Industria y Comerci
SUPERINTENDENCI
República de Colombi
Ministerio de Comercio, Industria y Turism

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-111688- -00000-0000
Fecha: 2012-07-04 14:40:39 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYli Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 170

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

SOLICITUD DE

PATENTE DE INVENCION
PCT ENTRADA EN FASE NACIONAL

21. EXPEDIENTE No. _____

54. TITULO: **DERIVADOS DE SULFONAMIDA COMO AGENTES INDUCTORES DE APOPTOSIS CON SELECTIVIDAD POR Bcl-2 PARA EL TRATAMIENTO DE CANCER Y ENFERMEDADES INMUNES**

52. CLASIFICACION INTERNACIONAL: **C07D 405/12, A61K 31/404, A61P 35/00, C07D 209/32, C07D 211/96, C07D 213/64, C07D 215/20, C07D 217/16, C07D 235/26, C07D 249/04, C07D 295/14, C07D 309/14, C07D 401/12, C07D 295/125, C07D 231/56, C07D 405/14**

71. SOLICITANTE: **ABBOTT LABORATORIES**

DOMICILIO: **100 Abbott Park Road, Abbott Park, Illinois 60064, ESTADOS UNIDOS DE AMERICA**

74. APODERADO: **Dra. MARGARITA CASTELLANOS A.**

22. BOGOTA, D.C., _____

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-111688 -00000-0000
Fecha: 2012-07-04 14:40:39 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 170

ición

DIRECCIÓN DE NUEVAS CREACIONES
SOLICITUD FASE NACIONAL -PCT

1	(12) TIPO DE SOLICITUD	X Patente de invención X Capítulo I	___ Patente de Modelo de Utilidad ___ Capitulo II

2 DATOS SOLICITUD INTERNACIONAL PCT (86)

Solicitud Internacional No.	**PCT/US2010/036919**	**Fecha**	**01/06/2010**
Publicación Internacional No.	**WO 2011/068561 A1**	**Fecha**	**09/06/2011**

3 (54) TÍTULO DE LA INVENCIÓN (200 caracteres o espacios máximos)

DERIVADOS DE SULFONAMIDA COMO AGENTES INDUCTORES DE APOPTOSIS CON SELECTIVIDAD POR Bcl-2 PARA EL TRATAMIENTO DE CANCER Y ENFERMEDADES INMUNES

4 CLASIFICACIÓN INTERNACIONAL (51) CIP

C07D 405/12, A61K 31/404, A61P 35/00, C07D 209/32, C07D 211/96, C07D 213/64, C07D 215/20, C07D 217/16, C07D 235/26, C07D 249/04, C07D 295/14, C07D 309/14, C07D 401/12, C07D 295/125, C07D 231/56, C07D 405/14

5 (71) SOLICITANTE (S) ___ Esta persona también es inventor. Para datos adicionales utilizar hoja de información complementaria

APELLIDOS O RAZÓN SOCIAL	NOMBRE	IDENTIFICACIÓN	TIPO
ABBOTT LABORATORIES			

6 DATOS DEL SOLICITANTE

DIRECCIÓN	**100 Abbott Park Road**	No. TELÉFONO	
CIUDAD	**Abbott Park**	E-MAIL	
DEPARTAMENTO/ESTADO	**Illinois 60064**	NACIONALIDAD O LUGAR DE CONSTITUCIÓN	**ESTADOS UNIDOS DE AMERICA**
PAÍS DE RESIDENCIA	**ESTADOS UNIDOS DE AMERICA**		

7 (72) INVENTOR (ES) complementaria Para datos adicionales utilizar hoja de información

APELLIDOS	NOMBRES	NACIONALIDAD
1. BRUNCKO	**MILAN**	**ESTADOUNIDENSE**
2. DING	**HONG**	**CHINA**
3. DOHERTY	**GEORGE A.**	**ESTADOUNIDENSE**
4. ELMORE	**STEVEN W.**	**ESTADOUNIDENSE**
5. HASVOLD	**LISA**	**ESTADOUNIDENSE**
6. HEXAMER	**LAURA**	**ESTADOUNIDENSE**

DIRECCIÓN DE CORREO ELECTRÓNICO:

8 DATOS INVENTOR (ES)

PAÍS RESIDENCIA	DEPARTAMENTO/ESTADO	CIUDAD	DIRECCIÓN
1. ESTADOS UNIDOS	**Illinois 60048**	**Green Oaks**	**31231 Prairie Ridge**
2. ESTADOS UNIDOS	**Illinois 60031**	**Gurnee**	**7465 Clem Drive**
3. ESTADOS UNIDOS	**Illinois 60048**	**Libertyville**	**1605 Bush Court**
4. ESTADOS UNIDOS	**Illinois 60062**	**Northbrook**	**239 Ash Lane**
5. ESTADOS UNIDOS	**Illinois 60030**	**Grayslake**	**552 Shakespeare Drive**
6. ESTADOS UNIDOS	**Illinois 60030**	**Grayslake**	**439 Gatewood Lane**

OTRO(S) SOLICITANTE(S) Y/O (OTRO(S)) INVENTOR(ES)

☐ Los demás solicitantes y/o (demás) inventores se indican en una hoja a continuación.

9 (74) ___ **REPRESENTANTE** X **APODERADO**

APELLIDOS	NOMBRES	IDENTIFICACIÓN
CASTELLANOS ABONDANO	**MARGARITA**	C.C . **39.779.654** T.P . **70.819**

DIRECCIÓN	**CALLE 94 A No. 7 A-09**	No. TELÉFONO	**7560770**
CIUDAD	**BOGOTA**	E-MAIL	**info@castellanosyco.co**
PAÍS	**COLOMBIA**	No. DE PROTOCOLO EN LA OFICINA	

000002

10	(30) DECLARACIONES DE PRIORIDAD	X SI ___ NO		
	(33) PAÍS DE ORIGEN	CÓDIGO PAÍS	(31) NÚMERO	(32) FECHA (AAAA/MM/DD)
	1. ESTADOS UNIDOS DE AMERICA	**US**	**12/631.404**	**2009/12/04**
	2.			
	3.			

11 DECLARACIÓN SOBRE USO DE RECURSOS GENÉTICOS O BIOLÓGICOS

Declaro que el objeto de la presente solicitud de patente fue obtenido a partir de recursos genéticos o biológicos de los que cualquiera de los países miembros de la Comunidad Andina es país de origen.

___ SI X NO

Nota: En caso afirmativo deberá anexar copia del contrato de acceso de recursos genéticos o productos derivados, o certificado o número de registro, expedido por la Autoridad competente.

12 DECLARACIÓN SOBRE USO DE CONOCIMIENTOS TRADICIONALES

Declaro que el objeto de la presente solicitud de patente fue obtenido a partir de conocimientos tradicionales de comunidades indígenas, afroamericanas o locales de países miembros de la Comunidad Andina.

___ SI X NO

Nota: En caso afirmativo deberá anexar la licencia o autorización de uso de conocimiento tradicional, o certificado, o número de registro expedido por la Autoridad competente.

13 REDUCCIÓN DE TASAS

Declaro que carezco de medios económicos para presentar la solicitud de patente.

___ SI X NO

Nota: En caso de ser persona natural y carecer de medios económicos, y por lo tanto, aplique la reducción de tasas a que se refiere la resolución vigente en tarifas, debe firmar la presente solicitud bajo la gravedad de juramento.

Micro, pequeñas y medianas empresas	**Universidades públicas o privadas**	**Entidades sin ánimo de lucro**
___ Copia simple de la declaración de renta del año inmediatamente anterior, o en su defecto prueba documental idónea. ___ Documento de constancia de cumplimiento con lo establecido en la ley 905 de 2004.	___ Copia acto de reconocimiento institucional emitido por el Ministerio de Educación. Acreditación Colciencias.	___ Copia de registro vigente en Cámara de comercio. ___ Hoja de información complementaria. ___ Otros, especificar

14 AUTORIZACIÓN DE NOTIFICACIÓN EN LÍNEA ___ SI X NO

Manifiesto que he leído y entendido perfectamente los términos y condiciones de uso de medios electrónicos para las notificaciones en línea a través de Internet de los actos administrativos proferidos por la Superintendencia de Industria y Comercio que deben ser notificados personalmente y, en consecuencia, autorizo el servicio de notificación a través de internet.

14	**COMPROBANTE DE PAGO O PAGO ELECTRÓNICO**	**N° 12-0056763, 12-0056765**	**Fecha Junio 6 de 2012**

15 FIRMA DEL SOLICITANTE, DEL APODERADO O DEL REPRESENTANTE LEGAL
Junto a cada firma, indicar el nombre del firmante y su calidad (si tal calidad no es obvia al leer el petitorio)

MARGARITA CASTELLANOS ABONDANO – APODERADO 04 JUL. 2012

16 ORDEN Y RELACIÓN DE DOCUMENTOS QUE ACOMPAÑAN LA SOLICITUD

Documentación Técnica
Solicitud Internacional en castellano

1. X Descripción — N° de folios: **719**
2. X Reivindicaciones — N° Reivindicaciones: **14**
3. ___ Dibujos y/o figuras — N° folios:
4. X Resumen.
5. ___ Certificado de depósito de material biológico si fuera el caso.
6. ___ Listado de secuencias de nucleótidos y/o aminoácidos en forma digital si fuera el caso.
7. ___ Arte final 12 x 12.
8. X Anexo formatos digitales (Dos CD'S: **1.** contiene el texto de la publicación internacional y **2.** contiene el texto de la descripción y reivindicaciones en español)

Documentación Jurídica

9. X Poderes, si fuera el caso.
10. ___ Documento que legalmente pruebe la cesión del inventor al solicitante o a su causante
11. ___ Copia del contrato de acceso de recursos genéticos o productos derivados, certificado o número de registro, si fuera el caso.
12. ___ Copia de la licencia o autorización de Conocimientos Tradicionales, certificado o número de registro, si fuera el caso.
13. ___ Documento que acredita la existencia y representación legal, cuando el solicitante es persona jurídica
14. X Comprobante de pago de la tasa de presentación de la solicitud.
15. ___ Comprobante de pago por reivindicación de prioridad.
16. ___ Comprobante de pago de la tasa por concepto de excedente de palabras en la publicación.
17. X Comprobante de pago por reivindicación adicional a 10.

Industria y Comercio
SUPERINTENDENCIA

HOJA DE INFORMACIÓN COMPLEMENTARIA PCT

1	(12) TIPO DE SOLICITUD	NUMERO DE RADICACIÓN
___ Patente de invención ___ Patente de Modelo de Utilidad		FECHA DE PRESENTACIÓN

4 (71) SOLICITANTE (S)

APELLIDOS O RAZÓN SOCIAL	NOMBRE	IDENTIFICACIÓN	TIPO
2. 3. 4.			

5 DATOS DEL SOLICITANTE

PAÍS DE RESIDENCIA	DEPARTAMENTO/ESTADO	CIUDAD	DIRECCIÓN
2. 3. 4.			

TELÉFONO	FAX	E-MAIL	NACIONALIDAD
2. 3. 4.			

6 (72) INVENTOR (ES)

APELLIDOS	NOMBRE	NACIONALIDAD
7. KUNZER	AARON	ESTADOUNIDENSE
8. MANTEI	ROBERT A.	ESTADOUNIDENSE
9. McCLELLAN	WILLIAM J.	ESTADOUNIDENSE
10. PARK	CHEOL-MIN	KOREANA
11. PETROS	ANDREW M.	ESTADOUNIDENSE
12. SONG	XIAOHONG	CHINA
13. SOUERS	ANDREW J.	ESTADOUNIDENSE

7 DATOS INVENTOR (ES)

DIRECCIÓN	CIUDAD	DEPARTAMENTO/ ESTADO	PAÍS RESIDENCIA
7. 615 W. Burr Oak Drive	Arlington Heights	Illinois 60004	ESTADOS UNIDOS
8. 4203 Carolyn Court	Franklin	Wisconsin 53132	ESTADOS UNIDOS
9. 1212 North Sheridan Road	Waukegan	Illinois 60085	ESTADOS UNIDOS
10. 5312 F. George Court	Gurnee	Illinois 60031	ESTADOS UNIDOS
11. 940 Ambria Drive	Mundelein	Illinois 60060	ESTADOS UNIDOS
12. 34037 Sulkey Drive	Grayslake	Illinois 60030	ESTADOS UNIDOS
13. 901 Hinman, Apt. 3 A	Evanston	Illinois 60202	ESTADOS UNIDOS

9 (30) DECLARACIONES DE PRIORIDAD

PAÍS DE ORIGEN	CÓDIGO PAÍS	NÚMERO	FECHA (AAAA/MM/DD)
4. 5. 6. 7. 8. 9. 10.			

Industria y Comercio
SUPERINTENDENCIA

HOJA DE INFORMACIÓN COMPLEMENTARIA PCT

1	(12) TIPO DE SOLICITUD	NUMERO DE RADICACIÓN
___ Patente de invención ___ Patente de Modelo de Utilidad		FECHA DE PRESENTACIÓN

4 (71) SOLICITANTE (S)

APELLIDOS O RAZÓN SOCIAL	NOMBRE	IDENTIFICACIÓN	TIPO
2. 3. 4.			

5 DATOS DEL SOLICITANTE

PAÍS DE RESIDENCIA	DEPARTAMENTO/ESTADO	CIUDAD	DIRECCIÓN
2. 3. 4.			

TELÉFONO	FAX	E-MAIL	NACIONALIDAD
2. 3. 4.			

6 (72) INVENTOR (ES)

APELLIDOS	NOMBRE	NACIONALIDAD
14. SULLIVAN	GERARD M.	ESTADOUNIDENSE
15. TAO	ZHI-FU	CHINA
16. WANG	GARY T.	ESTADOUNIDENSE
17. WANG	LE	ESTADOUNIDENSE
18. WANG	XILU	ESTADOUNIDENSE
19. WENDT	MICHAEL D.	ESTADOUNIDENSE
20. HANSEN	TODD M.	ESTADOUNIDENSE
21. PARK	CHANG H.	ESTADOUNIDENSE

7 DATOS INVENTOR (ES)

DIRECCIÓN	CIUDAD	DEPARTAMENTO/ ESTADO	PAÍS RESIDENCIA
14. 1212 Tulip Tree Court	Lake Villa	Illinois 60046	ESTADOS UNIDOS
15. 1532 Vineyard Drive	Gurnee	Illinois 60031	ESTADOS UNIDOS
16. 1904 Darnell Street	Libertyville	Illinois 60048	ESTADOS UNIDOS
17. 338 East Colonial Drive	Vernon Hills	Illinois 60061	ESTADOS UNIDOS
18. 34056 Sulkey Drive	Grayslake	Illinois 60030	ESTADOS UNIDOS
19. 1445 Maidstone Drive	Vernon Hills	Illinois 60061	ESTADOS UNIDOS
20. 191 Seymour Avenue	Grayslake	Illinois 60030	ESTADOS UNIDOS
21. 2871 North Southern Hills	Wadsworth	Illinois 60083	ESTADOS UNIDOS

9 (30) DECLARACIONES DE PRIORIDAD

PAÍS DE ORIGEN	CÓDIGO PAÍS	NÚMERO	FECHA (AAAA/MM/DD)
4. 5. 6. 7. 8. 9. 10.			

000005

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 12 - 0056765

Bogotá D.C., Junio 06 de 2012 - 14:36:15

RECIBIDO DE : CASTELLANOS Y Y CO NI 800.174.641

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	380505532	05/06/2012	8.540.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICACION EN MARCAS Y LEMAS COMERCIALES	120.000.00	120.000.00
				$120.000.00

SON: **CIENTO VEINTE MIL PESOS MONEDA CORRIENTE***

Responsable: _____
-*********-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-111688- -00000-0000
Fecha: 2012-07-04 14:40:39 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve. 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 170

000006

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 12 - 0056763

Bogotá D.C., Junio 06 de 2012 - 14:36:15

RECIBIDO DE : CASTELLANOS Y Y CO NI 800.174.641

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	380505532	05/06/2012	8.540.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCION	590.000.00	590.000.00
				$590.000.00

SON: **QUINIENTOS NOVENTA MIL PESOS MONEDA CORRIENTE***

Responsable: _____
-*******-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-111688--00000-0000
Fecha: 2012-07-04 14:40:39 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 170

000007

21661

COLOMBIA

PODER

El (los)

ABBOTT LABORATORIES

Domiciliados en

100 Abbott Park Road
Abbott Park
Illinois 60064
E.U.A.

Nombran por el presente a **XIMENA CASTELLANOS A. y/o MARGARITA CASTELLANOS A.** abogadas con oficinas en la Calle 94A No. 7A-09, Bogotá-Colombia para

y para obtener la protección de mi (nuestra) propiedad Industrial y con este fin autorizamos a dichos apoderados para que nos representen ante cualesquiera autoridades o personas de los órdenes administrativo, contencioso –administrativo y judicial en todo lo relacionado con los siguientes actos y gestiones:

a) Obtención de patentes de invención, modelos y dibujos industriales; registro de marcas de fabrica, de servicio, colectivas o defensivas y de denominaciones de origen, depósito de nombres y enseñas comerciales; su renovación, prórroga, inscripción de traspaso y cambio de nombre o domicilio, cancelación voluntaria y el registro de licencias de uso de esos derechos;
b) Para la obtención de registros sanitarios;
c) Acciones de oposición, observación, cancelación, nulidad, medidas cautelares y en general los juicios civiles, penales, administrativos o contencioso - administrativos que promovamos o se nos promuevan.

Pudiendo en todos los actos y gestiones arriba mencionados sustituir éste mandato, transigir, desistir, recibir, cancelar, renunciar, aceptar notificaciones y nombrar apoderados judiciales y extrajudiciales.

Finalmente, este poder ratifica la validez de todos los actos y solicitudes que, a nombre de la poderdante hubieren realizado los apoderados en relación con las facultades anteriormente enumeradas, antes de la suscripción del presente poder

Dado y firmado hoy 19 de Noviembre de 2008

en Abbott Park, Illinois,
ESTADOS UNIDOS DE AMERICA

por ABBOTT LABORATORIES
(firma ilegible) Paul D. Yasger
(El notario debe suscribir el documento en la pagina siguiente)

(Se requiere legalización consular o mediante apostilla)

POWER OF ATTORNEY

I (we) the undersigned

ABBOTT LABORATORIES

Of

100 Abbott Park Road
Abbott Park
Illinois 60064
USA

hereby grant(s) Power of Attorney to **XIMENA CASTELLANOS A. and /or MARGARITA CASTELLANOS** a. attorneys residing at Calle 94A No. 7A-09, Bogotá- Colombia, to

and to obtain the protection of my (our Industrial Property, for which purpose we authorize the said attorneys to represent us before any authorities, or persons, specially those, administrative, contentious and judicial, in all matters concerning the following:

a) Obtainment of patents, models and designs, registration of trademarks, service, collective and defensive marks, and of designations of origin; the deposit of trade names and ensigns; its renewal, extension, recordal of assignments, change of name or domicile, voluntary cancellation, and the registration of licenses of use of the above rights;
b) For the obtainment of Sanitary registrations;
c) Actions of opposition, cancellation, nullity, infringement, granting of licenses; and in general the civil, criminal and administrative suits related to those rights; actions and suits instituted by us or against us;

In all the above matters ~~they~~ may substitute this power of attorney, compromise, desist, cancel, receive, renounce, accept notifications and appoint attorneys in fact, in or out of court.

Finally, this power of attorney ratifies the validity of all acts and applications made by the representatives in the name of the signatory of this power of attorney, with regard to the faculties above given, before the execution of the present power of attorney.

Given and signed this 19 day of November, 2008

in Abbott Park, Illinois, USA 60064

by Paul D. Yasger, Assistant Secretary, DVP, Associate General Counsel
(Notary shall execute on the other side)

(Consular legalization or apostille is required)

CASTELLANOS & CO
ABOGADOS COLOMBIA
Calle 94A No. 7A-09- P.O.Box 6349 - Bogotá, Colombia
Tels.: (571) 610 74 20 / - Fax (571) 610 07 06 - e-mail info@castellanosyco.com

* Abbott at its sole discretion

COLOMBIA

CERTIFICADO NOTARIAL (Sociedad)

Hoy 19de Nov. del año 2008
compareció (eron) personalmente
Paul D. Yasger

a quienes conozco como la(s) personas que firma(n) en representación de la Sociedad (Compañía) denominada **ABBOTT LABORATORIES**

Certifico :

a) Que **ABBOTT LABORATORIES**

es una sociedad/Compañía legalmente constituida y existente de acuerdo con las leyes de Estados Unidos de América

b) Que el domicilio de dicha Sociedad/Compañía es

100 Abbott Park Road
Abbott Park
Illinois 60064
EUA

c) Que el objeto u objetos para los cuales se otorga el presente poder están comprendidos dentro del objeto social de la mencionada Sociedad /Compañía.

d) Que el Sr. Paul D. Yasger

esta autorizado para otorgar el presente poder. Lo anterior esta probado por medio de los siguientes documentos, que certifico he visto*

(Ciudad) Abbott Park

(Estado) Illinois

Hoy 19del Noviembre de 2008

(Notario Público)

*Los documentos debe identificarse con fecha y origen.

NOTARIAL CERTIFICATION (Corporation)

On this 19 day of November of 2008
personally appeared Paul D. Yasger,
whom I know to be the person(s) who signed this document as representative(s) of the Corporation /Company named
ABBOTT LABORATORIES

I certify:

a) That **ABBOTT LABORATORIES**

is a corporation (Company legally constituted and in existence in accordance with the laws of United States of America

b) That the domicile of said Corporation/Company is

100 Abbott Park Road
Abbott Park
Illinois 60064
USA

c) That the purpose or purposes for which the present Power of Attorney is granted are comprised within the object set forth in the charter of the mentioned Corporation/Company.

d) That Mr. Paul D. Yasger

is (are) authorized to grant the present Power of Attorney. The aforementioned was duly proven through the following documents and I duly certify having seen them*:Appointment of Corporate Officer dated March 6, 2008 and signed by Mile D. White, Chairman of the Board and Chief Executive Office of Abbott Laboratories

(City) Abbott Park

(State) Illinois

this 19th day of November of the year 2008

(Notary Public)

*Documents must be identified with date and origin

OFFICIAL SEAL
LINDA S LUTZ
NOTARY PUBLIC - STATE OF ILLINOIS
MY COMMISSION EXPIRES:07/23/11

CASTELLANOS & CO
ABOGADOS COLOMBIA
Calle 94A No. 7A-09- P.O.Box 6349 - Bogotá, Colombia
Tels.: (571) 610 74 20 / - Fax (571) 610 07 06 - e-mail info@castellanosyco.com

000009

STATE OF ILLINOIS

SECRETARY OF STATE

SPRINGFIELD, ILLINOIS

APOSTILLE

(Convention de La Haye du 5 Octobre 1961)

1. Country: United States of America

This public document

2. has been signed by LINDA S LUTZ

3. acting in the capacity of NOTARY PUBLIC, MCHENRY COUNTY

4. bears the seal/stamp of STATE OF ILLINOIS

Certified

5. Springfield, Illinois

6. NOVEMBER 26, 2008

7. by the Secretary of State, State of Illinois

8. No. S08DL14032

9. Seal/Stamp:



10. Signature:

Jesse White

JESSE WHITE
SECRETARY OF STATE
STATE OF ILLINOIS

Printed on recycled paper. Printed by authority of the State of Illinois. May 2008 — 50M — I 168.2

----------TRADUCCION OFICIAL No. 081205----------

de un documento escrito en INGLES, el cual para su identificación lleva el sello de la Traductora e Intérprete Oficial, Res. 2755/68 y 01144/97 de Minjusticia, al igual que la presente.----------

(Adjunto a un documento de PODER de Abbott Laboratories)

(fdo) ilegible

Notario Público

SELLO OFICIAL

Notario Público – Estado de Illinois

LINDA S. LUTZ

Mi comisión vence 07/23/11

ESTADO DE ILLINOIS

Secretario de Estado

Springfield, Illinois

APOSTILLA

(Convención de La Haya de 5 de Octubre de 1961)

1. País: Estados Unidos de América

Este documento público

2. ha sido firmado por LINDA S. LUTZ
3. actuando en su calidad de Notario Público, Condado de McHenry
4. lleva el sello del Estado de Illinois

CERTIFICADO

5. en Springfield, Illinois
6. El día 26 de Noviembre de 2008
7. Por el Secretario de Estado, Estado de Illinois
8. No. S08DL14032
9. Sello
10. Firma: (fdo) Jesse White

JESSE WHITE

Secretario de Estado

Estado de Illinois (Sello en oblea dorada)

ES TRADUCCION FIEL Y COMPLETA, a la cual me remito,

Bogotá, D. C., Diciembre 17, 2008

MINISTERIO DE
RELACIONES EXTERIORES

2008 DIC 17 P 12:14

JEFE DE LEGALIZACIONES
BOGOTA D.C.

NO SE ASUME
RESPONSABILIDAD
DEL TEXTO

854400

Doc Pague

ESE EN EL
DOCUMENTO DESEMPEÑA
AS FUNCIONES INDICADAS

13644254 1/4

C00012

000013

PATENT COOPERATION TREATY

PCT/US2010/036919

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

YASGER, Paul, D.
Abbott Laboratories
100 Abbott Park Road
Abbott Park, IL 60064
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*
08 August 2011 (08.08.2011)

Applicant's or agent's file reference
9696WOO2

IMPORTANT NOTIFICATION

International application No.
PCT/US2010/036919

International filing date *(day/month/year)*
01 June 2010 (01.06.2010)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address

PARK, Chang, H.
2871 North Southern Hills
Wadsworth, Illinois 60083
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address

PARK, Chang, H.
2871 North Southern Hills
Wadsworth, Illinois 60083
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:
☐ Notifications by e-mail authorized

3. Further observations, if necessary:
The person identified in Box 2 has been recorded as applicant for US only and inventor for all designated States.

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 87 20

Authorized officer
Adelise Andre
e-mail pt03.pct@wipo.int
Telephone No. +41 22 338 74 03

000014

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 June 2011 (09.06.2011)

PCT

(10) International Publication Number
WO 2011/068561 A1

(51) International Patent Classification:
C07D 405/12 (2006.01) *C07D 235/26* (2006.01)
A61K 31/404 (2006.01) *C07D 249/04* (2006.01)
A61P 35/00 (2006.01) *C07D 295/14* (2006.01)
C07D 209/32 (2006.01) *C07D 309/14* (2006.01)
C07D 211/96 (2006.01) *C07D 401/12* (2006.01)
C07D 213/64 (2006.01) *C07D 295/125* (2006.01)
C07D 215/20 (2006.01) *C07D 231/56* (2006.01)
C07D 217/16 (2006.01) *C07D 405/14* (2006.01)

(21) International Application Number:
PCT/US2010/036919

(22) International Filing Date:
1 June 2010 (01.06.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
12/631,404 4 December 2009 (04.12.2009) US

(71) Applicant *(for all designated States except US)*: **ABBOTT LABORATORIES** [US/US]; 100 Abbott Park Road, Abbott Park, Illinois 60064 (US).

(72) Inventor; and
(71) Applicant : **PARK, Chang, H.** [US/US]; 2871 North Southern Hills, Wadsworth, Illinois 60083 (US).

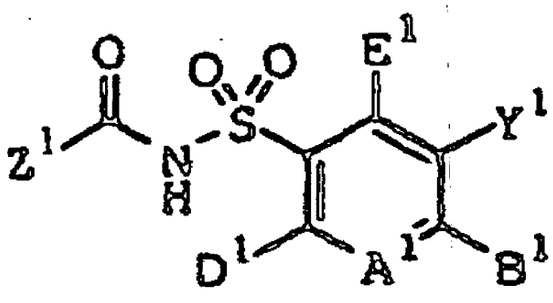
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BRUNCKO, Milan** [US/US]; 31231 Prairie Ridge, Green Oaks, Illinois 60048 (US). **DING, Hong** [CN/US]; 7465 Clem Drive, Gurnee, Illinois 60031 (US). **DOHERTY, George A.** [US/US]; 1605 Bush Court, Libertyville, Illinois 60048 (US). **ELMORE, Steven, W.** [US/US]; 239 Ash Lane, Northbrook, Illinois 60062 (US). **HASVOLD, Lisa** [US/US]; 552 Shakespeare Drive, Grayslake, Illinois 60030 (US). **HEXAMER, Laura** [US/US]; 439 Gatewood Lane, Grayslake, Illinois 60030 (US). **KUNZER, Aaron** [US/US]; 615 W. Burr Oak Drive, Arlington Heights, Illinois 60004 (US). **MANTEI, Robert, A.** [US/US]; 4203 Carolyn Court, Franklin, Wisconsin 53132 (US). **McCLELLAN, William, J.** [US/US]; 1212 North Sheridan Road, Waukegan, Illinois 60085 (US). **PARK, Cheol-Min** [KR/US]; 5312 F. George Court, Gurnee, Illinois 60031 (US). **PETROS, Andrew, M.** [US/US]; 940 Ambria Drive, Mundelein, Illinois 60060 (US). **SONG, Xiaohong** [CN/US]; 34037 Sulkey Drive, Grayslake, Illinois 60030 (US). **SOUERS, Andrew, J.** [US/US]; 901 Hinman, Apt. 3A, Evanston, Illinois 60202 (US). **SULLIVAN, Gerard, M.** [US/US]; 1212 Tulip Tree Court, Lake Villa, Illinois 60046 (US). **TAO, Zhi-Fu** [CN/US]; 1532 Vineyard Drive, Gurnee, Illinois 60031 (US). **WANG, Gary, T.** [US/US]; 1904 Darnell Street, Libertyville, Illinois 60048 (US). **WANG, Le** [US/US]; 338 East Colonial Drive, Vernon Hills, Illinois 60061 (US). **WANG, Xilu** [US/US]; 34056 Sulkey Drive, Grayslake, Illinois 60030 (US). **WENDT, Michael, D.** [US/US]; 1445 Maidstone Drive, Vernon Hills, Illinois 60061 (US). **HANSEN, Todd, M.** [US/US]; 191 Seymour Avenue, Grayslake, Illinois 60030 (US).

(74) Agents: **YASGER, Paul, D.** et al.; Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ,

[Continued on next page]

(54) Title: SULFONAMIDE DERIVATIVES AS BCL-2-SELECTIVE APOPTOSIS-INDUCING AGENTS FOR THE TREATMENT OF CANCER AND IMMUNE DISEASES



(I)

(57) Abstract: Disclosed are compounds (I) which inhibit the activity of anti-apoptotic Bcl-2 or Bcl xL proteins, compositions containing the compounds and methods of treating diseases during which are expressed anti apoptotic Bcl-2 protein.

WO 2011/068561 A1

WO 2011/068561 A1

CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to the identity of the inventor (Rule 4.17(i))*

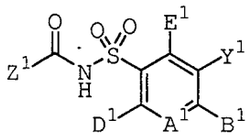
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *with international search report (Art. 21(3))*

WHAT IS CLAIMED IS:

1. A compound having formula I



(I),

or a therapeutically acceptable salt, prodrug or salt of prodrug thereof ,

A^1 is N or $C(A^2)$;

one or two or three or each of A^2, B^1, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$; and

Y^1 is H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ or $NHSO_2R^{17}$;

or

B^1 and Y^1, together with the atoms to which they are attached, are imidazole or triazole; and

one or two or each of A^2, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$;

R^1 is R^2, R^3, R^4 or R^5;

R^{1A} is C_1-C_6-alkyl, C_3-C_6-alkenyl or C_3-C_6-alkynyl;

R^2 is phenyl which is unfused or fused with arene, heteroarene or R^{2A}; R^{2A} is cycloalkane or heterocycloalkane;

R^3 is heteroaryl which is unfused or fused with benzene, heteroarene or R^{3A}; R^{3A} is cycloalkane or heterocycloalkane;

R^4 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with arene, heteroarene or R^{4A}; R^{4A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^5 is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^6 is C_2-C_5-spiroalkyl, each of which is unsubstituted or substituted with OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ or $N(CH_3)_2$;

R^{6A} and R^{6B} are independently selected alkyl or, together with the N to which they are attached, R^{6C};

R^{6C} is aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, each having one CH_2 moiety unreplaced or replaced with O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH;

R^7 is R^8, R^9, R^{10} or R^{11};

R^8 is phenyl which is unfused or fused with arene, heteroarene or R^{8A};

R^{8A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^9 is heteroaryl which is unfused or fused with arene, heteroarene or R^{9A}; R^{9A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{10} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{10A}; R^{10A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{11} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{12} is R^{13}, R^{14}, R^{15} or R^{16};

R^{13} is phenyl which is unfused or fused with arene, heteroarene or R^{13A}; R^{13A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{14} is heteroaryl, each of which is unfused or fused with arene, heteroarene or R^{14A}; R^{14A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{15} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene, each of which is unfused or fused with arene, heteroarene or R^{15A}; R^{15A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{16} is alkyl, alkenyl or alkynyl;

R^{17} is R^{18}, R^{19}, R^{20} or R^{21};

R^{18} is phenyl which is unfused or fused with arene, heteroarene or R^{18A}; R^{18A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{19} is heteroaryl which is unfused or fused with arene, heteroarene or R^{19A}; R^{19A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{20} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{20A}; R^{20A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{21} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{22} is R^{23}, R^{24} or R^{25};

R^{23} is phenyl which is unfused or fused with arene, heteroarene or R^{23A}; R^{23A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{24} is heteroarene which is unfused or fused with arene, heteroarene or R^{24A}; R^{24A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{25} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{25A}; R^{25A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

Z^1 is R^{26} or R^{27}, each of which is substituted with R^{28}, R^{29} or R^{30}, each of which is substituted with F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} or $N(R^{32})R^{37}$;

R^{26} is phenyl which is unfused or fused with arene or heteroarene;

R^{27} is heteroarene which is unfused or fused with arene or heteroarene;

R^{28} is phenyl which is unfused or fused with arene, heteroarene or R^{28A}; R^{28A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{29} is heteroaryl or R^{29A}; R^{29A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{30} is cycloalkyl or cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{30A}; R^{30A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{31} and R^{31A} are independently F, Cl, Br or alkyl or are taken together and are C_2-C_5-spiroalkyl;

R^{32} is R^{33}, $C(O)R^{33}$ or $C(O)OR^{33}$;

R^{33} is R^{34} or R^{35};

R^{34} is phenyl which is unfused or fused with aryl, heteroaryl or R^{34A}; R^{34A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{35} is alkyl which is unsubstituted or substituted with R^{36};

R^{36} is phenyl which is unfused or fused with arene, heteroarene or R^{36A}; R^{36A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{37} is R^{38}, R^{39} or R^{40}, each of which is substituted with F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ or SO_2R^{41};

R^{38} is phenyl which is unfused or fused with arene, heteroarene or R^{38A}; R^{38A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{39} is heteroaryl which is unfused or fused with arene, heteroarene or R^{39A}; R^{39A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{40} is C_3-C_8-cycloalkyl or C_4-C_8-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{40A}; R^{40A} cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{41} is R^{42}, R^{43}, R^{44} or R^{45};

R^{42} is phenyl which is unfused or fused with arene, heteroarene or R^{42A}; R^{42A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{43} is heteroaryl which is unfused or fused with arene, heteroarene or R^{43A}; R^{43A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{44} is C_3-C_9-cycloalkyl or C_4-C_7-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2

or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{44A}; R^{44A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{45} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two independently selected R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{46} is R^{47}, R^{48} or R^{49};

R^{47} is phenyl which is unfused or fused with arene, heteroarene or R^{47A}; R^{47A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{48} is heteroaryl or R^{48A}; R^{48A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{49} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{49A}; R^{49A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein the moieties represented by R^{26} and R^{27} are further substituted by one or two or three of independently selected R^{50A}, OR^{50A}, SR^{50A}, $S(O)R^{50A}$, SO_2R^{50A} or NHR^{50A};

R^{50A} is R^{51A}, R^{52A}, R^{53A} or R^{54A};

R^{51A} is phenyl which is unfused or fused with benzene, heteroarene or R^{51AA},

wherein R^{51AA} is cycloalkane, cycloalkene or heterocycloalkane heterocycloalkene,

R^{52A} is heteroaryl;

R^{53A} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl; each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{53AA};

wherein R^{53AA} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{54A} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{55AA}, OR^{55AA}, SR^{55AA}, $S(O)R^{55AA}$, SO_2R^{55AA}, NHR^{55AA}, $N(R^{55AA})_2$, $C(O)R^{55AA}$, $C(O)NH_2$, $C(O)NHR^{55AA}$, $NHC(O)R^{55AA}$, $NHSO_2R^{55AA}$, $NHC(O)OR^{55AA}$, SO_2NH_2, SO_2NHR^{55AA}, $SO_2N(R^{55AA})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55AA}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{55AA} is alkyl, alkenyl, alkynyl, phenyl or heteroaryl, or R^{56A};

R^{56A} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N;

wherein moieties represented by R^2, R^3, R^4, R^6, R^{6C}, R^8, R^{8A}, R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{18}, R^{19}, R^{20}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{34}, R^{36}, R^{38}, R^{39}, R^{40}, R^{42}, R^{43}, R^{44}, R^{47}, R^{48}, and R^{49} are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five independently selected R^{50AA}, R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{50AA} is spirocyclyl;

R^{50} is R^{51}, R^{52}, R^{53} or R^{54};

R^{51} is phenyl which is unfused or fused with arene, heteroarene or R^{51B}; R^{51B} is cycloalkane, cycloalkene; heterocycloalkane or heterocycloalkene;

R^{52} is heteroaryl;

R^{53} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{53B};

wherein R^{53B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

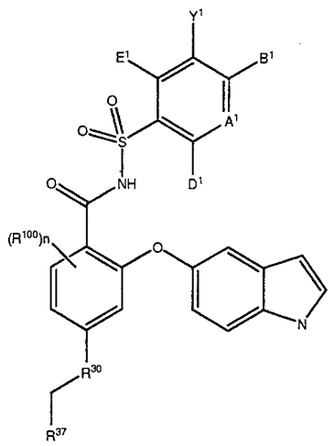
R^{54} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{55} is alkyl, alkenyl, alkynyl, phenyl, heteroaryl or R^{56};

wherein the alkyl, alkenyl, alkynyl are unsubstituted or substituted with OCH_3; and

R^{56} is C_3-C_8-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N.

2. A compound having formula II



(II),

or a therapeutically acceptable salt, prodrug or salt of prodrug thereof ,

wherein

R^{100} is as described for substituents on R^{26};

n is 0, 1, 2, or 3;

A^1 is N or $C(A^2)$;.

one or two or three or each of A^2, B^1, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$; and

Y^1 is H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ or $NHSO_2R^{17}$;

or

B^1 and Y^1, together with the atoms to which they are attached, are imidazole or triazole; and

one or two or each of A^2, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$;

R^1 is R^2, R^3, R^4 or R^5;

R^{1A} is C_1-C_6-alkyl, C_3-C_6-alkenyl or C_3-C_6-alkynyl;

R^2 is phenyl which is unfused or fused with arene, heteroarene or R^{2A}; R^{2A} is cycloalkane or heterocycloalkane;

R^3 is heteroaryl which is unfused or fused with benzene, heteroarene or R^{3A}; R^{3A} is cycloalkane or heterocycloalkane;

R^4 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with arene, heteroarene or R^{4A}; R^{4A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^5 is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^6 is C_2-C_5-spiroalkyl, each of which is unsubstituted or substituted with OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ or $N(CH_3)_2$;

R^{6A} and R^{6B} are independently selected alkyl or, together with the N to which they are attached, R^{6C};

R^{6C} is aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, each having one CH_2 moiety unreplaced or replaced with O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH;

R^7 is R^8, R^9, R^{10} or R^{11};

R^8 is phenyl which is unfused or fused with arene, heteroarene or R^{8A};

R^{8A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^9 is heteroaryl which is unfused or fused with arene, heteroarene or R^{9A}; R^{9A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{10} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{10A}; R^{10A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{11} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{12} is R^{13}, R^{14}, R^{15} or R^{16};

R^{13} is phenyl which is unfused or fused with arene, heteroarene or R^{13A}; R^{13A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{14} is heteroaryl, each of which is unfused or fused with arene, heteroarene or R^{14A}; R^{14A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{15} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene, each of which is unfused or fused with arene, heteroarene or R^{15A}; R^{15A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{16} is alkyl, alkenyl or alkynyl;

R^{17} is R^{18}, R^{19}, R^{20} or R^{21};

R^{18} is phenyl which is unfused or fused with arene, heteroarene or R^{18A}; R^{18A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{19} is heteroaryl which is unfused or fused with arene, heteroarene or R^{19A}; R^{19A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{20} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{20A}; R^{20A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{21} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{22} is R^{23}, R^{24} or R^{25};

R^{23} is phenyl which is unfused or fused with arene, heteroarene or R^{23A}; R^{23A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{24} is heteroarene which is unfused or fused with arene, heteroarene or R^{24A}; R^{24A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{25} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{25A}; R^{25A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{30} is cycloalkyl or cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and

one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{30A}; R^{30A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; each of which is substituted with F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} or $N(R^{32})R^{37}$;

R^{31} and R^{31A} are independently F, Cl, Br or alkyl or are taken together and are C_2-C_5-spiroalkyl;

R^{32} is R^{33}, $C(O)R^{33}$ or $C(O)OR^{33}$;

R^{33} is R^{34} or R^{35};

R^{34} is phenyl which is unfused or fused with aryl, heteroaryl or R^{34A}; R^{34A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{35} is alkyl which is unsubstituted or substituted with R^{36};

R^{36} is phenyl which is unfused or fused with arene, heteroarene or R^{36A}; R^{36A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{37} is R^{38}, R^{39} or R^{40}, each of which is substituted with F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ or SO_2R^{41};

R^{38} is phenyl which is unfused or fused with arene, heteroarene or R^{38A}; R^{38A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{39} is heteroaryl which is unfused or fused with arene, heteroarene or R^{39A}; R^{39A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{40} is C_3-C_8-cycloalkyl or C_4-C_8-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{40A}; R^{40A} cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{41} is R^{42}, R^{43}, R^{44} or R^{45};

R^{42} is phenyl which is unfused or fused with arene, heteroarene or R^{42A}; R^{42A} is cycloalkane, cycloalkene; heterocycloalkane or heterocycloalkene;

R^{43} is heteroaryl which is unfused or fused with arene, heteroarene or R^{43A}; R^{43A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{44} is C_3-C_9-cycloalkyl or C_4-C_7-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{44A}; R^{44A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{45} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two independently selected R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{46} is R^{47}, R^{48} or R^{49};

R^{47} is phenyl which is unfused or fused with arene, heteroarene or R^{47A}; R^{47A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{48} is heteroaryl or R^{48A}; R^{48A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{49} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{49A}; R^{49A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein moieties represented by R^2 R^3 R^4, R^6, R^{6C}, R^8, R^{8A} R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{18}, R^{19}, R^{20}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{34}, R^{36}, R^{38}, R^{39}, R^{40}, R^{42}, R^{43}, R^{44}, R^{47}, R^{48}, and R^{49} are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five independently selected R^{50AA}, R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, C(N)NH_2, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{50AA} is spirocyclyl;

R^{50} is R^{51}, R^{52}, R^{53} or R^{54};

R^{51} is phenyl which is unfused or fused with arene, heteroarene or R^{51B}; R^{51B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{52} is heteroaryl;

R^{53} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{53B};

wherein R^{53B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

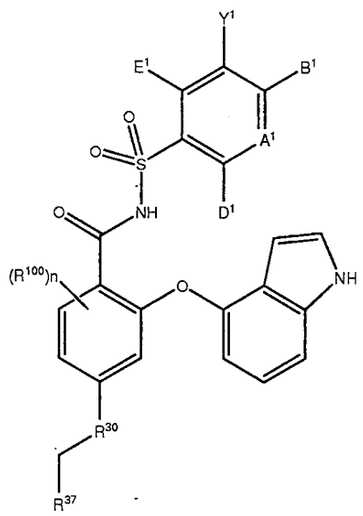
R^{54} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{55} is alkyl, alkenyl, alkynyl, phenyl, heteroaryl or R^{56};

wherein the alkyl, alkenyl, alkynyl are unsubstituted or substituted with OCH_3; and

R^{56} is C_3-C_8-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N.

3. A compound having formula III



(III),

or a therapeutically acceptable salt, prodrug or salt of prodrug thereof ,

wherein

R^{100} is as described for substituents on R^{26};

n is 0, 1, 2, or 3;

A^1 is N or $C(A^2)$;

one or two or three or each of A^2, B^1, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$,

$NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$; and

Y^1 is H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ or $NHSO_2R^{17}$;

or

B^1 and Y^1, together with the atoms to which they are attached, are imidazole or triazole; and

one or two or each of A^2, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$;

R^1 is R^2, R^3, R^4 or R^5;

R^{1A} is C_1-C_6-alkyl, C_3-C_6-alkenyl or C_3-C_6-alkynyl;

R^2 is phenyl which is unfused or fused with arene, heteroarene or R^{2A}; R^{2A} is cycloalkane or heterocycloalkane;

R^3 is heteroaryl which is unfused or fused with benzene, heteroarene or R^{3A}; R^{3A} is cycloalkane or heterocycloalkane;

R^4 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with arene, heteroarene or R^{4A}; R^{4A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^5 is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^6 is C_2-C_5-spiroalkyl, each of which is unsubstituted or substituted with OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ or $N(CH_3)_2$;

R^{6A} and R^{6B} are independently selected alkyl or, together with the N to which they are attached, R^{6C};

R^{6C} is aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, each having one CH_2 moiety unreplaced or replaced with O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH;

R^7 is R^8, R^9, R^{10} or R^{11};

R^8 is phenyl which is unfused or fused with arene, heteroarene or R^{8A};

R^{8A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^9 is heteroaryl which is unfused or fused with arene, heteroarene or R^{9A}; R^{9A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{10} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{10A}; R^{10A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{11} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{12} is R^{13}, R^{14}, R^{15} or R^{16};

R^{13} is phenyl which is unfused or fused with arene, heteroarene or R^{13A}; R^{13A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{14} is heteroaryl, each of which is unfused or fused with arene, heteroarene or R^{14A}; R^{14A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{15} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene, each of which is unfused or fused with arene, heteroarene or R^{15A}; R^{15A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{16} is alkyl, alkenyl or alkynyl;

R^{17} is R^{18}, R^{19}, R^{20} or R^{21};

R^{18} is phenyl which is unfused or fused with arene, heteroarene or R^{18A}; R^{18A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{19} is heteroaryl which is unfused or fused with arene, heteroarene or R^{19A}; R^{19A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{20} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{20A}; R^{20A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{21} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{22} is R^{23}, R^{24} or R^{25};

R^{23} is phenyl which is unfused or fused with arene, heteroarene or R^{23A}; R^{23A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{24} is heteroarene which is unfused or fused with arene, heteroarene or R^{24A}; R^{24A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{25} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{25A}; R^{25A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{30} is cycloalkyl or cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{30A}; R^{30A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; each of which is substituted with F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} or $N(R^{32})R^{37}$;

R^{31} and R^{31A} are independently F, Cl, Br or alkyl or are taken together and are C_2-C_5-spiroalkyl;

R^{32} is R^{33}, $C(O)R^{33}$ or $C(O)OR^{33}$;

R^{33} is R^{34} or R^{35};

R^{34} is phenyl which is unfused or fused with aryl, heteroaryl or R^{34A}; R^{34A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{35} is alkyl which is unsubstituted or substituted with R^{36};

R^{36} is phenyl which is unfused or fused with arene, heteroarene or R^{36A}; R^{36A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{37} is R^{38}, R^{39} or R^{40}, each of which is substituted with F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ or SO_2R^{41};

R^{38} is phenyl which is unfused or fused with arene, heteroarene or R^{38A}; R^{38A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{39} is heteroaryl which is unfused or fused with arene, heteroarene or R^{39A}; R^{39A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{40} is C_3-C_8-cycloalkyl or C_4-C_8-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{40A}; R^{40A} cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{41} is R^{42}, R^{43}, R^{44} or R^{45};

R^{42} is phenyl which is unfused or fused with arene, heteroarene or R^{42A}; R^{42A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{43} is heteroaryl which is unfused or fused with arene, heteroarene or R^{43A}; R^{43A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{44} is C_3-C_9-cycloalkyl or C_4-C_7-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{44A}; R^{44A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{45} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two independently selected R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{46} is R^{47}, R^{48} or R^{49};

R^{47} is phenyl which is unfused or fused with arene, heteroarene or R^{47A}; R^{47A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{48} is heteroaryl or R^{48A}; R^{48A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{49} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{49A}; R^{49A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein moieties represented by R^2 R^3 R^4, R^6, R^{6C}, R^8, R^{8A} R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{18}, R^{19}, R^{20}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{34}, R^{36}, R^{38}, R^{39}, R^{40}, R^{42}, R^{43}, R^{44}, R^{47}, R^{48}, and R^{49} are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five independently selected R^{50AA}, R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50},

$N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{50AA} is spirocyclyl;

R^{50} is R^{51}, R^{52}, R^{53} or R^{54};

R^{51} is phenyl which is unfused or fused with arene, heteroarene or R^{51B}; R^{51B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{52} is heteroaryl;

R^{53} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{53B};

wherein R^{53B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

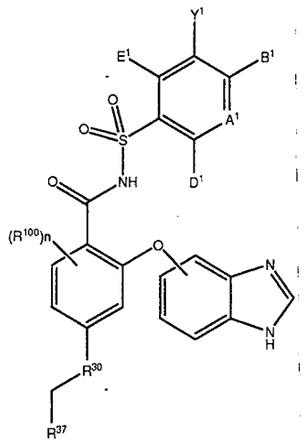
R^{54} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{55} is alkyl, alkenyl, alkynyl, phenyl, heteroaryl or R^{56};

wherein the alkyl, alkenyl, alkynyl are unsubstituted or substituted with OCH_3; and

R^{56} is C_3-C_8-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N.

4. A compound having formula IV



(IV),

or a therapeutically acceptable salt, prodrug or salt of prodrug thereof ,

wherein

R^{100} is as described for substituents on R^{26};

n is 0, 1, 2, or 3;

A^1 is N or $C(A^2)$;

one or two or three or each of A^2, B^1, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CN, CF_3, C(O)OH; $C(O)NH_2$ or $C(O)OR^{1A}$; and

Y^1 is H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ or $NHSO_2R^{17}$;

or

B^1 and Y^1, together with the atoms to which they are attached, are imidazole or triazole; and

one or two or each of A^2, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$;

R^1 is R^2, R^3, R^4 or R^5;

R^{1A} is C_1-C_6-alkyl, C_3-C_6-alkenyl or C_3-C_6-alkynyl;

R^2 is phenyl which is unfused or fused with arene, heteroarene or R^{2A}; R^{2A} is cycloalkane or heterocycloalkane;

R^3 is heteroaryl which is unfused or fused with benzene, heteroarene or R^{3A}; R^{3A} is cycloalkane or heterocycloalkane;

R^4 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with arene, heteroarene or R^{4A}; R^{4A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^5 is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^6 is C_2-C_5-spiroalkyl, each of which is unsubstituted or substituted with OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ or $N(CH_3)_2$;

R^{6A} and R^{6B} are independently selected alkyl or, together with the N to which they are attached, R^{6C};

R^{6C} is aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, each having one CH_2 moiety unreplaced or replaced with O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH;

R^7 is R^8, R^9, R^{10} or R^{11};

R^8 is phenyl which is unfused or fused with arene, heteroarene or R^{8A};

R^{8A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^9 is heteroaryl which is unfused or fused with arene, heteroarene or R^{9A}; R^{9A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{10} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{10A}; R^{10A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{11} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{12} is R^{13}, R^{14}, R^{15} or R^{16};

R^{13} is phenyl which is unfused or fused with arene, heteroarene or R^{13A}; R^{13A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{14} is heteroaryl, each of which is unfused or fused with arene, heteroarene or R^{14A}; R^{14A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{15} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene, each of which is unfused or fused with arene, heteroarene or R^{15A}; R^{15A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{16} is alkyl, alkenyl or alkynyl;

R^{17} is R^{18}, R^{19}, R^{20} or R^{21};

R^{18} is phenyl which is unfused or fused with arene, heteroarene or R^{18A}; R^{18A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{19} is heteroaryl which is unfused or fused with arene, heteroarene or R^{19A}; R^{19A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{20} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{20A}; R^{20A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{21} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{22} is R^{23}, R^{24} or R^{25};

R^{23} is phenyl which is unfused or fused with arene, heteroarene or R^{23A}; R^{23A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{24} is heteroarene which is unfused or fused with arene, heteroarene or R^{24A}; R^{24A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{25} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{25A}; R^{25A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{30} is cycloalkyl or cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and

one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{30A}; R^{30A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; each of which is substituted with F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} or $N(R^{32})R^{37}$;

R^{31} and R^{31A} are independently F, Cl, Br or alkyl or are taken together and are C_2-C_5-spiroalkyl;

R^{32} is R^{33}, $C(O)R^{33}$ or $C(O)OR^{33}$;

R^{33} is R^{34} or R^{35};

R^{34} is phenyl which is unfused or fused with aryl, heteroaryl or R^{34A}; R^{34A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{35} is alkyl which is unsubstituted or substituted with R^{36};

R^{36} is phenyl which is unfused or fused with arene, heteroarene or R^{36A}; R^{36A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{37} is R^{38}, R^{39} or R^{40}, each of which is substituted with F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ or SO_2R^{41};

R^{38} is phenyl which is unfused or fused with arene, heteroarene or R^{38A}; R^{38A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{39} is heteroaryl which is unfused or fused with arene, heteroarene or R^{39A}; R^{39A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{40} is C_3-C_8-cycloalkyl or C_4-C_8-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{40A}; R^{40A} cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{41} is R^{42}, R^{43}, R^{44} or R^{45};

R^{42} is phenyl which is unfused or fused with arene, heteroarene or R^{42A}; R^{42A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{43} is heteroaryl which is unfused or fused with arene, heteroarene or R^{43A}; R^{43A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{44} is C_3-C_9-cycloalkyl or C_4-C_7-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{44A}; R^{44A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{45} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two independently selected R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{46} is R^{47}, R^{48} or R^{49};

R^{47} is phenyl which is unfused or fused with arene, heteroarene or R^{47A}; R^{47A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{48} is heteroaryl or R^{48A}; R^{48A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{49} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{49A}; R^{49A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein moieties represented by R^2 R^3 R^4, R^6, R^{6C}, R^8, R^{8A} R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{18}, R^{19}, R^{20}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{34}, R^{36}, R^{38}, R^{39}, R^{40}, R^{42}, R^{43}, R^{44}, R^{47}, R^{48}, and R^{49} are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five independently selected R^{50AA}, R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{50AA} is spirocyclyl;

R^{50} is R^{51}, R^{52}, R^{53} or R^{54};

R^{51} is phenyl which is unfused or fused with arene, heteroarene or R^{51B}; R^{51B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{52} is heteroaryl;

R^{53} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{53B};

wherein R^{53B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

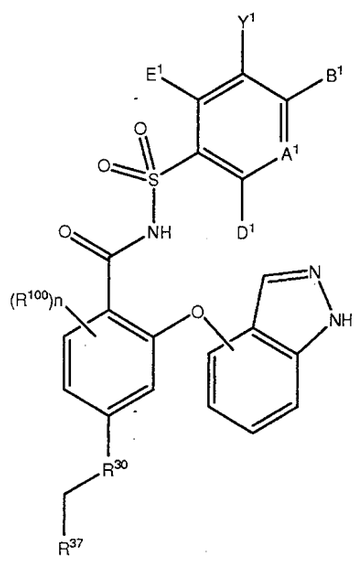
R^{54} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{55} is alkyl, alkenyl, alkynyl, phenyl, heteroaryl or R^{56};

wherein the alkyl, alkenyl, alkynyl are unsubstituted or substituted with OCH_3; and

R^{56} is C_3-C_8-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N.

5. A compound having formula V



(V),

or a therapeutically acceptable salt, prodrug or salt of prodrug thereof , wherein

R^{100} is as described for substituents on R^{26};

n is 0, 1, 2, or 3;

A^1 is N or $C(A^2)$;

one or two or three or each of A^2, B^1, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$,

$NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$; and

Y^1 is H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ or $NHSO_2R^{17}$;

or

B^1 and Y^1, together with the atoms to which they are attached, are imidazole or triazole; and

one or two or each of A^2, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$;

R^1 is R^2, R^3, R^4 or R^5;

R^{1A} is C_1-C_6-alkyl, C_3-C_6-alkenyl or C_3-C_6-alkynyl;

R^2 is phenyl which is unfused or fused with arene, heteroarene or R^{2A}; R^{2A} is cycloalkane or heterocycloalkane;

R^3 is heteroaryl which is unfused or fused with benzene, heteroarene or R^{3A}; R^{3A} is cycloalkane or heterocycloalkane;

R^4 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with arene, heteroarene or R^{4A}; R^{4A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^5 is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^6 is C_2-C_5-spiroalkyl, each of which is unsubstituted or substituted with OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ or $N(CH_3)_2$;

R^{6A} and R^{6B} are independently selected alkyl or, together with the N to which they are attached, R^{6C};

R^{6C} is aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, each having one CH_2 moiety unreplaced or replaced with O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH;

R^7 is R^8, R^9, R^{10} or R^{11};

R^8 is phenyl which is unfused or fused with arene, heteroarene or R^{8A};

R^{8A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^9 is heteroaryl which is unfused or fused with arene, heteroarene or R^{9A}; R^{9A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{10} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{10A}; R^{10A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{11} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{12} is R^{13}, R^{14}, R^{15} or R^{16};

R^{13} is phenyl which is unfused or fused with arene, heteroarene or R^{13A}; R^{13A} is cycloalkane, cycloalkene; heterocycloalkane or heterocycloalkene;

R^{14} is heteroaryl, each of which is unfused or fused with arene, heteroarene or R^{14A}; R^{14A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{15} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene, each of which is unfused or fused with arene, heteroarene or R^{15A}; R^{15A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{16} is alkyl, alkenyl or alkynyl;

R^{17} is R^{18}, R^{19}, R^{20} or R^{21};

R^{18} is phenyl which is unfused or fused with arene, heteroarene or R^{18A}; R^{18A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{19} is heteroaryl which is unfused or fused with arene, heteroarene or R^{19A}; R^{19A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{20} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{20A}; R^{20A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{21} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{22} is R^{23}, R^{24} or R^{25};

R^{23} is phenyl which is unfused or fused with arene, heteroarene or R^{23A}; R^{23A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{24} is heteroarene which is unfused or fused with arene, heteroarene or R^{24A}; R^{24A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{25} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{25A}; R^{25A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{30} is cycloalkyl or cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{30A}; R^{30A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; each of which is substituted with F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} or $N(R^{32})R^{37}$;

R^{31} and R^{31A} are independently F, Cl, Br or alkyl or are taken together and are C_2-C_5-spiroalkyl;

R^{32} is R^{33}, $C(O)R^{33}$ or $C(O)OR^{33}$;

R^{33} is R^{34} or R^{35};

R^{34} is phenyl which is unfused or fused with aryl, heteroaryl or R^{34A}; R^{34A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{35} is alkyl which is unsubstituted or substituted with R^{36};

R^{36} is phenyl which is unfused or fused with arene, heteroarene or R^{36A}; R^{36A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{37} is R^{38}, R^{39} or R^{40}, each of which is substituted with F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ or SO_2R^{41};

R^{38} is phenyl which is unfused or fused with arene, heteroarene or R^{38A}; R^{38A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{39} is heteroaryl which is unfused or fused with arene, heteroarene or R^{39A}; R^{39A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{40} is C_3-C_8-cycloalkyl or C_4-C_8-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{40A}; R^{40A} cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{41} is R^{42}, R^{43}, R^{44} or R^{45};

R^{42} is phenyl which is unfused or fused with arene, heteroarene or R^{42A}; R^{42A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{43} is heteroaryl which is unfused or fused with arene, heteroarene or R^{43A}; R^{43A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{44} is C_3-C_9-cycloalkyl or C_4-C_7-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{44A}; R^{44A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{45} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two independently selected R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{46} is R^{47}, R^{48} or R^{49};

R^{47} is phenyl which is unfused or fused with arene, heteroarene or R^{47A}; R^{47A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{48} is heteroaryl or R^{48A}; R^{48A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{49} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{49A}; R^{49A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein moieties represented by R^2 R^3 R^4, R^6, R^{6C}, R^8, R^{8A} R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{18}, R^{19}, R^{20}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{34}, R^{36}, R^{38}, R^{39}, R^{40}, R^{42}, R^{43}, R^{44}, R^{47}, R^{48}, and R^{49} are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five independently selected R^{50AA}, R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50},

$N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{50AA} is spirocyclyl;

R^{50} is R^{51}, R^{52}, R^{53} or R^{54};

R^{51} is phenyl which is unfused or fused with arene, heteroarene or R^{51B}; R^{51B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{52} is heteroaryl;

R^{53} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{53B};

wherein R^{53B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{54} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{55} is alkyl, alkenyl, alkynyl, phenyl, heteroaryl or R^{56};

wherein the alkyl, alkenyl, alkynyl are unsubstituted or substituted with OCH_3; and

R^{56} is C_3-C_8-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N.

6. The compound of claim 1, claim 2, claim 3, claim 4, or claim 5, wherein

A^1 is $C(A^2)$; and

A^2 is H.

7. The compound of claim 1, claim 2, claim 3, claim 4, or claim 5, wherein

A^1 is $C(A^2)$ or N;

A^2 is H; and

B^1 is NHR^1.

8. The compound of claim 1, claim 2, claim 3, claim 4, or claim 5, wherein
A^1 is $C(A^2)$ or N;
A^2 is H;
B^1 is NHR^1; and
D^1 is H.

9. The compound of claim 1, claim 2, claim 3, claim 4, or claim 5, wherein
A^1 is $C(A^2)$ or N;
A^2 is H;
B^1 is NHR^1;
D^1 is H; and
E^1 is H.

10. The compound of claim 1, claim 2, claim 3, claim 4, or claim 5, wherein
A^1 is $C(A^2)$ or N;
A^2 is H;
B^1 is NHR^1;
D^1 is H;
E^1 is H; and
Y^1 is NO_2.

11. A compound of claim 1, wherein the compound is chosen from:
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;
2-(benzyloxy)-4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(2-phenylethoxy)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(phenylthio)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(phenylthio)-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-(phenylthio)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(phenylsulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(phenylsulfinyl)benzamide;

2-benzyl-4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

2-benzyl-4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

2-benzyl-4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(2-phenylethyl)benzamide;

2-(benzylamino)-4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

2-anilino-4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

2-anilino-4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-methoxy-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indazol-5-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indazol-5-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-(1,2,3,4-tetrahydroquinolin-6-yloxy)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)-2-(1,2,3,4-tetrahydroquinolin-6-yloxy)benzamide;

4-(4-((4'-chloro-4-(pyrrolidin-1-ylmethyl)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-pyrrolidin-1-ylethyl)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((1-cyclopentylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)-3-isobutylpiperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-(2,4-dioxo-3-azabicyclo(3.2.0)hept-3-yl)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-(3,3-dimethyl-2-oxoazetidin-1-yl)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-(4-nitro-2H-1,2,3-triazol-2-yl)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((2-(2-piperidin-1-ylethoxy)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-((((1-ethylpyrrolidin-2-yl)methyl)amino)carbonyl)-4-methoxyphenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1-naphthyloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(2-naphthyloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-(2-naphthyloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(2-naphthyloxy)-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(quinolin-7-yloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(quinolin-6-yloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(isoquinolin-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(isoquinolin-5-yloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(quinolin-6-yloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-6-yloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(isoquinolin-7-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(isoquinolin-7-yloxy)benzamide;

4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-4-yloxy)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-4-yloxy)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-methoxyphenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-methylphenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
N-((3-((chloro(difluoro)methyl)sulfonyl)-4-((3-(dimethylamino)propyl)amino)phenyl)sulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

2-(1H-indol-4-yloxy)-4-(4-((2-(4-methoxyphenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4,4-dimethyl-2-(4-(trifluoromethyl)phenyl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4,4-dimethyl-2-(4-(trifluoromethoxy)phenyl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4,4-dimethyl-2-(3-(trifluoromethyl)phenyl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(3-fluorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-fluorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

N-((3-((chloro(difluoro)methyl)sulfonyl)-4-((1-methylpiperidin-4-yl)amino)phenyl)sulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-((2-(4-chlorophenyl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(phenoxymethyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(pyridin-3-yloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(pyridin-3-yloxy)-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-(((1R)-3-(dimethylamino)-1-((phenylthio)methyl)propyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(pyridin-4-yloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-(pyridin-3-yloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-(pyridin-4-yloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((2-(4-methylpiperazin-1-yl)ethyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(4-methylpiperazin-1-yl)propyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)(methyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-(((1-methylpiperidin-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-cyano-4-((3-(dimethylamino)propyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-(trifluoromethyl)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(isopropyl(methyl)amino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-(3-(dimethylamino)propoxy)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((2-(4-methylpiperazin-1-yl)ethyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((3-(4-methylpiperazin-1-yl)propyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((3-(4-methylpiperazin-1-yl)propyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-(3-(dimethylamino)propoxy)-3-nitrophenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((2-(4-methylpiperazin-1-yl)ethyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-(((1-methylpiperidin-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-(((1-methylpiperidin-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-(3-(dimethylamino)propoxy)-3-nitrophenyl)sulfonyl)-2-(1H-indol-4-yloxy)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-(4-methylpiperazin-1-yl)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((1-(2,2,2-trifluoroethyl)piperidin-4-yl)amino)phenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-(((4-(dimethylamino)-1-methylpiperidin-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(2,3-dihydro-1,4-benzodioxin-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;
5-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-1,1'-biphenyl-2-carboxamide;

5-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-1,1'-biphenyl-2-carboxamide;

4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-4-(3-piperidin-1-ylpropoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-4-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-4-(3-(dimethylamino)propoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-4-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(3-piperidin-1-ylpropoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(3-(dimethylamino)propoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-3-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-3-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((1-(2,2,2-trifluoroethyl)piperidin-4-yl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-4-(2-pyrrolidin-1-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-4-(2-(diisopropylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(2,3-dihydro-1H-indol-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)cyclohept-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)cyclooct-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)cyclopent-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclopent-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)cyclooct-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)cyclohept-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)cyclopent-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)cyclohept-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((2-(dimethylamino)ethyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((4-(dimethylamino)butyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((1-(phenylsulfonyl)piperidin-4-yl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((1-(quinolin-8-ylsulfonyl)piperidin-4-yl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((1-(phenylsulfonyl)piperidin-4-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((1-(quinolin-8-ylsulfonyl)piperidin-4-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-(((1S)-3-(dimethylamino)-1-thien-2-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((thien-2-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((2-(1H-1,2,3-triazol-1-yl)ethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((2-(2H-1,2,3-triazol-2-yl)ethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(2-naphthyloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((2-(2-oxopyridin-1(2H)-yl)ethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((2-(pyridin-2-yloxy)ethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((2-pyridin-4-ylethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-(trifluoromethyl)phenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((3-cyano-4-((3-(dimethylamino)propyl)amino)phenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1*H*-indol-5-yloxy)-*N*-((3-nitro-4-((1-tetrahydro-2*H*-pyran-4-ylpiperidin-4-yl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1*H*-indol-5-yloxy)-*N*-((4-((4-methylpiperazin-1-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-(1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl)piperazin-1-yl)-2-(1*H*-indol-4-yloxy)-*N*-((3-nitro-4-((tetrahydro-2*H*-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

N-((4-(((4-aminotetrahydro-2*H*-pyran-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1*H*-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(2-methoxyethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(3S)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(3R)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-hydroxy-1-methylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-3-fluoro-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-3-fluoro-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-hydroxy-1-methylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

N-[(4-{[(3S,4R)-1-benzyl-3-hydroxypiperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

N-[(4-{[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[1-(2-methoxyethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(2-hydroxyethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[1-(2-methoxyethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(3-hydroxypropyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-[4-({4'-chloro-3-[3-(dimethylamino)propyl]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(3-hydroxypropyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-{4-[(4'-chloro-4-morpholin-4-yl-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-[4-({4'-chloro-3-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(diethylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(dimethylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(diethylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-[4-({4'-chloro-3-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-{4-[1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(dimethylamino)tetrahydro-2H-pyran-4-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;

N-({4-[(2-aminocyclohexyl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-[4-({4'-chloro-4-[3-(dimethylamino)prop-1-ynyl]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(3-nitro-4-{[1-(4,4,4-trifluorobutyl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[2-(4-hydroxy-1-methylpiperidin-4-yl)ethyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[1-(1,3-thiazol-2-yl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[4'-chloro-4-(2-hydroxyethoxy)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(cyclopropylmethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[1-(4,4,4-trifluorobutyl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide;

4-{4-[1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-(hydroxymethyl)piperazin-1-yl]-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-(hydroxymethyl)piperazin-1-yl]-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-(4-{[4'-chloro-4-(2-hydroxyethoxy)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[3-(3-oxopiperazin-1-yl)propyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(3-nitro-4-{[3-(3-oxopiperazin-1-yl)propyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-5-hydroxycyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-5-hydroxycyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-5-hydroxycyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(2,3-dihydro-1H-inden-2-yl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(2,3-dihydro-1H-inden-2-yl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(1-morpholin-4-ylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[1-(1,3-thiazol-2-ylmethyl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[1-(1,3-thiazol-4-ylmethyl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(2-hydroxyethyl)piperazin-1-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(3S)-1-methylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(3-fluoropropyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-(hydroxymethyl)piperazin-1-yl]-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

N-[(4-{[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-(hydroxymethyl)piperazin-1-yl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(2-methoxyethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-hydroxy-1-tetrahydro-2H-pyran-4-ylethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-({1-[2-(1H-pyrazol-1-yl)ethyl]piperidin-4-yl}amino)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(methylamino)-3-nitrophenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[4-(methylamino)-3-nitrophenyl]sulfonyl}benzamide;

4-{4-[1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-5-hydroxycyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-5-morpholin-4-ylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

N-[(4-{[(1-aminocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[2-(2-oxopyrrolidin-1-yl)ethyl]amino}phenyl)sulfonyl]benzamide;

4-{4-[1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{1-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]ethyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{1-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]ethyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-{4-[(1R)-1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-{4-[(1S)-1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{1-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]ethyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{1-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]ethyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(morpholin-4-ylamino)-3-nitrophenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-3-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[4-(morpholin-4-ylamino)-3-nitrophenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylamino)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(3-methyloxetan-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methoxycyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(1,1-dioxidothiomorpholin-4-yl)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[2-(2-oxopiperidin-1-yl)ethyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[2-(2-oxoimidazolidin-1-yl)ethyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(2-pyridin-4-ylethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-morpholin-4-yl-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(4-methoxypiperidin-1-yl)-3-nitrophenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-5-pyrrolidin-1-ylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[2-(3-oxopiperazin-1-yl)ethyl]amino}phenyl)sulfonyl]benzamide;

4-[4-({4'-chloro-4-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1,1-dioxidotetrahydrothien-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[2-(1,3-dioxolan-2-yl)ethyl]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(3-nitro-4-{[2-(3-oxopiperazin-1-yl)ethyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methyl-5-oxopyrrolidin-3-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methyl-6-oxopiperidin-3-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[3-nitro-4-(piperidin-1-ylamino)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(piperidin-1-ylamino)phenyl]sulfonyl}benzamide;

4-(4-{[4-(4-chlorophenyl)-1-methyl-1H-pyrazol-5-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(3-methyloxetan-3-yl)methoxy]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(1-oxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1,3-thiazol-5-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(2-tetrahydro-2H-pyran-4-ylethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(3-nitro-4-{[2-(trifluoromethoxy)ethyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[2-(2-methoxyethoxy)ethyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[3-(methylsulfonyl)propyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(1,1-dioxidothiomorpholin-4-yl)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(2-tetrahydro-2H-pyran-4-ylethyl)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[2-(2-methoxyethoxy)ethyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[2-(trifluoromethoxy)ethyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2,2-difluoroethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4,4-difluorocyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-1-isopropyl-6-oxo-1,6-dihydropyridin-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(tetrahydro-2H-pyran-4-ylmethyl)amino]carbonyl}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(2-methoxyethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[3-nitro-4-(2-tetrahydro-2H-pyran-4-ylethoxy)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(2-methoxyethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[3-(methylsulfonyl)propoxy]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(3-methoxypropyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(3-methoxypropyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-cyanoethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-cyanoethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(3R)-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[Cis-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(3,3,3-trifluoropropyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(3,3,3-trifluoropropyl)amino]phenyl}sulfonyl)benzamide;

N-({5-bromo-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1,1-dioxidotetrahydrothien-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-(methylamino)-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

N-{[5-bromo-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6-isopropoxypyridin-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[6-(tetrahydro-2H-pyran-4-ylmethoxy)-5-(1,3-thiazol-2-yl)pyridin-3-yl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(2-methoxyethyl)amino]carbonyl}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;

N-({4-[(1-acetylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[1-(methylsulfonyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

N-({4-[(1-acetylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[1-(methylsulfonyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[4'-chloro-5-(trifluoromethyl)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[4'-chloro-5-(trifluoromethyl)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}benzamide;

4-{4-[(5-tert-butyl-4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-{4-[(5-tert-butyl-4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-{[(tetrahydro-2H-pyran-4-ylmethyl)amino]carbonyl}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2R)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2S)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

N-({5-bromo-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(2-morpholin-4-ylethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)oxy]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[4-(4-chlorophenyl)-1-(3-hydroxypropyl)-1,2,5,6-tetrahydropyridin-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

benzyl 4-({[4-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzoyl]amino}sulfonyl)-2-nitrophenyl]amino}methyl)piperidine-1-carboxylate;

N-{[3-(aminocarbonyl)-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[4'-chloro-5-(trifluoromethyl)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-{4-[(5-tert-butyl-4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(1-methyl-1H-imidazol-5-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(morpholin-4-ylsulfonyl)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidothiomorpholin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

N-{[5-bromo-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-5-(1,3-thiazol-2-yl)pyridin-3-yl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3,3-dimethylbutyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1S)-1-(hydroxymethyl)-3-methylbutyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(2R)-tetrahydrofuran-2-ylmethyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1R)-1-(hydroxymethyl)-2-methylpropyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methoxyphenyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

N-[(4-{[2-(1,3-benzodioxol-5-yl)ethyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-hydroxyphenyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

N-{[4-({2-[4-(aminosulfonyl)phenyl]ethyl}amino)-3-nitrophenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(1H-imidazol-1-yl)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(1S)-1-phenylethyl]amino}phenyl)sulfonyl]benzamide;

N-({2-chloro-5-fluoro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[2-(2-methoxyethoxy)ethyl]thio}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[2-(2-methoxyethoxy)ethyl]thio}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(methylsulfonyl)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[4-(methylsulfonyl)phenyl]sulfonyl}benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2,2-dimethyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-4-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-4-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(2-morpholin-4-ylethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)oxy]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-morpholin-4-ylbut-2-ynyl)oxy]-3-nitrophenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-ethynyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-4-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(2-morpholin-4-ylethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-4-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-indol-4-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-hydroxy-4-methoxyphenyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(2,3-dihydro-1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(pyridin-3-ylamino)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)-2-(pyridin-3-ylamino)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)-2-(pyridin-3-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1,2,3,4-tetrahydroisoquinolin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-5-(trifluoromethyl)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyclopropylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4,4-difluorocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

N-[(5-chloro-6-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

Trans-N-({5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(2,2-difluoroethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-fluoro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

N-[(5-chloro-6-{[1-(cyanomethyl)-4-fluoropiperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydrofuran-3-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

Trans-N-({5-chloro-6-[(4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-[(5-chloro-6-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]oxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-N-[(5-chloro-6-{[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

2-(1H-benzimidazol-4-yloxy)-N-[(5-chloro-6-{[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

N-[(5-chloro-6-{[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-[(5-chloro-6-{[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(cyanomethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({(3R)-1-[2-(2-methoxyethoxy)ethyl]pyrrolidin-3-yl}amino)-3-nitrophenyl]sulfonyl}benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(N,N-dimethylglycyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(cyanomethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyclopropylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(4-oxetan-3-ylmorpholin-2-yl)methyl]amino}phenyl)sulfonyl]benzamide;

N-{[5-chloro-6-({(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl}oxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydrofuran-3-ylmethyl)amino]phenyl}sulfonyl)benzamide;

Trans-2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-fluoro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

N-{[5-chloro-6-({(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl}methoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-[(5-chloro-6-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(1-cyclopropylpiperidin-4-yl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-N-({5-chloro-6-[(1-cyclopropylpiperidin-4-yl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

Trans-2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-methylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[({(2R)-4-[2-(2-methoxyethoxy)ethyl]morpholin-2-yl}methyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4,4-difluorocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

N-[(4-{[(4-acetylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(methylsulfonyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[6-({4-fluoro-1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl}methoxy)-5-(trifluoromethyl)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(2-tetrahydrofuran-2-ylethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

Trans-2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyanocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-N-({5-chloro-6-[(4,4-difluorocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-*N*-{[5-cyano-6-(2-tetrahydro-2*H*-pyran-4-ylethoxy)pyridin-3-yl]sulfonyl}-2-(1*H*-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(1R,5S)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxy-4-(4-{(3-phenylpropanoyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamide;

N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-phenoxy-4-(4-{(3-phenylpropanoyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamide;

N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxy-4-(4-{(3-phenylpropyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamide;

N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-phenoxy-4-(4-{(3-phenylpropyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamide;

4-[4-(2-{[(1R,5S)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]amino}benzyl)piperazin-1-yl]-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-phenoxybenzamide;

4-[4-(2-{[(1R,5S)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]amino}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide;

4-{4-[2-(3-azabicyclo[3.2.2]non-3-yl)benzyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide;

4-{4-[2-(3-azabicyclo[3.2.2]non-3-yl)benzyl]piperazin-1-yl}-2-phenoxy-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-{4-[2-(3-azabicyclo[3.2.2]non-3-yl)benzyl]piperazin-1-yl}-2-phenoxy-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-{4-[2-(3-azabicyclo[3.2.2]non-3-yl)benzyl]piperazin-1-yl}-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-phenoxybenzamide;

4-(4-{2-[(4R,7S)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-5-yl]benzyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide;

4-[4-(2-{5-[(1R,5S)-8-azabicyclo[3.2.1]oct-8-ylmethyl]thien-2-yl}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide;

4-[4-(2-{5-[(1R,5S)-8-azabicyclo[3.2.1]oct-8-ylmethyl]thien-2-yl}benzylidene)piperidin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide;

4-[4-(3-{5-[(1R,5S)-8-azabicyclo[3.2.1]oct-8-ylmethyl]thien-2-yl}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide;

N-({5-chloro-6-[(4,4-difluorocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({6-[(trans-4-carbamoylcyclohexyl)methoxy]-5-chloropyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-cyanocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[2-(1H-imidazol-1-yl)ethoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(1-methyl-1H-imidazol-5-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-fluoro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

N-{[5-chloro-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(4,4-difluoro-1-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(2,2-difluorocyclopropyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(trans-4-cyanocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-(trifluoromethyl)phenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-chloro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

N-{[3-chloro-4-(1,4-dioxan-2-ylmethoxy)phenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-N-[(5-chloro-6-{[(2S)-4-cyclopropylmorpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

N-[(5-chloro-6-{[(2S)-4-cyclopropylmorpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

methyl 2-{[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}morpholine-4-carboxylate;

2-{[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide;

2-{[(4-{[2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}-N-ethyl-N-methylmorpholine-4-carboxam
ide;

N-({5-chloro-6-[(trans-4-ethyl-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(cis-4-ethyl-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

5-chloro-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamid
e;

5-chloro-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(cis-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamid
e;

N-({5-chloro-6-[(trans-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzam
ide;

2-(1H-benzotriazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzotriazol-4-yloxy)-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-chloro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}benzamide;

N-[(3-chloro-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(cis-1-fluoro-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzotriazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)benzamide;

N-[(5-chloro-6-{[(1R,2R,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-[(5-chloro-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzotriazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzotriazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S)-4-cyclopropylmorpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

N-[(5-chloro-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S)-4-cyclopropylmorpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S)-4-cyclopropylmorpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-cyano-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-{[3-nitro-4-(2-oxaspiro[3.5]non-7-ylmethoxy)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-cyano-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-{[3-nitro-4-({[(2S)-4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)phenyl]sulfonyl}benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-({[(2S)-4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)phenyl]sulfonyl}benzamide;

N-[(5-chloro-6-{[trans-4-(2-hydroxypropan-2-yl)cyclohexyl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]phenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-({5-nitro-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)benzamide;

2-(1H-benzotriazol-4-yloxy)-N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

N-({3-chloro-4-[(cis-4-cyano-1-fluorocyclohexyl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({3-chloro-4-[(trans-4-cyano-1-fluorocyclohexyl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(cis-4-cyano-1-fluorocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(trans-4-cyano-1-fluorocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzami
de;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-chloro-6-{[1-(1,3-thiazol-2-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(6-{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-5-nitropyridin-3-yl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-indazol-4-yloxy)benz
amide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

N-(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)-4-cyanopiperidine-1-carboxamide; and therapeutically acceptable salts, prodrugs, salts of prodrugs and metabolites thereof.

12. A composition for treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer, said composition comprising an excipient and a therapeutically effective amount of the compound of claim 1.

13. A method of treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies

of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer in a patient, said method comprising administering to the patient a therapeutically effective amount of a compound of claim 1.

14. A method of treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer in a patient, said method comprising administering to the patient therapeutically effective amount of the compound of claim 1 and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/036919

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D405/12 A61K31/404 A61P35/00 C07D209/32 C07D211/96
C07D213/64 C07D215/20 C07D217/16 C07D235/26 C07D249/04
C07D295/14 C07D309/14 C07D401/12 C07D295/125 C07D231/56

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2010/065865 A2 (ABBOTT LAB [US]; BRUNCKO MILAN [US]; DING HONG [US]; DOHERTY GEORGE A) 10 June 2010 (2010-06-10) claims examples 1-481	1-14
E	WO 2010/083441 A2 (ABBOTT LAB [US]; HEXAMER LAURA [US]; DING HONG [US]; ELMORE STEVEN W [] 22 July 2010 (2010-07-22) claims examples	1-14
X	US 2007/072860 A1 (BRUNCKO MILAN [US] ET AL) 29 March 2007 (2007-03-29) the whole document	1-14

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 August 2010	19/08/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Fax: (+31–70) 340–3016	Kollmannsberger, M

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/036919

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/030836 A2 (ABBOTT LAB [US]; ELMORE STEVEN W [US]; ROSENBERG SAUL [US]; GORDON GAR) 13 March 2008 (2008-03-13) page 8, line 11 - page 15, line 24	1-14
Y	CHEOL-MIN PARK ET AL: "Discovery of an orally bioavailable small molecule inhibitor of prosurvival B-cell lymphoma 2 proteins" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US LNKD-DOI:10.1021/JM800669S, vol. 51, no. 21, 13 November 2008 (2008-11-13), pages 6902-6915, XP002574160 ISSN: 0022-2623 [retrieved on 2008-10-08] page 6905, column 2 - page 6907, column 1 compounds 1-34	1-14
Y	BRUNCKO M ET AL: "Studies leading to potent, dual inhibitors of Bcl-2 and Bcl-xL" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US LNKD-DOI:10.1021/JM061152T, vol. 50, no. 4, 22 February 2007 (2007-02-22), pages 641-662, XP002574161 ISSN: 0022-2623 [retrieved on 2007-01-26] * abstract compounds 1-2, 23i-23z, 43a, 43b, 8a-8n, 10a-10k,	1-14
X	US 2005/159427 A1 (BRUNCKO MILAN [US] ET AL) 21 July 2005 (2005-07-21) the whole document	1-14
X	US 2007/015787 A1 (BRUNCKO MILAN [US] ET AL) 18 January 2007 (2007-01-18) the whole document	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2010/036919

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010065865 A2	10-06-2010	US 2010152183 A1	17-06-2010
WO 2010083441 A2	22-07-2010	US 2010184750 A1	22-07-2010
US 2007072860 A1	29-03-2007	NONE	
WO 2008030836 A2	13-03-2008	CA 2662320 A1	13-03-2008
		CN 101534904 A	16-09-2009
		EP 2061560 A2	27-05-2009
		JP 2010502727 T	28-01-2010
		US 2008076779 A1	27-03-2008
US 2005159427 A1	21-07-2005	US 2006128706 A1	15-06-2006
US 2007015787 A1	18-01-2007	NONE	

DERIVADOS DE SULFONAMIDA COMO AGENTES INDUCTORES DE APOPTOSIS CON SELECTIVIDAD POR Bcl-2 PARA EL TRATAMIENTO DE CÁNCER Y ENFERMEDADES INMUNES

La presente solicitud es una continuación parcial de la solicitud de patente estadounidense No. 12/631,404, presentada el 4 de diciembre de 2009, que invoca prioridad sobre las solicitudes estadounidense No. 61/120,275, presentada el 5 de diciembre de 2008, y la solicitud provisional de patente estadounidense No. 61/181,180, presentada el 26 de mayo 2009, las cuales están incorporadas en la presente en su totalidad.

CAMPO DE LA INVENCIÓN

La presente invención se refiere a compuestos que inhiben de manera selectiva la actividad de familia de proteínas anti-apoptóticas Bcl-2, composiciones que contienen dichos compuestos, y métodos para tratar enfermedades durante las cuales se expresan las proteínas anti-apoptóticas Bcl-2.

ANTECEDENTES DE LA INVENCIÓN

Las proteínas anti-apoptóticas de la familia Bcl-2 se asocian con diversas enfermedades y están siendo investigadas como potenciales objetivos para fármacos terapéuticas. Dichos objetivos para la terapia intervencionista incluyen, por ejemplo, a la familia de proteínas Bcl-2 Bcl-2, Bcl-X_L y Bcl-w. Recientemente, los inhibidores de la familia de proteínas Bcl-2 han sido informados en PCT/US/2004/36770, publicada como WO 2005/049593 y PCT/US/2004/367911, publicada como WO 2005/049594, de propiedad conjunta. Aunque en dicho arte se describen inhibidores con alto grado de unión a la proteína objetivo, la afinidad de unión del compuesto es solo uno de muchos parámetros que se deben tomar en consideración. Una meta consiste en producir compuestos que se unan a una proteína con preferencia sobre otra proteína, es decir, que se unan con selectividad por la primera. Para mostrar dicha selectividad, se sabe bien que un compuesto no solo muestra una alta afinidad de unión por una proteína en particular sino además una menor afinidad de unión por otros miembros.

Una medida típica de la afinidad de unión de un inhibidor de proteína anti-apoptótica es el equilibrio entre los procesos de unión y de disociación entre la proteína y el inhibidor (K_i). La constante de inhibición (K_i) es la constante de disociación de un complejo enzima-inhibidor o un complejo de proteína/moléculas pequeñas, donde las moléculas pequeñas inhiben la unión de una proteína a otra proteína. Por lo tanto, un valor K_i grande indica una baja afinidad de unión, y un valor K_i pequeño indica una alta afinidad de unión.

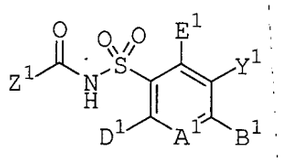
Una medida típica de la actividad celular de un inhibidor de proteína anti-apoptótica es la concentración que causa un 50% del efecto en la célula (EC_{50}).

Por lo tanto, los inventores han descubierto que aunque los compuestos divulgados en el arte son útiles para el tratamiento de diversos tipos de cáncer y enfermedades inmunes, los mismos no poseen selectividad por las proteínas anti-apoptóticas Bcl-2 sobre las proteínas anti-apoptóticas Bcl-X_L y que por lo tanto presentan una mayor probabilidad de causar efectos secundarios caracterizados por la inhibición de proteínas anti-apoptóticas Bcl-X_L tales como trombocitopenia.

Por lo tanto, la presente invención comprende una serie de compuestos que muestran propiedades inesperadas con respecto a su selectividad por unirse a la proteína anti-apoptótica Bcl-2, e inhibir su actividad, respecto de la proteína anti-apoptótica Bcl-X_L que es significativamente mayor que las de los compuestos divulgados en PCT/US/2004/36770 y PCT/US/2004/367911.

SÍNTESIS DE LA INVENCIÓN

Una realización de esta invención, por lo tanto, se refiere a compuestos o sus sales, profármacos, o sales de profármacos terapéuticamente aceptables, que son útiles como inhibidores selectivos de uno o más miembros de la familia de proteínas anti-apoptóticas, donde los compuestos tienen la Fórmula (I)



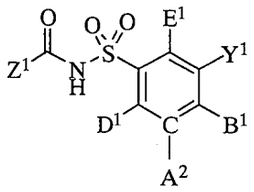
(I),

en donde A^1 es N o $C(A^2)$;

uno o dos o tres o cada uno de A^2, B^1, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1,

REIVINDICACIONES:

1. Un compuesto CARACTERIZADO PORQUE tiene la Fórmula I



(I),

o una sal, profármaco o sal de profármaco terapéuticamente aceptable del mismo ,

A^1 es N o $C(A^2)$;

uno o dos o tres o cada uno de A^2, B^1, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes se seleccionan en forma independiente entre H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$; y

Y^1 es H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ o $NHSO_2R^{17}$;

o

B^1 y Y^1, junto con los átomos a los cuales están unidos , son imidazol o triazol; y

uno o dos o cada uno de A^2, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes se seleccionan en forma independiente entre H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$;

R^1 es R^2, R^3, R^4 o R^5;

R^{1A} es C_1-C_6-alquilo, C_3-C_6-alquenilo o C_3-C_6-alquinilo;

R^2 es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{2A}; R^{2A} es cicloalcano o heterocicloalcano;

R^3 es heteroarilo que no está fusionado o está fusionado con benceno, heteroareno o R^{3A}; R^{3A} es cicloalcano o heterocicloalcano;

R^4 es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{4A}; R^{4A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^5 es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^6 es C_2-C_5-espiroalquilo, cada uno de los cuales no esta sustituido o está sustituido con OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ o $N(CH_3)_2$;

R^{6A} y R^{6B} se seleccionan en forma independiente entre alquilo o, junto con el N al cual están unidos, R^{6C};

R^{6C} es aziridin-1–ilo, azetidin-1–ilo, pirrolidin-1–ilo o piperidin-1–ilo, teniendo cada uno una unidad CH_2 no reemplazada o reemplazada con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH;

R^7 es R^8, R^9, R^{10} o R^{11};

R^8 es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{8A};

R^{8A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^9 es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{9A}; R^{9A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{10} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{10A}; R^{10A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{11} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I;

R^{12} es R^{13}, R^{14}, R^{15} o R^{16};

R^{13} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{13A}; R^{13A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{14} es heteroarilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{14A}; R^{14A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{15} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{15A}; R^{15A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{16} es alquilo, alquenilo o alquinilo;

R^{17} es R^{18}, R^{19}, R^{20} o R^{21};

R^{18} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{18A}; R^{18A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{19} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{19A}; R^{19A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{20} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{20A}; R^{20A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{21} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{22} es R^{23}, R^{24} o R^{25};

R^{23} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{23A}; R^{23A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{24} es heteroareno que no está fusionado o está fusionado con areno, heteroareno o R^{24A}; R^{24A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{25} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{25A}; R^{25A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

Z^1 es R^{26} o R^{27}, cada uno de los cuales está sustituido con R^{28}, R^{29} o R^{30}, cada uno de los cuales está sustituido con F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} o $N(R^{32})R^{37}$;

R^{26} es fenilo que no está fusionado o está fusionado con areno o heteroareno;

R^{27} es heteroareno que no está fusionado o está fusionado con areno o heteroareno;

R^{28} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{28A}; R^{28A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno

R^{29} es heteroarilo o R^{29A}; R^{29A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{30} es cicloalquilo o cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{30A}; R^{30A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{31} y R^{31A} son en forma independiente F, Cl, Br o alquilo o se toman juntos y son C_2-C_5-espiroalquilo;

R^{32} es R^{33}, $C(O)R^{33}$ o $C(O)OR^{33}$;

R^{33} es R^{34} o R^{35};

R^{34} es fenilo que no está fusionado o está fusionado con arilo, heteroarilo o R^{34A}; R^{34A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{35} es alquilo que no está sustituido o está sustituido con R^{36};

R^{36} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{36A}; R^{36A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{37} es R^{38}, R^{39} o R^{40}, cada uno de los cuales está sustituido con F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ o SO_2R^{41};

R^{38} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{38A}; R^{38A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{39} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{39A}; R^{39A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{40} es C_3-C_8-cicloalquilo o C_4-C_8-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{40A}; R^{40A} cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{41} es R^{42}, R^{43}, R^{44} o R^{45};

R^{42} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{42A}; R^{42A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{43} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{43A}; R^{43A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{44} es C_3-C_9-cicloalquilo o C_4-C_7-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{44A}; R^{44A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{45} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos sustituyentes seleccionados en forma independiente entre: R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{46} es R^{47}, R^{48} o R^{49};

R^{47} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{47A}; R^{47A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{48} es heteroarilo o R^{48A}; R^{48A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{49} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{49A}; R^{49A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

en donde las unidades representadas por R^{26} y R^{27} se sustituyen adicionalmente con uno o dos o tres sustituyentes seleccionados en forma independiente entre: R^{50A}, OR^{50A}, SR^{50A}, $S(O)R^{50A}$, SO_2R^{50A} o NHR^{50A},

R^{50A} es R^{51A}, R^{52A}, R^{53A} o R^{54A};

R^{51A} es fenilo que no está fusionado o está fusionado con benceno, heteroareno o R^{51AA},

en donde R^{51AA} es cicloalcano, cicloalqueno o heterocicloalcano heterocicloalqueno,

R^{52A} es heteroarilo;

R^{53A} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo; donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{53AA};

en donde R^{53AA} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{54A} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre: R^{55AA}, OR^{55AA}, SR^{55AA}, $S(O)R^{55AA}$, SO_2R^{55AA}, NHR^{55AA}, $N(R^{55AA})_2$, $C(O)R^{55AA}$, $C(O)NH_2$, $C(O)NHR^{55AA}$, $NHC(O)R^{55AA}$, $NHSO_2R^{55AA}$, $NHC(O)OR^{55AA}$, SO_2NH_2, SO_2NHR^{55AA}, $SO_2N(R^{55AA})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55AA}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{55AA} es alquilo, alquenilo, alquinilo, fenilo o heteroarilo, o R^{56A};

R^{56A} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N;

en donde las unidades representadas por R^2 R^3 R^4, R^6, R^{6C}, R^8, R^{8A} R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{18}, R^{19}, R^{20}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{34}, R^{36}, R^{38}, R^{39}, R^{40}, R^{42}, R^{43}, R^{44}, R^{47}, R^{48}, y R^{49} son en forma independiente no sustituidas, adicionalmente no sustituidas, sustituidas o adicionalmente sustituidas con uno o dos o tres o cuatro o cinco sustituyentes seleccionados en forma independiente entre $R^{50\,AA}$, R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{50AA} es espirociclilo;

R^{50} es R^{51}, R^{52}, R^{53} o R^{54};

R^{51} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{51B};

R^{51B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{52} es heteroarilo;

R^{53} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{53B};

en donde R^{53B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{54} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$,

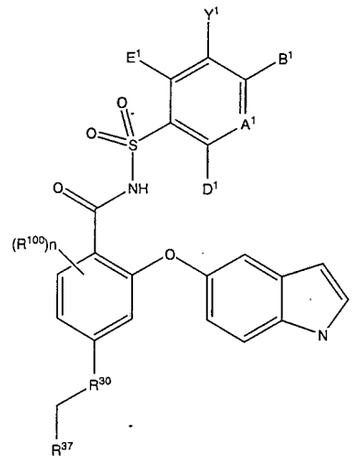
$C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{55} es alquilo, alquenilo, alquinilo, fenilo, heteroarilo o R^{56};

en donde el alquilo, alquenilo, alquinilo no están sustituidos o están sustituidos con OCH_3; y

R^{56} es C_3-C_8-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N.

2. Un compuesto CARACTERIZADO PORQUE tiene la Fórmula II



(II),

o una sal, profármaco o sal de profármaco terapéuticamente aceptable del mismo ,

en donde

R^{100} tiene los valores que se definen para los sustituyentes de R^{26};

n es 0, 1, 2, o 3;

A^1 es N o $C(A^2)$;

uno o dos o tres o cada uno de A^2, B^1, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1,

$SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes se seleccionan en forma independiente entre H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$; y

Y^1 es H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ o $NHSO_2R^{17}$;

o

B^1 y Y^1, junto con los átomos a los cuales están unidos , son imidazol o triazol; y

uno o dos o cada uno de A^2, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes se seleccionan en forma independiente entre H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$;

R^1 es R^2, R^3, R^4 o R^5;

R^{1A} es C_1-C_6-alquilo, C_3-C_6-alquenilo o C_3-C_6-alquinilo;

R^2 es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{2A}; R^{2A} es cicloalcano o heterocicloalcano;

R^3 es heteroarilo que no está fusionado o está fusionado con benceno, heteroareno o R^{3A}; R^{3A} es cicloalcano o heterocicloalcano;

R^4 es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{4A}; R^{4A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^5 es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^6 es C_2-C_5-espiroalquilo, cada uno de los cuales no esta sustituido o está sustituido con OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ o $N(CH_3)_2$;

R^{6A} y R^{6B} se seleccionan en forma independiente entre alquilo o, junto con el N al cual están unidos, R^{6C};

R^{6C} es aziridin-1–ilo, azetidin-1–ilo, pirrolidin-1–ilo o piperidin-1–ilo, teniendo cada uno una unidad CH_2 no reemplazada o reemplazada con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH;

R^7 es R^8, R^9, R^{10} o R^{11};

R^8 es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{8A};

R^{8A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^9 es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{9A}; R^{9A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{10} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{10A}; R^{10A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{11} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{12} es R^{13}, R^{14}, R^{15} o R^{16};

R^{13} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{13A}; R^{13A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{14} es heteroarilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{14A}; R^{14A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{15} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{15A}; R^{15A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{16} es alquilo, alquenilo o alquinilo;

R^{17} es R^{18}, R^{19}, R^{20} o R^{21};

R^{18} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{18A}; R^{18A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{19} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{19A}; R^{19A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{20} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH,

$CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{20A}; R^{20A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{21} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{22} es R^{23}, R^{24} o R^{25};

R^{23} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{23A}; R^{23A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{24} es heteroareno que no está fusionado o está fusionado con areno, heteroareno o R^{24A}; R^{24A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{25} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{25A}; R^{25A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{30} es cicloalquilo o cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{30A}; R^{30A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; cada uno de los cuales está sustituido con F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} o $N(R^{32})R^{37}$;

R^{31} y R^{31A} son en forma independiente F, Cl, Br o alquilo o se toman juntos y son C_2-C_5-espiroalquilo;

R^{32} es R^{33}, $C(O)R^{33}$ o $C(O)OR^{33}$;

R^{33} es R^{34} o R^{35};

R^{34} es fenilo que no está fusionado o está fusionado con arilo, heteroarilo o R^{34A}; R^{34A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{35} es alquilo que no está sustituido o está sustituido con R^{36};

R^{36} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{36A}; R^{36A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{37} es R^{38}, R^{39} o R^{40}, cada uno de los cuales está sustituido con F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ o SO_2R^{41};

R^{38} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{38A}; R^{38A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{39} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{39A}; R^{39A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{40} es C_3-C_8-cicloalquilo o C_4-C_8-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{40A}; R^{40A} cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{41} es R^{42}, R^{43}, R^{44} o R^{45};

R^{42} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{42A}; R^{42A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{43} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{43A}; R^{43A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{44} es C_3-C_9-cicloalquilo o C_4-C_7-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{44A}; R^{44A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{45} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos sustituyentes seleccionados en forma independiente entre: R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{46} es R^{47}, R^{48} o R^{49};

R^{47} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{47A}; R^{47A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{48} es heteroarilo o R^{48A}; R^{48A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{49} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con

N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{49A}; R^{49A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

en donde las unidades representadas por R^2 R^3 R^4, R^6, R^{6C}, R^8, R^{8A} R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{18}, R^{19}, R^{20}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{34}, R^{36}, R^{38}, R^{39}, R^{40}, R^{42}, R^{43}, R^{44}, R^{47}, R^{48}, y R^{49} son en forma independiente no sustituidas, adicionalmente no sustituidas, sustituidas o adicionalmente sustituidas con uno o dos o tres o cuatro o cinco sustituyentes seleccionados en forma independiente entre R^{50AA}, R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{50AA} es espirociclilo;

R^{50} es R^{51}, R^{52}, R^{53} o R^{54};

R^{51} es fenil que no está fusionado o está fusionado con areno, heteroareno o R^{51B}; R^{51B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{52} es heteroarilo;

R^{53} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, teniendo cada uno una o dos unidades CH_2 no reemplazadas o reemplazadas con O, C(O), CNOH, CNOCH#3, S, S(O), SO_2 o NH seleccionados en forma independiente y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{53B};

donde R^{53B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

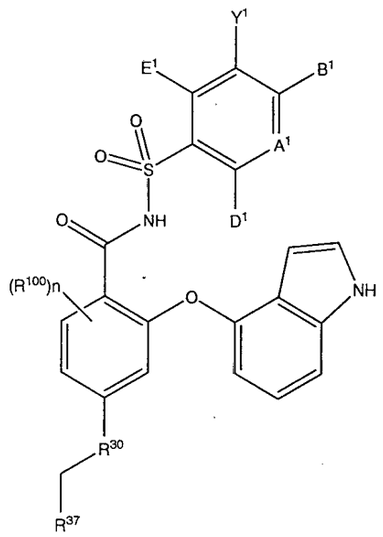
R^{54} es alquilo, alquenilo o alquinilo, cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados entre R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{55} es alquilo, alquenilo, alquinilo, fenilo, heteroarilo o R^{56};

donde el alquilo, alquenilo, alquinilo no están sustituidos o están sustituidos con OCH_3; y

R^{56} es C_3-C_8-cicloalquilo o C_4-C_6-cicloalquenilo, teniendo cada uno una o dos unidades CH_2 no reemplazadas o reemplazadas con O, C(O), CNOH, CNOCH#3, S, S(O), SO_2 o NH seleccionados en forma independiente y una o dos unidades CH no reemplazadas o reemplazadas con N.

3. Un compuesto CARACTERIZADO PORQUE tiene la fórmula III



(III),

o una sal terapéuticamente aceptable, profármaco o sal de profármaco del mismo , en donde

R^{100} tiene los valores descritos para los sustituyentes en R^{26};

n es 0, 1, 2, o 3;

A^1 es N o $C(A^2)$;

uno o dos o tres o cada uno de A^2, B^1, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes son sustituyentes seleccionados en forma independiente entre H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$ y ; y

Y^1 es H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ o $NHSO_2R^{17}$;

or

B^1 y Y^1, junto con los átomos a los cuales están unidos, son imidazol o triazol y ; y

uno o dos o cada uno de A^2, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1,

$SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes son sustituyentes seleccionados en forma independiente entre H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$;

R^1 es R^2, R^3, R^4 o R^5;

R^{1A} es C_1-C_6-alquilo, C_3-C_6-alquenilo o C_3-C_6-alquinil;

R^2 es fenil que no está fusionado o está fusionado con areno, heteroareno o R^{2A}; R^{2A} es cicloalcano o heterocicloalcano;

R^3 es heteroarilo que no está fusionado o está fusionado con benceno, heteroareno o R^{3A}; R^{3A} es cicloalcano o heterocicloalcano;

R^4 es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{4A}; R^{4A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^5 es alquilo, alquenilo o alquinilo, cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados entre R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^6 es C_2-C_5-espiroalquilo, cada uno de los cuales no está sustituido o está sustituido con OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ o $N(CH_3)_2$;

R^{6A} y R^{6B} se seleccionan en forma independiente entre alquilo o, junto con el N al cual están unidos, R^{6C};

R^{6C} es aziridin-1-ilo, azetidin-1-ilo, pirrolidin-1-il o piperidin-1-ilo, teniendo cada uno una unidad CH_2 no reemplazada o reemplazada con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH;

R^7 es R^8, R^9, R^{10} o R^{11};

R^8 es fenil que no está fusionado o está fusionado con areno, heteroareno o R^{8A};

R^{8A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^9 es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{9A}; R^{9A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{10} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, teniendo cada uno una o dos unidades CH_2 no reemplazadas o reemplazadas con O, C(O), CNOH, CNOCH#3, S, S(O), SO_2 o NH seleccionados en forma independiente y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno,

heteroareno o R^{10A}; R^{10A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{11} es alquilo, alquenilo o alquinilo, cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados entre R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{12} es R^{13}, R^{14}, R^{15} o R^{16};

R^{13} es fenil que no está fusionado o está fusionado con areno, heteroareno o R^{13A}; R^{13A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{14} es heteroarilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{14A}; R^{14A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{15} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{15A}; R^{15A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{16} es alquilo, alquenilo o alquinil;

R^{17} es R^{18}, R^{19}, R^{20} o R^{21};

R^{18} es fenil que no está fusionado o está fusionado con areno, heteroareno o R^{18A}; R^{18A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{19} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{19A}; R^{19A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{20} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, teniendo cada uno una o dos unidades CH_2 no reemplazadas o reemplazadas con O, C(O), CNOH, CNOCH#3, S, S(O), SO_2 o NH seleccionados en forma independiente y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{20A}; R^{20A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{21} es alquilo, alquenilo o alquinilo, cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados entre R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{22} es R^{23}, R^{24} o R^{25};

R^{23} es fenil que no está fusionado o está fusionado con areno, heteroareno o R^{23A}; R^{23A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{24} es heteroareno que no está fusionado o está fusionado con areno, heteroareno o R^{24A}; R^{24A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{25} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, teniendo cada uno una o dos unidades CH_2 no reemplazadas o reemplazadas con O, C(O), CNOH, CNOCH#3, S, S(O), SO_2 o NH seleccionados en forma independiente y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{25A}; R^{25A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{30} es cicloalquilo o cicloalquenilo, teniendo cada uno una o dos unidades CH_2 no reemplazadas o reemplazadas con O, C(O), CNOH, CNOCH#3, S, S(O), SO_2 o NH seleccionados en forma independiente y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{30A}; R^{30A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; cada uno de los cuales está sustituido con F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} o $N(R^{32})R^{37}$;

R^{31} y R^{31A} son en forma independiente F, Cl, Br o alquilo o son taken togeter y son C_2-C_5-espiroalquilo;

R^{32} es R^{33}, $C(O)R^{33}$ o $C(O)OR^{33}$;

R^{33} es R^{34} o R^{35};

R^{34} es fenil que no está fusionado o está fusionado con arilo, heteroarilo o R^{34A}; R^{34A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{35} es alquilo which no está sustituido o está sustituido con R^{36};

R^{36} es fenil que no está fusionado o está fusionado con areno, heteroareno o R^{36A}; R^{36A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{37} es R^{38}, R^{39} o R^{40}, cada uno de los cuales está sustituido con F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ o SO_2R^{41};

R^{38} es fenil que no está fusionado o está fusionado con areno, heteroareno o R^{38A}; R^{38A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{39} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{39A}; R^{39A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{40} es C_3-C_8-cicloalquilo o C_4-C_8-cicloalquenilo, teniendo cada uno una o dos unidades CH_2 no reemplazadas o reemplazadas con O, C(O), CNOH, CNOCH#3, S, S(O), SO_2 o NH seleccionados en forma independiente y una o dos unidades CH no reemplazadas o

reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{40A}; R^{40A} cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{41} es R^{42}, R^{43}, R^{44} o R^{45};

R^{42} es fenil que no está fusionado o está fusionado con areno, heteroareno o R^{42A}; R^{42A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{43} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{43A}; R^{43A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{44} es C_3-C_9-cicloalquilo o C_4-C_7-cicloalquenilo, teniendo cada uno una o dos unidades CH_2 no reemplazadas o reemplazadas con O, C(O), CNOH, CNOCH#3, S, S(O), SO_2 o NH seleccionados en forma independiente y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{44A}; R^{44A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{45} es alquilo, alquenilo o alquinilo, cada uno de los cuales no está sustituido o está sustituido con uno o dos sustituyentes seleccionados en forma independiente entre R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{46} es R^{47}, R^{48} o R^{49};

R^{47} es fenil que no está fusionado o está fusionado con areno, heteroareno o R^{47A}; R^{47A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{48} es heteroarilo o R^{48A}; R^{48A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{49} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, teniendo cada uno una o dos unidades CH_2 no reemplazadas o reemplazadas con O, C(O), CNOH, CNOCH#3, S, S(O), SO_2 o NH seleccionados en forma independiente y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{49A}; R^{49A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

donde las unidades representadas por R^2 R^3 R^4, R^6, R^{6C}, R^8, R^{8A} R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{18}, R^{19}, R^{20}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{34}, R^{36}, R^{38}, R^{39}, R^{40}, R^{42}, R^{43}, R^{44}, R^{47}, R^{48}, y R^{49} en forma independiente no están sustituidas , no están adicionalmente sustituidas, están sustituidas o adicionalmente sustituidas con uno o dos o tres o cuatro o cinco sustituyentes seleccionados en forma independiente entre R^{50AA}, R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$,

$C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{50AA} es espirociclilo;

R^{50} es R^{51}, R^{52}, R^{53} o R^{54};

R^{51} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{51B};

R^{51B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{52} es heteroarilo;

R^{53} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{53B};

en donde R^{53B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

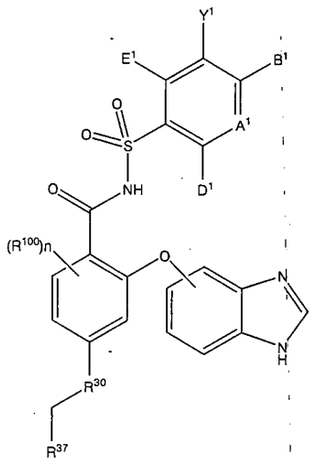
R^{54} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{55} es alquilo, alquenilo, alquinilo, fenilo, heteroarilo o R^{56};

en donde el alquilo, alquenilo, alquinilo no están sustituidos o están sustituidos con OCH_3; y

R^{56} es C_3-C_8-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N.

4. Un compuesto CARACTERIZADO PORQUE tiene la Fórmula IV



(IV),

o una sal, profármaco o sal de profármaco terapéuticamente aceptable del mismo ,

en donde

R^{100} tiene los valores que se definen para los sustituyentes de R^{26};

n es 0, 1, 2, o 3;

A^1 es N o $C(A^2)$;

uno o dos o tres o cada uno de A^2, B^1, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes se seleccionan en forma independiente entre H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$; y

Y^1 es H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ o $NHSO_2R^{17}$;

o

B^1 y Y^1, junto con los átomos a los cuales están unidos , son imidazol o triazol; y

uno o dos o cada uno de A^2, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes se seleccionan en forma independiente entre H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$;

R^1 es R^2, R^3, R^4 o R^5;

R^{1A} es C_1-C_6-alquilo, C_3-C_6-alquenilo o C_3-C_6-alquinilo;

R^2 es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{2A}; R^{2A} es cicloalcano o heterocicloalcano;

R^3 es heteroarilo que no está fusionado o está fusionado con benceno, heteroareno o R^{3A}; R^{3A} es cicloalcano o heterocicloalcano;

R^4 es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{4A}; R^{4A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^5 es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^6 es C_2-C_5-espiroalquilo, cada uno de los cuales no esta sustituido o está sustituido con OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ o $N(CH_3)_2$;

R^{6A} y R^{6B} se seleccionan en forma independiente entre alquilo o, junto con el N al cual están unidos, R^{6C};

R^{6C} es aziridin-1–ilo, azetidin-1–ilo, pirrolidin-1–ilo o piperidin-1–ilo, teniendo cada uno una unidad CH_2 no reemplazada o reemplazada con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH;

R^7 es R^8, R^9, R^{10} o R^{11};

R^8 es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{8A};

R^{8A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^9 es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{9A}; R^{9A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{10} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{10A}; R^{10A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{11} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma

independiente: R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{12} es R^{13}, R^{14}, R^{15} o R^{16};

R^{13} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{13A}; R^{13A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{14} es heteroarilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{14A}; R^{14A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{15} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{15A}; R^{15A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{16} es alquilo, alquenilo o alquinilo;

R^{17} es R^{18}, R^{19}, R^{20} o R^{21};

R^{18} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{18A}; R^{18A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{19} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{19A}; R^{19A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{20} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{20A}; R^{20A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{21} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{22} es R^{23}, R^{24} o R^{25};

R^{23} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{23A}; R^{23A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{24} es heteroareno que no está fusionado o está fusionado con areno, heteroareno o R^{24A}; R^{24A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{25} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con

N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{25A}; R^{25A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{30} es cicloalquilo o cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{30A}; R^{30A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; cada uno de los cuales está sustituido con F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} o $N(R^{32})R^{37}$;

R^{31} y R^{31A} son en forma independiente F, Cl, Br o alquilo o se toman juntos y son C_2-C_5-espiroalquilo;

R^{32} es R^{33}, $C(O)R^{33}$ o $C(O)OR^{33}$;

R^{33} es R^{34} o R^{35};

R^{34} es fenilo que no está fusionado o está fusionado con arilo, heteroarilo o R^{34A}; R^{34A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{35} es alquilo que no está sustituido o está sustituido con R^{36};

R^{36} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{36A}; R^{36A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{37} es R^{38}, R^{39} o R^{40}, cada uno de los cuales está sustituido con F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ o SO_2R^{41};

R^{38} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{38A}; R^{38A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{39} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{39A}; R^{39A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{40} es C_3-C_8-cicloalquilo o C_4-C_8-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{40A}; R^{40A} cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{41} es R^{42}, R^{43}, R^{44} o R^{45};

R^{42} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{42A}; R^{42A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{43} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{43A}; R^{43A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{44} es C_3-C_9-cicloalquilo o C_4-C_7-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{44A}; R^{44A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{45} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos sustituyentes seleccionados en forma independiente entre: R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{46} es R^{47}, R^{48} o R^{49};

R^{47} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{47A}; R^{47A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{48} es heteroarilo o R^{48A}; R^{48A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{49} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{49A}; R^{49A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

en donde las unidades representadas por R^2 R^3 R^4, R^6, R^{6C}, R^8, R^{8A} R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{18}, R^{19}, R^{20}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{34}, R^{36}, R^{38}, R^{39}, R^{40}, R^{42}, R^{43}, R^{44}, R^{47}, R^{48}, y R^{49} son en forma independiente no sustituidas, adicionalmente no sustituidas, sustituidas o adicionalmente sustituidas con uno o dos o tres o cuatro o cinco sustituyentes seleccionados en forma independiente entre $R^{50\,AA}$, R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{50AA} es espirociclilo;

R^{50} es R^{51}, R^{52}, R^{53} o R^{54};

R^{51} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{51B}; R^{51B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{52} es heteroarilo;

R^{53} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{53B};

en donde R^{53B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

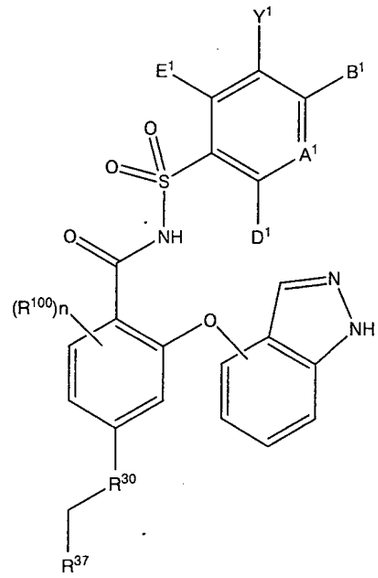
R^{54} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{55} es alquilo, alquenilo, alquinilo, fenilo, heteroarilo o R^{56};

en donde el alquilo, alquenilo, alquinilo no están sustituidos o están sustituidos con OCH_3; y

R^{56} es C_3-C_8-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N.

5. Un compuesto CARACTERIZADO PORQUE tiene la Fórmula V



(V),

o una sal, profármaco o sal de profármaco terapéuticamente aceptable del mismo ,

en donde

R^{100} tiene los valores que se definen para los sustituyentes de R^{26};

n es 0, 1, 2, o 3;

A^1 es N o $C(A^2)$;

uno o dos o tres o cada uno de A^2, B^1, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes se seleccionan en forma independiente entre H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$; y

Y^1 es H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}; NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ o $NHSO_2R^{17}$;

o

B^1 y Y^1, junto con los átomos a los cuales están unidos , son imidazol o triazol; y

uno o dos o cada uno de A^2, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes se seleccionan en forma independiente entre H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$;

R^1 es R^2, R^3, R^4 o R^5;

R^{1A} es C_1-C_6-alquilo, C_3-C_6-alquenilo o C_3-C_6-alquinilo;

R^2 es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{2A}; R^{2A} es cicloalcano o heterocicloalcano;

R^3 es heteroarilo que no está fusionado o está fusionado con benceno, heteroareno o R^{3A}; R^{3A} es cicloalcano o heterocicloalcano;

R^4 es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{4A}; R^{4A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^5 es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$,

$NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^6 es C_2-C_5-espiroalquilo, cada uno de los cuales no esta sustituido o está sustituido con OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ o $N(CH_3)_2$;

R^{6A} y R^{6B} se seleccionan en forma independiente entre alquilo o, junto con el N al cual están unidos, R^{6C};

R^{6C} es aziridin-1–ilo, azetidin-1–ilo, pirrolidin-1–ilo o piperidin-1–ilo, teniendo cada uno una unidad CH_2 no reemplazada o reemplazada con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH;

R^7 es R^8, R^9, R^{10} o R^{11};

R^8 es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{8A};

R^{8A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^9 es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{9A}; R^{9A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{10} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{10A}; R^{10A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{11} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{12} es R^{13}, R^{14}, R^{15} o R^{16};

R^{13} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{13A}; R^{13A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{14} es heteroarilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{14A}; R^{14A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{15} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{15A}; R^{15A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{16} es alquilo, alquenilo o alquinilo;

R^{17} es R^{18}, R^{19}, R^{20} o R^{21};

R^{18} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{18A}; R^{18A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{19} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{19A}; R^{19A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{20} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{20A}; R^{20A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{21} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{22} es R^{23}, R^{24} o R^{25};

R^{23} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{23A}; R^{23A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{24} es heteroareno que no está fusionado o está fusionado con areno, heteroareno o R^{24A}; R^{24A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{25} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{25A}; R^{25A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{30} es cicloalquilo o cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{30A}; R^{30A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; cada uno de los cuales está sustituido con F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} o $N(R^{32})R^{37}$;

R^{31} y R^{31A} son en forma independiente F, Cl, Br o alquilo o se toman juntos y son C_2-C_5-espiroalquilo;

R^{32} es R^{33}, $C(O)R^{33}$ o $C(O)OR^{33}$;

R^{33} es R^{34} o R^{35};

R^{34} es fenilo que no está fusionado o está fusionado con arilo, heteroarilo o R^{34A}; R^{34A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{35} es alquilo que no está sustituido o está sustituido con R^{36};

R^{36} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{36A}; R^{36A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{37} es R^{38}, R^{39} o R^{40}, cada uno de los cuales está sustituido con F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ o SO_2R^{41};

R^{38} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{38A}; R^{38A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{39} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{39A}; R^{39A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{40} es C_3-C_8-cicloalquilo o C_4-C_8-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{40A}; R^{40A} cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{41} es R^{42}, R^{43}, R^{44} o R^{45};

R^{42} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{42A}; R^{42A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{43} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{43A}; R^{43A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{44} es C_3-C_9-cicloalquilo o C_4-C_7-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{44A}; R^{44A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{45} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos sustituyentes seleccionados en forma independiente entre: R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{46} es R^{47}, R^{48} o R^{49};

R^{47} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{47A}; R^{47A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{48} es heteroarilo o R^{48A}; R^{48A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{49} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{49A}; R^{49A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

en donde las unidades representadas por R^2 R^3 R^4, R^6, R^{6C}, R^8, R^{8A} R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{18}, R^{19}, R^{20}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{34}, R^{36}, R^{38}, R^{39}, R^{40}, R^{42}, R^{43}, R^{44}, R^{47}, R^{48}, y R^{49} son en forma independiente no sustituidas, adicionalmente no sustituidas, sustituidas o adicionalmente sustituidas con uno o dos o tres o cuatro o cinco sustituyentes seleccionados en forma independiente entre $R^{50\,AA}$, R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{50AA} es espirociclilo;

R^{50} es R^{51}, R^{52}, R^{53} o R^{54};

R^{51} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{51B}; R^{51B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{52} es heteroarilo;

R^{53} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{53B};

en donde R^{53B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{54} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{55} es alquilo, alquenilo, alquinilo, fenilo, heteroarilo o R^{56};

en donde el alquilo, alquenilo, alquinilo no están sustituidos o están sustituidos con OCH_3; y

R^{56} es C_3-C_8-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N.

6. El compuesto de la reivindicación 1, la reivindicación 2, la reivindicación 3, la reivindicación 4, o la reivindicación 5, CARACTERIZADO PORQUE

A^1 es $C(A^2)$; y

A^2 es H.

7. El compuesto de la reivindicación 1, la reivindicación 2, la reivindicación 3, la reivindicación 4, o la reivindicación 5, CARACTERIZADO PORQUE

A^1 es $C(A^2)$ o N;

A^2 es H; y

B^1 es NHR^1.

8. El compuesto de la reivindicación 1, la reivindicación 2, la reivindicación 3, la reivindicación 4, o la reivindicación 5, CARACTERIZADO PORQUE

A^1 es $C(A^2)$;

A^2 es H;

B^1 es NHR^1; y

D^1 es H.

9. El compuesto de la reivindicación 1, la reivindicación 2, la reivindicación 3, la reivindicación 4, o la reivindicación 5, CARACTERIZADO PORQUE

A^1 es $C(A^2)$ o N;

A^2 es H;

B^1 es NHR^1;

D^1 es H; y

E^1 es H.

10. El compuesto de la reivindicación 1, la reivindicación 2, la reivindicación 3, la reivindicación 4, o la reivindicación 5, CARACTERIZADO PORQUE

A^1 es $C(A^2)$ o N;

A^2 es H;

B^1 es NHR^1;

D^1 es H;

E^1 es H; y

Y^1 es NO_2.

11. Un compuesto de la reivindicación 1, CARACTERIZADO PORQUE el compuesto se selecciona entre:

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;

benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

2-(benciloxi)-4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(2-feniletoxi)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(feniltio)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(feniltio)-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)-2-(feniltio)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(fenilsulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(fenilsulfinil)benzamida;

2-bencil-4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

2-bencil-4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

2-bencil-4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(2-feniletil)benzamida;

2-(bencilamino)-4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

2-anilino-4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

2-anilino-4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-metoxi-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;

4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indazol-5–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indazol-5–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)-2-(1,2,3,4-tetrahidroquinolin-6–iloxi)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)-2-(1,2,3,4-tetrahidroquinolin-6–iloxi)benzamida;

4-(4-((4'-cloro-4-(pirrolidin-1–ilmetil)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-4-(2-pirrolidin-1–iletil)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((1-ciclopentilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)-3-isobutilpiperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-(2,4-dioxo-3-azabiciclo(3.2.0)hept-3–il)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-(4-metil-6-oxo-1,4,5,6-tetrahidropiridazin-3–il)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-(3,3-dimetil-2-oxoazetidin-1–il)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-(4-nitro-2H-1,2,3-triazol-2–il)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((2-(2-piperidin-1–iletoxi)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-((((1-etilpirrolidin-2–il)metil)amino)carbonil)-4-metoxifenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1-naftiloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(2-naftiloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)-2-(2-naftiloxi)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(2-naftiloxi)-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(quinolin-7–iloxi)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(quinolin-6–iloxi)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(isoquinolin-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(isoquinolin-5–iloxi)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(quinolin-6–iloxi)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-4–iloxi)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-6–iloxi)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(isoquinolin-7–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(isoquinolin-7–iloxi)benzamida;

4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-4–iloxi)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-4–iloxi)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-metoxifenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-metilfenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;

N-((3-((cloro(difluoro)metil)sulfonil)-4-((3-(dimetilamino)propil)amino)fenil)sulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

2-(1H-indol-4–iloxi)-4-(4-((2-(4-metoxifenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;

4-(4-((4,4-dimetil-2-(4-(trifluorometil)fenil)ciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;

4-(4-((4,4-dimetil-2-(4-(trifluorometoxi)fenil)ciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;

4-(4-((4,4-dimetil-2-(3-(trifluorometil)fenil)ciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;

4-(4-((2-(3-fluorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;

4-(4-((2-(4-fluorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;

N-((3-((cloro(difluoro)metil)sulfonil)-4-((1-metilpiperidin-4–il)amino)fenil)sulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

4-(4-((2-(4-clorofenil)ciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(fenoximetil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(piridin-3–iloxi)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(piridin-3–iloxi)-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-(((1R)-3-(dimetilamino)-1-((feniltio)metil)propil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(piridin-4–iloxi)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)-2-(piridin-3–iloxi)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)-2-(piridin-4–iloxi)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((2-(4-metilpiperazin-1–il)etil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(4-metilpiperazin-1–il)propil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)(metil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-(((1-metilpiperidin-4–il)metil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-ciano-4-((3-(dimetilamino)propil)amino)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-(trifluorometil)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(isopropil(metil)amino)propil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-(3-(dimetilamino)propoxi)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((2-(4-metilpiperazin-1–il)etil)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((3-(4-metilpiperazin-1–il)propil)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((3-(4-metilpiperazin-1–il)propil)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-(3-(dimetilamino)propoxi)-3-nitrofenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((2-(4-metilpiperazin-1–il)etil)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-(((1-metilpiperidin-4–il)metil)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-(((1-metilpiperidin-4–il)metil)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-(3-(dimetilamino)propoxi)-3-nitrofenil)sulfonil)-2-(1H-indol-4–iloxi)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-(4-metilpiperazin-1–il)-3-nitrofenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((1-(2,2,2-trifluoroetil)piperidin-4–il)amino)fenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-(((4-(dimetilamino)-1-metilpiperidin-4–il)metil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(2,3-dihidro-1,4-benzodioxin-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

5-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-1,1'-bifenil-2-carboxamida;

5-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-1,1'-bifenil-2-carboxamida;

4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-4-(3-piperidin-1–ilpropoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-4-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-4-(3-(dimetilamino)propoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-4-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-4-(3-piperidin-1–ilpropoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-4-(3-(dimetilamino)propoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-4-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-4-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-3-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-3-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-4-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((1-(2,2,2-trifluoroetil)piperidin-4–il)amino)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-4-(2-pirrolidin-1–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-4-(2-(diisopropilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(2,3-dihidro-1H-indol-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)ciclohept-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)ciclooct-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)ciclopent-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclopent-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)ciclooct-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)ciclohept-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)ciclopent-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)ciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)ciclohept-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((2-(dimetilamino)etil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((4-(dimetilamino)butil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((1-(fenilsulfonil)piperidin-4–il)amino)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((1-(quinolin-8–ilsulfonil)piperidin-4–il)amino)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((1-(fenilsulfonil)piperidin-4–il)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((1-(quinolin-8–ilsulfonil)piperidin-4–il)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-(((1S)-3-(dimetilamino)-1-tien-2–ilpropil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tien-2–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((2-(1H-1,2,3-triazol-1–il)etil)amino)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((2-(2H-1,2,3-triazol-2–il)etil)amino)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(2-naftiloxi)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((2-(2-oxopiridin-1(2H)–il)etil)amino)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((2-(piridin-2–iloxi)etil)amino)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((2-piridin-4–iletil)amino)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-(trifluorometil)fenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((3-ciano-4-((3-(dimetilamino)propil)amino)fenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1*H*-indol-5–iloxi)-*N*-((3-nitro-4-((1-tetrahidro-2*H*-piran-4–ilpiperidin-4–il)amino)fenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1*H*-indol-5–iloxi)-*N*-((4-((4-metilpiperazin-1–il)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-(1-(4'-cloro-1,1'-bifenil-2–il)etil)piperazin-1–il)-2-(1*H*-indol-4–iloxi)-*N*-((3-nitro-4-((tetrahidro-2*H*-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

N-((4-(((4-aminotetrahidro-2*H*-piran-4–il)metil)amino)-3-nitrofenil)sulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1*H*-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-morfolin-4–ilciclohexil)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(2-metoxietil)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[(3S)-tetrahidro-2H-piran-3–ilmetil]amino}fenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[(3R)-tetrahidro-2H-piran-3–ilmetil]amino}fenil)sulfonil]benzamida;

4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-hidroxi-1-metilpiperidin-4–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-3-fluoro-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-3-fluoro-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-hidroxi-1-metilpiperidin-4–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;

N-[(4-{[(3S,4R)-1-bencil-3-hidroxipiperidin-4–il]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

N-[(4-{[(4-aminotetrahidro-2H-piran-4–il)metil]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[1-(2-metoxietil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(2-hidroxietil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[1-(2-metoxietil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(3-hidroxipropil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;

4-[4-({4'-cloro-3-[3-(dimetilamino)propil]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(3-hidroxipropil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-{4-[(4'-cloro-4-morfolin-4–il-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-[4-({4'-cloro-3-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(dietilamino)ciclohexil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(dimetilamino)ciclohexil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(dietilamino)ciclohexil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(4-morfolin-4–ilciclohexil)amino]-3-nitrofenil}sulfonil)benzamida;

4-[4-({4'-cloro-3-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-{4-[1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[4-(dimetilamino)tetrahidro-2H-piran-4–il]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida;

N-({4-[(2-aminociclohexil)amino]-3-nitrofenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

4-[4-({4'-cloro-4-[3-(dimetilamino)prop-1-ynil]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(3-nitro-4-{[1-(4,4,4-trifluorobutil)piperidin-4–il]amino}fenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[2-(4-hidroxi-1-metilpiperidin-4–il)etil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[1-(1,3-tiazol-2–il)piperidin-4–il]amino}fenil)sulfonil]benzamida;

4-(4-{[4'-cloro-4-(2-hidroxietoxi)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(ciclopropilmetil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[1-(4,4,4-trifluorobutil)piperidin-4–il]amino}fenil)sulfonil]benzamida;

4-{4-[1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-[4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}-3-(hidroximetil)piperazin-1–il]-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-[4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}-3-(hidroximetil)piperazin-1–il]-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;

4-(4-{[4'-cloro-4-(2-hidroxietoxi)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[3-(3-oxopiperazin-1–il)propil]amino}fenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(3-nitro-4-{[3-(3-oxopiperazin-1–il)propil]amino}fenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-5-hidroxiciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-5-hidroxiciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-5-hidroxiciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(2,3-dihidro-1H-inden-2–il)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(2,3-dihidro-1H-inden-2–il)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(1-morfolin-4–ilciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[1-(1,3-tiazol-2–ilmetil)piperidin-4–il]amino}fenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[1-(1,3-tiazol-4–ilmetil)piperidin-4–il]amino}fenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[4-(hidroximetil)tetrahidro-2H-piran-4–il]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(2-hidroxietil)piperazin-1–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(3S)-1-metilpirrolidin-3–il]amino}-3-nitrofenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(3-fluoropropil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-[4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}-3-(hidroximetil)piperazin-1–il]-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

N-[(4-{[(4-aminotetrahidro-2H-piran-4–il)metil]amino}-3-nitrofenil)sulfonil]-4-[4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}-3-(hidroximetil)piperazin-1–il]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1-hidroxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(2-metoxietil)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(hidroximetil)tetrahidro-2H-piran-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(hidroximetil)tetrahidro-2H-piran-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2-hidroxi-1-tetrahidro-2H-piran-4–iletil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-({1-[2-(1H-pirazol-1–il)etil]piperidin-4–il}amino)fenil]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(metilamino)-3-nitrofenil]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[4-(metilamino)-3-nitrofenil]sulfonil}benzamida;

4-{4-[1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-5-hidroxiciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-5-morfolin-4–ilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

N-[(4-{[(1-aminociclohexil)metil]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[2-(2-oxopirrolidin-1–il)etil]amino}fenil)sulfonil]benzamida;
4-{4-[1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{1-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]etil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{1-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]etil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida;
4-{4-[(1R)-1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-{4-[(1S)-1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{1-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]etil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{1-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]etil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(ciclohexilmetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(morfolin-4–ilamino)-3-nitrofenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-3–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[4-(morfolin-4–ilamino)-3-nitrofenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(tetrahidro-2H-piran-4–ilamino)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(3-metiloxetan-3–il)metil]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-metoxiciclohexil)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[3-(1,1-dioxidotiomorfolin-4–il)propil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[2-(2-oxopiperidin-1–il)etil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[2-(2-oxoimidazolidin-1–il)etil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(2-piridin-4–iletil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-morfolin-4–il-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(4-metoxipiperidin-1–il)-3-nitrofenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-5-pirrolidin-1–ilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[2-(3-oxopiperazin-1–il)etil]amino}fenil)sulfonil]benzamida;
4-[4-({4'-cloro-4-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1,1-dioxidotetrahidrotien-3–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1,1-dioxidotetrahidrotien-3–il)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-[(tetrahidro-2H-piran-4–ilmetil)amino]-3-(trifluorometil)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[2-(1,3-dioxolan-2–il)etil]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(tetrahidro-2H-piran-4–ilmetoxi)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(3-nitro-4-{[2-(3-oxopiperazin-1–il)etil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metil-5-oxopirrolidin-3–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metil-6-oxopiperidin-3–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[3-nitro-4-(piperidin-1–ilamino)fenil]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(piperidin-1–ilamino)fenil]sulfonil}benzamida;

4-(4-{[4-(4-clorofenil)-1-metil-1H-pirazol-5–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(3-metiloxetan-3–il)metoxi]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[(1-oxidotetrahidro-2H-tiopiran-4–il)metil]amino}fenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1,3-tiazol-5–ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[3-nitro-4-(tetrahidro-2H-piran-4–ilmetoxi)fenil]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(2-tetrahidro-2H-piran-4–iletil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(3-nitro-4-{[2-(trifluorometoxi)etil]amino}fenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[2-(2-metoxietoxi)etil]amino}-3-nitrofenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[3-(metilsulfonil)propil]amino}-3-nitrofenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[3-(1,1-dioxidotiomorfolin-4–il)propil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(2-tetrahidro-2H-piran-4–iletil)fenil]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-(1,4-dioxan-2–ilmetoxi)-3-nitrofenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[2-(2-metoxietoxi)etil]amino}-3-nitrofenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1,1-dioxidotetrahidrotien-3–il)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[2-(trifluorometoxi)etil]amino}fenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1,1-dioxidotetrahidro-2H-tiopiran-4–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2,2-difluoroetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4,4-difluorociclohexil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[4-(4-clorofenil)-1-isopropil-6-oxo-1,6-dihidropiridin-3–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(tetrahidro-2H-piran-4–ilmetil)amino]carbonil}fenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(2-metoxietil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-hidroxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(4-metoxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-hidroxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(4-metoxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[3-nitro-4-(2-tetrahidro-2H-piran-4–iletoxi)fenil]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(2-metoxietil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[3-(metilsulfonil)propoxi]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(3-metoxipropil)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(3-metoxipropil)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2-cianoetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2-cianoetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[(3R)-4-hidroxi-1-adamantil]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[Cis-4-hidroxi-1-adamantil]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(3,3,3-trifluoropropil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(3,3,3-trifluoropropil)amino]fenil}sulfonil)benzamida;

N-({5-bromo-6-[(tetrahidro-2H-piran-4–ilmetil)amino]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1,1-dioxidotetrahidrotien-3–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-(metilamino)-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;

N-{[5-bromo-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[4-(4-clorofenil)-6-isopropoxipiridin-3–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[6-(tetrahidro-2H-piran-4–ilmetoxi)-5-(1,3-tiazol-2–il)piridin-3–il]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(2-metoxietil)amino]carbonil}fenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-ciano-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indol-5–iloxi)benzamida;

N-({4-[(1-acetilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[1-(metilsulfonil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1,4-dioxan-2–ilmetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;

N-({4-[(1-acetilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[1-(metilsulfonil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]benzamida;

4-(4-{[4'-cloro-5-(trifluorometil)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[4'-cloro-5-(trifluorometil)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(tetrahidro-2H-piran-4–ilmetoxi)fenil]sulfonil}benzamida;

4-{4-[(5-tert-butil-4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-{4-[(5-tert-butil-4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(tetrahidro-2H-piran-4–ilmetoxi)fenil]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(2,2,2-trifluoroetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(2,2,2-trifluoroetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-{[(tetrahidro-2H-piran-4–ilmetil)amino]carbonil}fenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2R)-1,4-dioxan-2–ilmetoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2S)-1,4-dioxan-2–ilmetoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;

N-({5-bromo-6-[(tetrahidro-2H-piran-4–ilmetil)amino]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(2-morfolin-4–iletil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-ciano-6-[(tetrahidro-2H-piran-4–ilmetil)amino]piridin-3–il}sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)oxi]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)metoxi]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[4-(4-clorofenil)-1-(3-hidroxipropil)-1,2,5,6-tetrahidropiridin-3–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-({[4-({[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzoil]amino}sulfonil)-2-nitrofenil]amino}metil)piperidin-1-carboxilato de bencilo ;

N-{[3-(aminocarbonil)-4-(tetrahidro-2H-piran-4–ilmetoxi)fenil]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[4'-cloro-5-(trifluorometil)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;

4-{4-[(5-tert-butil-4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(1-metil-1H-imidazol-5–il)metil]amino}-3-nitrofenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(morfolin-4–ilsulfonil)fenil]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1,1-dioxidotiomorfolin-4–il)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-morfolin-4–ilciclohexil)amino]-3-nitrofenil}sulfonil)benzamida;

N-{[5-bromo-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[6-[(tetrahidro-2H-piran-4–ilmetil)amino]-5-(1,3-tiazol-2–il)piridin-3–il]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-ciano-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-ciano-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(3,3-dimetilbutil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1S)-1-(hidroximetil)-3-metilbutil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[(2R)-tetrahidrofuran-2–ilmetil]amino}fenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1R)-1-(hidroximetil)-2-metilpropil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-metoxifenil)amino]-3-nitrofenil}sulfonil)benzamida;

N-[(4-{[2-(1,3-benzodioxol-5–il)etil]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[3-(2-oxopirrolidin-1–il)propil]amino}fenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-hidroxifenil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;

N-{[4-({2-[4-(aminosulfonil)fenil]etil}amino)-3-nitrofenil]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[3-(1H-imidazol-1–il)propil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[(1S)-1-feniletil]amino}fenil)sulfonil]benzamida;

N-({2-cloro-5-fluoro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[2-(2-metoxietoxi)etil]tio}-3-nitrofenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[2-(2-metoxietoxi)etil]tio}-3-nitrofenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(metilsulfonil)fenil]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[4-(metilsulfonil)fenil]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2,2-dimetiltetrahidro-2H-piran-4–il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-ciano-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-ciano-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-cloro-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-ciano-6-(2-morfolin-4–iletoxi)piridin-3–il]sulfonil}-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)oxi]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-morfolin-4–ilbut-2-ynil)oxi]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-etinil-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-ciano-6-(2-morfolin-4–iletoxi)piridin-3–il]sulfonil}-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-ciano-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(3-hidroxi-4-metoxifenil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(2,3-dihidro-1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)-2-(piridin-3–ilamino)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)-2-(piridin-3–ilamino)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)-2-(piridin-3–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(1,2,3,4-tetrahidroisoquinolin-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;

Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)-N-({4-[(4-morfolin-4–ilciclohexil)amino]-3-nitrofenil}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-ciano-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-2-(1H-indazol-4–iloxi)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(3R)-1-(2,2-difluoroetil)pirrolidin-3–il]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-fluorotetrahidro-2H-piran-4–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]-5-(trifluorometil)piridin-3–il]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-ciclopropilmorfolin-2–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4,4-difluorociclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4–iloxi)benzamida;

N-[(5-cloro-6-{[(4-fluorotetrahidro-2H-piran-4–il)metil]amino}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

Trans-N-({5-cloro-6-[(4-metoxiciclohexil)metoxi]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[4-(2,2-difluoroetil)morfolin-2–il]metil}amino)-3-nitrofenil]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-fluoro-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-2-(1H-indazol-4–iloxi)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;

N-[(5-cloro-6-{[1-(cianometil)-4-fluoropiperidin-4–il]metoxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-cloro-6-(tetrahidrofuran-3–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;

Trans-N-({5-cloro-6-[(4-hidroxiciclohexil)metoxi]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

N-[(5-cloro-6-{[(3R)-1-(2,2-difluoroetil)pirrolidin-3–il]oxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

2-(1H-benzimidazol-4–iloxi)-N-[(5-cloro-6-{[(2S)-4-(N,N-dimetilglicil)morfolin-2–il]metoxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)benzamida;

2-(1H-benzimidazol-4–iloxi)-N-[(5-cloro-6-{[(2R)-4-(N,N-dimetilglicil)morfolin-2–il]metoxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)benzamida;

N-[(5-cloro-6-{[(2S)-4-(N,N-dimetilglicil)morfolin-2–il]metoxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

N-[(5-cloro-6-{[(2R)-4-(N,N-dimetilglicil)morfolin-2–il]metoxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-cloro-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(3R)-1-(cianometil)pirrolidin-3–il]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({(3R)-1-[2-(2-metoxietoxi)etil]pirrolidin-3–il}amino)-3-nitrofenil]sulfonil}benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(3R)-1-(N,N-dimetilglicil)pirrolidin-3–il]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[4-(cianometil)morfolin-2–il]metil}amino)-3-nitrofenil]sulfonil}benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-ciclopropilmorfolin-2–il)metil]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(3-nitro-4-{[(4-oxetan-3–ilmorfolin-2–il)metil]amino}fenil)sulfonil]benzamida;

N-{[5-cloro-6-({(3R)-1-[2-fluoro-1-(fluorometil)etil]pirrolidin-3–il}oxi)piridin-3–il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({(3R)-1-[2-fluoro-1-(fluorometil)etil]pirrolidin-3–il}amino)-3-nitrofenil]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1-ciclopropilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)-2-(1H-indazol-4–iloxi)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[(2R)-4-(N,N-dimetilglicil)morfolin-2–il]metil}amino)-3-nitrofenil]sulfonil}benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[(2S)-4-(N,N-dimetilglicil)morfolin-2–il]metil}amino)-3-nitrofenil]sulfonil}benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(tetrahidrofuran-3–ilmetil)amino]fenil}sulfonil)benzamida;

Trans-2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-metoxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-fluorotetrahidro-2H-piran-4–il)metil]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-fluoro-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)benzamida;

N-{[5-cloro-6-({(3R)-1-[2-fluoro-1-(fluorometil)etil]pirrolidin-3–il}metoxi)piridin-3–il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

N-[(5-cloro-6-{[(3R)-1-(2,2-difluoroetil)pirrolidin-3–il]metoxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)-N-[(4-{[(4-metoxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-(1,4-dioxan-2–ilmetoxi)-3-nitrofenil]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;

N-({5-cloro-6-[(1-ciclopropilpiperidin-4–il)amino]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

2-(1H-benzimidazol-4–iloxi)-N-({5-cloro-6-[(1-ciclopropilpiperidin-4–il)amino]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1,4-dioxan-2–ilmetil)amino]-3-nitrofenil}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1-ciclopropilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;

Trans-2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-morfolin-4–ilciclohexil)amino]-3-nitrofenil}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1-metilpiperidin-4–il)metil]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[({(2R)-4-[2-(2-metoxietoxi)etil]morfolin-2–il}metil)amino]-3-nitrofenil}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4,4-difluorociclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;

N-[(4-{[(4-acetilmorfolin-2–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[4-(metilsulfonil)morfolin-2–il]metil}amino)-3-nitrofenil]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[6-({4-fluoro-1-[2-fluoro-1-(fluorometil)etil]piperidin-4–il}metoxi)-5-(trifluorometil)piridin-3–il]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-cloro-6-(2-tetrahidrofuran-2–iletoxi)piridin-3–il]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;

Trans-2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-cianociclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-N-({5-cloro-6-[(4,4-difluorociclohexil)metoxi]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)benzamida;

N-({3-cloro-4-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-*N*-{[5-ciano-6-(2-tetrahidro-2*H*-piran-4–iletoxi)piridin-3–il]sulfonil}-2-(1*H*-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(1R,5S)-8-metil-8-azabiciclo[3.2.1]oct-3–il]amino}-3-nitrofenil)sulfonil]benzamida;

N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxi-4-(4-{(3-fenilpropanoil)[(1S,2S,3S,5R)-2,6,6-trimetilbiciclo[3.1.1]hept-3–il]amino}piperidin-1–il)benzamida;

N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)-2-fenoxi-4-(4-{(3-fenilpropanoil)[(1S,2S,3S,5R)-2,6,6-trimetilbiciclo[3.1.1]hept-3–il]amino}piperidin-1–il)benzamida;

N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxi-4-(4-{(3-fenilpropil)[(1S,2S,3S,5R)-2,6,6-trimetilbiciclo[3.1.1]hept-3–il]amino}piperidin-1–il)benzamida;

N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)-2-fenoxi-4-(4-{(3-fenilpropil)[(1S,2S,3S,5R)-2,6,6-trimetilbiciclo[3.1.1]hept-3–il]amino}piperidin-1–il)benzamida;

4-[4-(2-{[(1R,5S)-8-metil-8-azabiciclo[3.2.1]oct-3–il]amino}bencil)piperazin-1–il]-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)-2-fenoxibenzamida;

4-[4-(2-{[(1R,5S)-8-metil-8-azabiciclo[3.2.1]oct-3–il]amino}bencil)piperazin-1–il]-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida;

4-{4-[2-(3-azabiciclo[3.2.2]non-3–il)bencil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida;

4-{4-[2-(3-azabiciclo[3.2.2]non-3–il)bencil]piperazin-1–il}-2-fenoxi-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;

4-{4-[2-(3-azabiciclo[3.2.2]non-3–il)bencil]piperazin-1–il}-2-fenoxi-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-{4-[2-(3-azabiciclo[3.2.2]non-3–il)bencil]piperazin-1–il}-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)-2-fenoxibenzamida;

4-(4-{2-[(4R,7S)-2,3,3a,4,7,7a-hexahidro-1H-4,7-metanoinden-5–il]bencil}piperazin-1–il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida;

4-[4-(2-{5-[(1R,5S)-8-azabiciclo[3.2.1]oct-8–ilmetil]tien-2–il}bencil)piperazin-1–il]-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida;

4-[4-(2-{5-[(1R,5S)-8-azabiciclo[3.2.1]oct-8–ilmetil]tien-2–il}benciliden)piperidin-1–il]-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida;

4-[4-(3-{5-[(1R,5S)-8-azabiciclo[3.2.1]oct-8–ilmetil]tien-2–il}bencil)piperazin-1–il]-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida;

N-({5-cloro-6-[(4,4-difluorociclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({6-[(trans-4-carbamoilciclohexil)metoxi]-5-cloropiridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(trans-4-cianociclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[2-(1H-imidazol-1-il)etoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(1-metil-1H-imidazol-5-il)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[5-fluoro-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil}-2-(1H-indazol-4-iloxi)benzamida;

N-{[5-cloro-6-(1,4-dioxan-2-ilmetoxi)piridin-3-il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(4,4-difluoro-1-hidroxiciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(2,2-difluorociclopropil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(trans-4-cianociclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(cis-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({3-cloro-4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]fenil}sulfonil)-4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]-3-(trifluorometil)fenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-cloro-4-(tetrahidro-2H-piran-4-ilmetoxi)fenil]sulfonil}-2-(1H-indazol-4-iloxi)benzamida;

2-(1H-benzimidazol-4-iloxi)-N-({3-cloro-4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida;

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[5-cloro-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-ciano-4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]fenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida;

N-{[3-cloro-4-(1,4-dioxan-2-ilmetoxi)fenil]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

2-(1H-benzimidazol-4-iloxi)-N-[(5-cloro-6-{[(2S)-4-ciclopropilmorfolin-2-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida;

N-[(5-cloro-6-{[(2S)-4-ciclopropilmorfolin-2-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

2-{[(4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzoil]sulfamoil}-2-nitrofenil)amino]metil}morfolin-4-carboxilato de metilo ;

2-{[(4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzoil]sulfamoil}-2-nitrofenil)amino]metil}-N-etil-N-metilmorfolin-4-carboxamida;

2-{[(4-{[2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzoil]sulfamoil}-2-nitrofenil)amino]metil}-N-etil-N-metilmorfolin-4-carboxam

ide;

N-({5-cloro-6-[(trans-4-etil-4-hidroxiciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(cis-4-etil-4-hidroxiciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

5-cloro-N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamid

e;

5-cloro-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4-fluorotetrahidro-2H-piran-4-il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(cis-1-fluoro-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamid

e;

N-({5-cloro-6-[(trans-1-fluoro-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzam

ide;

2-(1H-benzotriazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4-fluorotetrahidro-2H-piran-4-il)metil]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzotriazol-4-iloxi)-N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida;

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-cloro-4-(tetrahidro-2H-piran-4-ilmetoxi)fenil]sulfonil}benzamida;

N-[(3-cloro-4-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}fenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(cis-1-fluoro-4-hidroxiciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

2-(1H-benzotriazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]-3-nitrofenil}sulfonil)benzamida;

N-[(5-cloro-6-{[(1R,2R,4R,5R)-5-hidroxi-5-metilbiciclo[2.2.1]hept-2-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-
iloxi)benzamida;

N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-[(5-cloro-6-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

2-(1H-benzotriazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(trans-4-hidroxi-4-metilciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(cis-4-hidroxi-4-metilciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;

2-(1H-benzotriazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({[(2S)-4-ciclopropilmorfolin-2-il]metil}amino)-3-nitrofenil]sulfonil}benzamida;

N-[(5-cloro-6-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({[(2S)-4-ciclopropilmorfolin-2-il]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-indazol-4-iloxi)benzamida;

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({[(2S)-4-ciclopropilmorfolin-2-il]metil}amino)-3-nitrofenil]sulfonil}benzamida;

N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(cis-4-hidroxi-4-metilciclohexil)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(trans-4-hidroxi-4-metilciclohexil)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-ciano-4-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}fenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-{[3-nitro-4-(2-oxaspiro[3.5]non-7-ilmetoxi)fenil]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[5-cloro-6-(5,6,7,8-tetrahidroimidazo[1,2-a]piridin-6-ilmetoxi)piridin-3-il]sulfonil}-2-(1H-indazol-4-iloxi)benzami

de;

2-(1H-benzimidazol-4-iloxi)-N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(5-ciano-6-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}piridin-3-il)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-5-(metoximetil)-5-metilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)b

enzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-{[3-nitro-4-({[(2S)-4-(oxetan-3-il)morfolin-2-il]metil}amino)fenil]sulfonil}benzamida;

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-nitro-4-({[(2S)-4-(oxetan-3-il)morfolin-2-il]metil}amino)fenil]sulfonil}benzamida;

N-[(5-cloro-6-{[trans-4-(2-hidroxipropan-2-il)ciclohexil]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-ciano-4-[(trans-4-hidroxi-4-metilciclohexil)metoxi]fenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({5-ciano-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-({5-nitro-6-[(tetrahidro-2H-piran-4-ilmetil)amino]piridin-3-il}sulfonil)benzamida;

2-(1H-benzotriazol-4-iloxi)-N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida;

N-({3-cloro-4-[(cis-4-ciano-1-fluorociclohexil)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({3-cloro-4-[(trans-4-ciano-1-fluorociclohexil)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(cis-4-ciano-1-fluorociclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(trans-4-ciano-1-fluorociclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzami

de;

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(trans-4-hidroxi-4-metilciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;

N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-5-metoxi-5-metilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(5-cloro-6-{[1-(1,3-tiazol-2-il)piperidin-4-il]metoxi}piridin-3-il)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(6-{[(cis-4-hidroxi-4-metilciclohexil)metil]amino}-5-nitropiridin-3-il)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]-5-(trifluorometil)piridin-3-il}sulfonil)-2-(1H-indazol-4-iloxi)benz

amida;

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(cis-4-hidroxi-4-metilciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;

N-(4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzoil]sulfamoil}-2-nitrofenil)-4-cianopiperidin-1-carboxamida;y sus sales, profármacos, sales de profármacos y metabolitos terapéuticamente aceptables.

12. Una composición para tratar cáncer de vejiga, cáncer de cerebro, cáncer de mamas, cáncer de médula ósea, cáncer cervical, leucemia linfocítica crónica, cáncer colorrectal, cáncer de esófago, cáncer hepatocelular, leucemia linfoblástica, linfoma folicular,

malignidades linfoides originadas en células T o células B, melanoma, leucemia mielógena, mieloma, cáncer oral, cáncer de ovarios, cáncer de pulmón de células no pequeñas, leucemia linfocítica crónica, mieloma, cáncer de próstata, cáncer de pulmón o cáncer de bazo de células pequeñas, CARACTERIZADA PORQUE dicha composición comprende un excipiente y una cantidad terapéuticamente efectiva del compuesto de la reivindicación 1.

13. Un método para tratar cáncer de vejiga, cáncer de cerebro, cáncer de mamas, cáncer de médula ósea, cáncer cervical, leucemia linfocítica crónica, cáncer colorrectal, cáncer de esófago, cáncer hepatocelular, leucemia linfoblástica, linfoma folicular, malignidades linfoides originadas en células T o células B, melanoma, leucemia mielógena, mieloma, cáncer oral, cáncer de ovarios, cáncer de pulmón de células no pequeñas, leucemia linfocítica crónica, mieloma, cáncer de próstata, cáncer de pulmón o cáncer de bazo de células pequeñas en un paciente, CARACTERIZADO PORQUE dicho método comprende administrar al paciente una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1.

14. Un método para tratar cáncer de vejiga, cáncer de cerebro, cáncer de mamas, cáncer de médula ósea, cáncer cervical, leucemia linfocítica crónica, cáncer colorrectal, cáncer de esófago, cáncer hepatocelular, leucemia linfoblástica, linfoma folicular, malignidades linfoides originadas en células T o células B, melanoma, leucemia mielógena, mieloma, cáncer oral, cáncer de ovarios, cáncer de pulmón de células no pequeñas, leucemia linfocítica crónica, mieloma, cáncer de próstata, cáncer de pulmón o cáncer de bazo de células pequeñas en un paciente, CARACTERIZADO PORQUE dicho método comprende administrar al paciente una cantidad terapéuticamente efectiva del compuesto de la reivindicación 1 y una cantidad terapéuticamente efectiva de un agente terapéutico adicional o más de un agente terapéutico adicional.

AGENTES INDUCTORES DE APOPTOSIS CON SELECTIVIDAD POR Bcl-2 PARA EL TRATAMIENTO DE CÁNCER Y ENFERMEDADES INMUNES

RESUMEN

Compuestos que inhiben la actividad de las proteínas anti-apoptóticas Bcl-2 o Bcl-X_L, composiciones que contienen dichos compuestos y métodos para tratar enfermedades durante las cuales se expresa la proteína anti-apoptótica Bcl-2.

9696 02_Listado de secuencias
SEQUENCE LISTING

<110> BRUNCKO, MILAN
DING, HONG
DOHERTY, GEORGE A.
ELMORE, STEVEN W.
HASVOLD, LISA
HEXAMER, LAURA
KUNZER, AARON R.
MANTEI, ROBERT A.
MCCLELLAN, WILLIAM J.
PARK, CHANG H.
PARK, CHEOL-MIN
PETROS, ANDREW M.
SONG, XIAOHONG
SOUERS, ANDREW J.
SULLIVAN, GERARD M.
TAO, ZHI-FU
WANG, GARY T.
WANG, LE
WANG, XILU
WENDT, MICHAEL D.
HANSEN, TODD M.

<120> AGENTES INDUCTORES DE APOPTOSIS CON SELECTIVIDAD POR BCL-2 PARA EL TRATAMIENTO DE CÁNCER Y ENFERMEDADES INMUNES

<130> 9696USP1

<140> 12/793,418
<141> 2010-06-03

<150> 12/631,404
<151> 2009-12-04

<150> 61/181,180
<151> 2009-05-26

<150> 61/120,275
<151> 2008-12-05

<160> 2

<170> PatentIn version 3.5

<210> 1
<211> 13
<212> PRT
<213> Secuencia artificial

<220>
<223> Descripción de la secuencia artificial: sonda sintética

<400> 1
Gly Gln Val Gly Arg Gln Leu Ala Ile Ile Gly Asp Lys
1 5 10

<210> 2
<211> 3
<212> PRT
<213> Secuencia artificial

<220>
<223> Descripción de la secuencia artificial: sonda sintética

<400> 2
Ile Asn Arg
1

000109
168

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO PROPIETARIOS

PATENTE DE INVENCION ___ PCT __X__ MODELO DE UTILIDAD ___ DISEÑO INDUSTRIAL ___

(21) Nº de solicitud:
(22) Fecha de solicitud:
(51) Clasificación Internacional :

(71)Solicitante(s) **ABBOTT LABORATORIES**

(72) Inventor(es) **BRUNCKO, Milan; DING, Hong; DOHERTY, George A.; ELMORE, Steven W.; HASVOLD, Lisa; HEXAMER, Laura; KUNZER, Aaron; MANTEI, Robert A.; McCLELLAN, William J.; PARK, Cheol-Min; PETROS, Andrew M.; SONG, Xiaohong; SOUERS, Andrew J.; SULLIVAN, Gerard M.; TAO, Zhi-Fu; WANG, Gary T. ; WANG, Le; WANG, Xilu; WENDT, Michael D. ; HANSEN, Todd M.; PARK, Chang H.**

(74) Apoderado: **DRA. MARGARITA CASTELLANOS ABONDANO**

(30) Prioridad	(31)	No. Prioridad	32)	Fecha	(33)	País
		12/631.404		04/12/2009		US

(85) Fecha inicio fase nacional:
(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: **01/06/2010**
No. de solicitud **PCT/US2010/036919**

(87) Publicación internacional
Fecha: **09/06/2011**
Nº publicación: **WO 2011/068561 A1**

(54) Titulo: **DERIVADOS DE SULFONAMIDA COMO AGENTES INDUCTORES DE APOPTOSIS CON SELECTIVIDAD POR Bcl-2 PARA EL TRATAMIENTO DE CANCER Y ENFERMEDADES INMUNES**

Industria y Comercio
SUPERINTENDENCIA

EXTRACTO PARA PUBLICACIÓN

___ **Patente de Invención** ___ **Patente modelo de utilidad** _X_ **PCT**

(21) No. De solicitud	(51) int. Cl:
(22) Fecha de solicitud	(71) Solicitante (s) **ABBOTT LABORATORIES**
(30) Prioridad (31) No. Prioridad **12/631.404** (32) Fecha **04/12/2009** (33) País **US**	(72) Interventor (es) **BRUNCKO, Milan** **DING, Hong** **DOHERTY, George A.** **ELMORE, Steven W.** **HASVOLD, Lisa** **Y OTROS** (74) Apoderado (s) **DRA. MARGARITA CASTELLANOS ABONDANO**

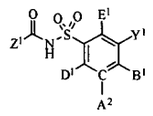
(54) Título
DERIVADOS DE SULFONAMIDA COMO AGENTES INDUCTORES DE APOPTOSIS CON SELECTIVIDAD POR Bcl-2 PARA EL TRATAMIENTO DE CANCER Y ENFERMEDADES INMUNES

Las casillas identificadas con 85, 86 y 87 sólo aplican para PCT

(85) Fecha límite inicio Fase Nacional	
(86) Datos relativos a la presentación de la solicitud PCT Fecha de presentación de la solicitud **01/06/2010** No. de solicitud **PCT/US2010/036919**	(87) Publicación internacional Fecha **09/06/2011** No. Publicación **WO 2011/068561 A1**

Resumen reivindicación (es):

1. Un compuesto CARACTERIZADO PORQUE tiene la Fórmula I



(I),

o una sal, profármaco o sal de profármaco terapéuticamente aceptable del mismo ,
A^1 es N o $C(A^2)$;
uno o dos o tres o cada uno de A^2, B^1, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes se seleccionan en forma independiente entre H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$; y
Y^1 es H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ o $NHSO_2R^{17}$;
o
B^1 y Y^1, junto con los átomos a los cuales están unidos , son imidazol o triazol; y
uno o dos o cada uno de A^2, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes se seleccionan en forma independiente entre H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$;
R^1 es R^2, R^3, R^4 o R^5;
R^{1A} es C_1-C_6-alquilo, C_3-C_6-alquenilo o C_3-C_6-alquinilo;
R^2 es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{2A}; R^{2A} es cicloalcano o heterocicloalcano;
R^3 es heteroarilo que no está fusionado o está fusionado con benceno, heteroareno o R^{3A}; R^{3A} es cicloalcano o heterocicloalcano;
R^4 es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{4A}; R^{4A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;
R^5 es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;
R^6 es C_2-C_5-espiroalquilo, cada uno de los cuales no esta sustituido o está sustituido con OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ o $N(CH_3)_2$;
R^{6A} y R^{6B} se seleccionan en forma independiente entre alquilo o, junto con el N al cual están unidos, R^{6C};
R^{6C} es aziridin-1–ilo, azetidin-1–ilo, pirrolidin-1–ilo o piperidin-1–ilo, teniendo cada uno una unidad CH_2 no reemplazada o reemplazada con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH;
R^7 es R^8, R^9, R^{10} o R^{11}; ...

Industria y Comercio
SUPERINTENDENCIA

PLANILLA DE RADICACIÓN - DIGITALIZACIÓN DIARIA
RELACIÓN DE ANEXOS

Dependencia:	Fecha:	Recorrido:

Tipo de Radicación: Entrada: Salida: Traslado: Convenio:

Radicador:	Planilla:

ID	No. Radicación	Cons	Item
1			
2			
3	12-111688-0		
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			

Item	Unidad de Conservación
1	CD
2	Disquetes
3	DVD
4	Fotos
5	Libro
6	Muestra Física
7	Otros
8	Planos
9	Periódico
10	Publicación Periódica
11	Sobre blanco tamaño carta
12	Sobre blanco tamaño oficio
13	Sobre de manila

Observaciones
Folio 170 Sobre blanco.

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-111688- -00000-0000
Fecha: 2012-07-04 14:40:39 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 170

PATENTE DE INVENCIÓN _____ MODELO DE UTILIDAD _____ Art 33 Decisión 486/00

Indicación que se solicita una patente.
Datos de identificación del solicitante o de la persona que presenta la solicitud
Descripción de la invención
Dibujos de ser estos pertinentes
Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)
Completa _____ Incompleta _____

PATENTE DE INVENCIÓN PCT _X_ MODELO DE UTILIDAD PCT ___ Art.33 Decisión 486/00, Circular Única

X Indicación que se solicita una PCT
X Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
Dibujos de ser estos pertinentes
X Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa _X_ Incompleta _____

DISEÑO INDUSTRIAL _____ (Art. 119 Decisión 486/00)

Indicación que se solicita Diseño industrial
Datos de identificación del solicitante o de la persona que presenta la solicitud
Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño

Comprobante de pago de las tasas establecidas
Completa _____ Incompleta _____

ESQUEMA DE TRAZADO _____ (Art. 92 Decisión 486/00)

Indicación que se solicita un esquema de trazado

Datos de identificación del solicitante o de la persona que presenta la solicitud

Representación gráfica de un esquema de trazado

Comprobante de pago de las tasas establecidas

Completa _____ Incompleta _____

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 June 2011 (09.06.2011)

PCT

(10) International Publication Number
WO 2011/068561 A1

(51) International Patent Classification:
C07D 405/12 (2006.01) *C07D 235/26* (2006.01)
A61K 31/404 (2006.01) *C07D 249/04* (2006.01)
A61P 35/00 (2006.01) *C07D 295/14* (2006.01)
C07D 209/32 (2006.01) *C07D 309/14* (2006.01)
C07D 211/96 (2006.01) *C07D 401/12* (2006.01)
C07D 213/64 (2006.01) *C07D 295/125* (2006.01)
C07D 215/20 (2006.01) *C07D 231/56* (2006.01)
C07D 217/16 (2006.01) *C07D 405/14* (2006.01)

(21) International Application Number:
PCT/US2010/036919

(22) International Filing Date:
1 June 2010 (01.06.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
12/631,404 4 December 2009 (04.12.2009) US

(71) Applicant *(for all designated States except US)*: **ABBOTT LABORATORIES** [US/US]; 100 Abbott Park Road, Abbott Park, Illinois 60064 (US).

(72) Inventor; and
(71) Applicant : **PARK, Chang, H.** [US/US]; 2871 North Southern Hills, Wadsworth, Illinois 60083 (US).

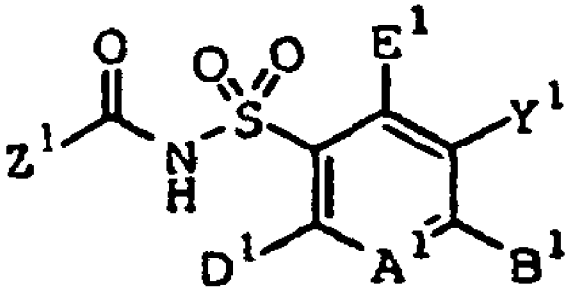
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BRUNCKO, Milan** [US/US]; 31231 Prairie Ridge, Green Oaks, Illinois 60048 (US). **DING, Hong** [CN/US]; 7465 Clem Drive, Gurnee, Illinois 60031 (US). **DOHERTY, George A.** [US/US]; 1605 Bush Court, Libertyville, Illinois 60048 (US). **ELMORE, Steven, W.** [US/US]; 239 Ash Lane, Northbrook, Illinois 60062 (US). **HASVOLD, Lisa** [US/US]; 552 Shakespeare Drive, Grayslake, Illinois 60030 (US). **HEXAMER, Laura** [US/US]; 439 Gatewood Lane, Grayslake, Illinois 60030 (US). **KUNZER, Aaron** [US/US]; 615 W. Burr Oak Drive, Arlington Heights, Illinois 60004 (US). **MANTEI, Robert, A.** [US/US]; 4203 Carolyn Court, Franklin, Wisconsin 53132 (US). **McCLELLAN, William, J.** [US/US]; 1212 North Sheridan Road, Waukegan, Illinois 60085 (US). **PARK, Cheol-Min** [KR/US]; 5312 F. George Court, Gurnee, Illinois 60031 (US). **PETROS, Andrew, M.** [US/US]; 940 Ambria Drive, Mundelein, Illinois 60060 (US). **SONG, Xiaohong** [CN/US]; 34037 Sulkey Drive, Grayslake, Illinois 60030 (US). **SOUERS, Andrew, J.** [US/US]; 901 Hinman, Apt. 3A, Evanston, Illinois 60202 (US). **SULLIVAN, Gerard, M.** [US/US]; 1212 Tulip Tree Court, Lake Villa, Illinois 60046 (US). **TAO, Zhi-Fu** [CN/US]; 1532 Vineyard Drive, Gurnee, Illinois 60031 (US). **WANG, Gary, T.** [US/US]; 1904 Darnell Street, Libertyville, Illinois 60048 (US). **WANG, Le** [US/US]; 338 East Colonial Drive, Vernon Hills, Illinois 60061 (US). **WANG, Xilu** [US/US]; 34056 Sulkey Drive, Grayslake, Illinois 60030 (US). **WENDT, Michael, D.** [US/US]; 1445 Maidstone Drive, Vernon Hills, Illinois 60061 (US). **HANSEN, Todd, M.** [US/US]; 191 Seymour Avenue, Grayslake, Illinois 60030 (US).

(74) Agents: **YASGER, Paul, D.** et al.; Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ,

[Continued on next page]

(54) Title: SULFONAMIDE DERIVATIVES AS BCL-2-SELECTIVE APOPTOSIS-INDUCING AGENTS FOR THE TREATMENT OF CANCER AND IMMUNE DISEASES



(I)

(57) Abstract: Disclosed are compounds (I) which inhibit the activity of anti-apoptotic Bc1-2 or Bc1 xL proteins, compositions containing the compounds and methods of treating diseases during which are expressed anti apoptotic Bc1-2 protein.

WO 2011/068561 A1

CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to the identity of the inventor (Rule 4.17(i))*

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *with international search report (Art. 21(3))*

SULFONAMIDE DERIVATIVES AS BCL-2-SELECTIVE APOPTOSIS-INDUCING AGENTS FOR THE TREATMENT OF CANCER AND IMMUNE DISEASES

This application claims priority to U.S. Patent Application Serial No. 12/631,404, filed December 4, 2009, which is incorporated by reference in its entirety.

FIELD OF THE INVENTION

This invention pertains to compounds which selectively inhibit the activity of anti-apoptotic Bcl-2 family proteins, compositions containing the compounds, and methods of treating diseases during which anti-apoptotic Bcl-2 proteins are expressed.

BACKGROUND OF THE INVENTION

Anti-apoptotic Bcl-2 family proteins are associated with a number of diseases and are under investigation as potential therapeutic drug targets. These targets for interventional therapy include, for example, the Bcl-2 family proteins Bcl-2, Bcl-X_L and Bcl-w. Recently, inhibitors of Bcl-2 family proteins have been reported in commonly-owned PCT/US/2004/36770, published as WO 2005/049593 and PCT/US/2004/367911, published as WO 2005/049594. While this art teaches inhibitors having high binding to the target protein, compound binding affinity is only one of many parameters to be considered. One goal is to produce compounds that preferentially bind to, that is, are selective for, one protein over another protein. To exhibit this selectivity, it is well known that a compound not only displays a high binding affinity to a particular protein but a lower binding affinity for another member as well.

A typical measure of binding affinity of an anti-apoptotic protein inhibitor is the balance between the binding and dissociation processes between the protein and the inhibitor (K_i). The inhibition constant (K_i) is the dissociation constant of an enzyme-inhibitor complex or a protein/small molecule complex, wherein the small molecule is inhibiting binding of one protein to another protein. So a large K_i value indicates a low binding affinity, and a small K_i value indicates a high binding affinity.

A typical measure of cellular activity of an anti-apoptotic protein inhibitor is the concentration eliciting 50% cellular effect (EC_{50}).

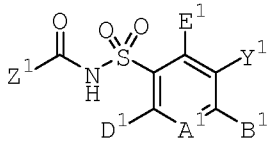
Accordingly, the inventors have discovered that while compounds taught in the art have utility for the treatment of various cancers and immune diseases, they are not selective

for anti-apoptotic Bcl-2 proteins over anti-apoptotic Bcl-X_L proteins and thereby result in a higher probability of side effects characterized by inhibition of anti-apoptotic Bcl-X_L proteins such as, thrombocytopenia.

This invention therefore comprises a series of compounds that demonstrate unexpected properties with respect to their selectivity for binding to, and inhibiting the activity of anti-apoptotic Bcl-2 protein over anti-apoptotic Bcl-X_L protein as significantly higher than those of the compounds taught in PCT/US/2004/36770 and PCT/US/2004/367911.

SUMMARY OF THE INVENTION

One embodiment of this invention, therefore, pertains to compounds or therapeutically acceptable salts, prodrugs or salts of prodrugs thereof, which are useful as selective inhibitors one or more than one anti-apoptotic protein family member, the compounds having Formula (I)



(I),

wherein

A^1 is N or $C(A^2)$;

one or two or three or each of A^2, B^1, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$; and

Y^1 is H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ or $NHSO_2R^{17}$;

or

B^1 and Y^1, together with the atoms to which they are attached, are imidazole or triazole; and

one or two or each of A^2, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$,

$NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$;

R^1 is R^2, R^3, R^4 or R^5;

R^{1A} is C_1-C_6-alkyl, C_3-C_6-alkenyl or C_3-C_6-alkynyl;

R^2 is phenyl which is unfused or fused with arene, heteroarene or R^{2A}; R^{2A} is cycloalkane or heterocycloalkane;

R^3 is heteroaryl which is unfused or fused with benzene, heteroarene or R^{3A}; R^{3A} is cycloalkane or heterocycloalkane;

R^4 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with arene, heteroarene or R^{4A}; R^{4A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^5 is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^6 is C_2-C_5-spiroalkyl, each of which is unsubstituted or substituted with OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ or $N(CH_3)_2$;

R^{6A} and R^{6B} are independently selected alkyl or, together with the N to which they are attached, R^{6C};

R^{6C} is aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, each having one CH_2 moiety unreplaced or replaced with O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH;

R^7 is R^8, R^9, R^{10} or R^{11};

R^8 is phenyl which is unfused or fused with arene, heteroarene or R^{8A};

R^{8A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^9 is heteroaryl which is unfused or fused with arene, heteroarene or R^{9A}; R^{9A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{10} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{10A}; R^{10A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{11} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{12} is R^{13}, R^{14}, R^{15} or R^{16};

R^{13} is phenyl which is unfused or fused with arene, heteroarene or R^{13A}; R^{13A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{14} is heteroaryl, each of which is unfused or fused with arene, heteroarene or R^{14A}; R^{14A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{15} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene, each of which is unfused or fused with arene, heteroarene or R^{15A}; R^{15A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{16} is alkyl, alkenyl or alkynyl;

R^{17} is R^{18}, R^{19}, R^{20} or R^{21};

R^{18} is phenyl which is unfused or fused with arene, heteroarene or R^{18A}; R^{18A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{19} is heteroaryl which is unfused or fused with arene, heteroarene or R^{19A}; R^{19A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{20} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{20A}; R^{20A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{21} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{22} is R^{23}, R^{24} or R^{25};

R^{23} is phenyl which is unfused or fused with arene, heteroarene or R^{23A}; R^{23A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{24} is heteroarene which is unfused or fused with arene, heteroarene or R^{24A}; R^{24A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{25} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is

unfused or fused with arene, heteroarene or R^{25A}; R^{25A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

Z^1 is R^{26} or R^{27}, each of which is substituted with R^{28}, R^{29} or R^{30}, each of which is substituted with F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} or $N(R^{32})R^{37}$;

R^{26} is phenyl which is unfused or fused with arene or heteroarene;

R^{27} is heteroarene which is unfused or fused with arene or heteroarene;

R^{28} is phenyl which is unfused or fused with arene, heteroarene or R^{28A}; R^{28A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{29} is heteroaryl or R^{29A}; R^{29A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{30} is cycloalkyl or cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{30A}; R^{30A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{31} and R^{31A} are independently F, Cl, Br or alkyl or are taken together and are C_2-C_5-spiroalkyl;

R^{32} is R^{33}, $C(O)R^{33}$ or $C(O)OR^{33}$;

R^{33} is R^{34} or R^{35};

R^{34} is phenyl which is unfused or fused with aryl, heteroaryl or R^{34A}; R^{34A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{35} is alkyl which is unsubstituted or substituted with R^{36};

R^{36} is phenyl which is unfused or fused with arene, heteroarene or R^{36A}; R^{36A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{37} is R^{38}, R^{39} or R^{40}, each of which is substituted with F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ or SO_2R^{41};

R^{38} is phenyl which is unfused or fused with arene, heteroarene or R^{38A}; R^{38A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{39} is heteroaryl which is unfused or fused with arene, heteroarene or R^{39A}; R^{39A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{40} is C_3-C_8-cycloalkyl or C_4-C_8-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is

unfused or fused with arene, heteroarene or R^{40A}; R^{40A} cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{41} is R^{42}, R^{43}, R^{44} or R^{45};

R^{42} is phenyl which is unfused or fused with arene, heteroarene or R^{42A}; R^{42A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{43} is heteroaryl which is unfused or fused with arene, heteroarene or R^{43A}; R^{43A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{44} is C_3-C_9-cycloalkyl or C_4-C_7-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{44A}; R^{44A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{45} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two independently selected R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{46} is R^{47}, R^{48} or R^{49};

R^{47} is phenyl which is unfused or fused with arene, heteroarene or R^{47A}; R^{47A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{48} is heteroaryl or R^{48A}; R^{48A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{49} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{49A}; R^{49A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein the moieties represented by R^{26} and R^{27} are further substituted by one or two or three of independently selected R^{50A}, OR^{50A}, SR^{50A}, $S(O)R^{50A}$, SO_2R^{50A} or NHR^{50A};

R^{50A} is R^{51A}, R^{52A}, R^{53A} or R^{54A};

R^{51A} is phenyl which is unfused or fused with benzene, heteroarene or R^{51AA}, wherein R^{51AA} is cycloalkane, cycloalkene or heterocycloalkane heterocycloalkene,

R^{52A} is heteroaryl;

R^{53A} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl; each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2

or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{53AA};

wherein R^{53AA} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{54A} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{55AA}, OR^{55AA}, SR^{55AA}, $S(O)R^{55AA}$, SO_2R^{55AA}, NHR^{55AA}, $N(R^{55AA})_2$, $C(O)R^{55AA}$, $C(O)NH_2$, $C(O)NHR^{55AA}$, $NHC(O)R^{55AA}$, $NHSO_2R^{55AA}$, $NHC(O)OR^{55AA}$, SO_2NH_2, SO_2NHR^{55AA}, $SO_2N(R^{55AA})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55AA}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{55AA} is alkyl, alkenyl, alkynyl, phenyl or heteroaryl, or R^{56A};

R^{56A} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N;

wherein moieties represented by R^2 R^3 R^4, R^6, R^{6C}, R^8, R^{8A} R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{18}, R^{19}, R^{20}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{34}, R^{36}, R^{38}, R^{39}, R^{40}, R^{42}, R^{43}, R^{44}, R^{47}, R^{48}, and R^{49} are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five independently selected R^{50AA}, R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{50AA} is spirocyclyl;

R^{50} is R^{51}, R^{52}, R^{53} or R^{54};

R^{51} is phenyl which is unfused or fused with arene, heteroarene or R^{51B}; R^{51B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{52} is heteroaryl;

R^{53} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{53B};

wherein R^{53B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

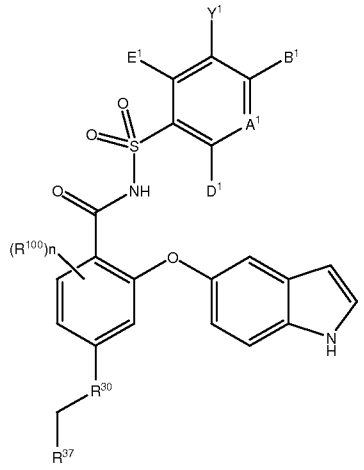
R^{54} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{55} is alkyl, alkenyl, alkynyl, phenyl, heteroaryl or R^{56};

wherein the alkyl, alkenyl, alkynyl are unsubstituted or substituted with OCH_3; and

R^{56} is C_3-C_8-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N.

Another embodiment of this invention pertains to compounds or therapeutically acceptable salts, prodrugs or salts of prodrugs thereof, which are useful as selective inhibitors of anti-apoptotic Bcl-2 proteins, the compounds having Formula (II)



(II),

wherein

R^{100} is as described for substituents on R^{26};

n is 0, 1, 2, or 3;

A^1 is N or $C(A^2)$;

one or two or three or each of A^2, B^1, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$; and

Y^1 is H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ or $NHSO_2R^{17}$;

or

B^1 and Y^1, together with the atoms to which they are attached, are imidazole or triazole; and

one or two or each of A^2, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$;

R^1 is R^2, R^3, R^4 or R^5;

R^{1A} is C_1-C_6-alkyl, C_3-C_6-alkenyl or C_3-C_6-alkynyl;

R^2 is phenyl which is unfused or fused with arene, heteroarene or R^{2A}; R^{2A} is cycloalkane or heterocycloalkane;

R^3 is heteroaryl which is unfused or fused with benzene, heteroarene or R^{3A}; R^{3A} is cycloalkane or heterocycloalkane;

R^4 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with arene, heteroarene or R^{4A}; R^{4A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^5 is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^6 is C_2-C_5-spiroalkyl, each of which is unsubstituted or substituted with OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ or $N(CH_3)_2$;

R^{6A} and R^{6B} are independently selected alkyl or, together with the N to which they are attached, R^{6C};

R^{6C} is aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, each having one CH_2 moiety unreplaced or replaced with O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH;

R^7 is R^8, R^9, R^{10} or R^{11};

R^8 is phenyl which is unfused or fused with arene, heteroarene or R^{8A};

R^{8A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{9} is heteroaryl which is unfused or fused with arene, heteroarene or R^{9A}; R^{9A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{10} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{10A}; R^{10A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{11} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{12} is R^{13}, R^{14}, R^{15} or R^{16};

R^{13} is phenyl which is unfused or fused with arene, heteroarene or R^{13A}; R^{13A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{14} is heteroaryl, each of which is unfused or fused with arene, heteroarene or R^{14A}; R^{14A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{15} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene, each of which is unfused or fused with arene, heteroarene or R^{15A}; R^{15A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{16} is alkyl, alkenyl or alkynyl;

R^{17} is R^{18}, R^{19}, R^{20} or R^{21};

R^{18} is phenyl which is unfused or fused with arene, heteroarene or R^{18A}; R^{18A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{19} is heteroaryl which is unfused or fused with arene, heteroarene or R^{19A}; R^{19A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{20} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{20A}; R^{20A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{21} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{22} is R^{23}, R^{24} or R^{25};

R^{23} is phenyl which is unfused or fused with arene, heteroarene or R^{23A}; R^{23A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{24} is heteroarene which is unfused or fused with arene, heteroarene or R^{24A}; R^{24A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{25} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{25A}; R^{25A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{30} is cycloalkyl or cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{30A}; R^{30A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; each of which is substituted with F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} or $N(R^{32})R^{37}$;

R^{31} and R^{31A} are independently F, Cl, Br or alkyl or are taken together and are C_2-C_5-spiroalkyl;

R^{32} is R^{33}, $C(O)R^{33}$ or $C(O)OR^{33}$;

R^{33} is R^{34} or R^{35};

R^{34} is phenyl which is unfused or fused with aryl, heteroaryl or R^{34A}; R^{34A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{35} is alkyl which is unsubstituted or substituted with R^{36};

R^{36} is phenyl which is unfused or fused with arene, heteroarene or R^{36A}; R^{36A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{37} is R^{38}, R^{39} or R^{40}, each of which is substituted with F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ or SO_2R^{41};

R^{38} is phenyl which is unfused or fused with arene, heteroarene or R^{38A}; R^{38A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{39} is heteroaryl which is unfused or fused with arene, heteroarene or R^{39A}; R^{39A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{40} is C_3-C_8-cycloalkyl or C_4-C_8-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is

unfused or fused with arene, heteroarene or R^{40A}; R^{40A} cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{41} is R^{42}, R^{43}, R^{44} or R^{45};

R^{42} is phenyl which is unfused or fused with arene, heteroarene or R^{42A}; R^{42A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{43} is heteroaryl which is unfused or fused with arene, heteroarene or R^{43A}; R^{43A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{44} is C_3-C_9-cycloalkyl or C_4-C_7-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{44A}; R^{44A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{45} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two independently selected R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{46} is R^{47}, R^{48} or R^{49};

R^{47} is phenyl which is unfused or fused with arene, heteroarene or R^{47A}; R^{47A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{48} is heteroaryl or R^{48A}; R^{48A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{49} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{49A}; R^{49A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein moieties represented by R^2, R^{2A}, R^3, R^{3A}, R^4, R^{4A}, R^6, R^{6C}, R^8, R^{8A}, R^9, R^{10}, R^{10A}, R^{13}, R^{13A}, R^{14}, R^{14A}, R^{15}, R^{15A}, R^{18}, R^{18A}, R^{19}, R^{19A}, R^{20}, R^{20A}, R^{23}, R^{23A}, R^{24}, R^{24A}, R^{25}, R^{25A}, R^{26}, R^{27}, R^{28}, R^{28A}, R^{29}, R^{29A}, R^{30}, R^{30A}, R^{34}, R^{34A}, R^{36}, R^{36A}, R^{38}, R^{38A}, R^{39}, R^{39A}, R^{40}, R^{40A}, R^{42}, R^{42A}, R^{43}, R^{43A}, R^{44}, R^{44A}, R^{47}, R^{47A}, R^{48}, R^{48A}, R^{49}, and R^{49A} are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five independently selected R^{50AA}, R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$,

$C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{50AA} is spirocyclyl;

R^{50} is R^{51}, R^{52}, R^{53} or R^{54};

R^{51} is phenyl which is unfused or fused with arene, heteroarene or R^{51B}; R^{51B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{52} is heteroaryl;

R^{53} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{53B};

wherein R^{53B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

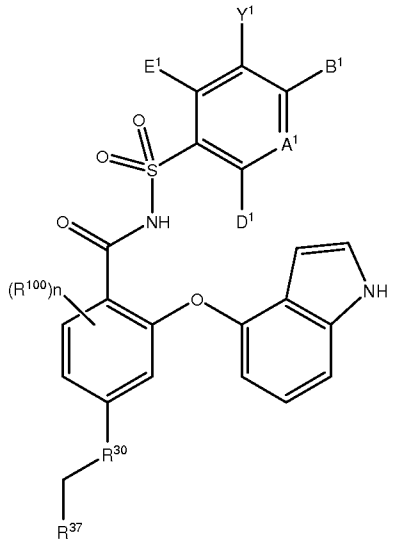
R^{54} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{55} is alkyl, alkenyl, alkynyl, phenyl, heteroaryl or R^{56};

wherein the alkyl, alkenyl, alkynyl are unsubstituted or substituted with OCH_3; and

R^{56} is C_3-C_8-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N.

Another embodiment of this invention pertains to compounds or therapeutically acceptable salts, prodrugs or salts of prodrugs thereof, which are useful as selective inhibitors of anti-apoptotic Bcl-2 proteins, the compounds having Formula (III)



(III),

wherein

R^{100} is as described for substituents on R^{26};

n is 0, 1, 2, or 3;

A^1 is N or $C(A^2)$;

one or two or three or each of A^2, B^1, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$; and

Y^1 is H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ or $NHSO_2R^{17}$;

or

B^1 and Y^1, together with the atoms to which they are attached, are imidazole or triazole; and

one or two or each of A^2, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$;

R^1 is R^2, R^3, R^4 or R^5;

R^{1A} is C_1-C_6-alkyl, C_3-C_6-alkenyl or C_3-C_6-alkynyl;

R^2 is phenyl which is unfused or fused with arene, heteroarene or R^{2A}; R^{2A} is cycloalkane or heterocycloalkane;

R^3 is heteroaryl which is unfused or fused with benzene, heteroarene or R^{3A}; R^{3A} is cycloalkane or heterocycloalkane;

R^4 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with arene, heteroarene or R^{4A}; R^{4A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^5 is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^6 is C_2-C_5-spiroalkyl, each of which is unsubstituted or substituted with OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ or $N(CH_3)_2$;

R^{6A} and R^{6B} are independently selected alkyl or, together with the N to which they are attached, R^{6C};

R^{6C} is aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, each having one CH_2 moiety unreplaced or replaced with O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH;

R^7 is R^8, R^9, R^{10} or R^{11};

R^8 is phenyl which is unfused or fused with arene, heteroarene or R^{8A};

R^{8A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^9 is heteroaryl which is unfused or fused with arene, heteroarene or R^{9A}; R^{9A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{10} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{10A}; R^{10A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{11} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{12} is R^{13}, R^{14}, R^{15} or R^{16};

R^{13} is phenyl which is unfused or fused with arene, heteroarene or R^{13A}; R^{13A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{14} is heteroaryl, each of which is unfused or fused with arene, heteroarene or R^{14A}; R^{14A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{15} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene, each of which is unfused or fused with arene, heteroarene or R^{15A}; R^{15A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{16} is alkyl, alkenyl or alkynyl;

R^{17} is R^{18}, R^{19}, R^{20} or R^{21};

R^{18} is phenyl which is unfused or fused with arene, heteroarene or R^{18A}; R^{18A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{19} is heteroaryl which is unfused or fused with arene, heteroarene or R^{19A}; R^{19A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{20} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{20A}; R^{20A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{21} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{22} is R^{23}, R^{24} or R^{25};

R^{23} is phenyl which is unfused or fused with arene, heteroarene or R^{23A}; R^{23A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{24} is heteroarene which is unfused or fused with arene, heteroarene or R^{24A}; R^{24A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{25} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{25A}; R^{25A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{30} is cycloalkyl or cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused

with arene, heteroarene or R^{30A}; R^{30A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; each of which is substituted with F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} or $N(R^{32})R^{37}$;

R^{31} and R^{31A} are independently F, Cl, Br or alkyl or are taken together and are C_2-C_5-spiroalkyl;

R^{32} is R^{33}, $C(O)R^{33}$ or $C(O)OR^{33}$;

R^{33} is R^{34} or R^{35};

R^{34} is phenyl which is unfused or fused with aryl, heteroaryl or R^{34A}; R^{34A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{35} is alkyl which is unsubstituted or substituted with R^{36};

R^{36} is phenyl which is unfused or fused with arene, heteroarene or R^{36A}; R^{36A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{37} is R^{38}, R^{39} or R^{40}, each of which is substituted with F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ or SO_2R^{41};

R^{38} is phenyl which is unfused or fused with arene, heteroarene or R^{38A}; R^{38A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{39} is heteroaryl which is unfused or fused with arene, heteroarene or R^{39A}; R^{39A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{40} is C_3-C_8-cycloalkyl or C_4-C_8-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{40A}; R^{40A} cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{41} is R^{42}, R^{43}, R^{44} or R^{45};

R^{42} is phenyl which is unfused or fused with arene, heteroarene or R^{42A}; R^{42A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{43} is heteroaryl which is unfused or fused with arene, heteroarene or R^{43A}; R^{43A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{44} is C_3-C_9-cycloalkyl or C_4-C_7-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{44A}; R^{44A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{45} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two independently selected R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{46} is R^{47}, R^{48} or R^{49};

R^{47} is phenyl which is unfused or fused with arene, heteroarene or R^{47A}; R^{47A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{48} is heteroaryl or R^{48A}; R^{48A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{49} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{49A}; R^{49A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein moieties represented by R^2, R^{2A}, R^3, R^{3A}, R^4, R^{4A}, R^6, R^{6C}, R^8, R^{8A}, R^9, R^{10}, R^{10A}, R^{13}, R^{13A}, R^{14}, R^{14A}, R^{15}, R^{15A}, R^{18}, R^{18A}, R^{19}, R^{19A}, R^{20}, R^{20A}, R^{23}, R^{23A}, R^{24}, R^{24A}, R^{25}, R^{25A}, R^{26}, R^{27}, R^{28}, R^{28A}, R^{29}, R^{29A}, R^{30}, R^{30A}, R^{34}, R^{34A}, R^{36}, R^{36A}, R^{38}, R^{38A}, R^{39}, R^{39A}, R^{40}, R^{40A}, R^{42}, R^{42A}, R^{43}, R^{43A}, R^{44}, R^{44A}, R^{47}, R^{47A}, R^{48}, R^{48A}, R^{49}, and R^{49A} are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five independently selected R^{50AA}, R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{50AA} is spirocyclyl;

R^{50} is R^{51}, R^{52}, R^{53} or R^{54};

R^{51} is phenyl which is unfused or fused with arene, heteroarene or R^{51B}; R^{51B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{52} is heteroaryl;

R^{53} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{53B};

wherein R^{53B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

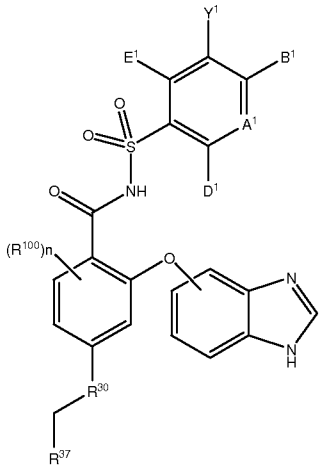
R^{54} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{55} is alkyl, alkenyl, alkynyl, phenyl, heteroaryl or R^{56};

wherein the alkyl, alkenyl, alkynyl are unsubstituted or substituted with OCH_3; and

R^{56} is C_3-C_8-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N.

Another embodiment of this invention pertains to compounds or therapeutically acceptable salts, prodrugs or salts of prodrugs thereof, which are useful as selective inhibitors of anti-apoptotic Bcl-2 proteins, the compounds having Formula (IV)



(IV),

wherein

R^{100} is as described for substituents on R^{26};

n is 0, 1, 2, or 3;

A^1 is N or $C(A^2)$;

one or two or three or each of A^2, B^1, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$; and

Y^1 is H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ or $NHSO_2R^{17}$;

or

B^1 and Y^1, together with the atoms to which they are attached, are imidazole or triazole; and

one or two or each of A^2, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$;

R^1 is R^2, R^3, R^4 or R^5;

R^{1A} is C_1-C_6-alkyl, C_3-C_6-alkenyl or C_3-C_6-alkynyl;

R^2 is phenyl which is unfused or fused with arene, heteroarene or R^{2A}; R^{2A} is cycloalkane or heterocycloalkane;

R^3 is heteroaryl which is unfused or fused with benzene, heteroarene or R^{3A}; R^{3A} is cycloalkane or heterocycloalkane;

R^4 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with arene, heteroarene or R^{4A}; R^{4A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^5 is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^6 is C_2-C_5-spiroalkyl, each of which is unsubstituted or substituted with OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ or $N(CH_3)_2$;

R^{6A} and R^{6B} are independently selected alkyl or, together with the N to which they are attached, R^{6C};

R^{6C} is aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, each having one CH_2 moiety unreplaced or replaced with O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH;

R^7 is R^8, R^9, R^{10} or R^{11};

R^8 is phenyl which is unfused or fused with arene, heteroarene or R^{8A};

R^{8A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{9} is heteroaryl which is unfused or fused with arene, heteroarene or R^{9A}; R^{9A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{10} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{10A}; R^{10A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{11} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{12} is R^{13}, R^{14}, R^{15} or R^{16};

R^{13} is phenyl which is unfused or fused with arene, heteroarene or R^{13A}; R^{13A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{14} is heteroaryl, each of which is unfused or fused with arene, heteroarene or R^{14A}; R^{14A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{15} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene, each of which is unfused or fused with arene, heteroarene or R^{15A}; R^{15A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{16} is alkyl, alkenyl or alkynyl;

R^{17} is R^{18}, R^{19}, R^{20} or R^{21};

R^{18} is phenyl which is unfused or fused with arene, heteroarene or R^{18A}; R^{18A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{19} is heteroaryl which is unfused or fused with arene, heteroarene or R^{19A}; R^{19A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{20} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{20A}; R^{20A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{21} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{22} is R^{23}, R^{24} or R^{25};

R^{23} is phenyl which is unfused or fused with arene, heteroarene or R^{23A}; R^{23A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{24} is heteroarene which is unfused or fused with arene, heteroarene or R^{24A}; R^{24A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{25} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{25A}; R^{25A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{30} is cycloalkyl or cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{30A}; R^{30A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; each of which is substituted with F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} or $N(R^{32})R^{37}$;

R^{31} and R^{31A} are independently F, Cl, Br or alkyl or are taken together and are C_2-C_5-spiroalkyl;

R^{32} is R^{33}, $C(O)R^{33}$ or $C(O)OR^{33}$;

R^{33} is R^{34} or R^{35};

R^{34} is phenyl which is unfused or fused with aryl, heteroaryl or R^{34A}; R^{34A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{35} is alkyl which is unsubstituted or substituted with R^{36};

R^{36} is phenyl which is unfused or fused with arene, heteroarene or R^{36A}; R^{36A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{37} is R^{38}, R^{39} or R^{40}, each of which is substituted with F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ or SO_2R^{41};

R^{38} is phenyl which is unfused or fused with arene, heteroarene or R^{38A}; R^{38A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{39} is heteroaryl which is unfused or fused with arene, heteroarene or R^{39A}; R^{39A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{40} is C_3-C_8-cycloalkyl or C_4-C_8-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is

unfused or fused with arene, heteroarene or R^{40A}; R^{40A} cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{41} is R^{42}, R^{43}, R^{44} or R^{45};

R^{42} is phenyl which is unfused or fused with arene, heteroarene or R^{42A}; R^{42A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{43} is heteroaryl which is unfused or fused with arene, heteroarene or R^{43A}; R^{43A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{44} is C_3-C_9-cycloalkyl or C_4-C_7-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{44A}; R^{44A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{45} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two independently selected R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{46} is R^{47}, R^{48} or R^{49};

R^{47} is phenyl which is unfused or fused with arene, heteroarene or R^{47A}; R^{47A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{48} is heteroaryl or R^{48A}; R^{48A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{49} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{49A}; R^{49A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein moieties represented by R^2, R^{2A}, R^3, R^{3A}, R^4, R^{4A}, R^6, R^{6C}, R^8, R^{8A}, R^9, R^{10}, R^{10A}, R^{13}, R^{13A}, R^{14}, R^{14A}, R^{15}, R^{15A}, R^{18}, R^{18A}, R^{19}, R^{19A}, R^{20}, R^{20A}, R^{23}, R^{23A}, R^{24}, R^{24A}, R^{25}, R^{25A}, R^{26}, R^{27}, R^{28}, R^{28A}, R^{29}, R^{29A}, R^{30}, R^{30A}, R^{34}, R^{34A}, R^{36}, R^{36A}, R^{38}, R^{38A}, R^{39}, R^{39A}, R^{40}, R^{40A}, R^{42}, R^{42A}, R^{43}, R^{43A}, R^{44}, R^{44A}, R^{47}, R^{47A}, R^{48}, R^{48A}, R^{49}, and R^{49A} are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five independently selected R^{50AA}, R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$,

$C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{50AA} is spirocyclyl;

R^{50} is R^{51}, R^{52}, R^{53} or R^{54};

R^{51} is phenyl which is unfused or fused with arene, heteroarene or R^{51B}; R^{51B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{52} is heteroaryl;

R^{53} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{53B};

wherein R^{53B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

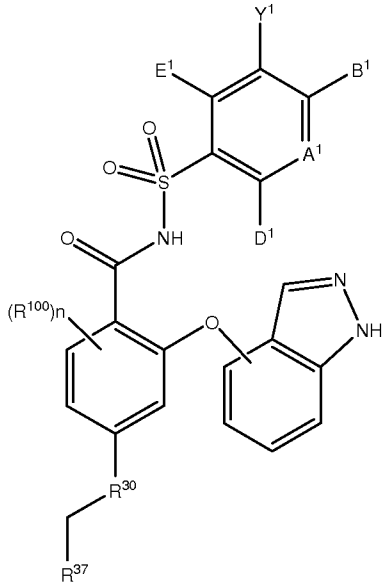
R^{54} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{55} is alkyl, alkenyl, alkynyl, phenyl, heteroaryl or R^{56};

wherein the alkyl, alkenyl, alkynyl are unsubstituted or substituted with OCH_3; and

R^{56} is C_3-C_8-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N.

Another embodiment of this invention pertains to compounds or therapeutically acceptable salts, prodrugs or salts of prodrugs thereof, which are useful as selective inhibitors of anti-apoptotic Bcl-2 proteins, the compounds having Formula (V)



(V),

wherein

R^{100} is as described for substituents on R^{26};

n is 0, 1, 2, or 3;

A^1 is N or $C(A^2)$;

one or two or three or each of A^2, B^1, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$; and

Y^1 is H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ or $NHSO_2R^{17}$;

or

B^1 and Y^1, together with the atoms to which they are attached, are imidazole or triazole; and

one or two or each of A^2, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$;

R^1 is R^2, R^3, R^4 or R^5;

R^{1A} is C_1-C_6-alkyl, C_3-C_6-alkenyl or C_3-C_6-alkynyl;

R^2 is phenyl which is unfused or fused with arene, heteroarene or R^{2A}; R^{2A} is cycloalkane or heterocycloalkane;

R^3 is heteroaryl which is unfused or fused with benzene, heteroarene or R^{3A}; R^{3A} is cycloalkane or heterocycloalkane;

R^4 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with arene, heteroarene or R^{4A}; R^{4A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^5 is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^6 is C_2-C_5-spiroalkyl, each of which is unsubstituted or substituted with OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ or $N(CH_3)_2$;

R^{6A} and R^{6B} are independently selected alkyl or, together with the N to which they are attached, R^{6C};

R^{6C} is aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, each having one CH_2 moiety unreplaced or replaced with O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH;

R^7 is R^8, R^9, R^{10} or R^{11};

R^8 is phenyl which is unfused or fused with arene, heteroarene or R^{8A};

R^{8A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^9 is heteroaryl which is unfused or fused with arene, heteroarene or R^{9A}; R^{9A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{10} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{10A}; R^{10A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{11} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{12} is R^{13}, R^{14}, R^{15} or R^{16};

R^{13} is phenyl which is unfused or fused with arene, heteroarene or R^{13A}; R^{13A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{14} is heteroaryl, each of which is unfused or fused with arene, heteroarene or R^{14A}; R^{14A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{15} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene, each of which is unfused or fused with arene, heteroarene or R^{15A}; R^{15A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{16} is alkyl, alkenyl or alkynyl;

R^{17} is R^{18}, R^{19}, R^{20} or R^{21};

R^{18} is phenyl which is unfused or fused with arene, heteroarene or R^{18A}; R^{18A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{19} is heteroaryl which is unfused or fused with arene, heteroarene or R^{19A}; R^{19A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{20} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{20A}; R^{20A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{21} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{22} is R^{23}, R^{24} or R^{25};

R^{23} is phenyl which is unfused or fused with arene, heteroarene or R^{23A}; R^{23A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{24} is heteroarene which is unfused or fused with arene, heteroarene or R^{24A}; R^{24A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{25} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{25A}; R^{25A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{30} is cycloalkyl or cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused

with arene, heteroarene or R^{30A}; R^{30A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; each of which is substituted with F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} or $N(R^{32})R^{37}$;

R^{31} and R^{31A} are independently F, Cl, Br or alkyl or are taken together and are C_2-C_5-spiroalkyl;

R^{32} is R^{33}, $C(O)R^{33}$ or $C(O)OR^{33}$;

R^{33} is R^{34} or R^{35};

R^{34} is phenyl which is unfused or fused with aryl, heteroaryl or R^{34A}; R^{34A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{35} is alkyl which is unsubstituted or substituted with R^{36};

R^{36} is phenyl which is unfused or fused with arene, heteroarene or R^{36A}; R^{36A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{37} is R^{38}, R^{39} or R^{40}, each of which is substituted with F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ or SO_2R^{41};

R^{38} is phenyl which is unfused or fused with arene, heteroarene or R^{38A}; R^{38A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{39} is heteroaryl which is unfused or fused with arene, heteroarene or R^{39A}; R^{39A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{40} is C_3-C_8-cycloalkyl or C_4-C_8-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{40A}; R^{40A} cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{41} is R^{42}, R^{43}, R^{44} or R^{45};

R^{42} is phenyl which is unfused or fused with arene, heteroarene or R^{42A}; R^{42A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{43} is heteroaryl which is unfused or fused with arene, heteroarene or R^{43A}; R^{43A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{44} is C_3-C_9-cycloalkyl or C_4-C_7-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{44A}; R^{44A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{45} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two independently selected R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{46} is R^{47}, R^{48} or R^{49};

R^{47} is phenyl which is unfused or fused with arene, heteroarene or R^{47A}; R^{47A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{48} is heteroaryl or R^{48A}; R^{48A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{49} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{49A}; R^{49A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein moieties represented by R^2, R^{2A}, R^3, R^{3A}, R^4, R^{4A}, R^6, R^{6C}, R^8, R^{8A}, R^9, R^{10}, R^{10A}, R^{13}, R^{13A}, R^{14}, R^{14A}, R^{15}, R^{15A}, R^{18}, R^{18A}, R^{19}, R^{19A}, R^{20}, R^{20A}, R^{23}, R^{23A}, R^{24}, R^{24A}, R^{25}, R^{25A}, R^{26}, R^{27}, R^{28}, R^{28A}, R^{29}, R^{29A}, R^{30}, R^{30A}, R^{34}, R^{34A}, R^{36}, R^{36A}, R^{38}, R^{38A}, R^{39}, R^{39A}, R^{40}, R^{40A}, R^{42}, R^{42A}, R^{43}, R^{43A}, R^{44}, R^{44A}, R^{47}, R^{47A}, R^{48}, R^{48A}, R^{49}, and R^{49A} are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five independently selected R^{50AA}, R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{50AA} is spirocyclyl;

R^{50} is R^{51}, R^{52}, R^{53} or R^{54};

R^{51} is phenyl which is unfused or fused with arene, heteroarene or R^{51B}; R^{51B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{52} is heteroaryl;

R^{53} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{53B};

wherein R^{53B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{54} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{55} is alkyl, alkenyl, alkynyl, phenyl, heteroaryl or R^{56};

wherein the alkyl, alkenyl, alkynyl are unsubstituted or substituted with OCH_3; and

R^{56} is C_3-C_8-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N.

Another embodiment pertains to compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) wherein A^1 is $C(A^2)$; and A^2 is H.

Another embodiment pertains to compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) wherein A^1 is $C(A^2)$ or N; A^2 is H; and B^1 is NHR^1.

Another embodiment pertains to compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) wherein A^1 is $C(A^2)$ or N; A^2 is H; B^1 is NHR^1; and D^1 is H.

Another embodiment pertains to compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) wherein A^1 is $C(A^2)$ or N; A^2 is H; B^1 is NHR^1;D^1 is H; and E^1 is H.

Another embodiment pertains to compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) wherein A^1 is $C(A^2)$ or N; A^2 is H; B^1 is NHR^1;D^1 is H; E^1 is H; and Y^1 is NO_2.

Still another embodiment pertains to compounds having Formula I which are

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

2-(benzyloxy)-4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(2-phenylethoxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(phenylthio)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(phenylthio)-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-(phenylthio)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(phenylsulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(phenylsulfinyl)benzamide;
2-benzyl-4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;
2-benzyl-4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;
2-benzyl-4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(2-phenylethyl)benzamide;
2-(benzylamino)-4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;
2-anilino-4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;
2-anilino-4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-methoxy-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indazol-5-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indazol-5-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-(1,2,3,4-tetrahydroquinolin-6-yloxy)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)-2-(1,2,3,4-tetrahydroquinolin-6-yloxy)benzamide;

4-(4-((4'-chloro-4-(pyrrolidin-1-ylmethyl)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-pyrrolidin-1-ylethyl)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((1-cyclopentylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)-3-isobutylpiperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-(2,4-dioxo-3-azabicyclo(3.2.0)hept-3-yl)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-(3,3-dimethyl-2-oxoazetidin-1-yl)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-(4-nitro-2H-1,2,3-triazol-2-yl)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((2-(2-piperidin-1-ylethoxy)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-((((1-ethylpyrrolidin-2-yl)methyl)amino)carbonyl)-4-methoxyphenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1-naphthyloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(2-naphthyloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-(2-naphthyloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(2-naphthyloxy)-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(quinolin-7-yloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(quinolin-6-yloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(isoquinolin-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(isoquinolin-5-yloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(quinolin-6-yloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-6-yloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(isoquinolin-7-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(isoquinolin-7-yloxy)benzamide;

4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-4-yloxy)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-4-yloxy)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-methoxyphenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-methylphenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
N-((3-((chloro(difluoro)methyl)sulfonyl)-4-((3-(dimethylamino)propyl)amino)phenyl)sulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

2-(1H-indol-4-yloxy)-4-(4-((2-(4-methoxyphenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4,4-dimethyl-2-(4-(trifluoromethyl)phenyl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4,4-dimethyl-2-(4-(trifluoromethoxy)phenyl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4,4-dimethyl-2-(3-(trifluoromethyl)phenyl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(3-fluorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-fluorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

N-((3-((chloro(difluoro)methyl)sulfonyl)-4-((1-methylpiperidin-4-yl)amino)phenyl)sulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-((2-(4-chlorophenyl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(phenoxymethyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(pyridin-3-yloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(pyridin-3-yloxy)-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-(((1R)-3-(dimethylamino)-1-((phenylthio)methyl)propyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(pyridin-4-yloxy)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-(pyridin-3-yloxy)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-(pyridin-4-yloxy)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((2-(4-methylpiperazin-1-yl)ethyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(4-methylpiperazin-1-yl)propyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)(methyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-(((1-methylpiperidin-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-cyano-4-((3-(dimethylamino)propyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-(trifluoromethyl)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(isopropyl(methyl)amino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-(3-(dimethylamino)propoxy)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((2-(4-methylpiperazin-1-yl)ethyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((3-(4-methylpiperazin-1-yl)propyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((3-(4-methylpiperazin-1-yl)propyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-(3-(dimethylamino)propoxy)-3-nitrophenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((2-(4-methylpiperazin-1-yl)ethyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-(((1-methylpiperidin-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-(((1-methylpiperidin-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-(3-(dimethylamino)propoxy)-3-nitrophenyl)sulfonyl)-2-(1H-indol-4-yloxy)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-(4-methylpiperazin-1-yl)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((1-(2,2,2-trifluoroethyl)piperidin-4-yl)amino)phenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-(((4-(dimethylamino)-1-methylpiperidin-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(2,3-dihydro-1,4-benzodioxin-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;
5-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-1,1'-biphenyl-2-carboxamide;

5-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-1,1'-biphenyl-2-carboxamide;
4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-4-(3-piperidin-1-ylpropoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-4-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-4-(3-(dimethylamino)propoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-4-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-4-(3-piperidin-1-ylpropoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-4-(3-(dimethylamino)propoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-3-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-3-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((1-(2,2,2-trifluoroethyl)piperidin-4-yl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-4-(2-pyrrolidin-1-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-4-(2-(diisopropylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(2,3-dihydro-1H-indol-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)cyclohept-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)cyclooct-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)cyclopent-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclopent-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)cyclooct-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)cyclohept-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)cyclopent-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)cyclohept-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((2-(dimethylamino)ethyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((4-(dimethylamino)butyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((1-(phenylsulfonyl)piperidin-4-yl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((1-(quinolin-8-ylsulfonyl)piperidin-4-yl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((1-(phenylsulfonyl)piperidin-4-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((1-(quinolin-8-ylsulfonyl)piperidin-4-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-(((1S)-3-(dimethylamino)-1-thien-2-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((thien-2-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((2-(1H-1,2,3-triazol-1-yl)ethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((2-(2H-1,2,3-triazol-2-yl)ethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(2-naphthyloxy)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((2-(2-oxopyridin-1(2H)-yl)ethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((2-(pyridin-2-yloxy)ethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((2-pyridin-4-ylethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-(trifluoromethyl)phenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((3-cyano-4-((3-(dimethylamino)propyl)amino)phenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1*H*-indol-5-yloxy)-*N*-((3-nitro-4-((1-tetrahydro-2*H*-pyran-4-ylpiperidin-4-yl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1*H*-indol-5-yloxy)-*N*-((4-((4-methylpiperazin-1-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-(1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl)piperazin-1-yl)-2-(1*H*-indol-4-yloxy)-*N*-((3-nitro-4-((tetrahydro-2*H*-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

N-((4-(((4-aminotetrahydro-2*H*-pyran-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1*H*-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(2-methoxyethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(3S)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(3R)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-hydroxy-1-methylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-3-fluoro-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-3-fluoro-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-hydroxy-1-methylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

N-[(4-{[(3S,4R)-1-benzyl-3-hydroxypiperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

N-[(4-{[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[1-(2-methoxyethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(2-hydroxyethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[1-(2-methoxyethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(3-hydroxypropyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-[4-({4'-chloro-3-[3-(dimethylamino)propyl]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(3-hydroxypropyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-{4-[(4'-chloro-4-morpholin-4-yl-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-[4-({4'-chloro-3-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(diethylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(dimethylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(diethylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-[4-({4'-chloro-3-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-{4-[1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(dimethylamino)tetrahydro-2H-pyran-4-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;

N-({4-[(2-aminocyclohexyl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-[4-({4'-chloro-4-[3-(dimethylamino)prop-1-ynyl]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(3-nitro-4-{[1-(4,4,4-trifluorobutyl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[2-(4-hydroxy-1-methylpiperidin-4-yl)ethyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[1-(1,3-thiazol-2-yl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[4'-chloro-4-(2-hydroxyethoxy)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(cyclopropylmethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[1-(4,4,4-trifluorobutyl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide;

4-{4-[1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-(hydroxymethyl)piperazin-1-yl]-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-(hydroxymethyl)piperazin-1-yl]-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-(4-{[4'-chloro-4-(2-hydroxyethoxy)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[3-(3-oxopiperazin-1-yl)propyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(3-nitro-4-{[3-(3-oxopiperazin-1-yl)propyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-5-hydroxycyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-5-hydroxycyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-5-hydroxycyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(2,3-dihydro-1H-inden-2-yl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(2,3-dihydro-1H-inden-2-yl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(1-morpholin-4-ylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[1-(1,3-thiazol-2-ylmethyl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[1-(1,3-thiazol-4-ylmethyl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(2-hydroxyethyl)piperazin-1-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(3S)-1-methylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(3-fluoropropyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-(hydroxymethyl)piperazin-1-yl]-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

N-[(4-{[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-(hydroxymethyl)piperazin-1-yl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(2-methoxyethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-hydroxy-1-tetrahydro-2H-pyran-4-ylethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-({1-[2-(1H-pyrazol-1-yl)ethyl]piperidin-4-yl}amino)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(methylamino)-3-nitrophenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[4-(methylamino)-3-nitrophenyl]sulfonyl}benzamide;

4-{4-[1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-5-hydroxycyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-5-morpholin-4-ylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

N-[(4-{[(1-aminocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[2-(2-oxopyrrolidin-1-yl)ethyl]amino}phenyl)sulfonyl]benzamide;

4-{4-[1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{1-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]ethyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{1-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]ethyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-{4-[(1R)-1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-{4-[(1S)-1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{1-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]ethyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{1-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]ethyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(morpholin-4-ylamino)-3-nitrophenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-3-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[4-(morpholin-4-ylamino)-3-nitrophenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylamino)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(3-methyloxetan-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methoxycyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(1,1-dioxidothiomorpholin-4-yl)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[2-(2-oxopiperidin-1-yl)ethyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[2-(2-oxoimidazolidin-1-yl)ethyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(2-pyridin-4-ylethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-morpholin-4-yl-3-nitrophenyl)sulfonyl]benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(4-methoxypiperidin-1-yl)-3-nitrophenyl]sulfonyl}benzamide;
4-(4-{[2-(4-chlorophenyl)-5-pyrrolidin-1-ylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[2-(3-oxopiperazin-1-yl)ethyl]amino}phenyl)sulfonyl]benzamide;
4-[4-({4'-chloro-4-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1,1-dioxidotetrahydrothien-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl]sulfonyl}benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[2-(1,3-dioxolan-2-yl)ethyl]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(3-nitro-4-{[2-(3-oxopiperazin-1-yl)ethyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methyl-5-oxopyrrolidin-3-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methyl-6-oxopiperidin-3-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[3-nitro-4-(piperidin-1-ylamino)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(piperidin-1-ylamino)phenyl]sulfonyl}benzamide;

4-(4-{[4-(4-chlorophenyl)-1-methyl-1H-pyrazol-5-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(3-methyloxetan-3-yl)methoxy]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(1-oxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1,3-thiazol-5-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(2-tetrahydro-2H-pyran-4-ylethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(3-nitro-4-{[2-(trifluoromethoxy)ethyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[2-(2-methoxyethoxy)ethyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[3-(methylsulfonyl)propyl]amino}-3-nitrophenyl)sulfonyl]benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(1,1-dioxidothiomorpholin-4-yl)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(2-tetrahydro-2H-pyran-4-ylethyl)phenyl]sulfonyl}benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[2-(2-methoxyethoxy)ethyl]amino}-3-nitrophenyl)sulfonyl]benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-4-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[2-(trifluoromethoxy)ethyl]amino}phenyl)sulfonyl]benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2,2-difluoroethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4,4-difluorocyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-1-isopropyl-6-oxo-1,6-dihydropyridin-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(tetrahydro-2H-pyran-4-ylmethyl)amino]carbonyl}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(2-methoxyethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[3-nitro-4-(2-tetrahydro-2H-pyran-4-ylethoxy)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(2-methoxyethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[3-(methylsulfonyl)propoxy]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(3-methoxypropyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(3-methoxypropyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-cyanoethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-cyanoethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-4-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(3R)-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[Cis-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(3,3,3-trifluoropropyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(3,3,3-trifluoropropyl)amino]phenyl}sulfonyl)benzamide;
N-({5-bromo-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1,1-dioxidotetrahydrothien-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-(methylamino)-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;
N-{[5-bromo-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[4-(4-chlorophenyl)-6-isopropoxypyridin-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[6-(tetrahydro-2H-pyran-4-ylmethoxy)-5-(1,3-thiazol-2-yl)pyridin-3-yl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(2-methoxyethyl)amino]carbonyl}phenyl)sulfonyl]benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;
N-({4-[(1-acetylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[1-(methylsulfonyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
N-({4-[(1-acetylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[1-(methylsulfonyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;
4-(4-{[4'-chloro-5-(trifluoromethyl)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[4'-chloro-5-(trifluoromethyl)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}benzamide;
4-{4-[(5-tert-butyl-4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
4-{4-[(5-tert-butyl-4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-{[(tetrahydro-2H-pyran-4-ylmethyl)amino]carbonyl}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2R)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2S)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

N-({5-bromo-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(2-morpholin-4-ylethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)oxy]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[4-(4-chlorophenyl)-1-(3-hydroxypropyl)-1,2,5,6-tetrahydropyridin-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

benzyl 4-({[4-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzoyl]amino}sulfonyl)-2-nitrophenyl]amino}methyl)piperidine-1-carboxylate;

N-{[3-(aminocarbonyl)-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[4'-chloro-5-(trifluoromethyl)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-{4-[(5-tert-butyl-4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(1-methyl-1H-imidazol-5-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(morpholin-4-ylsulfonyl)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidothiomorpholin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

N-{[5-bromo-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-5-(1,3-thiazol-2-yl)pyridin-3-yl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3,3-dimethylbutyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1S)-1-(hydroxymethyl)-3-methylbutyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(2R)-tetrahydrofuran-2-ylmethyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1R)-1-(hydroxymethyl)-2-methylpropyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methoxyphenyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

N-[(4-{[2-(1,3-benzodioxol-5-yl)ethyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-hydroxyphenyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

N-{[4-({2-[4-(aminosulfonyl)phenyl]ethyl}amino)-3-nitrophenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(1H-imidazol-1-yl)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(1S)-1-phenylethyl]amino}phenyl)sulfonyl]benzamide;

N-({2-chloro-5-fluoro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[2-(2-methoxyethoxy)ethyl]thio}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[2-(2-methoxyethoxy)ethyl]thio}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(methylsulfonyl)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[4-(methylsulfonyl)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2,2-dimethyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(2-morpholin-4-ylethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)oxy]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-morpholin-4-ylbut-2-ynyl)oxy]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-ethynyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(2-morpholin-4-ylethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-hydroxy-4-methoxyphenyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(2,3-dihydro-1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(pyridin-3-ylamino)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)-2-(pyridin-3-ylamino)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)-2-(pyridin-3-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1,2,3,4-tetrahydroisoquinolin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-5-(trifluoromethyl)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyclopropylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4,4-difluorocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

N-[(5-chloro-6-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

Trans-N-({5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(2,2-difluoroethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-fluoro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

N-[(5-chloro-6-{[1-(cyanomethyl)-4-fluoropiperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydrofuran-3-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

Trans-N-({5-chloro-6-[(4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-[(5-chloro-6-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]oxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-N-[(5-chloro-6-{[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

2-(1H-benzimidazol-4-yloxy)-N-[(5-chloro-6-{[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

N-[(5-chloro-6-{[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-[(5-chloro-6-{[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(cyanomethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({(3R)-1-[2-(2-methoxyethoxy)ethyl]pyrrolidin-3-yl}amino)-3-nitrophenyl]sulfonyl}benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(N,N-dimethylglycyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(cyanomethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyclopropylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(4-oxetan-3-ylmorpholin-2-yl)methyl]amino}phenyl)sulfonyl]benzamide;

N-{[5-chloro-6-({(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl}oxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydrofuran-3-ylmethyl)amino]phenyl}sulfonyl)benzamide;

Trans-2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-fluoro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

N-{[5-chloro-6-({(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl}methoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-[(5-chloro-6-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(1-cyclopropylpiperidin-4-yl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-N-({5-chloro-6-[(1-cyclopropylpiperidin-4-yl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

Trans-2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-methylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[({(2R)-4-[2-(2-methoxyethoxy)ethyl]morpholin-2-yl}methyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4,4-difluorocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

N-[(4-{[(4-acetylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(methylsulfonyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[6-({4-fluoro-1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl}methoxy)-5-(trifluoromethyl)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(2-tetrahydrofuran-2-ylethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

Trans-2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyanocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-N-({5-chloro-6-[(4,4-difluorocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-*N*-{[5-cyano-6-(2-tetrahydro-2*H*-pyran-4-ylethoxy)pyridin-3-yl]sulfonyl}-2-(1*H*-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(1R,5S)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxy-4-(4-{(3-phenylpropanoyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamide;

N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-phenoxy-4-(4-{(3-phenylpropanoyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamide;

N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxy-4-(4-{(3-phenylpropyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamide;

N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-phenoxy-4-(4-{(3-phenylpropyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamide;

4-[4-(2-{[(1R,5S)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]amino}benzyl)piperazin-1-yl]-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-phenoxybenzamide;

4-[4-(2-{[(1R,5S)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]amino}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide;

4-{4-[2-(3-azabicyclo[3.2.2]non-3-yl)benzyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide;

4-{4-[2-(3-azabicyclo[3.2.2]non-3-yl)benzyl]piperazin-1-yl}-2-phenoxy-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-{4-[2-(3-azabicyclo[3.2.2]non-3-yl)benzyl]piperazin-1-yl}-2-phenoxy-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-{4-[2-(3-azabicyclo[3.2.2]non-3-yl)benzyl]piperazin-1-yl}-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-phenoxybenzamide;

4-(4-{2-[(4R,7S)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-5-yl]benzyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide;

4-[4-(2-{5-[(1R,5S)-8-azabicyclo[3.2.1]oct-8-ylmethyl]thien-2-yl}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide;

4-[4-(2-{5-[(1R,5S)-8-azabicyclo[3.2.1]oct-8-ylmethyl]thien-2-yl}benzylidene)piperidin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide;

4-[4-(3-{5-[(1R,5S)-8-azabicyclo[3.2.1]oct-8-ylmethyl]thien-2-yl}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide;

N-({5-chloro-6-[(4,4-difluorocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({6-[(trans-4-carbamoylcyclohexyl)methoxy]-5-chloropyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-cyanocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[2-(1H-imidazol-1-yl)ethoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(1-methyl-1H-imidazol-5-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-fluoro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

N-{[5-chloro-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(4,4-difluoro-1-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(2,2-difluorocyclopropyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(trans-4-cyanocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-(trifluoromethyl)phenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-chloro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

N-{[3-chloro-4-(1,4-dioxan-2-ylmethoxy)phenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-N-[(5-chloro-6-{[(2S)-4-cyclopropylmorpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

N-[(5-chloro-6-{[(2S)-4-cyclopropylmorpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

methyl 2-{[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}morpholine-4-carboxylate;

2-{[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide;

2-{[(4-{[2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide;

N-({5-chloro-6-[(trans-4-ethyl-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(cis-4-ethyl-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

5-chloro-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamid
e;

5-chloro-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(cis-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(trans-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzotriazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzotriazol-4-yloxy)-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-chloro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}benzamide;

N-[(3-chloro-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(cis-1-fluoro-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzotriazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)benzamide;

N-[(5-chloro-6-{[(1R,2R,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-[(5-chloro-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzotriazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzotriazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S)-4-cyclopropylmorpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

N-[(5-chloro-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S)-4-cyclopropylmorpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S)-4-cyclopropylmorpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-cyano-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-{[3-nitro-4-(2-oxaspiro[3.5]non-7-ylmethoxy)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-cyano-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-{[3-nitro-4-({[(2S)-4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)phenyl]sulfonyl}benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-({[(2S)-4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)phenyl]sulfonyl}benzamide;

N-[(5-chloro-6-{[trans-4-(2-hydroxypropan-2-yl)cyclohexyl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]phenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-({5-nitro-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)benzamide;

2-(1H-benzotriazol-4-yloxy)-N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

N-({3-chloro-4-[(cis-4-cyano-1-fluorocyclohexyl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({3-chloro-4-[(trans-4-cyano-1-fluorocyclohexyl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(cis-4-cyano-1-fluorocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(trans-4-cyano-1-fluorocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-chloro-6-{[1-(1,3-thiazol-2-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(6-{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-5-nitropyridin-3-yl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

N-(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)-4-cyanopiperidine-1-carboxamide;

and therapeutically acceptable salts, prodrugs, salts of prodrugs and metabolites thereof.

Another embodiment pertains to a composition for treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer, said composition comprising an excipient and a therapeutically effective amount of the compound of Formula (I).

Another embodiment pertains to a method of treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer in a patient, said method comprising administering to the patient a therapeutically effective amount of Formula (I).

Another embodiment pertains to a method of treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular

lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer in a patient, said method comprising administering to the patient therapeutically effective amount of the compound of Formula (I) and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

DETAILED DESCRIPTION OF THE INVENTION

Variable moieties herein are represented by identifiers (capital letters with numerical and/or alphabetical superscripts) and may be specifically embodied.

It is meant to be understood that proper valences are maintained for all moieties and combinations thereof, that monovalent moieties having more than one atom are drawn from left to right and are attached through their left ends, and that divalent moieties are also drawn from left to right.

It is also meant to be understood that a specific embodiment of a variable moiety herein may be the same or different as another specific embodiment having the same identifier.

The term "alkenyl" as used herein, means a straight or branched hydrocarbon chain containing from 2 to 10 carbons and containing at least one carbon-carbon double bond. The term "C_x-C_y alkyl" means a straight or branched hydrocarbon chain containing at least one carbon-carbon double bond containing x to y carbon atoms. The term "C_3-C_6 alkenyl" means an alkenyl group containing 3-6 carbon atoms. Representative examples of alkenyl include, but are not limited to, buta-2,3-dienyl, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, 2-methyl-1-heptenyl, and 3-decenyl.

The term "alkenylene" means a divalent group derived from a straight or branched chain hydrocarbon of 2 to 4 carbon atoms and contains at least one carbon-carbon double bond. The term "C_x-C_y alkylene" means a divalent group derived from a straight or branched hydrocarbon chain containing at least one carbon-carbon double bond and containing x to y carbon atoms. Representative examples of alkenylene include, but are not limited to, -CH=CH- and -CH_2CH=CH-.

The term "alkyl" as used herein, means a straight or branched, saturated hydrocarbon chain containing from 1 to 10 carbon atoms. The term "C_X-C_y alkyl" means a straight or branched chain, saturated hydrocarbon containing x to y carbon atoms. For example "C_1-C_6 alkyl" means a straight or branched chain, saturated hydrocarbon containing 2 to 6 carbon

atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, n-heptyl, n-octyl, n-nonyl, and n-decyl.

The term "alkylene" means a divalent group derived from a straight or branched, saturated hydrocarbon chain of 1 to 10 carbon atoms, for example, of 1 to 4 carbon atoms. The term "C_X-C_y alkylene" means a divalent group derived from a straight or branched chain, saturated hydrocarbon containing x to y carbon atoms. For example "C_2-C_6 alkylene" means a straight or branched chain, saturated hydrocarbon containing 2 to 6 carbon atoms. Representative examples of alkylene include, but are not limited to, -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2$-, and -$CH_2CH(CH_3)CH_2$-.

The term "alkynyl" as used herein, means a straight or branched chain hydrocarbon group containing from 2 to 10 carbon atoms and containing at least one carbon-carbon triple bond. The term "C_x-C_y alkynyl" means a straight or branched chain hydrocarbon group containing from x to y carbon atoms. For example "C_3-C_6 alkynyl" means a straight or branched chain hydrocarbon group containing from 3 to 6 carbon atoms and containing at least one carbon-carbon triple bond. Representative examples of alkynyl include, but are not limited to, acetylenyl, 1-propynyl, 2-propynyl, 3-butynyl, 2-pentynyl, and 1-butynyl.

The term "alkynylene," as used herein, means a divalent radical derived from a straight or branched chain hydrocarbon group containing from 2 to 10 carbon atoms and containing at least one carbon-carbon triple bond.

The term "aryl" as used herein, means phenyl.

The term "cyclic moiety," as used herein, means benzene, phenyl, phenylene, cycloalkane, cycloalkyl, cycloalkylene, cycloalkene, cycloalkenyl, cycloalkenylene, cycloalkyne, cycloalkynyl, cycloalkynylene, heteroarene, heteroaryl, heterocycloalkane, heterocycloalkyl, heterocycloalkene, heterocycloalkenyl and spiroalkyl.

The term "cycloalkylene" or cycloalkyl" or "cycloalkane" as used herein, means a monocyclic or bridged hydrocarbon ring system. The monocyclic cycloalkyl is a carbocyclic ring system containing three to ten carbon atoms, zero heteroatoms and zero double bonds. Examples of monocyclic ring systems include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. The monocyclic ring may contain one or two alkylene bridges, each consisting of one, two, or three carbon atoms, each linking two non-adjacent carbon atoms of the ring system. Representative examples of such bridged cycloalkyl ring systems include, but are not limited to, bicyclo[3.1.1]heptane,

bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.1]octane, bicyclo[3.2.2]nonane, bicyclo[3.3.1]nonane, bicyclo[4.2.1]nonane, tricyclo[3.3.1.$0^{3,7}$]nonane (octahydro-2,5-methanopentalene or noradamantane), and tricyclo[3.3.1.$1^{3,7}$]decane (adamantane). The monocyclic and bridged cycloalkyl can be attached to the parent molecular moiety through any substitutable atom contained within the ring system.

The term "cycloalkenylene," or "cycloalkenyl" or "cycloalkene" as used herein, means a monocyclic or a bridged hydrocarbon ring system. The monocyclic cycloalkenyl has four to ten carbon atoms and zero heteroatoms. The four-membered ring systems have one double bond, the five-or six-membered ring systems have one or two double bonds, the seven- or eight-membered ring systems have one, two, or three double bonds, and the nine- or ten-membered rings have one, two, three, or four double bonds. Representative examples of monocyclic cycloalkenyl groups include, but are not limited to, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. The monocyclic cycloalkenyl ring may contain one or two alkylene bridges, each consisting of one, two, or three carbon atoms, each linking two non-adjacent carbon atoms of the ring system. Representative examples of the bridged cycloalkenyl groups include, but are not limited to, bicyclo[2.2.1]hept-2-ene, 4,5,6,7-tetrahydro-3aH-indene, octahydronaphthalenyl, and 1,6-dihydro-pentalene. The monocyclic and bridged cycloalkenyl can be attached to the parent molecular moiety through any substitutable atom contained within the ring systems.

The term "cycloalkyne," or "cycloalkynyl," or "cycloalkynylene," as used herein, means a monocyclic or a bridged hydrocarbon ring system. The monocyclic cycloalkynyl has eight or more carbon atoms, zero heteroatoms, and one or more triple bonds. The monocyclic cycloalkynyl ring may contain one or two alkylene bridges, each consisting of one, two, or three carbon atoms, each linking two non-adjacent carbon atoms of the ring system. The monocyclic and bridged cycloalkynyl can be attached to the parent molecular moiety through any substitutable atom contained within the ring systems.

The term "heteroarene," or "heteroaryl," or "heteroarylene," as used herein, means a five-membered or six-membered aromatic ring having at least one carbon atom and one or more than one independently selected nitrogen, oxygen or sulfur atom. The heteroarenes of this invention are connected through any adjacent atoms in the ring, provided that proper valences are maintained. Representative examples of heteroaryl include, but are not limited to, furanyl (including, but not limited thereto, furan-2-yl), imidazolyl (including, but not limited thereto, 1H-imidazol-1-yl), isoxazolyl, isothiazolyl, oxadiazolyl, 1,3-oxazolyl, pyridinyl (e.g. pyridin-4-yl, pyridin-2-yl, pyridin-3-yl), pyridazinyl, pyrimidinyl, pyrazinyl,

pyrazolyl, pyrrolyl, tetrazolyl, thiadiazolyl, 1,3-thiazolyl, thienyl (including, but not limited thereto, thien-2-yl, thien-3-yl), triazolyl, and triazinyl.

The term "heterocycloalkane," or "heterocycloalkyl," or "heterocycloalkylene," as used herein, means monocyclic or bridged three-, four-, five-, six-, seven-, or eight-membered ring containing at least one heteroatom independently selected from the group consisting of O, N, and S and zero double bonds. The monocyclic and bridged heterocycloalkane are connected to the parent molecular moiety through any substitutable carbon atom or any substitutable nitrogen atom contained within the rings. The nitrogen and sulfur heteroatoms in the heterocycle rings may optionally be oxidized and the nitrogen atoms may optionally be quarternized. Representative examples of heterocycloalkane groups include, but are not limited to, 8-azabicyclo[3.2.1]octane, 3-azabicyclo[3.2.2]nonane, morpholinyl, tetrahydropyranyl, pyrrolidinyl, piperidinyl, dioxolanyl, tetrahydrofuranyl, thiomorpholinyl, 1,4-dioxanyl, tetrahydrothienyl, tetrahydrothiopyranyl, oxetanyl, piperazinyl, imidazolidinyl, azetidine, azepanyl, aziridinyl, diazepanyl, dithiolanyl, dithianyl, isoxazolidinyl, isothiazolidinyl, oxadiazolidinyl, oxazolidinyl, pyrazolidinyl, tetrahydrothienyl, thiadiazolidinyl, thiazolidinyl, thiomorpholinyl, trithianyl, and trithianyl.

The term "heterocycloalkene," or "heterocycloalkenyl," or "heterocycloalkenylene," as used herein, means monocyclic or bridged three-, four-, five-, six-, seven-, or eight-membered ring containing at least one heteroatom independently selected from the group consisting of O, N, and S and one or more double bonds. The monocyclic and bridged heterocycloalkene are connected to the parent molecular moiety through any substitutable carbon atom or any substitutable nitrogen atom contained within the rings. The nitrogen and sulfur heteroatoms in the heterocycle rings may optionally be oxidized and the nitrogen atoms may optionally be quarternized. Representative examples of heterocycloalkene groups include, but are not limited to, 1,4,5,6-tetrahydropyridazinyl, 1,2,3,6-tetrahydropyridinyl, dihydropyranyl, imidazolinyl, isothiazolinyl, oxadiazolinyl, isoxazolinyl, oxazolinyl, pyranyl, pyrazolinyl, pyrrolinyl, thiadiazolinyl, thiazolinyl, and thiopyranyl.

The term "phenylene," as used herein, means a divalent radical formed by removal of a hydrogen atom from phenyl.

The term "spiroalkyl," as used herein, means alkylene, both ends of which are attached to the same carbon atom and is exemplified by C_2-spiroalkyl, C_3-spiroalkyl, C_4-spiroalkyl, C_5-spiroalkyl, C_6-spiroalkyl, C_7-spiroalkyl, C_8-spiroalkyl, C_9-spiroalkyl and the like.

The term "spiroheteroalkyl," as used herein, means spiroalkyl having one or two CH_2 moieties replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N.

The term "spiroheteroalkenyl," as used herein, means spiroalkenyl having one or two CH_2 moieties replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N and also means spiroalkenyl having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties replaced with N.

The term, "spirocyclo," as used herein, means two substituents on the same carbon atom, that, together with the carbon atom to which they are attached, form a cycloalkane, heterocycloalkane, cycloalkene, or heterocycloalkene ring.

The term "C_2-C_5-spiroalkyl," as used herein, means C_2-spiroalkyl, C_3-spiroalkyl, C_4-spiroalkyl, and C_5-spiroalkyl.

The term "C_2-spiroalkyl," as used herein, means eth-1,2-ylene, both ends of which replace hydrogen atoms of the same CH_2 moiety.

The term "C_3-spiroalkyl," as used herein, means prop-1,3-ylene, both ends of which replace hydrogen atoms of the same CH_2 moiety.

The term "C_4-spiroalkyl," as used herein, means but-1,4-ylene, both ends of which replace hydrogen atoms of the same CH_2 moiety.

The term "C_5-spiroalkyl," as used herein, means pent-1,5-ylene, both ends of which replace hydrogen atoms of the same CH_2 moiety.

The term "C_6-spiroalkyl," as used herein, means hex-1,6-ylene, both ends of which replace hydrogen atoms of the same CH_2 moiety.

The term "NH protecting group," as used herein, means trichloroethoxycarbonyl, tribromoethoxycarbonyl, benzyloxycarbonyl, para-nitrobenzylcarbonyl, ortho-bromobenzyloxycarbonyl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, phenylacetyl, formyl, acetyl, benzoyl, tert-amyloxycarbonyl, tert-butoxycarbonyl, para-methoxybenzyloxycarbonyl, 3,4-dimethoxybenzyl-oxycarbonyl, 4-(phenylazo)benzyloxycarbonyl, 2-furfuryl-oxycarbonyl, diphenylmethoxycarbonyl, 1,1-dimethylpropoxy-carbonyl, isopropoxycarbonyl, phthaloyl, succinyl, alanyl, leucyl, 1-adamantyloxycarbonyl, 8-quinolyloxycarbonyl, benzyl, diphenylmethyl, triphenylmethyl, 2-nitrophenylthio, methanesulfonyl, para-toluenesulfonyl, N,N-dimethylaminomethylene, benzylidene, 2-hydroxybenzylidene, 2-hydroxy-5-chlorobenzylidene, 2-hydroxy-1-naphthyl-

methylene, 3-hydroxy-4-pyridylmethylene, cyclohexylidene, 2-ethoxycarbonylcyclohexylidene, 2-ethoxycarbonylcyclopentylidene, 2-acetylcyclohexylidene, 3,3-dimethyl-5-oxycyclo-hexylidene, diphenylphosphoryl, dibenzylphosphoryl, 5-methyl-2-oxo-2H-1,3-dioxol-4-yl-methyl, trimethylsilyl, triethylsilyl, and triphenylsilyl.

The term "C(O)OH protecting group," as used herein, means methyl, ethyl, n-propyl, isopropyl, 1,1-dimethylpropyl, n-butyl, tert-butyl, phenyl, naphthyl, benzyl, diphenylmethyl, triphenylmethyl, para-nitrobenzyl, para-methoxybenzyl, bis(para-methoxyphenyl)methyl, acetylmethyl, benzoylmethyl, para-nitrobenzoylmethyl, para-bromobenzoylmethyl, para-methanesulfonylbenzoylmethyl, 2-tetrahydropyranyl 2-tetrahydrofuranyl, 2,2,2-trichloro-ethyl, 2-(trimethylsilyl)ethyl, acetoxymethyl, propionyloxymethyl, pivaloyloxymethyl, phthalimidomethyl, succinimidomethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methoxymethyl, methoxyethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, benzyloxymethyl, methylthiomethyl, 2-methylthioethyl, phenylthiomethyl, 1,1-dimethyl-2-propenyl, 3-methyl-3-butenyl, allyl, trimethylsilyl, triethylsilyl, triisopropylsilyl, diethylisopropylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, diphenylmethylsilyl, and tert-butylmethoxyphenylsilyl.

The term "OH or SH protecting group," as used herein, means benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, 1,1-dimethylpropoxycarbonyl, isopropoxycarbonyl, isobutyloxycarbonyl, diphenylmethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2,2,2-tribromoethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, 2-(phenylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphonio)ethoxycarbonyl, 2-furfuryloxycarbonyl, 1-adamantyloxycarbonyl, vinyloxycarbonyl, allyloxycarbonyl, S-benzylthiocarbonyl, 4-ethoxy-1-naphthyloxycarbonyl, 8-quinolyloxycarbonyl, acetyl, formyl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, methoxyacetyl, phenoxyacetyl, pivaloyl, benzoyl, methyl, tert-butyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 1,1-dimethyl-2-propenyl, 3-methyl-3-butenyl, allyl, benzyl (phenylmethyl), para-methoxybenzyl, 3,4-dimethoxybenzyl, diphenylmethyl, triphenylmethyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiopyranyl, methoxymethyl, methylthiomethyl, benzyloxymethyl, 2-methoxyethoxymethyl, 2,2,2-trichloro-ethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, 1-ethoxyethyl, methanesulfonyl, para-toluenesulfonyl, trimethylsilyl, triethylsilyl, triisopropylsilyl, diethylisopropylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, diphenylmethylsilyl, and tert-butylmethoxyphenylsilyl.

Compounds

Geometric isomers may exist in the present compounds. Compounds of this invention may contain carbon-carbon double bonds or carbon-nitrogen double bonds in the E or Z configuration, wherein the term "E" represents higher order substituents on opposite sides of the carbon-carbon or carbon-nitrogen double bond and the term "Z" represents higher order substituents on the same side of the carbon-carbon or carbon-nitrogen double bond as determined by the Cahn-Ingold-Prelog Priority Rules. The compounds of this invention may also exist as a mixture of "E" and "Z" isomers. Substituents around a cycloalkyl or heterocycloalkyl are designated as being of cis or trans configuration. Furthermore, the invention contemplates the various isomers and mixtures thereof resulting from the disposal of substituents around an adamantane ring system. Two substituents around a single ring within an adamantane ring system are designated as being of Z or E relative configuration. For examples, see C. D. Jones, M. Kaselj, R. N. Salvatore, W. J. le Noble *J. Org. Chem.* **1998**, 63, 2758-2760 and E. L. Eliel, and S.H. Wilen. (1994) *Stereochemistry of Organic Compounds*. New York, NY: John Wiley & Sons, Inc.

Compounds of this invention contain asymmetrically substituted carbon atoms in the R or S configuration, in which the terms "R" and "S" are as defined by the IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem. (1976) 45, 13-10. Compounds having asymmetrically substituted carbon atoms with equal amounts of R and S configurations are racemic at those carbon atoms. Atoms with an excess of one configuration over the other are assigned the configuration present in the higher amount, preferably an excess of about 85%-90%, more preferably an excess of about 95%-99%, and still more preferably an excess greater than about 99%. Accordingly, this invention includes racemic mixtures, relative and absolute stereoisomers, and mixtures of relative and absolute stereoisomers.

Compounds of this invention containing NH, C(O)OH, OH or SH moieties may have attached thereto prodrug-forming moieties. The prodrug-forming moieties are removed by metabolic processes and release the compounds having the freed hydroxyl, amino or carboxylic acid in vivo. Prodrugs are useful for adjusting such pharmacokinetic properties of the compounds as solubility and/or hydrophobicity, absorption in the gastrointestinal tract, bioavailability, tissue penetration, and rate of clearance.

Isotope Enriched or Labeled Compounds

Compounds of the invention can exist in isotope-labeled or -enriched form containing one or more atoms having an atomic mass or mass number different from the atomic mass or mass number most abundantly found in nature. Isotopes can be radioactive or non-radioactive isotopes. Isotopes of atoms such as hydrogen, carbon, phosphorous, sulfur, fluorine, chlorine, and iodine include, but are not limited to, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, and ^{125}I. Compounds that contain other isotopes of these and/or other atoms are within the scope of this invention.

In another embodiment, the isotope-labeled compounds contain deuterium (^{2}H), tritium (^{3}H) or ^{14}C isotopes. Isotope-labeled compounds of this invention can be prepared by the general methods well known to persons having ordinary skill in the art. Such isotope-labeled compounds can be conveniently prepared by carrying out the procedures disclosed in the Examples disclosed herein and Schemes by substituting a readily available isotope-labeled reagent for a non-labeled reagent. In some instances, compounds may be treated with isotope-labeled reagents to exchange a normal atom with its isotope, for example, hydrogen for deuterium can be exchanged by the action of a deuteric acid such as D_2SO_4/D_2O. In addition to the above, relevant procedures and intermediates are disclosed, for instance, in Lizondo, J et al., *Drugs Fut*, 21(11), 1116 (1996); Brickner, S J *et al., J Med Chem*, 39(3), 673 (1996); Mallesham, B et al., *Org Lett*, 5(7), 963 (2003); PCT publications WO1997010223, WO2005099353, WO1995007271, WO2006008754; US Patent Nos. 7538189; 7534814; 7531685; 7528131; 7521421; 7514068; 7511013; and US Patent Application Publication Nos. 20090137457; 20090131485; 20090131363; 20090118238; 20090111840; 20090105338; 20090105307; 20090105147; 20090093422; 20090088416; and 20090082471, the methods are hereby incorporated by reference.

The isotope-labeled compounds of the invention may be used as standards to determine the effectiveness of Bcl-2 inhibitors in binding assays. Isotope containing compounds have been used in pharmaceutical research to investigate the in vivo metabolic fate of the compounds by evaluation of the mechanism of action and metabolic pathway of the nonisotope-labeled parent compound (Blake et al. *J. Pharm. Sci.* 64, 3, 367-391 (1975)). Such metabolic studies are important in the design of safe, effective therapeutic drugs, either because the *in vivo* active compound administered to the patient or because the metabolites produced from the parent compound prove to be toxic or carcinogenic (Foster et al., Advances in Drug Research Vol. 14, pp. 2-36, Academic press, London, 1985; Kato et al., J. *Labelled Comp. Radiopharmaceut.*, 36(10):927-932 (1995); Kushner et al., *Can. J. Physiol. Pharmacol.*, 77, 79-88 (1999).

In addition, non-radio active isotope containing drugs, such as deuterated drugs called "heavy drugs," can be used for the treatment of diseases and conditions related to Bcl-2 activity. Increasing the amount of an isotope present in a compound above its natural abundance is called enrichment. Examples of the amount of enrichment include from about 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 21, 25, 29, 33, 37, 42, 46, 50, 54, 58, 63, 67, 71, 75, 79, 84, 88, 92, 96, to about 100 mol %. Replacement of up to about 15% of normal atom with a heavy isotope has been effected and maintained for a period of days to weeks in mammals, including rodents and dogs, with minimal observed adverse effects (Czajka D M and Finkel A J, Ann. N.Y. Acad. Sci. 1960 84: 770; Thomson J F, Ann. New York Acad. Sci 1960 84: 736; Czakja D M et al., Am. J. Physiol. 1961 201: 357). Acute replacement of as high as 15%-23% in human fluids with deuterium was found not to cause toxicity (Blagojevic N et al. in "Dosimetry & Treatment Planning for Neutron Capture Therapy", Zamenhof R, Solares G and Harling O Eds. 1994. Advanced Medical Publishing, Madison Wis. pp.125-134; Diabetes Metab. 23: 251 (1997)).

Stable isotope labeling of a drug can alter its physico-chemical properties such as pKa and lipid solubility. These effects and alterations can affect the pharmacodynamic response of the drug molecule if the isotopic substitution affects a region involved in a ligand-receptor interaction. While some of the physical properties of a stable isotope-labeled molecule are different from those of the unlabeled one, the chemical and biological properties are the same, with one important exception: because of the increased mass of the heavy isotope, any bond involving the heavy isotope and another atom will be stronger than the same bond between the light isotope and that atom. Accordingly, the incorporation of an isotope at a site of metabolism or enzymatic transformation will slow said reactions potentially altering the pharmacokinetic profile or efficacy relative to the non-isotopic compound.

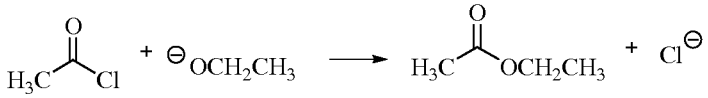
Amides, Esters and Prodrugs

Prodrugs are derivatives of an active drug designed to ameliorate some identified, undesirable physical or biological property. The physical properties are usually solubility (too much or not enough lipid or aqueous solubility) or stability related, while problematic biological properties include too rapid metabolism or poor bioavailability which itself may be related to a physicochemical property.

Prodrugs are usually prepared by: a) formation of ester, hemi esters, carbonate esters, nitrate esters, amides, hydroxamic acids, carbamates, imines, Mannich bases, phosphates, phosphate esters, and enamines of the active drug, b) functionalizing the drug with azo, glycoside, peptide, and ether functional groups, c) use of aminals, hemi-aminals, polymers, salts, complexes, phosphoramides, acetals, hemiacetals, and ketal forms of the drug. For example, see Andrejus Korolkovas`s, "Essentials of Medicinal Chemistry", John Wiley-Interscience Publications, John Wiley and Sons, New York (1988), pp. 97-118, which is incorporated in its entirety by reference herein.

Esters can be prepared from substrates of formula (I) containing either a hydroxyl group or a carboxy group by general methods known to persons skilled in the art. The typical reactions of these compounds are substitutions replacing one of the heteroatoms by another atom, for example:

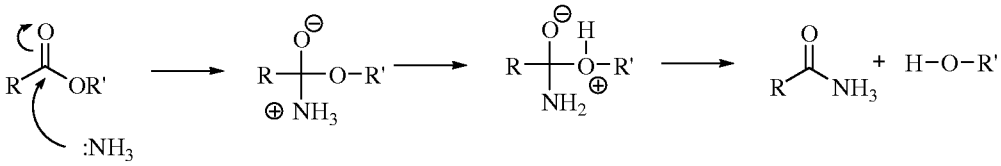
Scheme 1



Acyl Chloride Alkoxide Ester

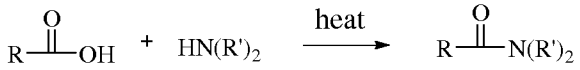
Amides can be prepared from substrates of formula (I) containing either an amino group or a carboxy group in similar fashion. Esters can also react with amines or ammonia to form amides.

Scheme 2



Another way to make amides from compounds of formula (I) is to heat carboxylic acids and amines together.

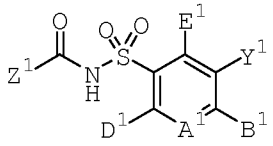
Scheme 3



In Schemes 2 and 3 above, R and R' are independently substrates of formula (I), alkyl or hydrogen.

Suitable groups for A^1, B^1, D^1, E^1, Y^1, and Z^1 in compounds of Formula (I) are independently selected. The described embodiments of the present invention may be combined. Such combination is contemplated and within the scope of the present invention. For example, it is contemplated that embodiments for any of A^1, B^1, D^1, E^1, Y^1, and Z^1 can be combined with embodiments defined for any other of A^1, B^1, D^1, E^1, Y^1, and Z^1.

One embodiment of this invention, therefore, pertains to compounds or therapeutically acceptable salts, prodrugs or salts of prodrugs thereof, which are useful as selective inhibitors one or more than one anti-apoptotic protein family member, the compounds having formula (I)



(I),

wherein

A^1 is N or $C(A^2)$;

one or two or three or each of A^2, B^1, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$; and

Y^1 is H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ or $NHSO_2R^{17}$;

or

B^1 and Y^1, together with the atoms to which they are attached, are imidazole or triazole; and

one or two or each of A^2, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$,

$NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$;

R^1 is R^2, R^3, R^4 or R^5;

R^{1A} is C_1-C_6-alkyl, C_3-C_6-alkenyl or C_3-C_6-alkynyl;

R^2 is phenyl which is unfused or fused with arene, heteroarene or R^{2A}; R^{2A} is cycloalkane or heterocycloalkane;

R^3 is heteroaryl which is unfused or fused with benzene, heteroarene or R^{3A}; R^{3A} is cycloalkane or heterocycloalkane;

R^4 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with arene, heteroarene or R^{4A}; R^{4A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^5 is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^6 is C_2-C_5-spiroalkyl, each of which is unsubstituted or substituted with OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ or $N(CH_3)_2$;

R^{6A} and R^{6B} are independently selected alkyl or, together with the N to which they are attached, R^{6C};

R^{6C} is aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, each having one CH_2 moiety unreplaced or replaced with O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH;

R^7 is R^8, R^9, R^{10} or R^{11};

R^8 is phenyl which is unfused or fused with arene, heteroarene or R^{8A};

R^{8A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^9 is heteroaryl which is unfused or fused with arene, heteroarene or R^{9A}; R^{9A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{10} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{10A}; R^{10A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{11} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{12} is R^{13}, R^{14}, R^{15} or R^{16};

R^{13} is phenyl which is unfused or fused with arene, heteroarene or R^{13A}; R^{13A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{14} is heteroaryl, each of which is unfused or fused with arene, heteroarene or R^{14A}; R^{14A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{15} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene, each of which is unfused or fused with arene, heteroarene or R^{15A}; R^{15A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{16} is alkyl, alkenyl or alkynyl;

R^{17} is R^{18}, R^{19}, R^{20} or R^{21};

R^{18} is phenyl which is unfused or fused with arene, heteroarene or R^{18A}; R^{18A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{19} is heteroaryl which is unfused or fused with arene, heteroarene or R^{19A}; R^{19A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{20} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{20A}; R^{20A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{21} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{22} is R^{23}, R^{24} or R^{25};

R^{23} is phenyl which is unfused or fused with arene, heteroarene or R^{23A}; R^{23A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{24} is heteroarene which is unfused or fused with arene, heteroarene or R^{24A}; R^{24A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{25} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is

unfused or fused with arene, heteroarene or R^{25A}; R^{25A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

Z^1 is R^{26} or R^{27}, each of which is substituted with R^{28}, R^{29} or R^{30}, each of which is substituted with F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} or $N(R^{32})R^{37}$;

R^{26} is phenyl which is unfused or fused with arene or heteroarene;

R^{27} is heteroarene which is unfused or fused with arene or heteroarene;

R^{28} is phenyl which is unfused or fused with arene, heteroarene or R^{28A}; R^{28A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene

R^{29} is heteroaryl or R^{29A}; R^{29A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{30} is cycloalkyl or cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{30A}; R^{30A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{31} and R^{31A} are independently F, Cl, Br or alkyl or are taken together and are C_2-C_5-spiroalkyl;

R^{32} is R^{33}, $C(O)R^{33}$ or $C(O)OR^{33}$;

R^{33} is R^{34} or R^{35};

R^{34} is phenyl which is unfused or fused with aryl, heteroaryl or R^{34A}; R^{34A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{35} is alkyl which is unsubstituted or substituted with R^{36};

R^{36} is phenyl which is unfused or fused with arene, heteroarene or R^{36A}; R^{36A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{37} is R^{38}, R^{39} or R^{40}, each of which is substituted with F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ or SO_2R^{41};

R^{38} is phenyl which is unfused or fused with arene, heteroarene or R^{38A}; R^{38A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{39} is heteroaryl which is unfused or fused with arene, heteroarene or R^{39A}; R^{39A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{40} is C_3-C_8-cycloalkyl or C_4-C_8-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is

unfused or fused with arene, heteroarene or R^{40A}; R^{40A} cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{41} is R^{42}, R^{43}, R^{44} or R^{45};

R^{42} is phenyl which is unfused or fused with arene, heteroarene or R^{42A}; R^{42A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{43} is heteroaryl which is unfused or fused with arene, heteroarene or R^{43A}; R^{43A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{44} is C_3-C_9-cycloalkyl or C_4-C_7-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{44A}; R^{44A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{45} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two independently selected R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{46} is R^{47}, R^{48} or R^{49};

R^{47} is phenyl which is unfused or fused with arene, heteroarene or R^{47A}; R^{47A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{48} is heteroaryl or R^{48A}; R^{48A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{49} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{49A}; R^{49A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein the moieties represented by R^{26} and R^{27} are further substituted by one or two or three of independently selected R^{50A}, OR^{50A}, SR^{50A}, $S(O)R^{50A}$, SO_2R^{50A} or NHR^{50A},

R^{50A} is R^{51A}, R^{52A}, R^{53A} or R^{54A};

R^{51A} is phenyl which is unfused or fused with benzene, heteroarene or R^{51AA}, wherein R^{51AA} is cycloalkane, cycloalkene or heterocycloalkane heterocycloalkene,

R^{52A} is heteroaryl;

R^{53A} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl; each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2

or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{53AA};

wherein R^{53AA} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{54A} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{55AA}, OR^{55AA}, SR^{55AA}, $S(O)R^{55AA}$, SO_2R^{55AA}, NHR^{55AA}, $N(R^{55AA})_2$, $C(O)R^{55AA}$, $C(O)NH_2$, $C(O)NHR^{55AA}$, $NHC(O)R^{55AA}$, $NHSO_2R^{55AA}$, $NHC(O)OR^{55AA}$, SO_2NH_2, SO_2NHR^{55AA}, $SO_2N(R^{55AA})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55AA}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{55AA} is alkyl, alkenyl, alkynyl, phenyl or heteroaryl, or R^{56A};

R^{56A} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N;

wherein moieties represented by R^2, R^{2A}, R^3, R^{3A}, R^4, R^{4A}, R^6, R^{6C}, R^8, R^{8A}, R^9, R^{10}, R^{10A}, R^{13}, R^{13A}, R^{14}, R^{14A}, R^{15}, R^{15A}, R^{18}, R^{18A}, R^{19}, R^{19A}, R^{20}, R^{20A}, R^{23}, R^{23A}, R^{24}, R^{24A}, R^{25}, R^{25A}, R^{26}, R^{27}, R^{28}, R^{28A}, R^{29}, R^{29A}, R^{30}, R^{30A}, R^{34}, R^{34A}, R^{36}, R^{36A}, R^{38}, R^{38A}, R^{39}, R^{39A}, R^{40}, R^{40A}, R^{42}, R^{42A}, R^{43}, R^{43A}, R^{44}, R^{44A}, R^{47}, R^{47A}, R^{48}, R^{48A}, R^{49}, and R^{49A} are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five independently selected R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{50} is R^{51}, R^{52}, R^{53} or R^{54};

R^{51} is phenyl which is unfused or fused with arene, heteroarene or R^{51B}; R^{51B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{52} is heteroaryl;

R^{53} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{53B};

wherein R^{53B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{54} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$,

$C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{55} is alkyl, alkenyl, alkynyl, phenyl, heteroaryl or R^{56}; and

wherein the alkyl, alkenyl, alkynyl are unsubstituted or substituted with OCH_3; and

R^{56} is C_3-C_8-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N.

Another embodiment of this invention pertains to compounds of Formula (I), wherein

A^1 is N or $C(A^2)$;

one or two or three or each of A^2, B^1, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$; and

Y^1 is H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ or $NHSO_2R^{17}$;

or

B^1 and Y^1, together with the atoms to which they are attached, are imidazole or triazole; and

one or two or each of A^2, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$;

R^1 is R^2, R^3, R^4 or R^5;

R^{1A} is C_1-C_6-alkyl, C_3-C_6-alkenyl or C_3-C_6-alkynyl;

R^2 is phenyl which is unfused or fused with arene, heteroarene or R^{2A}; R^{2A} is cycloalkane or heterocycloalkane;

R^3 is heteroaryl which is unfused or fused with benzene, heteroarene or R^{3A}; R^{3A} is cycloalkane or heterocycloalkane;

R^4 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with arene, heteroarene or R^{4A}; R^{4A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^5 is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^6 is C_2-C_5-spiroalkyl, each of which is unsubstituted or substituted with OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ or $N(CH_3)_2$;

R^{6A} and R^{6B} are independently selected alkyl or, together with the N to which they are attached, R^{6C};

R^{6C} is aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, each having one CH_2 moiety unreplaced or replaced with O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH;

R^7 is R^8, R^9, R^{10} or R^{11};

R^8 is phenyl which is unfused or fused with arene, heteroarene or R^{8A};

R^{8A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^9 is heteroaryl which is unfused or fused with arene, heteroarene or R^{9A}; R^{9A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{10} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{10A}; R^{10A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{11} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{12} is R^{13}, R^{14}, R^{15} or R^{16};

R^{13} is phenyl which is unfused or fused with arene, heteroarene or R^{13A}; R^{13A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{14} is heteroaryl, each of which is unfused or fused with arene, heteroarene or R^{14A}; R^{14A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{15} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene, each of which is unfused or fused with arene, heteroarene or R^{15A}; R^{15A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{16} is alkyl, alkenyl or alkynyl;

R^{17} is R^{18}, R^{19}, R^{20} or R^{21};

R^{18} is phenyl which is unfused or fused with arene, heteroarene or R^{18A}; R^{18A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{19} is heteroaryl which is unfused or fused with arene, heteroarene or R^{19A}; R^{19A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{20} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{20A}; R^{20A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{21} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{22} is R^{23}, R^{24} or R^{25};

R^{23} is phenyl which is unfused or fused with arene, heteroarene or R^{23A}; R^{23A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{24} is heteroarene which is unfused or fused with arene, heteroarene or R^{24A}; R^{24A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{25} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{25A}; R^{25A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

Z^1 is R^{26} or R^{27}, each of which is substituted with R^{28}, R^{29} or R^{30}, each of which is substituted with F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} or $N(R^{32})R^{37}$;

R^{26} is phenyl which is unfused or fused with arene or heteroarene;

R^{27} is heteroarene which is unfused or fused with arene or heteroarene;

R^{28} is phenyl which is unfused or fused with arene, heteroarene or R^{28A}; R^{28A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene

R^{29} is heteroaryl or R^{29A}; R^{29A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{30} is cycloalkyl or cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{30A}; R^{30A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{31} and R^{31A} are independently F, Cl, Br or alkyl or are taken together and are C_2-C_5-spiroalkyl;

R^{32} is R^{33}, $C(O)R^{33}$ or $C(O)OR^{33}$;

R^{33} is R^{34} or R^{35};

R^{34} is phenyl which is unfused or fused with aryl, heteroaryl or R^{34A}; R^{34A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{35} is alkyl which is unsubstituted or substituted with R^{36};

R^{36} is phenyl which is unfused or fused with arene, heteroarene or R^{36A}; R^{36A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{37} is R^{38}, R^{39} or R^{40}, each of which is substituted with F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ or SO_2R^{41};

R^{38} is phenyl which is unfused or fused with arene, heteroarene or R^{38A}; R^{38A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{39} is heteroaryl which is unfused or fused with arene, heteroarene or R^{39A}; R^{39A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{40} is C_3-C_8-cycloalkyl or C_4-C_8-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{40A}; R^{40A} cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{41} is R^{42}, R^{43}, R^{44} or R^{45};

R^{42} is phenyl which is unfused or fused with arene, heteroarene or R^{42A}; R^{42A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{43} is heteroaryl which is unfused or fused with arene, heteroarene or R^{43A}; R^{43A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{44} is C_3-C_9-cycloalkyl or C_4-C_7-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2

or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{44A}; R^{44A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{45} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two independently selected R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), $C(O)OH$, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{46} is R^{47}, R^{48} or R^{49};

R^{47} is phenyl which is unfused or fused with arene, heteroarene or R^{47A}; R^{47A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{48} is heteroaryl or R^{48A}; R^{48A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{49} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{49A}; R^{49A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein the moieties represented by R^{26} and R^{27} are further substituted with OR^{50A};

R^{50A} is R^{51A};

R^{51A} is phenyl which is fused with heteroarene;

wherein moieties represented by R^2, R^{2A}, R^3, R^{3A}, R^4, R^{4A}, R^6, R^{6C}, R^8, R^{8A}, R^9, R^{10}, R^{10A}, R^{13}, R^{13A}, R^{14}, R^{14A}, R^{15}, R^{15A}, R^{18}, R^{18A}, R^{19}, R^{19A}, R^{20}, R^{20A}, R^{23}, R^{23A}, R^{24}, R^{24A}, R^{25}, R^{25A}, R^{26}, R^{27}, R^{28}, R^{28A}, R^{29}, R^{29A}, R^{30}, R^{30A}, R^{34}, R^{34A}, R^{36}, R^{36A}, R^{38}, R^{38A}, R^{39}, R^{39A}, R^{40}, R^{40A}, R^{42}, R^{42A}, R^{43}, R^{43A}, R^{44}, R^{44A}, R^{47}, R^{47A}, R^{48}, R^{48A}, R^{49}, and R^{49A} are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five independently selected R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, $C(O)NHOH$, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{50} is R^{51}, R^{52}, R^{53} or R^{54};

R^{51} is phenyl which is unfused or fused with arene, heteroarene or R^{51B}; R^{51B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{52} is heteroaryl;

R^{53} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{53B};

wherein R^{53B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{54} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{55} is alkyl, alkenyl, alkynyl, phenyl, heteroaryl or R^{56}; and

wherein the alkyl, alkenyl, alkynyl are unsubstituted or substituted with OCH_3; and

R^{56} is C_3-C_8-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N.

A^1 is N or $C(A^2)$;

one or two or three or each of A^2, B^1, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$; and

Y^1 is H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ or $NHSO_2R^{17}$;

or

B^1 and Y^1, together with the atoms to which they are attached, are imidazole or triazole; and

one or two or each of A^2, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$;

R^1 is R^2, R^3, R^4 or R^5;

R^{1A} is C_1-C_6-alkyl, C_3-C_6-alkenyl or C_3-C_6-alkynyl;

R^2 is phenyl which is unfused or fused with arene, heteroarene or R^{2A}; R^{2A} is cycloalkane or heterocycloalkane;

R^3 is heteroaryl which is unfused or fused with benzene, heteroarene or R^{3A}; R^{3A} is cycloalkane or heterocycloalkane;

R^4 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with arene, heteroarene or R^{4A}; R^{4A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^5 is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^6 is C_2-C_5-spiroalkyl, each of which is unsubstituted or substituted with OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ or $N(CH_3)_2$;

R^{6A} and R^{6B} are independently selected alkyl or, together with the N to which they are attached, R^{6C};

R^{6C} is aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, each having one CH_2 moiety unreplaced or replaced with O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH;

R^7 is R^8, R^9, R^{10} or R^{11};

R^8 is phenyl which is unfused or fused with arene, heteroarene or R^{8A};

R^{8A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^9 is heteroaryl which is unfused or fused with arene, heteroarene or R^{9A}; R^{9A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{10} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{10A}; R^{10A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{11} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{12} is R^{13}, R^{14}, R^{15} or R^{16};

R^{13} is phenyl which is unfused or fused with arene, heteroarene or R^{13A}; R^{13A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{14} is heteroaryl, each of which is unfused or fused with arene, heteroarene or R^{14A}; R^{14A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{15} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene, each of which is unfused or fused with arene, heteroarene or R^{15A}; R^{15A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{16} is alkyl, alkenyl or alkynyl;

R^{17} is R^{18}, R^{19}, R^{20} or R^{21};

R^{18} is phenyl which is unfused or fused with arene, heteroarene or R^{18A}; R^{18A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{19} is heteroaryl which is unfused or fused with arene, heteroarene or R^{19A}; R^{19A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{20} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{20A}; R^{20A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{21} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{22} is R^{23}, R^{24} or R^{25};

R^{23} is phenyl which is unfused or fused with arene, heteroarene or R^{23A}; R^{23A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{24} is heteroarene which is unfused or fused with arene, heteroarene or R^{24A}; R^{24A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{25} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{25A}; R^{25A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

Z^1 is R^{26} or R^{27}, each of which is substituted with R^{28}, R^{29} or R^{30}, each of which is substituted with F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} or $N(R^{32})R^{37}$;

R^{26} is phenyl which is unfused or fused with arene or heteroarene;

R^{27} is heteroarene which is unfused or fused with arene or heteroarene;

R^{28} is phenyl which is unfused or fused with arene, heteroarene or R^{28A}; R^{28A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{29} is heteroaryl or R^{29A}; R^{29A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{30} is cycloalkyl or cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{30A}; R^{30A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{31} and R^{31A} are independently F, Cl, Br or alkyl or are taken together and are C_2-C_5-spiroalkyl;

R^{32} is R^{33}, $C(O)R^{33}$ or $C(O)OR^{33}$;

R^{33} is R^{34} or R^{35};

R^{34} is phenyl which is unfused or fused with aryl, heteroaryl or R^{34A}; R^{34A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{35} is alkyl which is unsubstituted or substituted with R^{36};

R^{36} is phenyl which is unfused or fused with arene, heteroarene or R^{36A}; R^{36A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{37} is R^{38}, R^{39} or R^{40}, each of which is substituted with F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ or SO_2R^{41};

R^{38} is phenyl which is unfused or fused with arene, heteroarene or R^{38A}; R^{38A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{39} is heteroaryl which is unfused or fused with arene, heteroarene or R^{39A}; R^{39A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{40} is C_3-C_8-cycloalkyl or C_4-C_8-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{40A}; R^{40A} cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{41} is R^{42}, R^{43}, R^{44} or R^{45};

R^{42} is phenyl which is unfused or fused with arene, heteroarene or R^{42A}; R^{42A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{43} is heteroaryl which is unfused or fused with arene, heteroarene or R^{43A}; R^{43A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{44} is C_3-C_9-cycloalkyl or C_4-C_7-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{44A}; R^{44A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{45} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two independently selected R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{46} is R^{47}, R^{48} or R^{49};

R^{47} is phenyl which is unfused or fused with arene, heteroarene or R^{47A}; R^{47A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{48} is heteroaryl or R^{48A}; R^{48A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{49} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{49A}; R^{49A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein the moieties represented by R^{26} and R^{27} are further substituted by one or two or three of independently selected R^{50A}, OR^{50A}, SR^{50A}, $S(O)R^{50A}$, SO_2R^{50A} or NHR^{50A};

R^{50A} is R^{51A}, R^{52A}, R^{53A} or R^{54A};

R^{51A} is phenyl which is unfused or fused with benzene, heteroarene or R^{51AA},

wherein R^{51AA} is cycloalkane, cycloalkene or heterocycloalkane heterocycloalkene,

R^{52A} is heteroaryl;

R^{53A} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl; each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{53AA};

wherein R^{53AA} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{54A} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{55AA}, OR^{55AA}, SR^{55AA}, $S(O)R^{55AA}$, SO_2R^{55AA}, NHR^{55AA}, $N(R^{55AA})_2$, $C(O)R^{55AA}$, $C(O)NH_2$, $C(O)NHR^{55AA}$, $NHC(O)R^{55AA}$, $NHSO_2R^{55AA}$,

$NHC(O)OR^{55AA}$, SO_2NH_2, SO_2NHR^{55AA}, $SO_2N(R^{55AA})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55AA}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{55AA} is alkyl, alkenyl, alkynyl, phenyl or heteroaryl, or R^{56A};

R^{56A} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N;

wherein moieties represented by R^2 R^3 R^4, R^6, R^{6C}, R^8, R^{8A} R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{18}, R^{19}, R^{20}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{34}, R^{36}, R^{38}, R^{39}, R^{40}, R^{42}, R^{43}, R^{44}, R^{47}, R^{48}, and R^{49} are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five independently selected R^{50AA}, R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{50AA} is spirocyclyl;

R^{50} is R^{51}, R^{52}, R^{53} or R^{54};

R^{51} is phenyl which is unfused or fused with arene, heteroarene or R^{51B}; R^{51B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{52} is heteroaryl;

R^{53} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{53B};

wherein R^{53B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{54} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{55} is alkyl, alkenyl, alkynyl, phenyl, heteroaryl or R^{56};

wherein the alkyl, alkenyl, alkynyl are unsubstituted or substituted with OCH_3; and

R^{56} is C_3-C_8-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N.

In one embodiment of Formula (I),

A^1 is N or $C(A^2)$;

one or two or three or each of A^2, B^1, D^1 and E^1 are independently selected R^1, OR^1, SR^1, SO_2R^1, $NHC(O)R^1$, NHR^1, $N(R^1)_2$, or $C(O)NHR^1$, and the remainder are independently selected H, F, Cl, Br, or I;

Y^1 is H, CN, NO_2, F, Cl, Br, I, CF_3, R^{17}, $NHC(O)R^{17}$, or $C(O)NH_2$;

R^1 is R^2, R^3, R^4 or R^5;

R^2 is phenyl;

R^3 is heteroaryl;

R^4 is cycloalkyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{4A}; R^{4A} is cycloalkane;

R^5 is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^6, R^7, OR^7, SR^7, SO_2R^7, $N(R^7)_2$, OH, CN, CF_3, F, Cl, Br or I substituents;

R^6 is C_2-C_5-spiroalkyl;

R^7 is R^8, R^9, R^{10} or R^{11};

R^8 is phenyl which is unfused or fused with R^{8A};

R^{8A} is heterocycloalkane;

R^9 is heteroaryl;

R^{10} is C_3-C_{10}-cycloalkyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N; and each of which is unfused or fused with heteroarene;

R^{11} is alkyl, each of which is unsubstituted or substituted with one or two or three independently selected OR^{12}, F, Cl, Br or I substituents;

R^{12} is R^{16};

R^{16} is alkyl;

R^{17} is R^{19} or R^{21};

R^{19} is heteroaryl which is unfused or fused with arene, heteroarene or R^{19A}; R^{19A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{21} is alkynyl;

Z^1 is R^{26}, each of which is substituted with R^{30}, each of which is substituted with F, Cl, Br, I, CH_2R^{37}, or $CH(R^{31})(R^{37})$;

R^{26} is phenyl;

R^{30} is cycloalkyl, each having two CH_2 moieties unreplaced or replaced with NH;

R^{31} and R^{31A} are independently alkyl;

R^{37} is R^{38}, R^{39} or R^{40}, each of which is substituted with F, Cl, Br, I, NHR^{41}, or R^{41};

R^{38} is phenyl;

R^{39} is heteroaryl;

R^{40} is C_3-C_8-cycloalkyl or C_4-C_8-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH;

R^{41} is R^{42}, R^{43}, or R^{44};

R^{42} is phenyl;

R^{43} is heteroaryl;

R^{44} is C_3-C_9-cycloalkyl or C_4-C_7-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with R^{44A}; R^{44A} is cycloalkane;

wherein the moiety represented by R^{26} is further substituted by one or two or three of independently selected R^{50A}, OR^{50A}, SR^{50A}, $S(O)R^{50A}$, SO_2R^{50A} or NHR^{50A};

R^{50A} is R^{51A}, R^{52A} or R^{54A};

R^{51A} is phenyl which is unfused or fused with benzene, heteroarene or R^{51AA};

wherein R^{51AA} is heterocycloalkane;

R^{52A} is heteroaryl;

R^{54A} is alkyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{55AA}, or OR^{55AA};

R^{55AA} is phenyl;

wherein moieties represented by R^2, R^3, R^4, R^{4A}, R^6, R^8, R^{8A}, R^9, R^{10}, R^{19}, R^{26}, R^{30}, R^{38}, R^{39}, R^{40}, R^{42}, R^{43}, R^{44}, and R^{44A} are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five independently selected R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, NH_2, NHR^{50}, $C(O)NH_2$, $C(O)N(R^{50})_2$, SO_2NH_2, OH, (O), CN, CF_3, OCF_3, F, Cl, Br or I substituents;

R^{50} is R^{51}, R^{52}, or R^{54};

R^{51} is phenyl which is unfused or fused with arene, heteroarene or R^{51B}; R^{51B} is heterocycloalkane;

R^{52} is heteroaryl;

R^{53} is C_3-C_6-cycloalkyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, and one or two CH moieties unreplaced or replaced with N;

R^{54} is alkyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{55}, OR^{55}, $N(R^{55})_2$, OH, CN, F, Cl, Br or I substituents; and

R^{55} is alkyl or phenyl;

wherein the alkyl is unsubstituted or substituted with OCH_3; and

R^{56} is C_3-C_8-cycloalkyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected NH and one or two CH moieties unreplaced or replaced with N.

In one embodiment of Formula (I), A^1 is N. In another embodiment of Formula (I), A^1 is $C(A^2)$. In another embodiment of Formula (I), A^1 is $C(A^2)$, and A^2 is H.

In one embodiment of Formula (I), B^1 is R^1, OR^1, SR^1, SO_2R^1, $NHC(O)R^1$, NHR^1, $N(R^1)_2$, or $C(O)NHR^1$. In another embodiment of Formula (I), B^1 is NHR^1. In another embodiment of Formula (I), B^1 is NHR^1, and A^1 is $C(A^2)$, and A^2 is H. In another embodiment of Formula (I), B^1 is NHR^1, and A^1 is $C(A^2)$ or N, and A^2 is H. In another embodiment of Formula (I), B^1 is OR^1. In another embodiment of Formula (I), B^1 is OR^1, and A^1 is $C(A^2)$, and A^2 is H. In another embodiment of Formula (I), B^1 is OR^1, and A^1 is $C(A^2)$ or N, and A^2 is H.

In one embodiment of Formula (I), D^1 and E^1 are H. In another embodiment of Formula (I), B^1 is NHR^1, and A^1 is $C(A^2)$, A^2 is H, and D^1 and E^1 are H. In another embodiment of Formula (I), B^1 is NHR^1, and A^1 is $C(A^2)$ or N, A^2 is H, and D^1 and E^1 are H. In another embodiment of Formula (I), B^1 is OR^1, and A^1 is $C(A^2)$, A^2 is H, and D^1 and E^1 are H. In another embodiment of Formula (I), B^1 is OR^1, and A^1 is $C(A^2)$ or N, A^2 is H, and D^1 and E^1 are H.

In one embodiment of Formula (I), Y^1 is H, CN, NO_2, F, Cl, Br, I, CF_3, R^{17}, $NHC(O)R^{17}$, or $C(O)NH_2$. In another embodiment of Formula (I), Y^1 is NO_2. In another embodiment of Formula (I), Y^1 is Cl. In another embodiment of Formula (I), B^1 is NHR^1, and A^1 is $C(A^2)$, A^2 is H, D^1 and E^1 are H, and Y^1 is NO_2. In another embodiment of Formula (I), B^1 is NHR^1, and A^1 is $C(A^2)$ or N, A^2 is H, D^1 and E^1 are H, and Y^1 is NO_2. In another embodiment of Formula (I), B^1 is OR^1, and A^1 is $C(A^2)$, A^2 is H, D^1 and E^1 are H, and Y^1 is Cl. In another embodiment of Formula (I), B^1 is OR^1, and A^1 is $C(A^2)$ or N, A^2 is H, D^1 and E^1 are H, and Y^1 is Cl.

In one embodiment of Formula (I), R^1 is R^2, R^3, R^4 or R^5. In another embodiment of Formula (I), R^1 is R^2, and R^2 is phenyl.

In one embodiment of Formula (I), R^1 is R^3, and R^3 is heteroaryl. In another embodiment of Formula (I), R^3 is triazolyl.

In one embodiment of Formula (I), R^1 is R^4. In another embodiment of Formula (I), R^1 is R^4, and R^4 is cycloalkyl. In another embodiment of Formula (I), R^1 is R^4, and R^4 is cyclohexyl. In another embodiment of Formula (I), R^1 is R^4, and R^4 is heterocycloalkyl. In another embodiment of Formula (I), R^1 is R^4, and R^4 is 8-azabicyclo[3.2.1]octane, azetidinyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydropyranyl, or tetrahydrothiophenyl. In another embodiment of Formula (I), R^1 is R^4, and R^4 is heterocycloalkenyl. In another embodiment of Formula (I), R^1 is R^4, and R^4 is tetrahydropyridazinyl.

In one embodiment of Formula (I), R^1 is R^5. In another embodiment of Formula (I), R^1 is R^5 and R^5 is alkyl or alkynyl. In another embodiment of Formula (I), R^1 is R^5 and R^5 is alkyl which is unsubstituted. In another embodiment of Formula (I), R^1 is R^5 and R^5 is alkyl which is substituted with one or two or three independently selected R^6, R^7, OR^7, SR^7, SO_2R^7, $N(R^7)_2$, OH, CN, CF_3, F, Cl, Br or I substituents. In another embodiment of Formula (I), R^1 is R^5 and R^5 is alkyl which is substituted with R^7.

In one embodiment of Formula (I), R^7 is R^8, R^9, R^{10} or R^{11}. In another embodiment of Formula (I), R^7 is R^8, and R^8 is phenyl which is unfused or fused with R^{8A}, and R^{8A} is heterocycloalkane. In another embodiment of Formula (I), R^7 is R^8, and R^8 is phenyl which is unfused. In another embodiment of Formula (I), R^7 is R^9, and R^9 is heteroaryl. In another embodiment of Formula (I), R^7 is R^9, and R^9 is furanyl, imidazolyl, isothiazolyl, isoxazolyl, 1,2,3-oxadiazoyl, 1,2,5-oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrazolyl, thiazolyl, thiophenyl, triazinyl or 1,2,3-triazolyl. In another embodiment of Formula (I), R^7 is R^9, and R^9 is pyridinyl, thiazolyl, imidazoyl, and 1,2,3-triazolyl. In another embodiment of Formula (I), R^7 is R^{10}, and R^{10} is C_3-C_{10}-cycloalkyl. In another embodiment of Formula (I), R^7 is R^{10}, and R^{10} is C_3, C_6, C_7 or C_{10}-cycloalkyl. In another embodiment of Formula (I), R^7 is R^{10}, and R^{10} is cyclopropyl, cyclohexyl, bicyclo[2.2.1]heptanyl, or adamantanyl. In another embodiment of Formula (I), R^7 is R^{10}, and R^{10} is morpholinyl, piperazinyl, piperidinyl, tetrahydro-2H-pyranyl, 1,2-dihydropyridinyl, pyranyl, pyridin-1(H)-yl, pyrrolidinyl, oxetanyl, thiomorpholinyl, imidazolidinyl, tetrahydrothiophenyl, dioxolanyl, tetrahydrothiopyranyl, dioxanyl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl, or tetrahydrofuranyl. In another embodiment of Formula

(I), R^7 is R^{10}, and R^{10} is morpholinyl, piperazinyl, piperidinyl, tetrahydro-2H-pyranyl, 1,2-dihydropyridinyl, pyrrolidinyl, oxetanyl, thiomorpholinyl, imidazolidinyl, tetrahydrothiophenyl, dioxolanyl, tetrahydrothiopyranyl, dioxanyl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl, or tetrahydrofuranyl. In another embodiment of Formula (I), R^7 is R^{11}, and R^{11} is alkyl which is unsubstituted or substituted. In another embodiment of Formula (I), R^7 is R^{11}, and R^{11} is alkyl which is unsubstituted. In another embodiment of Formula (I), R^7 is R^{11}, and R^{11} is alkyl which is substituted. In another embodiment of Formula (I), R^7 is R^{11}, and R^{11} is alkyl which is substituted with one or two or three independently selected OR^{12}, F, Cl, Br or I substituents. In another embodiment of Formula (I), R^7 is R^{11}, R^{11} is alkyl which is substituted with OR^{12}, R^{12} is R^{16}, and R^{16} is alkyl.

In one embodiment of Formula (I), R^{17} is R^{19} or R^{21}. In another embodiment of Formula (I), R^{17} is R^{19}, and R^{19} is heteroaryl. In another embodiment of Formula (I), R^{17} is R^{19}, and R^{19} is thiazolyl. In another embodiment of Formula (I), R^{17} is R^{21}, and R^{21} is alkynyl. In another embodiment of Formula (I), R^{17} is R^{21}, and R^{21} is ethynyl.

Still another embodiment pertains to compounds having Formula I which are

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

2-(benzyloxy)-4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(2-phenylethoxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(phenylthio)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(phenylthio)-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-(phenylthio)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(phenylsulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(phenylsulfinyl)benzamide;

2-benzyl-4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

2-benzyl-4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

2-benzyl-4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(2-phenylethyl)benzamide;

2-(benzylamino)-4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

2-anilino-4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

2-anilino-4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-methoxy-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indazol-5-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indazol-5-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-(1,2,3,4-tetrahydroquinolin-6-yloxy)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)-2-(1,2,3,4-tetrahydroquinolin-6-yloxy)benzamide;

4-(4-((4'-chloro-4-(pyrrolidin-1-ylmethyl)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-pyrrolidin-1-ylethyl)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((1-cyclopentylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)-3-isobutylpiperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-(2,4-dioxo-3-azabicyclo(3.2.0)hept-3-yl)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-(3,3-dimethyl-2-oxoazetidin-1-yl)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-(4-nitro-2H-1,2,3-triazol-2-yl)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((2-(2-piperidin-1-ylethoxy)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-((((1-ethylpyrrolidin-2-yl)methyl)amino)carbonyl)-4-methoxyphenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1-naphthyloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(2-naphthyloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-(2-naphthyloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(2-naphthyloxy)-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(quinolin-7-yloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(quinolin-6-yloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(isoquinolin-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(isoquinolin-5-yloxy)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(quinolin-6-yloxy)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-4-yloxy)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-6-yloxy)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(isoquinolin-7-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(isoquinolin-7-yloxy)benzamide;
4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-4-yloxy)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-methoxyphenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-methylphenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
N-((3-((chloro(difluoro)methyl)sulfonyl)-4-((3-(dimethylamino)propyl)amino)phenyl)sulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;
2-(1H-indol-4-yloxy)-4-(4-((2-(4-methoxyphenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;
4-(4-((4,4-dimethyl-2-(4-(trifluoromethyl)phenyl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;
4-(4-((4,4-dimethyl-2-(4-(trifluoromethoxy)phenyl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;
4-(4-((4,4-dimethyl-2-(3-(trifluoromethyl)phenyl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(3-fluorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;
4-(4-((2-(4-fluorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;
N-((3-((chloro(difluoro)methyl)sulfonyl)-4-((1-methylpiperidin-4-yl)amino)phenyl)sulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-((2-(4-chlorophenyl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(phenoxymethyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(pyridin-3-yloxy)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(pyridin-3-yloxy)-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-(((1R)-3-(dimethylamino)-1-((phenylthio)methyl)propyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(pyridin-4-yloxy)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-(pyridin-3-yloxy)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-(pyridin-4-yloxy)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((2-(4-methylpiperazin-1-yl)ethyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(4-methylpiperazin-1-yl)propyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)(methyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-(((1-methylpiperidin-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-cyano-4-((3-(dimethylamino)propyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-(trifluoromethyl)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(isopropyl(methyl)amino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-(3-(dimethylamino)propoxy)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((2-(4-methylpiperazin-1-yl)ethyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((3-(4-methylpiperazin-1-yl)propyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((3-(4-methylpiperazin-1-yl)propyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-(3-(dimethylamino)propoxy)-3-nitrophenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((2-(4-methylpiperazin-1-yl)ethyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-(((1-methylpiperidin-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-(((1-methylpiperidin-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-(3-(dimethylamino)propoxy)-3-nitrophenyl)sulfonyl)-2-(1H-indol-4-yloxy)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-(4-methylpiperazin-1-yl)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((1-(2,2,2-trifluoroethyl)piperidin-4-yl)amino)phenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-(((4-(dimethylamino)-1-methylpiperidin-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(2,3-dihydro-1,4-benzodioxin-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;
5-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-1,1'-biphenyl-2-carboxamide;
5-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-1,1'-biphenyl-2-carboxamide;
4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-4-(3-piperidin-1-ylpropoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-4-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-4-(3-(dimethylamino)propoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-4-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(3-piperidin-1-ylpropoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(3-(dimethylamino)propoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-3-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-3-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((1-(2,2,2-trifluoroethyl)piperidin-4-yl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-4-(2-pyrrolidin-1-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-4-(2-(diisopropylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(2,3-dihydro-1H-indol-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)cyclohept-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)cyclooct-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)cyclopent-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclopent-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)cyclooct-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)cyclohept-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)cyclopent-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)cyclohept-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((2-(dimethylamino)ethyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((4-(dimethylamino)butyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((1-(phenylsulfonyl)piperidin-4-yl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((1-(quinolin-8-ylsulfonyl)piperidin-4-yl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((1-(phenylsulfonyl)piperidin-4-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((1-(quinolin-8-ylsulfonyl)piperidin-4-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-(((1S)-3-(dimethylamino)-1-thien-2-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((thien-2-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((2-(1H-1,2,3-triazol-1-yl)ethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((2-(2H-1,2,3-triazol-2-yl)ethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(2-naphthyloxy)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((2-(2-oxopyridin-1(2H)-yl)ethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((2-(pyridin-2-yloxy)ethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((2-pyridin-4-ylethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-(trifluoromethyl)phenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((3-cyano-4-((3-(dimethylamino)propyl)amino)phenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1*H*-indol-5-yloxy)-*N*-((3-nitro-4-((1-tetrahydro-2*H*-pyran-4-ylpiperidin-4-yl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1*H*-indol-5-yloxy)-*N*-((4-((4-methylpiperazin-1-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-(1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl)piperazin-1-yl)-2-(1*H*-indol-4-yloxy)-*N*-((3-nitro-4-((tetrahydro-2*H*-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

N-((4-(((4-aminotetrahydro-2*H*-pyran-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1*H*-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(2-methoxyethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(3S)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(3R)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-hydroxy-1-methylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-3-fluoro-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-3-fluoro-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-hydroxy-1-methylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

N-[(4-{[(3S,4R)-1-benzyl-3-hydroxypiperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

N-[(4-{[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[1-(2-methoxyethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(2-hydroxyethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[1-(2-methoxyethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(3-hydroxypropyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-[4-({4'-chloro-3-[3-(dimethylamino)propyl]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(3-hydroxypropyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-{4-[(4'-chloro-4-morpholin-4-yl-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-[4-({4'-chloro-3-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(diethylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(dimethylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(diethylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-[4-({4'-chloro-3-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-{4-[1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(dimethylamino)tetrahydro-2H-pyran-4-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;

N-({4-[(2-aminocyclohexyl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-[4-({4'-chloro-4-[3-(dimethylamino)prop-1-ynyl]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(3-nitro-4-{[1-(4,4,4-trifluorobutyl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[2-(4-hydroxy-1-methylpiperidin-4-yl)ethyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[1-(1,3-thiazol-2-yl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[4'-chloro-4-(2-hydroxyethoxy)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(cyclopropylmethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[1-(4,4,4-trifluorobutyl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide;

4-{4-[1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-(hydroxymethyl)piperazin-1-yl]-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-(hydroxymethyl)piperazin-1-yl]-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-(4-{[4'-chloro-4-(2-hydroxyethoxy)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[3-(3-oxopiperazin-1-yl)propyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(3-nitro-4-{[3-(3-oxopiperazin-1-yl)propyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-5-hydroxycyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-5-hydroxycyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-5-hydroxycyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(2,3-dihydro-1H-inden-2-yl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(2,3-dihydro-1H-inden-2-yl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(1-morpholin-4-ylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[1-(1,3-thiazol-2-ylmethyl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[1-(1,3-thiazol-4-ylmethyl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(2-hydroxyethyl)piperazin-1-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(3S)-1-methylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(3-fluoropropyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-(hydroxymethyl)piperazin-1-yl]-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

N-[(4-{[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-(hydroxymethyl)piperazin-1-yl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(2-methoxyethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-hydroxy-1-tetrahydro-2H-pyran-4-ylethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-({1-[2-(1H-pyrazol-1-yl)ethyl]piperidin-4-yl}amino)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(methylamino)-3-nitrophenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[4-(methylamino)-3-nitrophenyl]sulfonyl}benzamide;

4-{4-[1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-5-hydroxycyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-5-morpholin-4-ylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

N-[(4-{[(1-aminocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[2-(2-oxopyrrolidin-1-yl)ethyl]amino}phenyl)sulfonyl]benzamide;

4-{4-[1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{1-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]ethyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{1-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]ethyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-{4-[(1R)-1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-{4-[(1S)-1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{1-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]ethyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{1-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]ethyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(morpholin-4-ylamino)-3-nitrophenyl]sulfonyl}benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-3-ylmethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[4-(morpholin-4-ylamino)-3-nitrophenyl]sulfonyl}benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylamino)phenyl]sulfonyl}benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(3-methyloxetan-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methoxycyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(1,1-dioxidothiomorpholin-4-yl)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[2-(2-oxopiperidin-1-yl)ethyl]amino}phenyl)sulfonyl]benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[2-(2-oxoimidazolidin-1-yl)ethyl]amino}phenyl)sulfonyl]benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(2-pyridin-4-ylethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-morpholin-4-yl-3-nitrophenyl)sulfonyl]benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(4-methoxypiperidin-1-yl)-3-nitrophenyl]sulfonyl}benzamide;
4-(4-{[2-(4-chlorophenyl)-5-pyrrolidin-1-ylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[2-(3-oxopiperazin-1-yl)ethyl]amino}phenyl)sulfonyl]benzamide;

4-[4-({4'-chloro-4-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1,1-dioxidotetrahydrothien-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[2-(1,3-dioxolan-2-yl)ethyl]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(3-nitro-4-{[2-(3-oxopiperazin-1-yl)ethyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methyl-5-oxopyrrolidin-3-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methyl-6-oxopiperidin-3-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[3-nitro-4-(piperidin-1-ylamino)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(piperidin-1-ylamino)phenyl]sulfonyl}benzamide;

4-(4-{[4-(4-chlorophenyl)-1-methyl-1H-pyrazol-5-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(3-methyloxetan-3-yl)methoxy]-3-nitrophenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(1-oxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}phenyl)sulfonyl]benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1,3-thiazol-5-ylmethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}benzamide;
4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(2-tetrahydro-2H-pyran-4-ylethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(3-nitro-4-{[2-(trifluoromethoxy)ethyl]amino}phenyl)sulfonyl]benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[2-(2-methoxyethoxy)ethyl]amino}-3-nitrophenyl)sulfonyl]benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[3-(methylsulfonyl)propyl]amino}-3-nitrophenyl)sulfonyl]benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(1,1-dioxidothiomorpholin-4-yl)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(2-tetrahydro-2H-pyran-4-ylethyl)phenyl]sulfonyl}benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[2-(2-methoxyethoxy)ethyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[2-(trifluoromethoxy)ethyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2,2-difluoroethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4,4-difluorocyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-1-isopropyl-6-oxo-1,6-dihydropyridin-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(tetrahydro-2H-pyran-4-ylmethyl)amino]carbonyl}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(2-methoxyethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[3-nitro-4-(2-tetrahydro-2H-pyran-4-ylethoxy)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(2-methoxyethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[3-(methylsulfonyl)propoxy]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(3-methoxypropyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(3-methoxypropyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-cyanoethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-cyanoethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(3R)-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[Cis-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(3,3,3-trifluoropropyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(3,3,3-trifluoropropyl)amino]phenyl}sulfonyl)benzamide;
N-({5-bromo-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1,1-dioxidotetrahydrothien-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-(methylamino)-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;
N-{[5-bromo-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[4-(4-chlorophenyl)-6-isopropoxypyridin-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[6-(tetrahydro-2H-pyran-4-ylmethoxy)-5-(1,3-thiazol-2-yl)pyridin-3-yl]sulfonyl}benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(2-methoxyethyl)amino]carbonyl}phenyl)sulfonyl]benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;
N-({4-[(1-acetylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[1-(methylsulfonyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
N-({4-[(1-acetylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[1-(methylsulfonyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;
4-(4-{[4'-chloro-5-(trifluoromethyl)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[4'-chloro-5-(trifluoromethyl)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}benzamide;
4-{4-[(5-tert-butyl-4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
4-{4-[(5-tert-butyl-4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-{[(tetrahydro-2H-pyran-4-ylmethyl)amino]carbonyl}phenyl)sulfonyl]benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2R)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2S)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

N-({5-bromo-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(2-morpholin-4-ylethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)oxy]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[4-(4-chlorophenyl)-1-(3-hydroxypropyl)-1,2,5,6-tetrahydropyridin-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

benzyl 4-({[4-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzoyl]amino}sulfonyl)-2-nitrophenyl]amino}methyl)piperidine-1-carboxylate;

N-{[3-(aminocarbonyl)-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[4'-chloro-5-(trifluoromethyl)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-{4-[(5-tert-butyl-4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(1-methyl-1H-imidazol-5-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(morpholin-4-ylsulfonyl)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidothiomorpholin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

N-{[5-bromo-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-5-(1,3-thiazol-2-yl)pyridin-3-yl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3,3-dimethylbutyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1S)-1-(hydroxymethyl)-3-methylbutyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(2R)-tetrahydrofuran-2-ylmethyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1R)-1-(hydroxymethyl)-2-methylpropyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methoxyphenyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

N-[(4-{[2-(1,3-benzodioxol-5-yl)ethyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-hydroxyphenyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

N-{[4-({2-[4-(aminosulfonyl)phenyl]ethyl}amino)-3-nitrophenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(1H-imidazol-1-yl)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(1S)-1-phenylethyl]amino}phenyl)sulfonyl]benzamide;

N-({2-chloro-5-fluoro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[2-(2-methoxyethoxy)ethyl]thio}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[2-(2-methoxyethoxy)ethyl]thio}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(methylsulfonyl)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[4-(methylsulfonyl)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2,2-dimethyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(2-morpholin-4-ylethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)oxy]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-morpholin-4-ylbut-2-ynyl)oxy]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-ethynyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(2-morpholin-4-ylethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-hydroxy-4-methoxyphenyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(2,3-dihydro-1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(pyridin-3-ylamino)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)-2-(pyridin-3-ylamino)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)-2-(pyridin-3-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1,2,3,4-tetrahydroisoquinolin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-5-(trifluoromethyl)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyclopropylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4,4-difluorocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

N-[(5-chloro-6-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

Trans-N-({5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(2,2-difluoroethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-fluoro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

N-[(5-chloro-6-{[1-(cyanomethyl)-4-fluoropiperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydrofuran-3-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

Trans-N-({5-chloro-6-[(4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-[(5-chloro-6-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]oxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-N-[(5-chloro-6-{[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

2-(1H-benzimidazol-4-yloxy)-N-[(5-chloro-6-{[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

N-[(5-chloro-6-{[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-[(5-chloro-6-{[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(cyanomethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({(3R)-1-[2-(2-methoxyethoxy)ethyl]pyrrolidin-3-yl}amino)-3-nitrophenyl]sulfonyl}benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(N,N-dimethylglycyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(cyanomethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyclopropylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(4-oxetan-3-ylmorpholin-2-yl)methyl]amino}phenyl)sulfonyl]benzamide;

N-{[5-chloro-6-({(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl}oxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydrofuran-3-ylmethyl)amino]phenyl}sulfonyl)benzamide;

Trans-2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-fluoro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

N-{[5-chloro-6-({(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl}methoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-[(5-chloro-6-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(1-cyclopropylpiperidin-4-yl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-N-({5-chloro-6-[(1-cyclopropylpiperidin-4-yl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

Trans-2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-methylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[({(2R)-4-[2-(2-methoxyethoxy)ethyl]morpholin-2-yl}methyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4,4-difluorocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

N-[(4-{[(4-acetylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(methylsulfonyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[6-({4-fluoro-1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl}methoxy)-5-(trifluoromethyl)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(2-tetrahydrofuran-2-ylethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

Trans-2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyanocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-N-({5-chloro-6-[(4,4-difluorocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-*N*-{[5-cyano-6-(2-tetrahydro-2*H*-pyran-4-ylethoxy)pyridin-3-yl]sulfonyl}-2-(1*H*-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(1R,5S)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxy-4-(4-{(3-phenylpropanoyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamide;

N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-phenoxy-4-(4-{(3-phenylpropanoyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamide;

N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxy-4-(4-{(3-phenylpropyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamide;

N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-phenoxy-4-(4-{(3-phenylpropyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamide;

4-[4-(2-{[(1R,5S)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]amino}benzyl)piperazin-1-yl]-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-phenoxybenzamide;

4-[4-(2-{[(1R,5S)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]amino}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide;

4-{4-[2-(3-azabicyclo[3.2.2]non-3-yl)benzyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide;

4-{4-[2-(3-azabicyclo[3.2.2]non-3-yl)benzyl]piperazin-1-yl}-2-phenoxy-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-{4-[2-(3-azabicyclo[3.2.2]non-3-yl)benzyl]piperazin-1-yl}-2-phenoxy-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-{4-[2-(3-azabicyclo[3.2.2]non-3-yl)benzyl]piperazin-1-yl}-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-phenoxybenzamide;

4-(4-{2-[(4R,7S)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-5-yl]benzyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide;

4-[4-(2-{5-[(1R,5S)-8-azabicyclo[3.2.1]oct-8-ylmethyl]thien-2-yl}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide;

4-[4-(2-{5-[(1R,5S)-8-azabicyclo[3.2.1]oct-8-ylmethyl]thien-2-yl}benzylidene)piperidin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide;

4-[4-(3-{5-[(1R,5S)-8-azabicyclo[3.2.1]oct-8-ylmethyl]thien-2-yl}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide;

N-({5-chloro-6-[(4,4-difluorocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({6-[(trans-4-carbamoylcyclohexyl)methoxy]-5-chloropyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-cyanocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[2-(1H-imidazol-1-yl)ethoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(1-methyl-1H-imidazol-5-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-fluoro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

N-{[5-chloro-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(4,4-difluoro-1-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(2,2-difluorocyclopropyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(trans-4-cyanocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-(trifluoromethyl)phenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-chloro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

N-{[3-chloro-4-(1,4-dioxan-2-ylmethoxy)phenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-N-[(5-chloro-6-{[(2S)-4-cyclopropylmorpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

N-[(5-chloro-6-{[(2S)-4-cyclopropylmorpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

methyl 2-{[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}morpholine-4-carboxylate;

2-{[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide;

2-{[(4-{[2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide;

N-({5-chloro-6-[(trans-4-ethyl-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(cis-4-ethyl-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

5-chloro-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

5-chloro-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(cis-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(trans-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzotriazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzotriazol-4-yloxy)-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-chloro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}benzamide;

N-[(3-chloro-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(cis-1-fluoro-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzotriazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)benzamide;

N-[(5-chloro-6-{[(1R,2R,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-[(5-chloro-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzotriazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzotriazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S)-4-cyclopropylmorpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

N-[(5-chloro-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S)-4-cyclopropylmorpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S)-4-cyclopropylmorpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-cyano-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-{[3-nitro-4-(2-oxaspiro[3.5]non-7-ylmethoxy)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-cyano-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-{[3-nitro-4-({[(2S)-4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)phenyl]sulfonyl}benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-({[(2S)-4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)phenyl]sulfonyl}benzamide;

N-[(5-chloro-6-{[trans-4-(2-hydroxypropan-2-yl)cyclohexyl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]phenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-({5-nitro-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)benzamide;

2-(1H-benzotriazol-4-yloxy)-N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

N-({3-chloro-4-[(cis-4-cyano-1-fluorocyclohexyl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({3-chloro-4-[(trans-4-cyano-1-fluorocyclohexyl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(cis-4-cyano-1-fluorocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(trans-4-cyano-1-fluorocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-chloro-6-{[1-(1,3-thiazol-2-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

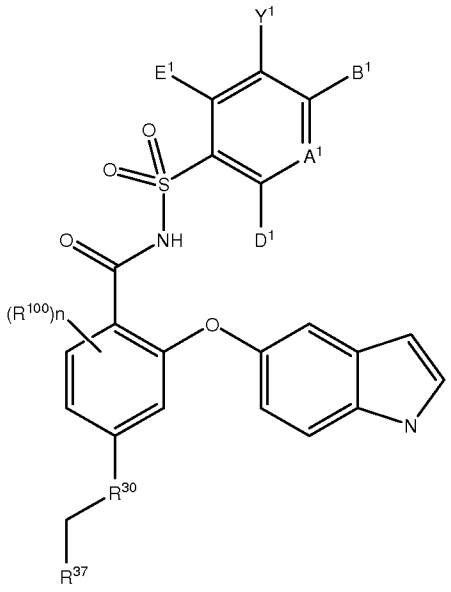
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(6-{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-5-nitropyridin-3-yl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

N-(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)-4-cyanopiperidine-1-carboxamide; and therapeutically acceptable salts, prodrugs, salts of prodrugs and metabolites thereof.

In another aspect, the present invention provides compounds of Formula (II)



(II)

and therapeutically acceptable salts, prodrugs, salts of prodrugs and metabolites thereof, wherein A^1, B^1, D^1, E^1, Y^1, R^{30}, and R^{37} are as described herein for Formula (I), n is 0, 1, 2, or 3; describing the number of substituents on R^{26}, and R^{100} is as described for substituents on R^{26}.

In one embodiment of Formula (II), A^1 is N. In another embodiment of Formula (II), A^1 is $C(A^2)$. In another embodiment of Formula (II), A^1 is $C(A^2)$, and A^2 is H.

In one embodiment of Formula (II), B^1 is R^1, OR^1, SR^1, SO_2R^1, $NHC(O)R^1$, NHR^1, $N(R^1)_2$, or $C(O)NHR^1$. In another embodiment of Formula (II), B^1 is NHR^1. In another embodiment of Formula (II), B^1 is NHR^1, and A^1 is $C(A^2)$, and A^2 is H. In another embodiment of Formula (II), B^1 is NHR^1, and A^1 is $C(A^2)$ or N, and A^2 is H. In another embodiment of Formula (II), B^1 is OR^1. In another embodiment of Formula (II), B^1 is OR^1, and A^1 is $C(A^2)$, and A^2 is H. In another embodiment of Formula (II), B^1 is OR^1. In another embodiment of Formula (II), B^1 is OR^1, and A^1 is $C(A^2)$ or N, and A^2 is H.

In one embodiment of Formula (II), D^1 and E^1 are H. In another embodiment of Formula (II), B^1 is NHR^1, and A^1 is $C(A^2)$, A^2 is H, and D^1 and E^1 are H. In another embodiment of Formula (II), B^1 is NHR^1, and A^1 is $C(A^2)$ or N, A^2 is H, and D^1 and E^1 are H.

In another embodiment of Formula (II), B^1 is OR^1, and A^1 is $C(A^2)$, A^2 is H, and D^1 and E^1 are H. In another embodiment of Formula (II), B^1 is OR^1, and A^1 is $C(A^2)$ or N, A^2 is H, and D^1 and E^1 are H.

In one embodiment of Formula (II), Y^1 is H, CN, NO_2, F, Cl, Br, I, CF_3, R^{17}, $NHC(O)R^{17}$, or $C(O)NH_2$. In another embodiment of Formula (II), Y^1 is NO_2. In another embodiment of Formula (II), Y^1 is Cl. In another embodiment of Formula (II), B^1 is NHR^1, and A^1 is $C(A^2)$, A^2 is H, D^1 and E^1 are H, and Y^1 is NO_2. In another embodiment of Formula (II), B^1 is NHR^1, and A^1 is $C(A^2)$ or N, A^2 is H, D^1 and E^1 are H, and Y^1 is NO_2. In another embodiment of Formula (II), B^1 is OR^1, and A^1 is $C(A^2)$, A^2 is H, D^1 and E^1 are H, and Y^1 is Cl. In another embodiment of Formula (II), B^1 is OR^1, and A^1 is $C(A^2)$ or N, A^2 is H, D^1 and E^1 are H, and Y^1 is Cl.

In one embodiment of Formula (II), R^1 is R^2, R^3, R^4 or R^5. In another embodiment of Formula (II), R^1 is R^2, and R^2 is phenyl.

In one embodiment of Formula (II), R^1 is R^3, and R^3 is heteroaryl. In another embodiment of Formula (II), R^3 is triazolyl.

In one embodiment of Formula (II), R^1 is R^4. In another embodiment of Formula (II), R^1 is R^4, and R^4 is cycloalkyl. In another embodiment of Formula (II), R^1 is R^4, and R^4 is cyclohexyl. In another embodiment of Formula (II), R^1 is R^4, and R^4 is heterocycloalkyl. In another embodiment of Formula (II), R^1 is R^4, and R^4 is 8-azabicyclo[3.2.1]octane, azetidinyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydropyranyl, or tetrahydrothiophenyl. In another embodiment of Formula (II), R^1 is R^4, and R^4 is heterocycloalkenyl. In another embodiment of Formula (II), R^1 is R^4, and R^4 is tetrahydropyridazinyl.

In one embodiment of Formula (II), R^1 is R^5. In another embodiment of Formula (II), R^1 is R^5 and R^5 is alkyl or alkynyl. In another embodiment of Formula (II), R^1 is R^5 and R^5 is alkyl which is unsubstituted. In another embodiment of Formula (II), R^1 is R^5 and R^5 is alkyl which is substituted with one or two or three independently selected R^6, R^7, OR^7, SR^7, SO_2R^7, $N(R^7)_2$, OH, CN, CF_3, F, Cl, Br or I substituents. In another embodiment of Formula (II), R^1 is R^5 and R^5 is alkyl which is substituted with R^7.

In one embodiment of Formula (II), R^7 is R^8, R^9, R^{10} or R^{11}. In another embodiment of Formula (II), R^7 is R^8, and R^8 is phenyl which is unfused or fused with R^{8A}, and R^{8A} is heterocycloalkane. In another embodiment of Formula (II), R^7 is R^8, and R^8 is phenyl which is unfused. In another embodiment of Formula (II), R^7 is R^9, and R^9 is heteroaryl. In another embodiment of Formula (II), R^7 is R^9, and R^9 is furanyl, imidazolyl, isothiazolyl, isoxazolyl,

1,2,3-oxadiazoyl, 1,2,5-oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrazolyl, thiazolyl, thiophenyl, triazinyl or 1,2,3-triazolyl. In another embodiment of Formula (II), R^7 is R^9, and R^9 is pyridinyl, thiazolyl, imidazoyl, and 1,2,3-triazolyl. In another embodiment of Formula (II), R^7 is R^{10}, and R^{10} is C_3-C_{10}-cycloalkyl. In another embodiment of Formula (II), R^7 is R^{10}, and R^{10} is C_3, C_6, C_7 or C_{10}-cycloalkyl. In another embodiment of Formula (II), R^7 is R^{10}, and R^{10} is cyclopropyl, cyclohexyl, bicyclo[2.2.1]heptanyl, or adamantanyl. In another embodiment of Formula (II), R^7 is R^{10}, and R^{10} is morpholinyl, piperazinyl, piperidinyl, tetrahydro-2H-pyranyl, 1,2-dihydropyridinyl, pyranyl, pyridin-1(H)-yl, pyrrolidinyl, oxetanyl, thiomorpholinyl, imidazolidinyl, tetrahydrothiophenyl, dioxolanyl, tetrahydrothiopyranyl, dioxanyl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl, or tetrahydrofuranyl. In another embodiment of Formula (II), R^7 is R^{10}, and R^{10} is morpholinyl, piperazinyl, piperidinyl, tetrahydro-2H-pyranyl, 1,2-dihydropyridinyl, pyrrolidinyl, oxetanyl, thiomorpholinyl, imidazolidinyl, tetrahydrothiophenyl, dioxolanyl, tetrahydrothiopyranyl, dioxanyl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl, or tetrahydrofuranyl. In another embodiment of Formula (II), R^7 is R^{11}, and R^{11} is alkyl which is unsubstituted or substituted. In another embodiment of Formula (II), R^7 is R^{11}, and R^{11} is alkyl which is unsubstituted. In another embodiment of Formula (II), R^7 is R^{11}, and R^{11} is alkyl which is substituted. In another embodiment of Formula (II), R^7 is R^{11}, and R^{11} is alkyl which is substituted with one or two or three independently selected OR^{12}, F, Cl, Br or I substituents. In another embodiment of Formula (II), R^7 is R^{11}, R^{11} is alkyl which is substituted with OR^{12}, R^{12} is R^{16}, and R^{16} is alkyl.

In one embodiment of Formula (II), R^{17} is R^{19} or R^{21}. In another embodiment of Formula (II), R^{17} is R^{19}, and R^{19} is heteroaryl. In another embodiment of Formula (II), R^{17} is R^{19}, and R^{19} is thiazolyl. In another embodiment of Formula (II), R^{17} is R^{21}, and R^{21} is alkynyl. In another embodiment of Formula (II), R^{17} is R^{21}, and R^{21} is ethynyl.

Still another embodiment pertains to compounds having Formula II which are 4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((1-cyclopentylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide 4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide; 4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide; 4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
N-((3-((chloro(difluoro)methyl)sulfonyl)-4-((3-(dimethylamino)propyl)amino)phenyl)sulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;
N-((3-((chloro(difluoro)methyl)sulfonyl)-4-((1-methylpiperidin-4-yl)amino)phenyl)sulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-((2-(4-chlorophenyl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((2-(4-methylpiperazin-1-yl)ethyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((3-(4-methylpiperazin-1-yl)propyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-(3-(dimethylamino)propoxy)-3-nitrophenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-(((1-methylpiperidin-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-(4-methylpiperazin-1-yl)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-(((4-(dimethylamino)-1-methylpiperidin-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-4-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-3-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-4-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(2,3-dihydro-1H-indol-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)cyclohept-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-(trifluoromethyl)phenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((3-cyano-4-((3-(dimethylamino)propyl)amino)phenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1*H*-indol-5-yloxy)-*N*-((3-nitro-4-((1-tetrahydro-2*H*-pyran-4-ylpiperidin-4-yl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1*H*-indol-5-yloxy)-*N*-((4-((4-methylpiperazin-1-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(2-methoxyethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(3S)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(3R)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-hydroxy-1-methylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-3-fluoro-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-3-fluoro-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

N-[(4-{[(3S,4R)-1-benzyl-3-hydroxypiperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

N-[(4-{[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[1-(2-methoxyethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-5-fluoro-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-5-fluoro-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(3-hydroxypropyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(diethylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(dimethylamino)tetrahydro-2H-pyran-4-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;

N-({4-[(2-aminocyclohexyl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[2-(4-hydroxy-1-methylpiperidin-4-yl)ethyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[1-(1,3-thiazol-2-yl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(cyclopropylmethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[1-(4,4,4-trifluorobutyl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide;

4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-(hydroxymethyl)piperazin-1-yl]-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-(hydroxymethyl)piperazin-1-yl]-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[3-(3-oxopiperazin-1-yl)propyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-5-hydroxycyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-5-hydroxycyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-5-hydroxycyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(2,3-dihydro-1H-inden-2-yl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(1-morpholin-4-ylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[1-(1,3-thiazol-2-ylmethyl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[1-(1,3-thiazol-4-ylmethyl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(2-hydroxyethyl)piperazin-1-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(3S)-1-methylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(3-fluoropropyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-(hydroxymethyl)piperazin-1-yl]-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

N-[(4-{[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-(hydroxymethyl)piperazin-1-yl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-hydroxy-1-tetrahydro-2H-pyran-4-ylethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-({1-[2-(1H-pyrazol-1-yl)ethyl]piperidin-4-yl}amino)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(methylamino)-3-nitrophenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-5-hydroxycyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-5-morpholin-4-ylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

N-[(4-{[(1-aminocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[2-(2-oxopyrrolidin-1-yl)ethyl]amino}phenyl)sulfonyl]benzamide;

4-{4-[1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{1-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]ethyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{1-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]ethyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;
4-(4-{1-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]ethyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide;
4-(4-{1-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]ethyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(morpholin-4-ylamino)-3-nitrophenyl]sulfonyl}benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-3-ylmethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylamino)phenyl]sulfonyl}benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(3-methyloxetan-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methoxycyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(1,1-dioxidothiomorpholin-4-yl)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[2-(2-oxopiperidin-1-yl)ethyl]amino}phenyl)sulfonyl]benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[2-(2-oxoimidazolidin-1-yl)ethyl]amino}phenyl)sulfonyl]benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(2-pyridin-4-ylethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-morpholin-4-yl-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(4-methoxypiperidin-1-yl)-3-nitrophenyl]sulfonyl}benzamide;
4-(4-{[2-(4-chlorophenyl)-5-pyrrolidin-1-ylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[2-(3-oxopiperazin-1-yl)ethyl]amino}phenyl)sulfonyl]benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1,1-dioxidotetrahydrothien-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl]sulfonyl}benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[2-(1,3-dioxolan-2-yl)ethyl]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methyl-5-oxopyrrolidin-3-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methyl-6-oxopiperidin-3-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(piperidin-1-ylamino)phenyl]sulfonyl}benzamide;
4-(4-{[4-(4-chlorophenyl)-1-methyl-1H-pyrazol-5-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(3-methyloxetan-3-yl)methoxy]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(1-oxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1,3-thiazol-5-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(2-tetrahydro-2H-pyran-4-ylethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(2-tetrahydro-2H-pyran-4-ylethyl)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[2-(2-methoxyethoxy)ethyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[2-(trifluoromethoxy)ethyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2,2-difluoroethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4,4-difluorocyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-1-isopropyl-6-oxo-1,6-dihydropyridin-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(tetrahydro-2H-pyran-4-ylmethyl)amino]carbonyl}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(2-methoxyethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(3-methoxypropyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-cyanoethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(3R)-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(3R)-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(3,3,3-trifluoropropyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-(methylamino)-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

N-{[5-bromo-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6-isopropoxypyridin-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[6-(tetrahydro-2H-pyran-4-ylmethoxy)-5-(1,3-thiazol-2-yl)pyridin-3-yl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(2-methoxyethyl)amino]carbonyl}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;

N-({4-[(1-acetylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[1-(methylsulfonyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[4'-chloro-5-(trifluoromethyl)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[4'-chloro-5-(trifluoromethyl)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}benzamide;

4-{4-[(5-tert-butyl-4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-{4-[(5-tert-butyl-4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-{[(tetrahydro-2H-pyran-4-ylmethyl)amino]carbonyl}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2R)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2S)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;
N-({5-bromo-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(2-morpholin-4-ylethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)oxy]-3-nitrophenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)benzamide;
benzyl 4-({[4-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzoyl]amino}sulfonyl)-2-nitrophenyl]amino}methyl)piperidine-1-carboxylate;
N-{[3-(aminocarbonyl)-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[4'-chloro-5-(trifluoromethyl)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;
4-{4-[(5-tert-butyl-4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(1-methyl-1H-imidazol-5-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(morpholin-4-ylsulfonyl)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidothiomorpholin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3,3-dimethylbutyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1S)-1-(hydroxymethyl)-3-methylbutyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(2R)-tetrahydrofuran-2-ylmethyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1R)-1-(hydroxymethyl)-2-methylpropyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methoxyphenyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

N-[(4-{[2-(1,3-benzodioxol-5-yl)ethyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-hydroxyphenyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

N-{[4-({2-[4-(aminosulfonyl)phenyl]ethyl}amino)-3-nitrophenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(1H-imidazol-1-yl)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(1S)-1-phenylethyl]amino}phenyl)sulfonyl]benzamide;

N-({2-chloro-5-fluoro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[2-(2-methoxyethoxy)ethyl]thio}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(methylsulfonyl)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2,2-dimethyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(2-morpholin-4-ylethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)oxy]phenyl}sulfonyl)benzamide;

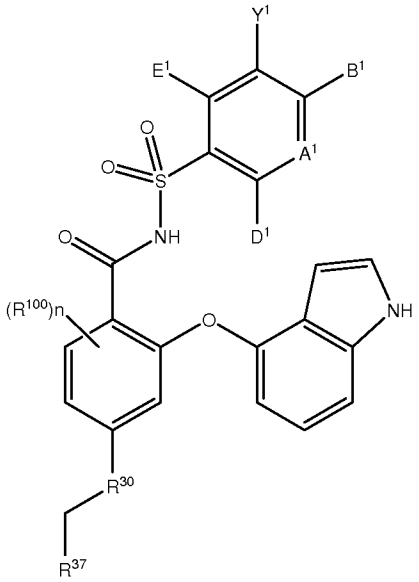
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-morpholin-4-ylbut-2-ynyl)oxy]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-hydroxy-4-methoxyphenyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(1R,5S)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]amino}-3-

nitrophenyl)sulfonyl]benzamide;and therapeutically acceptable salts, prodrugs, salts of prodrugs and metabolites thereof.

In another aspect, the present invention provides compounds of Formula (III)



(III)

and therapeutically acceptable salts, prodrugs, salts of prodrugs and metabolites thereof, wherein A^1, B^1, D^1, E^1, Y^1, R^{30}, and R^{37} are as described herein for Formula (I), n is 0, 1, 2, or 3; describing the number of substituents on R^{26}, and R^{100} is as described for substituents on R^{26}.

In one embodiment of Formula (III), A^1 is N. In another embodiment of Formula (III), A^1 is $C(A^2)$. In another embodiment of Formula (III), A^1 is $C(A^2)$, and A^2 is H.

In one embodiment of Formula (III), B^1 is R^1, OR^1, SR^1, SO_2R^1, $NHC(O)R^1$, NHR^1, $N(R^1)_2$, or $C(O)NHR^1$. In another embodiment of Formula (III), B^1 is NHR^1. In another embodiment of Formula (III), B^1 is NHR^1, and A^1 is $C(A^2)$, and A^2 is H. In another embodiment of Formula (III), B^1 is NHR^1, and A^1 is $C(A^2)$ or N, and A^2 is H. In another embodiment of Formula (III), B^1 is OR^1. In another embodiment of Formula (III), B^1 is OR^1, and A^1 is $C(A^2)$, and A^2 is H. In another embodiment of Formula (III), B^1 is OR^1, and A^1 is $C(A^2)$ or N, and A^2 is H.

In one embodiment of Formula (III), D^1 and E^1 are H. In another embodiment of Formula (III), B^1 is NHR^1, and A^1 is $C(A^2)$, A^2 is H, and D^1 and E^1 are H. In another embodiment of Formula (III), B^1 is NHR^1, and A^1 is $C(A^2)$ or N, A^2 is H, and D^1 and E^1 are H. In another embodiment of Formula (III), B^1 is OR^1, and A^1 is $C(A^2)$, A^2 is H, and D^1 and

E^1 are H. In another embodiment of Formula (III), B^1 is OR^1, and A^1 is $C(A^2)$ or N, A^2 is H, and D^1 and E^1 are H.

In one embodiment of Formula (III), Y^1 is H, CN, NO_2, F, Cl, Br, I, CF_3, R^{17}, $NHC(O)R^{17}$, or $C(O)NH_2$. In another embodiment of Formula (III), Y^1 is NO_2. In another embodiment of Formula (III), Y^1 is Cl. In another embodiment of Formula (III), B^1 is NHR^1, and A^1 is $C(A^2)$, A^2 is H, D^1 and E^1 are H, and Y^1 is NO_2. In another embodiment of Formula (III), B^1 is NHR^1, and A^1 is $C(A^2)$ or N, A^2 is H, D^1 and E^1 are H, and Y^1 is NO_2. In another embodiment of Formula (III), B^1 is OR^1, and A^1 is $C(A^2)$, A^2 is H, D^1 and E^1 are H, and Y^1 is Cl. In another embodiment of Formula (III), B^1 is OR^1, and A^1 is $C(A^2)$ or N, A^2 is H, D^1 and E^1 are H, and Y^1 is Cl.

In one embodiment of Formula (III), R^1 is R^2, R^3, R^4 or R^5. In another embodiment of Formula (III), R^1 is R^2, and R^2 is phenyl.

In one embodiment of Formula (III), R^1 is R^3, and R^3 is heteroaryl. In another embodiment of Formula (III), R^3 is triazolyl.

In one embodiment of Formula (III), R^1 is R^4. In another embodiment of Formula (III), R^1 is R^4, and R^4 is cycloalkyl. In another embodiment of Formula (III), R^1 is R^4, and R^4 is cyclohexyl. In another embodiment of Formula (III), R^1 is R^4, and R^4 is heterocycloalkyl. In another embodiment of Formula (III), R^1 is R^4, and R^4 is 8-azabicyclo[3.2.1]octane, azetidinyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydropyranyl, or tetrahydrothiophenyl. In another embodiment of Formula (III), R^1 is R^4, and R^4 is heterocycloalkenyl. In another embodiment of Formula (III), R^1 is R^4, and R^4 is tetrahydropyridazinyl.

In one embodiment of Formula (III), R^1 is R^5. In another embodiment of Formula (III), R^1 is R^5 and R^5 is alkyl or alkynyl. In another embodiment of Formula (III), R^1 is R^5 and R^5 is alkyl which is unsubstituted. In another embodiment of Formula (III), R^1 is R^5 and R^5 is alkyl which is substituted with one or two or three independently selected R^6, R^7, OR^7, SR^7, SO_2R^7, $N(R^7)_2$, OH, CN, CF_3, F, Cl, Br or I substituents. In another embodiment of Formula (III), R^1 is R^5 and R^5 is alkyl which is substituted with R^7.

In one embodiment of Formula (III), R^7 is R^8, R^9, R^{10} or R^{11}. In another embodiment of Formula (III), R^7 is R^8, and R^8 is phenyl which is unfused or fused with R^{8A}, and R^{8A} is heterocycloalkane. In another embodiment of Formula (III), R^7 is R^8, and R^8 is phenyl which is unfused. In another embodiment of Formula (III), R^7 is R^9, and R^9 is heteroaryl. In another embodiment of Formula (III), R^7 is R^9, and R^9 is furanyl, imidazolyl, isothiazolyl, isoxazolyl, 1,2,3-oxadiazoyl, 1,2,5-oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl,

pyrimidinyl, pyrrolyl, tetrazolyl, thiazolyl, thiophenyl, triazinyl or 1,2,3-triazolyl. In another embodiment of Formula (III), R^7 is R^9, and R^9 is pyridinyl, thiazolyl, imidazoyl, and 1,2,3-triazolyl. In another embodiment of Formula (III), R^7 is R^{10}, and R^{10} is C_3-C_{10}-cycloalkyl. In another embodiment of Formula (III), R^7 is R^{10}, and R^{10} is C_3, C_6, C_7 or C_{10}-cycloalkyl. In another embodiment of Formula (III), R^7 is R^{10}, and R^{10} is cyclopropyl, cyclohexyl, bicyclo[2.2.1]heptanyl, or adamantanyl. In another embodiment of Formula (III), R^7 is R^{10}, and R^{10} is morpholinyl, piperazinyl, piperidinyl, tetrahydro-2H-pyranyl, 1,2-dihydropyridinyl, pyranyl, pyridin-1(H)-yl, pyrrolidinyl, oxetanyl, thiomorpholinyl, imidazolidinyl, tetrahydrothiophenyl, dioxolanyl, tetrahydrothiopyranyl, dioxanyl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl, or tetrahydrofuranyl. In another embodiment of Formula (III), R^7 is R^{10}, and R^{10} is morpholinyl, piperazinyl, piperidinyl, tetrahydro-2H-pyranyl, 1,2-dihydropyridinyl, pyrrolidinyl, oxetanyl, thiomorpholinyl, imidazolidinyl, tetrahydrothiophenyl, dioxolanyl, tetrahydrothiopyranyl, dioxanyl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl, or tetrahydrofuranyl. In another embodiment of Formula (III), R^7 is R^{11}, and R^{11} is alkyl which is unsubstituted or substituted. In another embodiment of Formula (III), R^7 is R^{11}, and R^{11} is alkyl which is unsubstituted. In another embodiment of Formula (III), R^7 is R^{11}, and R^{11} is alkyl which is substituted. In another embodiment of Formula (III), R^7 is R^{11}, and R^{11} is alkyl which is substituted with one or two or three independently selected OR^{12}, F, Cl, Br or I substituents. In another embodiment of Formula (III), R^7 is R^{11}, R^{11} is alkyl which is substituted with OR^{12}, R^{12} is R^{16}, and R^{16} is alkyl.

In one embodiment of Formula (III), R^{17} is R^{19} or R^{21}. In another embodiment of Formula (III), R^{17} is R^{19}, and R^{19} is heteroaryl. In another embodiment of Formula (III), R^{17} is R^{19}, and R^{19} is thiazolyl. In another embodiment of Formula (III), R^{17} is R^{21}, and R^{21} is alkynyl. In another embodiment of Formula (III), R^{17} is R^{21}, and R^{21} is ethynyl.

Still another embodiment pertains to compounds having Formula (III) which are

4-(4-((4'-chloro-4-(pyrrolidin-1-ylmethyl)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-pyrrolidin-1-ylethyl)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-4-yloxy)benzamide;
4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-4-yloxy)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-4-yloxy)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
2-(1H-indol-4-yloxy)-4-(4-((2-(4-methoxyphenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;
4-(4-((4,4-dimethyl-2-(4-(trifluoromethyl)phenyl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;
4-(4-((4,4-dimethyl-2-(4-(trifluoromethoxy)phenyl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;
4-(4-((4,4-dimethyl-2-(3-(trifluoromethyl)phenyl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;
4-(4-((2-(3-fluorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;
4-(4-((2-(4-fluorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((3-(4-methylpiperazin-1-yl)propyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((2-(4-methylpiperazin-1-yl)ethyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-(((1-methylpiperidin-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-(3-(dimethylamino)propoxy)-3-nitrophenyl)sulfonyl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((1-(2,2,2-trifluoroethyl)piperidin-4-yl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-3-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)cyclohept-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)cyclooct-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)cyclopent-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclopent-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)cyclooct-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)cyclohept-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)cyclopent-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-(1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl)piperazin-1-yl)-2-(1*H*-indol-4-yloxy)-*N*-((3-nitro-4-((tetrahydro-2*H*-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

N-((4-(((4-aminotetrahydro-2*H*-pyran-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1*H*-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-hydroxy-1-methylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(2-hydroxyethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[1-(2-methoxyethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(3-hydroxypropyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-[4-({4'-chloro-3-[3-(dimethylamino)propyl]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-{4-[(4'-chloro-4-morpholin-4-yl-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-[4-({4'-chloro-3-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-{4-[1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(dimethylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(diethylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-[4-({4'-chloro-3-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-{4-[1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-[4-({4'-chloro-4-[3-(dimethylamino)prop-1-ynyl]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(3-nitro-4-{[1-(4,4,4-trifluorobutyl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[4'-chloro-4-(2-hydroxyethoxy)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-{4-[1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[4'-chloro-4-(2-hydroxyethoxy)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(3-nitro-4-{[3-(3-oxopiperazin-1-yl)propyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(2,3-dihydro-1H-inden-2-yl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(2-methoxyethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[4-(methylamino)-3-nitrophenyl]sulfonyl}benzamide;

4-{4-[1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-{4-[(1R)-1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-{4-[(1S)-1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[4-(morpholin-4-ylamino)-3-nitrophenyl]sulfonyl}benzamide;

4-[4-({4'-chloro-4-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(3-nitro-4-{[2-(3-oxopiperazin-1-yl)ethyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[3-nitro-4-(piperidin-1-ylamino)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(3-nitro-4-{[2-(trifluoromethoxy)ethyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[2-(2-methoxyethoxy)ethyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[3-(methylsulfonyl)propyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(1,1-dioxidothiomorpholin-4-yl)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(2-methoxyethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[3-nitro-4-(2-tetrahydro-2H-pyran-4-ylethoxy)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[3-(methylsulfonyl)propoxy]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(3-methoxypropyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-cyanoethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(3,3,3-trifluoropropyl)amino]phenyl}sulfonyl)benzamide;

N-({5-bromo-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1,1-dioxidotetrahydrothien-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

N-({4-[(1-acetylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[1-(methylsulfonyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-(4-{[4-(4-chlorophenyl)-1-(3-hydroxypropyl)-1,2,5,6-tetrahydropyridin-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

N-{[5-bromo-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-5-(1,3-thiazol-2-yl)pyridin-3-yl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[2-(2-methoxyethoxy)ethyl]thio}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[4-(methylsulfonyl)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-4-yloxy)benzamide;

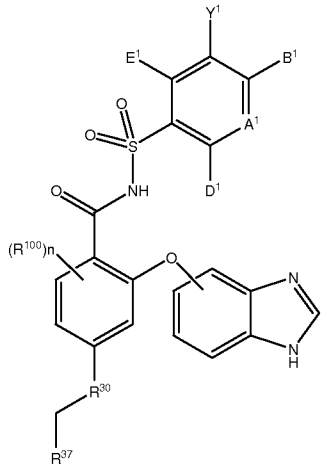
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-ethynyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(2-morpholin-4-ylethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-indol-4-yloxy)benzamide;

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)benzamide; and therapeutically acceptable salts, prodrugs, salts of prodrugs and metabolites thereof.

In another aspect, the present invention provides compounds of Formula (IV)



(IV)

and therapeutically acceptable salts, prodrugs, salts of prodrugs and metabolites thereof, wherein A^1, B^1, D^1, E^1, Y^1, R^{30}, and R^{37} are as described herein for Formula (I), n is 0, 1, 2, or 3; describing the number of substituents on R^{26}, and R^{100} is as described for substituents on R^{26}.

In one embodiment of Formula (IV), A^1 is N. In another embodiment of Formula (IV), A^1 is $C(A^2)$. In another embodiment of Formula (IV), A^1 is $C(A^2)$, and A^2 is H.

In one embodiment of Formula (IV), B^1 is R^1, OR^1, SR^1, SO_2R^1, $NHC(O)R^1$, NHR^1, $N(R^1)_2$, or $C(O)NHR^1$. In another embodiment of Formula (IV), B^1 is NHR^1. In another embodiment of Formula (IV), B^1 is NHR^1, and A^1 is $C(A^2)$, and A^2 is H. In another embodiment of Formula (IV), B^1 is NHR^1, and A^1 is $C(A^2)$ or N, and A^2 is H. In another embodiment of Formula (IV), B^1 is OR^1. In another embodiment of Formula (IV), B^1 is OR^1, and A^1 is $C(A^2)$, and A^2 is H. In another embodiment of Formula (IV), B^1 is OR^1, and A^1 is $C(A^2)$ or N, and A^2 is H.

In one embodiment of Formula (IV), D^1 and E^1 are H. In another embodiment of Formula (IV), B^1 is NHR^1, and A^1 is $C(A^2)$, A^2 is H, and D^1 and E^1 are H. In another embodiment of Formula (IV), B^1 is NHR^1, and A^1 is $C(A^2)$ or N, A^2 is H, and D^1 and E^1 are H. In another embodiment of Formula (IV), B^1 is OR^1, and A^1 is $C(A^2)$, A^2 is H, and D^1 and E^1 are H. In another embodiment of Formula (IV), B^1 is OR^1, and A^1 is $C(A^2)$ or N, A^2 is H, and D^1 and E^1 are H.

In one embodiment of Formula (IV), Y^1 is H, CN, NO_2, F, Cl, Br, I, CF_3, R^{17}, $NHC(O)R^{17}$, or $C(O)NH_2$. In another embodiment of Formula (IV), Y^1 is NO_2. In another embodiment of Formula (IV), Y^1 is Cl. In another embodiment of Formula (IV), B^1 is NHR^1,

and A^1 is $C(A^2)$, A^2 is H, D^1 and E^1 are H, and Y^1 is NO_2. In another embodiment of Formula (IV), B^1 is NHR^1, and A^1 is $C(A^2)$ or N, A^2 is H, D^1 and E^1 are H, and Y^1 is NO_2. In another embodiment of Formula (IV), B^1 is OR^1, and A^1 is $C(A^2)$, A^2 is H, D^1 and E^1 are H, and Y^1 is Cl. In another embodiment of Formula (IV), B^1 is OR^1, and A^1 is $C(A^2)$ or N, A^2 is H, D^1 and E^1 are H, and Y^1 is Cl.

In one embodiment of Formula (IV), R^1 is R^2, R^3, R^4 or R^5. In another embodiment of Formula (IV), R^1 is R^2, and R^2 is phenyl.

In one embodiment of Formula (IV), R^1 is R^3, and R^3 is heteroaryl. In another embodiment of Formula (IV), R^3 is triazolyl.

In one embodiment of Formula (IV), R^1 is R^4. In another embodiment of Formula (IV), R^1 is R^4, and R^4 is cycloalkyl. In another embodiment of Formula (IV), R^1 is R^4, and R^4 is cyclohexyl. In another embodiment of Formula (IV), R^1 is R^4, and R^4 is heterocycloalkyl. In another embodiment of Formula (IV), R^1 is R^4, and R^4 is 8-azabicyclo[3.2.1]octane, azetidinyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydropyranyl, or tetrahydrothiophenyl. In another embodiment of Formula (IV), R^1 is R^4, and R^4 is heterocycloalkenyl. In another embodiment of Formula (IV), R^1 is R^4, and R^4 is tetrahydropyridazinyl.

In one embodiment of Formula (IV), R^1 is R^5. In another embodiment of Formula (IV), R^1 is R^5 and R^5 is alkyl or alkynyl. In another embodiment of Formula (IV), R^1 is R^5 and R^5 is alkyl which is unsubstituted. In another embodiment of Formula (IV), R^1 is R^5 and R^5 is alkyl which is substituted with one or two or three independently selected R^6, R^7, OR^7, SR^7, SO_2R^7, $N(R^7)_2$, OH, CN, CF_3, F, Cl, Br or I substituents. In another embodiment of Formula (IV), R^1 is R^5 and R^5 is alkyl which is substituted with R^7.

In one embodiment of Formula (IV), R^7 is R^8, R^9, R^{10} or R^{11}. In another embodiment of Formula (IV), R^7 is R^8, and R^8 is phenyl which is unfused or fused with R^{8A}, and R^{8A} is heterocycloalkane. In another embodiment of Formula (IV), R^7 is R^8, and R^8 is phenyl which is unfused. In another embodiment of Formula (IV), R^7 is R^9, and R^9 is heteroaryl. In another embodiment of Formula (IV), R^7 is R^9, and R^9 is furanyl, imidazolyl, isothiazolyl, isoxazolyl, 1,2,3-oxadiazoyl, 1,2,5-oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrazolyl, thiazolyl, thiophenyl, triazinyl or 1,2,3-triazolyl. In another embodiment of Formula (IV), R^7 is R^9, and R^9 is pyridinyl, thiazolyl, imidazoyl, and 1,2,3-triazolyl. In another embodiment of Formula (IV), R^7 is R^{10}, and R^{10} is C_3-C_{10}-cycloalkyl. In another embodiment of Formula (IV), R^7 is R^{10}, and R^{10} is C_3, C_6, C_7 or C_{10}-cycloalkyl. In another embodiment of Formula (IV), R^7 is R^{10}, and R^{10} is cyclopropyl,

cyclohexyl, bicyclo[2.2.1]heptanyl, or adamantanyl. In another embodiment of Formula (IV), R^7 is R^{10}, and R^{10} is morpholinyl, piperazinyl, piperidinyl, tetrahydro-2H-pyranyl, 1,2-dihydropyridinyl, pyranyl, pyridin-1(H)-yl, pyrrolidinyl, oxetanyl, thiomorpholinyl, imidazolidinyl, tetrahydrothiophenyl, dioxolanyl, tetrahydrothiopyranyl, dioxanyl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl, or tetrahydrofuranyl. In another embodiment of Formula (IV), R^7 is R^{10}, and R^{10} is morpholinyl, piperazinyl, piperidinyl, tetrahydro-2H-pyranyl, 1,2-dihydropyridinyl, pyrrolidinyl, oxetanyl, thiomorpholinyl, imidazolidinyl, tetrahydrothiophenyl, dioxolanyl, tetrahydrothiopyranyl, dioxanyl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl, or tetrahydrofuranyl. In another embodiment of Formula (IV), R^7 is R^{11}, and R^{11} is alkyl which is unsubstituted or substituted. In another embodiment of Formula (IV), R^7 is R^{11}, and R^{11} is alkyl which is unsubstituted. In another embodiment of Formula (IV), R^7 is R^{11}, and R^{11} is alkyl which is substituted. In another embodiment of Formula (IV), R^7 is R^{11}, and R^{11} is alkyl which is substituted with one or two or three independently selected OR^{12}, F, Cl, Br or I substituents. In another embodiment of Formula (IV), R^7 is R^{11}, R^{11} is alkyl which is substituted with OR^{12}, R^{12} is R^{16}, and R^{16} is alkyl.

In one embodiment of Formula (IV), R^{17} is R^{19} or R^{21}. In another embodiment of Formula (IV), R^{17} is R^{19}, and R^{19} is heteroaryl. In another embodiment of Formula (IV), R^{17} is R^{19}, and R^{19} is thiazolyl. In another embodiment of Formula (IV), R^{17} is R^{21}, and R^{21} is alkynyl. In another embodiment of Formula (IV), R^{17} is R^{21}, and R^{21} is ethynyl.

Still another embodiment pertains to compounds having Formula (IV) which are

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(2,2-difluoroethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-N-[(5-chloro-6-{[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

2-(1H-benzimidazol-4-yloxy)-N-[(5-chloro-6-{[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(cyanomethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({(3R)-1-[2-(2-methoxyethoxy)ethyl]pyrrolidin-3-yl}amino)-3-nitrophenyl]sulfonyl}benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(N,N-dimethylglycyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(cyanomethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyclopropylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(4-oxetan-3-ylmorpholin-2-yl)methyl]amino}phenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydrofuran-3-ylmethyl)amino]phenyl}sulfonyl)benzamide;

Trans-2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-fluoro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

2-(1H-benzimidazol-4-yloxy)-N-({5-chloro-6-[(1-cyclopropylpiperidin-4-yl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

Trans-2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-methylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[({(2R)-4-[2-(2-methoxyethoxy)ethyl]morpholin-2-yl}methyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4,4-difluorocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

N-[(4-{[(4-acetylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(methylsulfonyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

Trans-2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyanocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-N-({5-chloro-6-[(4,4-difluorocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

2-(1H-benzimidazol-4-yloxy)-N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}benzamide;

2-(1H-benzimidazol-4-yloxy)-N-[(5-chloro-6-{[(2S)-4-cyclopropylmorpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

2-{[(4-{[2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-chloro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S)-4-cyclopropylmorpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

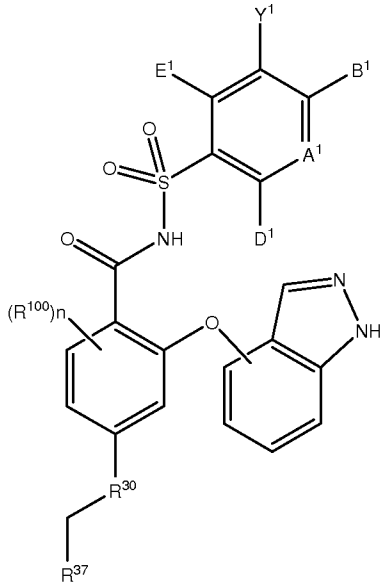
2-(1H-benzimidazol-4-yloxy)-N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-({[(2S)-4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)phenyl]sulfonyl}benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;and therapeutically acceptable salts, prodrugs, salts of prodrugs and metabolites thereof.

In another aspect, the present invention provides compounds of Formula (V)



(V)

and therapeutically acceptable salts, prodrugs, salts of prodrugs and metabolites thereof, wherein A^1, B^1, D^1, E^1, Y^1, R^{30}, and R^{37} are as described herein for Formula (I), n is 0, 1, 2, or 3; describing the number of substituents on R^{26}, and R^{100} is as described for substituents on R^{26}.

In one embodiment of Formula (V), A^1 is N. In another embodiment of Formula (V), A^1 is $C(A^2)$. In another embodiment of Formula (V), A^1 is $C(A^2)$, and A^2 is H.

In one embodiment of Formula (V), B^1 is R^1, OR^1, SR^1, SO_2R^1, $NHC(O)R^1$, NHR^1, $N(R^1)_2$, or $C(O)NHR^1$. In another embodiment of Formula (V), B^1 is NHR^1. In another embodiment of Formula (V), B^1 is NHR^1, and A^1 is $C(A^2)$, and A^2 is H. In another embodiment of Formula (V), B^1 is NHR^1, and A^1 is $C(A^2)$ or N, and A^2 is H. In another embodiment of Formula (V), B^1 is OR^1. In another embodiment of Formula (V), B^1 is OR^1, and A^1 is $C(A^2)$, and A^2 is H. In another embodiment of Formula (V), B^1 is OR^1, and A^1 is $C(A^2)$ or N, and A^2 is H.

In one embodiment of Formula (V), D^1 and E^1 are H. In another embodiment of Formula (V), B^1 is NHR^1, and A^1 is $C(A^2)$, A^2 is H, and D^1 and E^1 are H. In another embodiment of Formula (V), B^1 is NHR^1, and A^1 is $C(A^2)$ or N, A^2 is H, and D^1 and E^1 are H. In another embodiment of Formula (V), B^1 is OR^1, and A^1 is $C(A^2)$, A^2 is H, and D^1 and E^1 are H. In another embodiment of Formula (V), B^1 is OR^1, and A^1 is $C(A^2)$ or N, A^2 is H, and D^1 and E^1 are H.

In one embodiment of Formula (V), Y^1 is H, CN, NO_2, F, Cl, Br, I, CF_3, R^{17}, $NHC(O)R^{17}$, or $C(O)NH_2$. In another embodiment of Formula (V), Y^1 is NO_2. In another embodiment of Formula (V), Y^1 is Cl. In another embodiment of Formula (V), B^1 is NHR^1, and A^1 is $C(A^2)$, A^2 is H, D^1 and E^1 are H, and Y^1 is NO_2. In another embodiment of Formula (V), B^1 is NHR^1, and A^1 is $C(A^2)$ or N, A^2 is H, D^1 and E^1 are H, and Y^1 is NO_2. In another embodiment of Formula (V), B^1 is OR^1, and A^1 is $C(A^2)$, A^2 is H, D^1 and E^1 are H, and Y^1 is Cl. In another embodiment of Formula (V), B^1 is OR^1, and A^1 is $C(A^2)$ or N, A^2 is H, D^1 and E^1 are H, and Y^1 is Cl.

In one embodiment of Formula (V), R^1 is R^2, R^3, R^4 or R^5. In another embodiment of Formula (V), R^1 is R^2, and R^2 is phenyl.

In one embodiment of Formula (V), R^1 is R^3, and R^3 is heteroaryl. In another embodiment of Formula (V), R^3 is triazolyl.

In one embodiment of Formula (V), R^1 is R^4. In another embodiment of Formula (V), R^1 is R^4, and R^4 is cycloalkyl. In another embodiment of Formula (V), R^1 is R^4, and R^4 is cyclohexyl. In another embodiment of Formula (V), R^1 is R^4, and R^4 is heterocycloalkyl. In

another embodiment of Formula (V), R^1 is R^4, and R^4 is 8-azabicyclo[3.2.1]octane, azetidinyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydropyranyl, or tetrahydrothiophenyl. In another embodiment of Formula (V), R^1 is R^4, and R^4 is heterocycloalkenyl. In another embodiment of Formula (V), R^1 is R^4, and R^4 is tetrahydropyridazinyl.

In one embodiment of Formula (V), R^1 is R^5. In another embodiment of Formula (V), R^1 is R^5 and R^5 is alkyl or alkynyl. In another embodiment of Formula (V), R^1 is R^5 and R^5 is alkyl which is unsubstituted. In another embodiment of Formula (V), R^1 is R^5 and R^5 is alkyl which is substituted with one or two or three independently selected R^6, R^7, OR^7, SR^7, SO_2R^7, $N(R^7)_2$, OH, CN, CF_3, F, Cl, Br or I substituents. In another embodiment of Formula (V), R^1 is R^5 and R^5 is alkyl which is substituted with R^7.

In one embodiment of Formula (V), R^7 is R^8, R^9, R^{10} or R^{11}. In another embodiment of Formula (V), R^7 is R^8, and R^8 is phenyl which is unfused or fused with R^{8A}, and R^{8A} is heterocycloalkane. In another embodiment of Formula (V), R^7 is R^8, and R^8 is phenyl which is unfused. In another embodiment of Formula (V), R^7 is R^9, and R^9 is heteroaryl. In another embodiment of Formula (V), R^7 is R^9, and R^9 is furanyl, imidazolyl, isothiazolyl, isoxazolyl, 1,2,3-oxadiazoyl, 1,2,5-oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrazolyl, thiazolyl, thiophenyl, triazinyl or 1,2,3-triazolyl. In another embodiment of Formula (V), R^7 is R^9, and R^9 is pyridinyl, thiazolyl, imidazoyl, and 1,2,3-triazolyl. In another embodiment of Formula (V), R^7 is R^{10}, and R^{10} is C_3-C_{10}-cycloalkyl. In another embodiment of Formula (V), R^7 is R^{10}, and R^{10} is C_3, C_6, C_7 or C_{10}-cycloalkyl. In another embodiment of Formula (V), R^7 is R^{10}, and R^{10} is cyclopropyl, cyclohexyl, bicyclo[2.2.1]heptanyl, or adamantanyl. In another embodiment of Formula (V), R^7 is R^{10}, and R^{10} is morpholinyl, piperazinyl, piperidinyl, tetrahydro-2H-pyranyl, 1,2-dihydropyridinyl, pyranyl, pyridin-1(H)-yl, pyrrolidinyl, oxetanyl, thiomorpholinyl, imidazolidinyl, tetrahydrothiophenyl, dioxolanyl, tetrahydrothiopyranyl, dioxanyl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl, or tetrahydrofuranyl. In another embodiment of Formula (V), R^7 is R^{10}, and R^{10} is morpholinyl, piperazinyl, piperidinyl, tetrahydro-2H-pyranyl, 1,2-dihydropyridinyl, pyrrolidinyl, oxetanyl, thiomorpholinyl, imidazolidinyl, tetrahydrothiophenyl, dioxolanyl, tetrahydrothiopyranyl, dioxanyl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl, or tetrahydrofuranyl. In another embodiment of Formula (V), R^7 is R^{11}, and R^{11} is alkyl which is unsubstituted or substituted. In another embodiment of Formula (V), R^7 is R^{11}, and R^{11} is alkyl which is unsubstituted. In another embodiment of Formula (V), R^7 is R^{11}, and R^{11} is alkyl which is substituted. In another embodiment of

Formula (V), R^7 is R^{11}, and R^{11} is alkyl which is substituted with one or two or three independently selected OR^{12}, F, Cl, Br or I substituents. In another embodiment of Formula (V), R^7 is R^{11}, R^{11} is alkyl which is substituted with OR^{12}, R^{12} is R^{16}, and R^{16} is alkyl.

In one embodiment of Formula (V), R^{17} is R^{19} or R^{21}. In another embodiment of Formula (V), R^{17} is R^{19}, and R^{19} is heteroaryl. In another embodiment of Formula (V), R^{17} is R^{19}, and R^{19} is thiazolyl. In another embodiment of Formula (V), R^{17} is R^{21}, and R^{21} is alkynyl. In another embodiment of Formula (V), R^{17} is R^{21}, and R^{21} is ethynyl.

Still another embodiment pertains to compounds having Formula (V) which are

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-5-(trifluoromethyl)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyclopropylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4,4-difluorocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

N-[(5-chloro-6-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

Trans-N-({5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-fluoro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

N-[(5-chloro-6-{[1-(cyanomethyl)-4-fluoropiperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydrofuran-3-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

Trans-N-({5-chloro-6-[(4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-[(5-chloro-6-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]oxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-[(5-chloro-6-{[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-[(5-chloro-6-{[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

N-{[5-chloro-6-({(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl}oxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

N-{[5-chloro-6-({(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl}methoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-[(5-chloro-6-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(1-cyclopropylpiperidin-4-yl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-N-({5-chloro-6-[(1-cyclopropylpiperidin-4-yl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[6-({4-fluoro-1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl}methoxy)-5-(trifluoromethyl)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(2-tetrahydrofuran-2-ylethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-*N*-{[5-cyano-6-(2-tetrahydro-2*H*-pyran-4-ylethoxy)pyridin-3-yl]sulfonyl}-2-(1*H*-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(4,4-difluorocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({6-[(trans-4-carbamoylcyclohexyl)methoxy]-5-chloropyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-cyanocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[2-(1H-imidazol-1-yl)ethoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(1-methyl-1H-imidazol-5-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-fluoro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

N-{[5-chloro-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(4,4-difluoro-1-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(2,2-difluorocyclopropyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(trans-4-cyanocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-(trifluoromethyl)phenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-chloro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

N-{[3-chloro-4-(1,4-dioxan-2-ylmethoxy)phenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-[(5-chloro-6-{[(2S)-4-cyclopropylmorpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

methyl 2-{[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}morpholine-4-carboxylate;

2-{[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide;

N-({5-chloro-6-[(trans-4-ethyl-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(cis-4-ethyl-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

5-chloro-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

5-chloro-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(cis-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(trans-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-[(3-chloro-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(cis-1-fluoro-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-[(5-chloro-6-{[(1R,2R,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-[(5-chloro-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

N-[(5-chloro-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S)-4-cyclopropylmorpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-cyano-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-{[3-nitro-4-(2-oxaspiro[3.5]non-7-ylmethoxy)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-cyano-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-{[3-nitro-4-({[(2S)-4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)phenyl]sulfonyl}benzamide;

N-[(5-chloro-6-{[trans-4-(2-hydroxypropan-2-yl)cyclohexyl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]phenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-({5-nitro-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)benzamide;

N-({3-chloro-4-[(cis-4-cyano-1-fluorocyclohexyl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({3-chloro-4-[(trans-4-cyano-1-fluorocyclohexyl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(cis-4-cyano-1-fluorocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(trans-4-cyano-1-fluorocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

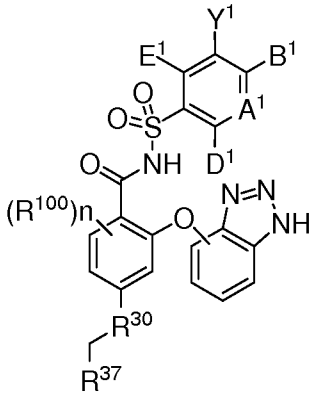
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-chloro-6-{[1-(1,3-thiazol-2-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(6-{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-5-nitropyridin-3-yl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide; and therapeutically acceptable salts,

N-(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)-4-cyanopiperidine-1-carboxamide; prodrugs, salts of prodrugs and metabolites thereof.

In another aspect, the present invention provides compounds of Formula (VI)



(VI)

and therapeutically acceptable salts, prodrugs, salts of prodrugs and metabolites thereof, wherein A^1, B^1, D^1, E^1, Y^1, R^{30}, and R^{37} are as described herein for Formula (VI), n is 0, 1, 2, or 3; describing the number of substituents on R^{26}, and R^{100} is as described for substituents on R^{26}.

In one embodiment of Formula (VI), A^1 is N. In another embodiment of Formula (VI), A^1 is $C(A^2)$. In another embodiment of Formula (VI), A^1 is $C(A^2)$, and A^2 is H.

In one embodiment of Formula (VI), B^1 is R^1, OR^1, SR^1, SO_2R^1, $NHC(O)R^1$, NHR^1, $N(R^1)_2$, or $C(O)NHR^1$. In another embodiment of Formula (VI), B^1 is NHR^1. In another embodiment of Formula (VI), B^1 is NHR^1, and A^1 is $C(A^2)$, and A^2 is H. In another embodiment of Formula (VI), B^1 is NHR^1, and A^1 is $C(A^2)$ or N, and A^2 is H. In another embodiment of Formula (VI), B^1 is OR^1. In another embodiment of Formula (VI), B^1 is OR^1,

and A^1 is $C(A^2)$, and A^2 is H. In another embodiment of Formula (VI), B^1 is OR^1, and A^1 is $C(A^2)$ or N, and A^2 is H.

In one embodiment of Formula (VI), D^1 and E^1 are H. In another embodiment of Formula (VI), B^1 is NHR^1, and A^1 is $C(A^2)$, A^2 is H, and D^1 and E^1 are H. In another embodiment of Formula (VI), B^1 is NHR^1, and A^1 is $C(A^2)$ or N, A^2 is H, and D^1 and E^1 are H. In another embodiment of Formula (VI), B^1 is OR^1, and A^1 is $C(A^2)$, A^2 is H, and D^1 and E^1 are H. In another embodiment of Formula (VI), B^1 is OR^1, and A^1 is $C(A^2)$ or N, A^2 is H, and D^1 and E^1 are H.

In one embodiment of Formula (VI), Y^1 is H, CN, NO_2, F, Cl, Br, I, CF_3, R^{17}, $NHC(O)R^{17}$, or $C(O)NH_2$. In another embodiment of Formula (VI), Y^1 is NO_2. In another embodiment of Formula (VI), Y^1 is Cl. In another embodiment of Formula (VI), B^1 is NHR^1, and A^1 is $C(A^2)$, A^2 is H, D^1 and E^1 are H, and Y^1 is NO_2. In another embodiment of Formula (VI), B^1 is NHR^1, and A^1 is $C(A^2)$ or N, A^2 is H, D^1 and E^1 are H, and Y^1 is NO_2. In another embodiment of Formula (VI), B^1 is OR^1, and A^1 is $C(A^2)$, A^2 is H, D^1 and E^1 are H, and Y^1 is Cl. In another embodiment of Formula (VI), B^1 is OR^1, and A^1 is $C(A^2)$ or N, A^2 is H, D^1 and E^1 are H, and Y^1 is Cl.

In one embodiment of Formula (VI), R^1 is R^2, R^3, R^4 or R^5. In another embodiment of Formula (VI), R^1 is R^2, and R^2 is phenyl.

In one embodiment of Formula (VI), R^1 is R^3, and R^3 is heteroaryl. In another embodiment of Formula (VI), R^3 is triazolyl.

In one embodiment of Formula (VI), R^1 is R^4. In another embodiment of Formula (VI), R^1 is R^4, and R^4 is cycloalkyl. In another embodiment of Formula (VI), R^1 is R^4, and R^4 is cyclohexyl. In another embodiment of Formula (VI), R^1 is R^4, and R^4 is heterocycloalkyl. In another embodiment of Formula (VI), R^1 is R^4, and R^4 is 8-azabicyclo[3.2.1]octane, azetidinyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydropyranyl, or tetrahydrothiophenyl. In another embodiment of Formula (VI), R^1 is R^4, and R^4 is heterocycloalkenyl. In another embodiment of Formula (VI), R^1 is R^4, and R^4 is tetrahydropyridazinyl.

In one embodiment of Formula (VI), R^1 is R^5. In another embodiment of Formula (VI), R^1 is R^5 and R^5 is alkyl or alkynyl. In another embodiment of Formula (VI), R^1 is R^5 and R^5 is alkyl which is unsubstituted. In another embodiment of Formula (VI), R^1 is R^5 and R^5 is alkyl which is substituted with one or two or three independently selected R^6, R^7, OR^7, SR^7, SO_2R^7, $N(R^7)_2$, OH, CN, CF_3, F, Cl, Br or I substituents. In another embodiment of Formula (VI), R^1 is R^5 and R^5 is alkyl which is substituted with R^7.

In one embodiment of Formula (VI), R^7 is R^8, R^9, R^{10} or R^{11}. In another embodiment of Formula (VI), R^7 is R^8, and R^8 is phenyl which is unfused or fused with R^{8A}, and R^{8A} is heterocycloalkane. In another embodiment of Formula (VI), R^7 is R^8, and R^8 is phenyl which is unfused. In another embodiment of Formula (VI), R^7 is R^9, and R^9 is heteroaryl. In another embodiment of Formula (VI), R^7 is R^9, and R^9 is furanyl, imidazolyl, isothiazolyl, isoxazolyl, 1,2,3-oxadiazoyl, 1,2,5-oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrazolyl, thiazolyl, thiophenyl, triazinyl or 1,2,3-triazolyl. In another embodiment of Formula (VI), R^7 is R^9, and R^9 is pyridinyl, thiazolyl, imidazoyl, and 1,2,3-triazolyl. In another embodiment of Formula (VI), R^7 is R^{10}, and R^{10} is C_3-C_{10}-cycloalkyl. In another embodiment of Formula (VI), R^7 is R^{10}, and R^{10} is C_3, C_6, C_7 or C_{10}-cycloalkyl. In another embodiment of Formula (VI), R^7 is R^{10}, and R^{10} is cyclopropyl, cyclohexyl, bicyclo[2.2.1]heptanyl, or adamantanyl. In another embodiment of Formula (VI), R^7 is R^{10}, and R^{10} is morpholinyl, piperazinyl, piperidinyl, tetrahydro-2H-pyranyl, 1,2-dihydropyridinyl, pyranyl, pyridin-1(H)-yl, pyrrolidinyl, oxetanyl, thiomorpholinyl, imidazolidinyl, tetrahydrothiophenyl, dioxolanyl, tetrahydrothiopyranyl, dioxanyl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl, or tetrahydrofuranyl. In another embodiment of Formula (VI), R^7 is R^{10}, and R^{10} is morpholinyl, piperazinyl, piperidinyl, tetrahydro-2H-pyranyl, 1,2-dihydropyridinyl, pyrrolidinyl, oxetanyl, thiomorpholinyl, imidazolidinyl, tetrahydrothiophenyl, dioxolanyl, tetrahydrothiopyranyl, dioxanyl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl, or tetrahydrofuranyl. In another embodiment of Formula (VI), R^7 is R^{11}, and R^{11} is alkyl which is unsubstituted or substituted. In another embodiment of Formula (VI), R^7 is R^{11}, and R^{11} is alkyl which is unsubstituted. In another embodiment of Formula (VI), R^7 is R^{11}, and R^{11} is alkyl which is substituted. In another embodiment of Formula (VI), R^7 is R^{11}, and R^{11} is alkyl which is substituted with one or two or three independently selected OR^{12}, F, Cl, Br or I substituents. In another embodiment of Formula (VI), R^7 is R^{11}, R^{11} is alkyl which is substituted with OR^{12}, R^{12} is R^{16}, and R^{16} is alkyl.

In one embodiment of Formula (VI), R^{17} is R^{19} or R^{21}. In another embodiment of Formula (VI), R^{17} is R^{19}, and R^{19} is heteroaryl. In another embodiment of Formula (VI), R^{17} is R^{19}, and R^{19} is thiazolyl. In another embodiment of Formula (VI), R^{17} is R^{21}, and R^{21} is alkynyl. In another embodiment of Formula (VI), R^{17} is R^{21}, and R^{21} is ethynyl.

Still another embodiment pertains to compounds having Formula (V) which are 2-(1H-benzotriazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzotriazol-4-yloxy)-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

2-(1H-benzotriazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)benzamide;

2-(1H-benzotriazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

2-(1H-benzotriazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S)-4-cyclopropylmorpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

2-(1H-benzotriazol-4-yloxy)-N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide; and therapeutically acceptable salts, prodrugs, salts of prodrugs and metabolites thereof.

Pharmaceutical Compositions, Combination Therapies, Methods of Treatment, and Administration

Another embodiment comprises pharmaceutical compositions comprising a compound having Formula (I) and an excipient.

Still another embodiment comprises methods of treating cancer in a mammal comprising administering thereto a therapeutically acceptable amount of a compound having Formula (I).

Still another embodiment comprises methods of treating autoimmune disease in a mammal comprising administering thereto a therapeutically acceptable amount of a compound having Formula (I).

Still another embodiment pertains to compositions for treating diseases during which anti-apoptotic Bcl-2 proteins are expressed, said compositions comprising an excipient and a therapeutically effective amount of the compound having Formula (I).

Still another embodiment pertains to methods of treating disease in a patient during which anti-apoptotic Bcl-2 proteins are expressed, said methods comprising administering to the patient a therapeutically effective amount of a compound having Formula (I).

Still another embodiment pertains to compositions for treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia,

colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer or spleen cancer, said compositions comprising an excipient and a therapeutically effective amount of the compound having Formula (I).

Still another embodiment pertains to methods of treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer or spleen cancer in a patient, said methods comprising administering to the patient a therapeutically effective amount of a compound having Formula (I).

Still another embodiment pertains to compositions for treating diseases during which are expressed anti-apoptotic Bcl-2 proteins, said compositions comprising an excipient and a therapeutically effective amount of the compound having Formula (I) and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

Still another embodiment pertains to methods of treating disease in a patient during which are expressed anti-apoptotic Bcl-2 proteins, said methods comprising administering to the patient a therapeutically effective amount of a compound having Formula (I) and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

Still another embodiment pertains to compositions for treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer, said compositions comprising an excipient and a therapeutically effective amount of the compound having Formula (I) and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

Still another embodiment pertains to methods of treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular

lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer in a patient, said methods comprising administering to the patient a therapeutically effective amount of the compound having Formula (I) and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

Metabolites of compounds having Formula I, produced by in vitro or in vivo metabolic processes, may also have utility for treating diseases associated with anti-apoptotic Bcl-2 protein.

Certain precursor compounds which may be metabolized in vitro or in vivo to form compounds having Formula I may also have utility for treating diseases associated with expression of anti-apoptotic Bcl-2 protein.

Compounds having Formula I may exist as acid addition salts, basic addition salts or zwitterions. Salts of the compounds are prepared during isolation or following purification of the compounds. Acid addition salts of the compounds are those derived from the reaction of the compounds with an acid. For example, the acetate, adipate, alginate, bicarbonate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsufonate, digluconate, formate, fumarate, glycerophosphate, glutamate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, lactobionate, lactate, maleate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, phosphate, picrate, propionate, succinate, tartrate, thiocyanate, trichloroacetic, trifluoroacetic, para-toluenesulfonate, and undecanoate salts of the compounds and prodrugs thereof are contemplated as being embraced by this invention. Basic addition salts of the compounds are those derived from the reaction of the compounds with the hydroxide, carbonate or bicarbonate of cations such as lithium, sodium, potassium, calcium, and magnesium.

The compounds having Formula I may be administered, for example, bucally, ophthalmically, orally, osmotically, parenterally (intramuscularly, intraperitoneally intrasternally, intravenously, subcutaneously), rectally, topically, transdermally, or vaginally.

Therapeutically effective amounts of compounds having Formula I depend on the recipient of the treatment, the disorder being treated and the severity thereof, the composition containing the compound, the time of administration, the route of administration, the duration of treatment, the compound potency, its rate of clearance and whether or not another drug is

co-administered. The amount of a compound of this invention having Formula I used to make a composition to be administered daily to a patient in a single dose or in divided doses is from about 0.03 to about 200 mg/kg body weight. Single dose compositions contain these amounts or a combination of submultiples thereof.

Compounds having Formula I may be administered with or without an excipient. Excipients include, for example, encapsulating materials or additives such as absorption accelerators, antioxidants, binders, buffers, coating agents, coloring agents, diluents, disintegrating agents, emulsifiers, extenders, fillers, flavoring agents, humectants, lubricants, perfumes, preservatives, propellants, releasing agents, sterilizing agents, sweeteners, solubilizers, wetting agents and mixtures thereof.

Excipients for preparation of compositions comprising a compound having Formula I to be administered orally in solid dosage form include, for example, agar, alginic acid, aluminum hydroxide, benzyl alcohol, benzyl benzoate, 1,3-butylene glycol, carbomers, castor oil, cellulose, cellulose acetate, cocoa butter, corn starch, corn oil, cottonseed oil, cross-povidone, diglycerides, ethanol, ethyl cellulose, ethyl laureate, ethyl oleate, fatty acid esters, gelatin, germ oil, glucose, glycerol, groundnut oil, hydroxypropylmethyl cellulose, isopropanol, isotonic saline, lactose, magnesium hydroxide, magnesium stearate, malt, mannitol, monoglycerides, olive oil, peanut oil, potassium phosphate salts, potato starch, povidone, propylene glycol, Ringer's solution, safflower oil, sesame oil, sodium carboxymethyl cellulose, sodium phosphate salts, sodium lauryl sulfate, sodium sorbitol, soybean oil, stearic acids, stearyl fumarate, sucrose, surfactants, talc, tragacanth, tetrahydrofurfuryl alcohol, triglycerides, water, and mixtures thereof. Excipients for preparation of compositions comprising a compound of this invention having Formula I to be administered ophthalmically or orally in liquid dosage forms include, for example, 1,3-butylene glycol, castor oil, corn oil, cottonseed oil, ethanol, fatty acid esters of sorbitan, germ oil, groundnut oil, glycerol, isopropanol, olive oil, polyethylene glycols, propylene glycol, sesame oil, water and mixtures thereof. Excipients for preparation of compositions comprising a compound of this invention having Formula I to be administered osmotically include, for example, chlorofluorohydrocarbons, ethanol, water and mixtures thereof. Excipients for preparation of compositions comprising a compound of this invention having Formula I to be administered parenterally include, for example, 1,3-butanediol, castor oil, corn oil, cottonseed oil, dextrose, germ oil, groundnut oil, liposomes, oleic acid, olive oil, peanut oil, Ringer's solution, safflower oil, sesame oil, soybean oil, U.S.P. or isotonic sodium chloride solution, water and mixtures thereof. Excipients for preparation of compositions

comprising a compound of this invention having Formula I to be administered rectally or vaginally include, for example, cocoa butter, polyethylene glycol, wax and mixtures thereof.

Compounds having Formula (I) are expected to be useful when used with alkylating agents, angiogenesis inhibitors, antibodies, antimetabolites, antimitotics, antiproliferatives, antivirals, aurora kinase inhibitors, other apoptosis promoters (for example, Bcl-xL, Bcl-w and Bfl-1) inhibitors, activators of death receptor pathway, Bcr-Abl kinase inhibitors, BiTE (Bi-Specific T cell Engager) antibodies, antibody drug conjugates, biologic response modifiers, cyclin-dependent kinase inhibitors, cell cycle inhibitors, cyclooxygenase-2 inhibitors, DVDs, leukemia viral oncogene homolog (ErbB2) receptor inhibitors, growth factor inhibitors, heat shock protein (HSP)-90 inhibitors, histone deacetylase (HDAC) inhibitors, hormonal therapies, immunologicals, inhibitors of inhibitors of apoptosis proteins (IAPs), intercalating antibiotics, kinase inhibitors, kinesin inhibitors, Jak2 inhibitors, mammalian target of rapamycin inhibitors, microRNA's, mitogen-activated extracellular signal-regulated kinase inhibitors, multivalent binding proteins, non-steroidal anti-inflammatory drugs (NSAIDs), poly ADP (adenosine diphosphate)-ribose polymerase (PARP) inhibitors, platinum chemotherapeutics, polo-like kinase (Plk) inhibitors, phosphoinositide-3 kinase (PI3K) inhibitors, proteosome inhibitors, purine analogs, pyrimidine analogs, receptor tyrosine kinase inhibitors, etinoids/deltoids plant alkaloids, small inhibitory ribonucleic acids (siRNAs), topoisomerase inhibitors, ubiquitin ligase inhibitors, and the like, and in combination with one or more of these agents .

BiTE antibodies are bi-specific antibodies that direct T-cells to attack cancer cells by simultaneously binding the two cells. The T-cell then attacks the target cancer cell. Examples of BiTE antibodies include adecatumumab (Micromet MT201), blinatumomab (Micromet MT103) and the like. Without being limited by theory, one of the mechanisms by which T-cells elicit apoptosis of the target cancer cell is by exocytosis of cytolytic granule components, which include perforin and granzyme B. In this regard, Bcl-2 has been shown to attenuate the induction of apoptosis by both perforin and granzyme B. These data suggest that inhibition of Bcl-2 could enhance the cytotoxic effects elicited by T-cells when targeted to cancer cells (V.R. Sutton, D.L. Vaux and J.A. Trapani, *J. of Immunology* **1997**, 158 (12), 5783).

SiRNAs are molecules having endogenous RNA bases or chemically modified nucleotides. The modifications do not abolish cellular activity, but rather impart increased stability and/or increased cellular potency. Examples of chemical modifications include phosphorothioate groups, 2'-deoxynucleotide, 2'-OCH_3-containing ribonucleotides, 2'-F-

ribonucleotides, 2'-methoxyethyl ribonucleotides, combinations thereof and the like. The siRNA can have varying lengths (e.g., 10-200 bps) and structures (e.g., hairpins, single/double strands, bulges, nicks/gaps, mismatches) and are processed in cells to provide active gene silencing. A double-stranded siRNA (dsRNA) can have the same number of nucleotides on each strand (blunt ends) or asymmetric ends (overhangs). The overhang of 1-2 nucleotides can be present on the sense and/or the antisense strand, as well as present on the 5'- and/ or the 3'-ends of a given strand. For example, siRNAs targeting Mcl-1 have been shown to enhance the activity of ABT-263, (i.e., N-(4-(4-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide) or ABT-737 (i.e., N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide) in multiple tumor cell lines (Tse et. al, *Cancer Research* **2008**, 68(9), 3421 and references therein).

Multivalent binding proteins are binding proteins comprising two or more antigen binding sites. Multivalent binding proteins are engineered to have the three or more antigen binding sites and are generally not naturally occurring antibodies. The term "multispecific binding protein" means a binding protein capable of binding two or more related or unrelated targets. Dual variable domain (DVD) binding proteins are tetravalent or multivalent binding proteins binding proteins comprising two or more antigen binding sites. Such DVDs may be monospecific (i.e., capable of binding one antigen) or multispecific (i.e., capable of binding two or more antigens). DVD binding proteins comprising two heavy chain DVD polypeptides and two light chain DVD polypeptides are referred to as DVD Ig's. Each half of a DVD Ig comprises a heavy chain DVD polypeptide, a light chain DVD polypeptide, and two antigen binding sites. Each binding site comprises a heavy chain variable domain and a light chain variable domain with a total of 6 CDRs involved in antigen binding per antigen binding site. Multispecific DVDs include DVD binding proteins that bind DLL4 and VEGF, or C-met and EFGR or ErbB3 and EGFR.

Alkylating agents include altretamine, AMD-473, AP-5280, apaziquone, bendamustine, brostallicin, busulfan, carboquone, carmustine (BCNU), chlorambucil, CLORETAZINE® (laromustine, VNP 40101M), cyclophosphamide, decarbazine, estramustine, fotemustine, glufosfamide, ifosfamide, KW-2170, lomustine (CCNU), mafosfamide, melphalan, mitobronitol, mitolactol, nimustine, nitrogen mustard N-oxide,

ranimustine, temozolomide, thiotepa, TREANDA® (bendamustine), treosulfan, rofosfamide and the like.

Angiogenesis inhibitors include endothelial-specific receptor tyrosine kinase (Tie-2) inhibitors, epidermal growth factor receptor (EGFR) inhibitors, insulin growth factor-2 receptor (IGFR-2) inhibitors, matrix metalloproteinase-2 (MMP-2) inhibitors, matrix metalloproteinase-9 (MMP-9) inhibitors, platelet-derived growth factor receptor (PDGFR) inhibitors, thrombospondin analogs, vascular endothelial growth factor receptor tyrosine kinase (VEGFR) inhibitors and the like.

Antimetabolites include ALIMTA® (pemetrexed disodium, LY231514, MTA), 5-azacitidine, XELODA® (capecitabine), carmofur, LEUSTAT® (cladribine), clofarabine, cytarabine, cytarabine ocfosfate, cytosine arabinoside, decitabine, deferoxamine, doxifluridine, eflornithine, EICAR (5-ethynyl-1-β -D-ribofuranosylimidazole-4-carboxamide), enocitabine, ethnylcytidine, fludarabine, 5-fluorouracil alone or in combination with leucovorin, GEMZAR® (gemcitabine), hydroxyurea, ALKERAN®(melphalan), mercaptopurine, 6-mercaptopurine riboside, methotrexate, mycophenolic acid, nelarabine, nolatrexed, ocfosfate, pelitrexol, pentostatin, raltitrexed, Ribavirin, triapine, trimetrexate, S-1, tiazofurin, tegafur, TS-1, vidarabine, UFT and the like.

Antivirals include ritonavir, hydroxychloroquine and the like.

Aurora kinase inhibitors include ABT-348, AZD-1152, MLN-8054, VX-680, Aurora A-specific kinase inhibitors, Aurora B-specific kinase inhibitors and pan-Aurora kinase inhibitors and the like.

Bcl-2 protein inhibitors include AT-101 ((-)gossypol), GENASENSE® (G3139 or oblimersen (Bcl-2-targeting antisense oligonucleotide)), IPI-194, IPI-565, N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide) (ABT-737), N-(4-(4-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide (ABT-263), GX-070 (obatoclax) and the like.

Bcr-Abl kinase inhibitors include DASATINIB® (BMS-354825), GLEEVEC® (imatinib) and the like.

CDK inhibitors include AZD-5438, BMI-1040, BMS-032, BMS-387, CVT-2584, flavopyridol, GPC-286199, MCS-5A, PD0332991, PHA-690509, seliciclib (CYC-202, R-roscovitine), ZK-304709 and the like.

COX-2 inhibitors include ABT-963, ARCOXIA® (etoricoxib), BEXTRA® (valdecoxib), BMS347070, CELEBREX® (celecoxib), COX-189 (lumiracoxib), CT-3, DERAMAXX® (deracoxib), JTE-522, 4-methyl-2-(3,4-dimethylphenyl)-1-(4-sulfamoylphenyl-1H-pyrrole), MK-663 (etoricoxib), NS-398, parecoxib, RS-57067, SC-58125, SD-8381, SVT-2016, S-2474, T-614, VIOXX® (rofecoxib) and the like.

EGFR inhibitors include ABX-EGF, anti-EGFR immunoliposomes, EGF-vaccine, EMD-7200, ERBITUX® (cetuximab), HR3, IgA antibodies, IRESSA® (gefitinib), TARCEVA® (erlotinib or OSI-774), TP-38, EGFR fusion protein, TYKERB® (lapatinib) and the like.

ErbB2 receptor inhibitors include CP-724-714, CI-1033 (canertinib), HERCEPTIN® (trastuzumab), TYKERB® (lapatinib), OMNITARG® (2C4, petuzumab), TAK-165, GW-572016 (ionafarnib), GW-282974, EKB-569, PI-166, dHER2 (HER2 vaccine), APC-8024 (HER-2 vaccine), anti-HER/2neu bispecific antibody, B7.her2IgG3, AS HER2 trifunctional bispecfic antibodies, mAB AR-209, mAB 2B-1 and the like.

Histone deacetylase inhibitors include depsipeptide, LAQ-824, MS-275, trapoxin, suberoylanilide hydroxamic acid (SAHA), TSA, valproic acid and the like.

HSP-90 inhibitors include 17-AAG-nab, 17-AAG, CNF-101, CNF-1010, CNF-2024, 17-DMAG, geldanamycin, IPI-504, KOS-953, MYCOGRAB® (human recombinant antibody to HSP-90), NCS-683664, PU24FCl, PU-3, radicicol, SNX-2112, STA-9090 VER49009 and the like.

Inhibitors of inhibitors of apoptosis proteins include HGS1029, GDC-0145, GDC-0152, LCL-161, LBW-242 and the like.

Antibody drug conjugates include anti-CD22-MC-MMAF, anti-CD22-MC-MMAE, anti-CD22-MCC-DM1, CR-011-vcMMAE, PSMA-ADC, MEDI-547, SGN-19Am SGN-35, SGN-75 and the like

Activators of death receptor pathway include TRAIL, antibodies or other agents that target TRAIL or death receptors (e.g., DR4 and DR5) such as Apomab, conatumumab, ETR2-ST01, GDC0145, (lexatumumab), HGS-1029, LBY-135, PRO-1762 and trastuzumab.

Kinesin inhibitors include Eg5 inhibitors such as AZD4877, ARRY-520; CENPE inhibitors such as GSK923295A and the like.

JAK-2 inhibitors include CEP-701 (lesaurtinib), XL019 and INCB018424 and the like.

MEK inhibitors include ARRY-142886, ARRY-438162 PD-325901, PD-98059 and the like.

mTOR inhibitors include AP-23573, CCI-779, everolimus, RAD-001, rapamycin, temsirolimus, ATP-competitive TORC1/TORC2 inhibitors, including PI-103, PP242, PP30, Torin 1 and the like.

Non-steroidal anti-inflammatory drugs include AMIGESIC® (salsalate), DOLOBID® (diflunisal), MOTRIN® (ibuprofen), ORUDIS® (ketoprofen), RELAFEN® (nabumetone), FELDENE® (piroxicam), ibuprofen cream, ALEVE® (naproxen) and NAPROSYN® (naproxen), VOLTAREN® (diclofenac), INDOCIN® (indomethacin), CLINORIL® (sulindac), TOLECTIN® (tolmetin), LODINE® (etodolac), TORADOL® (ketorolac), DAYPRO® (oxaprozin) and the like.

PDGFR inhibitors include C-451, CP-673, CP-868596 and the like.

Platinum chemotherapeutics include cisplatin, ELOXATIN® (oxaliplatin) eptaplatin, lobaplatin, nedaplatin, PARAPLATIN® (carboplatin), satraplatin, picoplatin and the like.

Polo-like kinase inhibitors include BI-2536 and the like.

Phosphoinositide-3 kinase (PI3K) inhibitors include wortmannin, LY294002, XL-147, CAL-120, ONC-21, AEZS-127, ETP-45658, PX-866, GDC-0941, BGT226, BEZ235, XL765 and the like.

Thrombospondin analogs include ABT-510, ABT-567, ABT-898, TSP-1 and the like.

VEGFR inhibitors include AVASTIN® (bevacizumab), ABT-869, AEE-788, ANGIOZYME™ (a ribozyme that inhibits angiogenesis (Ribozyme Pharmaceuticals (Boulder, CO.) and Chiron, (Emeryville, CA)) , axitinib (AG-13736), AZD-2171, CP-547,632, IM-862, MACUGEN (pegaptamib), NEXAVAR® (sorafenib, BAY43-9006), pazopanib (GW-786034), vatalanib (PTK-787, ZK-222584), SUTENT® (sunitinib, SU-11248), VEGF trap, ZACTIMA™ (vandetanib, ZD-6474), GA101, ofatumumab, ABT-806 (mAb-806), ErbB3 specific antibodies, BSG2 specific antibodies, DLL4 specific antibodies and C-met specific antibodies, and the like.

Antibiotics include intercalating antibiotics aclarubicin, actinomycin D, amrubicin, annamycin, adriamycin, BLENOXANE® (bleomycin), daunorubicin, CAELYX® or MYOCET® (liposomal doxorubicin), elsamitrucin, epirbucin, glarbuicin, ZAVEDOS® (idarubicin), mitomycin C, nemorubicin, neocarzinostatin, peplomycin, pirarubicin, rebeccamycin, stimalamer, streptozocin, VALSTAR® (valrubicin), zinostatin and the like.

Topoisomerase inhibitors include aclarubicin, 9-aminocamptothecin, amonafide, amsacrine, becatecarin, belotecan, BN-80915, CAMPTOSAR® (irinotecan hydrochloride), camptothecin, CARDIOXANE® (dexrazoxine), diflomotecan, edotecarin, ELLENCE® or

PHARMORUBICIN® (epirubicin), etoposide, exatecan, 10-hydroxycamptothecin, gimatecan, lurtotecan, mitoxantrone, orathecin, pirarbucin, pixantrone, rubitecan, sobuzoxane, SN-38, tafluposide, topotecan and the like.

Antibodies include AVASTIN® (bevacizumab), CD40-specific antibodies, chTNT-1/B, denosumab, ERBITUX® (cetuximab), HUMAX-CD4® (zanolimumab), IGF1R-specific antibodies, lintuzumab, PANOREX® (edrecolomab), RENCAREX® (WX G250), RITUXAN® (rituximab), ticilimumab, trastuzimab, CD20 antibodies types I and II and the like.

Hormonal therapies include ARIMIDEX® (anastrozole), AROMASIN® (exemestane), arzoxifene, CASODEX® (bicalutamide), CETROTIDE® (cetrorelix), degarelix, deslorelin, DESOPAN® (trilostane), dexamethasone, DROGENIL® (flutamide), EVISTA® (raloxifene), AFEMA™ (fadrozole), FARESTON® (toremifene), FASLODEX® (fulvestrant), FEMARA® (letrozole), formestane, glucocorticoids, HECTOROL® (doxercalciferol), RENAGEL® (sevelamer carbonate), lasofoxifene, leuprolide acetate, MEGACE® (megesterol), MIFEPREX® (mifepristone), NILANDRON™ (nilutamide), NOLVADEX® (tamoxifen citrate), PLENAXIS™ (abarelix), prednisone, PROPECIA® (finasteride), rilostane, SUPREFACT® (buserelin), TRELSTAR® (luteinizing hormone releasing hormone (LHRH)), VANTAS® (Histrelin implant), VETORYL® (trilostane or modrastane), ZOLADEX® (fosrelin, goserelin) and the like.

Deltoids and retinoids include seocalcitol (EB1089, CB1093), lexacalcitrol (KH1060), fenretinide, PANRETIN® (aliretinoin), ATRAGEN® (liposomal tretinoin), TARGRETIN® (bexarotene), LGD-1550 and the like.

PARP inhibitors include ABT-888 (veliparib), olaparib, KU-59436, AZD-2281, AG-014699, BSI-201, BGP-15, INO-1001, ONO-2231 and the like.

Plant alkaloids include, but are not limited to, vincristine, vinblastine, vindesine, vinorelbine and the like.

Proteasome inhibitors include VELCADE® (bortezomib), MG132, NPI-0052, PR-171 and the like.

Examples of immunologicals include interferons and other immune-enhancing agents. Interferons include interferon alpha, interferon alpha-2a, interferon alpha-2b, interferon beta, interferon gamma-1a, ACTIMMUNE® (interferon gamma-1b) or interferon gamma-n1, combinations thereof and the like. Other agents include ALFAFERONE® ,(IFN-α), BAM-002 (oxidized glutathione), BEROMUN® (tasonermin), BEXXAR® (tositumomab),

CAMPATH® (alemtuzumab), CTLA4 (cytotoxic lymphocyte antigen 4), decarbazine, denileukin, epratuzumab, GRANOCYTE® (lenograstim), lentinan, leukocyte alpha interferon, imiquimod, MDX-010 (anti-CTLA-4), melanoma vaccine, mitumomab, molgramostim, MYLOTARG™ (gemtuzumab ozogamicin), NEUPOGEN® (filgrastim), OncoVAC-CL, OVAREX® (oregovomab), pemtumomab (Y-muHMFG1), PROVENGE® (sipuleucel-T), sargaramostim, sizofilan, teceleukin, THERACYS® (Bacillus Calmette-Guerin), ubenimex, VIRULIZIN® (immunotherapeutic, Lorus Pharmaceuticals), Z-100 (Specific Substance of Maruyama (SSM)), WF-10 (Tetrachlorodecaoxide (TCDO)), PROLEUKIN® (aldesleukin), ZADAXIN® (thymalfasin), ZENAPAX® (daclizumab), ZEVALIN® (90Y-Ibritumomab tiuxetan) and the like.

Biological response modifiers are agents that modify defense mechanisms of living organisms or biological responses, such as survival, growth or differentiation of tissue cells to direct them to have anti-tumor activity and include krestin, lentinan, sizofiran, picibanil PF-3512676 (CpG-8954), ubenimex and the like.

Pyrimidine analogs include cytarabine (ara C or Arabinoside C), cytosine arabinoside, doxifluridine, FLUDARA® (fludarabine), 5-FU (5-fluorouracil), floxuridine, GEMZAR® (gemcitabine), TOMUDEX® (ratitrexed), TROXATYL™ (triacetyluridine troxacitabine) and the like.

Purine analogs include LANVIS® (thioguanine) and PURI-NETHOL® (mercaptopurine).

Antimitotic agents include batabulin, epothilone D (KOS-862), N-(2-((4-hydroxyphenyl)amino)pyridin-3-yl)-4-methoxybenzenesulfonamide, ixabepilone (BMS 247550), paclitaxel, TAXOTERE® (docetaxel), PNU100940 (109881), patupilone, XRP-9881 (larotaxel), vinflunine, ZK-EPO (synthetic epothilone) and the like.

Ubiquitin ligase inhibitors include MDM2 inhibitors, such as nutlins, NEDD8 inhibitors such as MLN4924 and the like.

Compounds of this invention can also be used as radiosensitizers that enhance the efficacy of radiotherapy. Examples of radiotherapy include external beam radiotherapy, teletherapy, brachytherapy and sealed, unsealed source radiotherapy and the like.

Additionally, compounds having Formula (I) may be combined with other chemotherapeutic agents such as ABRAXANE™ (ABI-007), ABT-100 (farnesyl transferase inhibitor), ADVEXIN® (Ad5CMV-p53 vaccine), ALTOCOR® or MEVACOR® (lovastatin), AMPLIGEN® (poly I:poly C12U, a synthetic RNA), APTOSYN® (exisulind), AREDIA® (pamidronic acid), arglabin, L-asparaginase, atamestane (1-methyl-3,17-dione-androsta-1,4-

diene), AVAGE® (tazarotene), AVE-8062 (combreastatin derivative) BEC2 (mitumomab), cachectin or cachexin (tumor necrosis factor), canvaxin (vaccine), CEAVAC® (cancer vaccine), CELEUK® (celmoleukin), CEPLENE® (histamine dihydrochloride), CERVARIX® (human papillomavirus vaccine), CHOP® (C: CYTOXAN® (cyclophosphamide); H: ADRIAMYCIN® (hydroxydoxorubicin); O: Vincristine (ONCOVIN®); P: prednisone), CYPAT™ (cyproterone acetate), combrestatin A4P, DAB(389)EGF (catalytic and translocation domains of diphtheria toxin fused via a His-Ala linker to human epidermal growth factor) or TransMID-107R™ (diphtheria toxins), dacarbazine, dactinomycin, 5,6-dimethylxanthenone-4-acetic acid (DMXAA), eniluracil, EVIZON™ (squalamine lactate), DIMERICINE® (T4N5 liposome lotion), discodermolide, DX-8951f (exatecan mesylate), enzastaurin, EPO906 (epithilone B), GARDASIL® (quadrivalent human papillomavirus (Types 6, 11, 16, 18) recombinant vaccine), GASTRIMMUNE®, GENASENSE®, GMK (ganglioside conjugate vaccine), GVAX® (prostate cancer vaccine), halofuginone, histerelin, hydroxycarbamide, ibandronic acid, IGN-101, IL-13-PE38, IL-13-PE38QQR (cintredekin besudotox), IL-13-pseudomonas exotoxin, interferon-α, interferon-γ, JUNOVAN™ or MEPACT™ (mifamurtide), lonafarnib, 5,10-methylenetetrahydrofolate, miltefosine (hexadecylphosphocholine), NEOVASTAT®(AE-941), NEUTREXIN® (trimetrexate glucuronate), NIPENT® (pentostatin), ONCONASE® (a ribonuclease enzyme), ONCOPHAGE® (melanoma vaccine treatment), ONCOVAX® (IL-2 Vaccine), ORATHECIN™ (rubitecan), OSIDEM® (antibody-based cell drug), OVAREX® MAb (murine monoclonal antibody), paclitaxel, PANDIMEX™ (aglycone saponins from ginseng comprising 20(S)protopanaxadiol (aPPD) and 20(S)protopanaxatriol (aPPT)), panitumumab, PANVAC®-VF (investigational cancer vaccine), pegaspargase, PEG Interferon A, phenoxodiol, procarbazine, rebimastat, REMOVAB® (catumaxomab), REVLIMID® (lenalidomide), RSR13 (efaproxiral), SOMATULINE® LA (lanreotide), SORIATANE® (acitretin), staurosporine (Streptomyces staurospores), talabostat (PT100), TARGRETIN® (bexarotene), TAXOPREXIN® (DHA-paclitaxel), TELCYTA® (canfosfamide, TLK286), temilifene, TEMODAR® (temozolomide), tesmilifene, thalidomide, THERATOPE® (STn-KLH), thymitaq (2-amino-3,4-dihydro-6-methyl-4-oxo-5-(4-pyridylthio)quinazoline dihydrochloride), TNFERADE™ (adenovector: DNA carrier containing the gene for tumor necrosis factor-α), TRACLEER® or ZAVESCA® (bosentan), tretinoin (Retin-A), tetrandrine, TRISENOX® (arsenic trioxide), VIRULIZIN®, ukrain (derivative of alkaloids from the greater celandine plant), vitaxin (anti-alphavbeta3 antibody), XCYTRIN® (motexafin gadolinium), XINLAY™ (atrasentan), XYOTAX™ (paclitaxel poliglumex), YONDELIS®

(trabectedin), ZD-6126, ZINECARD® (dexrazoxane), ZOMETA® (zolendronic acid), zorubicin and the like.

Data

Determination of the utility of compounds having Formula I as binders to and inhibitors of anti-apoptotic Bcl-2 and Bcl-xL proteins was performed using the Time Resolved-Fluorescence Resonance Energy Transfer (TR-FRET) Assay. Tb-anti-GST antibody was purchased from Invitrogen (Catalog No. PV4216).

Probe Synthesis

All reagents were used as obtained from the vendor unless otherwise specified. Peptide synthesis reagents including diisopropylethylamine (DIEA), dichloromethane (DCM), N-methylpyrrolidone (NMP), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), N-hydroxybenzotriazole (HOBt) and piperidine were obtained from Applied Biosystems, Inc. (ABI), Foster City, CA or American Bioanalytical, Natick, MA. Preloaded 9-Fluorenylmethyloxycarbonyl (Fmoc) amino acid cartridges (Fmoc-Ala-OH, Fmoc-Cys(Trt)-OH, Fmoc-Asp(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Phe-OH, Fmoc-Gly-OH, Fmoc-His(Trt)-OH, Fmoc-Ile-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Met-OH, Fmoc-Asn(Trt)-OH, Fmoc-Pro-OH, Fmor-Gln(Trt)-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Thr(tBu)-OH, Fmoc-Val-OH, Fmoc-Trp(Boc)-OH, Fmoc-Tyr(tBu)-OH) were obtained from ABI or Anaspec, San Jose, CA. The peptide synthesis resin (Fmoc-Rink amide MBHA resin) and Fmoc-Lys(Mtt)-OH were obtained from Novabiochem, San Diego, CA. Single-isomer 6-carboxyfluorescein succinimidyl ester (6-FAM-NHS) was obtained from Anaspec. Trifluoroacetic acid (TFA) was obtained from Oakwood Products, West Columbia, SC. Thioanisole, phenol, triisopropylsilane (TIS), 3,6-dioxa-1,8-octanedithiol (DODT) and isopropanol were obtained from Aldrich Chemical Co., Milwaukee, WI. Matrix-assisted laser desorption ionization mass-spectra (MALDI-MS) were recorded on an Applied Biosystems Voyager DE-PRO MS). Electrospray mass-spectra (ESI-MS) were recorded on Finnigan SSQ7000 (Finnigan Corp., San Jose, CA) in both positive and negative ion mode.

General Procedure For Solid-Phase Peptide Synthesis (SPPS)

Peptides were synthesized with, at most, 250 µmol preloaded Wang resin/vessel on an ABI 433A peptide synthesizer using 250 µmol scale Fastmoc™ coupling cycles. Preloaded cartridges containing 1 mmol standard Fmoc-amino acids, except for the position of attachment of the fluorophore, where 1 mmol Fmoc-Lys(Mtt)-OH was placed in the

cartridge, were used with conductivity feedback monitoring. N-terminal acetylation was accomplished by using 1 mmol acetic acid in a cartridge under standard coupling conditions.

Removal of 4-Methyltrityl (Mtt) From Lysine

The resin from the synthesizer was washed thrice with dichloromethane and kept wet. 150 mL of 95:4:1 dichloromethane:triisopropylsilane:trifluoroacetic acid was flowed through the resin bed over 30 minutes. The mixture turned deep yellow then faded to pale yellow. 100 mL of DMF was flowed through the bed over 15 minutes. The resin was then washed thrice with DMF and filtered. Ninhydrin tests showed a strong signal for primary amine.

Resin Labeling With 6-Carboxyfluorescein-NHS (6-FAM-NHS)

The resin was treated with 2 equivalents 6-FAM-NHS in 1% DIEA/DMF and stirred or shaken at ambient temperature overnight. When complete, the resin was drained, washed thrice with DMF, thrice with (1% DCM and 1% methanol) and dried to provide an orange resin that was negative by ninhydrin test.

General Procedure For Cleavage And Deprotection Of Resin-Bound Peptide

Peptides were cleaved from the resin by shaking for 3 hours at ambient temperature in a cleavage cocktail consisting of 80% TFA, 5% water, 5% thioanisole, 5% phenol, 2.5% TIS, and 2.5% EDT (1 mL/0.1 g resin). The resin was removed by filtration and rinsing twice with TFA. The TFA was evaporated from the filtrates, and product was precipitated with ether (10 mL/0.1 g resin), recovered by centrifugation, washed twice with ether (10 mL/0.1 g resin) and dried to give the crude peptide.

General Procedure For Purification Of Peptides

The crude peptides were purified on a Gilson preparative HPLC system running Unipoint® analysis software (Gilson, Inc., Middleton, WI) on a radial compression column containing two 25 × 100 mm segments packed with Delta-Pak™ C18 15 μm particles with 100 Å pore size and eluted with one of the gradient methods listed below. One to two milliliters of crude peptide solution (10 mg/mL in 90% DMSO/water) was purified per injection. The peaks containing the product(s) from each run were pooled and lyophilized. All preparative runs were run at 20 mL/min with eluents as buffer A: 0.1% TFA-water and buffer B: acetonitrile.

General Procedure For Analytical HPLC

Analytical HPLC was performed on a Hewlett-Packard 1200 series system with a diode-array detector and a Hewlett-Packard 1046A fluorescence detector running HPLC 3D ChemStation software version A.03.04 (Hewlett-Packard. Palo Alto, CA) on a 4.6 × 250 mm

YMC column packed with ODS-AQ 5 μm particles with a 120 Å pore size and eluted with one of the gradient methods listed below after preequilibrating at the starting conditions for 7 minutes. Eluents were buffer A: 0.1% TFA-water and buffer B: acetonitrile. The flow rate for all gradients was 1 mL/min.

F-Bak: Peptide Probe: Acetyl--(SEQ ID NO: 1)GQVGRQLAIIGDK(6-FAM)-(SEQ ID NO: 2) INR-NH_2

Fmoc-Rink amide MBHA resin was extended using the general peptide synthesis procedure to provide the protected resin-bound peptide (1.020 g). The Mtt group was removed, labeled with 6-FAM-NHS and cleaved and deprotected as described hereinabove to provide the crude product as an orange solid (0.37 g). This product was purified by RP-HPLC. Fractions across the main peak were tested by analytical RP-HPLC, and the pure fractions were isolated and lyophilized, with the major peak providing the title compound (0.0802 g) as a yellow solid; MALDI-MS m/z = 2137.1 ($(M+H)^+$).

Alternative Synthesis of Peptide Probe F-Bak: Acetyl--(SEQ ID NO: 1)GQVGRQLAIIGDK(6-FAM)- -(SEQ ID NO: 2)INR-NH_2

The protected peptide was assembled on 0.25 mmol Fmoc-Rink amide MBHA resin (Novabiochem) on an Applied Biosystems 433A automated peptide synthesizer running Fastmoc™ coupling cycles using pre-loaded 1 mmol amino acid cartridges, except for the fluorescein(6-FAM)-labeled lysine, where 1 mmol Fmoc-Lys(4-methyltrityl) was weighed into the cartridge. The N-terminal acetyl group was incorporated by putting 1 mmol acetic acid in a cartridge and coupling as described hereinabove. Selective removal of the 4-methyltrityl group was accomplished with a solution of 95:4:1 DCM:TIS:TFA (v/v/v) flowed through the resin over 15 minutes, followed by quenching with a flow of dimethylformamide. Single-isomer 6-carboxyfluorescein-NHS was reacted with the lysine side-chain in 1% DIEA in DMF and confirmed complete by ninhydrin testing. The peptide was cleaved from the resin and side-chains deprotected by treating with 80:5:5:5:2.5:2.5 TFA:water: phenol: thioanisole:triisopropylsilane: 3,6-dioxa-1,8-octanedithiol (v/v/v/v/v/v), and the crude peptide was recovered by precipitation with diethyl ether. The crude peptide was purified by reverse-phase high-performance liquid chromatography, and its purity and identity were confirmed by analytical reverse-phase high-performance liquid chromatography and matrix-assisted laser-desorption mass-spectrometry (m/z = 2137.1 ($(M+H)^+$)).

Time Resolved-Fluorescence Resonance Energy Transfer (TR-FRET) Assay

Representative compounds were serially diluted in dimethyl sulfoxide (DMSO) starting at 50 μM (2× starting concentration; 10% DMSO) and 10 μL were transferred into a 384-well plate. Then 10 μL of a protein/probe/antibody mix was added to each well at final concentrations listed in TABLE 1.

TABLE 1. Protein, Probe And Antibody Used For TR-FRET Assays

Protein	Probe	Protein (nM)	Probe (nM)	Antibody	Antibody (nM)
GST-Bcl-2	F-Bak(SEQ. ID. No. 1) (GQVGRQLAIIGDK(6-FAM) (SEQ ID No.2)INR-amide)	1	100	Tb-anti-GST	1
GST-Bcl-X_L	F-Bak(SEQ. ID. No. 1) (GQVGRQLAIIGDK(6-FAM) (SEQ ID No.2)INR-amide)	1	100	Tb-anti-GST	1

6-FAM = 6- carboxyfluorescein.; Tb = terbium; GST = glutathione S-transferase

The samples were then mixed on a shaker for 1 minute and incubated for an additional 3 hours at room temperature. For each assay, the probe/antibody and protein/probe/antibody were included on each assay plate as negative and positive controls, respectively. Fluorescence was measured on the Envision (Perkin Elmer) using a 340/35 nm excitation filter and 520/525 (F-Bak peptide) and 495/510 nm (Tb-labeled anti-Histidine antibody) emission filters.

Inhibition constants (K_i) for compounds according to the invention and ABT-737, and the binding selectivity ratio (Bcl-X_L K_i:Bcl-2 K_i) for each are shown in TABLE 2 below. The inhibition constant (K_i) is the dissociation constant of an enzyme-inhibitor complex or a protein/small molecule complex, wherein the small molecule is inhibiting binding of one protein to another protein or peptide. Where the K_i for a compound is represented as ">" (greater than) a certain numerical value, it is intended to mean that the binding affinity value (e.g., for Bcl-X_L) is greater than the limits of detection of the assay used. Where the binding selectivity ratio for a compound is represented as ">" (greater than) a certain numerical value, it is intended to mean that the selectivity of a particular compound for Bcl-2 over Bcl-X_L is at least as great as the number indicated. Where the K_i for a compound is represented as "<" (less than) a certain numerical value, it is intended to mean that the binding affinity value

(e.g., for Bcl-2) is lower than the limit of detection of the assay used. Inhibition constants were determined using Wang's equation (Wang Z-X., An Exact Mathematical Expression For Describing Competitive Binding Of Two Different Ligands To A Protein Molecule. *FEBS Lett.* **1995**, 360:111-4).

TABLE 2. TR-FRET Binding Affinity

Example	Bcl-2 K_i , (μM)	Bcl-X_L K_i (μM)	Binding selectivity ratio (Bcl-X_L K_i /Bcl-2 K_i)
ABT-737	0.000088	0.00008	0.9
1	0.006773	0.57833	85.4
18	0.000238	0.008131	34.2
19	0.000847	0.020027	23.6
20	0.002365	0.077593	32.8
21	0.005428	0.19038	35.1
22	0.006218	0.1253	20.2
23	0.006639	0.16782	25.3
24	0.000194	>0.66	>3402.1
25	0.00005	0.20519	4103.8
26	0.00014	>0.66	>4714.3
28	0.033705	>0.66	>19.6
29	0.011911	>0.66	>55.4
30	0.10292	>0.66	>6.4
31	0.036614	>0.66	>18.0
32	0.061123	>0.66	>10.8
33	0.006684	0.33339	49.9
34	0.001986	0.088007	44.3
36	0.000796	0.008995	11.3
37	0.000464	0.044422	95.7
40	0.000534	>0.66	>1236.0
42	0.000048	0.003841	80

45	0.000828	>0.66	>797.1
46	0.000159	0.018958	119.2
47	0.00663	0.10428	15.7
50	0.000471	0.090073	191.2
51	0.000252	0.015646	62.1
52	0.000239	0.079805	333.9
53	0.000081	0.004845	59.8
54	0.000757	0.082015	108.3
55	0.000196	0.02488	126.9
56	0.000268	0.012924	48.2
57	0.000068	0.004674	68.7
58	0.001085	0.28807	265.5
59	0.000672	1.255	1867.6
60	0.01893	>0.66	>34.9
61	0.05221	>0.66	>12.6
62	0.003516	0.5711	162.4
64	0.000523	0.040334	77.1
65	0.004558	0.021805	4.8
67	0.28867	>0.66	>2.3
68	0.001227	0.013969	11.4
69	0.001245	0.092074	74
70	0.001192	0.074407	62.4
71	0.006233	>0.66	>105.9
72	0.003022	0.052359	17.3
73	0.001697	0.016885	9.9
74	0.00002	0.025249	1262.5
75	0.000125	0.10653	852.2
76	0.000051	0.003288	64.5
78	0.11251	>0.66	>5.9
79	0.00205	0.0972	47.4
85	0.000236	0.011521	48.8
86	0.000212	0.010522	49.6

87	0.000762	0.40679	533.8
88	0.000069	0.004642	67.3
89	0.000129	0.007453	57.8
90	0.002134	0.28384	133
91	0.000193	0.010191	52.8
92	0.004375	0.34857	79.7
93	0.000231	0.013861	60
94	0.00007	0.002317	33.1
95	0.00006	0.015699	261.7
96	0.000047	0.008781	186.8
97	0.000027	0.002611	96.7
98	0.000013	>0.66	>50769.2
99	0.00004	0.00553	138.3
100	0.000116	0.008288	71.4
101	0.000092	0.011152	121.2
102	0.000035	0.002242	64.1
103	0.000056	0.11738	2096.1
104	0.000077	0.049106	637.7
105	0.00008	0.005016	62.7
107	0.002087	0.13041	62.5
108	0.002342	0.059639	25.5
109	0.000161	>0.66	>4099.4
114	0.000096	0.014325	149.2
115	0.000176	0.027527	156.4
116	0.000036	0.008305	230.7
117	0.002299	>0.66	>287.1
118	0.000769	>0.66	>858.3
119	0.000622	0.23029	370.2
120	0.000443	0.099593	224.8
121	0.000001	0.000388	388
122	0.000058	0.012144	209.4
123	0.000015	0.001372	91.5

124	0.000335	0.073725	220.1
125	0.000003	0.011637	3879
126	0.000012	0.1629	13575
127	0.000459	>0.66	>1437.9
128	0.000051	0.363	7117.6
129	0.000056	>0.66	>11785.7
130	0.00014	>0.66	>4714.3
131	0.000106	0.24297	2292.2
132	0.000553	0.31529	570.1
133	0.000009	0.000281	31.2
134	0.000052	0.01805	347.1
135	0.000008	0.006239	779.9
136	0.000259	0.061863	238.9
137	0.000305	0.015977	52.4
138	0.000009	0.005174	574.9
139	0.000101	0.010416	103.1
140	0.004726	>0.66	>139.7
141	0.000673	0.028642	42.6
142	0.003664	0.10184	27.8
143	0.002232	0.075383	33.8
144	0.053902	>0.66	>12.2
145	0.00003	0.012029	401
146	0.044184	>0.66	>14.9
147	0.000514	>0.66	>1284.0
148	0.00289	>0.66	>228.4
149	0.000265	>0.66	>2490.6
150	0.000014	0.009338	667
151	0.000162	>0.66	>4074.1
152	0.000026	0.000412	15.8
153	0.000265	0.093006	351
154	0.000133	0.005375	40.4
155	0.000484	0.037667	77.8

156	0.000116	0.006155	53.1
157	0.004454	>0.66	>148.2
158	0.06478	>0.66	>10.2
161	0.00171	>0.66	>386.0
162	0.001348	0.16692	123.8
163	0.005616	>0.66	>117.5
164	0.000963	0.13795	143.3
165	0.000823	0.036585	44.5
166	0.000459	0.00327	7.1
169	0.00097	0.088637	91.4
170	0.000126	0.003802	30.2
171	0.002942	0.052053	17.7
172	0.002048	0.06569	32.1
173	0.000108	0.022102	204.6
174	0.000105	0.062087	591.3
175	0.0001	>0.660	>6600
176	0.00018	0.032	177.8
177	0.000165	0.132	799.7
178	0.000226	>0.660	>2915.8
179	0.000181	>0.660	>3642.4
180	0.000192	>0.660	>3438.6
181	0.000291	>0.660	>2271.9
182	0.000087	>0.660	>7595.8
183	0.000039	0.009428	240.5
184	0.000281	>0.660	>2345.3
185	0.000228	0.082582	361.5
186	0.00001	0.011199	1069.2
187	0.000329	>0.660	>2003.9
188	0.000102	0.11529	1135.4
189	0.000144	0.051724	358.6
190	0.000512	0.097064	189.6
191	0.000073	0.009162	125.2

194	0.000151	0.032029	212.4
195	0.000039	0.00671	170.2
196	0.000032	>0.660	>20552.4
197	0.000025	0.004837	193
198	0.003966	>0.660	>166.4
199	0.000014	0.005231	369.8
200	0.0001	>0.660	>6588.8
201	0.000125	0.024585	196.6
202	0.000052	0.005073	97.1
203	0.000031	0.004305	139.5
204	0.000145	0.042341	291.3
205	0.000005	0.003573	658.6
206	0.000083	>0.660	>7916.4
207	0.000218	>0.660	>3021.3
208	0.000589	>0.660	>1120.6
209	0.000267	>0.660	>2476.0
210	0.000624	>0.660	>1057.6
211	0.000009	0.005612	651.1
212	0.000737	>0.660	>895.1
213	< 0.00001	>0.660	>66000
214	0.000082	0.064044	776.6
215	0.000503	0.060768	120.8
216	0.000615	>0.660	>1073.2
217	0.000262	0.044761	171.1
218	0.000131	0.096873	738.2
219	0.000236	0.029861	126.8
220	0.000192	0.031387	163.7
221	0.000057	0.1701	3005.2
222	0.000107	0.13661	1275.3
223	0.000169	0.097266	574.1
224	<0.00001	0.000999	>99.9
225	0.00001	0.003482	>348.2

226	0.000017	0.009928	577.7
227	0.006831	>0.660	>96.6
228	0.004669	>0.660	>141.4
229	0.049413	>0.660	>13.4
230	0.008819	>0.660	>74.8
231	0.000918	>0.660	>718.8
232	0.00046	0.19749	429.1
233	0.000243	>0.660	>2714.3
234	0.000369	0.024503	66.3
235	0.000252	0.058196	231.4
236	0.000369	>0.660	>1787.6
237	0.000401	0.268	668.3
238	0.00043	>0.660	>1534.3
239	0.000252	0.10842	430.9
240	0.00083	>0.660	>795.4
241	0.006091	>0.660	>108.3
242	0.001796	>0.660	>367.6
243	0.00028	>0.660	>2357.6
244	0.00016	>0.660	>4136.9
245	0.001617	>0.660	>408.2
246	0.000783	0.38418	490.9
247	0.000188	0.027265	145.3
248	0.000013	0.15503	12079.6
249	0.00009	>0.660	>7302.0
250	0.000266	0.21547	811
251	0.000328	0.47166	1438.5
252	0.000077	>0.660	>8570.3
253	0.000142	>0.660	>4663.3
254	0.000126	0.053315	421.7
255	0.007834	>0.660	>84.2
256	0.00012	>0.660	>5519.8
257	0.000171	0.017126	100.2

258	0.000048	0.004085	86
259	0.001995	>0.660	>330.9
260	0.001087	>0.660	>607.2
261	0.000088	>0.660	>7530.1
262	0.003001	>0.660	219.9
263	0.000316	>0.660	>2090.0
264	0.000235	>0.660	>2808.4
265	0.001698	>0.660	>388.8
266	0.000183	>0.660	>3607.7
267	0.000454	>0.660	>1453.3
268	0.000092	0.14465	1563.9
269	nd	nd	nd
270	0.003314	>0.660	>199.1
271	0.006156	>0.660	>107.2
272	0.000011	>0.660	>58011.8
273	0.000076	0.18104	2396.1
274	0.000135	0.032908	244.6
275	0.000097	>0.660	>6832.4
276	0.000144	0.38147	2650.8
277	0.029684	>0.660	>22.2
278	0.00071	>0.660	>929.4
279	0.000095	>0.660	>6923.2
280	0.000178	0.19477	1097.2
281	0.000076	0.11925	1558.9
282	0.000164	0.56153	3434.4
283	0.047464	>0.660	>13.9
284	0.001552	>0.660	>425.2
285	0.006994	>0.660	>94.4
286	0.000567	>0.660	>1165.0
287	nd	nd	nd
288	0.000177	>0.660	>3730.9
289	0.000112	>0.660	>5917.7

290	0.000365	>0.660	>1808.5
291	0.00056	>0.660	>1179.1
292	0.000598	>0.660	>1104.2
293	0.000516	0.2604	505.1
294	0.000258	0.065126	252
295	0.000183	0.10971	599.4
296	0.000651	>0.660	>1014.4
297	0.000128	0.28281	2209.5
298	0.000315	0.44593	1415.7
299	0.000425	0.24551	577.7
300	nd	>0.660	nd
301	0.000291	>0.660	>2268.0
302	0.000504	>0.660	>1309.5
303	0.00148	>0.660	>445.9
304	0.000678	>0.660	>973.5
305	0.003684	>0.660	>179.2
306	0.000077	0.047895	622
307	0.003727	>0.660	>177.1
308	0.057376	>0.660	>11.5
309	0.004417	>0.660	>149.4
310	0.000049	>0.660	>13469.4
311	0.00026	>0.660	>2538.5
312	0.00034	>0.660	>1941.2
313	0.000044	0.066	1500
314	0.003066	>0.660	>215.3
315	0.003461	>0.660	>190.7
316	0.000149	0.079528	533.7
317	0.002798	>0.660	>235.9
318	0.001468	0.15067	102.6
319	0.000413	0.20791	503.4
320	0.001243	0.12873	103.6
321	0.000689	>0.660	>957.9

322	0.000184	>0.660	>3591.4
323	0.000949	>0.660	>695.2
324	0.001481	>0.660	>445.7
325	0.002331	>0.660	>283.1
326	0.000116	>0.660	>5708.8
327	0.000031	0.095575	3035.4
328	0.001859	>0.660	>355.0
329	0.000285	>0.660	>2319.5
330	0.074915	>0.660	>8.8
331	0.008266	>0.660	>79.8
332	0.012582	>0.660	>52.5
333	0.000089	>0.660	>7415.7
334	0.000179	>0.660	>3697.5
335	0.000438	>0.660	>1508.2
336	0.000105	0.24152	2301.3
337	0.000535	>0.660	>1233.3
338	0.000403	>0.660	>1637.7
339	0.014136	>0.660	>46.7
340	0.007593	>0.660	>86.9
341	0.012998	>0.660	>50.8
342	0.025752	>0.660	>25.6
343	0.000576	>0.660	>1145.9
344	0.000284	0.44708	1576.9
345	0.001146	>0.660	>575.9
346	0.000018	0.20364	11405.2
347	0.000243	0.30556	1256.7
348	0.000302	0.029266	97.1
349	0.000467	0.024235	51.9
350	0.00597	>0.660	>110.6
351	0.001576	>0.660	>418.7
352	0.006825	>0.660	>96.7
353	0.000292	>0.660	>2260.0

354	0.000036	0.00541	148.8
355	0.00012	>0.660	>5489.5
356	0.005015	>0.660	>131.6
357	0.001336	>0.660	>493.9
358	0.005417	>0.660	>121.8
359	0.013481	>0.660	>49.0
360	0.000228	0.14423	633.9
361	0.007128	>0.660	>92.6
362	0.000082	0.28999	3548.2
363	0.00018	>0.660	>3670.5
364	0.000006	0.07596	12197.3
365	0.001077	>0.660	>612.9
366	0.005457	>0.660	>121.0
367	0.004608	>0.660	>143.2
368	>1.195	>0.660	nd
369	0.8382	>0.660	>0.8
370	0.000904	>0.660	>729.9
371	0.008376	>0.660	>78.8
372	>1.195	>0.660	nd
374	0.002266	>0.660	>291.2
375	0.011254	>0.660	>58.6
376	0.022405	>0.660	>29.5
377	0.00014	0.32457	2317.4
378	0.063003	>0.660	>10.5
379	0.25595	>0.660	>2.6
380	0.000083	0.17491	2107.3
381	0.000054	0.024207	448.3
382	0.00115	>0.660	>573.9
383	0.00217	>0.660	>304.1
384	0.000076	>0.660	>8684.2
385	0.000062	0.12998	2096.5
386	0.000239	0.11818	494.5

387	0.000162	0.27983	1723.4
388	0.000188	0.034845	185.1
389	0.000098	0.067181	685.5
390	0.000341	0.11581	339.6
391	0.00354	>0.660	>186.4
392	0.00038	0.121691	320.2
393	0.000083	0.0921	1109.6
394	0.002507	> 660	> 263262.9
395	0.000798	0.018843	23.6
396	0.11567	> 660	>5705.9
397	0.022972	> 660	>28730.6
398	0.001233	0.083449	67.7
399	0.002923	> 660	> 225764.5
400	< 0.00001	0.036438	> 3643.8
401	< 0.00001	0.001621	> 162.1
402	0.00003	0.004152	137.4
403	0.000003	0.024340	8250.6
404	0.000012	0.030268	2423.5
405	0.000040	0.055325	1394.8
406	0.000035	0.044553	1263.8
407	0.000015	0.074556	4930.6
408	0.000002	0.028131	13701.7
409	< 0.000010	0.017485	1748.5
410	0.000055	0.101630	1838.6
411	0.000003	0.007453	2352.3
412	0.000021	0.135210	6545.5
413	0.000120	0.096802	803.8
414	0.000007	0.095640	13930.5
415	0.000002	0.026900	17326.9
416	0.000023	0.059112	2569.0
417	0.000046	0.003986	87.1
418	0.000004	0.001566	404.7

419	0.000197	0.211240	1070.8
420	0.000063	0.072108	1153.3
421	0.000026	0.054039	2089.5
422	0.000071	0.289500	4073.4
423	< 0.000010	0.007566	756.6
424	< 0.000010	0.007825	782.5
425	0.000003	0.003995	1282.2
426	0.000007	0.004311	604.2
427	0.000002	0.085636	34408.6
428	0.000003	0.015643	5832.2
429	< 0.000010	0.001407	140.7
430	< 0.000010	0.000998	99.8
431	< 0.000010	0.006774	677.4
432	0.000023	0.009298	408.8
433	< 0.000010	0.002286	228.55
434	0.000052	0.075474	1459.4
435	0.000017	0.032896	1935.1
436	0.000011	0.006500	590.9
437	< 0.000010	0.000514	51.4
438	< 0.000010	0.000345	34.5
439	< 0.000010	0.014968	1496.8
440	< 0.000010	0.045491	4549.1
441	< 0.000010	0.024219	2421.9
442	< 0.000010	0.033589	3358.9
443	< 0.000010	0.019357	1935.7
444	0.000112	0.081494	727.6
445	0.000028	0.013557	484.2
446	0.000038	0.019318	508.4
447	0.000028	0.065838	2373.1
448	0.000005	0.014610	3119.3
449	0.000240	0.017841	74.4
450	0.000299	0.032065	107.3

451	< 0.000010	0.003599	359.9
452	< 0.000010	0.006004	600.4
453	< 0.000010	0.003630	363.0
454	0.000026	0.018906	735.2
455	0.000004	0.000619	139.4
456	< 0.000010	0.000540	54.0
457	0.000045	0.330930	7413.6
458	< 0.000010	0.002372	237.2
459	< 0.000010	0.005416	541.6
460	0.000049	0.028982	586.5
461	0.000093	0.003650	39.4
462	0.000026	0.018425	710.8
463	0.000007	0.043884	6042.9
464	0.000081	0.521110	6431.8
465	0.000025	0.037216	1472.4
467	0.000080	0.13291	1653.0
473	0.079276	0.19124	2.4
474	0.0081	nd	nd
475	nd	nd	nd
476	nd	nd	nd
477	0.0085	nd	nd
478	nd	nd	nd
479	nd	nd	nd
480	nd	nd	nd
481	nd	nd	nd
482	0.000064	0.349890	5442.9
483	< 0.000010	0.005630	>563.0
484	< 0.000010	0.034339	>3433.9
485	0.000167	0.054207	324.0
486	0.000328	0.025460	77.6
487	0.000033	0.075419	2287.2
488	< 0.000010	0.023459	>2345.9

490	0.001144	0.106070	92.7
491	0.000017	0.077183	4600.5
492	< 0.000010	0.045096	>4509.6
493	< 0.000010	0.041883	>4188.3
494	< 0.000010	0.015566	>1556.6
496	0.000078	0.043348	558.9
497	0.000082	0.124230	1517.4
498	< 0.000010	0.124910	>12491.0
499	< 0.000010	0.104150	>10415.0
500	< 0.000010	0.147340	>14734.0
501	0.000027	0.162530	6025.7
502	0.000025	0.144860	5754.1
503	0.000062	0.146640	2356.5
504	< 0.000010	0.005499	>549.9
505	< 0.000010	0.004861	>486.1
506	< 0.000010	0.004457	>445.7
507	< 0.000010	0.033347	>3334.7
508	< 0.000010	0.043152	>4315.2
509	0.006300	0.229180	36.4
510	0.000674	0.173870	257.8
511	< 0.000010	0.021592	>2159.2
512	< 0.000010	0.017338	>1733.8
513	< 0.000010	0.006462	>646.2
514	< 0.000010	0.010413	>1041.3
515	< 0.000010	0.139940	>13994.0
516	< 0.000010	0.004823	>482.3
517	< 0.000010	0.006077	>607.7
518	< 0.000010	0.002546	>254.6
519	0.000012	0.310940	25935.4
520	< 0.000010	0.015378	>1537.8
521	< 0.000010	0.004669	>466.9
522	< 0.000010	0.002079	>207.9

523	< 0.000010	0.049444	>4944.4
524	< 0.000010	0.022184	>2218.4
525	< 0.000010	0.018984	>1898.4
526	< 0.000010	0.004679	>467.9
527	< 0.000010	0.004219	>421.9
528	< 0.000010	0.003669	>366.9
529	< 0.000010	0.008284	>828.4
530	< 0.000010	0.076660	>7666.0
531	< 0.000010	0.012578	>1257.8
532	< 0.000010	0.009812	>981.2
533	< 0.000010	0.010443	>1044.3
534	< 0.000010	0.046039	>4603.9
535	< 0.000010	0.002505	>250.5
536	0.000025	0.022152	886.1
538	< 0.000010	0.008001	>800.1
539	< 0.000010	0.040843	>4084.3
540	< 0.000010	0.001247	>124.7
541	< 0.000010	0.001382	>138.2
542	0.000023	0.124230	5359.8
543	< 0.000010	0.150470	>15047.0
544	< 0.000010	0.067003	>6700.3
545	< 0.000010	0.003566	>356.6
546	< 0.000010	0.006699	>669.9
547	0.000015	0.062949	4287.5
548	0.000014	0.028544	2111.7
549	< 0.000010	0.014820	>1482.0
550	0.000016	0.027218	1738.4
551	< 0.000010	0.016246	>1624.6
552	< 0.000010	0.010447	>1044.7
553	< 0.000010	0.013383	>1338.3
554	0.000034	0.057243	1674.6
555	< 0.000010	0.006298	>629.8

556	0.000034	0.091831	2730.2
557	0.000069	0.013166	189.8
538	0.000064	0.349890	5442.9
539	< 0.000010	0.005630	>563.0
540	< 0.000010	0.034339	>3433.9
541	0.000167	0.054207	324.0
542	0.000328	0.025460	77.6
543	0.000033	0.075419	2287.2
544	< 0.000010	0.023459	>2345.9
545	0.0001749	0.13811	789.7
546	0.001144	0.106070	92.7
547	0.000017	0.077183	4600.5
548	< 0.000010	0.045096	>4509.6
549	< 0.000010	0.041883	>4188.3
550	< 0.000010	0.015566	>1556.6
551	0.000078	0.043348	558.9
552	0.000082	0.124230	1517.4
553	< 0.000010	0.124910	>12491.0
554	< 0.000010	0.104150	>10415.0
555	< 0.000010	0.147340	>14734.0
556	0.000027	0.162530	6025.7
557	0.000025	0.144860	5754.1
558	nd	nd	nd

nd = not determined

TABLE 2 shows the utility of compounds having Formula I to functionally inhibit anti-apoptotic Bcl-2 protein. It also surprisingly demonstrates these compounds having comparatively less affinity for anti-apoptotic Bcl-xL protein, which in turn gives rise to high binding selectivity ratios (Bcl-xL K_i / Bcl-2 K_i) ranging from >2 to > 250,000. This selectivity for Bcl-2 protein is significantly greater than compounds previously disclosed in PCT US 2004/36770 and PCT US 2004/367911, as exemplified by ABT-737 in TABLE 2.

For some compounds (e.g., 192 and 193), the assay did not detect any activity against either Bcl-2 or Bcl-XL under the conditions stated above in the experimental description for

the FRET assay . As those skilled in the art will appreciate, the upper and lower limits of detection in an assay are influenced by the assay conditions, and for the FRET assay specifically, by the concentration of the probe that is used. Since compounds represented by Examples 192 and 193 show K_i values that are greater than the limits of detection in the assay format used, it can be stated that their affinity for Bcl-2 and Bcl-XL is less than the upper limit of detection of the assays. However, they may still have affinity for one or both proteins, and the inventors expect that they also have selectivity for Bcl-2.

Platelet Cell Viability Assay

Platelet-rich plasma (PRP) (prepared in-house according to conventional techniques) was incubated with ABT-737 (4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-(((1R)-3-(dimethylamino)-1-((phenylthio)methyl)propyl)amino)-3-nitrophenyl)sulfonyl)benzamide) or compounds of the invention at various concentrations for five hours at 37°C. After the incubation, platelets were equilibrated to room temperature for 20 minutes and then an equal volume of Cell Titer Glo reagent (Promega Corporation) was added. Samples were mixed for two minutes and then allowed to equilibrate for an additional 10 minutes at room temperature. The luminescence generated from the samples was quantitated using an LJL Analyst plate reader. IC_{50} values are concentrations of compound needed for 50% inhibition of cellular viability.

FL5.12/Bcl-2 cell viability assay

FL5.12 is an IL-3 dependent prolymphocytic murine cell line that undergoes apoptosis upon IL-3 withdrawal as a result of the upregulation of pro-apoptotic Bcl-2 proteins such as Bim and Puma. Stable overexpression of anti-apoptotic Bcl-2 protein (FL5.12/Bcl-2) protects against apoptosis induced by IL-3 withdrawal by sequestration of Bim and Puma. [Refs. Harada, et.al. *PNAS* 101, 15313 (2004); Certo, et.al. *Cancer Cell* 9, 351 (2006).] The ability of compounds to kill FL5.12/Bcl-2 cells upon IL-3 withdrawal is a direct measure of the compounds' ability to inhibit anti-apoptotic Bcl-2 protein function.

Wild type FL5.12/Bcl-2 overexpressing stable transfectants were cultured in RPMI-1640 supplemented with 2 mM L-glutamine, 10% FBS, 1 mM sodium pyruvate, 2 mM HEPES, 1% penicillin/streptomycin (Invitrogen), 57 μM β-ME, and 10% WEHI-3B conditioned medium (source of IL-3) and maintained at 37 °C containing 5% CO_2. $1x10^6$ cells/ml were washed 1 x PBS and resuspended in medium not supplemented with 10% WEHI-3B for 48 hrs prior to cytotoxicity assays. Cells were then treated for an additional 24 hrs in the presence of various concentrations of the indicated compounds. Cell viability was

assessed by CellTitre Glo assay (Promega Corp.) according to the manufacturer's recommendations.

Data analysis was performed using GraphPad Prism 4.0 and results are shown in TABLE 3 below.

TABLE 3. Cellular Activity

	FL5.12/Bcl-2	Canine platelets	Selectivity Ratio
	EC_{50} (μM)	EC_{50} (μM)	(Platelet EC_{50} / FL5.12/Bcl-2 EC_{50})
ABT-737	0.025	0.282	11
18	0.123	29.69	241
21	1.01	>50	>49
22	0.825	>50	>61
23	1.44	>50	>35
24	0.055	>50	>906
25	0.049	>50	>1020
26	0.035	>50	>1429
40	0.165	>50	>303
45	0.139	>50	>360
46	0.041	30	725
52	0.016	>50	>3164
53	0.011	18.325	1697
54	0.064	>50	>785
55	0.022	36	1614
56	0.049	27	554
57	0.016	16.8	1077
68	0.044	>50	>1144
69	0.075	>50	>666
70	0.111	>50	>450
71	0.46	>50	>107

72	0.154	>50	>325
73	0.14	23.22	166
74	0.008	16.71	1989
75	0.022	17.73	821
76	0.039	8.66	221
86	0.074	36.27	489
88	0.032	19.87	613
89	0.065	31.95	495
94	0.04	23.85	590
96	0.011	22.27	2043
97	0.013	14.1	1052
98	0.004	17.94	4849
99	0.009	21.72	2440
100	0.015	31.25	2029
102	0.02	20.21	996
103	0.014	31.35	2305
104	0.021	>50	>2392
105	0.013	30.31	2262
106	0.009	15.24	1657
109	0.036	>50	>1404
120	0.319	>50	>157
121	0.038	0.309	8
122	0.04	>50	>1259
123	0.087	2.81	32
125	0.01	44.83	4719
126	0.031	>50	>1618
128	0.025	>50	>2000
129	0.021	>50	>2415
130	0.197	>50	>254
131	0.031	>50	>1597
132	0.042	>50	>1196
133	0.02	0.095	5

134	0.048	4.72	98
135	0.042	4.55	108
136	0.19	>50	>263
137	0.281	>50	>178
138	0.029	17.75	616
139	0.046	38.5	841
140	2.13	>50	>23
141	0.076	>50	>661
142	0.27	>50	>185
143	0.199	>50	>251
144	0.046	40.02	864
145	0.004	3.21	730
146	0.152	21.97	145
147	0.009	17.62	1895
148	0.071	19.77	278
149	0.013	16.74	1298
150	0.006	2.9	509
151	0.049	31.4	642
152	0.009	2.66	283
154	0.085	29	343
155	0.421	>50	>119
166	0.153	>50	>327
170	0.015	7.35	507
171	0.276	>50	>181
172	0.194	>50	>257
173	0.011	>50	>4587
174	0.011	19.5	1857
175	0.0062	nd	nd
176	0.0585	nd	nd
177	0.01966	nd	nd
178	0.0186	nd	nd
179	0.02346	nd	nd

180	0.02047	nd	nd
181	0.03353	nd	nd
182	0.01242	nd	nd
183	0.03077	nd	nd
184	0.02698	nd	nd
185	0.06335	nd	nd
186	0.02036	nd	nd
187	0.34128	nd	nd
188	0.02466	nd	nd
189	0.01489	nd	nd
190	0.02421	nd	nd
191	0.01172	nd	nd
192	> 0.5	nd	nd
193	> 0.5	nd	nd
194	0.02697	nd	nd
195	0.01124	nd	nd
196	0.01236	nd	nd
197	0.00618	nd	nd
198	nd	nd	nd
199	0.02854	nd	nd
200	0.00629	nd	nd
201	0.0174	nd	nd
202	0.01383	nd	nd
203	0.0223	nd	nd
204	0.02738	nd	nd
205	0.03753	nd	nd
206	0.00501	nd	nd
207	0.1199	nd	nd
208	0.26403	nd	nd
209	0.13896	nd	nd
210	0.25691	nd	nd
211	0.01713	nd	nd

212	> 0.5	nd	nd
213	0.43216	nd	nd
214	0.01569	nd	nd
215	0.11576	nd	nd
216	0.03985	nd	nd
217	0.02083	nd	nd
218	0.033	nd	nd
219	0.02296	nd	nd
220	0.02403	nd	nd
221	0.14872	nd	nd
222	0.02366	nd	nd
223	0.03713	nd	nd
224	0.02116	nd	nd
225	0.02989	nd	nd
226	0.02301	nd	nd
227	> 0.5	nd	nd
228	> 0.5	nd	nd
229	> 0.5	nd	nd
230	0.17755	nd	nd
231	0.0509	nd	nd
232	0.01228	nd	nd
233	nd	nd	nd
234	nd	nd	nd
235	nd	nd	nd
236	nd	nd	nd
237	nd	nd	nd
238	0.05896	nd	nd
239	0.01764	nd	nd
240	0.20943	nd	nd
241	nd	nd	nd
242	0.16457	nd	nd
243	0.028	nd	nd

244	0.02025	nd	nd
245	0.07244	nd	nd
246	0.048	nd	nd
247	0.01607	nd	nd
248	0.04981	nd	nd
249	0.0412	nd	nd
250	0.07951	nd	nd
251	0.07812	nd	nd
252	0.00662	nd	nd
253	0.00758	nd	nd
254	0.01693	nd	nd
255	> 0.5	nd	nd
256	0.00889	nd	nd
257	0.00934	nd	nd
258	0.00911	nd	nd
259	> 0.5	nd	nd
260	0.05944	nd	nd
261	0.01701	nd	nd
262	0.17622	nd	nd
263	0.02835	nd	nd
264	0.02571	nd	nd
265	0.24417	nd	nd
266	0.01148	nd	nd
267	0.05643	nd	nd
268	0.06822	nd	nd
269	nd	nd	nd
270	0.42893	nd	nd
271	> 0.5	nd	nd
272	0.19406	nd	nd
273	0.07001	nd	nd
274	0.15519	nd	nd
275	0.03801	nd	nd

276	0.06218	nd	nd
277	> 0.5	nd	nd
278	0.15272	nd	nd
279	0.01623	nd	nd
280	0.24715	nd	nd
281	0.06022	nd	nd
282	0.09216	nd	nd
283	> 0.5	nd	nd
284	> 0.5	nd	nd
285	> 0.5	nd	nd
286	0.27896	nd	nd
287	nd	nd	nd
288	0.06432	nd	nd
289	0.02736	nd	nd
290	0.04468	nd	nd
291	0.05801	nd	nd
292	0.06916	nd	nd
293	0.06806	nd	nd
294	0.05981	nd	nd
295	0.04634	nd	nd
296	0.18237	nd	nd
297	0.01321	nd	nd
298	0.01948	nd	nd
299	0.07725	nd	nd
300	0.06215	nd	nd
301	0.05945	nd	nd
302	0.03238	nd	nd
303	> 0.5	nd	nd
304	0.41529	nd	nd
305	> 0.5	nd	nd
306	0.00716	nd	nd
307	> 0.5	nd	nd

308	> 0.5	nd	nd
309	> 0.5	nd	nd
310	0.00451	nd	nd
311	0.0334	nd	nd
312	0.01924	nd	nd
313	0.08289	nd	nd
314	0.24014	nd	nd
315	> 0.5	nd	nd
316	0.06749	nd	nd
317	0.08309	nd	nd
318	0.07695	nd	nd
319	0.03141	nd	nd
320	0.04158	nd	nd
321	0.02909	nd	nd
322	0.04445	nd	nd
323	0.09208	nd	nd
324	0.13417	nd	nd
325	0.25639	nd	nd
326	0.03509	nd	nd
327	0.00657	nd	nd
328	> 0.5	nd	nd
329	0.12652	nd	nd
330	> 0.5	nd	nd
331	> 0.5	nd	nd
332	> 0.5	nd	nd
333	0.10932	nd	nd
334	0.06592	nd	nd
335	0.03897	nd	nd
336	0.00749	nd	nd
337	0.12389	nd	nd
338	0.07113	nd	nd
339	> 0.5	nd	nd

340	> 0.5	nd	nd
341	> 0.5	nd	nd
342	> 0.5	nd	nd
343	0.05489	nd	nd
344	0.07147	nd	nd
345	> 0.5	nd	nd
346	0.01747	nd	nd
347	0.04681	nd	nd
348	0.0872	nd	nd
349	0.14571	nd	nd
350	0.31119	nd	nd
351	0.34452	nd	nd
352	0.15632	nd	nd
353	0.05828	nd	nd
354	0.0056	nd	nd
355	> 0.5	nd	nd
356	> 0.5	nd	nd
357	> 0.5	nd	nd
358	> 0.5	nd	nd
359	> 0.5	nd	nd
360	0.10622	nd	nd
361	> 0.5	nd	nd
362	0.17126	nd	nd
363	0.08692	nd	nd
364	0.18474	nd	nd
365	> 0.5	nd	nd
366	> 0.5	nd	nd
367	> 0.5	nd	nd
368	> 0.5	nd	nd
369	> 0.5	nd	nd
370	0.26334	nd	nd
371	> 0.5	nd	nd

372	> 0.5	nd	nd
374	> 0.5	nd	nd
375	> 0.5	nd	nd
376	> 0.5	nd	nd
377	0.08573	nd	nd
378	> 0.5	nd	nd
379	> 0.5	nd	nd
380	0.06849	nd	nd
381	0.07185	nd	nd
382	> 0.5	nd	nd
383	> 0.5	nd	nd
384	0.10121	nd	nd
385	0.05636	nd	nd
386	0.15353	nd	nd
387	0.08652	nd	nd
388	0.08288	nd	nd
389	0.02812	nd	nd
390	0.04118	nd	nd
391	> 0.5	nd	nd
392	nd	nd	nd
393	nd	nd	nd
394	nd	nd	nd
395	nd	nd	nd
396	> 0.5	nd	nd
397	nd	nd	nd
398	0.33382	nd	nd
399	> 0.5	nd	nd
400	0.00847	nd	nd
401	0.00538	nd	nd
402	0.01336	nd	nd
403	0.00292	nd	nd
404	0.00234	nd	nd

405	0.01162	nd	nd
406	0.02046	nd	nd
407	0.0081	nd	nd
408	0.00239	nd	nd
409	0.0012	nd	nd
410	0.01386	nd	nd
411	0.01145	nd	nd
412	0.00948	nd	nd
474	0.0934	nd	nd
475	0.223	nd	nd
477	>1.67	nd	nd
478	>5.0	nd	nd

nd = not determined

TABLE 3 shows the utility of compounds having Formula I to functionally inhibit anti-apoptotic Bcl-2 protein in a cellular context. FL5.12 is an IL-3 dependent prolymphocytic murine cell line that undergoes apoptosis upon IL-3 withdrawal as a result of the upregulation of pro-apoptotic Bcl-2 family proteins such as Bim and Puma. Stable overexpression of anti-apoptotic Bcl-2 protein (FL5.12/Bcl-2) protects against apoptosis induced by IL-3 withdrawal by sequestration of Bim and Puma. (Refs. Harada, et.al. *PNAS* **2004**, 101, 15313; Certo, et.al. *Cancer Cell* **2006,** 9, 351.) The ability of compounds to kill FL5.12/Bcl-2 cells upon IL-3 withdrawal is a direct measure of the compounds ability to inhibit anti-apoptotic Bcl-2 protein function. Compounds of Formula I are very effective in killing FL5.12/Bcl-2 cells under IL-3 withdrawal as demonstrated by low EC_{50} values.

Compounds of this invention bind to anti-apoptotic Bcl-2 proteins with high affinity and potently inhibit the function of anti-apoptotic Bcl-2 protein in a cellular context and are therefore expected to have utility in treatment of diseases during which anti-apoptotic Bcl-2 protein is expressed.

The anti-apoptotic Bcl-xL protein has been disclosed elsewhere (*Cell* **March 23, 2007**, 128, 1173-1176.) to be the major regulator of the survival of circulating platelets in animals. Genetic mutations to Bcl-xL protein that decrease Bcl-xL protein stability and half-life causes a decrease in platelet survival and life-span in mice bearing these mutations. A potent pharmacologic inhibitor of Bcl-xL, ABT-737, causes a rapid, concentration dependant decrease in circulating platelets following injection into C57BL/6 mice or in beagle canines

(*Cell* **March 23, 2007**, 128, 1173-1176.; *Cell Death Differ.* **May 2007**;14(5), 943-51). Thus, without being limited by theory, compounds of this invention that have reduced affinity for Bcl-xL can be expected to show lower levels of platelet apoptosis than previously reported compounds with higher Bcl-xL affinity.

The effect of compounds on platelet survival can be directly evaluated ex vivo by examining the viability of isolated canine platelets in the presence of various concentrations of compound. The data in Table 3 shows that compounds of Formula I have significantly less to no effect on the viability of isolated canine platelets ex vivo (higher EC_{50} values) compared to compounds previously disclosed in PCT US 2004/36770 and PCT US 2004/367911, as exemplified by ABT-737. Furthermore, the functional selectivity ratio (canine platelet EC_{50} : FL5.12/Bcl-2 EC_{50}) for compounds of Formula I ranges from 32 to 4849, which is significantly higher than that for compounds previously disclosed in PCT US 2004/36770 and PCT US 2004/367911, as exemplified by ABT-737.

Because compounds having Formula I bind to anti-apoptotic Bcl-2 protein with comparatively lower binding to anti-apoptotic Bcl- X_L protein, the compounds would have utility as medicaments for the treatment of cancer and autoimmune and immune diseases with reduction of the side effect of thrombocytopenia (i.e., they would be circulating platelet-sparing). Involvement of Bcl- X_L in thrombocytopenia is disclosed in *Cell* **March 23, 2007**, 128, 1173-1176. As described herein and elsewhere, a potent inhibitor of Bcl- X_L, ABT-737, causes a dose-dependent decrease in circulating platelets following injection into C57BL/6 mice or in canines (*Cell Death Differ.* **May 2007**;14(5), 943-51). Compounds with reduced Bcl- X_L affinity exhibit substantially less to no decrease in circulating platelets. Thus, without being limited by theory, compounds of this invention that have reduced affinity for Bcl- X_L can be expected to show lower levels of platelet apoptosis than previously reported compounds with higher Bcl- X_L affinity. The EC_{50} data in TABLE 2 show the effects of administration of compounds of this invention, compared to ABT-737, on canine platelets.

Involvement of Bcl-2 protein in bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer spleen cancer, and the like is described in commonly-owned PCT US 2004/36770, published as WO 2005/049593, and PCT US 2004/37911, published as WO 2005/024636.

Involvement of Bcl-2 proteins in immune and autoimmune diseases is described in *Current Allergy and Asthma Reports* **2003**, 3, 378-384; *British Journal of Haematology* **2000**, 110(3), 584-90; *Blood* **2000,** 95(4), 1283-92; and *New England Journal of Medicine* **2004**, 351(14), 1409-1418.

Involvement of Bcl-2 protein in arthritis is disclosed in commonly-owned United States Provisional Patent Application Serial No. 60/988,479.

Involvement of Bcl-2 protein in bone marrow transplant rejection is disclosed in commonly-owned United States Patent Application Serial No. 11/941,196 (now U.S. Published Application 20080182845A1).

Overexpression of Bcl-2 protein correlates with resistance to chemotherapy, clinical outcome, disease progression, overall prognosis or a combination thereof in various cancers and disorders of the immune system. Cancers include, but are not limited to, hematologic and solid tumor types such as acoustic neuroma, acute leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia (monocytic, myeloblastic, adenocarcinoma, angiosarcoma, astrocytoma, myelomonocytic and promyelocytic), acute t-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, brain cancer, breast cancer (including estrogen-receptor positive breast cancer), bronchogenic carcinoma, Burkitt's lymphoma, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fibrosarcoma, gastric carcinoma, germ cell testicular cancer, gestational trophoblastic disease, glioblastoma, head and neck cancer, heavy chain disease, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, liposarcoma, lung cancer (including small cell lung cancer and non-small cell lung cancer), lymphangioendothelio-sarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma (lymphoma, including diffuse large B-cell lymphoma, follicular lymphoma, Hodgkin's lymphoma and non-Hodgkin's lymphoma), malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, leukemia, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, oligodendroglioma, oral cancer, osteogenic

sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, peripheral T-cell lymphoma, pinealoma, polycythemia vera, prostate cancer (including hormone-insensitive (refractory) prostate cancer), rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small cell lung carcinoma, solid tumors (carcinomas and sarcomas), stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, testicular cancer (including germ cell testicular cancer), thyroid cancer, Waldenström's macroglobulinemia, testicular tumors, uterine cancer, Wilms' tumor and the like.

It is also expected that compounds having Formula I would inhibit growth of cells expressing Bcl-2 protein derived from a pediatric cancer or neoplasm including embryonal rhabdomyosarcoma, pediatric acute lymphoblastic leukemia, pediatric acute myelogenous leukemia, pediatric alveolar rhabdomyosarcoma, pediatric anaplastic ependymoma, pediatric anaplastic large cell lymphoma, pediatric anaplastic medulloblastoma, pediatric atypical teratoid/rhabdoid tumor of the central nervous system, pediatric biphenotypic acute leukemia, pediatric Burkitts lymphoma, pediatric cancers of Ewing's family of tumors such as primitive neuroectodermal rumors, pediatric diffuse anaplastic Wilm's tumor, pediatric favorable histology Wilm's tumor, pediatric glioblastoma, pediatric medulloblastoma, pediatric neuroblastoma, pediatric neuroblastoma-derived myelocytomatosis, pediatric pre-B-cell cancers (such as leukemia), pediatric psteosarcoma, pediatric rhabdoid kidney tumor, pediatric rhabdomyosarcoma, and pediatric T-cell cancers such as lymphoma and skin cancer and the like.

Autoimmune disorders include acquired immunodeficiency disease syndrome (AIDS), autoimmune lymphoproliferative syndrome, hemolytic anemia, inflammatory diseases, and thrombocytopenia, acute or chronic immune disease associated with organ transplantation, Addison's disease, allergic diseases, alopecia, alopecia areata, atheromatous disease/arteriosclerosis, atherosclerosis, arthritis (including osteoarthritis, juvenile chronic arthritis, septic arthritis, Lyme arthritis, psoriatic arthritis and reactive arthritis), autoimmune bullous disease, abetalipoprotemia, acquired immunodeficiency-related diseases, acute immune disease associated with organ transplantation, acquired acrocyanosis, acute and chronic parasitic or infectious processes, acute pancreatitis, acute renal failure, acute rheumatic fever, acute transverse myelitis, adenocarcinomas, aerial ectopic beats, adult (acute) respiratory distress syndrome, AIDS dementia complex, alcoholic cirrhosis, alcohol-induced liver injury, alcohol-induced hepatitis, allergic conjunctivitis, allergic contact dermatitis, allergic rhinitis, allergy and asthma, allograft rejection, alpha-l- antitrypsin

deficiency, Alzheimer's disease, amyotrophic lateral sclerosis, anemia, angina pectoris, ankylosing spondylitis associated lung disease, anterior horn cell degeneration, antibody mediated cytotoxicity, antiphospholipid syndrome, anti-receptor hypersensitivity reactions, aortic and peripheral aneurysms, aortic dissection, arterial hypertension, arteriosclerosis, arteriovenous fistula, arthropathy, asthenia, asthma, ataxia, atopic allergy, atrial fibrillation (sustained or paroxysmal), atrial flutter, atrioventricular block, atrophic autoimmune hypothyroidism, autoimmune haemolytic anaemia, autoimmune hepatitis, type-1 autoimmune hepatitis (classical autoimmune or lupoid hepatitis), autoimmune mediated hypoglycaemia, autoimmune neutropaenia, autoimmune thrombocytopaenia, autoimmune thyroid disease, B cell lymphoma, bone graft rejection, bone marrow transplant (BMT) rejection, bronchiolitis obliterans, bundle branch block, burns, cachexia, cardiac arrhythmias, cardiac stun syndrome, cardiac tumors, cardiomyopathy, cardiopulmonary bypass inflammation response, cartilage transplant rejection, cerebellar cortical degenerations, cerebellar disorders, chaotic or multifocal atrial tachycardia, chemotherapy associated disorders, chlamydia, choleosatatis, chronic alcoholism, chronic active hepatitis, chronic fatigue syndrome, chronic immune disease associated with organ transplantation, chronic eosinophilic pneumonia, chronic inflammatory pathologies, chronic mucocutaneous candidiasis, chronic obstructive pulmonary disease (COPD), chronic salicylate intoxication, colorectal common varied immunodeficiency (common variable hypogammaglobulinaemia), conjunctivitis, connective tissue disease associated interstitial lung disease, contact dermatitis, Coombs positive haemolytic anaemia, cor pulmonale, Creutzfeldt-Jakob disease, cryptogenic autoimmune hepatitis, cryptogenic fibrosing alveolitis, culture negative sepsis, cystic fibrosis, cytokine therapy associated disorders, Crohn's disease, dementia pugilistica, demyelinating diseases, dengue hemorrhagic fever, dermatitis, dermatitis scleroderma, dermatologic conditions, dermatomyositis/polymyositis associated lung disease, diabetes, diabetic arteriosclerotic disease, diabetes mellitus, Diffuse Lewy body disease, dilated cardiomyopathy, dilated congestive cardiomyopathy, discoid lupus erythematosus, disorders of the basal ganglia, disseminated intravascular coagulation, Down's Syndrome in middle age, drug-induced interstitial lung disease, drug-induced hepatitis, drug-induced movement disorders induced by drugs which block CNS dopamine, receptors, drug sensitivity, eczema, encephalomyelitis, endocarditis, endocrinopathy, enteropathic synovitis, epiglottitis, Epstein-Barr virus infection, erythromelalgia, extrapyramidal and cerebellar disorders, familial hematophagocytic lymphohistiocytosis, fetal thymus implant rejection, Friedreich's ataxia, functional peripheral arterial disorders, female infertility, fibrosis, fibrotic lung disease, fungal sepsis, gas

gangrene, gastric ulcer, giant cell arteritis, glomerular nephritis, glomerulonephritides, Goodpasture's syndrome, goitrous autoimmune hypothyroidism (Hashimoto's disease), gouty arthritis, graft rejection of any organ or tissue, graft versus host disease, gram negative sepsis, gram positive sepsis, granulomas due to intracellular organisms, group B streptococci (GBS) infection, Grave's disease, haemosiderosis associated lung disease, hairy cell leukemia, hairy cell leukemia, Hallerrorden-Spatz disease, Hashimoto's thyroiditis, hay fever, heart transplant rejection, hemachromatosis, hematopoietic malignancies (leukemia and lymphoma), hemolytic anemia, hemolytic uremic syndrome/thrombolytic thrombocytopenic purpura, hemorrhage, Henoch-Schoenlein purpurea, Hepatitis A, Hepatitis B, Hepatitis C, HIV infection/HIV neuropathy, Hodgkin's disease, hypoparathyroidism, Huntington's chorea, hyperkinetic movement disorders, hypersensitivity reactions, hypersensitivity pneumonitis, hyperthyroidism, hypokinetic movement disorders, hypothalamic-pituitary-adrenal axis evaluation, idiopathic Addison's disease, idiopathic leucopaenia, idiopathic pulmonary fibrosis, idiopathic thrombocytopaenia, idiosyncratic liver disease, infantile spinal muscular atrophy, infectious diseases, inflammation of the aorta, inflammatory bowel disease, insulin dependent diabetes mellitus, interstitial pneumonitis, iridocyclitis/uveitis/optic neuritis, ischemia-reperfusion injury, ischemic stroke, juvenile pernicious anaemia, juvenile rheumatoid arthritis, juvenile spinal muscular atrophy, Kaposi's sarcoma, Kawasaki's disease, kidney transplant rejection, legionella, leishmaniasis, leprosy, lesions of the corticospinal system, linear IgA disease, lipidema, liver transplant rejection, Lyme disease, lymphederma, lymphocytic infiltrative lung disease, malaria, male infertility idiopathic or NOS, malignant histiocytosis, malignant melanoma, meningitis, meningococcemia, microscopic vasculitis of the kidneys, migraine headache, mitochondrial multi-system disorder, mixed connective tissue disease, mixed connective tissue disease associated lung disease, monoclonal gammopathy, multiple myeloma, multiple systems degenerations (Mencel Dejerine-Thomas Shi-Drager and Machado-Joseph), myalgic encephalitis/Royal Free Disease, myasthenia gravis, microscopic vasculitis of the kidneys, mycobacterium avium intracellulare, mycobacterium tuberculosis, myelodyplastic syndrome, myocardial infarction, myocardial ischemic disorders, nasopharyngeal carcinoma, neonatal chronic lung disease, nephritis, nephrosis, nephrotic syndrome, neurodegenerative diseases, neurogenic I muscular atrophies, neutropenic fever, Non-alcoholic Steatohepatitis, occlusion of the abdominal aorta and its branches, occlusive arterial disorders, organ transplant rejection, orchitis/epidydimitis, orchitis/vasectomy reversal procedures, organomegaly, osteoarthrosis, osteoporosis, ovarian failure, pancreas transplant rejection, parasitic diseases, parathyroid transplant rejection,

Parkinson's disease, pelvic inflammatory disease, pemphigus vulgaris, pemphigus foliaceus, pemphigoid, perennial rhinitis, pericardial disease, peripheral atherlosclerotic disease, peripheral vascular disorders, peritonitis, pernicious anemia, phacogenic uveitis, pneumocystis carinii pneumonia, pneumonia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome), post perfusion syndrome, post pump syndrome, post-MI cardiotomy syndrome, postinfectious interstitial lung disease, premature ovarian failure, primary biliary cirrhosis, primary sclerosing hepatitis, primary myxoedema, primary pulmonary hypertension, primary sclerosing cholangitis, primary vasculitis, Progressive supranucleo Palsy, psoriasis, psoriasis type 1, psoriasis type 2, psoriatic arthropathy, pulmonary hypertension secondary to connective tissue disease, pulmonary manifestation of polyarteritis nodosa, post-inflammatory interstitial lung disease, radiation fibrosis, radiation therapy, Raynaud's phenomenon and disease,, Refsum's disease, regular narrow QRS tachycardia, Reiter's disease, renal disease NOS, renovascular hypertension, reperfusion injury, restrictive cardiomyopathy, rheumatoid arthritis associated interstitial lung disease, rheumatoid spondylitis, sarcoidosis, Schmidt's syndrome, scleroderma, senile chorea, Senile Dementia of Lewy body type, sepsis syndrome, septic shock, seronegative arthropathies, shock, sickle cell anemia, Sjögren's disease associated lung disease, Sjörgren's syndrome, skin allograft rejection, skin changes syndrome, small bowel transplant rejection, sperm autoimmunity, multiple sclerosis (all subtypes), spinal ataxia, spinocerebellar degenerations, spondyloarthropathy, sporadic, polyglandular deficiency type I sporadic, polyglandular deficiency type II, Still's disease, streptococcal myositis, stroke, structural lesions of the cerebellum, Subacute sclerosing panencephalitis, sympathetic ophthalmia, Syncope, syphilis of the cardiovascular system, systemic anaphylaxis, systemic inflammatory response syndrome, systemic onset juvenile rheumatoid arthritis, systemic lupus erythematosus, systemic lupus erythematosus-associated lung disease, systemic sclerosis, systemic sclerosis-associated interstitial lung disease, T-cell or FAB ALL, Takayasu's disease/arteritis, Telangiectasia, Th2 Type and Th1 Type mediated diseases, thromboangitis obliterans, thrombocytopenia, thyroiditis, toxicity, toxic shock syndrome, transplants, trauma/hemorrhage, type-2 autoimmune hepatitis (anti-LKM antibody hepatitis), type B insulin resistance with acanthosis nigricans, type III hypersensitivity reactions, type IV hypersensitivity, ulcerative colitic arthropathy, ulcerative colitis, unstable angina, uremia, urosepsis, urticaria, uveitis, valvular heart diseases, varicose veins, vasculitis, vasculitic diffuse lung disease, venous diseases, venous thrombosis, ventricular fibrillation, vitiligo

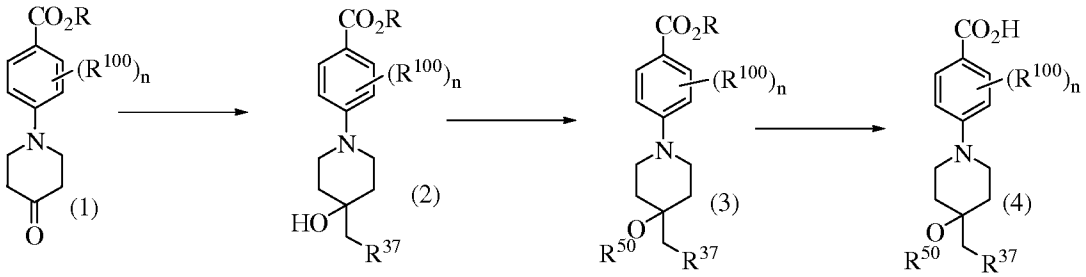
acute liver disease, viral and fungal infections, vital encephalitis/aseptic meningitis, vital-associated hemaphagocytic syndrome, Wegener's granulomatosis, Wernicke-Korsakoff syndrome, Wilson's disease, xenograft rejection of any organ or tissue, yersinia and salmonella-associated arthropathy and the like.

Schemes and Experimentals

The following schemes are presented to provide what is believed to be the most useful and readily understood description of procedures and conceptual aspects of this invention. Compounds of this invention may be made by synthetic chemical processes, examples of which are shown herein. It is meant to be understood that the order of the steps in the processes may be varied, that reagents, solvents and reaction conditions may be substituted for those specifically mentioned, and that vulnerable moieties may be protected and deprotected, as necessary.

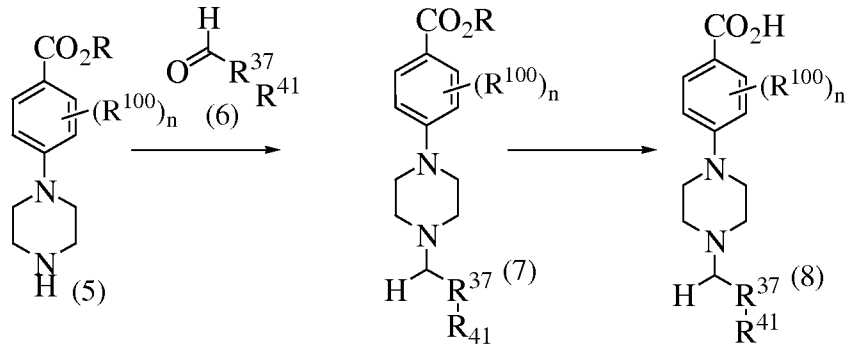
The following abbreviations have the meanings indicated. ADDP means 1,1'-(azodicarbonyl)dipiperidine; AD-mix-β means a mixture of $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, and K_2SO_4); 9-BBN means 9-borabicyclo(3.3.1)nonane; Boc means tert-butoxycarbonyl; $(DHQD)_2PHAL$ means hydroquinidine 1,4-phthalazinediyl diethyl ether; DBU means 1,8-diazabicyclo(5.4.0)undec-7-ene; DIBAL means diisobutylaluminum hydride; DIEA means diisopropylethylamine; DMAP means N,N-dimethylaminopyridine; DMF means N,N-dimethylformamide; dmpe means 1,2-bis(dimethylphosphino)ethane; DMSO means DMSO; dppb means 1,4-bis(diphenylphosphino)-butane; dppe means 1,2-bis(diphenylphosphino)ethane; dppf means 1,1'-bis(diphenylphosphino)ferrocene; dppm means 1,1-bis(diphenylphosphino)methane; EDAC·HCl means 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; Fmoc means fluorenylmethoxycarbonyl; HATU means O-(7-azabenzotriazol-1-yl)-N,N'N'N'-tetramethyluronium hexafluorophosphate; HMPA means hexamethylphosphoramide; IPA means isopropyl alcohol; MP-BH_3 means macroporous triethylammonium methylpolystyrene cyanoborohydride; TEA means triethylamine; TFA means trifluoroacetic acid; THF means tetrahydrofuran; NCS means N-chlorosuccinimide; NMM means N-methylmorpholine; NMP means N-methylpyrrolidine; PPh_3 means triphenylphosphine.

SCHEME 1



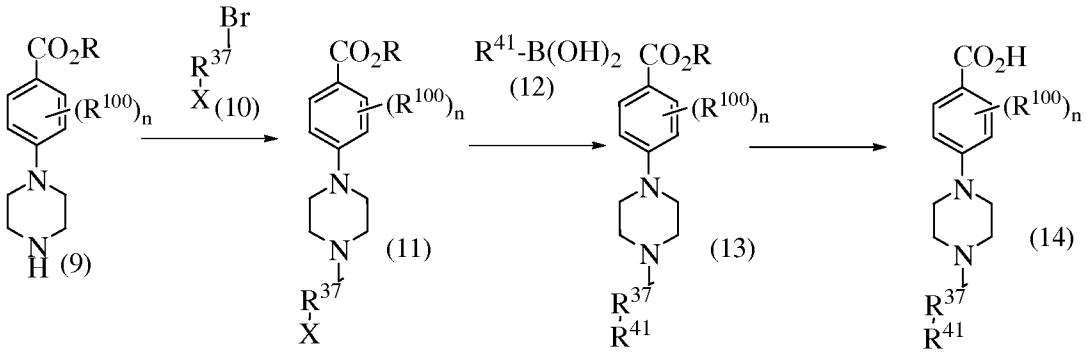
Compounds of Formula (4) can be prepared as shown in SCHEME 1, and can be used as described in SCHEME 7 to prepare compounds of Formula (I), which are representative of the compounds of the present invention. Compounds of Formula (1) wherein R is alkyl, R^{100} is as described for substituents on R^{26}, and n is 1, 2, or 3; can be converted to compounds of Formula (2) using $R^{37}CH^2MgX^1$, wherein X^1 is a halide, in a solvent such as but not limited to ether or tetrahydrofuran. Compounds of Formula (3) can be prepared from compounds of Formula (2) using a strong base such as NaH and $R^{50}X^2$, wherein X^2 is a halide and R^{50a} is as described herein. Compounds of Formula (3), when treated with aqueous NaOH or LiOH,will provide compounds of Formula (4).

SCHEME 2



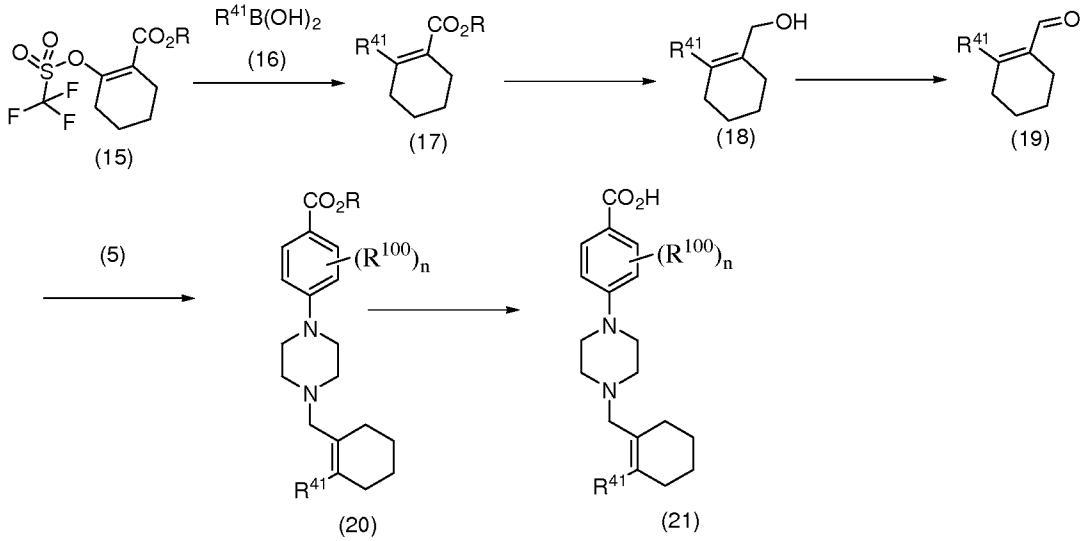
As shown in SCHEME 2, compounds of Formula (5) can be reacted with compounds of Formula (6) and a reducing agent to provide compounds of Formula (7). Examples of reducing agents include sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, polymer supported cyanoborohydride, and the like. The reaction is typically performed in a solvent such as but not limited to methanol, tetrahydrofuran, and dichloromethane or mixtures thereof. Compounds of Formula (8) can be prepared from compounds of Formula (7) as described in SCHEME 1, and can be used as described in SCHEME 7 to prepare compounds of Formula (I).

SCHEME 3



Compounds of Formula (9), when reacted with a compound a Formula (10) wherein X is a halide or triflate, and a base will provide a compound of Formula (11). Bases useful in the reaction include triethylamine, diisopropylethylamine and the like. Compounds of Formula (13), wherein R^{41} is as described herein for substituents on R^{37}, can be prepared from compounds of Formula (11) and compounds of Formula (12) using Suzuki coupling conditions known to those skilled in the art and readily available in the literature. Compounds of Formula (14) can be prepared from compounds of Formula (13) as described in SCHEME 1, and can be used as described in SCHEME 7 to prepare compounds of Formula (I).

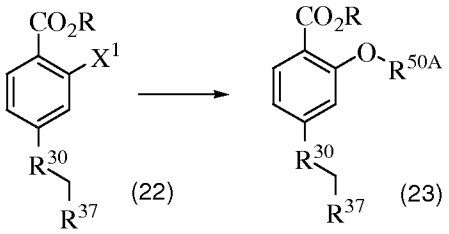
SCHEME 4



As shown in SCHEME 4, compounds of Formula (17) can be prepared from compounds of Formula (15) and compounds of Formula (16), wherein R is alkyl and R^{41} is as described herein, using Suzuki coupling conditions known to those skilled in the art and readily available in the literature. Compounds of Formula (17) can be reduced to compounds of

Formula (18) using a reducing agent such as $LiAlH_4$ in a solvent such as but not limited to diethyl ether or THF. Compounds of Formula (19) can be prepared from compounds of Formula (18) using Dess-Martin periodinane or Swern oxidation conditions known to those skilled in the art and readily available in the literature. Compounds of Formula (19) can be reacted with a compound of Formula (5) and a reducing agent to provide compounds of Formula (20). Examples of reducing agents include sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, polymer supported cyanoborohydride, and the like. The reaction is typically performed in a solvent such as but not limited to methanol, tetrahydrofuran, 1,2-dichloroethane, and dichloromethane or mixtures thereof. Compounds of Formula (21) can be prepared from compounds of Formula (20) as described in SCHEME 1, and can be used as described in SCHEME 7to prepare compounds of Formula (I).

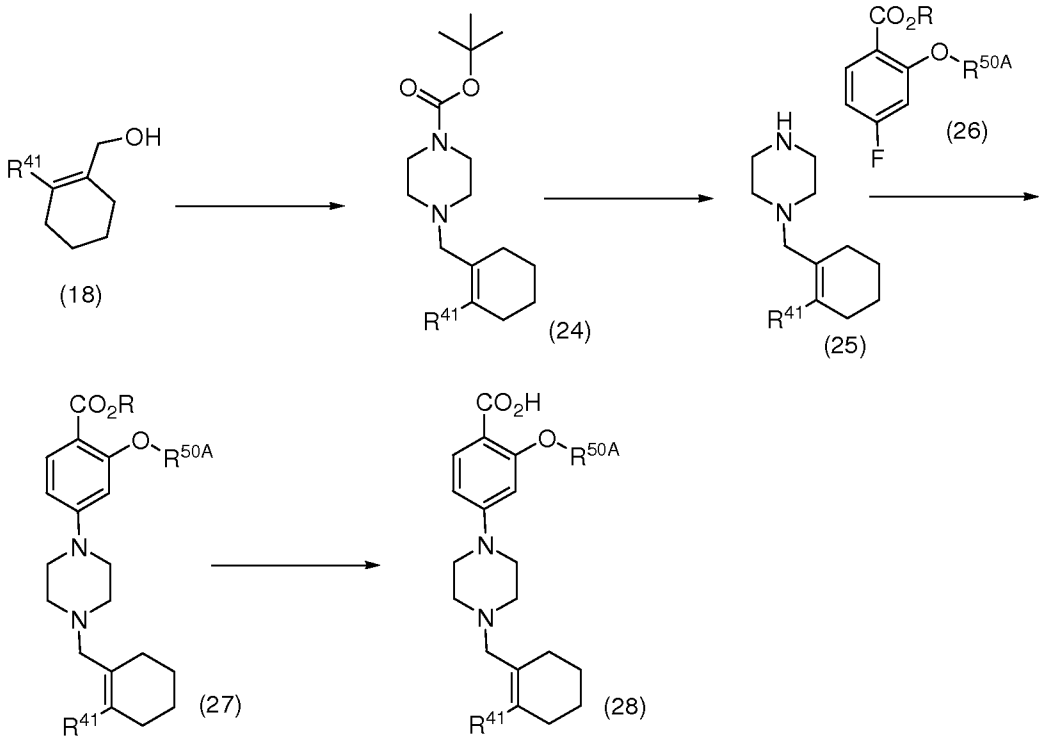
SCHEME 5



As shown in SCHEME 5, compounds of Formula (22), wherein R is alkyl, may be converted to compounds of Formula (23) by reacting the former, wherein X^1 is Cl, Br, I, or CF_3SO_3-, and compounds of Formula R^{50A}-OH and a catalyst, with or without a first base. Examples of catalysts include copper(I) trifluoromethanesulfonate toluene complex, $PdCl_2$, $Pd(OAc)_2$, and $Pd_2(dba)_3$. Examples of first bases include triethylamine, N,N-diisopropylethylamine, Cs_2CO_3, Na_2CO_3, K_3PO_4, and mixtures thereof.

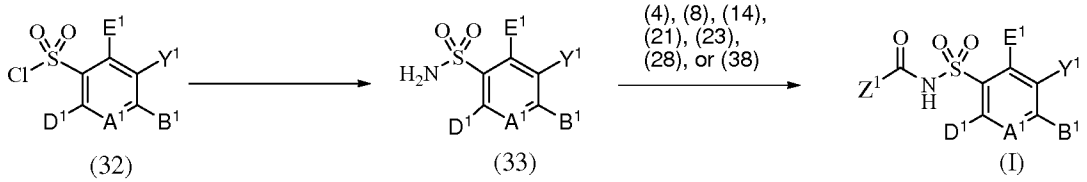
Compounds of Formula (22) may also be converted to compounds of Formula (23) by reacting the former, when X^1 is Cl, F, or NO_2, and compounds of Formula R^{50A}-OH with a first base. Examples of first bases include triethylamine, N,N-diisopropylethylamine, Cs_2CO_3, Na_2CO_3, K_3PO_4, and mixtures thereof.

SCHEME 6



Compounds of Formula (18) can be reacted with mesyl chloride and a base such as but not limited to triethylamine, followed by N-t-butoxycarbonylpiperazine, to provide compounds of Formula (24). Compounds of Formula (25) can be prepared by reacting compounds of Formula (24) with triethylsilane and trifluoroacetic acid. Compounds of Formula (25) can be reacted with compounds of Formula (26) and HK_2PO_4 to provide compounds of Formula (27) in a solvent such as but not limited to dimethylsulfoxide. Compounds of Formula (28) can be prepared from compounds of Formula (27) as described in SCHEME 1, and can be used as described in SCHEME 7 to prepare compounds of Formula (I).

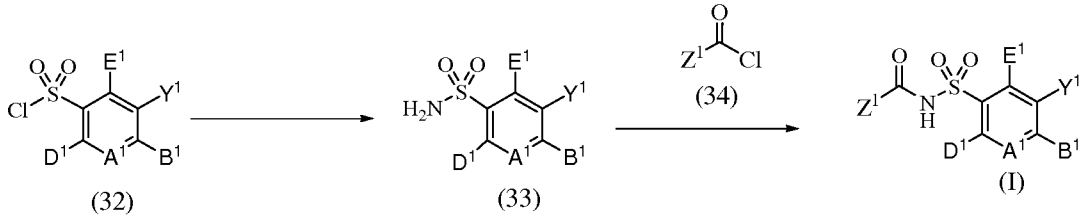
SCHEME 7



As shown in SCHEME 7, compounds of Formula (32), which can be prepared as described herein, may be converted to compounds of Formula (33) by reacting the former with ammonia. Compounds of Formula (33) may be converted to compounds of Formula (I) by

reacting the former and compounds of Formula (4), (8), (14), (21), (23), (28), or (38) and a coupling agent, with or without a first base. Examples of coupling agents include 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride, 1,1'-carbonyldiimidazole, and benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate. Examples of first bases include triethylamine, N,N-diisopropylethylamine, 4-(dimethylamino)pyridine, and mixtures thereof.

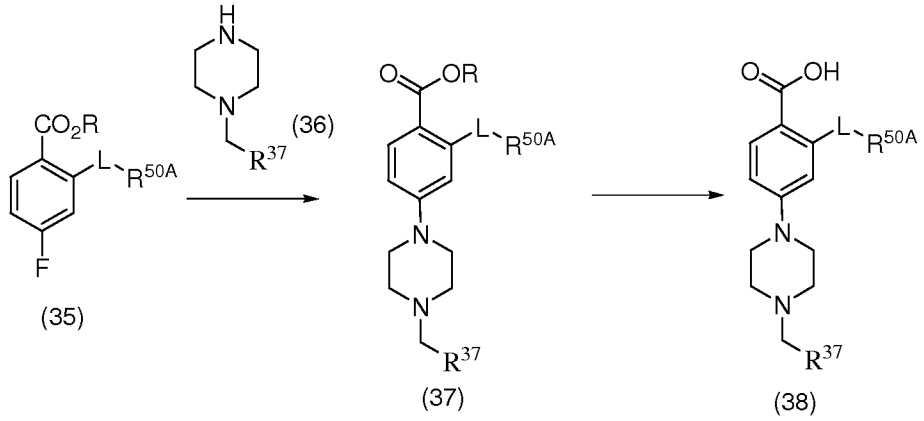
SCHEME 8



(32) (33) (34) (I)

Compounds of Formula (33), prepared as described in SCHEME 7, can also be converted to compounds of Formula (I) by reacting the former and compounds of Formula (34) and a first base. Examples of first bases include but are not limited to sodium hydride, triethylamine, N,N-diisopropylethylamine, 4-(dimethylamino)pyridine, and mixtures thereof.

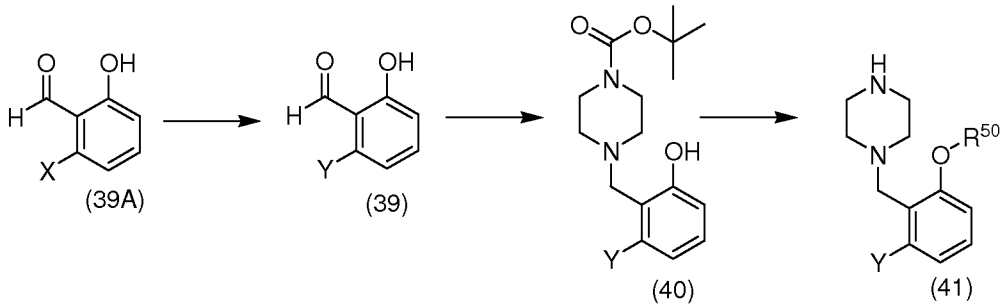
SCHEME 9



(35) (36) (37) (38)

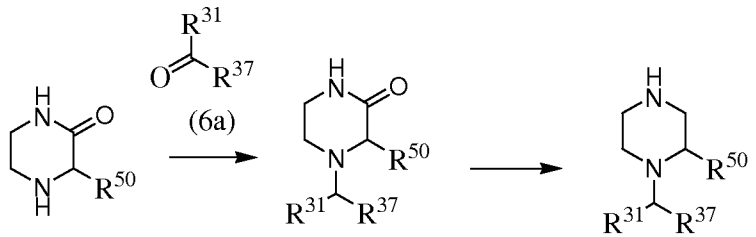
As shown in SCHEME 9, compounds of Formula (35), wherein L is a bond, alkyl, O, S, S(O), $S(O)_2$, NH, etc., can be reacted with compounds of Formula (36), to provide compounds of Formula (37). The reaction is typically performed at elevated temperatures in a solvent such as but not limited to dimethylsulfoxide, and may require the use of a base such as but not limited to potassium phosphate, potassium carbonate, and the like. Compounds of Formula (38) can be prepared from compounds of Formula (37) as described in SCHEME 1, and can be used as described in SCHEME 7 to prepare compounds of Formula (I).

SCHEME 10



Compounds of Formula (39), wherein Y is as described herein for substituents on R^{37}, can be prepared from compounds of Formula (39A) wherein X is a halide or triflate, and Y-$B(OH)_2$ using Suzuki coupling conditions known to those skilled in the art and readily available in the literature. Compounds of Formula (39) can be reacted with tert-butyl piperazine-1-carboxylate and a reducing agent such as sodium triacetoxyborohydride to provide compounds of Formula (40). The reaction is typically performed in a solvent such as but not limited to methylene chloride. Compounds of Formula (41) can be prepared from compounds of Formula (40) by reacting the latter with $R^{50}X$, wherein X is a halide, and NaH in a solvent such as N,N-dimethylformamide, and then the resulting material can be treated with triethylsilane and trifluoroacetic acid in dichloromethane. Compounds of Formula (41) can be used as described in Scheme 9 wherein CH_2R^{37} is as shown in Formula (41).

SCHEME 11



As shown in SCHEME 11, substituted piperazin-2-ones wherein R^{50} is alkyl, can be reacted with compounds of Formula (6a) and a reducing agent such as sodium triacetoxyborohydride in dichloromethane to provide compounds of Formula (42). Compounds of Formula (42) can be reduced to compounds of Formula (43) using a reducing agent such as but not limited to lithium aluminum hydride in a solvent such as but not limited to tetrahydrofuran. Compounds of Formula (43) can be used as described in Scheme 9 wherein CH_2R^{37} is as shown in Formula (43).

The following examples are presented to provide what is believed to be the most useful and readily understood description of procedures and conceptual aspects of this invention. The exemplified compounds were named using ACD/ChemSketch Version 5.06 (05 June 2001, Advanced Chemistry Development Inc. ,Toronto, Ontario), ACD/ChemSketch Version 12.01 (13 May 2009), or ChemDraw® Ver. 9.0.5 (CambridgeSoft, Cambridge, MA). Intermediates were named using ChemDraw® Ver. 9.0.5 (CambridgeSoft, Cambridge, MA).

EXAMPLE 1

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

EXAMPLE 1A

tert-butyl 4-((4'-chlorobiphenyl-2-yl)methyl)piperazine-1-carboxylate

4'-Chlorobiphenyl-2-carbaldehyde (EXAMPLE 27C) (4.1 g), tert-butyl piperazine-1-carboxylate (4.23 g), and sodium triacetoxyborohydride (5.61 g) in CH_2Cl_2 (60 mL) were combined stirred for 24 hours. The reaction was quenched with methanol and poured into ether. The solution was washed with water and brine, concentrated, and chromatographed on silica gel with 2-25% ethyl acetate/hexanes.

EXAMPLE 1B

1-((4'-chlorobiphenyl-2-yl)methyl)piperazine

EXAMPLE 1A (3.0 g) and triethylsilane (1 mL) were stirred in CH_2Cl_2 (30 mL) and trifluoroacetic acid (30 mL) for 2 hours, and the reaction was concentrated, and then taken up in ether and concentrated again. The product was used without further purification.

EXAMPLE 1C

methyl 4-fluoro-2-phenoxybenzoate

Methyl 2-bromo-4-fluorobenzoate (1 g), phenol (0.565 g), cesium carbonate (1.96 g), copper(I) triflate toluene complex (0.087 g), and ethyl acetate (0.034 mL) in toluene (12 mL) was stirred at 110°C for 24 hours. The reaction was cooled and chromatographed on silica gel with 5% ethyl acetate/hexanes.

EXAMPLE 1D

methyl 4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxybenzoate

EXAMPLE 1C (630 mg), EXAMPLE 1B , and K_2CO_3 (707 mg) were stirred in dimethylsulfoxide at 125°C for 5 hours. The reaction was cooled and chromatographed on silica gel with 10% ethyl acetate/hexanes.

EXAMPLE 1E

4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxybenzoic acid

EXAMPLE 1D (600 mg) was stirred in 25 mL 2:1 dioxane/1M NaOH at 60°C for 24 hours. The solution was cooled and adjusted to pH 4 with NaH_2PO_4 solution and concentrated HCl, and extracted with ethyl acetate. The extract was washed with brine and dried (Na_2SO_4), filtered and concentrated.

EXAMPLE 1F

3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

4-Fluoro-3-nitrobenzenesulfonamide (2.18 g), (tetrahydropyran-4-yl)methylamine (1.14 g), and triethylamine (1 g) were stirred in tetrahydrofuran (30 mL) for 24 hours. The solution was diluted with ethyl acetate, washed with NaH_2PO_4 solution and brine, and dried (Na_2SO_4), filtered and concentrated. The product was triturated from ethyl acetate.

EXAMPLE 1G

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

EXAMPLE 1E (90 mg), EXAMPLE 1F (45 mg), 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (65 mg), and 4-dimethylaminopyridine (22 mg) were stirred in CH_2Cl_2 (4 mL) for 24 hours. The reaction was cooled and chromatographed on silica gel with 20-100% ethyl acetate/hexanes. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.55 (brs, 1H), 8.63 (t, 1H), 8.47 (d, 1H), 7.75 (d, 1H), 7.46 (m, 6H), 7.35 (m, 2H), 7.24 (m, 3H), 7.15 (d, 1H), 6.99 (dd, 1H), 6.82 (d, 2H), 6.75 (d, 1H), 6.38 (d, 1H), 3.86 (br d, 2H), 3.49 (m, 2H), 3.37 (br s, 2H), 3.15 (br s, 4H), 2.34 (br s, 4H), 1.91 (br s, 4H), 1.64 (br d, 2H), 1.29 (m, 3H).

EXAMPLE 2

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-phenoxy-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 2A

4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

4-Aminobenzenesulfonamide (6.80 g), tetrahydropyran-4-carboxaldehyde (4.96 g), and sodium triacetoxyborohydride (16.74 g) in tetrahydrofuran (300 mL) and acetic acid (15 mL) were stirred in for 24 hours. The reaction was concentrated and taken up in ethyl acetate. The resulting solution was washed with water and brine, concentrated, and chromatographed on silica gel with 50% ethyl acetate/hexanes.

EXAMPLE 2B

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-phenoxy-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 2A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6/D_2O) δ 7.54 (d, 1H), 7.46 (m, 8H), 7.36 (m, 4H), 7.24 (d, 1H), 7.13 (dd, 1H), 6.93 (d, 2H), 6.75 (d, 1H), 6.55 (d, 2H), 6.30 (d, 1H), 3.86 (dd, 2H), 3.36 (s, 2H), 3.28 (t, 2H), 3.10 (br s, 4H), 2.96 (d, 2H), 2.32 (br s, 4H), 1.76 (m, 1H), 1.64 (d, 2H), 1.20 (m, 2H).

EXAMPLE 3

2-(benzyloxy)-4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 3A

methyl 2-(benzyloxy)-4-fluorobenzoate

Methyl 4-fluoro-2-hydroxybenzoate (2.00 g), benzyl bromide (1.54 mL), and cesium carbonate (4.60 g) in N,N-dimethylformamide (50 mL) were stirred for 24 hours. The reaction was taken up in ether and washed with 3x 1M NaOH solution, and brine, then concentrated to give the pure product.

EXAMPLE 3B

methyl 2-(benzyloxy)-4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 3A for EXAMPLE 1C in EXAMPLE 1D.

EXAMPLE 3C

2-(benzyloxy)-4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 3B for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 3D

2-(benzyloxy)-4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 3C for EXAMPLE 1E in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 10.90 (br s, 1H), 8.66 (m, 1H), 8.59 (s, 1H), 7.82 (d, 1H), 7.33-7.55 (m, 12H), 7.18-7.27 (m, 3H), 6.61 (s, 1H), 6.56 (d, 1H), 5.22 (s, 2H), 3.86 (br d, 2H), 3.40 (m, 2H), 3.31 (m, 8H), 2.34 (br s, 4H), 1.91 (br s, 2H), 1.64 (br d, 2H), 1.29 (m, 3H).

EXAMPLE 4

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(2-phenylethoxy)benzamide

EXAMPLE 4A

methyl 4-fluoro-2-phenethoxybenzoate

Methyl 4-fluoro-2-hydroxybenzoate (1.00 g) and phenethyl alcohol (0.64 mL) were added to triphenylphosphine (1.54 g) and diisopropylazodicarboxylate (1.04 mL) in tetrahydrofuran (20 mL) at 0°C, and the reaction was stirred at room temperature for 24 hours. The mixture was chromatographed on silica gel with 5% ethyl acetate/hexanes.

EXAMPLE 4B

methyl 4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-phenethoxybenzoate

The title compound was prepared by substituting EXAMPLE 4A for EXAMPLE 1C in EXAMPLE 1D.

EXAMPLE 4C

4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-phenethoxybenzoic acid

The title compound was prepared by substituting EXAMPLE 4B for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 4D

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(2-phenylethoxy)benzamide

The title compound was prepared by substituting EXAMPLE 4C for EXAMPLE 1E in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 10.75 (br s, 1H), 8.66 (m, 2H), 7.91 (d, 1H), 7.47 (m, 6H), 7.20-7.40 (m, 8H), 6.53 (d, 1H), 6.47 (s, 1H), 4.35 (t, 2H), 4.03 (m, 1H), 3.85 (br d, 2H), 3.38 (s, 2H), 3.25 (m, 8H), 3.13 (t, 2H), 2.36 (br s, 4H), 2.21 (br s, 2H), 1.62 (br d, 2H), 1.20 (m, 2H), 1.17 (m, 1H).

EXAMPLE 5

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(phenylthio)benzamide

EXAMPLE 5A

methyl 4-fluoro-2-(phenylthio)benzoate

5-Fluoro-2-(methoxycarbonyl)phenylboronic acid (1.00 g), 2-(phenylthio)isoindoline-1,3-dione (0.86 g), and (2-hydroxy-3,5-diisopropylbenzoyloxy)copper (0.29 g) were stirred in dioxane (15 mL) at 50°C for 24 hours. The reaction mixture was chromatographed on silica gel with 5% ethyl acetate/hexanes.

EXAMPLE 5B

methyl 4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-(phenylthio)benzoate

The title compound was prepared by substituting EXAMPLE 5A for EXAMPLE 1C in EXAMPLE 1D.

EXAMPLE 5C

4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-(phenylthio)benzoic acid

The title compound was prepared by substituting EXAMPLE 5B for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 5D

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(phenylthio)benzamide

The title compound was prepared by substituting EXAMPLE 5C for EXAMPLE 1E in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.95 (br s, 1H), 8.59 (m, 2H), 7.93 (d, 1H), 7.63 (d, 1H), 7.15-7.50 (m, 14H), 6.73 (d, 1H), 6.18 (s, 1H), 3.82 (dd, 2H), 3.36 (m, 4H), 3.32 (m, 2H), 2.94 (br s, 4H), 2.30 (br s, 4H), 1.64 (m, 1H), 1.61 (m, 2H), 1.25 (m, 2H).

EXAMPLE 6

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(phenylthio)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 5C for EXAMPLE 1E and EXAMPLE 2A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6/D_2O) δ 7.65 (d, 2H), 7.55 (d, 1H), 7.33-7.48 (m, 12H), 7.24 (m, 2H), 6.73 (d, 1H), 6.66 (d, 2H), 6.17 (d, 1H), 3.85 (dd, 2H), 3.34 (s, 2H), 3.26 (t, 2H), 2.98 (d, 2H), 2.92 (br s, 4H), 2.25 (br s, 4H), 1.78 (m, 1H), 1.63 (d, 2H), 1.20 (m, 2H).

EXAMPLE 7

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(phenylthio)benzamide

EXAMPLE 7A

4-(3-morpholinopropylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 3-(N-morpholinyl)-1-propylamine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 7B

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(phenylthio)benzamide

The title compound was prepared by substituting EXAMPLE 5C for EXAMPLE 1E and EXAMPLE 7A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 10.20 (br s, 1H), 8.69 (m, 1H), 8.57 (d, 1H), 7.95 (dd, 2H), 7.71 (m, 1H), 7.31-7.51 (m, 10H), 7.12-7.26 (m, 3H), 6.68 (dd, 1H), 6.07 (m, 1H), 4.06 (s, 2H), 3.68 (m, 4H), 3.50 (m, 2H), 3.32 (m, 6H), 2.88 (m, 4H), 2.27 (m, 4H), 1.91 (m, 2H).

EXAMPLE 8

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(phenylsulfonyl)benzamide

EXAMPLE 8A

methyl 4-fluoro-2-(phenylsulfonyl)benzoate

EXAMPLE 5A (0.30 g) and $KMnO_4$ (1.80 g) were stirred in acetic acid (40 mL) at 60°C for 24 hours. The reaction mixture was filtered through a plug of silica gel, concentrated, and chromatographed on silica gel with 50% ethyl acetate/hexanes.

EXAMPLE 8B

methyl 4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-(phenylsulfonyl)benzoate

The title compound was prepared by substituting EXAMPLE 8A for EXAMPLE 1C in EXAMPLE 1D.

EXAMPLE 8C

4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-(phenylsulfonyl)benzoic acid

The title compound was prepared by substituting EXAMPLE 8B for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 8D

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(phenylsulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 8C for EXAMPLE 1E in EXAMPLE 1G. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.95 (br s, 1H), 8.54 (s, 1H), 8.41 (dd, 1H), 7.90 (m, 2H), 7.82 (d, 1H), 7.76 (d, 1H), 7.66 (m, 1H), 7.46 (m, 5H), 7.40 (m, 4H), 7.11 (m, 2H), 6.67 (dd, 1H), 6.62 (m, 1H), 4.36 (m, 1H), 3.82 (dd, 2H), 3.39 (m, 6H), 3.19 (m, 6H), 2.37 (br s, 4H), 1.91 (m, 1H), 1.63 (m, 2H), 1.26 (m, 2H).

EXAMPLE 9

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(phenylsulfinyl)benzamide

EXAMPLE 9A

methyl 4-fluoro-2-(phenylsulfinyl)benzoate

OXONE® (Dupont) (5.60 g) was added portionwise over 1 hour to EXAMPLE 5A (1.00 g) in a mixture of acetic acid (30 mL), water (30 mL) and CH_2Cl_2 (20 mL), and the reaction was stirred for an additional 1 hour. The reaction mixture was taken up in ethyl acetate, washed with $Na_2S_2O_3$ solution, water, and brine, concentrated, and chromatographed on silica gel with 5-25% ethyl acetate/hexanes.

EXAMPLE 9B

methyl 4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-(phenylsulfinyl)benzoate

The title compound was prepared by substituting EXAMPLE 9A for EXAMPLE 1C in EXAMPLE 1D.

EXAMPLE 9C

4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-(phenylsulfinyl)benzoic acid

The title compound was prepared by substituting EXAMPLE 9B for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 9D

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(phenylsulfinyl)benzamide

The title compound was prepared by substituting EXAMPLE 9C for EXAMPLE 1E in EXAMPLE 1G. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6/D_2O) δ 8.51 (s,

1H), 7.85 (dd, 2H), 7.64 (d, 2H), 7.48 (m, 8H), 7.32 (m, 1H), 7.23 (m, 1H), 7.14 (m, 4H), 6.97 (d, 1H), 3.85 (dd, 2H), 3.35 (d, 2H), 3.34 (m, 6H), 3.27 (t, 2H), 2.74 (br s, 4H),1.93 (m, 1H), 1.64 (d, 2H), 1.28 (m, 2H).

EXAMPLE 10

2-benzyl-4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 10A

methyl 2-benzyl-4-fluorobenzoate

5-Fluoro-2-(methoxycarbonyl)phenylboronic acid (1.00 g), benzyl bromide (0.50 mL), K_2CO_3 (1.75 g), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) ($PdCl_2$(dppf)) (0.17 g) were stirred in tetrahydrofuran (20 mL) at 60°C for 24 hours. The reaction mixture was chromatographed on silica gel with 2% ethyl acetate/hexanes.

EXAMPLE 10B

methyl 2-benzyl-4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 10A for EXAMPLE 1C in EXAMPLE 1D.

EXAMPLE 10C

2-benzyl-4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 10B for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 10D

2-benzyl-4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 10C for EXAMPLE 1E in EXAMPLE 1G. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6/D_2O) δ 8.55 (d, 1H), 7.90 (d, 1H), 7.38-7.56 (m, 10H), 7.25 (m, 2H), 6.96 (d, 2H), 6.83 (s, 2H), 6.75 (d, 1H), 4.06 (s, 2H), 3.85 (dd, 2H), 3.48 (s, 2H), 3.37 (d, 2H), 3.25 (t, 2H), 3.20 (br s, 4H), 2.44 (br s, 4H), 1.91 (m, 1H), 1.63 (d, 2H), 1.29 (m, 2H).

EXAMPLE 11

2-benzyl-4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 10C for EXAMPLE 1E and EXAMPLE 2A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.70 (br s, 1H), 7.48 (m, 6H), 6.88 (m, 6H), 6.62 (m, 6H), 6.42 (dd, 2H), 3.83 (dd, 4H), 3.24 (m, 6H), 2.96 (m, 4H), 1.82 (m, 2H), 1.63 (m, 3H), 1.18 (m, 4H).

EXAMPLE 12

2-benzyl-4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 10C for EXAMPLE 1E and EXAMPLE 7A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.90 (br s, 1H), 8.80 (m, 1H), 8.54 (d, 1H), 7.91 (dd, 1H), 7.48 (m, 7H), 7.40 (d, 2H), 7.26 (d, 2H), 6.97 (dd, 2H), 6.86 (m, 2H), 6.76 (d, 1H), 4.04 (m, 5H), 3.72 (m, 4H), 3.56 (m, 2H), 3.40 (m, 8H), 3.21 (m, 4H), 2.34 (m, 2H), 1.98 (m, 2H).

EXAMPLE 13

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(2-phenylethyl)benzamide

EXAMPLE 13A

methyl 4-fluoro-2-phenethylbenzoate

Methyl 2-bromo-4-fluorobenzoate (1.00 g), (E)-styrylboronic acid (0.89 g), tetrakis(triphenylphosphine)palladium(0) (0.50 g), and K_3PO_4 (2.28 g) were stirred in dioxane (17 mL) at 90°C for 24 hours. The reaction mixture chromatographed on silica gel with 1-5% ethyl acetate/hexanes. The product in methanol (10 ml) was added to 20 wt% of fresh dry 5% Pd-C and stirred 4 days with H_2 in a pressure bottle. The mixture was filtered through a nylon membrane and concentrated.

EXAMPLE 13B

methyl 4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-phenethylbenzoate

The title compound was prepared by substituting EXAMPLE 13A for EXAMPLE 1C in EXAMPLE 1D.

EXAMPLE 13C

4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-phenethylbenzoic acid

The title compound was prepared by substituting EXAMPLE 13B for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 13D

4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-N-(3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)phenylsulfonyl)-2-phenethylbenzamide

The title compound was prepared by substituting EXAMPLE 13C for EXAMPLE 1E in EXAMPLE 1G. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6/D_2O) δ 8.62 (d, 1H), 7.95 (d, 1H), 7.91 (m, 1H), 7.35-7.52 (m, 6H), 7.19 (m, 2H), 7.13 (m, 2H), 6.99 (m, 4H), 6.83 (d, 1H), 6.70 (d, 1H), 6.65 (s, 1H), 3.80 (m, 2H), 3.24 (m, 2H), 3.18 (t, 2H), 3.11 (br s, 4H), 2.91 (t, 2H), 2.48 (m, 2H), 2.38 (br s, 4H), 1.81 (m, 1H), 1.54 (d, 2H), 1.23 (m, 2H).

EXAMPLE 14

2-(benzylamino)-4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 14A

methyl 2-(benzylamino)-4-fluorobenzoate

Methyl 2-amino-4-fluorobenzoate (0.90 g), benzaldehyde (0.54 mL), sodium triacetoxyborohydride (1.58 g) and acetic acid (0.3 mL) in CH_2Cl_2 (20 mL) were stirred for 3 hours. The reaction was quenched with methanol, concentrated, and chromatographed on silica gel with 5% ethyl acetate/hexanes.

EXAMPLE 14B

methyl 2-(benzylamino)-4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 14A for EXAMPLE 1C in EXAMPLE 1D.

EXAMPLE 14C

2-(benzylamino)-4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 14B for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 14D

2-(benzylamino)-4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 14C for EXAMPLE 1E in EXAMPLE 1G. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6/D_2O) δ 8.58 (d, 1H), 7.92 (d, 1H), 7.87 (m, 1H), 7.59 (d, 2H), 7.48 (m, 2H), 7.43 (m, 4H), 7.20-7.29 (m, 8H), 6.15 (d, 1H), 4.32 (s, 2H), 3.85 (m, 2H), 3.49 (m, 2H), 3.33 (m, 2H), 3.26 (t, 2H), 3.12 (br s, 4H), 2.39 (br s, 4H), 1.90 (m, 1H), 1.62 (d, 2H), 1.27 (m, 2H).

EXAMPLE 15

2-anilino-4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 15A

methyl 4-fluoro-2-(phenylamino)benzoate

Methyl 2-bromo-4-fluorobenzoate (1.00 g), aniline (0.47 mL), palladium(II) acetate (0.048 g), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.214 g) and Cs_2CO_3 (2.08 g) in toluene (12 mL) were stirred at 90°C for 24 hours. The reaction was concentrated and chromatographed on silica gel with 5-50% ethyl acetate/hexanes.

EXAMPLE 15B

methyl 4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-(phenylamino)benzoate

The title compound was prepared by substituting EXAMPLE 15A for EXAMPLE 1C in EXAMPLE 1D.

EXAMPLE 15C

4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-(phenylamino)benzoic acid

The title compound was prepared by substituting EXAMPLE 15B for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 15D

2-anilino-4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 15C for EXAMPLE 1E in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.55 (br s, 1H), 8.56 (m, 2H), 7.92 (d, 1H), 7.72 (d, 1H), 7.47 (m, 6H), 7.25 (m, 4H), 7.12 (d, 2H), 6.95 (m, 2H), 6.53 (s, 1H), 6.38 (dd, 1H), 3.81 (dd, 2H), 3.37 (br s, 4H), 3.12 (br s, 4H), 2.41 (br s, 4H), 1.91 (m, 1H), 1.61 (br d, 2H), 1.23 (m, 4H).

EXAMPLE 16

2-anilino-4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 15C for EXAMPLE 1E and EXAMPLE 2A for EXAMPLE 1F in EXMAPLE 1G. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6/D_2O) δ 7.78 (d, 1H), 7.52 (d, 2H), 7.47 (m, 6H), 7.36 (m, 3H), 7.27 (m, 3H), 7.11 (m, 2H), 6.90 (m, 1H), 6.61 (s, 1H), 6.53 (d, 1H), 6.31 (d, 1H), 4.46 (s, 1H), 3.82 (m, 2H), 3.37 (s, 2H), 3.26 (t, 2H), 3.05 (br s, 4H), 2.93 (d, 2H), 2.37 (br s, 4H), 1.77 (m, 1H), 1.63 (d, 2H), 1.20 (m, 2H).

EXAMPLE 17

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-methoxy-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 17A

methyl 4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-methoxybenzoate

Methyl 4-bromo-2-methoxybenzoic acid (700 mg), EXAMPLE 1B (983 mg), K_3PO_4 (909 mg), tris(dibenzylideneacetone)dipalladium(0) (78 mg), and 2-(di-t-butylphosphino)biphenyl (102 mg) were stirred in 1,2-dimethoxyethane (10 mL) at 80°C for

24 hours. The reaction mixture was chromatographed on silica gel with 20-50% ethyl acetate/hexanes.

EXAMPLE 17B

4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-methoxybenzoic acid

The title compound was prepared by substituting EXAMPLE 17A for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 17C

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-methoxy-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 17B for EXAMPLE 1E in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 10.81 (br s, 1H), 8.64 (m, 2H), 7.96 (d, 1H), 7.20-7.54(m, 10H), 6.52 (d, 1H), 6.46 (s, 1H), 3.90 (s, 3H), 3.40 (m, 4H), 3.27 (br s, 4H), 2.39 (br s, 4H), 1.91 (m, 1H), 1.62 (br d, 2H), 1.27 (m, 4H).

EXAMPLE 18

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-phenoxybenzamide

EXAMPLE 18A

methyl 4,4-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

To a suspension of hexane washed NaH (17 g) in dichloromethane (700 mL), 5,5-dimethyl-2-methoxycarbonylcyclohexanone (38.5 g) was added dropwise at 0°C. After stirring for 30 minutes, the mixture was cooled to –78°C and trifluoromethanesulfonic anhydride (40 mL) was added. The reaction mixture was warmed to room temperature and stirred for 24 hours. The organic layer was washed with brine, dried, and concentrated to give the product.

EXAMPLE 18B

methyl 2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enecarboxylate

EXAMPLE 18A (62.15g), 4-chlorophenylboronic acid (32.24 g), CsF (64 g) and tetrakis(triphenylphosphine)palladium(0) (2g) in 2:1 1,2-dimethoxyethane/methanol (600

mL) were heated to 70^{0}C for 24 hours. The mixture was concentrated. Ether (4x 200 mL) was added and the mixture was filtered. The combined ether solution was concentrated to give the product.

EXAMPLE 18C

(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methanol

To a mixture of $LiBH_4$ (13g), EXAMPLE 18B (53.8 g) and ether (400 mL), methanol (25 mL) was added slowly by syringe. The mixture was stirred at room temperature for 24 hours. The reaction was quenched with 1N HCl with ice-cooling. The mixture was diluted with water and extracted by ether (3x 100mL). The extracts were dried, and concentrated. The crude product was chromatographed on silica gel with 0-30% ethyl acetate/hexanes.

EXAMPLE 18D

methyl 2-bromo-4-(piperazin-1-yl)benzoate

The title compound was prepared by substituting piperazine for EXAMPLE 1B and methyl 2-bromo-4-fluorobenzoate for EXAMPLE 1C in EXAMPLE 1D.

EXAMPLE 18E

methyl 2-bromo-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

MsCl (7.5 mL) was added via syringe to EXAMPLE 18C (29.3 g) and triethylamine (30 mL) in CH_2Cl_2 (500 mL) at 0^{0}C, and the mixture was stirred for 1 minute. EXAMPLE 18D (25 g) was added and the reaction was stirred at room temperature for 24 hours. The suspension was washed with brine, dried, and concentrated. The crude product was chromatographed on silica gel with 10-20% ethyl acetate/hexanes.

EXAMPLE 18F

methyl 4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-phenoxybenzoate

EXAMPLE 18E (500 mg), phenol (195 mg), Cs_2CO_3 (674 mg), 1-naphthoic acid (356 mg), copper (I) triflate-toluene complex (45 mg), ethyl acetate (0.016 mL), and 4A sieves (50 mg) in toluene (2 mL) was stirred at 105°C for 24 hours. The reaction was cooled

and taken up in ethyl acetate (100 mL) and water (40 mL). The layers were separated and the organic layer was washed with 2x Na_2CO_3 solution and brine, dried, and concentrated. The crude product was chromatographed on silica gel with 20% ethyl acetate/hexanes.

EXAMPLE 18G

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-phenoxybenzoic acid

The title compound was prepared by substituting EXAMPLE 18F for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 18H

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-phenoxybenzamide

The title compound was prepared by substituting EXAMPLE 18G for EXAMPLE 1E and EXAMPLE 7A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.10 (br s, 1H), 8.76 (m, 1H), 8.46 (d, 1H), 7.76 (dd, 1H), 7.50 (d, 1H), 7.35 (d, 2H), 7.23 (d, 2H), 7.06 (dd, 2H), 6.99 (dd, 1H), 6.81 (d, 2H), 6.74 (d, 1H), 6.34 (s, 1H), 3.62 (m, 4H), 3.46 (m, 2H), 3.13 (m, 4H), 2.76 (m, 2H), 2.48 (m, 2H), 2.22 (m, 6H), 1.97 (m, 2H), 1.82 (m, 2H), 1.40 (t, 2H), 1.06 (m, 7H), 0.94 (s, 3H).

EXAMPLE 19

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-phenoxybenzamide

EXAMPLE 19A

methyl 5,5-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

The title compound was prepared by substituting 4,4-dimethyl-2-methoxycarbonylcyclohexanone for 5,5-dimethyl-2-methoxycarbonylcyclohexanone in EXAMPLE 18A.

EXAMPLE 19B

methyl 2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-enecarboxylate

The title compound was prepared by substituting EXAMPLE 19A for EXAMPLE 18A in EXAMPLE 18B.

EXAMPLE 19C

(2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-enyl)methanol

The title compound was prepared by substituting EXAMPLE 19B for EXAMPLE 18B in EXAMPLE 18C.

EXAMPLE 19D

methyl 2-bromo-4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 19C for EXAMPLE 18C in EXAMPLE 18E.

EXAMPLE 19E

methyl 4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-phenoxybenzoate

The title compound was prepared by substituting EXAMPLE 19D for EXAMPLE 18E in EXAMPLE 18F.

EXAMPLE 19F

4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-phenoxybenzoic acid

The title compound was prepared by substituting EXAMPLE 19E for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 19G

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-phenoxybenzamide

The title compound was prepared by substituting EXAMPLE 19F for EXAMPLE 1E and EXAMPLE 7A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.10 (br s, 1H), 8.71(m, 1H), 8.42 (d, 1H), 7.73 (dd, 1H), 7.53 (d, 1H), 7.34 (d, 2H), 7.21 (dd, 2H), 7.10 (d, 2H), 6.96 (dd, 1H), 6.78 (d, 2H), 6.70 (d,

1H), 6.32 (s, 1H), 3.61 (m, 4H), 3.44 (m, 2H), 3.09 (m, 4H), 2.71 (m, 2H), 2.44 (m, 4H), 2.21 (m, 4H), 1.96 (m, 2H), 1.79 (m, 2H), 1.47 (t, 2H), 1.17 (m, 3H), 1.08 (m, 4H), 0.95 (s, 3H).

EXAMPLE 20

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-5-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 20A

ethyl 2-(1H-indazol-5-yloxy)-4-fluorobenzoate

Ethyl 2,4-difluorobenzoate (1.14 g), K_3PO_4 (1.30 g) and 5-hydroxyindazole (0.90 g) were stirred at 110°C in diglyme (12 mL) for 24 hours. The reaction was cooled and poured into ether. The solution was washed three times with 1M NaOH solution, and brine, and dried. The solution was then concentrated, and the crude product was chromatographed on silica gel with 20% ethyl acetate/hexanes.

EXAMPLE 20B

tert-butyl 4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine-1-carboxylate

The title compound was prepared by substituting N-t-butoxycarbonylpiperazine for EXAMPLE 18D in EXAMPLE 18E.

EXAMPLE 20C

1-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine

This EXAMPLE was prepared by substituting EXAMPLE 20B for EXAMPLE 1A in EXAMPLE 1B.

EXAMPLE 20D

ethyl 2-(1H-indazol-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

EXAMPLE 20A (330 mg), EXAMPLE 20C (335 mg), and HK_2PO_4 (191 mg) were stirred in dimethylsulfoxide (5 mL) at 140°C for 24 hours. The reaction was diluted with ethyl acetate, washed three times with water, washed with brine, dried, and concentrated. The crude product was chromatographed on silica gel with 30% ethyl acetate/hexanes.

EXAMPLE 20E

2-(1H-indazol-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 20D for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 20F

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-5-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 20E for EXAMPLE 1E and EXAMPLE 7A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 13.03 (br s, 1H), 11.25 (br s, 1H), 8.70 (m, 1H), 8.48 (d, 1H), 7.94 (dd, 1H), 7.68 (dd, 1H), 7.52 (m, 2H), 7.34 (d, 2H), 7.06 (m, 4H), 6.96 (dd, 1H), 6.88 (d, 1H), 6.23 (s, 1H), 3.61 (m, 4H), 3.44 (m, 2H), 3.05 (m, 4H), 2.73 (m, 2H), 2.42 (m, 4H), 2.18 (m, 4H), 1.99 (m, 2H), 1.91 (d, 2H), 1.78 (m, 2H), 1.39 (t, 2H), 1.17 (m, 2H), 0.93 (s, 6H).

EXAMPLE 21

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 21A

4-(1-methylpiperidin-4-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 4-amino-N-methylpiperidine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 21B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 20E for EXAMPLE 1E and EXAMPLE 21A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 12.80 (br s, 1H), 10.70 (br s, 1H), 8.34 (s, 1H), 8.02 (d, 1H), 7.87 (d, 1H), 7.70 (dd, 1H), 7.55 (m, 2H), 7.36 (d, 2H), 7.06 (m, 2H), 6.95 (m, 1H),

6.72 (d, 1H), 6.62 (d, 1H), 6.24 (s, 1H), 3.35 (m, 4H), 3.18 (m, 2H), 3.00 (m, 2H), 2.80 (m, 4H), 2.73 (m, 2H), 2.20 (m, 4H), 1.99 (m, 2H), 1.91 (s, 3H), 1.54 (m, 1H), 1.41 (t, 2H), 1.22 (m, 2H), 1.09 (s, 6H).

EXAMPLE 22

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(1,2,3,4-tetrahydroquinolin-6-yloxy)benzamide

EXAMPLE 22A

ethyl 4-fluoro-2-(1,2,3,4-tetrahydroquinolin-6-yloxy)benzoate

The title compound was prepared by substituting 5-hydroxy-1,2,3,4-tetrahydroquinoline for 5-hydroxyindazole in EXAMPLE 20A.

EXAMPLE 22B

ethyl 4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1,2,3,4-tetrahydroquinolin-6-yloxy)benzoate

The title compound was prepared by substituting EXAMPLE 22A for EXAMPLE 20A in EXAMPLE 20D.

EXAMPLE 22C

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1,2,3,4-tetrahydroquinolin-6-yloxy)benzoic acid

The title compound was prepared by substituting EXAMPLE 22B for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 22D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(1,2,3,4-tetrahydroquinolin-6-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 22C for EXAMPLE 1E and EXAMPLE 7A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 10.95 (br s, 1H), 8.83 (m, 1H), 8.60(d, 1H), 7.90 (dd, 1H),

7.46 (d, 1H), 7.35 (d, 2H), 7.21 (dd, 2H), 7.06 (d, 2H), 6.62 (m, 2H), 6.42 (d, 1H), 6.11 (d, 1H), 5.61 (br s, 1H), 4.02 (m, 1H), 3.61 (m, 4H), 3.48 (m, 2H), 3.17 (m, 2H), 3.07 (m, 4H), 2.74 (m, 2H), 2.63 (m, 2H), 2.44 (m, 4H), 2.19 (m, 4H), 1.97 (m, 4H), 1.79 (m, 4H), 1.41 (t, 2H), 1.17 (m, 4H), 0.94 (s, 6H).

EXAMPLE 23

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1,2,3,4-tetrahydroquinolin-6-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 22C for EXAMPLE 1E and EXAMPLE 21A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.10 (br s, 1H), 8.71(m, 1H), 8.42 (d, 1H), 7.73 (dd, 1H), 7.53 (d, 1H), 7.34 (d, 2H), 7.21 (dd, 2H), 7.10 (d, 2H), 6.96 (dd, 1H), 6.78 (d, 2H), 6.70 (d, 1H), 6.32 (s, 1H), 3.61 (m, 4H), 3.44 (m, 2H), 3.09 (m, 4H), 2.71 (m, 2H), 2.44 (m, 4H), 2.21 (m, 4H), 1.96 (m, 2H), 1.79 (m, 2H), 1.47 (t, 2H), 1.17 (m, 3H), 1.08 (m, 4H), 0.95 (s, 3H).

EXAMPLE 24

4-(4-{[4'-chloro-4-(pyrrolidin-1-ylmethyl)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 24A

methyl 5-formyl-2-(trifluoromethylsulfonyloxy)benzoate

Triflic anhydride (7.74 mL) was added to methyl 5-formyl-2-hydroxybenzoate (7.5 g) in 150 mL CH_2Cl_2 at 0°C, and the reaction was stirred and allowed to warm to room temperature over 3 hours. The reaction was diluted with CH_2Cl_2 (150 mL), washed with 3x brine, dried over Na_2SO_4, and concentrated. The product was used without further purification.

EXAMPLE 24B

methyl 4'-chloro-4-formylbiphenyl-2-carboxylate

EXAMPLE 24A (14.5 g), 4-chlorophenylboronic acid (6.88 g) CsF (12.2 g), and tetrakis(triphenylphosphine)palladium(0) were stirred at 70°C for 24 hours. The reaction

was cooled, filtered, and concentrated. The crude product was taken up in ethyl acetate (250 mL), washed with 3x 1M NaOH, and brine, concentrated, and chromatographed on silica gel with 10% ethyl acetate/hexanes.

EXAMPLE 24C

methyl 4'-chloro-4-(pyrrolidin-1-ylmethyl)biphenyl-2-carboxylate

The title compound was prepared by substituting EXAMPLE 24B for 4'-chlorobiphenyl-2-carboxaldehyde and pyrrolidine for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 24D

(4'-chloro-4-(pyrrolidin-1-ylmethyl)biphenyl-2-yl)methanol

DIBAL in hexanes (1M, 5.9 mL) was added to EXAMPLE 24C (650 mg) in CH_2Cl_2 (30 mL) at 0°C, and the reaction was stirred for 20 minutes. The reaction was quenched by the slow addition of methanol (2 mL), and 1M NaOH (10 mL), and the resulting solution was extracted twice with ethyl acetate. The extracts were washed with brine, dried over Na_2SO_4, and concentrated. The product was used without further purification.

EXAMPLE 24E

4'-chloro-4-(pyrrolidin-1-ylmethyl)biphenyl-2-carbaldehyde

Dess-Martin periodinane (1.30 g) was added to EXAMPLE 24D (770 mg) in CH_2Cl_2 (30 mL) at room temperature and the reaction was stirred for 24 hours. The reaction mixture was concentrated and chromatographed on silica gel with 1% triethylamine in 25% ethyl acetate/hexanes.

EXAMPLE 24F

methyl 2-(1H-indol-4-yloxy)-4-fluorobenzoate

The title compound was prepared by substituting 4-hydroxyindole for 5-hydroxyindazole and methyl 2,4-difluorobenzoate for ethyl 2,4-difluorobenzoate in EXAMPLE 20A.

EXAMPLE 24G

tert-butyl 4-(3-(1H-indol-4-yloxy)-4-(methoxycarbonyl)phenyl)piperazine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 24F for EXAMPLE 20A and tert-butyl piperazine-1-carboxylate for EXAMPLE 20C in EXAMPLE 20D.

EXAMPLE 24H

methyl 2-(1H-indol-4-yloxy)-4-(piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 24G for EXAMPLE 1A in EXAMPLE 1B.

EXAMPLE 24I

methyl 2-(1H-indol-4-yloxy)-4-(4-((4'-chloro-4-(pyrrolidin-1-ylmethyl)biphenyl-2-yl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 24E for 4'-chlorobiphenyl-2 carboxaldehyde and EXAMPLE 24H for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 24J

2-(1H-indol-4-yloxy)-4-(4-((4'-chloro-4-(pyrrolidin-1-ylmethyl)biphenyl-2-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 24I for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 24K

4-(4-{[4'-chloro-4-(pyrrolidin-1-ylmethyl)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 24J for EXAMPLE 1E in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.52 (br s, 1H), 11.26 (s, 1H), 10.68 (br s, 1H), 8.61 (dd, 1H), 8.49 (s, 1H), 8.19 (br s, 1H), 7.66 (d, 2H), 7.54 (m, 3H), 7.36 (m, 2H), 7.28 (s, 1H), 7.24 (d, 1H), 7.05 (d, 1H), 6.95 (dd, 1H), 6.75 (d, 1H), 6.35 (m, 2H), 6.26 (s, 1H), 4.38 (m, 3H), 3.85 (dd, 2H), 3.61 (m, 4H), 3.24 (m, 4H), 3.09 (m, 4H), 2.85 (m, 2H), 2.35 (m, 2H), 2.02 (m, 2H), 1.87 (m, 4H), 1.60 (m, 2H), 1.25 (m, 2H).

EXAMPLE 25

4-(4-{[4'-chloro-4-(2-pyrrolidin-1-ylethyl)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 25A

methyl 4'-chloro-4-(2-oxoethyl)biphenyl-2-carboxylate

To a solution of (methoxymethyl)diphenylphosphine oxide (1.62 g) in 40 mL tetrahydrofuran at -78°C, was added lithium diisopropylamide (2M, 3.3 mL), and after stirring 3 minutes, EXAMPLE 24B (1.57 g) was added, and the solution was warmed to room temperature. NaH (230 mg), and 40 mL N,N-dimethylformamide were added, and the mixture was heated to 60°C for 1 hours. The reaction was cooled and poured into NaH_2PO_4 solution. The resulting solution was extracted twice with ether, and the combined extracts were washed twice with water, and brine, and concentrated. The crude mixture of enol ethers was taken up in 1M HCl (50 mL) and dioxane (50 mL), and stirred at 60°C for 3 hours. The reaction was cooled and poured into $NaHCO_3$ solution. The resulting solution was extracted twice with ether, and the combined extracts were washed with water, and brine, and concentrated. The product was used without further purification.

EXAMPLE 25B

methyl 4'-chloro-4-(2-(pyrrolidin-1-yl)ethyl)biphenyl-2-carboxylate

The title compound was prepared by substituting EXAMPLE 25A for 4'-chlorobiphenyl-2-carboxaldehyde and pyrrolidine for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 25C

(4'-chloro-4-(2-(pyrrolidin-1-yl)ethyl)biphenyl-2-yl)methanol

The title compound was prepared by substituting EXAMPLE 25B for EXAMPLE 24C in EXAMPLE 24D.

EXAMPLE 25D

4'-chloro-4-(2-(pyrrolidin-1-yl)ethyl)biphenyl-2-carbaldehyde

The title compound was prepared by substituting EXAMPLE 25C for EXAMPLE 24D in EXAMPLE 24E.

EXAMPLE 25E

methyl 2-(1H-indol-4-yloxy)-4-(4-((4'-chloro-4-(2-(pyrrolidin-1-yl)ethyl)biphenyl-2-yl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 25D for 4'-chlorobiphenyl-2 carboxaldehyde and EXAMPLE 24H for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 25F

2-(1H-indol-4-yloxy)-4-(4-((4'-chloro-4-(2-(pyrrolidin-1-yl)ethyl)biphenyl-2-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 25E for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 25G

4-(4-{[4'-chloro-4-(2-pyrrolidin-1-ylethyl)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 25F for EXAMPLE 1E in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.15 (s, 1H), 8.47 (t, 1H), 8.42 (s, 1H), 7.68 (dd, 1H), 7.58 (d, 1H), 7.44 (m, 4H), 7.22 (m, 3H), 7.10 (d, 1H), 6.92 (m, 2H), 6.68 (d, 1H), 6.34 (d, 1H), 6.26 (s, 2H), 3.87 (dd, 2H), 3.61 (m, 4H), 3.10-3.24 (m, 11H), 2.97 (m, 4H), 2.31 (m, 4H), 1.89 (m, 4H), 1.61 (m, 2H), 1.26 (m, 2H).

EXAMPLE 26

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopentylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

EXAMPLE 26A

ethyl 2-(1H-indol-5-yloxy)-4-fluorobenzoate

The title compound was prepared by substituting 5-hydroxyindole for 5-hydroxyindazole in EXAMPLE 20A.

EXAMPLE 26B

ethyl 2-(1H-indol-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 26A for EXAMPLE 20A in EXAMPLE 20D.

EXAMPLE 26C

2-(1H-indol-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 26B for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 26D

4-(1-cyclopentylpiperidin-4-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 1-cyclopentylpiperidin-4-amine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 26E

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopentylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 26C for EXAMPLE 1E and EXAMPLE 26D for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.13 (br s, 1H), 8.52 (s, 1H), 8.14 (d, 1H), 7.80 (d, 1H), 7.52 (d, 1H), 7.35 (m, 4H), 7.04 (m, 4H), 6.80 (d, 1H), 6.61 (d, 1H), 6.36 (s, 1H), 6.14 (s, 1H), 5.76 (s, 1H), 3.84 (m, 2H), 3.24 (m, 4H), 2.99 (m, 4H), 2.85 (m, 2H), 2.71 (m, 2H), 2.16 (m, 6H), 1.95 (m, 4H), 1.50-1.70 (m, 6H), 1.38 (m, 2H), 1.17 (m, 2H), 0.93 (s, 6H).

EXAMPLE 27

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]-3-isobutylpiperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

EXAMPLE 27A

methyl 2-bromo-4-methylpentanoate

To concentrated HBr (48%) (20 mL) in water (214 mL), was added KBr (17.6 g, cooled to 0 °C, then sodium nitrite (5.2 g) all at once, then DL-leucine (5.2 g) in a few portions. The reaction was mechanically stirred at 0 °C for 1.5 hours, then extracted with 2 x 200 mL ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. After filtration and concentration, the resultant oil was dissolved in CH_2Cl_2/methanol and treated with 2.0*M* $(TMS)CHN_2$ in ether (30 mL) at room temperature for 10 minutes. The reaction was concentrated and then purified by flash chromatography using 97.5/2.5 hexane/ethyl acetate.

EXAMPLE 27B

3-isobutylpiperazin-2-one

EXAMPLE 27A (2.2 g) in ethanol (15 mL) was added dropwise over a period of 2.5 hours to a stirred refluxing solution of ethane-1,2-diamine (13.2 mL) in ethanol (60 mL). Heating was continued for another 2.5 hours, then NaOEt in ethanol was added (21% by wt, 4.0 mL) and heated for another 90 minutes. The reaction was then cooled and concentrated. After trituration with ether, the title compound was used without purification.

EXAMPLE 27C

4'-chlorobiphenyl-2-carbaldehyde

To 2-bromobenzaldehyde (2.3 ml) and tetrakis(triphenylphosphine)palladium(0) (0.35 g) in toluene (50 mL), was added 4-chlorophenylboronic acid (4.0 g) and 2M Na_2CO_3 (70 ml). The mixture was heated under reflux for one hour. The reaction was cooled, diluted with water and extracted with ethyl acetate. The organic layer was washed with brine and the combined aqueous layers back-extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4. The crude material was purified by flash chromatography using 97.5/2.5 hexane/ethyl acetate.

EXAMPLE 27D

4-((4'-chlorobiphenyl-2-yl)methyl)-3-isobutylpiperazin-2-one

The title compound was prepared by substituting EXAMPLE 27B for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 27E

1-((4'-chlorobiphenyl-2-yl)methyl)-2-isobutylpiperazine

To a solution of EXAMPLE 27D in tetrahydrofuran (3.6 mL) was added borane-methyl sulfide complex (10*M* in tetrahydrofuran) (0.24 mL). The reaction was heated under reflux for 16 hours, then cooled in an ice/water bath. Methanol (5 mL) was added carefully, and the mixture was stirred cold for 75 minutes. Then 4*N* HCl in dioxane (0.65 mL) was added and the reaction heated under reflux for 60 minutes. After cooling to room temperature, 1*N* NH_4OH (2.6 mL) was added and the reaction was stirred for 15 minutes. Then the reaction was concentrated, redissolved in methanol, concentrated, redissolved in toluene and concentrated. The crude solids were slurried in $CHCl_3$/methanol, the solids were filtered off, and the filtrate concentrated to afford the title compound.

EXAMPLE 27F

methyl 4-(4-((4'-chlorobiphenyl-2-yl)methyl)-3-isobutylpiperazin-1-yl)-2-phenoxybenzoate

The title compound was prepared by substituting EXAMPLE 27E for EXAMPLE 1B in EXAMPLE 1D.

EXAMPLE 27G

4-(4-((4'-chlorobiphenyl-2-yl)methyl)-3-isobutylpiperazin-1-yl)-2-phenoxybenzoic acid

The title compound was prepared by substituting EXAMPLE 27F for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 27H

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]-3-isobutylpiperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

EXAMPLE 27G (13 mg), EXAMPLE 1F (7 mg), 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (8 mg), and 4-dimethylaminopyridine (5 mg) were stirred in CH_2Cl_2 (1 mL) for 24 hours. The product was purified by preparative

HPLC using a C18 column, 250 x 50 mm, 10μ, and eluting with a gradient of 20-100% CH_3CN vs. 0.1% trifluoroacetic aicd in water, giving the product as a trifluoroacetate salt. ^1H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.62 (br s, 1H), 9.10 (br s, 1H), 8.65 (t, 1H), 8.47 (d, 1H), 7.77 (dd, 1H), 7.70 (br s, 1H), 7.50 (m, 5H), 7.39 (m, 3H), 7.25 (m, 2H), 7.18 (d, 1H), 7.01 (dd, 1H), 6.83 (m, 2H), 6.76 (m, 1H), 6.40 (br s, 1H), 4.70 and 4.15 (both v br s, total 1H), 3.85 (dd, 2H), 3.60 (v br s, 1H), 3.32, 3.27, 3.24, 3.06 (all m, total 11H), 1.90 (m, 1H), 1.62 (m, 3H), 1.30 (m, 4H), 0.70 (br m, 6H).

EXAMPLE 28

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-{[4-(2,4-dioxo-3-azabicyclo[3.2.0]hept-3-yl)phenyl]sulfonyl}-2-phenoxybenzamide

The title compound was prepared by substituting EXAMPLE 1E for EXAMPLE 27G and 4-(2,4-dioxo-3-azabicyclo[3.2.0]heptan-3-yl)bezenesulfonamide for EXAMPLE 1F in EXAMPLE 27H. ^1H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.87 (br s, 1H), 9.58 (br s, 1H), 7.93 (d, 2H), 7.71 (br s, 1H), 7.54 (m, 7H), 7.35 (m, 5H), 7.10 (dd, 1H), 6.89 (d, 2H), 6.78 (dd, 1H), 6.42 (s, 1H), 4.37 (br s, 1H), 3.78 (br s, 1H), 3.43 (m, 4H), 3.22, 3.00, 2.85 (all v br s, total 6H), 2.62 (m, 2H), 2.18 (m, 2H).

EXAMPLE 29

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-{[4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenyl]sulfonyl}-2-phenoxybenzamide

The title compound was prepared by substituting EXAMPLE 1E for EXAMPLE 27G and 4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)bezenesulfonamide for EXAMPLE 1F in EXAMPLE 27H. ^1H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.87 (br s, 1H), 11.20 (s, 1H), 9.58 (br s, 1H), 7.90 (d, 2H), 7.83 (d, 2H), 7.50 (m, 5H), 7.32 (m, 5H), 7.08 (dd, 1H), 6.85 (d, 2H), 6.76 (dd, 1H), 6.43 (s, 1H), 4.38 (br s, 1H), 3.80 (br s, 1H), 3.60 (m, 2H), 3.40 (m, 2H), 3.21, 3.00, 2.84 (all br s, total 6H), 2.75 (dd, 1H), 2.28 (d, 1H), 1.08 (d, 3H).

EXAMPLE 30

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-{[4-(3,3-dimethyl-2-oxoazetidin-1-yl)phenyl]sulfonyl}-2-phenoxybenzamide

The title compound was prepared by substituting EXAMPLE 1E for EXAMPLE 27G and 4-(3,3-dimethyl-2-oxoazetidin-1-yl)bezenesulfonamide for EXAMPLE 1F in EXAMPLE

27H. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.62 (br s, 1H), 9.58 (br s, 1H), 7.80 (d, 2H), 7.72 (br s, 1H), 7.50 (m, 5H), 7.40 (m, 4H), 7.33 (m, 3H), 7.08 (dd, 1H), 6.85 (d, 2H), 6.76 (dd, 1H), 6.41 (s, 1H), 4.38 (br s, 1H), 3.77 (br s, 1H), 3.58 (s, 2H), 3.45 (m, 2H), 3.21, 3.00, 2.84 (all br s, total 6H), 1.32 (s, 6H).

EXAMPLE 31

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-{[4-(4-nitro-2H-1,2,3-triazol-2-yl)phenyl]sulfonyl}-2-phenoxybenzamide

The title compound was prepared by substituting EXAMPLE 1E for EXAMPLE 27G and 4-(4-nitro-2*H*-1,2,3-triazol-2-yl)bezenesulfonamide for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.98 (br s, 1H), 9.58 (br s, 1H), 9.11 (s, 1H), 8.21 (d, 2H), 8.05 (d, 2H), 7.70 (br s, 1H), 7.50 (m, 5H), 7.39 (m, 2H), 7.30 (m, 1H), 7.24 (m, 2H), 7.00 (dd, 1H), 6.82 (d, 2H), 6.78 (dd, 1H), 6.43 (s, 1H), 4.38 (br s, 1H), 3.77 (br s, 1H), 3.45 (m, 2H), 3.21, 3.00, 2.84 (all br s, total 6H).

EXAMPLE 32

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-phenoxy-N-{[2-(2-piperidin-1-ylethoxy)phenyl]sulfonyl}benzamide

The title compound was prepared by substituting EXAMPLE 1E for EXAMPLE 27G and 2-(2-(piperidin-1-yl)ethoxy)bezenesulfonamide for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.65 (br s, 1H), 9.77 (br s, 1H), 8.95 (br s, 1H), 7.80 (dd, 1H), 7.70 (br s, 1H), 7.68 (m, 1H), 7.50 (m, 5H), 7.36 (m, 5H), 7.23 (d, 1H), 7.15 (m, 2H), 6.90 (d, 2H), 6.78 (dd, 1H), 6.42 (s, 1H), 4.40 (m, 3H), 3.80 (br s, 1H), 3.40, 3.20 3.00, 2.90 (all v br m, total 13H), 1.63 (m, 5H), 1.27 (v br s, 1H).

EXAMPLE 33

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-{[3-({[(1-ethylpyrrolidin-2-yl)methyl]amino}carbonyl)-4-methoxyphenyl]sulfonyl}-2-phenoxybenzamide

The title compound was prepared by substituting EXAMPLE 1E for EXAMPLE 27G and *N*-((1-ethylpyrrolidin-2-yl)methyl)-2-methoxy-5-sulfamoylbenzamide for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.75 (br s, 1H), 9.70 (br s, 1H), 9.25 (br s, 1H), 8.62 (t, 1H), 8.25 (d, 1H), 7.90 (dd, 1H), 7.70 (br s, 1H), 7.50 (m, 5H), 7.40 (m, 2H), 7.10 (m, 5H), 7.09 (dd, 1H), 6.85 (d, 2H), 6.76 (dd, 1H), 6.40 (s, 1H), 4.39 (br

s, 1H), 3.96 (s, 3H), 3.77 (br s, 1H), 3.60 (m, 4H), 3.55-2.80 (envelope, 10H), 2.12 (m, 1H), 2.00 (m, 1H), 1.85 (m, 2H), 1.23 (t, 3H).

EXAMPLE 34

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1-naphthyloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 34A

methyl 2-bromo-4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting methyl 2-bromo-4-fluorobenzoate for EXAMPLE 1C in EXAMPLE 1D.

EXAMPLE 34B

methyl 4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-(naphthalen-1-yloxy)benzoate

The title compound was prepared by substituting EXAMPLE 34A for EXAMPLE 18E and 1-naphthol for phenol in EXAMPLE 18F.

EXAMPLE 34C

4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-(naphthalen-1-yloxy)benzoic acid

The title compound was prepared by substituting EXAMPLE 34B for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 34D

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1-naphthyloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 34C for EXAMPLE 27G in EXAMPLE 27H. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.82 (br s, 1H), 9.50 (br s, 1H), 8.58 (t, 1H), 8.29 (d, 1H), 8.18 (d, 1H), 7.85 (d, 1H), 7.70 (br s, 1H), 7.50 (m, 8H), 7.38 (m, 4H), 7.20 (dd, 1H), 6.82 (m, 2H), 6.55 (s, 1H), 6.45 (d, 1H), 4.38 (br s, 1H), 3.85 (dd, 2H), 3.78 (br s, 1H), 3.27 (m, 6H), 3.22, 3.02, 2.85 (all br s, total 6H), 1.84 (m, 1H), 1.60 (m, 2H), 1.29 (m, 2H).

EXAMPLE 35

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(2-naphthyloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 35A

1-(difluoromethylsulfonyl)-2-fluorobenzene

The title compound was prepared by substituting EXAMPLE 34A for EXAMPLE 18E and 2-naphthol for phenol in EXAMPLE 18F.

EXAMPLE 35B

4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-(naphthalen-2-yloxy)benzoic acid

The title compound was prepared by substituting EXAMPLE 35A for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 35C

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(2-naphthyloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 35B for EXAMPLE 27G in EXAMPLE 27H. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.80 (br s, 1H), 9.55 (br s, 1H), 8.50 (t, 1H), 8.39 (d, 1H), 7.83 (m, 2H), 7.69 (br s, 1H), 7.64 (d, 1H), 7.50 (m, 6H), 7.37 (m, 5H), 7.18 (dd, 1H), 7.00 (d, 1H), 6.81 (dd, 1H), 6.77 (d, 1H), 6.56 (d, 1H), 4.38 (br s, 1H), 3.85 (dd, 2H), 3.78 (br s, 1H), 3.27 (m, 6H), 3.22, 3.02, 2.85 (all br s, total 6H), 1.84 (m, 1H), 1.60 (m, 2H), 1.29 (m, 2H).

EXAMPLE 36

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(2-naphthyloxy)benzamide

The title compound was prepared by substituting EXAMPLE 35B for EXAMPLE 27G and EXAMPLE 7A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.80 (br s, 1H), 9.61 (br s, 2H), 8.57 (t, 1H), 8.40 (d, 1H), 7.83 (m, 2H), 7.66 (m, 2H), 7.50 (m, 6H), 7.40 (m, 5H), 7.18 (dd, 1H), 7.02 (d, 1H), 6.81 (d, 1H), 6.57

(s, 1H), 4.38 (br s, 1H), 4.00 (m, 2H), 3.80 (br s, 1H), 3.40 (m, 8H), 3.30-2.80 (envelope, 10H), 1.92 (m, 2H).

EXAMPLE 37

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(2-naphthyloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 35B for EXAMPLE 27G and EXAMPLE 163A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.82 (br s, 1H), 9.58 (br s, 1H), 8.03 (d, 1H), 7.90 (m, 2H), 7.70 (d, 1H), 7.69 (br s, 1H), 7.65 (dd, 1H), 7.50 (m, 7H), 7.36 (m, 3H), 7.18 (m, 2H), 7.05 (d, 1H), 6.81 (dd, 1H), 6.75 (d, 1H), 6.56 (d, 1H), 4.38 (br s, 1H), 3.83 (dd, 2H), 3.78 (br s, 1H), 3.23 (m, 4H), 3.22, 3.02, 2.85 (all br s, total 6H), 3.15 (m, 2H), 1.80 (m, 1H), 1.55 (m, 2H), 1.22 (m, 2H).

EXAMPLE 38

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(quinolin-7-yloxy)benzamide

EXAMPLE 38A

methyl 4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-(quinolin-7-yloxy)benzoate

The title compound was prepared by substituting EXAMPLE 34A for EXAMPLE 18E and quinolin-7-ol for phenol in EXAMPLE 18F.

EXAMPLE 38B

4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-(quinolin-7-yloxy)benzoic acid

The title compound was prepared by substituting EXAMPLE 38A for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 38C

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(quinolin-7-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 38B for EXAMPLE 27G in EXAMPLE 27H. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 8.80 (d, 1H), 8.48 (t, 1H), 8.35 (d, 1H), 8.32 (d, 1H), 7.90 (d, 1H), 7.74 (m, 1H), 7.59 (m, 2H), 7.50 (m, 4H), 7.45 (dd, 1H), 7.38 (d, 2H), 7.30 (m, 2H), 6.95 (d, 1H), 6.86 (dd, 1H), 6.83 (d, 1H), 6.71 (d, 1H), 4.38 (br s, 1H), 3.85 (dd, 2H), 3.78 (br s, 1H), 3.30-2.80 (envelope, 12H), 1.84 (m, 1H), 1.60 (m, 2H), 1.25 (m, 2H).

EXAMPLE 39

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(quinolin-6-yloxy)benzamide

EXAMPLE 39A

methyl 4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-(quinolin-6-yloxy)benzoate

The title compound was prepared by substituting EXAMPLE 34A for EXAMPLE 18E and quinolin-6-ol for phenol in EXAMPLE 18F.

EXAMPLE 39B

4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-(quinolin-6-yloxy)benzoic acid

The title compound was prepared by substituting EXAMPLE 39A for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 39C

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(quinolin-6-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 39B for EXAMPLE 27G in EXAMPLE 27H. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) 11.90 (br s, 1H), 9.65 (br s, 1H), 8.80 (d, 1H), 8.46 (t, 1H), 8.35 (d, 1H), 7.90 (d, 1H), 7.72 (m, 1H), 7.50 (m, 6H), 7.45 (dd, 1H), 7.37 (m, 4H), 7.02 (d, 1H), 6.83 (dd, 1H), 6.79 (d, 1H), 6.63 (d, 1H), 4.38 (br

s, 1H), 3.85 (dd, 2H), 3.78 (br s, 1H), 3.40-2.80 (envelope 12H), 1.87 (m, 1H), 1.62 (m, 2H), 1.26 (m, 2H).

EXAMPLE 40

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 40A

1-(triisopropylsilyl)-1H-indol-5-ol

5-Benzyloxy-indole (1.0 g) was treated with NaH (135 mg) and triisopropylsilyl chloride (1.0 g) in tetrahydrofuran for 1 hour, purified by flash chromatography (98/2 ethyl acetate/hexanes), then debenzylated in ethanol (35 mL) using Pearlman's catalyst (0.19 g) and a hydrogen balloon.

EXAMPLE 40B

methyl 2-(1H-indol-5-yloxy)-4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 34A for EXAMPLE 18E and EXAMPLE 40A for phenol in EXAMPLE 18F. In this example, the crude material from the ether formation was desilylated using tetrabutyl ammonium fluoride in tetrahydrofuran/water 95/5 prior to purification.

EXAMPLE 40C

2-(1H-indol-5-yloxy)-4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 40B for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 40D

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 40C for EXAMPLE 27G in EXAMPLE 27H. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.40 (br s, 1H), 11.17 (s, 1H), 9.50 (v br s, 1H), 8.61 (t, 1H), 8.57 (d, 1H), 7.77 (dd, 1H), 7.70 (br s, 1H), 7.50 (m, 5H), 7.36 (m, 5H), 7.10 (s, 1H), 7.08 (d, 1H), 6.83 (dd, 1H), 6.69 (dd, 1H), 6.37 (m, 1H), 6.21 (d, 1H), 4.30 (br s, 1H), 3.84 (dd, 2H), 3.70 (br s, 1H), 3.30 (m, 6H), 3.20, 2.95, 2.80 (all br s, total 6H), 1.86 (m, 1H), 1.60 (m, 2H), 1.25 (m, 2H).

EXAMPLE 41

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(isoquinolin-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 41A

methyl 4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-(isoquinolin-5-yloxy)benzoate

The title compound was prepared by substituting EXAMPLE 34A for EXAMPLE 18E and isoquinolin-5-ol for phenol in EXAMPLE 18F.

EXAMPLE 41B

4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-(isoquinolin-5-yloxy)benzoic acid

The title compound was prepared by substituting EXAMPLE 41A for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 41C

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(isoquinolin-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 41B for EXAMPLE 27G in EXAMPLE 27H. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.90 (br s, 1H), 9.55 (v br s, 1H), 9.26 (s, 1H), 8.47 (m, 2H), 8.14 (d, 1H), 7.99 (d, 1H), 7.65 (br s, 1H), 7.60 (d, 1H), 7.45 (m, 6H), 7.29 (m, 4H), 6.80 (m, 2H), 6.60 (m, 2H), 4.38 (br s, 1H), 3.85 (dd, 2H), 3.78 (br s, 1H), 3.24 (m, 6H), 3.22,3.00, 2.85 (all br s, total 6H), 1.87 (m, 1H), 1.62 (m, 2H), 1.26 (m, 2H).

EXAMPLE 42

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(4-{[3-(dimethylamino)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(isoquinolin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 41B for EXAMPLE 27G and EXAMPLE 154A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (300 MHz,

dimethylsulfoxide-d_6) δ 11.90 (br s, 1H), 9.38 (v br s, 1H), 9.22 (s, 1H), 8.54 (t, 1H), 8.45 (d, 1H), 8.16 (d, 1H), 7.96 (d, 1H), 7.62 (br s, 1H), 7.56 (d, 1H), 7.50 (d, 1H), 7.45 (m, 5H), 7.29 (m, 4H), 6.80 (m, 2H), 6.60 (m, 2H), 4.23 (br s, 1H), 3.78 (br s, 1H), 3.40 (m, 2H), 3.35-2.80 (envelope, 8H), 3.08 (m, 2H), 2.72, 2.70 (both s, total 6H), 1.87 (m, 2H).

EXAMPLE 43

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(4-{[3-(dimethylamino)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(quinolin-6-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 39B for EXAMPLE 27G and EXAMPLE 154A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.96 (br s, 1H), 9.38 (v br s, 1H), 8.77 (dd, 1H), 8.51 (t, 1H), 8.35 (d, 1H), 8.05 (d,1H), 7.90 (d, 1H), 7.70 (br s, 1H), 7.50 (m, 6H), 7.38 (m, 5H), 6.98 (d, 1H), 6.83 (dd, 1H), 6.79 (d, 1H), 6.63 (d, 1H), 4.38 (br s, 1H), 3.78 (br s, 1H), 3.42 (m, 2H), 3.35-2.80 (envelope, 8H), 3.15 (m, 2H), 2.81, 2.79 (both s, total 6H), 1.93 (m, 2H).

EXAMPLE 44

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(4-{[3-(dimethylamino)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 40C for EXAMPLE 27G and EXAMPLE 154A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.40 (br s, 1H), 11.18 (s, 1H), 9.30 (v br s, 1H), 8.66 (t, 1H), 8.60 (d, 1H), 7.85 (dd, 1H), 7.52 (d, 1H), 7.50 (m, 5H), 7.40 (m, 4H), 7.30 (br s, 1H), 7.14 (s, 1H), 7.10 (d, 1H), 6.84 (dd, 1H), 6.67 (dd, 1H), 6.39 (m, 1H), 6.20 (s, 1H), 4.35 (br s, 1H), 3.78 (br s, 1H), 3.40 (m, 2H), 3.35-2.80 (envelope, 8H), 3.10 (m, 2H), 2.78, 2.76 (both s, total 6H), 1.95 (m, 2H).

EXAMPLE 45

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 45A

1-(triisopropylsilyl)-1H-indol-4-ol

4-Benzyloxy-indole (1.0 g) was treated with NaH (135 mg) and triisopropylsilyl chloride (1.0 g) in tetrahydrofuran for 1 hour, purified by flash chromatography (98/2 ethyl acetate/hexanes), then debenzylated in ethanol (35 mL) using Pearlman's catalyst (0.19 g) and a hydrogen balloon.

EXAMPLE 45B

methyl 2-(1H-indol-4-yloxy)-4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 34A for EXAMPLE 18E and EXAMPLE 45A for phenol in EXAMPLE 18F. Here the crude material from the ether formation was desilated using tetra-*n*-butylammonium fluoride in tetrahydrofuran/water 95/5 prior to purification.

EXAMPLE 45C

2-(1H-indol-4-yloxy)-4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 45B for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 45D

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 45C for EXAMPLE 27G in EXAMPLE 27H. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.50 (br s, 1H), 11.24 (s, 1H), 9.50 (v br s, 1H), 8.61 (t, 1H), 8.47 (d, 1H), 7.70 (br s, 1H), 7.64 (dd, 1H), 7.50 (m, 5H), 7.30 (m, 4H), 7.15 (d, 2H), 7.04 (d, 2H), 6.92 (dd, 1H), 6.75 (dd, 1H), 6.33 (m, 2H), 6.23 (s, 1H), 4.30 (br s, 1H), 3.84 (dd, 2H), 3.70 (br s, 1H), 3.30 (m, 6H), 3.20, 2.95, 2.80 (all br s, total 6H), 1.86 (m, 1H), 1.60 (m, 2H), 1.25 (m, 2H).

EXAMPLE 46

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(4-{[3-(dimethylamino)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 45C for EXAMPLE 27G and EXAMPLE 154A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (300 MHz,

dimethylsulfoxide-d_6) δ 11.50 (v br s, 1H), 11.24 (s, 1H), 9.30 (br s, 1H), 8.66 (t, 1H), 8.53 (d, 1H), 7.85 (dd, 1H), 7.55 (d, 1H), 7.50 (m, 5H), 7.39 (m, 2H), 7.30 (m, 2H), 7.148 (d, 1H), 7.10 (d, 1H), 6.96 (dd, 1H), 6.72 (dd, 1H), 6.41 (d, 1H), 6.32 (s, 1H), 6.23 (s, 1H), 4.35 (br s, 1H), 3.78 (br s, 1H), 3.40 (m, 2H), 3.35-2.80 (envelope, 8H), 3.10 (m, 2H), 2.78, 2.76 (both s, total 6H), 1.95 (m, 2H).

EXAMPLE 47

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(4-{[3-(dimethylamino)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-6-yloxy)benzamide

EXAMPLE 47A

1-(triisopropylsilyl)-1H-indol-6-ol

6-Benzyloxy-indole (1.0 g) was treated with NaH (135 mg) and triisopropylsilyl chloride (1.0 g) in tetrahydrofuran for 1 hour, purified by flash chromatography (98/2 ethyl acetate/hexanes), then debenzylated in ethanol (35 mL) using Pearlman's catalyst (0.19 g) and a hydrogen balloon.

EXAMPLE 47B

methyl 2-(1H-indol-6-yloxy)-4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 34A for EXAMPLE 18E and EXAMPLE 47A for phenol in EXAMPLE 18F. In this example, the crude material from the ether formation was desilated using tetrabutyl ammonium fluoride in tetrahydrofuran/water 95/5 prior to purification.

EXAMPLE 47C

2-(1H-indol-6-yloxy)-4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 47B for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 47D

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(4-{[3-(dimethylamino)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-6-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 47C for EXAMPLE 27G and EXAMPLE 154A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.50 (v br s, 1H), 11.00 (s, 1H), 9.38 (br s, 1H), 8.64 (t, 1H), 8.58 (d, 1H), 7.75 (dd, 1H), 7.65 (br s, 1H), 7.55 (d, 1H), 7.50 (m, 5H), 7.39 (m, 2H), 7.30 (m, 2H), 7.00 (d, 1H), 6.90 (s, 1H), 6.70 (m, 2H), 6.42 (m, 1H), 6.30 (s, 1H), 4.35 (br s, 1H), 3.78 (br s, 1H), 3.40 (m, 2H), 3.35-2.80 (envelope, 8H), 3.10 (m, 2H), 2.78, 2.76 (both s, total 6H), 1.95 (m, 2H).

EXAMPLE 48

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(isoquinolin-7-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 48A

This EXAMPLE was prepared by substituting EXAMPLE 34A for EXAMPLE 18E and isoquinolin-7-ol for phenol in EXAMPLE 18F.

EXAMPLE 48B

4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-(isoquinolin-7-yloxy)benzoic acid

This EXAMPLE was prepared by substituting EXAMPLE 48A for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 48C

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(isoquinolin-7-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 48B for EXAMPLE 27G and EXAMPLE 7A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.98 (v br s, 1H), 9.70 (v br s, 2H), 9.10 (s, 1H), 8.56 (t, 1H), 8.42 (d, 1H), 8.13 (d, 1H), 7.93 (d, 1H), 7.81 (d, 1H), 7.70 (br s, 1H), 7.60 (m, 2H), 7.50 (m, 5H), 7.40 (d, 2H), 7.35 (m, 1H), 7.14 (d, 1H), 6.84 (m, 2H), 6.70 (d, 1H), 4.38 (br s, 1H), 4.00 (m, 2H), 3.80 (br s, 1H), 3.40 (m, 4H), 3.30-2.80 (envelope, 10H), 3.20 (m, 4H), 1.92 (m, 2H).

EXAMPLE 49

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(4-{[3-(dimethylamino)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(isoquinolin-7-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 48B for EXAMPLE 27G and EXAMPLE 154A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.98 (v br s, 1H), 9.40 (br s, 2H), 9.10 (s, 1H), 8.56 (t, 1H), 8.40 (d, 1H), 8.13 (d, 1H), 7.93 (d, 1H), 7.81 (d, 1H), 7.70 (br s, 1H), 7.60 (m, 2H), 7.50 (m, 5H), 7.40 (d, 2H), 7.35 (m, 1H), 7.14 (d, 1H), 6.84 (m, 2H), 6.70 (d, 1H), 4.38 (br s, 1H), 3.78 (br s, 1H), 3.42 (m, 2H), 3.35-2.80 (envelope, 8H), 3.15 (m, 2H), 2.81, 2.79 (both s, total 6H), 1.93 (m, 2H).

EXAMPLE 50

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 50A

methyl 2-(1H-indol-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 19D for EXAMPLE 34A in EXAMPLE 40B.

EXAMPLE 50B

2-(1H-indol-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 50A for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 50C

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 50B for EXAMPLE 27G and EXAMPLE 7A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.98 (br s, 1H), 11.20 (s, 1H), 9.70 (v br s, 1H), 9.35 (v br s, 1H),

8.71 (t, 1H), 8.62 (d, 1H), 7.86 (dd, 1H), 7.54 (d, 1H), 7.40 (m, 4H), 7.12 (m, 4H), 6.87 (dd, 1H), 6.70 (dd, 1H), 6.40 (m, 1H), 6.20 (d, 1H), 3.98 (m, 2H), 3.50, 3.40, 3.30 (all m, total 12H), 3.19 (m, 2H), 3.00 (m, 4H), 2.75 (br s, 2H), 2.23 (br m, 2H), 1.97 (br m, 2H), 1.43 (br t, 2H), 0.98 (s, 6H).

EXAMPLE 51

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(dimethylamino)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 50B for EXAMPLE 27G and EXAMPLE 154A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.42 (br s, 1H), 11.20 (s, 1H), 9.40 (v br s, 1H), 9.30 (v br s, 1H), 8.66 (t, 1H), 8.61 (d, 1H), 7.86 (dd, 1H), 7.54 (d, 1H), 7.40 (m, 4H), 7.18 (d, 1H), 7.12 (m, 3H), 6.87 (dd, 1H), 6.70 (dd, 1H), 6.40 (s, 1H), 6.20 (s, 1H), 3.60 (br s, 2H), 3.50 (m, 4H), 3.35 (br s, 2H), 3.13 (m, 3H), 3.00 (br m, 2H), 2.78, 2.77 (both s, total 6H), 2.70 (br s, 1H), 2.12 (br m, 2H), 1.97 (m, 4H), 1.42 (br t, 2H), 0.97 (s, 6H).

EXAMPLE 52

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 26C for EXAMPLE 27G and EXAMPLE 7A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.40 (br s, 1H), 11.20 (s, 1H), 9.60 (v br s, 1H), 9.25 (v br s, 1H), 8.70 (t, 1H), 8.62 (d, 1H), 7.86 (dd, 1H), 7.54 (d, 1H), 7.40 (m, 4H), 7.18 (d, 1H), 7.13 (d, 1H), 7.09 (d, 2H), 6.87 (dd, 1H), 6.70 (dd, 1H), 6.40 (m, 1H), 6.20 (s, 1H), 3.98 (m, 2H), 3.50, 3.40, 3.30 (all m, total 12H), 3.19 (m, 2H), 3.00 (m, 4H), 2.75 (br s, 2H), 2.18 (br m, 2H), 2.00 (br m, 4H), 1.43 (br t, 2H), 0.96 (s, 6H).

EXAMPLE 53

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(dimethylamino)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 27G and EXAMPLE 154A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.41 (br s, 1H), 11.20 (s, 1H), 9.35 (v br s, 2H), 8.66 (t, 1H), 8.62

(d, 1H), 7.86 (dd, 1H), 7.54 (d, 1H), 7.40 (m, 4H), 7.18 (d, 1H), 7.13 (d, 1H), 7.09 (d, 2H), 6.87 (dd, 1H), 6.70 (dd, 1H), 6.40 (m, 1H), 6.20 (s, 1H), 3.50 (m, 4H), 3.35 (br s, 2H), 3.13 (m, 3H), 3.00 (br m, 2H), 2.78, 2.77 (both s, total 6H), 2.70 (br s, 1H), 2.20 (br m, 2H), 2.00 (m, 2H), 1.93 (m, 2H), 1.42 (br t, 2H), 0.97 (s, 6H).

EXAMPLE 54

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 54A

methyl 2-(1H-indol-4-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 19D for EXAMPLE 34A in EXAMPLE 45B.

EXAMPLE 54B

2-(1H-indol-4-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 54A for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 54C

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 54B for EXAMPLE 27G and EXAMPLE 7A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.50 (br s, 1H), 11.27 (s, 1H), 9.60 (v br s, 1H), 9.20 (v br s, 1H), 8.65 (t, 1H), 8.55 (d, 1H), 7.80 (dd, 1H), 7.57 (d, 1H), 7.40 (d, 2H), 7.30 (dd, 1H), 7.12 (d, 2H), 7.10 (d, 2H), 7.00 (dd, 1H), 6.73 (dd, 1H), 6.46 (d,1H), 6.30 (s, 1H), 6.23 (m, 1H), 3.98 (m, 2H), 3.60, 3.50, 3.40 (all m, total 12H), 3.19 (m, 2H), 3.00 (m, 4H), 2.75 (br s, 2H), 2.23 (br m, 2H), 1.97 (br m, 4H), 1.43 (br t, 2H), 0.98 (s, 6H).

EXAMPLE 55

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 55A

methyl 2-(1H-indol-4-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 45A for phenol in EXAMPLE 18F. Here the crude material from the ether formation was desilated using tetrabutyl ammonium fluoride in tetrahydrofuran/water 95/5 prior to purification.

EXAMPLE 55B

2-(1H-indol-4-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 55A for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 55C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 27G and EXAMPLE 7A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.50 (br s, 1H), 11.25 (s, 1H), 9.60 (v br s, 1H), 9.20 (v br s, 1H), 8.65 (t, 1H), 8.55 (d, 1H), 7.80 (dd, 1H), 7.57 (d, 1H), 7.40 (d, 2H), 7.30 (dd, 1H), 7.20 (d, 1H), 7.10 (m, 3H), 7.00 (dd, 1H), 6.73 (dd, 1H), 6.46 (d,1H), 6.30 (s, 1H), 6.23 (m, 1H), 3.98 (m, 2H), 3.60, 3.50, 3.40 (all m, total 12H), 3.19 (m, 2H), 3.00 (m, 4H), 2.75 (br s, 2H), 2.20 (br m, 2H), 2.00 (br m, 4H), 1.43 (br t, 2H), 0.98 (s, 6H).

EXAMPLE 56

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(dimethylamino)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 54B for EXAMPLE 27G and EXAMPLE 154A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (300 MHz,

dimethylsulfoxide-d_6) δ 11.55 (br s, 1H), 11.27 (s, 1H), 9.40 (v br s, 1H), 9.35 (v br s, 1H), 8.65 (t, 1H), 8.55 (d, 1H), 7.79 (dd, 1H), 7.57 (d, 1H), 7.40 (d, 2H), 7.30 (dd, 1H), 7.20 (d, 1H), 7.10 (m, 3H), 7.00 (dd, 1H), 6.73 (dd, 1H), 6.46 (d,1H), 6.30 (s, 1H), 6.23 (m, 1H), 3.50 (m, 4H), 3.35 (br s, 2H), 3.13 (m, 3H), 3.00 (br m, 2H), 2.78, 2.77 (both s, total 6H), 2.70 (br s, 1H), 2.22 (br m, 2H), 1.97 (m, 2H), 1.93 (m, 2H), 1.42 (br t, 2H), 0.97 (s, 6H).

EXAMPLE 57

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(dimethylamino)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 27G and EXAMPLE 154A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.50 (br s, 1H), 11.25 (s, 1H), 9.60 (v br s, 1H), 9.20 (v br s, 1H), 8.65 (t, 1H), 8.55 (d, 1H), 7.79 (dd, 1H), 7.57 (d, 1H), 7.40 (d, 2H), 7.30 (dd, 1H), 7.20 (d, 1H), 7.10 (m, 3H), 7.00 (dd, 1H), 6.73 (dd, 1H), 6.46 (d,1H), 6.30 (s, 1H), 6.23 (m, 1H), 3.50 (m, 4H), 3.35 (br s, 2H), 3.13 (m, 3H), 3.00 (br m, 2H), 2.78, 2.77 (both s, total 6H), 2.70 (br s, 1H), 2.20 (br m, 2H), 2.00 (m, 2H), 1.93 (m, 2H), 1.42 (br t, 2H), 0.97 (s, 6H).

EXAMPLE 58

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 45C for EXAMPLE 27G and EXAMPLE 7A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.50 (br s, 1H), 11.24 (s, 1H), 9.50 (v br s, 1H), 8.67 (t, 1H), 8.52 (d, 1H), 7.78 (dd, 1H), 7.70 (br s, 1H), 7.55 (d, 1H), 7.50 (m, 4H), 7.38 (d, 2H), 7.30 (dd, 2H), 7.18 (d, 1H), 7.08 (d, 1H), 6.96 (dd, 1H), 6.75 (dd, 1H), 6.40 (d, 1H), 6.33 (s, 1H), 6.23 (s, 1H), 4.38 (br s, 1H), 4.00 (m, 2H), 3.80 (br s, 1H), 3.40 (m, 4H), 3.30-2.80 (envelope, 10H), 3.20 (m, 4H), 1.95 (m, 2H).

EXAMPLE 59

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 40C for EXAMPLE 27G and EXAMPLE 7A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (300 MHz,

dimethylsulfoxide-d_6) δ 11.40 (br s, 1H), 11.19 (s, 1H), 9.60 (v br s, 1H), 8.69 (t, 1H), 8.60 (d, 1H), 7.83 (dd, 1H), 7.65 (br s, 1H), 7.50 (m, 5H), 7.38 (m, 5H), 7.12 (m, 2H), 6.83 (dd, 1H), 6.69 (dd, 1H), 6.39 (m, 1H), 6.20 (d, 1H), 4.38 (br s, 1H), 4.00 (m, 2H), 3.80 (br s, 1H), 3.40 (m, 4H), 3.30-2.80 (envelope, 10H), 3.20 (m, 4H), 1.96 (m, 2H).

EXAMPLE 60

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(4-methoxyphenyl)sulfonyl]-2-phenoxybenzamide

The title compound was prepared by substituting EXAMPLE 1E for EXAMPLE 27G and 4-methoxybenzenesulfonamide for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.57 (s, 1H), 7.74 (d, 2H), 7.50 (m, 5H), 7.35 (m, 6H), 7.10 (t, 1H), 7.02 (m, 2H), 6.87 (d, 2H), 6.75 (dd, 1H), 6.41 (s, 1H), 4.36 (m, 2H), 3.83 (s, 3H), 3.76 (m, 2H), 3.23 (m, 2H), 3.01 (m, 2H), 2.84 (m, 2H).

EXAMPLE 61

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(4-methylphenyl)sulfonyl]-2-phenoxybenzamide

The title compound was prepared by substituting EXAMPLE 1E for EXAMPLE 27G and 4-methylbenzenesulfonamide for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.64 (s, 1H), 7.68 (d, 2H), 7.50 (m, 5H), 7.38 (m, 2H), 7.32 (m, 6H), 7.11 (t, 1H), 6.87 (d, 2H), 6.75 (dd, 1H), 6.41 (s, 1H), 4.36 (m, 2H), 3.76 (m, 2H), 3.23 (m, 2H), 3.01 (m, 2H), 2.84 (m, 2H), 2.37 (s, 3H).

EXAMPLE 62

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 40C for EXAMPLE 27G and EXAMPLE 163A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.46 (s, 1H), 11.16 (s, 1H), 8.17 (d, 1H), 7.88 (dd, 1H), 7.68 (br s, 1H), 7.50 (m, 5H), 7.36 (m, 6H), 7.13 (s, 1H), 7.03 (d, 1H), 6.84 (dd, 1H), 6.68 (dd, 1H), 6.39 (m, 1H), 6.21 (br s, 1H), 4.32 (s, 2H), 3.84 (dd, 2H), 3.25 (m, 7H), 2.93 (m, 4H), 1.84 (m, 2H), 1.54 (m, 2H), 1.24 (m, 2H).

EXAMPLE 63

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 45C for EXAMPLE 27G and EXAMPLE 163A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.58 (s, 1H), 11.27 (s, 1H), 8.12 (d, 1H), 7.71 (m, 2H), 7.52 (m, 5H), 7.32 (m, 5H), 7.18 (d, 1H), 6.96 (m, 2H), 6.74 (dd, 1H), 6.36 (m, 2H), 6.26 (m, 1H), 4.32 (s, 2H), 3.84 (dd, 2H), 3.25 (m, 7H), 2.93 (m, 4H), 1.84 (m, 2H), 1.54 (m, 2H), 1.24 (m, 2H).

EXAMPLE 64

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({4-{[3-(dimethylamino)propyl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 40C and EXAMPLE 170A for EXAMPLE 27G and EXAMPLE 1F respectively, in EXAMPLE 27H. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.46 (br s, 1H), 11.18 (s, 1H), 8.21 (d, 1H), 7.98 (dd, 1H), 7.50 (m, 6H), 7.41 (m, 5H), 7.29 (br s, 1H), 7.17 (s, 1H), 7.08 (d, 1H), 6.84 (dd, 1H), 6.68 (dd, 1H), 6.40 (m, 1H), 6.18 (br s, 1H), 4.32 (br s, 2H), 3.59 (m, 4H), 3.25 (m, 2H), 3.05 (m, 4H), 2.90 (m, 2H), 2.77 (d, 6H), 1.88 (m, 2H).

EXAMPLE 65

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

EXAMPLE 65A

4-(3-morpholinopropylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 159C and 3-morpholinopropan-1-amine for 4-fluoro-3-nitrobenzenesulfonamide and (tetrahydropyran-4-yl)methylamine respectively, in EXAMPLE 1F.

EXAMPLE 65B

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 40C and EXAMPLE 65A for EXAMPLE 27G and EXAMPLE 1F respectively, in EXAMPLE 27H. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.46 (br s, 1H), 11.18 (s, 1H), 8.18 (d, 1H), 7.91 (m, 1H), 7.50 (m, 6H), 7.41 (m, 5H), 7.30 (m, 1H), 7.19 (d, 1H), 7.08 (m, 1H), 6.99 (m, 1H), 6.72 (dd, 1H), 6.48 (br s, 1H), 6.25 (m, 1H), 4.29 (br s, 2H), 4.01 (m, 2H), 3.59 (m, 2H), 3.41 (m, 4H), 3.05 (m, 10H), 2.58 (m, 2H), 1.91 (m, 2H).

EXAMPLE 66

N-[(3-{[chloro(difluoro)methyl]sulfonyl}-4-{[3-(dimethylamino)propyl]amino}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)benzamide

EXAMPLE 66A

(difluoromethyl)(2-fluorophenyl)sulfane

Powdered NaOH (31.2 g), tris(2-(2-methoxyethoxy)ethyl)amine (5 mL) and 2-fluorobenzene thiol (33.6 mL) in benzene (400 mL) was saturated with chlorodifluoromethane, stirred at 80°C for 30 minutes and filtered through diatomaceous earth (Celite®). The filtrate was washed with saturated $NaHCO_3$ and the water layer was extracted with diethyl ether. The extracts were combined and dried ($MgSO_4$), filtered and concentrated.

EXAMPLE 66B

1-(difluoromethylsulfonyl)-2-fluorobenzene

EXAMPLE 66A (46 g) in 1:1:2 CCl_4/CH_3CN/water (1.2L) at 25°C was treated with $NaIO_4$ (164.6 g) and $RuCl_3 \cdot xH_2O$ (534 mg), stirred for 18 hours, diluted with dichloromethane and filtered through diatomaceous earth (Celite®). The filtrate was washed with saturated $NaHCO_3$ and dried (Na_2SO_4), filtered and concentrated. The concentrate was filtered through silica gel.

EXAMPLE 66C

1-(chlorodifluoromethylsulfonyl)-2-fluorobenzene

EXAMPLE 66B (25 g) and N-chlorosuccinimide (17.55 g) in tetrahydrofuran (690 mL) at -78°C was treated with lithium hexamethyldisilazide (178.5 mL) over 1 hour, stirred for 1 hour and quenched with ammonium chloride. The mixture was extracted with ethyl acetate, and the extract was washed with brine and dried ($MgSO_4$), filtered and concentrated. The concentrate was chromatographed on silica gel with 0-5% ethyl acetate/hexanes.

EXAMPLE 66D

3-(chlorodifluoromethylsulfonyl)-4-fluorobenzene-1-sulfonyl chloride

EXAMPLE 66C (44 g) in chlorosulfonic acid (36.7 mL) at 120°C was stirred for 18 hours, cooled to 25°C, pipetted onto crushed ice and extracted with ethyl acetate. The extract was washed with water and brine and dried ($MgSO_4$), filtered and concentrated.

EXAMPLE 66E

3-(chlorodifluoromethylsulfonyl)-4-fluorobenzenesulfonamide

EXAMPLE 66D (22 g) in isopropanol (690 mL) at -78°C was treated with aqueous ammonia (90 mL) over 1 hour, stirred for another hour, quenched with 6M HCl (300 mL), warmed to 25°C and concentrated. The concentrate was mixed with water and extracted with ethyl acetate. The extract was dried ($MgSO_4$), filtered and concentrated. The concentrate was recrystallized from hexanes/ethyl acetate.

EXAMPLE 66F

3-(chlorodifluoromethylsulfonyl)-4-(3-(dimethylamino)propylamino)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 66E and N,N-dimethylpropane-1,3-diamine for 4-fluoro-3-nitrobenzenesulfonamide and (tetrahydropyran-4-yl)methylamine respectively, in EXAMPLE 1F.

EXAMPLE 66G

N-[(3-{[chloro(difluoro)methyl]sulfonyl}-4-{[3-(dimethylamino)propyl]amino}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 54B and EXAMPLE 66F for EXAMPLE 27G and EXAMPLE 1F respectively, in EXAMPLE 27H. ^1H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.20 (s, 1H), 8.28 (m,1H), 7.99 (m, 1H), 7.55 (m, 2H),

7.38 (m, 2H), 7.21 (m, 3H), 7.09 (d, 2H), 6.98 (m, 1H), 6.71 (m, 1H), 6.41 (m, 2H), 6.21 (m, 1H), 3.57 (m, 2H), 3.28 (m, 4H), 2.84 (m, 6H), 2.67 (m, 5H), 2.19 (m, 2H), 2.02 (m, 2H), 1.77 (br s, 2H), 1.61 (m, 2H), 1.46 (m, 2H), 0.94 (s, 6H).

EXAMPLE 67

N-[(3-{[chloro(difluoro)methyl]sulfonyl}-4-{[3-(dimethylamino)propyl]amino}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 26C and EXAMPLE 66F for EXAMPLE 27G and EXAMPLE 1F respectively, in EXAMPLE 27H. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.20 (s, 1H), 8.28 (m,1H), 8.05 (m, 1H), 7.99 (m, 1H), 7.55 (m, 2H), 7.38 (m, 2H), 7.21 (m, 3H), 7.09 (d, 2H), 6.98 (m, 1H), 6.71 (m, 1H), 6.41 (m, 2H), 6.21 (m, 1H), 3.57 (m, 2H), 3.28 (m, 4H), 3.05 (m, 2H), 2.96 (m, 2H), 2.88 (s, 3H), 2.78 (m, 2H), 2.68 (m, 3H), 2.19 (m, 2H), 2.01 (br s, 2H), 1.72 (m, 2H), 1.45 (m, 2H), 0.93 (s, 6H).

EXAMPLE 68

2-(1H-indol-4-yloxy)-4-(4-{[2-(4-methoxyphenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 68A

(2-bromo-4,4-dimethylcyclohex-1-enyl)methanol

N,N-dimethylformamide (18.41 ml) was taken up in chloroform (64 ml) and the resulting solution was cooled in an ice bath. Phosphorus tribromide (20.18 ml) was added dropwise over 15 minutes. The resulting suspension was then heated to 70 °C for 30 minutes. A solution of 3,3-dimethylcyclohexanone (10 g) in chloroform (21 ml) was added dropwise over 30 minutes. The mixture was stirred at 70 °C for another 2 hours. The mixture was then allowed to cool to room temperature. The solution was cautiously poured over ice. Solid sodium bicarbonate was added to neutralize acid. The mixture was extracted three times with ether, and the extracts were washed with water and brine and dried ($MgSO_4$). The solvent was removed under vacuum, and the crude material was flushed through a silica plug with ether as the eluent. After concentration, the crude material was dissolved in methanol.

Sodium borohydride (1.757 g) was added cautiously. The resulting mixture was stirred at room temperature overnight, and diluted with ethyl acetate. The mixture was washed with water and brine and dried ($MgSO_4$). The solvent was removed under vacuum, and the residue was purified by flash chromatography eluting with 20% ethyl acetate in hexanes to 100% ethyl acetate.

EXAMPLE 68B

methyl 2-(1H-indol-4-yloxy)-4-(piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 24F and piperazine for EXAMPLE 1C and EXAMPLE 1B respectively, in EXAMPLE 1D.

EXAMPLE 68C

methyl 2-(1H-indol-4-yloxy)-4-(4-((2-bromo-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 68A and EXAMPLE 68B for EXAMPLE 18C and EXAMPLE 18D respectively, in EXAMPLE 18E.

EXAMPLE 68D

methyl 2-(1H-indol-4-yloxy)-4-(4-((2-(4-methoxyphenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

EXAMPLE 68C (142mg), 4-methoxyphenylboronic acid (45.6 mg), bis(triphenylphosphine)palladium(II) dichloride (8.7 mg), and cesium fluoride (114 mg) were combined in dimethoxyethane (0.9 mL) and methanol (0.4 mL) and heated to 90°C for 2 hours. The reaction mixture was diluted with ethyl acetate and poured into water. The organic layer was washed with water and with brine, dried ($MgSO_4$), filtered, and concentrated. The resulting solid was triturated with methanol, and filtered.

EXAMPLE 68E

2-(1H-indol-4-yloxy)-4-(4-((2-(4-methoxyphenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 68D for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 68F

3-nitro-4-(3-(pyrrolidin-1-yl)propylamino)benzenesulfonamide

The title compound was prepared by substituting 3-(pyrrolidin-1-yl)propan-1-amine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 68G

2-(1H-indol-4-yloxy)-4-(4-{[2-(4-methoxyphenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 68E and EXAMPLE 68F for EXAMPLE 27G and EXAMPLE 1F respectively, in EXAMPLE 27H. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.56 (brs, 1H), 11.26 (s, 1H), 8.66 (t, 1H), 8.53 (d, 1H), 7.78 (dd, 1H), 7.56 (d, 1H), 7.29 (t, 1H), 7.19 (d, 1H), 7.10 (d, 1H), 6.98 (m, 3H), 6.88 (m, 2H), 6.74 (m, 1H), 6.43 (d, 1H), 6.36 (br s, 1H), 6.23 (m, 1H), 3.73 (s, 3H), 3.62 (m, 2H), 3.52 (m, 4H), 3.22 (m, 4H), 2.99 (m, 4H), 2.18 (m, 2H), 1.99 (m, 6H), 1.84 (m, 2H), 1.45 (m, 2H), 1.23 (m, 2H), 0.94 (s, 6H).

EXAMPLE 69

4-[4-({4,4-dimethyl-2-[4-(trifluoromethyl)phenyl]cyclohex-1-en-1-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 69A

methyl 2-(1H-indol-4-yloxy)-4-(4-((4,4-dimethyl-2-(4-(trifluoromethyl)phenyl)cyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting 4-(trifluoromethyl)phenylboronic acid for 4-methoxyphenylboronic acid in EXAMPLE 68D.

EXAMPLE 69B

2-(1H-indol-4-yloxy)-4-(4-((4,4-dimethyl-2-(4-(trifluoromethyl)phenyl)cyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 69A for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 69C

4-[4-({4,4-dimethyl-2-[4-(trifluoromethyl)phenyl]cyclohex-1-en-1-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 69B and EXAMPLE 68F for EXAMPLE 27G and EXAMPLE 1F respectively, in EXAMPLE 27H. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.55 (br s, 1H), 11.26 (s, 1H), 8.66 (t, 1H), 8.53 (d, 1H), 7.78 (m, 1H), 7.67 (m, 2H), 7.56 (m, 1H), 7.29 (m, 3H), 7.19 (d, 1H), 7.10 (d, 1H), 6.98 (m, 1H), 6.72 (m, 1H), 6.46 (m, 1H), 6.36 (br s, 1H), 6.23 (m, 1H), 3.62 (m, 4H), 3.52 (m, 4H), 3.18 (m, 4H), 3.02 (m, 4H), 2.19 (m, 2H), 2.02 (m, 6H), 1.82 (m, 2H), 1.47 (m, 2H), 0.94 (s, 6H).

EXAMPLE 70

4-[4-({4,4-dimethyl-2-[4-(trifluoromethoxy)phenyl]cyclohex-1-en-1-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 70A

methyl 2-(1H-indol-4-yloxy)-4-(4-((4,4-dimethyl-2-(4-(trifluoromethoxy)phenyl)cyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting 4-(trifluoromethoxy)phenylboronic acid for 4-methoxyphenylboronic acid in EXAMPLE 68D.

EXAMPLE 70B

2-(1H-indol-4-yloxy)-4-(4-((4,4-dimethyl-2-(4-(trifluoromethoxy)phenyl)cyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 70A for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 70C

4-[4-({4,4-dimethyl-2-[4-(trifluoromethoxy)phenyl]cyclohex-1-en-1-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 70B and EXAMPLE 68F for EXAMPLE 27G and EXAMPLE 1F respectively, in EXAMPLE 27H. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.56 (br s, 1H), 11.26 (s, 1H), 8.66 (t, 1H), 8.54 (d, 1H), 7.80 (m, 1H), 7.63 (m, 2H), 7.56 (m, 3H), 7.29 (m, 2H), 7.19 (m, 2H), 6.98 (m, 1H), 6.72 (m, 1H), 6.46 (m, 1H), 6.23 (m, 1H), 3.62 (m, 4H), 3.52 (m, 4H), 3.18 (m, 4H), 3.02 (m, 4H), 2.19 (m, 2H), 2.02 (m, 6H), 1.82 (m, 2H), 1.47 (m, 2H), 0.94 (s, 6H).

EXAMPLE 71

4-[4-({4,4-dimethyl-2-[3-(trifluoromethyl)phenyl]cyclohex-1-en-1-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 71A

methyl 2-(1H-indol-4-yloxy)-4-(4-((4,4-dimethyl-2-(3-(trifluoromethyl)phenyl)cyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting 3-(trifluoromethyl)phenylboronic acid for 4-methoxyphenylboronic acid in EXAMPLE 68D.

EXAMPLE 71B

2-(1H-indol-4-yloxy)-4-(4-((4,4-dimethyl-2-(3-(trifluoromethyl)phenyl)cyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 71A for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 71C

4-[4-({4,4-dimethyl-2-[3-(trifluoromethyl)phenyl]cyclohex-1-en-1-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 71B and EXAMPLE 68F for EXAMPLE 27G and EXAMPLE 1F respectively, in EXAMPLE 27H. ^{1}H NMR

(300MHz, dimethylsulfoxide-d_6) δ 11.55 (br s, 1H), 11.26 (s, 1H), 8.65 (t, 1H), 8.54 (d, 1H), 7.80 (dd, 1H), 7.63 (m, 2H), 7.56 (m, 3H), 7.38 (m, 2H), 7.29 (t, 1H), 7.19 (d, 1H), 7.11 (d, 1H), 6.98 (t, 1H), 6.72 (m, 1H), 6.46 (m, 1H), 6.31 (m, 1H), 6.23 (m, 1H), 3.58 (m, 7H), 3.18 (m, 4H), 3.02 (m, 4H), 2.19 (m, 3H), 2.02 (m, 6H), 1.82 (m, 2H), 1.47 (m, 2H), 0.96 (s, 6H).

EXAMPLE 72

4-(4-{[2-(3-fluorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 72A

methyl 2-(1H-indol-4-yloxy)-4-(4-((2-(3-fluorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting 3-fluorophenylboronic acid for 4-methoxyphenylboronic acid in EXAMPLE 68D.

EXAMPLE 72B

2-(1H-indol-4-yloxy)-4-(4-((2-(3-fluorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 72A for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 72C

4-(4-{[2-(3-fluorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 72B and EXAMPLE 68F for EXAMPLE 27G and EXAMPLE 1F respectively, in EXAMPLE 27H. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.55 (br s, 1H), 11.26 (s, 1H), 8.65 (t, 1H), 8.54 (d, 1H), 7.80 (m, 1H), 7.63 (m, 2H), 7.56 (m, 3H), 7.38 (m, 2H), 7.29 (t, 1H), 7.19 (d, 1H), 7.11 (d, 1H), 6.98 (m, 1H), 6.72 (m, 1H), 6.46 (m, 1H), 6.31 (m, 1H), 6.23 (m, 1H), 3.58 (m, 7H), 3.18 (m, 4H), 3.02 (m, 4H), 2.19 (m, 3H), 2.02 (m, 6H), 1.82 (m, 2H), 1.47 (m, 2H), 0.96 (s, 6H).

EXAMPLE 73

4-(4-{[2-(4-fluorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 73A

methyl 2-(1H-indol-4-yloxy)-4-(4-((2-(4-fluorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting 4-fluorophenylboronic acid for 4-methoxyphenylboronic acid in EXAMPLE 68D.

EXAMPLE 73B

2-(1H-indol-4-yloxy)-4-(4-((2-(4-fluorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 73A for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 73C

4-(4-{[2-(4-fluorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 73B and EXAMPLE 68F for EXAMPLE 27G and EXAMPLE 1F respectively, in EXAMPLE 27H. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.56 (br s, 1H), 11.26 (s, 1H), 8.66 (t, 1H), 8.54 (d, 1H), 7.80 (m, 1H), 7.63 (m, 2H), 7.56 (m, 3H), 7.29 (m, 2H), 7.19 (m, 2H), 6.98 (m, 1H), 6.72 (m, 1H), 6.46 (m, 1H), 6.23 (m, 1H), 3.62 (m, 4H), 3.52 (m, 4H), 3.18 (m, 4H), 3.02 (m, 4H), 2.19 (m, 2H), 2.02 (m, 6H), 1.82 (m, 2H), 1.47 (m, 2H), 0.94 (s, 6H).

EXAMPLE 74

N-({3-{[chloro(difluoro)methyl]sulfonyl}-4-[(1-methylpiperidin-4-yl)amino]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide

EXAMPLE 74A

3-(chlorodifluoromethylsulfonyl)-4-(1-methylpiperidin-4-ylamino)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 66E and 1-methylpiperidin-4-amine for 4-fluoro-3-nitrobenzenesulfonamide and (tetrahydropyran-4-yl)methylamine respectively, in EXAMPLE 1F.

EXAMPLE 74B

N-({3-{[chloro(difluoro)methyl]sulfonyl}-4-[(1-methylpiperidin-4-yl)amino]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 26C and EXAMPLE 74A for EXAMPLE 1E and EXAMPLE 1F respectively, in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.07 (s, 1H), 8.11 (d, 1H), 7.89 (dd, 1H), 7.50 (d, 1H), 7.34 (m, 4H), 7.05 (m, 3H), 6.96 (d, 1H), 6.78 (dd, 1H), 6.60 (m, 2H), 6.36 (s, 1H), 6.13 (d, 1H), 3.67 (m, 1H), 2.97 (m, 6H), 2.71 (s, 2H), 2.59 (m, 2H), 2.46 (s, 3H), 2.16 (m, 6H), 1.98 (m, 4H), 1.55 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 75

4-(4-{[2-(4-chlorophenyl)cyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 75A

methyl 2-(1H-indol-5-yloxy)-4-(4-((2-(4-chlorophenyl)cyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 149D and EXAMPLE 150A for 4'-chlorobiphenyl-2-carboxaldehyde and tert-butylpiperazine-1-carboxylate respectively, in EXAMPLE 1A.

EXAMPLE 75B

2-(1H-indol-5-yloxy)-4-(4-((2-(4-chlorophenyl)cyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 75A for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 75C

4-(4-{[2-(4-chlorophenyl)cyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 75B and EXAMPLE 21A for EXAMPLE 1E and EXAMPLE 1F respectively, in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.07 (s, 1H), 8.52 (d, 1H), 8.12 (d, 1H), 7.79 (dd, 1H), 7.52 (d, 1H), 7.34 (m, 4H), 7.05 (m, 4H), 6.79 (dd, 1H), 6.59 (dd, 1H), 6.36 (s, 1H), 6.13 (d, 1H), 3.72 (m, 1H), 2.97 (m, 6H), 2.69 (s, 2H), 2.59 (m, 2H), 2.46 (s, 3H), 2.16 (m, 6H), 2.11 (m, 2H), 1.98 (m, 2H), 1.70 (m, 2H), 1.62 (m, 4H).

EXAMPLE 76

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

EXAMPLE 76A

4-(1-methylpiperidin-4-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 159C and 1-methylpiperidin-4-amine for 4-fluoro-3-nitrobenzenesulfonamide and (tetrahydropyran-4-yl)methylamine respectively, in EXAMPLE 1F.

EXAMPLE 76B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 26C and EXAMPLE 76A for EXAMPLE 1E and EXAMPLE 1F respectively, in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.08 (s, 1H), 8.11 (d, 1H), 7.89 (dd, 1H), 7.50 (d, 1H), 7.34 (m, 4H), 7.05 (m, 3H), 6.98 (d, 1H), 6.78 (dd, 1H), 6.60 (m, 2H), 6.36 (t, 1H), 6.13 (d, 1H), 3.67 (br s, 1H), 2.97 (m, 6H), 2.71 (s, 3H), 2.63 (m, 1H), 2.47 (s, 3H), 2.17 (m, 6H), 1.98 (m, 4H), 1.60 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 77

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(phenoxymethyl)benzamide

EXAMPLE 77A

5-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)isobenzofuran-1(3H)-one

5-bromoisobenzofuran-1(3H)-one (400 mg), EXAMPLE 1B (646 mg), and potassium phosphate tribasic (558 mg) were added to 1,2-dimethoxyethane (10 mL). The solution was degassed under vacuum and flushed with nitrogen three times. Tris(dibenzylideneacetone)dipalladium(0) (51.6 mg) and 2-(di-tert-butylphosphino)biphenyl (67.2 mg) were added and the solution was heated to 80°C for 16 hours. The solution was cooled, filtered, concentrated, and purified by flash column chromatography on silica gel with 30% ethyl acetate in hexanes.

EXAMPLE 77B

4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-(hydroxymethyl)benzoic acid

EXAMPLE 77A (256 mg) and lithium hydroxide monohydrate (154 mg) were added to 1,4-dioxane (4 mL) and water (1 mL). The solution was heated to 65°C for 16 hours, cooled, concentrated under vacuum, and purified by flash column chromatography on silica gel with ethyl acetate. The solution was subsequently dried with anhydrous sodium sulfate to afford crude product of sufficient purity for subsequent use.

EXAMPLE 77C

methyl 4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-(hydroxymethyl)benzoate

Trimethylsilyldiazomethane (2M solution in diethyl ether, 0.214 mL) was added to EXAMPLE 77B (170 mg) dissolved in ethyl acetate (2 mL) and methanol (2 mL). The solution was mixed for 5 minutes after which the solvent was removed under vacuum to afford crude product of sufficient purity for subsequent use.

EXAMPLE 77D

methyl 4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-(phenoxymethyl)benzoate

Triphenylphosphine (93 mg) was added to tetrahydrofuran (3 mL) and cooled to 0°C. Diethylazodicarboxylate (40% solution, 0.161 mL) was added, and the solution was stirred at 0°C for 15 minutes. Phenol (33.3 mg) and EXAMPLE 77C (145 mg) were added,

and the solution was allowed to warm to room temperature and mix for 16 hours. The solution was concentrated on vacuum and purified by flash column chromatography on silica gel with 30% ethyl acetate (hexanes) increasing to 50% ethyl acetate (hexanes).

EXAMPLE 77E

4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-(phenoxymethyl)benzoic acid

The title compound was prepared by substituting EXAMPLE 77D for EXAMPLE 77A in EXAMPLE 77B.

EXAMPLE 77F

The title compound was prepared by substituting EXAMPLE 77E for EXAMPLE 1E in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 8.52 (m, 2H), 7.88 (dd, 1H), 7.84 (d, 1H), 7.50 (m, 2H), 7.48 (s, 3H), 7.37 (m, 2H), 7.26 - 7.10 (m, 4H), 7.01 (s, 1H), 6.87 (t, 1H), 6.83 - 6.75 (m, 3 H), 5.22 (broad s, 2H), 3.84 (dd, 2H), 3.41 - 3.10 (m, 10H), 2.39 (broad s, 4H), 1.89 (m, 1H), 1.60 (m, 2H), 1.32 - 1.18 (m, 2H).

EXAMPLE 78

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({4-[(3-morpholin-4-ylpropyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

EXAMPLE 78A

N-(4-sulfamoylphenyl)acrylamide

4-aminobenzenesulfonamide (1.00 g) and pyridine (1.41 mL) were added to 1,4-dioxane (30 mL). Acryloyl chloride (0.49 mL) was added dropwise and the solution was stirred for 3 hours at room temperature. 1M HCl was added, and the solution extracted with ethyl acetate. The extracts were dried using brine and anhydrous sodium sulfate and the solvent was removed to afford crude product of sufficient purity for subsequent use.

EXAMPLE 78B

3-morpholino-N-(4-sulfamoylphenyl)propanamide

EXAMPLE 78A (359 mg) and morpholine (1.38 mL) were added to acetonitrile (10 mL) and N,N-dimethylformamide (1 mL) and mixed at room temperature for 16 hours.

The solution was concentrated on vacuum, and purified by flash column chromatography on silica gel with 5% methanol in dichloromethane.

EXAMPLE 78C

4-(3-morpholinopropylamino)benzenesulfonamide

EXAMPLE 78B (268 mg) was added to tetrahydrofuran (4 mL). Borane (1M in tetrahydrofuran, 4.28 mL) was added slowly, and the solution was mixed at room temperature for 16 hours. The reaction was quenched slowly with methanol. N,N-diisopropylethylamine resin (3.42 mmol amine) was added and the solution was mixed at room temperature for 15 minutes. The solution was filtered, concentrated on vacuum, and purified by flash column chromatography on silica gel with 10% methanol in ethyl acetate.

EXAMPLE 78D

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({4-[(3-morpholin-4-ylpropyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

The title compound was prepared by substituting EXAMPLE 78C for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 10.98 (broad s, 1H), 7.51 - 7.44 (m, 9H), 7.40 - 7.31 (m, 3H), 7.26 - 7.21 (m, 1H), 7.13 (tt, 1H), 6.94 (dd, 2H), 6.75 (dd, 1H), 6.66 (t, 1H), 6.54 (d, 2H), 6.32 (d, 1H), 3.57 (t, 4H), 3.35 (m, 2H), 3.16 – 3.04 (m, 6H), 2.35 (m, 10H), 1.60 (m, 2H).

EXAMPLE 79

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(pyridin-3-yloxy)benzamide

EXAMPLE 79A

methyl 4-bromo-2-fluorobenzoate

4-Bromo-2-fluorobenzoic acid (5.00 g) was added to ethyl acetate (35 mL) and methanol (35 mL). Trimethylsilyldiazomethane (2M solution in diethyl ether, 12.56 mL) was added slowly and the solution was mixed at room temperature for 30 minutes. The solvent was removed under vacuum, and the crude material was dissolved in ethyl acetate. The solution was extracted with 0.5M sodium hydroxide and dried with brine then anhydrous

sodium sulfate. After filtration, the solvent was removed under vacuum to afford crude product of sufficient purity for subsequent use.

EXAMPLE 79B

methyl 4-bromo-2-(pyridin-3-yloxy)benzoate

EXAMPLE 79A (500 mg), pyridine-3-ol (204 mg), and potassium carbonate (385 mg) were added to N,N-dimethylacetamide (18 mL) and the mixture was heated to 145°C for 2 hours and then at 130°C for 16 hours. The solution was cooled, added to water (100 mL), extracted with 70% ethyl acetate in hexanes, and dried with anhydrous sodium sulfate. After filtration, the solution was concentrated under vacuum and purified by flash column chromatography on silica gel with 50-70% ethyl acetate in hexanes.

EXAMPLE 79C

methyl 4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-(pyridin-3-yloxy)benzoate

EXAMPLE 79B (367 mg), EXAMPLE 1B (410 mg), and potassium phosphate tribasic (379 mg) were added to 1,2-dimethoxyethane (6 mL). The solution was degassed under vacuum and flushed with nitrogen three times. Tris(dibenzylideneacetone)dipalladium(0) (32.7 mg) and 2-(di-tert-butylphosphino)biphenyl (42.6 mg) were added and the solution was heated to 80°C for 16 hours. The solution was cooled, filtered, concentrated, and purified by flash column chromatography on silica gel with 50-70% ethyl acetate in hexanes.

EXAMPLE 79D

4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-(pyridin-3-yloxy)benzoic acid

The title compound was prepared by substituting EXAMPLE 79C for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 79E

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(pyridin-3-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 79D for EXAMPLE 1E in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.72 (broad s, 1H), 8.64 (t, 1H), 8.46 (d, 1H), 8.15 (t, 2H), 7.75 (dd, 1H), 7.52 - 7.44 (m, 6H), 7.37 (m, 2H), 7.26 - 7.10

(m, 4H), 6.79 (dd, 1H), 6.50 (d, 1H), 3.87 (dd, 2H), 3.40 (s, 2H), 3.38 – 3.24 (m, 4H), 3.19 (broad s, 4H), 2.37 (broad s, 4H), 1.92 (m, 1H), 1.65 (d, 2H), 1.28 (m, 2H).

EXAMPLE 80

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(pyridin-3-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 79D for EXAMPLE 1E and EXAMPLE 2A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.34 (s, 1H), 8.27 (dd, 2H), 7.51 - 7.44 (m, 8H), 7.41 - 7.29 (m, 3H), 7.27 - 7.19 (m, 2H), 6.78 (dd, 1H), 6.72 (t, 1H), 6.56 (d, 2H), 6.44 (d, 1H), 3.86 (dd, 2H), 3.36 (s, 2H), 3.29 – 3.22 (m, 2H), 3.16 (m, 4H), 2.96 (t, 2H), 2.34 (m, 4H), 1.77 (m, 1H), 1.66 (d, 2H), 1.21 (m, 2H).

EXAMPLE 81

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-{[4-({(1R)-3-(dimethylamino)-1-[(phenylthio)methyl]propyl}amino)-3-nitrophenyl]sulfonyl}-2-phenoxybenzamide

EXAMPLE 81A

(R)-tert-butyl 3-(((9H-fluoren-9-yl)methoxy)carbonylamino)-4-hydroxybutanoate

Fmoc-D-Asp(OtBu)-OH (9.0g) and *N,N*-diisopropylethylamine (4.6 mL) were added to tetrahydrofuran (100 mL) and cooled to –40 °C. Isobutyl chloroformate (3.1 mL) was added, and the solution was gradually warmed to 0°C over 30 minutes. The solution was cooled to –20 °C, and to it was carefully added sodium borohydride (1.64 g, 43.6 mmol) and methanol (10 mL). The solution was gradually warmed to room temperature over two hours, diluted with ethyl acetate (200 mL), washed with water (100 mL) and brine (50 mL), dried with anhydrous magnesium sulfate, filtered, and concentrated to afford crude product of sufficient purity for subsequent use.

EXAMPLE 81B

(R)-tert-butyl 3-(((9H-fluoren-9-yl)methoxy)carbonylamino)-4-(phenylthio)butanoate

Tri-n-butylphosphine (90 μL) and 1,1'-(azodicarbonyl)dipiperidine (91 mg) were added to tetrahydrofuran (4 mL), treated with EXAMPLE 81A (90 mg) and thiophenol (21

mg), and stirred at room temperature for 18 hours. The solution was concentrated and purified by flash column chromatography on silica gel with 50% ethyl acetate in hexanes.

EXAMPLE 81C

(R)-tert-butyl 3-(2-nitro-4-sulfamoylphenylamino)-4-(phenylthio)butanoate

EXAMPLE 81B (600 mg), 4-fluoro-3-nitrobenzenesulfonamide (298 mg), and *N,N*-diisopropylethylamine (3 mL) were added to N,N-dimethylformamide (3 mL) and stirred at 60°C for 12 hours. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water (45 mL) and brine (10 mL), dried with anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel with 30% ethyl acetate in dichloromethane.

EXAMPLE 81D

(R)-3-(2-nitro-4-sulfamoylphenylamino)-4-(phenylthio)butanoic acid

EXAMPLE 81C (468 mg) and 4 M HCl in 1,4-dioxane (10 mL) were stirred at 50°C for 5 hours. The solution was concentrated to give the crude product of sufficient purity for subsequent use.

EXAMPLE 81E

(R)-N,N-dimethyl-3-(2-nitro-4-sulfamoylphenylamino)-4-(phenylthio)butanamide

The title compound was prepared by substituting EXAMPLE 81D for EXAMPLE 1E and dimethylamine (2M in tetrahydrofuran) for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 81F

(R)-4-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrobenzenesulfonamide

To EXAMPLE 81E (4.06 g) was added borane (1 M in tetrahydrofuran, 20.0 mL). The solution was stirred at room temperature for 16 hours. The reaction was quenched slowly with methanol (5.0 mL) and concentrated aqueous HCl (2.0 mL) was added. The solution was stirred at 80°C for three hours, cooled to room temperature, carefully basified with 4 M sodium carbonate, diluted with ethyl acetate (150 mL), washed with water (50 mL) and brine (10 mL), dried with anhydrous magnesium sulfate, and filtered. The solution was concentrated and purified by flash column chromatography on silica gel with 20% methanol in dichloromethane.

EXAMPLE 81G

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-{[4-({(1R)-3-(dimethylamino)-1-[(phenylthio)methyl]propyl}amino)-3-nitrophenyl]sulfonyl}-2-phenoxybenzamide

The title compound was prepared by substituting EXAMPLE 81F for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 8.33 (d, 1H), 8.28 (d, 1H), 7.61 (dd, 2H), 7.50 - 7.43 (m, 4H), 7.37 - 7.14 (m, 11H), 6.90 (t, 1H), 6.84 (d, 1H), 6.71 (d, 2H), 6.70 (dd, 1H), 6.32 (d, 1H), 4.06 (m, 1H), 3.36 (s, 2H), 3.33 – 3.30 (m, 2H), 3.08 (t, 4H), 2.86 (m, 2H), 2.53 (s, 6H), 2.35 (t, 4H), 2.04 (m, 2H).

EXAMPLE 82

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(pyridin-4-yloxy)benzamide

EXAMPLE 82A

methyl 4-bromo-2-(pyridin-4-yloxy)benzoate

EXAMPLE 79A (800 mg), pyridine-4-ol (359 mg), and potassium carbonate (617 mg) were added to N,N-dimethylacetamide (20 mL) and the mixture was heated to 125°C for 16 hours. The solution was concentrated on vacuum at 48°C and purified by flash column chromatography on silica gel with 20% methanol in dichloromethane.

EXAMPLE 82B

methyl 4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-(pyridin-4-yloxy)benzoate

The title compound was prepared by substituting EXAMPLE 82A for EXAMPLE 79B in EXAMPLE 79C.

EXAMPLE 82C

4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-(pyridin-4-yloxy)benzoic acid

The title compound was prepared by substituting EXAMPLE 82B for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 82D

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(pyridin-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 82C for EXAMPLE 1E in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 8.40 (t, 1H), 8.37 (d, 1H), 7.76 (dd, 1H), 7.65 (d, 1H), 7.54 - 7.48 (m, 1H), 7.47 (s, 3H), 7.42 - 7.35 (m, 5H), 7.27 - 7.23 (m, 1H), 7.06 (dd, 1H), 6.92 (dd, 1H), 6.88 (d, 1H), 5.91 (d, 2H), 3.85 (dd, 2H), 3.39 (s, 2H), 3.34 – 3.25 (m, 4H), 3.19 (broad, s, 4H), 2.39 (broad s, 4H), 1.92 (m, 1H), 1.65 (d, 2H), 1.27 (m, 2H).

EXAMPLE 83

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(pyridin-3-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 79D for EXAMPLE 1E and EXAMPLE 7A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 8.73 (t, 1H), 8.43 (d, 1H), 8.12 (t, 2H), 7.73 (dd, 1H), 7.55 (d, 1H), 7.51 - 7.44 (m, 4H), 7.37 (m, 2H), 7.25 - 7.17 (m, 3H), 7.07 (d, 2H), 6.78 (dd, 1H), 6.47 (d, 1H), 3.65 (t, 4H), 3.47 (q, 2H), 3.38 (s, 2H), 3.28 (m, 2H), 3.17 (br s, 4H), 2.57 (br s, 4H), 2.36 (br s, 4H), 1.84 (m, 2H).

EXAMPLE 84

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(pyridin-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 82C for EXAMPLE 1E and EXAMPLE 7A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 8.55 (t, 1H), 8.37 (d, 1H), 7.77 (dd, 1H), 7.65 (d, 1H), 7.54 - 7.43 (m, 5H), 7.42 – 7.32 (m, 4H), 7.26 - 7.22 (m, 1H), 7.01 (d, 1H), 6.91 (dd, 1H), 6.66 (d, 1H), 5.90 (d, 2H), 3.60 (t, 4H), 3.43 (q, 2H), 3.39 (s, 2H), 3.18 (br s, 4H), 2.38 (m, 10H), 1.80 (t, 2H).

EXAMPLE 85

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(4-{[2-(4-methylpiperazin-1-yl)ethyl]amino}-3-nitrophenyl)sulfonyl]-2-phenoxybenzamide

EXAMPLE 85A

4-(2-(4-methylpiperazin-1-yl)ethylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 2-(4-methylpiperazin-1-yl)ethanamine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 85B

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(4-{[2-(4-methylpiperazin-1-yl)ethyl]amino}-3-nitrophenyl)sulfonyl]-2-phenoxybenzamide

The title compound was prepared by substituting EXAMPLE 85A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 8.61 (t, 1H), 8.40 (d, 1H), 7.72 (dd, 1H), 7.57 (d, 1H), 7.51 - 7.44 (m, 5H), 7.36 (m, 2H), 7.26 - 7.15 (m, 3H), 6.95 (t, 2H), 6.75 (dd, 2H), 6.71 (dd, 1H), 6.34 (d, 1H), 3.45 (q, 2H), 3.36 (s, 2H), 3.34 (m, 2H), 3.10 (t, 4H), 2.79 (broad s, 4H), 2.68 (t, 2H), 2.60 (broad s, 2H), 2.49 (s, 3H), 2.35 (t, 4H).

EXAMPLE 86

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(4-{[3-(4-methylpiperazin-1-yl)propyl]amino}-3-nitrophenyl)sulfonyl]-2-phenoxybenzamide

EXAMPLE 86A

4-(3-(4-methylpiperazin-1-yl)propylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 3-(4-methylpiperazin-1-yl)propan-1-amine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 86B

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(4-{[3-(4-methylpiperazin-1-yl)propyl]amino}-3-nitrophenyl)sulfonyl]-2-phenoxybenzamide

The title compound was prepared by substituting EXAMPLE 86A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 8.57 (t, 1H), 8.38 (d, 1H), 7.71 (dd, 1H), 7.59 (d, 1H), 7.50 - 7.44 (m, 5H), 7.36 (m, 2H), 7.27 - 7.15 (m, 3H), 6.98 (d, 2H), 6.91 (t, 1H), 6.73 (dd, 2H), 6.70 (dd, 2H), 6.33 (d, 1H), 3.43 (q, 2H), 3.36 (s, 2H), 3.34 (m, 2H), 3.09 (t, 4H), 2.82 (broad s, 4H), 2.56 (broad s, 2H), 2.49 (s, 3H), 2.35 (t, 4H), 1.79 (t, 2H).

EXAMPLE 87

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({4-[[3-(dimethylamino)propyl](methyl)amino]-3-nitrophenyl}sulfonyl)-2-phenoxybenzamide

EXAMPLE 87A

4-((3-(dimethylamino)propyl)(methyl)amino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting N^1,N^1,N^3-trimethylpropane-1,3-diamine for 3-(pyrrolidin-1-yl)propan-1-amine in EXAMPLE 68F.

EXAMPLE 87B

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({4-[[3-(dimethylamino)propyl](methyl)amino]-3-nitrophenyl}sulfonyl)-2-phenoxybenzamide

The title compound was prepared by substituting EXAMPLE 87A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 8.01 (d, 1H), 7.68 (dd, 1H), 7.63 (d, 1H), 7.51 - 7.44 (m, 5H), 7.36 (m, 2H), 7.26 - 7.13 (m, 3H), 6.93 (t, 1H), 6.83 (m, 1H), 6.74 (dd, 2H), 6.69 (dd, 1H), 6.32 (d, 1H), 3.46 (q, 2H), 3.36 (s, 2H), 3.08 (t, 4H), 2.83 (t, 2H), 2.77 (s, 3H), 2.60 (s, 6H), 2.36 (t, 4H), 1.86 (m, 2H).

EXAMPLE 88

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(4-{[(1-methylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-phenoxybenzamide

EXAMPLE 88A

4-((1-methylpiperidin-4-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting (1-methylpiperidin-4-yl)methanamine for 3-(pyrrolidin-1-yl)propan-1-amine in EXAMPLE 68F.

EXAMPLE 88B

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(4-{[(1-methylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-phenoxybenzamide

The title compound was prepared by substituting EXAMPLE 88A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 8.44 (t, 1H), 8.35 (d, 1H),

7.79 (dd, 1H), 7.62 (d, 1H), 7.51 - 7.45 (m, 5H), 7.36 (m, 2H), 7.25 - 7.14 (m, 3H), 6.99 (d, 1H), 6.89 (t, 1H), 6.71 (d, 2H), 6.68 (dd, 1H), 6.31 (d, 1H), 3.36 (s, 2H), 3.34 (m, 4H), 3.07 (t, 4H), 2.73 (m, 2H), 2.62 (s, 3H), 2.36 (t, 4H), 1.90 – 1.82 (m, 3H), 1.47 – 1.31 (m, 2H).

EXAMPLE 89

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-phenoxybenzamide

The title compound was prepared by substituting EXAMPLE 21A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 8.38 (t, 1H), 8.09 (d, 1H), 7.73(m, 1H), 7.59 (d, 1H), 7.52 - 7.44 (m, 5H), 7.36 (m, 2H), 7.26 - 7.22 (m, 1H), 7.17 (t, 1H), 7.05 (d, 1H), 6.90 (t, 1H), 6.83 (m, 1H), 6.72 (d, 2H), 6.70 (dd, 1H), 6.33 (d, 1H), 3.36 (q, 2H), 3.36 (s, 2H), 3.24 – 3.12 (m, 2H), 3.09 (t, 4H), 2.80 (m, 1H), 2.59 (s, 3H), 2.36 (t, 4H), 2.08 (m, 2H), 1.77 (m, 2H).

EXAMPLE 90

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(3-cyano-4-{[3-(dimethylamino)propyl]amino}phenyl)sulfonyl]-2-phenoxybenzamide

EXAMPLE 90A

3-cyano-4-fluorobenzenesulfonamide

Concentrated ammonium hydroxide (28% solution in water, 3.17 mL) was cooled to 0°C and 3-cyano-4-fluorobenzene-1-sulfonyl chloride (1.00 g) was added. The solution was mixed at 0°C for four minutes. 4M HCl (10 mL) was added slowly and the solution was extracted with ethyl acetate. The extract was dried on brine and anhydrous sodium sulfate and the solvent removed under vacuum.

EXAMPLE 90B

3-cyano-4-(3-(dimethylamino)propylamino)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 90A for 4-chloro-3-nitrobenzenesulfonamide and N^1,N^1-dimethylpropane-1,3-diamine for 3-(pyrrolidin-1-yl)propan-1-amine in EXAMPLE 68F.

EXAMPLE 90C

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(3-cyano-4-{[3-(dimethylamino)propyl]amino}phenyl)sulfonyl]-2-phenoxybenzamide

The title compound was prepared by substituting EXAMPLE 90B for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 7.67 (s, 1H), 7.66 (dd, 1H), 7.59 (d, 1H), 7.51 - 7.44 (m, 5H), 7.36 (m, 2H), 7.28 - 7.20 (m, 3H), 6.98 (t, 2H), 6.77 (dd, 2H), 6.70 (d, 2H), 6.33 (d, 1H), 3.36 (s, 2H), 3.27 (q, 2H), 3.09 (t, 4H), 2.82 (t, 2H), 2.54 (s, 6H), 2.35 (t, 4H), 1.82 (m, 2H).

EXAMPLE 91

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

The title compound was prepared by substituting EXAMPLE 68F for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 8.49 (t, 1H), 8.37 (d, 1H), 7.72 (dd, 1H), 7.62 (d, 1H), 7.50 - 7.43 (m, 5H), 7.35 (m, 2H), 7.26 - 7.14 (m, 3H), 6.97 (d, 1H), 6.90 (t, 1H), 6.72 (d, 2H), 6.69 (dd, 1H), 6.31 (d, 1H), 3.47 (q, 2H), 3.36 (s, 2H), 3.20 (m, 2H), 3.07 (broad s, 8H), 2.35 (broad s, 4H), 1.95 – 1.83 (m, 6H).

EXAMPLE 92

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-{[4-{[3-(dimethylamino)propyl]amino}-3-(trifluoromethyl)phenyl]sulfonyl}-2-phenoxybenzamide

EXAMPLE 92A

4-fluoro-3-(trifluoromethyl)benzenesulfonamide

The title compound was prepared by substituting 4-fluoro-3-(trifluoromethyl)benzene-1-sulfonyl chloride for 3-cyano-4-fluorobenzene-1-sulfonyl chloride in EXAMPLE 90A.

EXAMPLE 92B

4-(3-(dimethylamino)propylamino)-3-(trifluoromethyl)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 92A for 4-fluoro-3-nitrobenzenesulfonamide and N^1,N^1-dimethylpropane-1,3-diamine for tetrahydropyran-4-yl)methylamine in EXAMPLE 1F

EXAMPLE 92C

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-{[4-{[3-(dimethylamino)propyl]amino}-3-(trifluoromethyl)phenyl]sulfonyl}-2-phenoxybenzamide

The title compound was prepared by substituting EXAMPLE 92B for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 7.77 (s, 1H), 7.68 (dd, 1H), 7.57 (d, 1H), 7.51 - 7.45 (m, 5H), 7.36 (m, 2H), 7.29 - 7.21 (m, 3H), 6.99 (t, 1H), 6.82 – 6.68 (m, 5H), 6.32 (d, 1H), 3.36 (s, 2H), 3.28 (q, 2H), 3.09 (t, 4H), 2.73 (m, 2H), 2.48 (s, 6H), 2.35 (t, 4H), 1.79 (m, 2H).

EXAMPLE 93

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-{[4-({3-[isopropyl(methyl)amino]propyl}amino)-3-nitrophenyl]sulfonyl}-2-phenoxybenzamide

EXAMPLE 93A

tert-butyl methyl(3-(2-nitro-4-sulfamoylphenylamino)propyl)carbamate

The title compound was prepared by substituting tert-butyl 3-aminopropyl(methyl)carbamate for 3-(pyrrolidin-1-yl)propan-1-amine in EXAMPLE 68F.

EXAMPLE 93B

tert-butyl 3-(4-(N-(4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxybenzoyl)sulfamoyl)-2-nitrophenylamino)propyl(methyl)carbamate

The title compound was prepared by substituting EXAMPLE 93A for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 93C

4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-N-(4-(3-(methylamino)propylamino)-3-nitrophenylsulfonyl)-2-phenoxybenzamide

EXAMPLE 93B (112 mg) and triethylsilane (0.082 mL) were added to dichloromethane (2 mL). Trifluoroacetic acid (0.198 mL) was added, the solution stirred at room temperature for one hour, and the solvent removed under vacuum.

EXAMPLE 93D

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-{[4-({3-[isopropyl(methyl)amino]propyl}amino)-3-nitrophenyl]sulfonyl}-2-phenoxybenzamide

EXAMPLE 93C (128 mg), acetone (0.014 mL), and sodium cyanoborohydride resin (2.15 mmol/g, 66 mg) were added to tetrahydrofuran (0.9 mL) and acetic acid (0.3 mL), and the soltuion was stirred at room temperature for 16 hours. More acetone (0.014 mL), and sodium cyanoborohydride resin (66 mg) were added, and the solution was stirred for 24 hours. The solution was purified by flash column chromatography on silica gel with 1% acetic acid and 10% methanol in dichloromethane. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.93 (broad s, 3H), 8.53 (broad s, 1H), 8.40 (d, 1H), 7.75 (dd, 1H), 7.60 (d, 1H), 7.51 - 7.45 (m, 5H), 7.36 (m, 2H), 7.25 - 7.16 (m, 3H), 7.02 (d, 1H), 6.92 (t, 1H), 6.74 (d, 2H), 6.70 (dd, 1H), 6.32 (d, 1H), 3.47 (m, 4H), 3.36 (s, 2H), 3.09 (t, 4H), 3.01 (broad s, 2H), 2.58 (s, 3H), 2.35 (t, 4H), 1.94 (m, 1H), 1.18 – 1.14 (m, 6H).

EXAMPLE 94

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({4-[3-(dimethylamino)propoxy]-3-nitrophenyl}sulfonyl)-2-phenoxybenzamide

EXAMPLE 94A

4-(3-(dimethylamino)propoxy)-3-nitrobenzenesulfonamide

Triphenylphosphine (1.398 g) was added to tetrahydrofuran (20 mL) and cooled to 0°C. Diethylazodicarboxylate (40% solution, 2.428 mL) was added, and the solution was stirred for at 0°C for 15 minutes. 4-Hydroxy-3-nitrobenzenesulfonamide (1.163 g) and 3-(dimethylamine)propan-1-ol (0.567 mL) were added, and the solution was allowed to warm to room temperature and stir for 16 hours. Solvent was removed under vacuum and the material recrystallized using 20% methanol (dichloromethane). The recrystallized solid was washed with dichloromethane, dissolved in methanol / dichloromethane, treated with triethylamine (0.13 mL, 0.924 mmol), and purified by flash column chromatography on silica gel with 10-20% methanol in dichloromethane.

EXAMPLE 94B

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({4-[3-(dimethylamino)propoxy]-3-nitrophenyl}sulfonyl)-2-phenoxybenzamide

The title compound was prepared by substituting EXAMPLE 94A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 8.06 (d, 1H), 7.84 (dd, 1H), 7.65 (d, 1H), 7.52 - 7.45 (m, 5H), 7.36 (m, 2H), 7.26 - 7.22 (m, 2H), 7.18 (td, 2H), 6.89 (t, 1H), 6.69 (d, 1H), 6.68 (d, 2H), 6.32 (d, 1H), 4.25 (t, 2H), 3.36 (s, 2H), 3.13 (t, 2H), 3.08 (t, 4H), 2.75 (s, 6H), 2.36 (t, 4H), 2.11 (m, 2H).

EXAMPLE 95

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[2-(4-methylpiperazin-1-yl)ethyl]amino}-3-nitrophenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 26C for EXAMPLE 1E and EXAMPLE 85A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.10 (s, 1H), 8.67 (t, 1H), 8.53 (d, 1H), 7.78 (dd, 1H), 7.52 (d, 1H), 7.39 – 7.31 (m, 4H), 7.08 – 7.02 (m, 3H), 6.94 (d, 1H), 6.80 (dd, 1H), 6.61 (dd, 1H), 6.36 (t, 1H), 6.14 (d, 1H), 3.42 (q, 2H), 2.99 (t, 4H), 2.71 (s, 2H), 2.70 – 2.48 (m, 10H), 2.39 (s, 3H), 2.16 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 96

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[3-(4-methylpiperazin-1-yl)propyl]amino}-3-nitrophenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 26C for EXAMPLE 1E and EXAMPLE 86A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.09 (s, 1H), 8.62 (t, 1H), 8.51 (d, 1H), 7.76 (dd, 1H), 7.53 (d, 1H), 7.38 – 7.31 (m, 4H), 7.05 (s, 1H), 7.02 (d, 2H), 6.96 (d, 1H), 6.79 (dd, 1H), 6.60 (dd, 1H), 6.35 (t, 1H), 6.14 (d, 1H), 3.40 (q, 2H), 2.98 (t, 4H), 2.71 (s, 2H), 2.67 (broad s, 4H), 2.55 – 2.40 (m, 6H), 2.39 (s, 3H), 2.16 (m, 6H), 1.95 (s, 2H), 1.77 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 97

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 26C for EXAMPLE 1E and EXAMPLE 68F for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.06 (s, 1H), 8.58 (t, 1H), 8.49 (d, 1H), 7.77 (dd, 1H), 7.54 (d, 1H), 7.36 – 7.31 (m, 4H), 7.06 – 7.01 (m, 3H), 6.95 (d, 1H), 6.76 (dd, 1H), 6.57 (dd, 1H), 6.35 (t, 1H), 6.14 (d, 1H), 3.44 (q, 2H), 2.97 (broad s, 10H), 2.71 (s, 2H), 2.16 (m, 6H), 1.95 (s, 2H), 1.90 – 1.80 (m, 6H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 98

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 26C for EXAMPLE 1E and EXAMPLE 21A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.08 (s, 1H), 8.51 (d, 1H), 8.13 (d, 1H), 7.78 (dd, 1H), 7.52 (d, 1H), 7.37 – 7.31 (m, 4H), 7.06 - 7.00 (m, 4H), 6.79 (dd, 1H), 6.59 (dd, 1H), 6.35 (t, 1H), 6.14 (d, 1H), 3.73 (m, 1H), 3.05 - 2.95 (m, 6H), 2.71 (s, 2H), 2.60 (m, 2H), 2.48 (s, 3H), 2.16 (m, 6H), 2.01 (m, 2H), 1.95 (s, 2H), 1.70 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 99

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[3-(4-methylpiperazin-1-yl)propyl]amino}-3-nitrophenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 1E and EXAMPLE 86A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.16 (s, 1H), 8.59 (t, 1H), 8.45 (d, 1H), 7.72 (dd, 1H), 7.55 (d, 1H), 7.34 (d, 2H), 7.23 (t, 1H), 7.12 (d, 1H), 7.02 (d, 2H), 6.95 (d, 1H), 6.94 (t, 1H), 6.64 (dd, 1H), 6.35 (d, 1H), 6.23 (m, 2H), 3.41 (q, 2H), 2.98 (t, 4H), 2.71 (broad s, 6H), 2.52 – 2.42 (m, 6H), 2.41 (s, 3H), 2.15 (m, 6H), 1.95 (s, 2H), 1.77 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 100

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[3-(dimethylamino)propoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 26C for EXAMPLE 1E and EXAMPLE 94A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz,

dimethylsulfoxide-d_6) δ 11.03 (s, 1H), 8.23 (d, 1H), 7.91 (dd, 1H), 7.56 (d, 1H), 7.36 – 7.29 (m, 4H), 7.19 (d, 1H), 7.05 (d, 2H), 6.97 (s, 1H), 6.73 (dd, 1H), 6.57 (dd, 1H), 6.33 (t, 1H), 6.15 (d, 1H), 4.23 (t, 2H), 3.04 (m, 2H), 2.96 (t, 4H), 2.72 (s, 2H), 2.67 (s, 6H), 2.22 – 2.02 (m, 8H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 101

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[2-(4-methylpiperazin-1-yl)ethyl]amino}-3-nitrophenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 1E and EXAMPLE 85A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.18 (s, 1H), 8.64 (t, 1H), 8.47 (d, 1H), 7.73 (dd, 2H), 7.56 (d, 1H), 7.34 (d, 2H), 7.24 (t, 1H), 7.04 (d, 2H), 6.96 (d, 1H), 6.94 (d, 1H), 6.65 (dd, 1H), 6.37 (d, 1H), 6.23 (m, 2H), 3.43 (q, 2H), 2.99 (t, 4H), 2.71 (s, 2H), 2.65 (m, 6H), 2.56 (m, 4H), 2.42 (s, 3H), 2.15 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 102

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 1E and EXAMPLE 68F for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.14 (s, 1H), 8.54 (t, 1H), 8.44 (d, 1H), 7.76 (dd, 1H), 7.59 (d, 1H), 7.34 (d, 2H), 7.22 (t, 1H), 7.10 (d, 1H), 7.05 (d, 2H), 6.98 – 6.89 (m, 2H), 6.62 (dd, 1H), 6.33 (d, 1H), 6.23 (t, 1H), 6.21 (d, 1H), 3.44 (q, 2H), 3.10 - 2.91 (m, 10H), 2.71 (s, 2H), 2.16 (m, 6H), 1.95 (s, 2H), 1.92 – 1.79 (m, 6H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 103

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 1E and EXAMPLE 21A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.14 (s, 1H), 8.44 (d, 1H), 8.11 (d, 1H), 7.75 (dd, 1H), 7.56 (d, 1H),

7.34 (d, 2H), 7.23 (t, 1H), 7.11 (d, 1H), 7.04 (d, 2H), 7.03 (d, 1H), 6.93 (t, 1H), 6.64 (dd, 1H), 6.34 (d, 1H), 6.22 (m, 2H), 3.73 (m, 1H), 3.08 - 2.93 (m, 6H), 2.71 (s, 2H), 2.70 – 2.56 (m, 2H), 2.48 (s, 3H), 2.16 (m, 6H), 2.02 (m, 2H), 1.95 (s, 2H), 1.70 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 104

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(1-methylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 26C for EXAMPLE 1E and EXAMPLE 88A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 10.99 (s, 1H), 8.39 (d, 1H), 8.32 (t, 1H), 7.65 (dd, 1H), 7.54 (d, 1H), 7.34 (d, 2H), 7.30 – 7.26 (m, 2H), 7.05 (d, 2H), 6.92 (d, 1H), 6.81 (d, 1H), 6.70 (dd, 1H), 6.53 (dd, 1H), 6.30 (t, 1H), 6.15 (d, 1H), 3.28 – 3.19 (m, 2H), 2.93 (t, 4H), 2.83 (m, 2H), 2.71 (s, 2H), 2.68 – 2.50 (m, 2H), 2.54 (s, 3H), 2.24 – 2.10 (m, 6H), 1.95 (broad s, 2H), 1.68 (d, 2H), 1.59 (m, 1H), 1.38 (t, 2H), 1.32 – 1.17 (m, 2H), 0.92 (s, 6H).

EXAMPLE 105

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[(1-methylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 1E and EXAMPLE 88A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.11 (s, 1H), 8.44 (t, 1H), 8.41 (d, 1H), 7.74 (dd, 1H), 7.59 (d, 1H), 7.34 (d, 2H), 7.21 (t, 1H), 7.11 – 7.02 (m, 3H), 6.98 – 6.90 (m, 2H), 6.61 (dd, 1H), 6.31 (d, 1H), 6.23 (t, 1H), 6.20 (d, 1H), 3.20 (m, 2H), 2.95 (t, 4H), 2.71 (s, 2H), 2.62 – 2.49 (m, 4H), 2.55 (s, 3H), 2.16 (m, 6H), 1.95 (s, 2H), 1.86 – 1.78 (m, 3H), 1.42 – 1.31 (m, 4H), 0.92 (s, 6H).

EXAMPLE 106

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[3-(dimethylamino)propoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 1E and EXAMPLE 94A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.10 (s, 1H), 8.16 (d, 1H), 7.90 (dd, 1H), 7.61 (d, 1H), 7.35 (d, 2H), 7.24 – 7.19 (m, 2H), 7.10 – 7.01 (m, 3H), 6.91 (t, 1H), 6.60 (dd, 1H), 6.28 (d, 1H), 6.23 (t, 1H), 6.20 (d, 1H), 4.23 (t, 2H), 3.03 (t, 2H), 2.95 (t, 4H), 2.72 (s, 2H), 2.67 (s, 6H), 2.17 (m, 6H), 2.07 (m, 2H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 107

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(4-methylpiperazin-1-yl)-3-nitrophenyl]sulfonyl}benzamide

EXAMPLE 107A

4-(4-methylpiperazin-1-yl)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 1-methylpiperazine for 3-(pyrrolidin-1-yl)propan-1-amine in EXAMPLE 68F.

EXAMPLE 107B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(4-methylpiperazin-1-yl)-3-nitrophenyl]sulfonyl}benzamide

The title compound was prepared by substituting EXAMPLE 26C for EXAMPLE 1E and EXAMPLE 107A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.21 (s, 1H), 8.18 (d, 1H), 7.77 (dd, 1H), 7.57 (d, 1H), 7.34 (d, 2H), 7.26 (t, 1H), 7.22 (d, 1H), 7.16 (d, 1H), 7.07 – 7.02 (m, 2H), 6.96 (t, 1H), 6.87 (dd, 1H), 6.39 (d, 1H), 6.25 (m, 2H), 3.16 (m, 4H), 3.01 (t, 4H), 2.73 (s, 2H), 2.66 (broad s, 4H), 2.39 (s, 3H), 2.18 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 108

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(3-nitro-4-{[1-(2,2,2-trifluoroethyl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide

EXAMPLE 108A

3-nitro-4-(1-(2,2,2-trifluoroethyl)piperidin-4-ylamino)benzenesulfonamide

4-chloro-3-nitrobenzenesulfonamide (1.300 g), 1-(2,2,2-trifluoroethyl)piperidin-4-amine hydrochloride (1.201 g), and triethylamine (2.30 mL) were added to 1,4-dioxane (50 mL) and water (5 mL) and heated at 90°C for 16 hours. The solution was concentrated on vacuum and purified by flash column chromatography on silica gel with ethyl acetate increasing to 5% methanol in ethyl acetate.

EXAMPLE 108B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(3-nitro-4-{[1-(2,2,2-trifluoroethyl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide

This EXAMPLE was prepared by substituting EXAMPLE 55B for EXAMPLE 1E and EXAMPLE 108A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.24 (s, 1H), 8.50 (d, 1H), 8.25 (d, 1H), 7.71 (dd, 1H), 7.52 (d, 1H), 7.34 (d, 2H), 7.27 (t, 1H), 7.17 (d, 1H), 7.11 (d, 1H), 7.04 (d, 2H), 6.97 (t, 1H), 6.71 (dd, 1H), 6.43 (d, 1H), 6.28 (d, 1H), 6.24 (t, 1H), 3.68 (m, 1H), 3.23(q, 2H), 3.06 (broad s, 4H), 2.95 - 2.87 (m, 2H), 2.78 – 2.71 (m, 2H), 2.58 (t, 2H), 2.25 – 2.11 (m, 6H), 1.98 – 1.85 (m, 4H), 1.64 (m, 2H), 1.39 (t, 2H), 0.92 (s, 6H).

EXAMPLE 109

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(dimethylamino)-1-methylpiperidin-4-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide

EXAMPLE 109A

4-((4-(dimethylamino)-1-methylpiperidin-4-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 4-(aminomethyl)-N,N,1-trimethylpiperidin-4-amine for 1-(2,2,2-trifluoroethyl)piperidin-4-amine hydrochloride in EXAMPLE 108A.

EXAMPLE 109B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(dimethylamino)-1-methylpiperidin-4-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 26C for EXAMPLE 1E and EXAMPLE 109A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.06 (s, 1H), 8.56 (broad s, 1H), 8.50 (d, 1H), 7.81 (dd, 1H), 7.54 (d, 1H), 7.36 – 7.31 (m, 4H), 7.08 – 7.02 (m, 4H), 6.77 (dd, 1H), 6.57 (dd, 1H), 6.34 (t, 1H), 6.13 (d, 1H), 3.50 (d, 2H), 3.04 (m, 2H), 2.96 (t, 4H), 2.87 (m, 2H), 2.71 (s, 2H), 2.58 (s, 3H), 2.28 (s, 6H), 2.16 (m, 6H), 1.98 (m, 2H), 1.95 (s, 2H), 1.65 – 1.54 (m, 2H), 1.38 (t, 2H), 0.94 (s, 6H).

EXAMPLE 110

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(2,3-dihydro-1,4-benzodioxin-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 110A

methyl 4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-(2,3-dihydrobenzo[b][1,4]dioxin-5-yloxy)benzoate

The title compound was prepared by substituting EXAMPLE 34A for EXAMPLE 18E and 2,3-dihydrobenzo[b][1,4]dioxin-5-ol for phenol in EXAMPLE 18F.

EXAMPLE 110B

4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-(2,3-dihydrobenzo[b][1,4]dioxin-5-yloxy)benzoic acid

The title compound was prepared by substituting EXAMPLE 110A for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 110C

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(2,3-dihydro-1,4-benzodioxin-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 110B for EXAMPLE 1E in EXAMPLE 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ ppm 11.40 (s, 1 H), 8.65 (t, 1 H), 8.55 (d, 1 H), 7.83 (dd, 1 H), 7.46 (m, 6 H), 7.36 (m, 2 H), 7.23 (m, 2 H), 6.77 (d, 1 H), 6.70 (dd, 1 H), 6.42 (m, 2 H), 6.27 (d, 1 H), 4.20 (s, 4 H), 3.85 (dd, 2 H), 3.37 (m, 4 H), 3.25 (m, 2 H), 3.13 (m, 4 H), 2.35 (m, 4 H), 1.90 (m, 1 H), 1.62 (dd, 2 H), 1.27 (m, 2 H).

EXAMPLE 111

5-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-1,1'-biphenyl-2-carboxamide

EXAMPLE 111A

methyl 5-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)biphenyl-2-carboxylate

EXAMPLE 34A (100 mg, 0.2 mmol) in tetrahydrofuran (1.5 mL) was treated with phenylboronic acid (36.6 mg, 0.3 mmol), tris(dibenzylideneacetone)dipalladium(0) (9.2 mg, 0.01 mmol), tri-tert-butylphosphonium tetrafluoroborate (5.8 mg, 0.02 mmol) and cesium fluoride (91 mg, 0.6 mmol), flushed with nitrogen and stirred overnight at ambient temperature. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The concentrate was purified by column chromatography on silica gel eluting with a gradient of 0 to 3% methanol in CH_2Cl_2 to give the product.

EXAMPLE 111B

5-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)biphenyl-2-carboxylic acid

The title compound was prepared by substituting EXAMPLE 111A for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 111C

5-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-1,1'-biphenyl-2-carboxamide

The title compound was prepared by substituting EXAMPLE 111B for EXAMPLE 27G in EXAMPLE 27H. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ ppm 12.09 (s, 1H), 8.72 (t, 1H), 8.46 (d, 1H), 7.79 (m, 2H), 7.52 (m, 4H), 7.35 (dd, 5H), 7.16 (m, 1H), 7.04 (m, 4H), 6.91 (dd, 1H), 6.78 (m, 1H), 4.39 (m, 1H), 3.88 (m, 3H), 3.42 (m, 4H), 3.27 (m, 4H), 2.96 (m, 4H), 1.95 (m, 1H), 1.67 (m, 2H), 1.31 (m, 2H).

EXAMPLE 112

5-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(4-{[3-(dimethylamino)propyl]amino}-3-nitrophenyl)sulfonyl]-1,1'-biphenyl-2-carboxamide

The title compound was prepared by substituting EXAMPLE 111B for EXAMPLE 27G and EXAMPLE 154A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ ppm 12.09 (s, 1H), 8.74 (t, 1H), 8.47 (d, 1H), 7.83 (dd, 1H), 7.70 (m, 1H), 7.40 (m, 8H), 7.27 (m, 1H), 7.20 (m, 1H), 7.07 (m, 4H), 6.91 (dd, 1H), 6.77 (m, 1H), 4.39 (m, 1H), 3.87 (m, 1H), 3.55 (m, 4H), 3.26 (m, 2H), 3.16 (m, 4H), 3.03 (m, 2H), 2.80 (m, 6H), 1.98 (m, 2H).

EXAMPLE 113

4-[4-({4'-chloro-4-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

EXAMPLE 113A

methyl 2-phenoxy-4-(piperazin-1-yl)benzoate

The title compound was made by substituting piperazine for EXAMPLE 1B in EXAMPLE 1D.

EXAMPLE 113B

methyl 4-(4-(2-bromo-5-hydroxybenzyl)piperazin-1-yl)-2-phenoxybenzoate

The title compound was made by substituting 2-bromo-5-hydroxybenzaldehyde for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 113A for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 113C

methyl 4-(4-(2-bromo-5-(2-(dimethylamino)ethoxy)benzyl)piperazin-1-yl)-2-phenoxybenzoate

A mixture of EXAMPLE 113B (170 mg), 2-chloro-N,N-dimethylethanamine hydrochloride salt (80 mg) and cesium carbonate (278 mg) was suspended in anhydrous N,N-dimethylformamide (3 mL). The reaction mixture was heated at 50°C overnight. The reaction mixture was cooled to room temperature and diluted with ethyl acetate. The organic phase was washed with water and brine, and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum to afford an oily residue which was used in the next step without further purification.

EXAMPLE 113D

methyl 4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxybenzoate

The title compound was made by substituting EXAMPLE 113C for EXAMPLE 68C and 4-chlorophenylboronic acid for 4-methoxyphenylboronic acid in EXAMPLE 68D.

EXAMPLE 113E

4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxybenzoic acid

The title compound was made by substituting EXAMPLE 113D for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 113F

4-[4-({4'-chloro-4-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

The title compound was made by substituting EXAMPLE 113E for EXAMPLE 1E in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.69 (br s, 1H), 9.87 (br s, 1H), 8.63 (t, 1H), 8.46 (d, 1H), 7.75 (dd, 1H), 7.50 (m, 3H), 7.34-7.23 (m, 6H), 7.14 (m, 2H), 6.98 (m, 1H), 6.78 (m, 3H), 6.44 (d, 1H), 4.37 (t, 2H), 3.86 (m, 2H), 3.60-3.41 (m, 10H), 3.34 (t, 4H), 3.28(m, 2H), 2.89 (s, 6H), 1.91 (m, 1H), 1.62 (m, 2H), 1.28 (m, 2H).

EXAMPLE 114

4-(4-{[4'-chloro-4-(3-piperidin-1-ylpropoxy)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

EXAMPLE 114A

methyl 4-(4-(2-bromo-5-(3-(piperidin-1-yl)propoxy)benzyl)piperazin-1-yl)-2-phenoxybenzoate

The title compound was made by substituting 1-(3-chloropropyl)piperidine hydrochloride salt for 2-chloro-N,N-dimethylethanamine hydrochloride salt in EXAMPLE 113C.

EXAMPLE 114B

methyl 4-(4-((4'-chloro-4-(3-(piperidin-1-yl)propoxy)biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxybenzoate

The title compound was made by substituting EXAMPLE 114A for EXAMPLE 68C and 4-chlorophenylboronic acid for 4-methoxyphenylboronic acid in EXAMPLE 68D.

EXAMPLE 114C

4-(4-((4'-chloro-4-(3-(piperidin-1-yl)propoxy)biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxybenzoic acid

The title compound was made by substituting EXAMPLE 114B for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 114D

4-(4-{[4'-chloro-4-(3-piperidin-1-ylpropoxy)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

The title compound was made by substituting EXAMPLE 114C for EXAMPLE 1E in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.69 (br s, 1H), 9.18 (br s, 1H), 8.63 (t, 1H), 8.46 (d, 1H), 7.75 (dd, 1H), 7.50 (m, 3H), 7.33-7.21 (m, 6H), 7.15 (d, 2H), 6.98 (m, 1H), 6.78 (m, 3H), 6.44 (d, 1H), 4.11 (t, 2H), 3.87 (dd, 2H), 3.60-3.38 (m, 10H), 3.34 (m, 4H), 3.25 (m, 4H), 2.92 (m, 2H), 2.17 (m, 2H), 1.85 (m, 3H), 1.64 (m, 6H), 1.29 (m, 2H).

EXAMPLE 115

4-(4-{[4'-chloro-4-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

EXAMPLE 115A

methyl 4-(4-(2-bromo-5-(2-morpholinoethoxy)benzyl)piperazin-1-yl)-2-phenoxybenzoate

The title compound was made by substituting 4-(2-chloroethyl)morpholine hydrochloride salt for 2-chloro-N,N-dimethylethanamine hydrochloride salt in EXAMPLE 113C.

EXAMPLE 115B

methyl 4-(4-((4'-chloro-4-(2-morpholinoethoxy)biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxybenzoate

The title compound was made by substituting EXAMPLE 115A for EXAMPLE 68C and 4-chlorophenylboronic acid for 4-methoxyphenylboronic acid in EXAMPLE 68D.

EXAMPLE 115C

4-(4-((4'-chloro-4-(2-morpholinoethoxy)biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxybenzoic acid

The title compound was made by substituting EXAMPLE 115B for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 115D

4-(4-{[4'-chloro-4-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

The title compound was made by substituting EXAMPLE 115C for EXAMPLE 1E in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.66 (br s, 1H), 8.63 (t, 1H), 8.46 (d, 1H), 7.75 (dd, 1H), 7.50 (m, 3H), 7.31 (m, 4H), 7.23 (m, 2H), 7.15 (m, 2H), 6.98 (m ,1H), 6.78 (m, 3H), 6.44 (d, 1H), 4.41 (m, 2H), 3.87 (m, 6H), 3.60-3.38 (m, 12H), 3.36-3.25 (m, 8H), 1.91 (m, 1H), 1.64 (m, 2H), 1.29 (m, 2H).

EXAMPLE 116

4-[4-({4'-chloro-4-[3-(dimethylamino)propoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

EXAMPLE 116A

methyl 4-(4-(2-bromo-5-(3-(dimethylamino)propoxy)benzyl)piperazin-1-yl)-2-phenoxybenzoate

The title compound was made by substituting 3-chloro-N,N-dimethylpropan-1-amine hydrochloride salt for 2-chloro-N,N-dimethylethanamine hydrochloride salt in EXAMPLE 113C.

EXAMPLE 116B

methyl 4-(4-((4'-chloro-4-(3-(dimethylamino)propoxy)biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxybenzoate

The title compound was made by substituting EXAMPLE 116A for EXAMPLE 68C and 4-chlorophenylboronic acid for 4-methoxyphenylboronic acid in EXAMPLE 68D.

EXAMPLE 116C

4-(4-((4'-chloro-4-(3-(dimethylamino)propoxy)biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxybenzoic acid

The title compound was made by substituting EXAMPLE 116B for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 116D

4-[4-({4'-chloro-4-[3-(dimethylamino)propoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

The title compound was made by substituting EXAMPLE 116C for EXAMPLE 1E in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.64 (br s, 1H), 9.52 (br s, 1H), 8.63 (t, 1H), 8.47 (d, 1H), 7.75 (dd, 1H), 7.50 (m, 3H), 7.34 (m, 2H), 7.23 (m, 4H), 7.14 (d, 1H), 6.98 (m, 2H), 6.78 (m, 3H), 6.42 (s, 1H), 4.09 (t, 2H), 3.86 (m, 2H), 3.50-3.36 (m, 8H), 3.28 (m, 8H), 2.83 (s, 6H), 2.12 (m, 2H), 1.91 (m, 1H), 1.62 (m, 2H), 1.29 (m, 2H).

EXAMPLE 117

4-(4-{[4'-chloro-4-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-phenoxy-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

The title compound was made by substituting EXAMPLE 115C for EXAMPLE 27G and EXAMPLE 163A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 8.11 (d, 1H), 7.86 (dd, 1H), 7.49 (m, 3H), 7.36-7.26 (m, 7H), 7.10 (m, 3H), 6.84 (d, 2H), 6.77 (dd, 1H), 6.41 (s, 1H), 4.38 (m, 2H), 3.84 (m, 4H), 3.55 (m, 2H), 3.50-3.30 (m, 10H), 3.28 (m, 8H), 3.20 (m, 2H), 1.86 (m, 1H), 1.55 (m, 2H), 1.26 (m, 2H).

EXAMPLE 118

4-(4-{[4'-chloro-4-(3-piperidin-1-ylpropoxy)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-phenoxy-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

The title compound was made by substituting EXAMPLE 114C for EXAMPLE 27G and EXAMPLE 163A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.65 (br s, 1H), 9.06 (br s, 1H), 8.11 (d, 1H), 7.86 (dd, 1H), 7.49 (m, 3H), 7.36-7.20 (m, 7H), 7.06 (m, 3H), 6.83 (d, 2H), 6.76 (dd, 1H), 6.41 (s, 1H), 4.10 (t, 2H), 3.85 (dd, 2H), 3.40-3.05 (m, 16H), 2.90 (m, 2H), 2.15 (m, 2H), 1.84 (m, 3H), 1.60 (m, 6H), 1.41 (m, 2H), 1.26 (m, 2H).

EXAMPLE 119

4-[4-({4'-chloro-4-[3-(dimethylamino)propoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-phenoxy-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

The title compound was made by substituting EXAMPLE 116C for EXAMPLE 27G and EXAMPLE 163A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 8.11 (d, 1H), 7.86 (dd, 1H), 7.49 (m, 3H), 7.36-7.26 (m, 7H), 7.06 (m, 3H), 6.84 (d, 2H), 6.76 (dd, 1H), 6.41 (d, 1H), 4.09 (t, 2H), 3.84 (dd, 2H), 3.50-3.24 (m, 14H), 3.10 (m, 2H), 2.83 (s, 6H), 2.12 (m, 2H), 1.86 (m, 1H), 1.55 (m, 2H), 1.26 (m, 2H).

EXAMPLE 120

4-[4-({4'-chloro-4-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-phenoxy-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

The title compound was made by substituting EXAMPLE 113E for EXAMPLE 27G and EXAMPLE 163A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.75 (br s, 1H), 9.90 (br s, 1H), 8.10 (d, 1H), 7.85 (dd, 1H), 7.49 (m, 3H), 7.38-7.25 (m, 7H), 7.11 (d, 2H), 7.03 (m, 1H), 6.82 (d, 2H), 6.77 (dd, 1H), 6.44 (s, 1H), 4.37 (t, 2H), 3.85 (m, 6H), 3.55 (m, 2H), 3.29 (m, 8H), 3.10 (m, 2H), 2.89 (s, 6H), 1.86 (m, 1H), 1.55 (m, 2H), 1.24 (m, 2H).

EXAMPLE 121

4-[4-({4'-chloro-4-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

The title compound was made by substituting EXAMPLE 113E for EXAMPLE 27G and EXAMPLE 68F for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.70 (br s, 1H), 9.95 (br s, 1H), 9.73 (br s, 1H), 8.69 (t, 1H), 8.49 (d, 1H), 7.79 (dd, 1H), 7.50 (m, 3H), 7.34 (m, 2H), 7.23 (m, 3H), 7.16 (d, 1H), 7.09 (m, 1H), 7.00 (m, 1H), 6.82 (d, 2H), 6.77 (dd, 1H), 6.42 (s, 1H), 4.37 (m, 2H), 3.70 (m, 6H), 3.54 (m, 8H), 3.21 (m, 4H), 3.19 (m, 2H), 2.88 (s, 6H), 1.97 (m, 4H), 1.85 (m, 2H).

EXAMPLE 122

4-[4-({4'-chloro-3-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

EXAMPLE 122A

methyl 4-(4-(2-bromo-6-hydroxybenzyl)piperazin-1-yl)-2-phenoxybenzoate

The title compound was made by substituting 2-bromo-6-hydroxybenzaldehyde for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE113A for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 122B

methyl 4-(4-((4'-chloro-3-hydroxybiphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxybenzoate

The title compound was made by substituting EXAMPLE 122A for EXAMPLE 68C and 4-chlorophenylboronic acid for 4-methoxyphenylboronic acid in EXAMPLE 68D.

EXAMPLE 122C

methyl 4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxybenzoate

EXAMPLE 122B (100 mg) and 2-chloro-N,N-dimethylethanamine hydrochloride salt (30 mg) was dissolved in mixed solvent of dichloromethane (1.5 mL) and 50% sodium hydroxide aqueous solution (0.5 mL), followed by addition of tetrabutylammonium iodide (15 mg). The reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate, and washed with water and brine. The organic phase

was dried over Na_2SO_4 and concentrated. Flash column purification was performed with 0-5% methanol/dichloromethane to afford the product.

EXAMPLE 122D

4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxybenzoic acid

The title compound was made by substituting EXAMPLE 122C for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 122E

4-[4-({4'-chloro-3-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

The title compound was made by substituting EXAMPLE 122D for EXAMPLE 1E in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 10.20 (br s, 1H), 9.46 (br s, 1H), 8.65 (t, 1H), 8.47 (d, 1H), 7.78 (d, 1H), 7.75(dd, 1H), 7.52 (m, 4H), 7.38 (m, 3H), 7.23 (m, 3H), 7.12 (m, 1H), 6.98 (m, 2H), 6.78 (d, 2H), 6.76 (dd, 1H), 6.43 (s, 1H), 4.43 (m, 2H), 3.87 (m, 2H), 3.62 (m, 4H), 3.35-3.15 (m, 12H), 2.90 (s, 6H), 1.90 (m, 1H), 1.62 (m, 2H), 1.27 (m, 2H).

EXAMPLE 123

4-[4-({4'-chloro-3-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

The title compound was made by substituting EXAMPLE 122C for EXAMPLE 1E and EXAMPLE 68F for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 10.01 (br s, 1H), 9.63 (br s, 1H), 9.32 (br s, 1H), 8.69(t, 1H), 8.49 (d, 1H), 7.80 (dd, 1H), 7.52 (m, 4H), 7.38 (m, 2H), 7.25 (m, 3H), 7.15 (d, 1H), 7.01 (m, 1H), 6.95 (m, 1H), 6.81 (d, 2H), 6.76 (m, 1H), 6.41 (s, 1H), 4.43 (m, 4H), 3.56-3.51 (m, 8H), 3.20 (m, 4H), 3.10 (m, 6H), 2.91 (s, 6H), 1.98 (m, 4H), 1.85 (m, 2H).

EXAMPLE 124

4-[4-({4'-chloro-3-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-phenoxy-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

The title compound was made by substituting EXAMPLE 122C for EXAMPLE 27G and EXAMPLE 163A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.71 (br s, 1H), 9.89 (br s, 1H), 9.14 (br s, 1H), 8.11(d, 1H), 7.86 (dd, 1H), 7.52 (m, 4H), 7.38 (m, 2H), 7.29 (m, 3H), 7.20 (m, 1H), 7.11 (d, 1H), 7.05 (m, 1H), 6.95 (m, 1H), 6.83 (d, 2H), 6.76 (dd, 1H), 6.40 (s, 1H), 4.41 (m, 2H), 3.85 (m, 2H), 3.59 (m, 4H), 3.44 (m, 2H), 3.28 (m, 8H), 3.06 (m, 2H), 2.91 (s, 6H), 1.84 (m, 1H), 1.55 (m, 2H), 1.26 (m, 2H).

EXAMPLE 125

4-[4-({4'-chloro-4-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 125A

4'-chloro-4-hydroxybiphenyl-2-carbaldehyde

The title compound was made by substituting 2-bromo-5-hydroxybenzaldehyde for EXAMPLE 68C and 4-chlorophenylboronic acid for 4-methoxyphenylboronic acid in EXAMPLE 68D.

EXAMPLE 125B

4'-chloro-4-(2-(dimethylamino)ethoxy)biphenyl-2-carbaldehyde

The title compound was made by substituting EXAMPLE 125A for EXAMPLE 122B in EXAMPLE 122C.

EXAMPLE 125C

methyl 2-(1H-indol-4-yloxy)-4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)biphenyl-2-yl)methyl)piperazin-1-yl)benzoate

The title compound was made by substituting EXAMPLE 125B for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 68B for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 125D

2-(1H-indol-4-yloxy)-4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)biphenyl-2-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was made by substituting EXAMPLE 125C for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 125E

4-[4-({4'-chloro-4-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was made by substituting EXAMPLE 125D for EXAMPLE 1E in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.46 (br s, 1H), 11.25 (s, 1H), 9.80 (br s, 1H), 8.60 (t, 1H), 8.48(d, 1H), 7.65 (dd, 1H), 7.55 (d, 1H), 7.46 (d, 2H), 7.28 (m, 5H), 7.15 (d, 1H), 7.10 (m, 1H), 7.04 (d, 1H), 6.94 (m, 1H), 6.73 (dd, 1H), 6.36 (m, 2H), 6.26 (m, 1H), 4.35 (t, 2H), 3.85 (m, 6H), 3.54 (m, 4H), 3.31 (m, 6H), 3.06 (m, 2H), 2.88 (s, 6H), 1.88 (m, 1H), 1.60 (m, 2H), 1.28 (m, 2H).

EXAMPLE 126

4-[4-({4'-chloro-4-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 126A

methyl 2-(1H-indol-5-yloxy)-4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)biphenyl-2-yl)methyl)piperazin-1-yl)benzoate

The title compound was made by substituting EXAMPLE 125B for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 150A for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 126B

2-(1H-indol-5-yloxy)-4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)biphenyl-2-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was made by substituting EXAMPLE 126A for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 126C

4-[4-({4'-chloro-4-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was made by substituting EXAMPLE 126B for EXAMPLE 1E in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.35 (br s, 1H), 11.17 (s, 1H), 9.85 (br s, 1H), 8.61 (t, 1H) 8.57(d, 1H), 7.77 (dd, 1H), 7.54 (d, 1H), 7.46 (d, 2H), 7.38 (m, 2H), 7.30 (m, 4H), 7.09 (m, 3H), 6.84 (dd, 1H), 6.69 (dd, 1H), 6.36 (m, 1H), 6.26 (m, 1H), 4.35 (t, 2H), 3.85 (m, 6H), 3.54 (m, 4H), 3.31 (m, 6H), 3.06 (m, 2H), 2.88 (s, 6H), 1.88 (m, 1H), 1.60 (m, 2H), 1.28 (m, 2H).

EXAMPLE 127

4-(4-{[4'-chloro-4-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 127A

4'-chloro-4-(2-morpholinoethoxy)biphenyl-2-carbaldehyde

The title compound was made by substituting EXAMPLE 125A for EXAMPLE 122B in and 4-(2-chloroethyl)morpholine hydrochloride salt for 2-chloro-N,N-dimethylethanamine hydrochloride salt EXAMPLE 122C.

EXAMPLE 127B

methyl 2-(1H-indol-5-yloxy)-4-(4-((4'-chloro-4-(2-morpholinoethoxy)biphenyl-2-yl)methyl)piperazin-1-yl)benzoate

The title compound was made by substituting EXAMPLE 127A for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 150A for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 127C

2-(1H-indol-5-yloxy)-4-(4-((4'-chloro-4-(2-morpholinoethoxy)biphenyl-2-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was made by substituting EXAMPLE 127Bfor EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 127D

4-(4-{[4'-chloro-4-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was made by substituting EXAMPLE 127C for EXAMPLE 1E in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.35 (br s, 1H), 11.17 (s, 1H), 8.61 (t, 1H), 8.57 (d, 1H), 7.77 (dd, 1H), 7.54 (d, 1H), 7.46 (d, 2H), 7.38 (m, 2H), 7.29 (m, 4H), 7.09 (m, 3H), 6.84 (dd, 1H), 6.69 (dd, 1H), 6.36 (m, 1H), 6.26 (d, 1H), 4.39 (t, 2H), 3.85 (m, 6H), 3.54 (m, 10H), 3.31 (m, 8H), 3.06 (m, 2H), 1.88 (m, 1H), 1.60 (m, 2H), 1.27 (m, 2H).

EXAMPLE 128

4-[4-({4'-chloro-3-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 128A

4'-chloro-3-hydroxybiphenyl-2-carbaldehyde

The title compound was made by substituting 2-bromo-6-hydroxybenzaldehyde for EXAMPLE 68C and 4-chlorophenylboronic acid for 4-methoxyphenylboronic acid in EXAMPLE 68D.

EXAMPLE 128B

4'-chloro-3-(2-(dimethylamino)ethoxy)biphenyl-2-carbaldehyde

The title compound was made by substituting EXAMPLE 128A for EXAMPLE 122B in EXAMPLE 122C.

EXAMPLE 128C

methyl 2-(1H-indol-4-yloxy)-4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)biphenyl-2-yl)methyl)piperazin-1-yl)benzoate

The title compound was made by substituting EXAMPLE 128B for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 68B for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 128D

2-(1H-indol-4-yloxy)-4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)biphenyl-2-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was made by substituting EXAMPLE 128C for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 128E

4-[4-({4'-chloro-3-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was made by substituting EXAMPLE 128D for EXAMPLE 1E in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.15 (s, 1H), 8.47 (t, 1H) 8.45 (d, 1H), 7.68 (dd, 1H), 7.57 (d, 1H), 7.50 (d, 2H), 7.42 (d, 2H), 7.32 (m, 1H), 7.24 (m, 1H), 7.12 (d, 1H), 7.05 (d, 1H), 6.94 (m, 2H), 6.84 (d, 1H), 6.66 (dd, 1H), 6.35 (d, 1H), 6.25 (m, 2H), 4.17 (t, 2H), 3.85 (m, 2H), 3.54 (m, 10H), 3.40 (m, 6H), 3.30 (s, 6H), 3.02 (m, 2H), 2.96 (m, 4H), 2.28 (m, 4H), 1.88 (m, 1H), 1.60 (m, 2H), 1.28 (m, 2H).

EXAMPLE 129

4-[4-({4'-chloro-3-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 129A

methyl 2-(1H-indol-5-yloxy)-4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)biphenyl-2-yl)methyl)piperazin-1-yl)benzoate

The title compound was made by substituting EXAMPLE 128B for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 150A for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 129B

2-(1H-indol-5-yloxy)-4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)biphenyl-2-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was made by substituting EXAMPLE 129A for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 129C

4-[4-({4'-chloro-3-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was made by substituting EXAMPLE 129B for EXAMPLE 1E in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.38 (br s, 1H), 11.19 (s, 1H), 10.00(br s, 1H), 8.61 (t, 1H) 8.58 (d, 1H), 7.79 (dd, 1H), 7.53 (m, 4H), 7.39 (m, 4H), 7.19 (m, 1H), 7.11 (m, 2H), 6.93 (d, 1H), 6.84 (dd, 1H), 6.69 (dd, 1H), 6.39 (m, 1H), 6.19 (d, 1H), 4.40 (m, 2H), 3.85 (m, 8H), 3.58 (m, 2H), 3.27 (m, 6H), 3.06 (m, 2H), 2.89 (s, 6H), 1.89 (m, 1H), 1.60 (m, 2H), 1.27 (m, 2H).

EXAMPLE 130

4-(4-{[4'-chloro-4-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 130A

methyl 2-(1H-indol-4-yloxy)-4-(4-((4'-chloro-4-(2-morpholinoethoxy)biphenyl-2-yl)methyl)piperazin-1-yl)benzoate

The title compound was made by substituting EXAMPLE 127A for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 68B for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 130B

2-(1H-indol-4-yloxy)-4-(4-((4'-chloro-4-(2-morpholinoethoxy)biphenyl-2-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was made by substituting EXAMPLE 130A for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 130C

4-(4-{[4'-chloro-4-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was made by substituting EXAMPLE 130B for EXAMPLE 1E in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.47(br s, 1H), 11.23 (s, 1H), 8.59 (t, 1H) 8.47 (d, 1H), 7.63 (dd, 1H), 7.54 (d, 1H), 7.47 (d, 2H), 7.27 (m, 6H), 7.13 (m, 2H), 7.03 (m, 1H), 6.93 (m, 1H), 6.74 (dd, 1H), 6.35 (m, 1H), 6.24 (m, 1H), 4.39 (t, 2H), 3.85 (m, 6H), 3.54 (m, 10H), 3.26 (m, 10H), 1.88 (m, 1H), 1.59 (m, 2H), 1.27 (m, 2H).

EXAMPLE 131

4-(4-{[4'-chloro-3-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 131A

4'-chloro-3-(2-morpholinoethoxy)biphenyl-2-carbaldehyde

The title compound was made by substituting EXAMPLE 128A for EXAMPLE 122B and 4-(2-chloroethyl)morpholine hydrochloride salt for 2-chloro-N,N-diemthylethanamine hydrochloride salt in EXAMPLE 122C.

EXAMPLE 131B

methyl 2-(1H-indol-4-yloxy)-4-(4-((4'-chloro-3-(2-morpholinoethoxy)biphenyl-2-yl)methyl)piperazin-1-yl)benzoate

The title compound was made by substituting EXAMPLE 131A for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 68B for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 131C

2-(1H-indol-4-yloxy)-4-(4-((4'-chloro-3-(2-morpholinoethoxy)biphenyl-2-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was made by substituting EXAMPLE 131B for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 131D

4-(4-{[4'-chloro-3-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was made by substituting EXAMPLE 131C for EXAMPLE 1E in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.49 (br s, 1H), 11.25 (s, 1H), 8.59 (t, 1H), 8.50 (d, 1H), 7.68 (dd, 1H), 7.52 (m, 4H), 7.34 (d, 2H), 7.28 (m, 1H), 7.18 (m, 2H), 7.06 (d, 1H), 6.94 (m, 2H), 6.73 (dd, 1H), 6.40 (d, 1H), 6.33 (d, 1H), 6.24 (m, 1H), 4.43(t, 2H), 3.85 (m, 10H), 3.61 (m, 6H), 3.27 (m, 8H), 3.02 (m, 2H), 1.88 (m, 1H), 1.60 (m, 2H), 1.28 (m, 2H).

EXAMPLE 132

4-(4-{[4'-chloro-3-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 132A

methyl 2-(1H-indol-5-yloxy)-4-(4-((4'-chloro-3-(2-morpholinoethoxy)biphenyl-2-yl)methyl)piperazin-1-yl)benzoate

The title compound was made by substituting EXAMPLE 131A for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 150A for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 132B

2-(1H-indol-5-yloxy)-4-(4-((4'-chloro-3-(2-morpholinoethoxy)biphenyl-2-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was made by substituting EXAMPLE 132A for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 132C

4-(4-{[4'-chloro-3-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was made by substituting EXAMPLE 132B for EXAMPLE 1E in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.34 (br s, 1H), 11.17 (s, 1H), 8.60 (t, 1H), 8.58 (d, 1H), 7.79 (dd, 1H), 7.50 (m, 4H), 7.39 (m, 4H), 7.19 (d, 1H), 7.14 (d, 1H), 7.09 (d, 1H), 6.93 (d, 1H), 6.84 (dd, 1H), 6.69 (dd, 1H), 6.39 (m, 1H), 6.19 (d, 1H), 4.40 (m, 2H), 3.85 (m, 6H), 3.48 (m, 8H), 3.27 (m, 10H), 3.06 (m, 2H), 1.89 (m, 1H), 1.60 (m, 2H), 1.27(m, 2H).

EXAMPLE 133

4-[4-({4'-chloro-4-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-phenoxybenzamide

The title compound was made by substituting EXAMPLE 113D for EXAMPLE 27G and EXAMPLE 21A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 8.34 (d, 1H), 8.05 (d, 1H), 7.69 (dd, 1H), 7.59 (d, 1H), 7.42 (m, 4H), 7.14 (m, 3H), 7.09 (d, 1H), 6.98 (d, 1H), 6.92 (dd, 1H), 6.87 (m, 1H), 6.84 (m, 3H), 6.30 (d, 1H), 4.16 (t, 2H), 3.07 (m, 6H), 2.95 (m, 4H), 2.56 (m, 2H), 2.45 (s, 3H), 2.35 (m, 4H), 2.03 (m, 2H), 1.68 (m, 2H).

EXAMPLE 134

4-[4-({4'-chloro-3-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)benzamide

The title compound was made by substituting EXAMPLE 129B for EXAMPLE 27G and EXAMPLE 68F for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.34 (br s, 1H), 11.17 (s, 1H), 9.65 (br s, 1H), 8.63 (t, 1H), 8.60 (d, 1H), 7.86 (dd, 1H), 7.53 (d, 2H), 7.41 (m, 6H), 7.15 (m, 3H), 6.92 (m, 1H), 6.84 (dd, 1H),

6.66 (dd, 1H), 6.38 (m, 1H), 6.16 (d, 1H), 4.37 (m, 2H), 3.50 (m, 12H), 3.17 (m, 4H), 2.97 (m, 4H), 2.88 (s, 6H), 1.95 (m, 4H), 1.85 (m, 2H).

EXAMPLE 135

4-[4-({4'-chloro-4-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)benzamide

The title compound was made by substituting EXAMPLE 126B for EXAMPLE 27G and EXAMPLE 68F for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.29 (br s, 1H), 11.16 (s, 1H), 9.56 (br s, 1H), 8.63 (t, 1H), 8.60 (d, 1H), 7.85 (dd, 1H), 7.53 (d, 1H), 7.41 (m, 4H), 7.32 (m, 3H), 7.24 (m, 1H), 7.12 (m, 3H), 6.84 (dd, 1H), 6.66 (dd, 1H), 6.38 (m, 1H), 6.18 (d, 1H), 4.33 (t, 2H), 3.50 (m, 12H), 3.17 (m, 4H), 2.97 (m, 4H), 2.86 (s, 6H), 1.95 (m, 4H), 1.85 (m, 2H).

EXAMPLE 136

4-(4-{[4'-chloro-4-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)benzamide

The title compound was made by substituting EXAMPLE 127C for EXAMPLE 27G and EXAMPLE 68F for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.29 (br s, 1H), 11.16 (s, 1H), 9.54 (br s, 1H), 8.63 (t, 1H), 8.60 (d, 1H), 7.85 (dd, 1H), 7.53 (d, 1H), 7.45 (d, 2H), 7.38 (m, 2H), 7.31(d, 2H), 7.23 (m, 2H), 7.12 (m, 3H), 6.84 (dd, 1H), 6.66 (dd, 1H), 6.38 (m, 1H), 6.18 (d, 1H), 4.36 (t, 2H), 3.82 (m, 4H), 3.50 (m, 8H), 3.17 (m, 10H), 2.98 (m, 4H), 1.95 (m, 6H), 1.85 (m, 2H).

EXAMPLE 137

4-[4-({4'-chloro-4-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-N-[(3-nitro-4-{[1-(2,2,2-trifluoroethyl)piperidin-4-yl]amino}phenyl)sulfonyl]-2-phenoxybenzamide

The title compound was made by substituting EXAMPLE 113E for EXAMPLE 27G and EXAMPLE 108A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.71 (br s, 1H), 9.81 (br s, 1H), 8.46(d, 1H), 8.29 (d, 1H), 7.75 (dd, 1H), 7.50 (m, 3H), 7.30 (m, 4H), 7.21(m, 3H), 7.10 (m, 1H), 6.97 (m, 1H), 6.77 (m, 3H), 6.43

(s, 1H), 4.36 (t, 2H), 3.72 (m, 2H), 3.58 (m, 4H), 3.23 (m, 6H), 2.95 (m, 4H), 2.89 (s, 6H), 2.60 (m, 2H), 1.92 (m, 2H), 1.68 (m, 2H).

EXAMPLE 138

4-(4-{[4'-chloro-4-(2-pyrrolidin-1-ylethoxy)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

EXAMPLE 138A

methyl 4-(4-((4'-chloro-4-hydroxybiphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxybenzoate

The title compound was made by substituting EXAMPLE 113B for EXAMPLE 68C and 4-chlorophenylboronic acid for 4-methoxyphenylboronic acid in EXAMPLE 68D.

EXAMPLE 138B

methyl 4-(4-((4'-chloro-4-(2-(pyrrolidin-1-yl)ethoxy)biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxybenzoate

The title compound was made by substituting EXAMPLE 138A for EXAMPLE 113B and 1-(2-chloroethyl)pyrrolidine HCl salt for 2-chloro-N,N-dimethylethanamine hydrochloride salt in EXAMPLE 113C.

EXAMPLE 138C

4-(4-((4'-chloro-4-(2-(pyrrolidin-1-yl)ethoxy)biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxybenzoic acid

The title compound was made by substituting EXAMPLE 138B for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 138D

4-(4-{[4'-chloro-4-(2-pyrrolidin-1-ylethoxy)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

The title compound was made by substituting EXAMPLE 138C for EXAMPLE 1E in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.64 (br s, 1H), 9.98 (br s, 1H), 8.62(d, 1H), 8.47 (d, 1H), 7.75(dd, 1H), 7.50 (m, 3H), 7.26 (m, 6H), 7.14 (m, 2H), 6.99 (m, 1H), 6.81 (d, 2H), 6.77 (dd, 1H), 6.43 (d, 1H), 4.36 (t, 2H), 3.86 (dd, 2H), 3.62 (m, 8H), 3.28 (m, 8H), 3.10 (m, 4H), 2.04 (m, 2H), 1.90(m, 3H), 1.65 (m, 2H), 1.29 (m, 2H).

EXAMPLE 139

4-[4-({4'-chloro-4-[2-(diisopropylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

EXAMPLE 139A

methyl 4-(4-((4'-chloro-4-(2-(diisopropylamino)ethoxy)biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxybenzoate

The title compound was made by substituting EXAMPLE 138A for EXAMPLE 113B and 2-diisopropylaminoethyl chloride hydrochloride salt for 2-chloro-N,N-dimethylethanamine hydrochloride salt in EXAMPLE 113C.

EXAMPLE 139B

4-(4-((4'-chloro-4-(2-(diisopropylamino)ethoxy)biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxybenzoic acid

The title compound was made by substituting EXAMPLE 139A for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 139C

4-[4-({4'-chloro-4-[2-(diisopropylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

The title compound was made by substituting EXAMPLE 139B for EXAMPLE 1E in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.65 (br s, 1H), 8.75 (br s, 1H), 8.62 (d, 1H), 8.47 (d, 1H), 7.75 (dd, 1H), 7.50 (m, 3H), 7.31 (m, 4H), 7.23 (m, 2H), 7.13 (m, 2H), 6.99 (m, 1H), 6.79 (m, 3H), 6.44 (m, 1H), 4.31 (t, 2H), 3.86 (dd, 2H), 3.62 (m, 10H), 3.28 (m, 6H), 1.91(m, 1H), 1.62 (m, 2H), 1.32(m, 14H).

EXAMPLE 140

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(2,3-dihydro-1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

A suspension of EXAMPLE 40D (22.57 mg) and sodium cyanoborohydride (25 mg) in acetic acid (5 ml) was stirred at room temperature for 2 hours. The product was

partitioned between dichloromethane and water. The organic layer was separated, dried over Na_2SO_4, and concentrated. The crude product was purified by RP HPLC (C8, 30 - 100 acetonitrile/water/0.1%trifluoroacetic acid). ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.56 (s, 1H), 9.60 (s, 1H), 8.66 (t, 1H), 8.57 (d, 1H), 7.85 (dd, 1H), 7.71 (s, 1H), 7.46 - 7.60 (m, 5H), 7.29 - 7.42 (m, 3H), 7.25 (d, 1H), 6.95 (s, 1H), 6.82 (s, 1H), 6.73 (d, 1H), 6.36 (s, 1H), 4.32 (bs, 2H), 3.85 (dd, 4H), 3.59 (t, 4H), 3.35 (t, 2H), 3.27 (t, 2H), 3.02 (t, 4H), 1.80 - 1.99 (m, 1H), 1.62 (d, 2H), 1.15 - 1.36 (m, 2H).

EXAMPLE 141

4-(4-{[2-(4-chlorophenyl)cyclohept-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 141A

(Z)-methyl 2-(trifluoromethylsulfonyloxy)cyclohept-1-enecarboxylate

The title compound was prepared by substituting methyl 2-oxocycloheptanecarboxylate for 5,5-dimethyl-2-methoxycarbonylcyclohexanone in EXAMPLE 18A.

EXAMPLE 141B

(Z)-methyl 2-(4-chlorophenyl)cyclohept-1-enecarboxylate

The title compound was prepared by substituting EXAMPLE 141A for EXAMPLE 18A in EXAMPLE 18B.

EXAMPLE 141C

(Z)-(2-(4-chlorophenyl)cyclohept-1-enyl)methanol

The title compound was prepared by substituting EXAMPLE 141B for EXAMPLE 18B in EXAMPLE 18C.

EXAMPLE 141D

(Z)-2-(4-chlorophenyl)cyclohept-1-enecarbaldehyde

The title compound was prepared by susbstituting EXAMPLE 141C for EXAMPLE 143C in EXAMPLE 143D.

EXAMPLE 141E

(Z)-ethyl 2-(1H-indol-4-yloxy)-4-(4-((2-(4-chlorophenyl)cyclohept-1-enyl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 141D for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 68B for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 141F

(Z)-2-(1H-indol-4-yloxy)-4-(4-((2-(4-chlorophenyl)cyclohept-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 141E for EXAMPLE 143E in EXAMPLE 143F.

EXAMPLE 141G

4-(4-{[2-(4-chlorophenyl)cyclohept-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 141F for EXAMPLE 1E and EXAMPLE 68F for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.45 (m, 1H), 10.03 (m, 1H), 8.58 (m, 2H), 8.30 (m, 1H), 7.26 (m, 11H), 6.25 (m, 2H), 3.14 (m, 12H), 2.73 (m, 5H), 1.94 (m, 12H), 1.54 (m, 5H).

EXAMPLE 142

4-(4-{[2-(4-chlorophenyl)cyclooct-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 142A

(Z)-ethyl 2-(trifluoromethylsulfonyloxy)cyclooct-1-enecarboxylate

The title compound was prepared by substituting ethyl 2-oxocyclooctanecarboxylate for 5,5-dimethyl-2-methoxycarbonylcyclohexanone in EXAMPLE 18A.

EXAMPLE 142B

(Z)-ethyl 2-(4-chlorophenyl)cyclooct-1-enecarboxylate

The title compound was prepared by substituting EXAMPLE 142A for EXAMPLE 18A in EXAMPLE 18B.

EXAMPLE 142C

(Z)-(2-(4-chlorophenyl)cyclooct-1-enyl)methanol

The title compound was prepared by substituting EXAMPLE 142B for EXAMPLE 18B in EXAMPLE 18C.

EXAMPLE 142D

(Z)-2-(4-chlorophenyl)cyclooct-1-enecarbaldehyde

The title compound was prepared by substituting EXAMPLE 142C for EXAMPLE 143C in EXAMPLE 143D.

EXAMPLE 142E

(Z)-ethyl 2-(1H-indol-4-yloxy)-4-(4-((2-(4-chlorophenyl)cyclooct-1-enyl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 142D for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 68B for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 142F

(Z)-2-(1H-indol-4-yloxy)-4-(4-((2-(4-chlorophenyl)cyclooct-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 142E for EXAMPLE 143E in EXAMPLE 143F.

EXAMPLE 142G

4-(4-{[2-(4-chlorophenyl)cyclooct-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 142F for EXAMPLE 1E and EXAMPLE 68F for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d6) δ 11.51 (m, 1H), 10.01 (m, 1H), 8.58 (m, 2H), 7.26 (m, 12H), 6.35 (m, 2H), 3.14 (m, 13H), 2.73 (m, 5H), 1.88 (m, 7H), 1.45 (m, 10H).

EXAMPLE 143

4-(4-{[2-(4-chlorophenyl)cyclopent-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 143A

ethyl 2-(trifluoromethylsulfonyloxy)cyclopent-1-enecarboxylate

The title compound was prepared by substituting ethyl 2-oxocyclopentanecarboxylate for 5,5-dimethyl-2-methoxycarbonylcyclohexanone in EXAMPLE 18A.

EXAMPLE 143B

ethyl 2-(4-chlorophenyl)cyclopent-1-enecarboxylate

The title compound was prepared by substituting EXAMPLE 143A for EXAMPLE 18A in EXAMPLE 18B.

EXAMPLE 143C

(2-(4-chlorophenyl)cyclopent-1-enyl)methanol

The title compound was prepared by substituting EXAMPLE 143B for EXAMPLE 18B in EXAMPLE 18C.

EXAMPLE 143D

2-(4-chlorophenyl)cyclopent-1-enecarbaldehyde

To a solution of oxalyl chloride (1.1g) in dichloromethane (30 ml) at -78°C was added dimethylsulfoxide (6.12 ml). The mixture was stirred at -78°C for 30 minutes, and then a solution of EXAMPLE 143C (1.2 g) in dichloromethane (10 ml) was added . The mixture was stirred at -78°C for 2 hours before the addition of triethylamine (10 ml). The mixture was stirred overnight and the temperature was allowed to rise to room temperature. The mixture was diluted with ether (300 ml) and washed with water, brine and dried over Na_2SO_4. Evaporation of solvent and column purification (5% ethyl acetate in hexane) to give the product.

EXAMPLE 143E

ethyl 2-(1H-indol-4-yloxy)-4-(4-((2-(4-chlorophenyl)cyclopent-1-enyl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 143D for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 68B for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 143F

2-(1H-indol-4-yloxy)-4-(4-((2-(4-chlorophenyl)cyclopent-1-enyl)methyl)piperazin-1-yl)benzoic acid

To a solution of EXAMPLE 143E (254 mg) in tetrahydrofuran (4 ml), methanol (2 ml) and water (2 ml) was added LiOH-H_2O (126 mg). The mixture was stirred overnight. The mixture was then neutralized with 5% HCl and diluted with ethyl acetate (200 ml). After washing with brine, it was dried over Na_2SO_4. Evaporation of solvent gave the product.

EXAMPLE 143G

4-(4-{[2-(4-chlorophenyl)cyclopent-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 143F for EXAMPLE 1E and EXAMPLE 68F for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d6) δ ppm 11.41 (m, 1H), 10.19 (m, 1H), 8.58 (m, 2H), 7.26 (m, 14H), 6.33 (m, 2H), 3.80 (m, 4H), 3.13 (m, 12H), 2.69 (m, 5H), 1.95 (m, 7H).

EXAMPLE 144

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclopent-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 144A

methyl 4,4-dimethyl-2-oxocyclopentanecarboxylate

This compound was prepared according to WO 2006/035061(page 53).

EXAMPLE 144B

methyl 4,4-dimethyl-2-(trifluoromethylsulfonyloxy)cyclopent-1-enecarboxylate

The title compound was prepared by substituting ethyl 2-oxocyclopentanecarboxylate for 5,5-dimethyl-2-methoxycarbonylcyclohexanone in EXAMPLE 18A.

EXAMPLE 144C

ethyl 2-(4-chlorophenyl)-4,4-dimethylcyclopent-1-enecarboxylate

The title compound was prepared by substituting EXAMPLE 144B for EXAMPLE 18A in EXAMPLE 18B.

EXAMPLE 144D

(2-(4-chlorophenyl)-4,4-dimethylcyclopent-1-enyl)methanol

The title compound was prepared by substituting EXAMPLE 144C for EXAMPLE 18B in EXAMPLE 18C.

EXAMPLE 144E

2-(4-chlorophenyl)-4,4-dimethylcyclopent-1-enecarbaldehyde

The title compound was prepared by substituting EXAMPLE 144D for EXAMPLE 143C in EXAMPLE 143D.

EXAMPLE 144F

ethyl 2-(1H-indol-4-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclopent-1-enyl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 144E for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 68B for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 144G

2-(1H-indol-4-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclopent-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 144F for EXAMPLE 143E in EXAMPLE 143F.

EXAMPLE 144H

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclopent-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 144G for EXAMPLE 1E and EXAMPLE 21A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d6) δ 11.59 (m, 1H), 11.25 (s, 1H), 9.53 (m, 1H), 8.50 (d, 1H), 8.16 (d, 1H), 8.16 (d, 1H), 7.80 (m, 1H), 7.56 (d, 1H), 7.26 (m, 7H), 6.95 (m, 1H), 6.77 (dd, 1H), 6.41 (m, 2H), 6.23 (s, 1H), 2.87 (m, 10H), 2.28 (m, 12H), 1.11 (m, 6H).

EXAMPLE 145

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 145A

methyl 6,6-dimethyl-4-oxotetrahydro-2H-pyran-3-carboxylate

To a suspension of hexane-washed NaH (0.72 g, 60%) in tetrahydrofuran (30 ml) was added a solution of 2,2-dimethyldihydro-2H-pyran-4(3H)-one (2.0 g) in tetrahydrofuran (20 ml). The suspension was stirred for 30 minutes. The dimethylcarbonate (6.31 ml) was added dropwise by syringe. The mixture was heated to reflux for 4 hours. The mixture was acidified with 5% HCl and extracted with dichloromethane (3x 100ml) and washed with water , brine and dried over Na_2SO_4. After evaporation, the crude product was loaded on a column and eluted with 10% ethyl acetate in hexane to give the product.

EXAMPLE 145B

methyl 6,6-dimethyl-4-(trifluoromethylsulfonyloxy)-5,6-dihydro-2H-pyran-3-carboxylate

The title compound was prepared by substituting EXAMPLE 145A for 5,5-dimethyl-2-methoxycarbonylcyclohexanone in EXAMPLE 18A.

EXAMPLE 145C

methyl 4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-carboxylate

The title compound was prepared by substituting EXAMPLE 145B for EXAMPLE 18A in EXAMPLE 18B.

EXAMPLE 145D

(4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methanol

The title compound was prepared by substituting EXAMPLE 145C for EXAMPLE 18B in EXAMPLE 18C.

EXAMPLE 145E

4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-carbaldehyde

The title compound was prepared by substituting EXAMPLE 145D for EXAMPLE 143C in EXAMPLE 143D.

EXAMPLE 145F

ethyl 2-(1H-indol-4-yloxy)-4-(4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 145E for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 68B for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 145G

2-(1H-indol-4-yloxy)-4-(4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 145F for EXAMPLE 143E in EXAMPLE 143F.

EXAMPLE 145H

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 145G for EXAMPLE 1E and EXAMPLE 21A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d6) δ 11.56 (m, 1H), 11.26 (s, 1H), 9.52 (m, 1H), 8.51 (m, 1H), 8.16 (d, 1H), 7.80 (dd, 1H), 7.55 (d, 1H), 7.41 (d, 2H), 7.28 (t, 1H), 7.17 (m, 4H), 6.96 (m, 2H),

6.74 (d, 1H), 6.39 (m, 2H), 6.23 (s, 1H), 4.18 (s, 2H), 3.85 (m, 3H), 2.93 (m, 10H), 2.10 (m, 7H), 1.22 (s, 6H).

EXAMPLE 146

4-(4-{[2-(4-chlorophenyl)cyclooct-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 142F for EXAMPLE 1E and EXAMPLE 21A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d6) δ 11.59 (s, 1H), 11.25 (s, 1H), 9.36 (m, 2H), 8.50 (d, 1H), 8.16 (d, 1H), 7.79 (dd, 1H), 7.55 (d, 1H), 7.40 (d, 2H), 7.28 (m, 1H), 7.14 (m, 5H), 6.96 (t, 1H), 6.74 (dd, 1H), 6.38 (m, 2H), 6.23 (s, 1H), 2.91 (m, 14H), 2.27 (m, 6H), 1.49 (m, 11H).

EXAMPLE 147

4-(4-{[2-(4-chlorophenyl)cyclohept-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 141F for EXAMPLE 1E and EXAMPLE 21A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d6) δ 11.60 (s, 1H), 11.26 (s, 1H), 9.32 (m, 2H), 8.51 (m, 1H), 8.16 (d, 1H), 7.79 (m, 1H), 7.55 (d, 1H), 7.39 (d, 2H), 7.29 (t, 1H), 7.14 (m, 4H), 6.97 (t, 1H), 6.75 (dd, 1H), 6.40 (m, 2H), 6.22 (s, 1H), 2.94 (m, 17H), 2.27 (m, 4H), 1.80 (m, 4H), 1.55 (m, 5H).

EXAMPLE 148

4-(4-{[2-(4-chlorophenyl)cyclopent-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 143F for EXAMPLE 1E and EXAMPLE 21A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d6) δ 11.60 (s, 1H), 11.26 (s, 1H), 9.47 (m, 2H), 8.51 (m, 1H), 8.16 (d, 1H), 7.77 (m, 1H), 7.56 (d, 1H), 7.43 (d, 2H), 7.20 (m, 6H), 6.96 (t, 1H), 6.77 (dd, 1H), 6.41 (m, 2H), 6.24 (s, 1H), 2.93 (m, 17H), 2.01 (m, 8H).

EXAMPLE 149

4-(4-{[2-(4-chlorophenyl)cyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 149A

ethyl 2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

The title compound was prepared by substituting ethyl 2-oxocyclohexanecarboxylate for 5,5-dimethyl-2-methoxycarbonylcyclohexanone in EXAMPLE 18A.

EXAMPLE 149B

ethyl 2-(4-chlorophenyl)cyclohex-1-enecarboxylate

The title compound was prepared by substituting EXAMPLE 149A for EXAMPLE 18A in EXAMPLE 18B.

EXAMPLE 149C

(2-(4-chlorophenyl)cyclohex-1-enyl)methanol

The title compound was prepared by substituting EXAMPLE 149B for EXAMPLE 18B in EXAMPLE 18C.

EXAMPLE 149D

2-(4-chlorophenyl)cyclohex-1-enecarbaldehyde

The title compound was prepared by substituting EXAMPLE 149C for EXAMPLE 143C in EXAMPLE 143D.

EXAMPLE 149E

ethyl 2-(1H-indol-4-yloxy)-4-(4-((2-(4-chlorophenyl)cyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 149D for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 68B for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 149F

2-(1H-indol-4-yloxy)-4-(4-((2-(4-chlorophenyl)cyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 149E for EXAMPLE 143E in EXAMPLE 143F.

EXAMPLE 149G

4-(4-{[2-(4-chlorophenyl)cyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 149F for EXAMPLE 1E and EXAMPLE 21A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d6) δ 11.14 (s, 1H), 8.44 (d, 1H), 8.10 (d, 1H), 7.74 (dd, 1H), 7.56 (d, 1H), 7.34 (d, 2H), 7.23 (m, 1H), 7.01 (m, 5H), 6.63 (dd, 1H), 6.34 (d, 1H), 6.22 (m, 2H), 3.74 (m, 1H), 3.03 (m, 7H), 2.67 (m, 5H), 2.07 (m, 11H), 1.67 (m, 7H).

EXAMPLE 150

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 150A

methyl 2-(1H-indol-5-yloxy)-4-(piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 26A for EXAMPLE 1C and piperazine for EXAMPLE 1B in EXAMPLE 1D.

EXAMPLE 150B

methyl 2-(1H-indol-5-yloxy)-4-(4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 145E for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 150A for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 150C

2-(1H-indol-5-yloxy)-4-(4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 150B for EXAMPLE 143E in EXAMPLE 143F.

EXAMPLE 150D

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 150C for EXAMPLE 1E and EXAMPLE 21A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d6) δ 11.00 (s, 1H), 8.42 (d, 1H), 8.07 (d, 1H), 7.67 (dd, 1H), 7.52 (d, 1H), 7.37 (d, 2H), 7.29 (m, 1H), 7.14 (d, 2H), 6.93 (d, 1H), 6.86 (d, 1H), 6.72 (dd, 1H), 6.55 (dd, 1H), 6.31 (s, 1H), 6.15 (d, 1H), 5.85 (m, 3H), 4.11 (s, 2H), 3.00 (m, 8H), 2.82 (s, 2H), 2.73 (m, 3 H), 2.23 (m, 8H), 1.57 (m, 2H), 1.18 (s, 6H).

EXAMPLE 151

4-(4-{[2-(4-chlorophenyl)cyclohept-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 151A

(Z)-methyl 2-(1H-indol-5-yloxy)-4-(4-((2-(4-chlorophenyl)cyclohept-1-enyl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 141D for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 150A for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 151B

(Z)-2-(1H-indol-5-yloxy)-4-(4-((2-(4-chlorophenyl)cyclohept-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 151A for EXAMPLE 143E in EXAMPLE 143F.

EXAMPLE 151C

4-(4-{[2-(4-chlorophenyl)cyclohept-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 151B for EXAMPLE 1E and EXAMPLE 21A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d6) δ 11.06 (s, 1H), 8.48 (d, 1H), 8.11 (d, 1H), 7.74 (dd, 1H), 7.52 (d, 1H), 7.33 (m, 4H), 7.01 (m, 4H), 6.76 (dd, 1H), 6.58 (dd, 1H), 6.34 (s, 1H), 6.14 (d, 1H), 5.75 (s, 1H), 3.69 (m, 1H), 2.96 (m, 6H), 2.71 (m, 2H), 2.36 (m, 8H), 2.21 (s, 5H), 1.98 (m, 2H), 1.63 (m, 8H).

EXAMPLE 152

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-phenoxybenzamide

This compound was made by substituting EXAMPLE 18G for EXAMPLE 1E and EXAMPLE 21A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 8.43 (m, 1H) 8.18 (d, 1H) 7.82 (dd, 1H) 7.52 (d, 1H) 7.40 (m, 2H) 7.22 (m, 3H) 7.11 (m, 2H) 7.01 (t, 1H) 6.79 (m, 3H) 6.45 (d, 1H) 3.06 (m, 14H) 2.20 (m, 4H) 2.04 (s, 3H) 1.85 (m, 2H) 1.47 (m, 2H) 0.96 (s, 6H).

EXAMPLE 153

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(4-{[2-(dimethylamino)ethyl]amino}-3-nitrophenyl)sulfonyl]-2-phenoxybenzamide

EXAMPLE 153A

4-(2-(dimethylamino)ethylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting N,N-dimethylethylenediamine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 153B

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(4-{[2-(dimethylamino)ethyl]amino}-3-nitrophenyl)sulfonyl]-2-phenoxybenzamide

The title compound was prepared by substituting EXAMPLE 153A for EXAMPLE 1F and EXAMPLE 1E for EXAMPLE 27G in EXAMPLE 27H. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.75 (br s, 1H), 9.78 (br s, 1H), 9.44 (br s, 1H), 8.66 (t, 1H), 8.49 (d, 1H), 7.83 (d, 1H), 7.70 (m, 2H), 7.51 (m, 4H), 7.38 (d, 2H), 7.33 (m, 1H), 7.24 (d, 2H), 7.18 (d, 1H), 7.02 (dd, 1H), 6.81 (d, 2H), 6.76 (d, 1H), 6.44 (s, 1H), 4.30 (m, 1H), 3.83 (m, 4H), 3.31 (m, 6H), 3.15 (m, 2H), 3.04 (m, 2H), 2.85 (s, 6H).

EXAMPLE 154

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(4-{[3-(dimethylamino)propyl]amino}-3-nitrophenyl)sulfonyl]-2-phenoxybenzamide

EXAMPLE 154A

4-(3-(dimethylamino)propylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting N,N-dimethyl-1,3-propanediamine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 154B

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(4-{[3-(dimethylamino)propyl]amino}-3-nitrophenyl)sulfonyl]-2-phenoxybenzamide

The title compound was prepared by substituting EXAMPLE 154A for EXAMPLE 1F and EXAMPLE 1E for EXAMPLE 27G in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.68 (br s, 1H), 9.38 (br s, 1H), 8.66 (t, 1H), 8.49 (d, 1H), 7.80 (d, 1H), 7.68 (m, 2H), 7.51 (m, 4H), 7.38 (d, 1H), 7.33 (m, 2H), 7.24 (d, 2H), 7.16 (d, 1H), 7.02 (dd, 1H), 6.81 (d, 2H), 6.76 (d, 1H), 6.43 (s, 1H), 4.25 (m, 1H), 3.50 (m, 4H), 3.30 (m, 4H), 3.12 (m, 6H), 2.78 (s, 6H), 1.95 (m, 2H).

EXAMPLE 155

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-phenoxybenzamide

The title compound was prepared by substituting EXAMPLE 7A for EXAMPLE 1F and EXAMPLE 1E for EXAMPLE 27G in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.70 (br s, 1H), 9.72 (br s, 1H), 8.68 (t, 1H), 8.49 (d, 1H), 7.81 (d, 1H), 7.70 (m, 2H), 7.51 (m, 4H), 7.37 (d, 2H), 7.33 (m, 1H), 7.24 (d, 2H), 7.15

(d, 1H), 7.03 (dd, 1H), 6.81 (d, 2H), 6.76 (d, 1H), 6.44 (s, 1H), 4.24 (m, 1H), 3.97 (m, 2H), 3.63 (m, 4H), 3.28 (m, 4H), 3.18 (m, 4H), 3.06 (m, 4H), 2.88 (m, 4H), 1.99 (m, 2H).

EXAMPLE 156

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(4-{[4-(dimethylamino)butyl]amino}-3-nitrophenyl)sulfonyl]-2-phenoxybenzamide

EXAMPLE 156A

4-(4-(dimethylamino)butylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting N,N-dimethyl-1,4-butanediamine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 156B

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(4-{[4-(dimethylamino)butyl]amino}-3-nitrophenyl)sulfonyl]-2-phenoxybenzamide

The title compound was prepared by substituting EXAMPLE 156A for EXAMPLE 1F and EXAMPLE 1E for EXAMPLE 27G in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.70 (br s, 1H), 9.34 (br s, 1H), 8.63 (t, 1H), 8.48 (d, 1H), 7.79 (d, 1H), 7.70 (m, 2H), 7.51 (m, 4H), 7.39 (d, 2H), 7.33 (m, 1H), 7.24 (d, 2H), 7.12 (d, 1H), 7.01 (dd, 1H), 6.80 (d, 2H), 6.75 (d, 1H), 6.44 (s, 1H), 4.28 (m, 1H), 3.83 (m, 4H), 3.45 (m, 10H), 3.10 (m, 4H), 2.85 (s, 6H), 1.66 (m, 4H).

EXAMPLE 157

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(3-nitro-4-{[1-(phenylsulfonyl)piperidin-4-yl]amino}phenyl)sulfonyl]-2-phenoxybenzamide

EXAMPLE 157A

tert-butyl 4-(2-nitro-4-sulfamoylphenylamino)piperidine-1-carboxylate

The title compound was prepared by substituting 1-Boc-4-aminopiperidine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 157B

3-nitro-4-(piperidin-4-ylamino)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 157A for EXAMPLE 1A in EXAMPLE 1B.

EXAMPLE 157C

3-nitro-4-(1-(phenylsulfonyl)piperidin-4-ylamino)benzenesulfonamide

A mixture of EXAMPLE 157B (84 mg), benzenesulfonyl chloride (46 mg), and triethylamine (101 mg) in CH_2Cl_2 (2 mL) was stirred for 1 hours. The product was chromatographed on silica gel with 25% ethyl acetate/hexanes.

EXAMPLE 157D

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(3-nitro-4-{[1-(phenylsulfonyl)piperidin-4-yl]amino}phenyl)sulfonyl]-2-phenoxybenzamide

The title compound was prepared by substituting EXAMPLE 157C for EXAMPLE 1F and EXAMPLE 1E for EXAMPLE 27G in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.68 (br s, 1H), 9.65 (br s, 1H), 8.42 (s, 1H), 8.19 (d, 1H), 7.78 (m, 2H), 7.70 (m, 4H), 7.51 (m, 5H), 7.37 (m, 3H), 7.19 (m, 3H), 6.94 (dd, 1H), 6.75 (m, 3H), 6.44 (s, 1H), 4.28 (m, 1H), 3.73 (m, 4H), 3.50 (m, 4H), 3.17 (m, 2H), 3.03 (m, 2H), 2.86 (m, 2H), 1.99 (m, 2H), 1.74 (m, 2H).

EXAMPLE 158

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(3-nitro-4-{[1-(quinolin-8-ylsulfonyl)piperidin-4-yl]amino}phenyl)sulfonyl]-2-phenoxybenzamide

EXAMPLE 158A

3-nitro-4-(1-(quinolin-8-ylsulfonyl)piperidin-4-ylamino)benzenesulfonamide

The title compound was prepared by substituting quinoline-8-sulfonyl chloride for benzenesulfonyl chloride in EXAMPLE 157C.

EXAMPLE 158B

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(3-nitro-4-{[1-(quinolin-8-ylsulfonyl)piperidin-4-yl]amino}phenyl)sulfonyl]-2-phenoxybenzamide

The title compound was prepared by substituting EXAMPLE 158A for EXAMPLE 1F and EXAMPLE 1E for EXAMPLE 27G in EXAMPLE 27H. ^{1}H NMR

(400MHz, dimethylsulfoxide-d_6) δ 11.66 (br s, 1H), 9.10 (dd, 1H), 8.55 (s, 1H), 8.41 (m, 2H), 8.32 (d, 1H), 8.20 (d, 1H), 7.78 (dd, 2H), 7.72 (d, 2H), 7.48 (m, 4H), 7.39 (dd, 2H), 7.33 (m, 1H), 7.17 (m, 3H), 6.95 (dd, 1H), 6.76 (m, 3H), 6.42 (s, 1H), 4.35 (m, 1H), 3.90 (d, 2H), 3.77 (m, 2H), 3.34 (m, 6H), 2.99 (m, 4H), 1.97 (m, 2H), 1.65 (m, 2H).

EXAMPLE 159

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-phenoxy-N-({4-{[1-(phenylsulfonyl)piperidin-4-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

EXAMPLE 159A

(2-fluorophenyl)(trifluoromethyl)sulfane

Methyl viologen hydrochloride (1.17 g) in N,N-dimethylformamide (80 mL) at 25°C was saturated with trifluoromethyl iodide, treated with 2-fluorobenzenethiol (9.7 mL) and triethylamine (20 mL), stirred for 24 hours, diluted with water (240 mL) and extracted with diethyl ether. The extract was washed with 1M NaOH, saturated ammonium chloride and brine and concentrated.

EXAMPLE 159B

1-fluoro-2-(trifluoromethylsulfonyl)benzene

EXAMPLE 159A (17.346 g) in 1:1:2 carbon tetrachloride:acetonitrile:water (800 mL) at 25°C was treated with sodium periodate (56.8 g) and ruthenium(III) chloride hydrate (183 mg), stirred for 18 hours, diluted with dichloromethane (100 mL) and filtered through diatomaceous earth (Celite®). The filtrate was washed with saturated sodium bicarbonate and extracted with dichloromethane. The extract was washed with brine and dried ($MgSO_4$), filtered and concentrated. The concentrate was filtered through silica gel.

EXAMPLE 159C

4-fluoro-3-(trifluoromethylsulfonyl)benzenesulfonamide

EXAMPLE 159B (37.3 g) in chlorosulfonic acid (32.8 mL) at 120°C was stirred for 18 hours, cooled to 25°C and pipetted onto crushed ice. The mixture was extracted with ethyl acetate, and the extract was washed with water and brine and dried ($MgSO_4$), filtered and concentrated. The crude product was taken up in isopropanol (706 mL) at -78°C, treated with

ammonium hydroxide (98 mL) over 1 hour, stirred for 1 hour, quenched with 6M HCl (353 mL), warmed to 25°C and concentrated. The concentrate was mixed with water and extracted with ethyl acetate. The extract was dried over $MgSO_4$, filtered and concentrated. The concentrate was recrystallized from ethyl acetate/hexane.

EXAMPLE 159D

tert-butyl 4-(4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino)piperidine-1-carboxylate

The title compound was prepared by substituting 1-Boc-4-aminopiperidine for (tetrahydropyran-4-yl)methylamine and EXAMPLE 159C for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 1F.

EXAMPLE 159E

4-(piperidin-4-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 159D for EXAMPLE 1A in EXAMPLE 1B.

EXAMPLE 159F

4-(1-(phenylsulfonyl)piperidin-4-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 159E for EXAMPLE 157B in EXAMPLE 157C.

EXAMPLE 159G

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-phenoxy-N-({4-{[1-(phenylsulfonyl)piperidin-4-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 159F for EXAMPLE 1F and EXAMPLE 1E for EXAMPLE 27G in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.72 (br s, 1H), 9.70 (br s, 1H), 8.07 (s, 1H), 7.67-7.82 (m, 7H), 7.52 (d, 2H), 7.47 (d, 2H), 7.36 (m, 3H), 7.24 (dd, 2H), 7.14 (d, 1H), 7.01 (m, 1H), 6.78 (d, 2H), 6.72 (m, 2H), 6.44 (d, 1H), 4.27 (m, 1H), 3.73 (m, 4H), 3.46 (m, 4H), 3.17 (m, 2H), 3.03 (m, 2H), 2.87 (m, 2H), 1.97 (m, 2H), 1.64 (m, 2H).

EXAMPLE 160

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-phenoxy-N-({4-{[1-(quinolin-8-ylsulfonyl)piperidin-4-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

EXAMPLE 160A

4-(1-(quinolin-8-ylsulfonyl)piperidin-4-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 159E for EXAMPLE 157B and quinoline-8-sulfonyl chloride for benzenesulfonyl chloride in EXAMPLE 157C.

EXAMPLE 160B

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-phenoxy-N-({4-{[1-(quinolin-8-ylsulfonyl)piperidin-4-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 160A for EXAMPLE 1F and EXAMPLE 1E for EXAMPLE 27G in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.74 (br s, 1H), 9.50 (br s, 1H), 9.08 (dd, 1H), 8.55 (s, 1H), 8.39 (d, 1H), 8.33 (d, 1H), 8.06 (s, 1H), 7.82 (dd, 2H), 7.70 (m, 1H), 7.50 (m, 3H), 7.40 (dd, 2H), 7.33 (m, 1H), 7.21 (m, 2H), 7.08 (m, 2H), 6.99 (dd, 1H), 6.95 (s, 1H), 6.78 (d, 1H), 6.73 (m, 2H), 6.42 (s, 1H), 4.35 (m, 1H), 3.75 (m, 4H), 3.34 (m, 6H), 3.05 (m, 4H), 1.93 (m, 2H), 1.55 (m, 2H..

EXAMPLE 161

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(4-{[(1S)-3-(dimethylamino)-1-thien-2-ylpropyl]amino}-3-nitrophenyl)sulfonyl]-2-phenoxybenzamide

EXAMPLE 161A

(S)-3-(benzyloxycarbonylamino)-3-(thiophen-2-yl)propanoic acid

(S)-3-amino-3-(thiophen-2-yl)propanoic acid (0.894 g) and benzyloxycarbonyl chloride 0.980 g) were stirred in 2M NaOH (8 mL) and dioxane (26 mL) at 0°C for 24 hours. The reaction mixture was acidified with concentrated aqueous HCl, extracted twice with ethyl acetate, and the extracts were dried over $MgSO_4$, filtered, concentrated, and chromatographed on silica gel with 50% ethyl acetate/hexanes.

EXAMPLE 161B

(S)-benzyl 3-(dimethylamino)-3-oxo-1-(thiophen-2-yl)propylcarbamate

The title compound was prepared by substituting EXAMPLE 161A for EXAMPLE 1E and dimethylamine for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 161C

(S)-N^1,N^1-dimethyl-3-(thiophen-2-yl)propane-1,3-diamine

A solution of EXAMPLE 161B (400 mg) and borane in tetrahydrofuran (1M, 2.5 mL) in tetrahydrofuran (6 mL) was stirred for 24 hours. The reaction was quenched with methanol, taken up in pH 7 buffer solution, and extracted three times with ethyl acetate. The combined extracts were washed with brine and concentrated. The crude product was taken up in HBr in acetic acid (1.1 mL) and stirred for 2 hours. The reaction was poured into CH_2Cl_2 (50 mL) and washed with 1M NaOH solution. The organic layer was dried over Na_2SO_4, and concentrated.

EXAMPLE 161D

(S)-4-(3-(dimethylamino)-1-(thiophen-2-yl)propylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 161C for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 161E

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(4-{[(1S)-3-(dimethylamino)-1-thien-2-ylpropyl]amino}-3-nitrophenyl)sulfonyl]-2-phenoxybenzamide

The title compound was prepared by substituting EXAMPLE 161D for EXAMPLE 1F and EXAMPLE 1E for EXAMPLE 27G in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6/D_2O) δ 11.72 (br s, 1H), 9.51 (br s, 1H), 8.60 (d, 1H), 8.48 (s, 1H), 7.75 (d, 1H), 7.70 (m, 1H), 7.51 (m, 4H), 7.38 (d, 2H), 7.32 (m, 1H), 7.25 (d, 1H), 7.16 (m, 3H), 7.06 (d, 1H), 6.92 (m, 1H), 6.75 (d, 3H), 6.44 (d, 1H), 5.31 (m, 1H), 4.30 (m, 1H), 3.54 (m, 8H), 3.20 (m, 2H), 3.07 (m, 2H), 2.80 (s, 6H), 2.35 (m, 2H).

EXAMPLE 162

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(thien-2-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

EXAMPLE 162A

3-nitro-4-(thiophen-2-ylmethylamino)benzenesulfonamide

The title compound was prepared by substituting 2-thiophenemethylamine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 162B

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(thien-2-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

The title compound was prepared by substituting EXAMPLE 162B for EXAMPLE 1F and EXAMPLE 1E for EXAMPLE 27G in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6/D_2O) δ 11.67 (br s, 1H), 9.55 (br s, 1H), 9.11 (t, 1H), 8.47 (s, 1H), 7.70 (m, 2H), 7.51 (m, 4H), 7.38 (d, 2H), 7.33 (m, 1H), 7.15 (m, 4H), 7.02 (d, 1H), 6.94 (m, 1H), 6.74 (d, 3H), 6.44 (d, 1H), 4.87 (m, 2H), 4.37 (m, 1H), 3.34 (m, 8H), 3.03 (m, 2H).

EXAMPLE 163

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-phenoxy-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

EXAMPLE 163A

4-((tetrahydro-2H-pyran-4-yl)methylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 159C for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 1F.

EXAMPLE 163B

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-phenoxy-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 163A for EXAMPLE 1F and EXAMPLE 1E for EXAMPLE 27G in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.71 (br s, 1H), 8.10 (d, 1H), 7.86 (d, 1H), 7.10 (m, 1H),

7.50 (m, 4H), 7.37 (m, 2H), 7.27 (m, 3H), 7.08 (m, 1H), 7.03 (dd, 1H), 6.95 (d, 1H), 6.82 (d, 1H), 6.76 (d, 1H), 6.43 (s, 1H), 4.35 (m, 1H), 3.84 (dd, 2H), 3.35 (m, 8H), 3.22 (m, 2H), 3.03 (m, 2H), 2.86 (m, 2H), 1.86 (m, 1H), 1.55 (m, 2H), 1.26 (m, 2H).

EXAMPLE 164

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(3-nitro-4-{[2-(1H-1,2,3-triazol-1-yl)ethyl]amino}phenyl)sulfonyl]-2-phenoxybenzamide

EXAMPLE 164A

4-(2-hydroxyethylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 2-aminoethanol for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 164B

4-(2-(tert-butyldimethylsilyloxy)ethylamino)-3-nitrobenzenesulfonamide

EXAMPLE 164A (131 mg), t-butyldimethylsilyl chloride (75 mg) and imidazole (68 mg) were stirred in CH_2Cl_2 (17 mL) for 24 hours. The reaction mixture was chromatographed on silica gel with 10% ethyl acetate/hexanes.

EXAMPLE 164C

N-(4-(2-(tert-butyldimethylsilyloxy)ethylamino)-3-nitrophenylsulfonyl)-4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxybenzamide

The title compound was prepared by substituting EXAMPLE 164B for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 164D

2-(4-(N-(4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxybenzoyl)sulfamoyl)-2-nitrophenylamino)ethyl 4-methylbenzenesulfonate

EXAMPLE 164C (150 mg) and concentrated aqueous HCl (0.020 mL) were stirred in tetrahydrofuran (1 mL) and methanol (1 mL) for 1 hours. The mixture was filtered through a short silica gel column. The product was taken up in CH_2Cl_2 (1 mL) and to it was added triethylamine (0.074 mL) and p-toluenesulfonic anhydride (58 mg) and the reaction was stirred for 24 hours. The reaction mixture was chromatographed on silica gel with 10% ethyl acetate/hexanes.

EXAMPLE 164E

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(3-nitro-4-{[2-(1H-1,2,3-triazol-1-yl)ethyl]amino}phenyl)sulfonyl]-2-phenoxybenzamide

EXAMPLE 164D (30 mg), 1,2,3-triazole (7 mg) and cesium carbonate (55 mg) were stirred in N,N-dimethylformamide (0.2 mL) for 24 hours. The reaction was quenched with ammonium chloride, and was extracted twice with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The product was purified by preparative HPLC using a C18 column, 250 x 50 mm, 10μ, and eluting with a gradient of 20-100% CH_3CN vs. 0.1% trifluoroacetic aicd in water, giving the product as a trifluoroacetate salt. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.75 (br s, 1H), 9.62 (br s, 1H), 8.66 (dd, 1H), 8.44 (d, 1H), 8.18 (s, 1H), 7.72 (m, 3H), 7.51 (m, 5H), 7.36 (m, 3H), 7.19 (dd, 2H), 7.06 (m, 1H), 6.93 (dd, 1H), 6.75 (d, 2H), 6.45 (s, 1H), 4.70 (t, 2H), 3.93 (dt, 2H), 3.61 (m, 4H), 3.22 (m, 2H), 3.01 (m, 2H), 2.84 (m, 2H).

EXAMPLE 165

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(3-nitro-4-{[2-(2H-1,2,3-triazol-2-yl)ethyl]amino}phenyl)sulfonyl]-2-phenoxybenzamide

The title compound was prepared in the same reaction as that for EXAMPLE 164E. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.75 (br s, 1H), 9.70 (br s, 1H), 8.67 (dd, 1H), 8.42 (s, 1H), 7.80 (s, 1H), 7.75 (m, 1H), 7.68 (d, 2H), 7.51 (m, 5H), 7.37 (m, 3H), 7.18 (dd, 2H), 6.97 (m, 1H), 6.92 (dd, 1H), 6.75 (d, 2H), 6.46 (s, 1H), 4.76 (t, 2H), 3.93 (dt, 2H), 3.67 (m, 4H), 3.22 (m, 2H), 3.03 (m, 2H), 2.84 (m, 2H).

EXAMPLE 166

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(4-{[3-(dimethylamino)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(2-naphthyloxy)benzamide

The title compound was prepared by substituting EXAMPLE 35B for EXAMPLE 27G and EXAMPLE 154A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.83 (br s, 1H), 9.46 (br s, 1H), 8.53 (t, 1H), 8.40 (s, 1H), 7.81 (d, 2H), 7.71 (m, 1H), 7.63 (m, 2H), 7.51 (m, 5H), 7.37 (m, 4H), 7.17 (d, 1H), 7.03 (s, 1H), 6.82 (d, 2H), 6.57 (d, 1H), 4.27 (m, 1H), 3.62 (m, 6H), 3.39 (m, 2H), 3.09 (m, 2H), 2.80-3.25 (m, 6H), 2.79 (s, 6H), 1.91 (m, 2H).

EXAMPLE 167

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(3-nitro-4-{[2-(2-oxopyridin-1(2H)-yl)ethyl]amino}phenyl)sulfonyl]-2-phenoxybenzamide

The title compound was prepared by substituting pyridin-2-ol for 1,2,3-triazole in EXAMPLE 164E. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.70 (br s, 1H), 9.65 (br s, 1H), 8.75 (t, 1H), 8.44 (d, 1H), 7.72 (d, 2H), 7.64 (d, 1H), 7.51 (m, 5H), 7.37 (m, 3H), 7.20 (m, 3H), 6.95 (t, 1H), 6.77 (d, 3H), 6.46 (s, 1H), 6.41 (d, 1H), 6.21 (t, 1H), 4.31 (m, 1H), 4.17 (t, 2H), 3.74 (dt, 2H), 3.60 (m, 6H), 3.20 (m, 2H), 3.03 (m, 2H), 2.87 (m, 2H).

EXAMPLE 168

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-[(3-nitro-4-{[2-(pyridin-2-yloxy)ethyl]amino}phenyl)sulfonyl]-2-phenoxybenzamide

The title compound was prepared by substituting pyridin-2-ol for 1,2,3-triazole in EXAMPLE 164E. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.71 (br s, 1H), 9.65 (br s, 1H), 8.84 (t, 1H), 8.44 (d, 1H), 8.19 (d, 1H), 7.74 (m, 3H), 7.51 (m, 5H), 7.37 (m, 3H), 7.20 (m, 3H), 7.00 (dd, 1H), 6.92 (t, 1H), 6.83 (d, 1H), 6.76 (m, 2H), 6.45 (d, 1H), 4.56 (t, 2H), 4.31 (m, 1H), 3.81 (dt, 2H), 3.71 (m, 6H), 3.23 (m, 2H), 3.04 (m, 2H), 2.89 (m, 2H).

EXAMPLE 169

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(2-pyridin-4-ylethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

EXAMPLE 169A

3-nitro-4-(2-(pyridin-4-yl)ethylamino)benzenesulfonamide

The title compound was prepared by substituting 2-(pyridin-4-yl)ethanamine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1E.

EXAMPLE 169B

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(2-pyridin-4-ylethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

The title compound was prepared by substituting EXAMPLE 169A for EXAMPLE 1F and EXAMPLE 1E for EXAMPLE 27G in EXAMPLE 27H. ^{1}H NMR

(400MHz, dimethylsulfoxide-d_6) δ 11.71 (br s, 1H), 9.70 (br s, 1H), 8.69 (d, 1H), 8.61 (t, 1H), 8.46 (s, 1H), 7.79 (dd, 1H), 7.72 (d, 3H), 7.51 (m, 5H), 7.37 (d, 2H), 7.32 (d, 1H), 7.21 (m, 3H), 6.95 (t, 1H), 6.78 (d, 2H), 6.75 (d, 1H), 6.44 (d, 1H), 4.23 (m, 1H), 3.76 (dt, 2H), 3.63 (m, 4H), 3.13 (t, 2H), 2.76-3.24 (m, 6H).

EXAMPLE 170

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-{[3-(dimethylamino)propyl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

EXAMPLE 170A

4-(3-(dimethylamino)propylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

The title compound was prepared by substituting N,N-dimethyl-1,3-propanediamine for (tetrahydropyran-4-yl)methylamine and EXAMPLE 159C for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 1F.

EXAMPLE 170B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-{[3-(dimethylamino)propyl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 170A for EXAMPLE 1F and EXAMPLE 26C for EXAMPLE 27G in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.42 (br s, 1H), 11.17 (s, 1H), 9.37 (br s, 1H), 8.22 (d, 1H), 7.98 (d, 1H), 7.52 (d, 1H), 7.35-7.45 (m, 4H), 7.19 (d, 1H), 7.08 (m, 3H), 6.85 (dd, 1H), 6.67 (dd, 1H), 6.40 (d, 1H), 6.19 (d, 1H), 3.55 (m, 8H), 3.04 (m, 4H), 2.77 (s, 6H), 2.72 (m, 2H), 2.17 (m, 2H), 2.00 (m, 2H), 1.88 (m, 2H), 1.44 (m, 2H), 0.93 (s, 6H).

EXAMPLE 171

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-{[3-(dimethylamino)propyl]amino}-3-(trifluoromethyl)phenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 26C for EXAMPLE 27G and EXAMPLE 92B for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR

(400MHz, dimethylsulfoxide-d_6) δ 11.19 (br s, 1H), 9.33 (br s, 1H), 7.94 (d, 1H), 7.85 (d, 1H), 7.54 (d, 1H), 7.35-7.45 (m, 4H), 7.20 (d, 1H), 7.07 (d, 2H), 6.88 (dd, 2H), 6.67 (dd, 1H), 6.58 (m, 1H), 6.41 (s, 1H), 6.18 (s, 1H), 3.57 (m, 6H), 3.33 (m, 2H), 3.09 (m, 2H), 3.04 (m, 2H), 2.77 (s, 6H), 2.74 (m, 2H), 2.17 (m, 2H), 2.00 (m, 2H), 1.87 (m, 2H), 1.44 (m, 2H), 0.93 (s, 6H).

EXAMPLE 172

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-cyano-4-{[3-(dimethylamino)propyl]amino}phenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 26C for EXAMPLE 27G and EXAMPLE 90B for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.19 (br s, 1H), 9.38 (br s, 1H), 7.98 (s, 1H), 7.81 (d, 1H), 7.55 (d, 1H), 7.35-7.45 (m, 4H), 7.20 (s, 1H), 7.16 (t, 1H), 7.07 (d, 2H), 6.86 (dd, 2H), 6.68 (dd, 1H), 6.41 (s, 1H), 6.18 (s, 1H), 3.57 (m, 6H), 3.31 (m, 2H), 3.09 (m, 2H), 3.04 (m, 2H), 2.77 (s, 6H), 2.74 (m, 2H), 2.17 (m, 2H), 2.00 (m, 2H), 1.87 (m, 2H), 1.44 (m, 2H), 0.93 (s, 6H).

EXAMPLE 173

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 173A

tert-butyl 1-(tetrahydro-2H-pyran-4-yl)piperidin-4-ylcarbamate

A mixture of tert-butyl piperidin-4-ylcarbamate (45 g) and dihydro-2H-pyran-4(3H)-one (24.74 g) in dichloromethane (1000 mL) was treated with sodium triacetoxyborohydride (61.9 g), stirred at room temperature for 16 hours, washed with 1M sodium hydroxide and dried with anhydrous sodium sulfate, filtered and concentrated. The concentrate was flash column chromatographed on silica gel with 10-20% methanol/dichloromethane.

EXAMPLE 173B

1-(tetrahydro-2H-pyran-4-yl)piperidin-4-amine

A solution of EXAMPLE 173A (52.57 g) in dichloromethane (900 mL) was treated with 4M HCl (462 mL), mixed vigorously at room temperature for 16 hours and concentrated.

EXAMPLE 173C

3-nitro-4-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-ylamino)benzenesulfonamide

A mixture of EXAMPLE 173B (22.12 g), water (43 mL), and triethylamine (43.6 mL) in 1,4-dioxane (300 mL) was stirred at room temperature until EXAMPLE 173B completely dissolved. The solution was then treated with 4-chloro-3-nitrobenzenesulfonamide, heated at 90°C for 16 hours, cooled and concentrated. 10% methanol in dichloromethane was added, and the solution was stirred vigorously at room temperature until a fine suspension existed and the mixture was filtered.

EXAMPLE 173D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide

A mixture of EXAMPLE 26C (3.95 g), EXAMPLE 173C (2.66 g), 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (2.66 g), and 4-dimethylaminopyridine (0.846 g) in dichloromethane (70 mL) and acetonitrile (20 mL) was stirred at 35°C for 24 hours, cooled and chromatographed on silica gel with 0-10% methanol in ethyl acetate, then 10% methanol in 1:1 ethyl acetate/dichloromethane. The combined fractions were concentrated, dissolved in of 5% methanol/ethyl acetate (1.5L), and the solution was washed with saturated NaH_2PO_4 solution and brine and dried over Na_2SO_4, filtered, concentrated to 300 mL, cooled, and filtered. The remaining solution was concentrated partway and filtered again to isolate more product. ^{1}H NMR (300MHz, dimethysulfoxide-d_6) δ 11.17 (brs, 1H), 10.70 (br s, 1H), 8.60 (d, 1H), 8.20 (br d, 1H), 7.88 (dd, 1H), 7.50 (d, 1H), 7.39 (m, 2H), 7.33 (d, 2H), 7.16 (m, 2H), 7.03 (d, 2H), 6.85 (dd, 1H), 6.65 (dd, 1H), 6.39 (s, 1H), 6.14 (s, 1H), 3.97 (m, 4H), 3.44 (m, 4H), 3.04 (m, 6H), 2.75 (m, 2H), 2.14 (m, 8H), 1.95 (m, 6H), 1.66 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 174

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 174A

4-(4-methylpiperazin-1-ylamino)-3-nitrobenzenesulfonamide

A mixture of 4-chloro-3-nitrobenzenesulfonamide (1 g), 4-methylpiperazin-1-amine dihydrochloride (1 g) and N^1,N^1,N^2,N^2-tetramethylethane-1,2-diamine (3 mL) in dioxane (10 mL) was refluxed for 12 hours, cooled to ambient temperature and filtered. The filtrate was added to a silica gel column (Analogix, SF65-200g) and purified by eluting with 1-5% methanol/dichloromethane).

EXAMPLE 174B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

A mixture of EXAMPLE 26C (0.108 g), EXAMPLE 174A (64 mg), 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (0.08 g) and 4-dimethylaminopyridine (0.08 g) in dichloromethane (3 mL) was stirred at ambient temperature overnight and concentrated. The concentrate was added to a preparative HPLC column and eluted with 20-100% acetonitrile/water with 0.1% trifluoroacetic aicd. The trifluoroacetic aicd salt solution was neutralized with $NaHCO_3$ and extracted with dichloromethane. This solution was washed with saturated $NaHCO_3$, dried over Na_2SO_4, and filtered and concentrated. ^1H NMR (500 MHz, dimethysulfoxide-d_6) δ 11.14 (s, 1H), 9.17 (s, 1H), 8.52 (s, 1H), 7.83 (m, 1H), 7.53 (m, 2H), 7.36 (m, 4H), 7.12 (s, 1H), 7.03 (d, 2H), 6.83 (m, 1H), 6.62 (m, 1H), 6.38 (s, 1H), 6.13 (m, 1H), 5.76 (s, 2H), 2.85 (m, 12H), 2.35 (m, 4H), 2.14 (m, 6H), 1.94 (m, 2H), 1.38 (m, 2H), 0.92 (s, 6H).

EXAMPLE 175

4-{4-[1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 175A

1-(4'-chlorobiphenyl-2-yl)ethanone

A mixture of 1-(2-bromophenyl)ethanone (3.1 g, 15.57 mmol)4-chlorophenylboronic acid (2.92 g), $(Ph_3P)_2PdCl_2$ (bis(triphenylphosphine)palladium(II) dichloride) (1.202 g) and Na_2CO_3 (3.30 g) in dimethoxyethane-ethanol-water (7:2:3, 50 mL) was heated at 100°C for 3 hours and concentrated. The concentrate was suspended in dichloromethane (30 mL) and the insoluble material was removed by filtration. The filtrate was loaded onto a silica gel column, eluted with 0% - 50% dichloromethane in hexane to provide the title compound.

EXAMPLE 175B

tert-butyl 4-(1-(4'-chlorobiphenyl-2-yl)ethyl)piperazine-1-carboxylate

EXAMPLE 175A (1.9 g) was dissolved in dichloromethane (3 mL) and titanium(IV) chloride (9.06 mL, 9.06 mmol) was added. The solution was cooled to 0°C and tert-butyl piperazine-1-carboxylate (3.07 g) was added. The resulting mixture was stirred at ambient temperature for 3 hours and $NaCNBH_3$ (0.828 g) in methanol (5 mL) was added. The resulting mixture was stirred at room temperature overnight and neutralized by aqueous NaOH, and then concentrated. To the concentrate was added ethyl acetate and the insoluble material was filtered off. The organic layer was washed with water and concentrated. The concentrate was dissolved in a mixture of methanol-trifluoroacetic aicd-dimethysulfoxide, loaded onto a reverse phase C18 column, and eluted with 0 - 80% acetonitrile in 0.1% trifluoroacetic aicd water over 70 minutes.

EXAMPLE 175C

1-(1-(4'-chlorobiphenyl-2-yl)ethyl)piperazine

To a solution of EXAMPLE 175B (650mg) in dichloromethane (6 mL) was added trifluoroacetic aicd (6 mL) at 0°C. The reaction mixture was stirred at 0°C for 50 minutes and concentrated. The concentrate was dissolved in dichloromethane, washed with aqueous $NaHCO_3$ and the organic layer was dried over Na_2SO_4, and concentrated.

EXAMPLE 175D

ethyl 2-(1H-indol-4-yloxy)-4-(4-(1-(4'-chlorobiphenyl-2-yl)ethyl)piperazin-1-yl)benzoate

EXAMPLE 175C (193mg) and ethyl 2-(1H-indol-4-yloxy)-4-fluorobenzoate (211 mg) in dimethysulfoxide (15 mL) was treated with potassium hydrogen phosphate (168 mg) at 135°C overnight and cooled. The reaction mixture was diluted with dichloromethane and washed with water. The organic layer was concentrated. The concentrate was dissolved in

dichloromethane, loaded onto a silica gel column, eluted with 0%-10% 10 M ammonia methanol in dichloromethane.

EXAMPLE 175E

2-(1H-indol-4-yloxy)-4-(4-(1-(4'-chlorobiphenyl-2-yl)ethyl)piperazin-1-yl)benzoic acid

EXAMPLE 175D (200mg) in tetrahydrofuran (10 mL) and methanol (10 mL) was treated with 10% NaOH (3 mL) at 50°C overnight and neutralized with HCl. The mixture was concentrated and the concentrate was taken up in water and extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and concentrated.

EXAMPLE 175F

4-(4-(1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl)piperazin-1-yl)-2-(1*H*-indol-4-yloxy)-*N*-((3-nitro-4-((tetrahydro-2*H*-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide

To a mixture of EXAMPLE 175E (66 mg), 3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide (75 mg) and 4-dimethylaminopyridine (58.4 mg) in dichloromethane (5 mL) was added 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (45.8 mg). The mixture was stirred at ambient temperature overnight and concentrated. The concentrate was purified by RP HPLC (10-70% acetonitrile in 0.1% trifluoroacetic aicd water / 70 minutes). The desired fractions were concentrated to remove acetonitrile and the concentrate was diluted with dichloromethane and neutralized with aqueous $NaHCO_3$. The dichloromethane layer was dried over Na_2SO_4 and concentrated to provide the title compound. ^{1}H NMR (500 MHz, dimethysulfoxide-d_6) δ ppm 11.31 (1 H, s), 11.25 (1 H, s), 8.62 (1 H, t), 8.50 (1 H, d), 7.68 (1 H, dd), 7.53 (2 H, d), 7.46 (2 H, d), 7.37 (1 H, t), 7.24 - 7.31 (4 H, m), 7.17 (1 H, d), 7.12 (1 H, dd), 7.07 (1 H, d), 6.96 (1 H, t), 6.69 (1 H, dd), 6.42 (1 H, d), 6.26 (2 H, s), 3.85 (2 H, dd), 3.21 - 3.33 (5 H, m), 3.01 (4 H, s), 2.29 - 2.39 (2 H, m), 2.15 - 2.22 (2 H, m), 1.83 - 1.94 (1 H, m), 1.57 - 1.68 (2 H, m), 1.22 - 1.31 (2 H, m), 1.17 (3 H, d).

EXAMPLE 176

N-[(4-{[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)benzamide

EXAMPLE 176A

4-((4-aminotetrahydro-2*H*-pyran-4-yl)methylamino)-3-nitrobenzenesulfonamide

A mixture of 4-chloro-3-nitrobenzenesulfonamide, 4-(aminomethyl)tetrahydro-2H-pyran-4-amine bis-hydrochloric acid salt and triethylamine in dioxane (10 mL) was heated at 110 °C overnight. After cooling, the reaction mixture was diluted with water (10 mL), and the solid was filtered to give the title compound.

EXAMPLE 176B

N-((4-(((4-aminotetrahydro-2*H*-pyran-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1*H*-indol-4-yloxy)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 55B for EXAMPLE 1F and EXAMPLE 176A (4-aminotetrahydro-2H-pyran-4-yl)methylamino)-3-nitrobenzenesulfonamide) for EXAMPLE 1G in EXAMPLE 1H. ^{1}H NMR (500MHz, dimethysulfoxide-d_6) δ 11.15 (s, 1H), 8.51 (s, 1H), 8.45 (d, J = 2.14 Hz, 1H), 7.70 (dd, J = 9.0, 1.98 Hz, 1H), 7.59 (d, J = 8.85 Hz, 1H), 7.34 (d, J = 8.24 Hz, 2H), 7.22 (t, J = 2.59 Hz, 1H), 7.11-7.12 (m, 2H), 7.04 (d, J = 8.54 Hz, 2H), 6.93 (t, J = 7.78 Hz, 1H), 6.62 (dd, J = 9.0, 1.98 Hz, 1H), 6.34 (d, J = 7.63 Hz, 1H), 6.20-6.23 (m, 2H), 3.55-3.70 (m, 6H), 2.96 (m, 3H), 2.71 (s, 2H), 2.16 (m, 6H), 1.95 (m, 2H), 1.70-1.74 (m, 2H), 1.55-1.59 (m, 2H), 1.37-1.39 (m, 2H), 0.92 (s, 6H).

EXAMPLE 177

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

A mixture of EXAMPLE 26C (2.85 g, 10 mmol), EXAMPLE 1F (1.577 g, 5 mmol), 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (1.917 g, 10 mmol), 4-(dimethylamino)pyridine (1.222 g, 10 mmol), and triethyl amine (2.8 mL, 20 mmol) was treated with CH_2Cl_2 (20 mL) and N,N-dimethylformamide (2 mL). The reaction mixture was stirred over night. The solvent was removed, and the residue was partitioned between water and ethyl acetate. The organic layers were washed with 1% HCl twice, then with sat $NaHCO_3$, brine, dried, filtered, and concentrated The residue was purified by reverse phase HPLC on a C18 column using a gradient of 40-60% acetonitrile/0.1% TFA in water to give

the title compound as the trifluoroacetate salt. The TFA salt was dissolved in dichloromethane (6 ml) and washed with 50% aqueous $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give the title compound. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.18 (s, 2H), 8.59-8.64 (m, 2H), 7.80 (dd, 1H), 7.52 (d, 1H), 7.39-7.42 (m, 2H), 7.33 (d, 2H), 7.16 (d, 1H), 7.10 (d,1H), 7.03 (d, 2H), 6.8 (dd, 1H), 6.65 (dd, 1H), 6.40)s, 1H), 6.14 (d, 1H), 3.85 (dd, 2H), 3.24-3.32 (m, 4H), 3.03 (s, 3H), 2.73 (s, 2H), 2.12-2.17 (m, 5H), 1.68-1.94 (m, 3H), 1.61 (d, 2H), 1.37 (t, 2H), 1.24-1.27 (m, 2H), 0.92 (s, 6H).

EXAMPLE 178

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 178A

Trans-4-(4-morpholinocyclohexylamino)-3-nitrobenzenesulfonamide

This EXAMPLE was prepared by substituting 4-amino-N-morpholinylpiperidine for 1-(tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 178B

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared as in EXAMPLE 177 by replacing EXAMPLE 1F with EXAMPLE 178A. ^{1}H NMR (500 MHz, pyridine-d_5) δ 12.29 (s, 1H), 9.29 (d, *J*=2.1 Hz, 1H), 8.37 (d, *J*=7.6 Hz, 1H), 8.32 (dd, *J*=9.3, 2.3 Hz, 1H), 8.18 (d, *J*=8.8 Hz, 1H), 7.52 - 7.57 (m, 2H), 7.39 - 7.47 (m, 3H), 7.10 (dd, *J*=8.7, 2.3 Hz, 1H), 7.05 - 7.08 (m, 2H), 6.90 (d, *J*=9.5 Hz, 1H), 6.74 (dd, *J*=9.0, 2.3 Hz, 1H), 6.59 - 6.63 (m, 1H), 6.55 (d, *J*=2.4 Hz, 1H), 3.72 - 3.78 (m, 4H), 3.33 - 3.43 (m, 1H), 2.99 - 3.09 (m, 4H), 2.76 (s, 2H), 2.46 - 2.54 (m, 4H), 2.16 - 2.29 (m, 3H), 2.09 - 2.14 (m, 4H), 2.05 (d, *J*=11.9 Hz, 2H), 1.97 (d, *J*=1.8 Hz, 2H), 1.87 (d, *J*=11.6 Hz, 2H), 1.19 - 1.42 (m, 6H), 0.93 (s, 6H).

EXAMPLE 179

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(2-methoxyethyl)amino]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 179A

4-(2-methoxyethylamino)-3-nitrobenzenesulfonamide

This EXAMPLE was prepared by substituting 2-methoxyethylamine for 1-(tetrahydropyran-4-yl)methylamine in EXAMPLE IF.

EXAMPLE 179B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(2-methoxyethyl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared as in EXAMPLE 177 by replacing EXAMPLE 1F with EXAMPLE 179A. ^{1}H NMR (400 MHz, DMSO- d_6) δ 11.20 (br. s, 1H) 11.15 (s, 1H) 8.59 (m, 2H) 7.81 (dd, 1H) 7.50 (d, 1H) 7.36 (m, 4H) 7.08 (m, 4H) 6.85 (dd, 1H) 6.65 (dd, 1H) 6.38 (m, 1H) 6.14 (m, 1H) 3.58 (m, 4H) 3.30 (s, 3H) 3.03 (m, 4H) 2.73 (s, 2H) 2.15 (m, 6H) 1.96 (s, 2H) 1.38 (t, 2H) 0.92 (s, 6H).

EXAMPLE 180

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(3S)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]benzamide

EXAMPLE 180A

(R)-3-nitro-4-((tetrahydro-2H-pyran-3-yl)methylamino)benzenesulfonamide and (S)-3-nitro-4-((tetrahydro-2H-pyran-3-yl)methylamino)benzenesulfonamide

This EXAMPLE was prepared by substituting (tetrahydro-2H-pyran-3-yl)methanamine for 1-(tetrahydropyran-4-yl)methylamine in EXAMPLE IF.

EXAMPLE 180B

(S)-3-nitro-4-((tetrahydro-2H-pyran-3-yl)methylamino)benzenesulfonamide

The racemic mixture of EXAMPLE 180A was resolved by chiral SFC on an AD column (21mm i.d.x 250 mm in length) using a gradient of 10-30% 0.1% diethylamine

methanol in CO_2 over 15 min (oven temperature: 40°C; flow rate: 40mL/min) to provide the title compound.

EXAMPLE 180C

(R)-3-nitro-4-((tetrahydro-2H-pyran-3-yl)methylamino)benzenesulfonamide

The racemic mixture of EXAMPLE 180A was resolved by chiral SFC on an AD column (21mm i.d.x 250 mm in length) using a gradient of 10-30% 0.1% diethylamine methanol in CO_2 over 15 min (oven temperature: 40°C; flow rate: 40mL/min) to provide the title compound.

EXAMPLE 180D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(3S)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]benzamide

The title compound was prepared as in EXAMPLE 177 by replacing EXAMPLE 1F with EXAMPLE 180B. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.17 (s, 2 H), 8.53 - 8.65 (m, 2 H), 7.80 (d, 1 H), 7.51 (d, 1 H), 7.38 - 7.44 (m, 2 H), 7.33 (d, 2 H), 7.15 (s, 1 H), 7.02 - 7.09 (m, 3 H), 6.82 - 6.92 (m, 1 H), 6.65 (d, 1 H), 6.39 (s, 1 H), 6.14 (s, 1 H), 3.68 - 3.82 (m, 2 H), 3.22 - 3.32 (m, 2 H), 3.13 - 3.22 (m, 1 H), 3.03 (s, 4 H), 2.72 (s, 2 H), 2.09 - 2.23 (m, 6 H), 1.78 - 1.98 (m, 4 H), 1.56 - 1.66 (m, 1 H), 1.43 - 1.51 (m, 1 H), 1.37 (t, 2 H), 1.22 - 1.33 (m, 1 H), 0.92 (s, 6 H).

EXAMPLE 181

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(3R)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]benzamide

The title compound was prepared as in EXAMPLE 177 by replacing EXAMPLE 1F with EXAMPLE 180C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.17 (s, 2 H), 8.53 - 8.65 (m, 2 H), 7.80 (d, 1 H), 7.51 (d, 1 H), 7.38 - 7.44 (m, 2 H), 7.33 (d, 2 H), 7.15 (s, 1 H), 7.02 - 7.09 (m, 3 H), 6.82 - 6.92 (m, 1 H), 6.65 (d, 1 H), 6.39 (s, 1 H), 6.14 (s, 1 H), 3.68 - 3.82 (m, 2 H), 3.22 - 3.32 (m, 2 H), 3.13 - 3.22 (m, 1 H), 3.03 (s, 4 H), 2.72 (s, 2 H), 2.09 - 2.23 (m, 6 H), 1.78 - 1.98 (m, 4 H), 1.56 - 1.66 (m, 1 H), 1.43 - 1.51 (m, 1 H), 1.37 (t, 2 H), 1.22 - 1.33 (m, 1 H), 0.92 (s, 6 H).

EXAMPLE 182

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared as in EXAMPLE 177 by replacing EXAMPLE 26C with EXAMPLE 150C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.20 (br s, 1H), 11.17(s, 1H), 8.63 (t, 1 H), 8.59 (d, 1 H), 7.79 (dd, 1 H), 7.51 (d, 1 H), 7.36 (m, 3 H), 7.13 (m, 2 H), 6.86 (dd, 1 H), 6.66 (dd, 1 H), 6.39 (s, 1 H), 6.15 (d, 1 H), 4.10 (s, 2 H), 3.85 (m, 3 H), 3.50 (m, 2 H), 3.42 (m, 2 H), 3.24 (m, 4 H), 3.02 (m, 4 H), 2.82 (m, 2 H), 2.16 (m, 2 H), 1.61 (m, 3 H), 1.25 (m, 4 H), 1.17 (s, 6 H).

EXAMPLE 183

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-hydroxy-1-methylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide

EXAMPLE 183A

4-((4-hydroxy-1-methylpiperidin-4-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 4-(aminomethyl)-1-methylpiperidin-4-ol for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 183B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-hydroxy-1-methylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 183A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.04 (s, 1H), 8.46-8.48 (m, 2H), 7.92 (s, 1H), 7.74 (d, 1H), 7.54 (d, 1H), 7.32-7.34 (m, 5H), 6.97-7.05 (m, 5H), 6.74-6.76 (m, 1H), 6.55-6.57 (m, 1H), 6.33 (s, 1H), 6.13 (d, 1H), 5.10 (s, 1H), 3.14-3.17 (m, 2H), 2.95 (br, 5H), 2.71 (br, 2H), 2.14-2.17 (m, 6H), 1.95 (br s, 2H), 1.70 (br, 4H), 1.36-1.39 (m, 2H), 1.24-1.26 (m, 2H), 0.92 (s, 6H).

EXAMPLE 184

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-3-fluoro-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 184A

ethyl 2-(1H-indol-5-yloxy)-3,4-difluorobenzoate

The title compound was prepared by substituting ethyl 2,3,4-trifluorobenzoate for ethyl 2,4-difluorobenzoate and 5-hydroxyindole for 5-hydroxyindazole in EXAMPLE 20A.

EXAMPLE 184B

ethyl 2-(1H-indol-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-3-fluorobenzoate

The title compound was prepared by substituting EXAMPLE 184A for EXAMPLE 20A in EXAMPLE 20D.

EXAMPLE 184C

2-(1H-indol-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-3-fluorobenzoic acid

The title compound was prepared by substituting EXAMPLE 184B for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 184D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-3-fluoro-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 184C for EXAMPLE 1E and EXAMPLE 21A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 10.98 (br s, 1H), 8.35 (d, 1H), 7.98 (dd, 1H), 7.59 (dd, 1H), 7.35 (m, 3H), 7.28 (t, 1H), 7.21 (d, 1H), 7.06 (d, 2H), 6.78 (m, 2H), 6.67 (m, 2H), 6.22 (s, 1H), 3.74 (dd, 2H), 3.39 (m, 4H), 3.06 (m, 3H), 2.97 (m, 4H), 2.79 (m, 2H), 2.73 (s, 3H), 2.29 (m, 2H), 2.18 (m, 2H), 2.05 (m, 2H), 1.81 (m, 2H), 1.41 (t, 2H), 0.94 (s, 6H).

EXAMPLE 185

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-3-fluoro-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 184C for EXAMPLE 1E and EXAMPLE 173C for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 10.98 (br s, 1H), 8.33 (d, 1H), 8.02 (dd, 1H), 7.50 (dd, 1H), 7.35 (m, 3H), 7.26 (t, 1H), 7.19 (d, 1H), 7.06 (d, 2H), 6.77 (dd, 2H), 6.67 (m, 2H), 6.22 (s, 1H), 3.90 (dd, 2H), 3.57 (m, 5H), 3.30 (dd, 2H), 3.06 (m, 3H), 2.94 (m, 4H), 2.78 (m, 2H), 2.27 (m, 4H), 2.18 (m, 2H), 1.98 (m, 4H), 1.80 (m, 2H), 1.55 (m, 2H), 1.41 (t, 2H), 0.94 (s, 6H).

EXAMPLE 186

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-hydroxy-1-methylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 183A for EXAMPLE 1F and EXAMPLE 55B for EXAMPLE 26C in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.12 (s, 1H), 8.49 (s, 1H), 8.42 (s, 1H), 7.73-7.75 (m, 1H), 7.58 (d, 1H), 7.34 (d, 2H), 7.22 (s, 1H), 7.09 (d, 1H), 7.01-7.05 (m, 3H), 6.92 (t, 1H), 6.61-6.62 (m, 1H), 6.31 (d, 1H), 6.23 (s, 1H), 6.20 (s, 1H), 5.16 (s, 1H), 4.05 (s, 3H), 2.95 (br s, 6H), 2.71 (br s, 2H), 2.62 (br, 3H), 2.16 (br s, 6H), 1.95 (br s, 2H), 1.72 (br, 4H), 1.37-1.39 (m, 2H), 0.92 (s, 6H).

EXAMPLE 187

N-[(4-{[(3S,4R)-1-benzyl-3-hydroxypiperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide

EXAMPLE 187A

2-(1H-indol-5-yloxy)-N-(4-chloro-3-nitrophenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzamide

The title compound was prepared by substituting 4-chloro-3-nitrobenzenesulfonamide for EXAMPLE 1F and EXAMPLE 26C for EXAMPLE 1E in EXAMPLE 1G.

EXAMPLE 187B

N-[(4-{[(3S,4R)-1-benzyl-3-hydroxypiperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide

A mixture of EXAMPLE 187A (0.158 g), (3S,4R)-4-amino-1-benzylpiperidin-3-ol, hydrochloric acid (0.049 g), and triethylamine (0.1 mL) in dioxane (2 mL) was heated at 100 °C overnight. The solvent was removed, and the residue was re-dissolved in 1:1 methanol:dimethylsulfoxide (3 mL). It was then purified by reverse phase Prep HPLC. The residue was purified by reverse phase HPLC on a C18 column using a gradient of 20-80% acetonitrile/0.1% TFA in water. The desired fractions were collected, and the organic solvent was partially removed under reduced pressure. The resulting mixture was treated with saturated aqueous $NaHCO_3$ mixture. It was then extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to give the desired product. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.14 (s, 1H), 8.69 (d, 1H), 8.14 (d, 1H), 7.77 (dd, 1H), 7.51 (d, 1H), 7.29-7.41 (m, 9H), 7.10-7.13 (m, 1H), 7.13 (d, 2H), 6.84 (dd, 1H), 6.63 (dd, 1H), 6.38 (s, 1H), 6.13 (d, 1H), 5.21-5.22 (br s, 1H), 3.82 (m, 2H), 3.62 (br s, 2H), 3.01 (br s, 4H), 2.71-2.82 (m , 4H), 2.12-2.15 (m, 7H), 1.94 (br s, 2H), 1.81 (br s, 2H), 1.36-1.39 (m, 2H), 0.92 (s, 6H).

EXAMPLE 188

N-[(4-{[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting 4-(aminomethyl)tetrahydro-2H-pyran-4-amine for (3S,4R)-4-amino-1-benzylpiperidin-3-ol hydrochloric acid in EXAMPLE 187B. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.08 (s, 1H), 8.60 (br s, 1H), 8.51 (d, 1H), 7.80 (dd, 1H), 7.54 (d, 1H), 7.32-7.36 (m, 4H), 7.12 (d, 1H), 7.03-7.05 (m, 3H), 6.77 (dd, 1H), 6.58 (dd, 1H), 6.35 (s, 1H), 6.13 (d, 1H), 3.61-3.70 (m, 4H), 3.53 (br s, 2H),

2.97 (br, 4H), 2.71 (br, 2H), 2.16 (br s, 6H), 1.94 (br s, 2H), 1.67-1.72 (m, 2H), 1.52-1.57 (m, 2H), 1.36-1.39 (m, 2H), 0.92 (s, 6H).

EXAMPLE 189

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[1-(2-methoxyethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]benzamide

EXAMPLE 189A

4-[1-(2-methoxy-ethyl)-piperidin-4-ylamino]-3-nitro-benzenesulfonamide

1-(2-Methoxy-ethyl)-piperidin-4-ylamine (2.01 g) and triethylamine (3.24 mL, 2.35 g) were added to 1,4-dioxane (60 mL). 4-Chloro-3-nitrobenzenesulfonamide (2.50 g) was added, and the mixture was heated to 90°C for 16 hours. The mixture was cooled and the material purified by flash column chromatography on silica gel using 10% methanol in dichloromethane.

EXAMPLE 189B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[1-(2-methoxyethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 26C for EXAMPLE 1E and EXAMPLE 189A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.12 (br s, 1H), 8.52 (d, 1H), 8.18 (d, 1H), 7.76 (dd, 1H), 7.51 (d, 1H), 7.39-7.31 (m, 4H), 7.08-7.05 (m, 4H), 6.80 (dd, 1H), 6.61, (dd, 1H), 6.36 (t, 1H), 6.14 (d, 1H), 3.70 (m, 1H), 3.50 (t, 2H), 3.27 (s, 3H), 2.99 (m, 6H), 2.71 (br s, 4H), 2.16 (m, 6H), 2.02-1.90 (m, 6H), 1.65 (m, 2H), 1.37 (t, 2H), 0.92 (s, 6H).

EXAMPLE 190

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 174A for EXAMPLE 1F and EXAMPLE 55B for EXAMPLE 26C in EXAMPLE 177. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 11.21 (br s, 1H), 9.14 (s, 1H), 8.45 (d, 1H), 7.71 (dd, 1H), 7.52 (m, 2H), 7.34 (m, 2H), 7.26 (m, 1H), 7.15 (d, 1H), 7.04 (m, 2H), 6.95 (t, 1H), 6.67 (m, 1H),

6.38 (d, 1H), 6.25 (m, 2H), 3.01 (m, 4H), 2.87 (m, 5H), 2.72 (m, 2H), 2.33 (m, 4H), 2.15 (m, 6H), 1.95 (s, 2H), 1.39 (m, 2H), 0.92 (s, 6H).

EXAMPLE 191

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(2-hydroxyethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide

EXAMPLE 191A

tert-butyl 4-(4-(N-(2-(1*H*-indol-4-yloxy)-4-(-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)piperidine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 1E and EXAMPLE 157A for EXAMPLE 1F in EXAMPLE 1G, except 5-7% methanol in CH_2Cl_2 was used for the chromatography.

EXAMPLE 191B

2-(1*H*-indol-4-yloxy)-N-(4-(1-(2-(*tert*-butyldimethylsilyloxy)ethyl)piperidin-4-ylamino)-3-nitrophenylsulfonyl)-4-(-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzamide

EXAMPLE 191A (400 mg) was dissolved in CH_2Cl_2 (2.5 mL) and 4*N* HCl in dioxane (2.5 mL), then stirred at room temperature for 30 minutes. The reaction was concentrated and then partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The organic layer was washed with brine and dried over Na_2SO_4. After filtration and concentration the resultant crude amine was slurried in CH_2Cl_2 (2.5 mL) and (*tert*-butyldimethylsilyloxy)acetaldehyde (73 mg) was added. After stirring for 15 minutes, sodium triacetoxyborohydride (400 mg) was added and the reaction was stirred at room temperature overnight. The reaction was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ The organic layer was washed with brine and dried over Na_2SO_4. The product was purified using column chromatography using 1.0-2.5 % methanol in CH_2Cl_2

EXAMPLE 191C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(2-hydroxyethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide

EXAMPLE 191B (46 mg) was dissolved in tetrahydrofuran (0.8 mL), then 1.0*M* tetrabutyl ammonium fluoride in 95/5 tetrahydrofuran/H_2O (0.075 mL) was added and the reaction stirred at room temperature overnight. The reaction was concentrated and purified with column chromatography using 2-6 % methanol in CH_2Cl_2. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.15 (br s, 1H), 8.44 (d, 1H), 8.13 (br d, 1H), 7.74 (dd, 1H), 7.55 (d, 1H), 7.33 (d, 2H), 7.23 (s, 1H), 7.11 (d, 1H), 7.03 (m, 3H), 6.93 (dd, 1H), 6.64 (d, 1H), 6.33 (d, 1H), 6.23 (s, 1H), 6.22 (s, 1H), 3.75 (br s, 1H), 3.61 (br s, 2H), 3.40 (br s, 2H), 3.10 (br s, 2H), 2.98 br s, 4H), 2.78 (br s, 2H), 2.71 (s, 2H), 2.16 (br m, 6H), 2.00 (br d, 2H), 1.95 (s, 2H), 1.72 (br s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 194

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[1-(2-methoxyethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 1E and EXAMPLE 189A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.19 (br s, 1H), 8.46 (d, 1H), 8.17 (d, 1H), 7.72 (dd, 1H), 7.55 (d, 1H), 7.35 (d, 2H), 7.25 (t, 1H), 7.12 (d, 1H), 7.07-7.02 (m, 3H), 6.94 (t, 1H), 6.66, (dd, 1H), 6.36 (d, 1H), 6.24 (m, 2H), 3.73 (m, 1H), 3.52 (t, 2H), 3.27 (s, 3H), 3.00 (m, 6H), 2.79 (m, 2H), 2.72 (br s, 2H), 2.16 (m, 6H), 2.04-1.93 (m, 6H), 1.68 (m, 2H), 1.37 (t, 2H), 0.92 (s, 6H).

EXAMPLE 195

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(3-hydroxypropyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide

EXAMPLE 195A

4-(1-(3-(tert-butyldimethylsilyloxy)propyl)piperidin-4-ylamino)-3-nitrobenzenesulfonamide

A mixture of EXAMPLE 157B (300 mg), (3-bromopropoxy)(tert-butyl)dimethylsilane (304 mg) and cesium carbonate (967 mg) was suspended in anhydrous N,N-dimethylformamide (5 mL). The reaction mixture was heated at 70°C overnight. The reaction mixture was cooled to room temperature and diluted with ethyl acetate. The organic phase was washed with water, brine, dried over anhydrous sodium sulfate, and concentrated. The crude material was purified using flash column purification with 3-10% methanol/dichloromethane to afford the title compound.

EXAMPLE 195B

2-(1H-indol-4-yloxy)-N-(4-(1-(3-(tert-butyldimethylsilyloxy)propyl)piperidin-4-ylamino)-3-nitrophenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 1E and EXAMPLE 195A for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 195C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(3-hydroxypropyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide

A mixture of EXAMPLE 195B (180 mg) in anhydrous tetrahydrofuran (1mL) and tetrabutyl ammonium fluoride (0.5 mL 1M in tetrahydrofuran) was stirred at room temperature for 2 hours. The solvent was removed under vacuum. The residue was purified by reverse phase HPLC on a C18 column using a gradient of 40-70% acetonitrile/0.1% trifluroacetic acid in water to give the title compound as the trifluoroacetate salt. The trifluroacetic acid salt was dissolved in dichloromethane (6 ml) and washed with 50% aqueous $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to give the title compound. ^1H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.16 (s, 1H), 8.43 (d, 1H), 8.10 (m, 1H), 7.74 (dd, 1H), 7.57 (d, 1H), 7.34 (d, 2H), 7.23 (m, 1H), 7.10 (m, 1H), 7.02 (m, 3H), 6.93 (m, 1H), 6.65 (dd, 1H), 6.34 (d, 1H), 6.22 (m, 2H), 3.74 (m, 2H), 3.47 (m, 4H), 3.14 (m, 2H), 2.97 (m, 4H), 2.74 (m, 4H), 2.60 (m, 1H), 2.17 (m, 4H), 1.97 (m, 4H), 1.69 (m, 4H), 1.40 (m, 2H), 0.93 (s, 6H).

EXAMPLE 196

4-[4-({4'-chloro-3-[3-(dimethylamino)propyl]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 196A

4'-chloro-3-hydroxybiphenyl-2-carbaldehyde

The title compound was prepared as described in EXAMPLE 175A by replacing 1-(2-bromophenyl)ethanone with 2-bromo-6-hydroxybenzaldehyde.

EXAMPLE 196B

tert-butyl 4-((4'-chloro-3-hydroxybiphenyl-2-yl)methyl)piperazine-1-carboxylate

The title compound was prepared as described in EXAMPLE 1A by replacing 4'-chlorobiphenyl-2-carboxaldehyde with EXAMPLE 196A.

EXAMPLE 196C

tert-butyl 4-((4'-chloro-3-(trifluoromethylsulfonyloxy)biphenyl-2-yl)methyl)piperazine-1-carboxylate

To a mixture of EXAMPLE 196B (390 mg) in pyridine (5 ml) at 0°C was added dropwise trifluoromethanesulfonic anhydride (0.326 ml). The reaction mixture was stirred in an ice bath for 1 hour and diluted with ethyl acetate. The resulting mixture was washed with brine extensively and the organic layer was dried over Na_2SO_4, filtered, and concentrated to provide the title compound.

EXAMPLE 196D

tert-butyl 4-((4'-chloro-3-(3-(dimethylamino)prop-1-ynyl)biphenyl-2-yl)methyl)piperazine-1-carboxylate

To a mixture of EXAMPLE 196C (380 mg), N,N-dimethylprop-2-yn-1-amine (0.227 ml), tetrakis(triphenylphosphine)palladium(0) (123 mg) and triethylamine (0.492) in N,N-dimethylformamide (1.5 ml) was added copper(I) iodide (27.1 mg) and ^tBuNI (394 mg). The reaction mixture was heated at 100°C for 4 hours, cooled and diluted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography, eluting with a mixture of methanol, dichloromethane and triethyl amine to provide the title compound.

EXAMPLE 196E

tert-butyl 4-((4'-chloro-3-(3-(dimethylamino)propyl)biphenyl-2-yl)methyl)piperazine-1-carboxylate

EXAMPLE 196D (200 mg) in methanol (8 ml) was treated with platinum(IV) oxide (29.1 mg) under H_2 atmosphere overnight. The insoluble material was filtered off and the filtrate was concentrated to provide the title compound.

EXAMPLE 196F

3-(4'-chloro-2-(piperazin-1-ylmethyl)biphenyl-3-yl)-N,N-dimethylpropan-1-amine

The title compound was prepared as described in EXAMPLE 175C by replacing EXAMPLE 175B with EXAMPLE 196E.

EXAMPLE 196G

ethyl 2-(1H-indol-4-yloxy)-4-(4-((4'-chloro-3-(3-(dimethylamino)propyl)biphenyl-2-yl)methyl)piperazin-1-yl)benzoate

The title compound was prepared as described in EXAMPLE 175D by replacing EXAMPLE 175C with EXAMPLE 196F.

EXAMPLE 196H

2-(1H-indol-4-yloxy)-4-(4-((4'-chloro-3-(3-(dimethylamino)propyl)biphenyl-2-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared as described in EXAMPLE 175E by replacing EXAMPLE 175D with EXAMPLE 196G.

EXAMPLE 196I

4-[4-({4'-chloro-3-[3-(dimethylamino)propyl]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared as described in EXAMPLE 175F by replacing EXAMPLE 175E with EXAMPLE 196H. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.11 (s, 1H), 8.38 - 8.44 (m, 2H), 7.68 (dd, 1H), 7.56 (d, 1H), 7.44 (d, 2H), 7.19 - 7.29 (m, 5H), 7.07 (d, 1H), 6.99 (dd, 1H), 6.87 - 6.93 (m, 2H), 6.59 (dd, 1H), 6.26 (d, 1H), 6.23 (s,

1H), 6.19 (d, 1H), 3.84 (dd, 2H), 3.22 - 3.29 (m, 4H), 2.87 (s, 6H), 2.69 - 2.75 (m, 2H), 2.59 (s, 5H), 2.14 (s, 4H), 1.83 - 1.92 (m, 3H), 1.56 - 1.65 (m, 2H), 1.19 - 1.31 (m, 4H), 0.81 - 0.90 (m, 1H)

EXAMPLE 197

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(3-hydroxypropyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide

EXAMPLE 197A

2-(1H-indol-5-yloxy)-N-(4-(1-(3-(tert-butyldimethylsilyloxy)propyl)piperidin-4-ylamino)-3-nitrophenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzamide

The title compound was prepared by substituting EXAMPLE 26C for EXAMPLE 1E and EXAMPLE 195A for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 197B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(3-hydroxypropyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 197A for EXAMPLE 195B in EXAMPLE 195C. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.07 (bs, 1H), 8.50 (d, 1H), 8.14 (d, , 1H), 7.75 (dd, 1H), 7.52 (d, 1H), 7.34 (m, 4H), 7.02 (m, 4H), 6.78 (dd, 1H), 6.59 (dd, 1H), 6.34 (m, 1H), 6.14 (d, 1H), 3.46 (m, 4H), 3.16 (m, 2H), 2.98 (m, 4H), 2.68 (m, 4H), 2.60 (m, 1H), 2.16 (m, 6H), 1.97 (m, 4H), 1.68 (m, 4H), 1.38 (t, 2H), 0.93 (s, 6H).

EXAMPLE 198

4-{4-[(4'-chloro-4-morpholin-4-yl-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 198A

tert-butyl 4-((4'-chloro-4-hydroxybiphenyl-2-yl)methyl)piperazine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 125A for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

EXAMPLE 198B

tert-butyl 4-((4'-chloro-4-(trifluoromethylsulfonyloxy)biphenyl-2-yl)methyl)piperazine-1-carboxylate

A mixture of EXAMPLE 198A (3.0 g), trifluoromethanesulfonic anhydride (3.14 g) in anhydrous pyridine (50 mL) mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate. The organic phase was washed with water, brine, dried over anhydrous sodium sulfate and concentrated. The residue was used in the next step without further purification.

EXAMPLE 198C

tert-butyl 4-((4'-chloro-4-morpholinobiphenyl-2-yl)methyl)piperazine-1-carboxylate

A suspension of EXAMPLE 198B (500 mg), morpholine (80 mg), palladium (II) acetate (22 mg), biphenyl-2-yldi-tert-butylphosphine (50 mg) and cesium carbonate (427 mg) in anhydrous tetrahydrofuran (6 mL) was heated at 50°C overnight. The reaction mixture was cooled to room temperature and diluted with ethyl acetate. The organic phase was washed with water, brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude material was purified by flash column purification with 30-50% ethyl acetate/hexane to afford the title compound.

EXAMPLE 198D

4-(4'-chloro-2-(piperazin-1-ylmethyl)biphenyl-4-yl)morpholine

The title compound was prepared by substituting EXAMPLE 198C for EXAMPLE 1A in EXAMPLE 1B.

EXAMPLE 198E

methyl 2-(1H-indol-4-yloxy)-4-(4-((4'-chloro-4-morpholinobiphenyl-2-yl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 24F for EXAMPLE 20A and EXAMPLE 198D for EXAMPLE 20C in EXAMPLE 20D.

EXAMPLE 198F

2-(1H-indol-4-yloxy)-4-(4-((4'-chloro-4-morpholinobiphenyl-2-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 198E for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 198G

4-{4-[(4'-chloro-4-morpholin-4-yl-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 198F for EXAMPLE 26C in EXAMPLE 177. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.26 (bs, 1H), 8.63 (t, 1H), 8.49 (d, 1H), 7.66 (dd, 1H), 7.54 (d, 1H), 7.40 (m, 4H), 7.29 (m, 1H), 7.02 (m, 6H), 6.73 (dd, 1H), 6.39 (d, 1H), 6.30 (m, 2H), 3.85 (dd, 2H), 3.74 (m, 4H), 3.24 (m, 6H), 3.10 (m, 8H), 2.29 (m, 4H), 1.89 (m, 1H), 1.63 (m, 2H), 1.28 (m, 2H).

EXAMPLE 199

4-[4-({4'-chloro-3-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 199A

tert-butyl 4-((4'-chloro-3-hydroxybiphenyl-2-yl)methyl)piperazine-1-carboxylate

The title compound was prepared as described in EXAMPLE 1A by replacing EXAMPLE 27C with EXAMPLE 196A.

EXAMPLE 199B

tert-butyl 4-((4'-chloro-3-(2-(dimethylamino)ethoxy)biphenyl-2-yl)methyl)piperazine-1-carboxylate

To a mixture of EXAMPLE 199A (1.5 g) in N,N-dimethylformamide (20 ml) was added 60% sodium hydride (0.596 g). The mixture was stirred at room temperature for 30 minutes and dimethylaminoethyl chloride hydrochloride salt (1.073 g) was added. After the resulting mixture was stirred overnight, additional 60% sodium hydride (0.596 g) and dimethylaminoethyl chloride hydrochloride salt (1.073 g) were added. The reaction mixture

was further stirred overnight, diluted with ethyl acetate and washed with water, saturated $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated to provide the title compound.

EXAMPLE 199C

2-(4'-chloro-2-(piperazin-1-ylmethyl)biphenyl-3-yloxy)-N,N-dimethylethanamine

To a mixture of EXAMPLE 199B (2 g) in dichloromethane (10 ml) was added trifluroacetic acid (10 ml) at 0°C. The reaction mixture was stirred at room temperature for 30 minutes and concentrated. The residue was loaded onto a C18 column, and eluted with 0-50% 0.1% trifluroacetic acid/water in acetonitrile. The title compound was obtained as a trifluroacetic acid salt.

EXAMPLE 199D

ethyl 2-(1H-indol-4-yloxy)-4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)biphenyl-2-yl)methyl)piperazin-1-yl)benzoate

The title compound was prepared as described in EXAMPLE 175D by replacing EXAMPLE 175C with EXAMPLE 199C.

EXAMPLE 199E

2-(1H-indol-4-yloxy)-4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)biphenyl-2-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared as described in EXAMPLE 175E by replacing EXAMPLE 175D with EXAMPLE 199D.

EXAMPLE 199F

4-[4-({4'-chloro-3-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared as described in EXAMPLE 175F by replacing EXAMPLE 175E and EXAMPLE 1F with EXAMPLE 199E and EXAMPLE 173C, respectively. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.13 (s, 1H), 8.41 (d, 1H), 8.12 (d, 1H), 7.70 (dd, 1H), 7.58 (d, 1H), 7.52 (d, 2H), 7.43 (d, 2H), 7.31 (t, 1H), 7.22 (t, 1H), 7.06 (dd, 2H), 6.89 - 6.97 (m, 2H), 6.84 (d, 1H), 6.64 (dd, 1H), 6.30 (d, 1H), 6.24 (dd, 2H), 4.14 (t,

2H), 3.90 (dd, 2H), 3.53 - 3.73 (m, 2H), 3.22 - 3.32 (m, 4H), 2.93 (s, 6H), 2.34 - 2.46 (m, 7H), 2.29 (s, 5H), 1.97 (d, 2H), 1.73 (d, 2H), 1.41 - 1.62 (m, 4H).

EXAMPLE 201

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(diethylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide

EXAMPLE 201A

4-(4-(diethylamino)cyclohexylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting N^1,N^1-diethylcyclohexane-1,4-diamine for 1-(2-methoxy-ethyl)-piperidin-4-ylamine in EXAMPLE 189A.

EXAMPLE 201B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(diethylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 26C for EXAMPLE 1E and EXAMPLE 201A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (500 MHz, pyridine-d_5) δ ppm 12.28 (s, 1H), 9.29 (d, 1H), 8.29 - 8.38 (m, 2H), 8.19 (d, 1H), 7.52 - 7.57 (m, 2H), 7.40 - 7.47 (m, 3H), 7.10 (dd, 1H), 7.06 (d, 2H), 6.92 (d, 1H), 6.74 (dd, 1H), 6.61 (s, 1H), 6.55 (d, 1H), 3.31 - 3.42 (m, 1H), 3.00 - 3.08 (m, 4H), 2.76 (s, 2H), 2.54 - 2.61 (m, 1H), 2.51 (q, 4H), 2.21 - 2.28 (m, 2H), 2.08 - 2.15 (m, 4H), 2.04 (d, 2H), 1.97 (s, 2H), 1.81 (d, 2H), 1.38 (t, 2H), 1.29 - 1.36 (m, 2H), 1.17 - 1.28 (m, 2H), 1.05 (t, 6H), 0.93 (s, 6H).

EXAMPLE 202

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(dimethylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide

EXAMPLE 202A

4-(4-(dimethylamino)cyclohexylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting N^1,N^1-dimethylcyclohexane-1,4-diamine for 1-(2-methoxy-ethyl)-piperidin-4-ylamine in EXAMPLE 189A.

EXAMPLE 202B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(dimethylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 1E and EXAMPLE 202A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (500 MHz, pyridine-d_5) δ ppm 12.45 (s, 1H), 9.21 (d, 1H), 8.33 (d, 1H), 8.27 (dd, 1H), 8.18 (d, 1H), 7.48 (t, 1H), 7.45 (d, 2H), 7.40 (d, 1H), 7.11 (t, 1H), 7.08 (d, 2H), 6.87 (d, 1H), 6.72 - 6.81 (m, 3H), 6.67 (d, 1H), 3.31 - 3.41 (m, 1H), 3.00 - 3.06 (m, 4H), 2.77 (s, 2H), 2.31 (s, 6H), 2.25 (t, 2H), 2.20 - 2.25 (m, 1H), 2.10 - 2.16 (m, 4H), 2.00 - 2.07 (d, 2H), 1.97 (s, 2H), 1.88 (d, 2H), 1.39 (t, 3H), 1.34 (d, 2H), 1.15 - 1.28 (m, 4H), 0.94 (s, 6H).

EXAMPLE 203

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(diethylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 1E and EXAMPLE 201A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (500 MHz, pyridine-d_5) δ 12.44 (s, 1H), 9.21 (d, 1H), 8.34 (d, 1H), 8.28 (dd, 1H), 8.18 (d, 1H), 7.47 - 7.50 (m, 1H), 7.45 (d, 2H), 7.40 (d, 1H), 7.11 (t, 1H), 7.08 (d, 2H), 6.90 (d, 1H), 6.73 - 6.81 (m, 3H), 6.67 (d, 1H), 3.32 - 3.40 (m, 1H), 2.99 - 3.06 (m, 4H), 2.76 (s, 2H), 2.52 - 2.60 (m, 1H), 2.49 (q, 4H), 2.25 (t, 2H), 2.09 - 2.16 (m, 4H), 2.04 (d, 2H), 1.97 (s, 2H), 1.79 (d, 2H), 1.29 - 1.42 (m, 4H), 1.16 - 1.28 (m, 2H), 1.04 (t, 6H), 0.92 - 0.95 (m, 6H).

EXAMPLE 204

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 204A

trans-4-(4-morpholinocyclohexylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting trans-4-morpholinocyclohexanamine for 1-(2-methoxy-ethyl)-piperidin-4-ylamine in EXAMPLE 189A.

EXAMPLE 204B

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 1E and EXAMPLE 204A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (500 MHz, pyridine-d_5) δ 12.45 (s, 1H), 9.21 (d, 1H), 8.36 (d, 1H), 8.26 (dd, 1H), 8.16 (d, 1H), 7.47 - 7.51 (m, 1H), 7.45 (d, 1H), 7.40 (d, 1H), 7.12 (t, 1H), 6.87 (d, 1H), 6.73 - 6.81 (m, 3H), 6.68 (d, 1H), 3.71 - 3.78 (m, 2H), 3.33 - 3.42 (m, 1H), 3.00 - 3.06 (m, 4H), 2.76 (s, 2H), 2.44 - 2.52 (m, 4H), 2.25 (t, 2H), 2.16 - 2.23 (m, 2H), 2.09 - 2.16 (m, 4H), 2.06 (d, 2H), 1.97 (s, 2H), 1.86 (s, 2H), 1.39 (t, 2H), 1.17 - 1.35 (m, 6H), 0.94 (s, 6H).

EXAMPLE 205

4-[4-({4'-chloro-3-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared as described in EXAMPLE 177 by replacing EXAMPLE 26C and EXAMPLE 1F with EXAMPLE 199E and EXAMPLE 21A, respectively. ^{1}H NMR (500 MHz, dichloromethane-d_2) δ 8.70 (d, 1H), 8.56 (s, 1H), 8.40 (d, 1H), 7.95 (dd, 1H), 7.91 (d, 1H), 7.46 (d, 2H), 7.24 - 7.35 (m, 5H), 7.15 (t, 1H), 6.90 (dd, 2H), 6.83 (d, 1H), 6.75 (d, 1H), 6.60 (dd, 1H), 6.41 (d, 1H), 6.19 (d, 1H), 4.05 (t, 2H), 3.58 (s, 1H), 3.32 (s, 2H), 2.95 - 3.02 (m, 4H), 2.66 - 2.80 (m, 4H), 2.30 - 2.35 (m, 4H), 2.24 - 2.29 (m, 9H), 2.15 - 2.23 (m, 2H), 2.05 (d, 2H), 1.63 - 1.73 (m, 2H)

EXAMPLE 206

4-{4-[1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared as described in EXAMPLE 177 by replacing EXAMPLE 26C and EXAMPLE 1F with EXAMPLE 175E and EXAMPLE 21A, respectively. ^{1}H NMR (400 MHz, dichloromethane-d_2) δ 8.70 (d, 1H), 8.51 (s, 1H), 8.40 (d, 1H), 7.94 (dd, 1H), 7.90 (d, 1H), 7.54 (d, 1H), 7.33 (t, 4H), 7.21 - 7.27 (m, 2H), 7.10 - 7.19 (m, 4H), 6.91 (d, 1H), 6.73 (d, 1H), 6.55 - 6.60 (m, 1H), 6.41 (s, 1H), 6.16 (d, 1H), 3.52 - 3.63 (m, 1H), 3.36 (q, 1H), 2.96 - 3.07 (m, 4H), 2.72 - 2.79 (m, 2H), 2.33 - 2.41 (m, 2H), 2.27 (s, 3H), 2.14 - 2.27 (m, 4H), 2.00 - 2.09 (m, 2H), 1.63 - 1.74 (m, 2H), 1.19 (d, 3H).

EXAMPLE 207

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(dimethylamino)tetrahydro-2H-pyran-4-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting 4-(aminomethyl)-N,N-dimethyltetrahydro-2H-pyran-4-amine for (3S,4R)-4-amino-1-benzylpiperidin-3-ol, hydrochloric acid in EXAMPLE 187B. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.17 (s, 1H), 8.84 (br s, 1H), 8.59 (d, 1H), 7.84 (dd, 1H), 7.51 (d, 1H), 7.39-7.43 (m, 2H), 7.33 (d, 2H), 7.17-7.21 (m, 2H), 7.03 (d, 2H), 6.89 (dd, Hz, 1H), 6.64 (d, 1H), 6.40 (s, 1H), 6.13 (d, 1H), 3.72-3.75 (m, 2H), 3.34-3.57 (m, 4H), 3.02 (br, 4H), 2.71 (br, 2H), 2.27 (s, 6H), 2.16 (br s, 6H), 1.94 (br s, 2H), 1.78-1.85 (m, 2H), 1.36-1.39 (m, 2H), 0.92 (s, 6H).

EXAMPLE 208

N-({4-[(2-aminocyclohexyl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide

EXAMPLE 208A

The title compound was prepared by substituting tert-butyl 2-aminocyclohexylcarbamate for (3S,4R)-4-amino-1-benzylpiperidin-3-ol, hydrochloric acid in EXAMPLE 187B.

EXAMPLE 208B

N-({4-[(2-aminocyclohexyl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide

EXAMPLE 208A (0.1 g) in dimethylsulfoxide (4 mL) was heated under microwave conditions (200 °C, 1 hour). The residue was purified by reverse phase HPLC on

a C18 column using a gradient of 30-70% acetonitrile/0.1% TFA in water. The desired fractions were collected, and the organic solvent was partially removed under reduced pressure. The resulting mixture was treated with saturated aqueous $NaHCO_3$ mixture. It was then extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to give the title compound. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.02 (s, 1H), 8.45 (s, 1H), 8.05 (d, 1H), 7.79-7.81 (m, 1H), 7.56 (d, 1H), 7.30-7.34 (m, 4H), 6.98-7.06 (m, 4H), 6.73 (d, 1H), 6.54 (dd, 1H), 6.33 (s, 1H), 6.11 (d, 1H), 3.64-3.70 (m, 1H), 2.93 (br, 4H), 2.71 (br, 2H), 2.14-2.16 (br s, 6H), 1.95 (br s, 2H), 1.67-1.73 (m, 2H), 1.36-1.39 (m, 2H), 0.92 (s, 6H).

EXAMPLE 209

4-[4-({4'-chloro-4-[3-(dimethylamino)prop-1-ynyl]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 209A

tert-butyl 4-((4'-chloro-4-(3-(dimethylamino)prop-1-ynyl)biphenyl-2-yl)methyl)piperazine-1-carboxylate

A suspension of EXAMPLE 198B (800 mg), N,N-dimethylprop-2-yn-1-amine (373 mg), copper(I) iodide (57 mg), tetrakis(triphenylphosphine)palladium(0) (259 mg), triethylamine (757 mg) and tert-butyl ammonium iodide (829 mg) in anhydrous N,N-dimethylformamide (5 mL) was heated at 100°C for 5 hours. The reaction mixture was cooled to room temperature and diluted with ethyl acetate. The organic phase was washed with water, brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude material was purified by flash column purification with 0-3% methanol/dichloromethane to afford the title compound.

EXAMPLE 209B

3-(4'-chloro-2-(piperazin-1-ylmethyl)biphenyl-4-yl)-N,N-dimethylprop-2-yn-1-amine

The title compound was prepared by substituting EXAMPLE 209A for EXAMPLE 1A in EXAMPLE 1B.

EXAMPLE 209C

methyl 2-(1H-indol-4-yloxy)-4-(4-((4'-chloro-4-(3-(dimethylamino)prop-1-ynyl)biphenyl-2-yl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 24F for EXAMPLE 20A and EXAMPLE 209B for EXAMPLE 20C in EXAMPLE 20D.

EXAMPLE 209D

2-(1H-indol-4-yloxy)-4-(4-((4'-chloro-4-(3-(dimethylamino)prop-1-ynyl)biphenyl-2-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 209C for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 209E

4-[4-({4'-chloro-4-[3-(dimethylamino)prop-1-ynyl]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 209D for EXAMPLE 26C in EXAMPLE 177. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.23 (bs, 1H), 8.57 (t, 1H), 8.47 (d, 1H), 7.67 (dd, 1H), 7.54 (m, 2H), 7.43 (m, 5H), 7.24 (m, 2H), 7.14 (m, 1H), 7.03 (m, 1H), 6.94 (m, 1H), 6.71 (d, 1H), 6.38 (d, 1H), 6.27 (d, 2H), 3.85 (m, 2H), 3.60 (m, 2H), 3.23 (m, 6H), 3.04 (m, 4H), 2.35 (s, 6H), 2.28 (m, 4H), 1.88 (m, 1H), 1.58 (m, 2H), 1.24 (m, 2H).

EXAMPLE 210

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(3-nitro-4-{[1-(4,4,4-trifluorobutyl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide

EXAMPLE 210A

3-nitro-4-(1-(4,4,4-trifluorobutyl)piperidin-4-ylamino)benzenesulfonamide

EXAMPLE 157B (600 mg) was combined with 1,1,1-trifluoro-4-iodobutane (595 mg) and potassium carbonate (829 mg) in acetonitrile (15 mL). The reaction was heated

to 70°C overnight. The reaction was concentrated, and then taken up in ether and concentrated again. The product was used in the next step without further purification.

EXAMPLE 210B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(3-nitro-4-{[1-(4,4,4-trifluorobutyl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 210A for EXAMPLE 1F and EXAMPLE 55B for EXAMPLE 1E in EXAMPLE 1G. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.20 (s, 1H), 8.47 (d, 1H), 8.20 (d, 1H), 7.72 (dd, 1H), 7.54 (d,1H), 7.34 (d, 2H), 7.25 (t, 1H), 7.14 (d, 1H), 7.05 (m, 3H), 6.95 (t, 1H), 6.68 (dd, 1H), 6.38 (d, 1H), 6.25 (s, 2H), 3.71 (m, 1H), 3.01 (m, 4H), 2.92 (m, 2H), 2.72 (s, 2H), 2.40 (m, 2H), 2.30 (m, 2H), 2.16 (m, 6H), 1.95 (m, 4H), 1.68 (m, 4H), 1.38 (t, 2H), 1.24 (br s, 1H), 0.92 (s, 6H).

EXAMPLE 211

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[2-(4-hydroxy-1-methylpiperidin-4-yl)ethyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting 4-(2-aminoethyl)-1-methylpiperidin-4-ol for (3S,4R)-4-amino-1-benzylpiperidin-3-ol, hydrochloric acid in EXAMPLE 187B. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.05 (s, 1H), 8.61 (s, 1H), 8.47 (d, 1H), 7.77 (dd, 1H), 7.54 (d, 1H), 7.32-7.34 (m, 4H), 7.04 (d, 2H), 7.01 (s, 1H), 6.90 (d, 2H), 6.76 (dd, 1H), 6.57 (dd, 1H), 6.33 (s, 1H), 6.13 (d, 1H), 4.92 (s, 1H), 3.43-3.46 (m, 2H), 2.95-3.01 (br, 8H), 2.71 (br, 2H), 2.65 (s, 3H), 2.12-2.16 (br s, 6H), 1.95 (br s, 2H), 1.77-1.80 (m, 2H), 1.67-1.71 (m, 4H), 1.36-1.39 (m, 2H), 0.92 (s, 6H).

EXAMPLE 212

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[1-(1,3-thiazol-2-yl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide

The title compound was prepared by substituting 4-(2-aminoethyl)-1-methylpiperidin-4-ol for (3S,4R)-4-amino-1-benzylpiperidin-3-ol, hydrochloric acid in

EXAMPLE 187B. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.16 (s, 1H), 8.58 (s, 1H), 8.28 (d, 1H), 7.82 (dd, 1H), 7.51 (d, 1H), 7.39-7.42 (m, 2H), 7.33 (d, 2H), 7.20 (d, 1H), 7.17 (d, 1H), 7.14 (d, 1H), 7.03 (d, 2H), 6.86 (d, 1H), 6.85 (d, 1H), 6.65 (dd, 1H), 6.39 (s, 1H), 6.15 (d, 1H), 3.87-3.90 (m, 2H), 3.20-3.24 (m, 2H), 3.04 (br, 4H), 2.73 (br, 2H), 2.11-2.17 (m, 5H), 1.95 (br s, 2H), 1.71-1.75 (m, 2H), 1.36-1.39 (m, 2H), 0.92 (s, 6H).

EXAMPLE 213

4-(4-{[4'-chloro-4-(2-hydroxyethoxy)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 213A

4-(2-(tert-butyldimethylsilyloxy)ethoxy)-4'-chlorobiphenyl-2-carbaldehyde

A mixture of EXAMPLE 125A (0.5 g), (2-bromoethoxy)(tert-butyl)dimethylsilane (0.771 g) and cesium carbonate (1.4 g) was suspended in anhydrous N,N-dimethylformamide (5 mL). The reaction mixture was heated at 70°C overnight. The reaction mixture was cooled to room temperature and diluted with ethyl acetate. The organic phase was washed with water, brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude material was purified by flash column purification with 0-5% ethyl acetate/hexane.to afford the title compound.

EXAMPLE 213B

methyl 2-(1H-indol-4-yloxy)-4-(4-((4-(2-(tert-butyldimethylsilyloxy)ethoxy)-4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)benzoate

The title compound was made by substituting EXAMPLE 213A for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 68B for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 213C

2-(1H-indol-4-yloxy)-4-(4-((4-(2-(tert-butyldimethylsilyloxy)ethoxy)-4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 213B for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 213D

2-(1H-indol-4-yloxy)-4-(4-((4-(2-(tert-butyldimethylsilyloxy)ethoxy)-4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-N-(3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)phenylsulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 213C for EXAMPLE 1E in EXAMPLE 1G.

EXAMPLE 213E

4-(4-{[4'-chloro-4-(2-hydroxyethoxy)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 213D for EXAMPLE 195B in EXAMPLE 195C. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.24 (m, 1H), 8.62 (t, 1H), 8.50 (d, 1H), 7.67 (dd, 1H), 7.54 (m, 1H), 7.43 (d, 2H), 7.37 (d, 2H), 7.28 (m, 1H), 7.15 (m, 2H), 7.05 (m, 2H), 6.96 (m, 1H), 6.90 (dd, 1H), 6.73 (dd, 1H), 6.40 (d, 1H), 6.31 (m, 1H), 6.27 (m, 1H), 4.82 (t, 1H), 3.99 (t, 2H), 3.86 (m, 2H), 3.71 (m, 2H), 3.26 (m, 6H), 2.66 (m, 2H), 2.31 (m, 5H), 1.89 (m, 1H), 1.63 (m, 2H), 1.27 (m, 2H).

EXAMPLE 214

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(cyclopropylmethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide

EXAMPLE 214A

tert-butyl 1-(cyclopropylmethyl)piperidin-4-ylcarbamate

The title compound was prepared by substituting cyclopropanecarbaldehyde for 4'-chlorobiphenyl-2-carboxaldehyde and tert-butyl piperidin-4-ylcarbamate for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 214B

1-(cyclopropylmethyl)piperidin-4-amine bis(2,2,2-trifluoroacetate)

The title compound was prepared by substituting EXAMPLE 214A for EXAMPLE 1A in EXAMPLE 1B.

EXAMPLE 214C

4-(1-(cyclopropylmethyl)piperidin-4-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 214B for 1-(2-Methoxy-ethyl)-piperidin-4-ylamine in EXAMPLE 189A.

EXAMPLE 214D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(cyclopropylmethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 26C for EXAMPLE 1E and EXAMPLE 214C for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (500 MHz, pyridine-d_5) δ 12.28 (s, 1H), 9.30 (d, 1H), 8.49 (d, 1H), 8.34 (dd, 1H), 8.18 (d, 1H), 7.52 - 7.56 (m, 2H), 7.41 - 7.46 (m, 3H), 7.09 (dd, 1H), 7.06 (d, 2H), 6.91 (d, 1H), 6.73 (dd, 1H), 6.61 (d, 1H), 6.54 (d, 1H), 3.45 - 3.56 (m, 1H), 3.00 - 3.08 (m, 4H), 2.87 (d, 2H), 2.76 (s, 2H), 2.25 (t, 2H), 2.19 (d, 4H), 2.09 - 2.14 (m, 4H), 1.97 (s, 4H), 1.63 - 1.73 (m, 2H), 1.38 (t, 2H), 0.84 - 0.91 (m, 1H), 0.43 - 0.50 (m, 2H), 0.11 (q, H).

EXAMPLE 215

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

EXAMPLE 215A

4-(4-methylpiperazin-1-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

The title compound was prepared by substituting 4-methylpiperazin-1-amine for (tetrahydropyran-4-yl)methanamine and EXAMPLE 159C for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 1F.

EXAMPLE 215B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 215A for EXAMPLE 1F and EXAMPLE 55B for EXAMPLE 26C in EXAMPLE 177. ^{1}H NMR (500 MHz, dimethylsulfoxide-d $_6$) δ 11.21 (br s, 1H), 8.09 (m, 1H), 7.98 (m, 1H), 7.83 (dd, 1H), 7.53 (d, 1H), 7.45 (d, 1H), 7.34 (d, 2H), 7.26 (t, 1H), 7.16 (d, 1H), 7.04 (d, 2H), 6.97 (t, 1H), 6.66 (dd, 1H), 6.39 (d, 1H), 6.24 (m, 2H), 2.87 (m, 13H), 2.38 (s, 3H), 2.17 (m, 6H), 1.95 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H)

EXAMPLE 216

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[1-(4,4,4-trifluorobutyl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 26C for EXAMPLE 1E and EXAMPLE 210A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d$_6$) δ 11.13 (s, 1H), 10.89 (br s, 1H), 8.55 (d, 1H), 8.22 (d, 1H), 7.79 (dd, 1H), 7.50 (d,1H), 7.34 (m, 4H), 7.07 (m, 4H), 6.83 (dd, 1H), 6.63 (dd, 1H), 6.37 (m, 1H), 6.15 (d, 1H), 3.71 (m, 1H), 3.01 (m, 4H), 2.92 (m, 2H), 2.72 (s, 2H), 2.40 (m, 2H), 2.30 (m, 2H), 2.16 (m, 6H), 1.95 (m, 4H), 1.68 (m, 4H), 1.38 (t, 2H), 1.24 (br s, 1H), 0.92 (s, 6H).

EXAMPLE 217

4-{4-[1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared as described in EXAMPLE 177 by replacing EXAMPLE 26C and EXAMPLE 1F with EXAMPLE 175E and EXAMPLE 174A, respectively. ^{1}H NMR (400 MHz, dimethylsulfoxide-d $_6$) δ 11.21 (s, 1H), 9.15 (s, 1H), 8.45 (d, 1H), 7.70 (dd, 1H), 7.43 - 7.56 (m, 5H), 7.34 - 7.41 (m, 1H), 7.24 - 7.31 (m, 4H), 7.10 - 7.16 (m, 2H), 6.94 (t, 1H), 6.66 (dd, 1H), 6.37 (d, 1H), 6.24 (dd, 2H), 2.80 - 3.02 (m, 10H), 2.28 - 2.39 (m, 5H), 2.14 - 2.24 (m, 2H), 1.16 (d, 3H).

EXAMPLE 218

4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-(hydroxymethyl)piperazin-1-yl]-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 218A

2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enecarbaldehyde

The title compound was prepared by substituting EXAMPLE 18C for EXAMPLE 143C in EXAMPLE 143D.

EXAMPLE 218B

tert-butyl 4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)-3-(hydroxymethyl)piperazine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 218A for EXAMPLE 27C and tert-butyl 3-(hydroxymethyl)piperazine-1-carboxylate for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 218C

(1-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-2-yl)methanol

The title compound was prepared by substituting EXAMPLE 218B for EXAMPLE 1A in EXAMPLE 1B.

EXAMPLE 218D

ethyl 2-(1H-indol-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)-3-(hydroxymethyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 218C for EXAMPLE 20C and EXAMPLE 26A for EXAMPLE 20A in EXAMPLE 20D.

EXAMPLE 218E

2-(1H-indol-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)-3-(hydroxymethyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 218D for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 218F

4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-(hydroxymethyl)piperazin-1-yl]-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 218E for EXAMPLE 26C and EXAMPLE 21A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.07 (s, 1H), 8.50 (d, 1H), 8.14 (d, 1H), 7.45 (d, J = 9.46 Hz, 1H), 7.52 (d, 1H), 7.32-7.35 (m, 4H), 6.99-7.05 (m, 4H), 6.78 (dd, 1H), 6.58-6.59 (m, 1H), 6.34 (s, 1H), 6.14 (d, 1H), 4.42-4.44 (m, 1H), 3.72 (br s, 1H), 3.10-3.25 (m, 6H), 3.00 (br, 2H), 2.58-2.69 (m, 6H), 1.82-2.01 (m, 6H), 1.70 (br, 2H), 1.36-1.39 (m, 2H), 0.92 (s, 6H).

EXAMPLE 219

4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-(hydroxymethyl)piperazin-1-yl]-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 218E for EXAMPLE 26C and EXAMPLE 173C for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.11 (s, 1H), 8.52 (d, 1H), 8.20 (d, 1H), 7.77 (dd, 1H), 7.52 (d, 1H), 7.32-7.38 (m, 4H), 7.03-7.07 (m, 4H), 6.81 (dd,, 1H), 6.58-6.60 (m, 1H), 6.36 (s, 1H), 6.14 (d, 1H), 4.44 (s, 1H), 3.92 (dd, 2H), 3.71 (br s, 1H), 3.41-3.43 (m, 2H), 3.02-3.06 (m, 4H), 2.55-2.72 (m, 6H), 2.18-2.24 (m, 2H), 1.91-2.00 (m, 8H), 1.76-1.80 (m, 2H), 1.63-1.65 (m, 2H), 1.49-1.51 (m, 2H), 1.35-1.38 (m, 2H), 0.92 (s, 6H).

EXAMPLE 220

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 215A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.14 (s, 1H), 8.15 (d, 1H), 8.04 (s, 1H), 7.95 (dd, 1H), 7.50 (t, 2H), 7.35 (m, 4H), 7.12 (d, 1H), 7.04 (d, 2H), 6.83 (dd, 1H), 6.61 (dd, 1H), 6.39 (m, 1H), 6.12 (d, 1H), 2.92 (m, 10H), 2.71 (s, 2H), 2.35 (s, 3H), 2.17 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 221

4-(4-{[4'-chloro-4-(2-hydroxyethoxy)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 221A

2-(1H-indol-4-yloxy)-4-(4-((4-(2-(tert-butyldimethylsilyloxy)ethoxy)-4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-N-(4-(1-methylpiperidin-4-ylamino)-3-nitrophenylsulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 213C for EXAMPLE 1E and EXAMPLE 21A for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 221B

4-(4-{[4'-chloro-4-(2-hydroxyethoxy)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 221A for EXAMPLE 195B in EXAMPLE 195. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.12 (s, 1H), 8.42 (d, 1H), 8.10 (d, 1H), 7.74 (dd, 1H), 7.58 (d, 1H), 7.40 (m, 4H), 7.21 (m, 1H), 7.06 (m, 4H), 6.90 (m, 2H), 6.65 (m, 1H), 6.31 (d, 1H), 6.23 (m, 2H), 4.84 (t, 1H), 4.00 (t, 2H), 3.71 (m, 3H), 3.24 (m, 4H), 3.02 (m, 6H), 2.66 (m, 2H), 2.32 (m, 5H), 2.00 (m, 2H), 1.69 (m, 2H).

EXAMPLE 222

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[3-(3-oxopiperazin-1-yl)propyl]amino}phenyl)sulfonyl]benzamide

EXAMPLE 222A

3-nitro-4-[3-(3-oxo-piperazin-1-yl)-propylamino]-benzenesulfonamide

4-(3-Amino-propyl)-piperazin-2-one (3.45 g) and triethylamine (5.18 mL, 3.76 g) were added to 1,4-dioxane (100 mL) and N,N-dimethylacetamide (20 mL) and mixed until dissolved. 4-Chloro-3-nitrobenzenesulfonamide (4.00 g) was added, and the mixture was heated to 90°C for 16 hours. The mixture was cooled and the solvent was removed under

vacuum. The material purified by recrystallization from 20% methanol in dichloromethane with subsequent washing of the recrystallized solid with 10% methanol in dichloromethane followed by washing with 100% dichloromethane.

EXAMPLE 222B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[3-(3-oxopiperazin-1-yl)propyl]amino}phenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 26C for EXAMPLE 1E and EXAMPLE 222A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.16 (br s, 1H), 8.85 (t, 1H), 8.58 (d, 1H), 7.79 (dd, 1H), 7.74 (br s, 1H), 7.51 (d, 1H), 7.43-7.37 (m, 2H), 7.34 (d, 2H), 7.16 (d, 1H), 7.07-7.01 (m, 3H), 6.86 (dd, 1H), 6.65, (d, 1H), 6.39 (t, 1H), 6.15 (d, 1H), 3.43 (q, 2H), 3.17 (t, 2H), 3.03 (m, 4H), 2.95 (s, 2H), 2.72 (s, 2H), 2.56 (t, 2H), 2.47 (t, 2H), 2.16 (m, 6H), 1.95 (br s, 2H), 1.79 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 223

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(3-nitro-4-{[3-(3-oxopiperazin-1-yl)propyl]amino}phenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 1E and EXAMPLE 222A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.24 (br s, 1H), 8.83 (t, 1H), 8.50 (d, 1H), 7.75 (br s, 1H), 7.68 (dd, 1H), 7.53 (d, 1H), 7.34 (d, 2H), 7.28 (t, 1H), 7.18 (d, 1H), 7.04 (d, 2H), 7.02-6.94 (m, 2H), 6.71 (dd, 1H), 6.42 (d, 1H), 6.29-6.23 (m, 2H), 3.43 (q, 2H), 3.17 (m, 2H), 3.05 (m, 4H), 2.96 (s, 2H), 2.72 (s, 2H), 2.57 (t, 2H), 2.48 (t, 2H), 2.17 (m, 6H), 1.95 (br s, 2H), 1.79 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 224

4-(4-{[2-(4-chlorophenyl)-5-hydroxycyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 224A

2-chloro-5-hydroxycyclohex-1-enecarbaldehyde

Phosphorus oxychloride(4.08 mL) was added to cooled (-10°C) N,N-dimethylformamide (20 mL). The temperature was maintained below 0°C. Stirring was continued for another 30 minutes before the addition of 4-(tert-butyldimethylsilyloxy)cyclohexanone (10 g). The mixture was then stirred at room temperature for 2 hours before it was diluted with ethyl acetate (300 mL) and washed with water (3x), brine and dried over Na_2SO_4. After filtration and concentration, the crude product was used directly in the next reaction without further purification.

EXAMPLE 224B

2-(4-chlorophenyl)-5-hydroxycyclohex-1-enecarbaldehyde

To a mixture of 4-chlorophenylboronic acid (6.88 g), EXAMPLE 224A (4.65 g), palladium(II) acetate (131 mg), K_2CO_3 (18.24 g) and tetrabutylammonium bromide (14.18 g) was added water (200 mL). The mixture was stirred at 50°C for 4 hours, cooled, and diluted with ethyl acetate (400 mL) and washed with water (3x) and brine and dried over Na_2SO_4. After filtration and concentration, the residue was loaded on a column and eluted with 5-20% ethyl acetate in hexane to give the title compound.

EXAMPLE 224C

methyl 2-(1H-indol-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5-hydroxycyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

To a mixture of EXAMPLE 224B (0.8 g) and EXAMPLE 150A (1.2 g) in dichloromethane (20 mL) was added sodium triacetoxyborohydride (1.2 g). The mixture was stirred overnight. The mixture was diluted with ethyl acetate (200 mL) and washed with 2% NaOH, water and brine. After drying over Na_2SO_4, the solvent was evaporated under vacuum and the residue was loaded on a column and eluted with 5-10% methanol in dichloromethane to give the title compound.

EXAMPLE 224D

2-(1H-indol-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5-hydroxycyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

To a mixture of EXAMPLE 224C (1.78 g) in tetrahydrofuran (30 mL), methanol (10 mL) and water (10 mL) was added $LiOH \cdot H_2O$ (0.262 g). The mixture was

stirred overnight. The mixture was then neutralized with 5% aqueous HCl and exacted with ethyl acetate (3x) and the combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of solvent gave the title compound.

EXAMPLE 224E

4-(4-{[2-(4-chlorophenyl)-5-hydroxycyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 224D for EXAMPLE 1E and EXAMPLE 21A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.08 (s, 1H), 8.50 (d, 1H), 8.13 (d, 1H), 7.77 (dd, 1H), 7.52 (d, 1H), 7.34 (m, 4H), 7.04 (m, 4H), 6.78 (dd, 1H), 6.59 (dd, 1H), 6.35 (s, 1H), 6.13 (d, 1H), 4.59 (d, 1H), 3.74 (m, 2H), 3.39 (m, 1H), 3.03 (m, 7H), 2.68 (m, 3H), 2.41 (m, 4H), 2.17 (m, 7H), 2.00 (m, 3H), 1.71 (m, 3H).

EXAMPLE 225

4-(4-{[2-(4-chlorophenyl)-5-hydroxycyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 224D for EXAMPLE 1E and EXAMPLE 173C for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.07 (s, 1H), 8.47 (d, 1H), 8.14 (d, 1H), 7.92 (s, 1H), 7.72 (dd, 1H), 7.52 (d, 1H), 7.46 (d, 1H), 7.33 (m, 4H), 7.07 (d, 2H), 6.98 (d, 1H), 6.77 (m, 1H), 6.58 (dd, 1H), 6.34 (s, 1H), 6.14 (d, 1H), 4.59 (m, 1H), 3.90 (dd, 2H), 3.70 (m, 1H), 3.01 (m, 8H), 2.71 (m, 6H), 2.56 (m, 8H), 2.19 (m, 4H), 1.94 (m, 3H), 1.56 (m, 3H).

EXAMPLE 226

4-(4-{[2-(4-chlorophenyl)-5-hydroxycyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 224D for EXAMPLE 1E and EXAMPLE 174A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.13 (s, 1H), 9.13 (s, 1H), 8.52 (d, 1H), 7.83 (dd, 1H), 7.53 (t, 2H), 7.36 (m, 4H), 7.09 (m, 3H), 6.83 (dd, 1H), 6.61 (dd, 1H), 6.38 (s, 1H), 6.12 (d, 1H), 4.59 (d, 1H), 3.75 (m, 1H), 2.81 (m, 12H), 2.27 (m, 12H), 1.79 (m, 4H).

EXAMPLE 227

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(2,3-dihydro-1H-inden-2-yl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide

EXAMPLE 227A

4-(1-indan-2-yl-piperidin-4-ylamino)-3-nitro-benzenesulfonamide

2-Aminoindane (12.84 g) and triethylamine (15.04 mL, 10.92 g) were added to 1,4-dioxane (150 mL) and the mixture was stirred until the solids were dissolved. 4-Chloro-3-nitrobenzenesulfonamide (12.77 g) was added, and the mixture was heated to 90°C for 16 hours. The mixture was cooled and the precipitate vacuum was filtered, washed with 20% methanol in dichloromethane, and washed with 100% dichloromethane.

EXAMPLE 227B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(2,3-dihydro-1H-inden-2-yl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 1E and EXAMPLE 227A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.20 (br s, 1H), 8.48 (d, 1H), 8.21 (d, 1H), 7.73 (dd, 1H), 7.54 (d, 1H), 7.34 (d, 2H), 7.26-7.21 (m, 3H), 7.16-7.12 (m, 2H), 7.09-7.02 (m, 3H), 6.95 (t, 2H), 6.68 (dd, 1H), 6.39 (d, 1H), 6.24 (m, 2H), 3.74 (m, 1H), 3.18-2.80 (m, 13H), 2.72 (br s, 2H), 2.16 (m, 6H), 2.03 (m, 2H), 1.95 (br s, 2H), 1.68 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 228

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(2,3-dihydro-1H-inden-2-yl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 26C for EXAMPLE 1E and EXAMPLE 227A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.12 (br s, 1H), 8.55 (d, 1H), 8.23 (d, 1H), 7.79 (dd, 1H), 7.51 (d, 1H), 7.41-7.31 (m, 4H), 7.22 (m, 2H), 7.16-7.09 (m, 3H), 7.07-7.01 (m, 3H), 6.83

(dd, 1H), 6.63 (dd, 1H), 6.37 (t, 1H), 6.15 (d, 1H), 3.73 (m, 1H), 3.16-2.82 (m, 13H), 2.71 (br s, 2H), 2.16 (m, 6H), 2.02 (m, 2H), 1.95 (br s, 2H), 1.67 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 229

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(1-morpholin-4-ylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide

The title compound was prepared by substituting (1-morpholinocyclohexyl)methanamine for (3S,4R)-4-amino-1-benzylpiperidin-3-ol, hydrochloric acid in EXAMPLE 187B. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.19 (s, 1H), 9.08 (s, 1H), 8.60 (d, 1H), 7.81 (dd, 1H), 7.51 (d, 1H), 7.43 (d, 1H), 7.39 (t, 1H), 7.33 (d, 2H), 7.16-7.18 (m, 2H), 7.03 (d, 2H), 6.88 (dd, 1H), 6.65 (dd, 1H), 6.40 (s, 1H), 6.13 (d, 1H), 3.60 (s, 4H), 3.42-3.43 (m, 2H), 3.01 (br s, 4H), 2.72 (br s, 2H), 2.57 (br s, 4H), 2.12-2.16 (m, 7H), 1.94 (br s, 2H), 1.46-1.60 (m, 12H), 1.36-1.39 (m, 2H), 0.92 (s, 6H).

EXAMPLE 230

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[1-(1,3-thiazol-2-ylmethyl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide

EXAMPLE 230A

tert-butyl 1-(thiazol-2-ylmethyl)piperidin-4-ylcarbamate

The title compound was prepared by substituting thiazole-2-carbaldehyde for EXAMPLE 27C and tert-butyl piperidin-4-ylcarbamate for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 230B

1-(thiazol-2-ylmethyl)piperidin-4-amine

The title compound was prepared by substituting EXAMPLE 230A for EXAMPLE 1A in EXAMPLE 1B.

EXAMPLE 230C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[1-(1,3-thiazol-2-ylmethyl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 230B for (3S,4R)-4-amino-1-benzylpiperidin-3-ol, hydrochloric acid in EXAMPLE 187B. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.14 (s, 1H), 8.23 (d, 1H), 7.76-7.79 (m, 2H), 7.65 (s, 1H), 7.53 (d, 1H), 7.38-7.40 (m, 2H), 7.34 (d, 2H), 7.17 (d, 1H), 7.11 (s, 1H), 7.04 (d, 2H), 6.82 (dd, 1H), 6.62 (d, 1H), 6.38 (s, 1H), 6.14 (d, 1H), 4.19 (s, 2H), 3.01 (s, 4H), 2.91-2.96 (m, 2H), 2.72 (s, 2H), 2.12-2.17 (m, 6H), 1.95-1.99 (m, 4H), 1.47-1.51 (m, 2H), 1.36-1.39 (m, 2H), 0.92 (s, 6H).

EXAMPLE 231

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[1-(1,3-thiazol-4-ylmethyl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide

EXAMPLE 231A

tert-butyl 1-(thiazol-4-ylmethyl)piperidin-4-ylcarbamate

The title compound was prepared by substituting thiazole-4-carbaldehyde for EXAMPLE 27C and tert-butyl piperidin-4-ylcarbamate for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 231B

1-(thiazol-4-ylmethyl)piperidin-4-amine

The title compound was prepared by substituting EXAMPLE 231A for EXAMPLE 1A in EXAMPLE 1B.

EXAMPLE 231C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[1-(1,3-thiazol-4-ylmethyl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 231B for (3S,4R)-4-amino-1-benzylpiperidin-3-ol, hydrochloric acid in EXAMPLE 187B. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.11 (s, 1H), 9.06 (s, 1H), 8.21 (d, 1H), 7.98 (s, 1H), 7.77 (dd, 1H), 7.54 (d, 1H), 7.33-7.38 (m, 4H), 7.13 (d, 2H), 7.03-7.07 (m, 3H), 6.79 (dd, 1H), 6.60 (dd, 1H), 6.37 (s, 1H), 6.14 (d, 1H), 4.23 (s, 2H), 2.99 (s, 4H), 2.89-2.94 (m, 2H), 2.71 (s, 2H), 2.12-2.17 (m, 6H), 1.95-1.99 (m, 4H), 1.47-1.51 (m, 2H), 1.36-1.39 (m, 2H), 0.92 (s, 6H).

EXAMPLE 232

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting (4-(aminomethyl)tetrahydro-2H-pyran-4-yl)methanol for (3S,4R)-4-amino-1-benzylpiperidin-3-ol, hydrochloric acid in EXAMPLE 187B. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.17 (s, 1H), 9.10 (t, 1H), 8.59 (d, 1H), 7.81 (dd, 1H), 7.51 (d, 1H), 7.42 (d, 1H), 7.39 (t, 1H), 7.16-7.18 (m, 2H), 7.03 (d, 2H), 6.87 (dd, 1H), 6.65 (d, 1H), 6.39 (s, 1H), 6.14 (d, 1H), 5.22 (t, 1H), 3.51-3.62 (m, 6H), 3.19 (d, 2H), 3.03 (s, 4H), 2.72 (s, 2H), 2.12-2.17 (m, 6H), 1.94 (s, 2H), 1.45-1.49 (m, 4H), 1.36-1.39 (m, 2H), 0.92 (s, 6H).

EXAMPLE 233

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(2-hydroxyethyl)piperazin-1-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide

EXAMPLE 233A

4-(4-(2-hydroxyethyl)piperazin-1-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 2-(4-aminopiperazin-1-yl)ethanol for (tetrahydro-2H-pyran-4-yl)methanamine in EXAMPLE 1F.

EXAMPLE 233B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(2-hydroxyethyl)piperazin-1-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 233A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.15 (s, 1H), 9.17 (m, 1H), 8.53 (d, 1H), 7.83 (dd, 1H), 7.56 (d, 1H), 7.51 (d, 1H), 7.36 (m, 4H), 7.13 (m, 1H), 7.03 (m, 2H), 6.84 (dd, 1H), 6.62 (dd, 1H), 6.38 (m, 1H), 6.12 (m, 1H), 4.57 (m, 1H), 3.54 (m, 2H), 2.95 (m, 10H), 2.71 (s, 2H), 2.57 (m, 2H), 2.15 (m, 6H), 1.94 (s, 2H), 1.38 (t, 2H), 0.93 (s, 6H)

EXAMPLE 234

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(3S)-1-methylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide

EXAMPLE 234A

(S)-tert-butyl 1-methylpyrrolidin-3-ylcarbamate

To a mixture of (S)-tert-butyl 1-methylpyrrolidin-3-ylcarbamate (438 mg) in methanol (10 mL) was added 37% formaldehyde mixture in water (0.53 mL) and sodium borohydride (267 mg). The reaction mixture was stirred overnight at room temperature and then concentrated. The residue was dissolved in chloroform (15 mL), washed with brine and $NaHCO_3$ solution, dried over $MgSO_4$, filtered and concentrated. The title compound was used in the next step without further purification.

EXAMPLE 234B

(S)-1-methylpyrrolidin-3-amine

The title compound was prepared by substituting EXAMPLE 234A for EXAMPLE 1A in EXAMPLE 1B.

EXAMPLE 234C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(3S)-1-methylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 234B for 1-(2-methoxy-ethyl)-piperidin-4-ylamine and EXAMPLE 310B for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 189A. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ

10.98 (s, 1H), 8.38 (d, 1H), 8.16 (d, 1H), 7.64 (dd, 1H), 7.53 (d, 1H), 7.34 (d, 2H), 7.28 (m, 2H), 7.05 (d, 2H), 6.89 (d, 1H), 6.72 (d, 1H), 6.68 (dd, 1H), 6.53 (dd, 1H), 6.29 (t, 1H), 6.15 (d, 1H), 4.14 (br s, 1H), 2.93 (m, 4H), 2.71 (m, 4H), 2.33 (m, 2H), 2.27 (s, 3H), 2.16 (m, 6H), 1.95 (s, 2H), 1.61 (m, 1H), 1.38 (t, 2H), 1.24 (br s, 1H), 0.92 (s, 6H).

EXAMPLE 235

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(3-fluoropropyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide

EXAMPLE 235A

4-(1-(3-fluoropropyl)piperidin-4-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 1-fluoro-3-iodopropane for 1,1,1-trifluoro-4-iodobutane in EXAMPLE 210A.

EXAMPLE 235B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(3-fluoropropyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 235A for EXAMPLE 1F and EXAMPLE 26C for EXAMPLE 1E in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.12 (s, 1H), 10.89 (br s, 1H), 8.48 (d, 1H), 8.152 (d, 1H), 7.79 (dd, 1H), 7.50 (d,1H), 7.34 (m, 4H), 7.03 (m, 4H), 6.83 (dd, 1H), 6.63 (dd, 1H), 6.37 (m, 1H), 6.15 (d, 1H), 3.71 (br s, 1H), 3.01 (m, 4H), 2.92 (m, 2H), 2.72 (m, 2H), 2.56 (m, 1H), 2.30 (m, 2H), 2.16 (m, 6H), 1.95 (m, 5H), 1.83 (m, 1H), 1.68 (m, 2H), 1.38 (m, 2H), 1.24 (br s, 1H), 0.92 (s, 6H).

EXAMPLE 236

4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-(hydroxymethyl)piperazin-1-yl]-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 218E for EXAMPLE 26C in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.17 (s,

2H), 8.62 (s, 1H), 8.58 (s, 1H), 7.78 (d, 1H), 7.52 (d, 1H), 7.39-7.42 (m, 2H), 7.33 (d, 1H), 7.14 (s, 1H), 7.09 (d, 1H), 7.04 (d, 1H), 6.86 (d, 1H), 6.62 (d, 1H), 6.39 (s, 1H), 6.14 (s, 1H), 4.46 (m, 1H), 3.85 (dd, 2H), 3.17-3.25 (m, 8H), 2.76 (br s, 2H), 2.58 (br s. 2H), 1.89-2.01 (m, 6H), 1.80 (br, 2H), 1.29-1.38 (m, 2H), 0.91 (s, 6H).

EXAMPLE 237

N-[(4-{[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-(hydroxymethyl)piperazin-1-yl]-2-(1H-indol-5-yloxy)benzamide

EXAMPLE 237A

4-((4-aminotetrahydro-2H-pyran-4-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 4-(aminomethyl)tetrahydro-2H-pyran-4-amine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 237B

N-[(4-{[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-(hydroxymethyl)piperazin-1-yl]-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 218E for EXAMPLE 26C and EXAMPLE 237A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.46 (s, 1H), 11.19 (s, 1H), 8.16 (d, 1H), 8.51-8.55 (m, 1H), 8.11 (s, 2H), 7.88 (d, 1H), 7.53 (d, 1H), 7.32-7.43 (m, 5H), 7.15 (s, 1H), 7.09 (d, 1H), 6.85 (dd, 1H), 6.68 (s, 1H), 6.40 (s, 1H), 6.21 (s, 1H), 3.81-3.82 (m, 2H), 3.70-3.72 (m, 4H), 3.10 (br s, 2H), 2.02-2.09 (m, 2H), 1.60-1.85 (m, 2H), 1.66-1.73 (m, 2H), 1.35-1.38 (m, 2H), 0.93 (s, 6H).

EXAMPLE 238

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting 1-(aminomethyl)cyclohexanol for (3S,4R)-4-amino-1-benzylpiperidin-3-ol, hydrochloric acid in EXAMPLE 187B. ^{1}H

NMR (500MHz, dimethylsulfoxide-d_6) δ 11.17 (s, 2H), 8.69 (t, 1H), 8.60 (d, 1H), 7.80 (dd, , 1H), 7.51 (d, 1H), 7.39-7.43 (m, 2H), 7.33 (d, 2H), 7.17 (d, 2H), 7.14 (d, 1H), 7.03 (d, 2H), 6.87 (dd, 1H), 6.65 (d, 1H), 6.40 (s, 1H), 6.14 (d, 1H), 4.73 (s, 1H), 3.03 (s, 4H), 2.74 (s, 2H), 2.12-2.18 (m, 6H), 1.94 (s, 2H), 1.54-1.58 (m, 4H), 1.36-1.43 (m, 7H), 0.92 (s, 6H).

EXAMPLE 239

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(2-methoxyethyl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 179A for EXAMPLE 1F and EXAMPLE 55B for EXAMPLE 26C in EXAMPLE 177. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.25 (s, 2H), 8.57 (m, 1H), 8.50 (d, 1H), 7.70 (dd, 1H), 7.52 (d, 1H), 7.34 (d, 2H), 7.28 (t, 1H), 7.17 (d, 1H), 7.05 (m, 3H), 6.97 (t, 1H), 6.71 (dd, 1H), 6.42 (d, 1H), 6.26 (m, 2H), 3.58 (m, 4H), 3.31 (s, 3H), 3.05 (m, 4H), 2.73 (s, 2H), 2.17 (m, 6H), 1.96 (s, 2H), 1.38 (t, 2H), 0.93 (s, 6H)

EXAMPLE 240

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide

EXAMPLE 240A

4-(4-(hydroxymethyl)tetrahydro-2H-pyran-4-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting (4-aminotetrahydro-2H-pyran-4-yl)methanol for (tetrahydropyran-4-yl)methylamine and 4-fluoro-3-nitrobenzenesulfonamide for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 1F.

EXAMPLE 240B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 240A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.14 (s, 2H), 8.63 (d, 1H), 8.50 (s, 1H), 7.92 (s, 1H), 7.79 (dd, 1H), 7.52 (d, 1H), 7.39-7.43 (m, 2H),

7.33-7.34 (m, 3H), 7.18 (s, 1H), 7.03 (d, 2H), 6.87 (dd, 1H), 6.65 (dd, 1H), 6.40 (s, 1H), 6.13 (d, 1H), 5.04 (t, 1H), 3.67-3.72 (m, 4H), 3.56 (t, 2H), 3.02 (s, 4H), 2.72 (br, 2H), 2.12-2.16 (m, 6H), 1.94-2.01 (m, 3H), 1.81-1.85 (m, 2H), 1.36-1.39 (m, 2H), 1.24 (m, 6H), 0.92 (s, 6H).

EXAMPLE 241

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 240A for EXAMPLE 1F and EXAMPLE 55B for EXAMPLE 26 C in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.26 (s, 2H), 8.55 (d, J = 2.14 Hz, 1H), 8.48 (s, 1H), 7.66 (dd, 1H), 7.54 (d, 1H), 7.34 (d, 2H), 7.27-7.29 (m, 2H), 7.19 (d, 2H), 7.03 (d, 2H), 6.99 (t, 1H), 6.70 (dd, 1H), 6.44 (d, 1H), 6.27 (s, 1H), 5.04 (t, 1H), 3.67-3.72 (m, 4H), 3.56 (t, 2H), 3.04 (s, 4H), 2.74 (s, 2H), 2.12-2.17 (m, 6H), 1.95-2.01 (m, 5H), 1.80-1.85 (m, 2H), 1.38 (t, 2H), 1.24 (m, 4H), 0.92 (s, 6H).

EXAMPLE 242

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-hydroxy-1-tetrahydro-2H-pyran-4-ylethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting 2-amino-2-(tetrahydro-2H-pyran-4-yl)ethanol for (3S,4R)-4-amino-1-benzylpiperidin-3-ol, hydrochloric acid in EXAMPLE 187B. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.18 (s, 1H), 8.60 (d, 1H), 8.57 (d, 1H), 7.79 (dd, 1H), 7.52 (d, 1H), 7.43 (d, 1H), 7.40 (t, 1H), 7.33 (d, 2H), 7.23 (d, 1H), 7.19 (d, 1H), 7.03 (d, 2H), 6.88 (dd, 1H), 6.65 (dd, 1H), 6.41 (s, 1H), 6.13 (d, 1H), 5.03 (t, 1H), 3.83-3.87 (m, 2H), 3.56-3.73 (m, 4H), 3.26 (t, 2H), 3.03 (s, 4H), 2.72 (s, 2H), 2.12-2.17 (br s, 4H), 1.58-1.62 (m, 2H), 1.36-1.39 (m, 2H), 0.92 (s, 6H).

EXAMPLE 243

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-({1-[2-(1H-pyrazol-1-yl)ethyl]piperidin-4-yl}amino)phenyl]sulfonyl}benzamide

EXAMPLE 243A

4-(1-(2-(1H-pyrazol-1-yl)ethyl)piperidin-4-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 1-(2-bromoethyl)-1H-pyrazole for 1,1,1-trifluoro-4-iodobutane in EXAMPLE 210A. After concentrating the reaction mixture, the title compound was collected by filtration of the ether slurry.

EXAMPLE 243B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-({1-[2-(1H-pyrazol-1-yl)ethyl]piperidin-4-yl}amino)phenyl]sulfonyl}benzamide

The title compound was prepared by substituting EXAMPLE 243A for EXAMPLE 1F and EXAMPLE 26C for EXAMPLE 1E in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.25 (br s, 1H), 11.14 (s, 1H), 8.55 (d, 1H), 8.22 (d, 1H), 7.74 (m, 2H), 7.50 (d, 1H), 7.40 (m, 3H), 7.33 (d, 2H), 7.10 (m, 1H), 7.03 (d, 2H), 6.83 (dd, 1H), 6.63 (dd, 1H), 6.38 (t, 1H), 6.22 (t, 1H), 6.15 (d, 1H), 4.24 (t, 2H), 3.65 (br s, 1H), 3.02 (m, 4H), 2.78 (m, 6H), 2.27 (m, 2H), 2.16 (m, 6H), 1.94 (m, 3H), 1.60 (m, 2H), 1.38 (t, 2H), 1.23 (br s, 1H), 0.92 (s, 6H).

EXAMPLE 244

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 26 C in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.26 (s, 2H), 8.61 (t, 1H), 8.50 (d, 1H), 7.69 (dd, 1H), 7.28 (t, 1H), 7.18 (d, 2H), 7.07 (d, 1H), 7.04 (d, 2H), 6.97 (t, 1H), 6.71 (dd, 1H), 6.43 (d, 1H), 6.28 (d, 1H), 6.26 (d, 1H), 5.04 (t, 1H), 3.85 (dd, 2H), 3.25-3.31 (m, 6H), 3.05 (s, 4H), 2.74 (s, 2H), 2.14-2.18 (m, 6H), 1.87-1.90 (m, 2H), 1.61-1.63 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 245

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(methylamino)-3-nitrophenyl]sulfonyl}benzamide

EXAMPLE 245A

4-(methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting methanamine for (tetrahydro-2H-pyran-4-yl)methanamine in EXAMPLE 1F.

EXAMPLE 245B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(methylamino)-3-nitrophenyl]sulfonyl}benzamide

The title compound was prepared by substituting EXAMPLE 245A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500 MHz, dimethylsulfoxide-d$_6$) δ 11.12 (m, 2H), 8.54 (m, 2H), 7.76 (m, 1H), 7.51 (d, 1H), 7.35 (m, 4H), 7.06 (m, 3H), 6.85 (m, 2H), 6.63 (d, 1H), 6.37 (m, 1H), 6.15 (d, 1H), 3.01 (m, 4H), 2.96 (d, 3H), 2.71 (s, 2H), 2.15 (m, 6H), 1.94 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H)

EXAMPLE 246

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[4-(methylamino)-3-nitrophenyl]sulfonyl}benzamide

The title compound was prepared by substituting EXAMPLE 245A for EXAMPLE 1F and EXAMPLE 55B for EXAMPLE 26C in EXAMPLE 177. ^{1}H NMR (500 MHz, dimethylsulfoxide-d$_6$) δ 11.32 (br s, 1H), 11.20 (br s, 1H), 8.54 (br s, 1H), 8.46 (s, 1H), 7.70 (dd, 1H), 7.53 (d, 1H), 7.34 (d, 2H), 7.26 (m, 1H), 7.14 (d, 1H), 7.04 (d, 2H), 6.94 (t, 1H), 6.87 (m, 1H), 6.67 (m, 1H), 6.37 (m, 1H), 6.25 (m, 2H), 3.02 (m, 4H), 2.97 (d, 3H), 2.72 (s, 2H), 2.16 (m, 6H), 1.94 (s, 2H), 1.38 (t, 2H), 0.93 (s, 6H).

EXAMPLE 247

4-{4-[1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 175E for EXAMPLE 1E and EXAMPLE 7A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (500 MHz, PYRIDINE-d$_5$) δ ppm 12.45 (s, 1H), 9.24 (d, 1H), 8.96 (t, 1H), 8.26 (dd, 1H), 8.16 (d, 1H), 7.65 (d, 1H), 7.46 (m, 5H), 7.35 (t, 1H), 7.30 (d, 2H), 7.24 (d, 1H), 7.15 (t, 1H), 6.86 (d, 1H), 6.79 (d, 1H), 6.74 (m, 2H), 6.61 (d, 1H), 3.78 (t, 4H), 3.41 (q, 1H), 3.31 (m, 2H), 2.94 (m, 4H), 2.34 (m, 6H), 2.24 (m, 2H), 2.10 (m, 2H), 1.72 (m, 2H), 1.15 (d, 3H).

EXAMPLE 248

4-(4-{[2-(4-chlorophenyl)-5-hydroxycyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 224D for EXAMPLE 1E in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.17 (s, 1H), 8.60 (m, 1H), 7.80 (dd, 1H), 7.52 (d, 1H), 7.38 (m, 4H), 7.11 (m, 4H), 6.87 (dd, 1H), 6.65 (dd, 1H), 6.40 (s, 1H), 6.13 (d, 1H), 4.59 (d, 1H), 3.85 (m, 2H), 3.28 (m, 6H), 3.03 (m, 2H), 2.72 (m, 2H), 2.18 (m, 3H), 1.87 (m, 3H), 1.53 (m, 5H), 1.26 (m, 7H).

EXAMPLE 249

4-(4-{[2-(4-chlorophenyl)-5-morpholin-4-ylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 249A

8-chloro-1,4-dioxaspiro[4.5]dec-7-ene-7-carbaldehyde

The title compound was prepared by substituting 1,4-dioxaspiro[4.5]decan-8-one for 4-(tert-butyldimethylsilyloxy)cyclohexanone in EXAMPLE 224A.

EXAMPLE 249B

8-(4-chlorophenyl)-1,4-dioxaspiro[4.5]dec-7-ene-7-carbaldehyde

The title compound was prepared by substituting EXAMPLE 249A for EXAMPLE 224A in EXAMPLE 224B.

EXAMPLE 249C

methyl 2-(1H-indol-5-yloxy)-4-(4-((8-(4-chlorophenyl)-1,4-dioxaspiro[4.5]dec-7-en-7-yl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 249B for EXAMPLE 224B in EXAMPLE 224C.

EXAMPLE 249D

2-(1H-indol-5-yloxy)-4-(4-((8-(4-chlorophenyl)-1,4-dioxaspiro[4.5]dec-7-en-7-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 249C for EXAMPLE 224C in EXAMPLE 224D.

EXAMPLE 249E

2-(1H-indol-5-yloxy)-4-(4-((8-(4-chlorophenyl)-1,4-dioxaspiro[4.5]dec-7-en-7-yl)methyl)piperazin-1-yl)-N-(3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)phenylsulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 249D for EXAMPLE 1E in EXAMPLE 1G.

EXAMPLE 249F

2-(1H-indol-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5-oxocyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)phenylsulfonyl)benzamide

A mixture of EXAMPLE 249E (20 mg) and pyridinium p-toluenesulfonate (16.8 mg) in acetone/H_2O (1:1, 3 mL) was heated in a microwave to 135°C for 8 minutes. The mixture was diluted with dichloromethane (100 mL), washed with water and brine, and dried over Na_2SO_4. Filtration and evaporation of solvent gave the product.

EXAMPLE 249G

4-(4-{[2-(4-chlorophenyl)-5-morpholin-4-ylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

To a mixture of EXAMPLE 249F (120 mg) in dichloromethane (2 mL) and methanol (0.5 mL) was added morpholine (37mg) and 2-picoline borane complex (15.04 mg). The mixture was stirred overnight. The mixture was then diluted with dichloromethane (200 mL) and washed with aqueous $NaHCO_3$, water, and brine, and dried over Na_2SO_4. The residue, after evaporation of solvent, was dissolved in dichloromethane and chromatographed with 0-10% 7N NH_3 in 5% methanol in dichloromethane to give the title compound. ^1H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.15 (s, 1H), 8.58 (m, 2H), 7.79 (dd, 1H), 7.53 (m, 1H), 7.35 (m, 4H), 7.17 (m, 1H), 7.07 (m, 2H), 6.85 (dd, 1H), 6.64 (dd, 1H), 6.39 (s, 1H), 6.13 (d,

1H), 3.84 (m, 2H), 3.58 (m, 5H), 3.01 (m, 5H), 2.63 (m, 6H), 2.10 (m, 14H), 1.61 (m, 3H), 1.26 (m, 3H).

EXAMPLE 250

N-[(4-{[(1-aminocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting 1-(aminomethyl)cyclohexanamine, 2hydrochloric acid for (3S,4R)-4-amino-1-benzylpiperidin-3-ol, hydrochloric acid in EXAMPLE 187B. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.04 (s, 1H), 8.47 (d, 1H), 8.39 (s, 1H), 7.79 (dd, 1H), 7.55 (d, 1H), 7.31-7.34 (m, 4H), 6.99-7.08 (m, 4H), 6.73 (dd, 1H), 6.65 (dd, 1H), 6.33 (s, 1H), 6.12 (d, 1H), 3.55 (d, 2H), 2.94 (s, 4H), 2.71 (s, 2H), 2.14-2.17 (m, 6H), 1.95 (s, 2H), 1.50-1.64 (m, 8H), 1.36-1.39 (m, 2H), 0.92 (s, 6H).

EXAMPLE 251

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[2-(2-oxopyrrolidin-1-yl)ethyl]amino}phenyl)sulfonyl]benzamide

The title compound was prepared by substituting 1-(2-aminoethyl)pyrrolidin-2-one for (3S,4R)-4-amino-1-benzylpiperidin-3-ol, hydrochloric acid in EXAMPLE 187B. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.17 (s, 1H), 8.58-8.60 (m, 2H), 7.84 (dd, 1H), 7.51 (d, 1H), 7.39-7.32 (m, 2H), 7.33 (d, 2H), 7.18 (d, 1H), 7.12 (d, 1H), 7.03 (d, 2H), 6.87 (dd, 1H), 6.65 (dd, 1H), 6.40 (s, 1H), 6.17 (d, 1H), 3.53-3.56 (m, 2H), 3.45 (t, 2H), 3.39 (t, 2H), 3.04 (s, 4H), 2.74 (s, 2H), 2.11-2.18 (m, 8H), 1.94 (s, 2H), 1.83-1.90 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 252

4-{4-[1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 252A

methyl 2-(1H-indol-5-yloxy)-4-(4-(1-(4'-chlorobiphenyl-2-yl)ethyl)piperazin-1-yl)benzoate

The title compound was prepared as described in EXAMPLE 175D by replacing ethyl 2-(1H-indol-4-yloxy)-4-fluorobenzoate with EXAMPLE 26A.

EXAMPLE 252B

2-(1H-indol-5-yloxy)-4-(4-(1-(4'-chlorobiphenyl-2-yl)ethyl)piperazin-1-yl)benzoic acid

The title compound was prepared as described in EXAMPLE 175E by replacing EXAMPLE 175D with v 252A.

EXAMPLE 252C

4-{4-[1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared as described in EXAMPLE 175F by replacing EXAMPLE 175E with EXAMPLE 252B. ^{1}H NMR (500 MHz, dimethylsulfoxide-d $_6$) δ 11.20 (s, 1H), 11.16 (s, 1H), 8.62 (t, 1H), 8.58 (d, 1H), 7.79 (dd, 1H), 7.48 - 7.54 (m, 2H), 7.45 (d, 2H), 7.35 - 7.41 (m, 3H), 7.25 - 7.29 (m, 3H), 7.15 (d, 1H), 7.08 - 7.13 (m, 2H), 6.86 (dd, 1H), 6.63 (dd, 1H), 6.38 (s, 1H), 6.13 (d, 1H), 3.85 (dd, 2H), 3.22 - 3.32 (m, 4H), 3.00 (s, 4H), 2.33 (s, 2H), 2.18 (s, 2H), 1.84 - 1.95 (m, 1H), 1.56 - 1.66 (m, 2H), 1.21 - 1.31 (m, 3H), 1.16 (d, 3H).

EXAMPLE 253

4-(4-{1-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]ethyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 253A

1-(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)ethanol

To a mixture of EXAMPLE 218A (3.52 g) in tetrahydrofuran (30 ml) was slowly added methylmagnesium chloride (3 M in tetrahydrofuran, 7.08 ml) at -78°C. After the addition was completed, the reaction mixture was stirred at 0°C for 30 minutes and ice-water was added. The resulting mixture was extracted with dichloromethane and the organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography, eluting with 0-100% dichloromethane in hexane to provide the title compound.

EXAMPLE 253B

1-(2-(4-chlorophenyl)-4, 4-dimethylcyclohex-1-enyl)ethanone

To a mixture of EXAMPLE 253A (1.18 g) in dichloromethane (20 ml) was slowly added Dess-Martin Periodinane (2.457 g). The reaction mixture was stirred at room temperature for 3 hours and diluted with ether. The resulting mixture was washed with aqueous NaOH and water. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography, eluting with 0-100% dichloromethane in hexane to provide the title compound.

EXAMPLE 253C

tert-butyl 4-(1-(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)ethyl)piperazine-1-carboxylate

EXAMPLE 253B (2.06 g) and tert-butyl piperazine-1-carboxylate (2.92 g) was treated with titanium(IV) isopropoxide (4.59 ml) at ambient temperature for 24 hours. Sodium cyanoborohydride (0.493 g) in methanol (10 ml) was added. The reaction mixture was stirred overnight and aqueous NaOH was added. The resulting mixture was diluted with ethyl acetate (300 ml). The precipitate was filtered off and washed with ethyl acetate. The organic layer was separated and washed with brine, dried over Na_2SO_4, filtered, and concentarted. The residue was dissolved in dichloromethane and loaded onto a silica gel column, eluted with 0-25% ethyl acetate in dichloromethane to provide the title compound.

EXAMPLE 253D

1-(1-(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)ethyl)piperazine

The title compound was prepared as described in EXAMPLE 175C by replacing EXAMPLE 175B with EXAMPLE 253C.

EXAMPLE 253E

ethyl 2-(1H-indol-5-yloxy)-4-(4-(1-(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)ethyl)piperazin-1-yl)benzoate

The title compound was prepared as described in EXAMPLE 175D by replacing ethyl 2-(1H-indol-4-yloxy)-4-fluorobenzoate and EXAMPLE 175C with EXAMPLE 26A and EXAMPLE 253D, respectively.

EXAMPLE 253F

2-(1H-indol-5-yloxy)-4-(4-(1-(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)ethyl)piperazin-1-yl)benzoic acid

The title compound was prepared as described in EXAMPLE 175E by replacing EXAMPLE 175D with EXAMPLE 253E.

EXAMPLE 253G

4-(4-{1-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]ethyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared as described in EXAMPLE 177 by replacing EXAMPLE 26C with EXAMPLE 253F. ^{1}H NMR (500 MHz, dimethylsulfoxide-d$_6$) δ 11.18 (s, 2H), 8.62 (t, 1H), 8.59 (d, 1H), 7.81 (dd, 1H), 7.52 (d, 1H), 7.38 - 7.44 (m, 2H), 7.34 (d, 2H), 7.17 (d, 1H), 7.11 (d, 1H), 7.01 (d, 2H), 6.87 (dd, 1H), 6.65 (dd, 1H), 6.40 (t, 1H), 6.13 (d, 1H), 3.85 (dd, 2H), 3.22 - 3.31 (m, 4H), 3.02 (s, 4H), 2.57 - 2.73 (m, 1H), 2.23 (s, 4H), 1.78 - 2.15 (m, 5H), 1.57 - 1.65 (m, 2H), 1.32 - 1.42 (m, 2H), 1.19 - 1.31 (m, 2H), 1.01 (d, 3H), 0.91 (d, 6H).

EXAMPLE 254

4-(4-{1-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]ethyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared as described in EXAMPLE 175F by replacing EXAMPLE 175E and EXAMPLE 1F with EXAMPLE 253F and EXAMPLE 174A. ^{1}H NMR (500 MHz, dimethylsulfoxide-d$_6$) δ 11.15 (s, 1H), 9.19 (s, 1H), 8.54 (d, 1H), 7.85 (dd, 1H), 7.57 (d, 1H), 7.52 (d, 1H), 7.37 - 7.41 (m, 2H), 7.34 (d, 2H), 7.14 (d, 1H), 7.01 (d, 2H), 6.84 (dd, 1H), 6.62 (dd, 1H), 6.39 (s, 1H), 6.12 (d, 1H), 2.81 - 3.04 (m, 10H), 2.58 - 2.67 (m, 1H), 2.29 - 2.45 (m, 5H), 2.15 - 2.28 (m, 4H), 1.92 - 2.13 (m, 3H), 1.82 (d, 1H), 1.29 - 1.41 (m, 2H), 1.00 (d, 3H), 0.91 (d, 6H).

EXAMPLE 255

4-{4-[(1R)-1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was obtained by the separation of the racemic mixture of EXAMPLE 175F on a chiral HPLC. ^{1}H NMR (500 MHz, dimethysulfoxide-d_6) δ 11.31 (1H, s), 11.25 (1H, s), 8.62 (1H, t), 8.50 (1H, d), 7.68 (1H, dd), 7.53 (2H, d), 7.46 (2H, d), 7.37 (1H, t), 7.24 - 7.31 (4H, m), 7.17 (1H, d), 7.12 (1H, dd), 7.07 (1H, d), 6.96 (1H, t), 6.69 (1H, dd), 6.42 (1H, d), 6.26 (2H, s), 3.85 (2H, dd), 3.21 - 3.33 (5H, m), 3.01 (4H, s), 2.29 - 2.39 (2H, m), 2.15 - 2.22 (2H, m), 1.83 - 1.94 (1H, m), 1.57 - 1.68 (2H, m), 1.22 - 1.31 (2H, m), 1.17 (3H, d).

EXAMPLE 256

4-{4-[(1S)-1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was obtained by the separation of the racemic mixture of EXAMPLE 175F on a chiral HPLC. ^{1}H NMR (500 MHz, dimethysulfoxide-d_6) δ 11.31 (1H, s), 11.25 (1H, s), 8.62 (1H, t), 8.50 (1H, d), 7.68 (1H, dd), 7.53 (2H, d), 7.46 (2H, d), 7.37 (1H, t), 7.24 - 7.31 (4H, m), 7.17 (1H, d), 7.12 (1H, dd), 7.07 (1H, d), 6.96 (1H, t), 6.69 (1H, dd), 6.42 (1H, d), 6.26 (2H, s), 3.85 (2H, dd), 3.21 - 3.33 (5H, m), 3.01 (4H, s), 2.29 - 2.39 (2H, m), 2.15 - 2.22 (2H, m), 1.83 - 1.94 (1H, m), 1.57 - 1.68 (2H, m), 1.22 - 1.31 (2H, m), 1.17 (3H, d).

EXAMPLE 257

4-(4-{1-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]ethyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared as described in EXAMPLE 175F by replacing EXAMPLE 175E and EXAMPLE 1F with EXAMPLE 253F and EXAMPLE 7A. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 8.79 (t, 1H), 8.57 (d, 1H), 7.80 (dd, 1H), 7.51 (d, 1H), 7.37 - 7.44 (m, 2H), 7.34 (d, 2H), 7.15 (d, 1H), 7.06 (d, 1H), 7.01 (d, 2H), 6.85 (dd, 1H), 6.63 (dd, 1H), 6.39 (s, 1H), 6.13 (d, 1H), 3.60 (t, 4H), 3.43 (q, 2H), 3.01 (s, 4H), 2.63 (d, 1H), 2.33 - 2.47 (m, 6H), 2.22 (d, 4H), 1.94 - 2.15 (m, 3H), 1.75 - 1.86 (m, 3H), 1.32 - 1.40 (m, 2H), 1.00 (d, 3H), 0.91 (s, 3H), 0.90 (s, 3H).

EXAMPLE 258

4-(4-{1-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]ethyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared as described in EXAMPLE 175F by replacing EXAMPLE 175E and EXAMPLE 1F with EXAMPLE 253F and EXAMPLE 173C. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.12 (s, 1H), 8.53 (d, 1H), 8.19 (d, 1H), 7.79 (dd, 1H), 7.52 (d, 1H), 7.32 - 7.40 (m, 4H), 6.99 - 7.12 (m, 4H), 6.81 (dd, 1H), 6.60 (dd, 1H), 6.37 (s, 1H), 6.13 (d, 1H), 3.92 (dd, 2H), 3.72 (s, 1H), 3.26 - 3.31 (m, 2H), 2.98 (s, 6H), 2.77 (s, 1H), 2.54 - 2.66 (m, 3H), 2.15 - 2.30 (m, 4H), 1.94 - 2.14 (m, 5H), 1.73 - 1.87 (m, 3H), 1.57 - 1.68 (m, 2H), 1.44 - 1.54 (m, 2H), 1.31 - 1.40 (m, 2H), 1.00 (d, 3H), 0.91 (d, 2H).

EXAMPLE 259

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

EXAMPLE 259A

4-(cyclohexylmethylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting cyclohexylmethylamine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 259B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 259A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.10 (s, 1H), 8.53 (m, 1H), 8.52 (d, 1H), 7.72 (dd, 1H), 7.44 (d, 1H), 7.32, (d, 1H), 7.31 (dd, 1H), 7.26 (d, 2H), 7.08 (d, 1H), 6.99 (d, 1H), 6.96 (d, 2H), 6.80 (dd, 1H), 6.58 (dd, 1H), 6.32 (s, 1H), 6.07 (d, 1H), 3.18 (t, 2H), 2.96 (br m, 4H), 2.65 (d, 2H), 2.06 (br m, 6H), 1.87 (s, 2H), 1.63 (m, 4H), 1.56 (m, 2H), 1.30 (t, 2H), 1.11 (m, 2H), 0.91 (m, 3H), 0.85 (s, 6H).

EXAMPLE 260

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(morpholin-4-ylamino)-3-nitrophenyl]sulfonyl}benzamide

EXAMPLE 260A

4-(morpholinoamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting morpholin-4-amine for 1-(2-methoxy-ethyl)-piperidin-4-ylamine in EXAMPLE 189A.

EXAMPLE 260B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(morpholin-4-ylamino)-3-nitrophenyl]sulfonyl}benzamide

The title compound was prepared by substituting EXAMPLE 26C for EXAMPLE 1E and EXAMPLE 260A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (500 MHz, pyridine-d5) δ 9.28 (s, 1H), 9.25 (d, 1H), 8.39 (dd, 1H), 8.18 (d, 1H), 7.66 (d, 1H), 7.52 - 7.56 (m, 2H), 7.40 - 7.46 (m, 3H), 7.09 (dd, 1H), 7.06 (d, 2H), 6.73 (dd, 1H), 6.60 (s, 1H), 6.54 (d, 1H), 3.87 (s, 2H), 3.74 (d, 2H), 3.00 - 3.08 (m, 4H), 2.89 (d, 4H), 2.76 (s, 2H), 2.24 (t, 2H), 2.08 - 2.15 (m, 4H), 1.97 (s, 2H), 1.38 (t, 2H), 0.93 (s, 6H).

EXAMPLE 261

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-3-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared as described in EXAMPLE 175F by replacing EXAMPLE 175E and EXAMPLE 1F with EXAMPLE 26C and EXAMPLE 180A, respectively. ^{1}H NMR (500 MHz, dimethylsulfoxide-d$_6$) δ 11.17 (s, 2H), 8.45 - 8.70 (m, 2H), 7.80 (dd, 1H), 7.51 (d, 1H), 7.38 - 7.42 (m, 2H), 7.33 (d, 2H), 7.16 (d, 1H), 7.07 (d, 1H), 7.03 (d, 2H), 6.86 (dd, 1H), 6.65 (dd, 1H), 6.39 (s, 1H), 6.14 (d, 1H), 3.79 (dd, 1H), 3.68 - 3.75 (m, 1H), 3.23 - 3.38 (m, 3H), 3.18 (dd, 1H), 3.03 (s, 4H), 2.72 (s, 2H), 2.07 - 2.21 (m, 6H), 1.79 - 1.96 (m, 4H), 1.57 - 1.64 (m, 1H), 1.41 - 1.51 (m, 1H), 1.37 (t, 2H), 1.22 - 1.33 (m, 1H), 0.92 (s, 6H).

EXAMPLE 262

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[4-(morpholin-4-ylamino)-3-nitrophenyl]sulfonyl}benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 1E and EXAMPLE 260A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (500 MHz, pyridine-d5) δ 12.45 (s, 1H), 9.26 (s, 1H), 9.17 (d, 1H), 8.27 (dd, 1H), 8.17 (d, 1H), 7.61 (d, 1H), 7.48 (t, 1H), 7.45 (d, 2H), 7.39 (d, 1H), 7.05 - 7.13 (m, 3H), 6.71 - 6.81 (m, 3H), 6.67 (d, *J*=2.1 Hz, 1H), 3.87 (s, 2H), 3.61 - 3.78 (m, 2H), 2.99 - 3.08 (m, 4H), 2.89 (d, 4H), 2.76 (s, 2H), 2.25 (t, 2H), 2.08 - 2.16 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

EXAMPLE 263

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylamino)phenyl]sulfonyl}benzamide

The title compound was prepared by substituting tetrahydro-2H-pyran-4-amine, hydrochloric acid for (3S,4R)-4-amino-1-benzylpiperidin-3-ol, hydrochloric acid in EXAMPLE 187B. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.15 (s, 2H), 8.57 (d, 1H), 8.24 (d, 1H), 7.78 (dd, 1H), 7.49 (d, 1H), 7.37-7.40 (m, 3H), 7.32 (d, 2H), 7.12-7.16 (m, 2H), 7.22 (d, 2H), 6.84 (dd, 1H), 6.64 (dd, 1H), 6.37 (s, 1H), 6.13 (d, 1H), 3.85-3.87 (m, 2H), 3.45 (t, 2H), 3.02 (s, 4H), 2.71 (s, 2H), 2.11-2.16 (m, 7H), 1.87-1.93 (m 4H), 1.58-1.62 (m, 2H), 1.36 (t, 2H), 0.90 (s, 6H).

EXAMPLE 264

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(3-methyloxetan-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide

The title compound was prepared by substituting (3-methyloxetan-3-yl)methanamine for (3S,4R)-4-amino-1-benzylpiperidin-3-ol, hydrochloric acid in EXAMPLE 187B. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.14 (s, 2H), 8.67 (t, 1H), 8.58 (d, 1H), 7.81 (dd, 1H), 7.49 (d, 1H), 7.36-7.39 (m, 2H), 7.32 (d, 2H), 7.12-7.14 (m, 2H), 7.02 (d, 2H), 6.84 (dd, 1H), 6.63 (dd, 1H), 6.37 (s, 1H), 6.13 (d, 1H), 4.44 (d, 2H), 4.30 (d, 2H), 3.55 (d, 2H), 3.01 (s, 4H), 2.70 (s, 2H), 2.11-2.15 (m, 7H), 1.93 (s 3H), 1.36 (t, 2H), 0.90 (s, 6H).

EXAMPLE 265

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methoxycyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting 4-methoxycyclohexanamine for (3S,4R)-4-amino-1-benzylpiperidin-3-ol, hydrochloric acid in EXAMPLE 187B. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.16 (s, 2H), 8.83 (d, 1H), 8.30 (d, 1H), 7.79 (dd, 1H), 7.50 (d, 1H), 7.37-7.41 (m, 2H), 7.33 (d, 2H), 7.10-7.14 (m, 2H), 7.03 (d, 2H), 6.85 (dd, 1H), 6.65 (dd, 1H), 6.39 (s, 1H), 6.14 (d, 1H), 3.24-3.25 (m, 5H), 3.03 (s, 4H), 2.72 (s, 2H), 2.14-2.17 (m, 8H), 1.92 (m 3H), 1.63-1.65 (m,2 H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 266

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(1,1-dioxidothiomorpholin-4-yl)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 187A for 4-chloro-3-nitrobenzene sulfonamide and 4-(3-aminopropyl)thiomorpholine-1,1-dioxide for 1-(2-methoxy-ethyl)-piperidin-4-ylamine in EXAMPLE 189A. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.16 (s, 1H), 8.86 (t, 1H), 8.58 (d, 1H), 7.82 (dd, 1H), 7.50 (t, 1H), 7.40 (m, 2H), 7.33 (d, 2H), 7.15 (m, 1H), 7.04 (m, 3H), 6.85 (dd, 1H), 6.64 (m, 1H), 6.38 (m, 1H), 6.13 (m, 1H), 3.43 (m, 2H), 3.12 (m, 4H), 3.01 (m, 4H), 2.89 (m, 4H), 2.72 (m, 2H), 2.57 (t, 2H), 2.16 (m, 6H), 1.94 (m, 2H), 1.78 (t, 2H), 1.37 (t, 2H), 0.93 (s, 6H).

EXAMPLE 267

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[2-(2-oxopiperidin-1-yl)ethyl]amino}phenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 187A for 4-chloro-3-nitrobenzene sulfonamide and 1-(2-aminoethyl)piperidine-2-one for 1-(2-methoxy-ethyl)-piperidin-4-ylamine in EXAMPLE 189A. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.12 (s, 1H), 8.61 (m, 1H), 8.52 (m, 1H), 7.78 (d, 1H), 7.51 (d, 1H), 7.37 (m, 2H), 7.33 (d, 2H), 7.10 (m, 2H), 7.04 (d, 2H), 6.81 (m, 1H), 6.61 (d, 1H), 6.37 (s, 1H), 6.13 (d, 1H), 3.52 (m, 4H), 3.28 (t, 2H), 3.00 (m, 4H), 2.71 (m, 2H), 2.17 (m, 8H), 1.94 (m, 2H), 1.63 (m, 4H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 268

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[2-(2-oxoimidazolidin-1-yl)ethyl]amino}phenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 187A for 4-chloro-3-nitrobenzene sulfonamide and 1-(2-aminoethyl)-2-imidazolidone for 1-(2-methoxy-ethyl)-piperidin-4-ylamine in EXAMPLE 189A. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.17 (s, 1H), 8.60 (t, 1H), 8.56 (d, 1H), 7.81 (dd, 1H), 7.50 (m, 1H), 7.39 (m, 2H), 7.33 (d, 2H), 7.15 (m, 1H), 7.08 (d, 1H), 7.02 (d, 2H), 6.85 (dd, 1H), 6.65 (m, 1H), 6.39 (m, 2H), 6.15 (m, 1H), 3.51 (m, 2H), 3.39 (t, 2H), 3.30 (m, 2H), 3.21 (t, 2H), 3.03 (m, 4H), 2.72 (m, 2H), 2.14 (m, 6H), 1.93 (m, 2H), 1.37 (t, 2H), 0.92 (s, 6H).

EXAMPLE 269

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(2-pyridin-4-ylethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting 4-(2-aminoethyl)pyridine for 1-(2-methoxyethyl)-piperidin-4-ylamine and EXAMPLE 187A for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 189A, except the material was purified by preparative HPLC on a Phenomenex Luna C8(2) 5 um 100Å AXIA column (30mm × 75mm). A gradient of acetonitrile and 0.1% trifluoroacetic acid in water was used, at a flow rate of 50 mL/minute (0-0.5 minutes 10% acetonitrile, 0.5-6.0 minutes linear gradient 10-100% acetonitrile, 6.0-7.0 minutes 100% acetonitrile, 7.0-8.0 minutes linear gradient 100-10% acetonitrile) to isolate the title compound as the bis trifluoroacetic acid salt. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.45 (br s, 1H), 11.18 (br s, 1H), 8.77 (d, 2H), 8.61 (t, 1H), 8.60 (d, 1H), 7.86 (dd, 1H), 7.84 (d, 2H), 7.54 (d, 1H), 7.43-7.37 (m, 4H), 7.22 (d, 1H), 7.15 (d, 1H), 7.08 (d, 2H), 6.85 (dd, 1H), 6.70 (dd, 1H), 6.38 (t, 1H), 6.22 (d, 1H), 3.77 (q, 2H), 3.68-3.54 (m, 4H), 3.27 (m, 2H), 3.16 (t, 2H), 3.00 (m, 2H), 2.74 (m, 2H), 2.18 (m, 2H), 2.01 (d, 2H), 1.45 (t, 2H), 0.94 (s, 6H).

EXAMPLE 270

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-morpholin-4-yl-3-nitrophenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 187A for 4-chloro-3-nitrobenzenesulfonamide and morpholine for 1-(2-methoxy-ethyl)-piperidin-4-ylamine in EXAMPLE 189A, except the crude material was purified by preparative HPLC using a C18 column, 250 x 50 mm, 10μ, and eluting with a gradient of 20-100% CH_3CN vs. 0.1% trifluoroacetic acid in water, giving the title compound as a trifluoroacetate salt. The salt was dissolved in dichloromethane (6 mL) and was washed with 50% aqueous $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to give the title compound. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.17 (s, 1H), 8.31 (d, 1H), 7.87 (dd, 1H), 7.53 (d, 1H), 7.41 (m, 2H), 7.33 (d, 2H), 7.24 (d, 1H), 7.16 (s, 1H), 7.02 (d, 2H), 6.85 (dd, 1H), 6.64 (dd, 1H), 6.40 (s, 1H), 6.14 (s, 1H), 3.69 (t, 4H), 3.13 (t, 4H), 3.03 (br s, 4H), 2.75 (s, 2H), 2.19 (br s, 4H), 2.14 (br t, 2H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 271

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(4-methoxypiperidin-1-yl)-3-nitrophenyl]sulfonyl}benzamide

The title compound was prepared by substituting EXAMPLE 187A for 4-chloro-3-nitrobenzenesulfonamide and 4-methoxy-piperidine for 1-(2-methoxy-ethyl)-piperidin-4-ylamine in EXAMPLE 189A, except the crude material was purified by preparative HPLC using a C18 column, 250 x 50 mm, 10μ, and eluting with a gradient of 20-100% CH_3CN vs. 0.1% trifluoroacetic acid in water, giving the product as a trifluoroacetate salt. The salt was dissolved in dichloromethane (6 mL) and washed with 50% aqueous $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to give the title compound. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.17 (s, 1H), 8.28 (d, 1H), 7.81 (dd, 1H), 7.53 (d, 1H), 7.41 (m, 2H), 7.33 (d, 2H), 7.22 (d, 1H), 7.16 (s, 1H), 7.04 (d, 2H), 6.86 (dd, 1H), 6.64 (dd, 1H), 6.40 (s, 1H), 6.14 (s, 1H), 3.42 (m, 1H), 3.27 (s, 3H), 3.25 (m, 2H), 3.00 (m, 6H), 2.73 (s, 2H), 2.18 (br s, 4H), 2.13 (br t, 2H), 1.94 (s, 2H), 1.91 (m, 2H), 1.56 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 272

4-(4-{[2-(4-chlorophenyl)-5-pyrrolidin-1-ylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting pyrrolidine for morpholine in EXAMPLE 249G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.04 (s, 1H), 8.44 (d, 1H), 8.42 (m, 1H), 7.70 (dd, 1H), 7.55 (d, 1H), 7.37 (d, 2H), 7.32 (m, 2H), 7.09 (d, 2H), 7.00 (d, 1H), 6.89 (d, 1H), 6.76 (d, 1H), 6.54 (d, 1H), 6.32 (d, 1H), 6.13 (d, 1H), 3.83 (m, 3H), 3.06 (m, 15H), 2.23 (m, 6H), 1.84 (m, 6H), 1.62 (m, 4H), 1.24 (m, 3H).

EXAMPLE 273

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[2-(3-oxopiperazin-1-yl)ethyl]amino}phenyl)sulfonyl]benzamide

EXAMPLE 273A

3-nitro-4-[2-(3-oxo-piperazin-1-yl)-ethylamino]-benzenesulfonamide

4-(2-Amino-ethyl)-piperazin-2-one (5.51 g) and triethylamine (9.07 mL, 6.59 g) were added to 1,4-dioxane (100 mL), N,N-dimethylacetamide (20 mL), and water (10 mL) and mixed until dissolved. 4-Chloro-3-nitrobenzenesulfonamide (7.00 g) was added, and the mixture was heated to 90°C for 16 hours. The mixture was cooled and the solvent was removed under vacuum. The crude material was purified by recrystallization from 20% methanol in dichloromethane with subsequent washing of the recrystallized solid with 10% methanol in dichloromethane followed by washing with 100% dichloromethane.

EXAMPLE 273B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[2-(3-oxopiperazin-1-yl)ethyl]amino}phenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 26C for EXAMPLE 1E and EXAMPLE 273A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.15 (br s, 1H), 8.73 (t, 1H), 8.58 (d, 1H), 7.82 (dd, 1H), 7.76 (br s, 1H), 7.51 (d, 1H), 7.42-7.38 (m, 2H), 7.34 (d, 2H), 7.16 (d, 1H), 7.06-7.01 (m, 3H), 6.85 (dd, 1H), 6.65 (dd, 1H), 6.38 (t, 1H), 6.15 (d, 1H), 3.48 (q, 2H), 3.17 (m, 2H), 3.04 (m, 6H), 2.72 (br s, 2H), 2.70-2.62 (m, 2H), 2.16 (m, 8H), 1.95 (br s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 274

4-[4-({4'-chloro-4-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 125D for EXAMPLE 26C and EXAMPLE 174A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.62 (s, 1H), 11.33 (s, 1H), 9.55 (d, 1H), 8.49 (d, 1H), 7.74 (dd, 1H), 7.55 (m, 5H), 7.35 (m, 2H), 7.30 (m, 1H), 7.19 (dd, 2H), 6.96 (m, 2H), 6.73 (dd, 1H), 6.40 (m, 1H), 6.33 (m, 1H), 6.24 (s, 1H), 4.37 (m, 2H), 3.53 (m, 8H), 3.30 (m, 8H), 3.23 (m, 4H), 2.90 (s, 6H), 2.84 (s, 3H).

EXAMPLE 275

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1,1-dioxidotetrahydrothien-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 187A for 4-chloro-3-nitrobenzene sulfonamide and (1,1-dioxidotetrahydrothien-3-yl)methylamine hydrochloride for 1-(2-methoxy-ethyl)-piperidin-4-ylamine in EXAMPLE 189A.^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.17 (s, 1H), 8.72 (t, 1H), 8.59 (d, 1H), 7.82 (dd, 1H), 7.51 (d, 1H), 7.40 (m, 2H), 7.33 (d, 2H), 7.16 (m, 2H), 7.03 (d, 2H), 6.86 (dd, 1H), 6.65 (dd, 1H), 6.40 (m, 1H), 6.14 (d, 1H), 3.55 (t, 2H), 3.28 (m, 1H), 3.23 (m, 1H), 3.05 (m, 5H), 2.91 (m, 1H), 2.74 (m, 3H), 2.27 (m, 1H), 2.15 (m, 6H), 1.95 (m, 2H), 1.86 (m, 1H), 1.38 (t, 2H), 0.91 (s, 6H).

EXAMPLE 276

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 187A for 4-chloro-3-nitrobenzene sulfonamide and 1,1-dioxidotetrahydrothiene-3ylamine for 1-(2-methoxy-ethyl)-piperidin-4-ylamine in EXAMPLE 189A. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.20 (bs, 1H), 11.15 (s, 1H), 8.59 (d, 1H), 8.50 (d, 1H), 7.86 (dd, 1H), 7.50 (d, 1H), 7.39 (m, 2H), 7.33 (d, 2H), 7.19 (d, 1H), 7.14 (m, 1H), 7.03 (d, 2H), 6.85

(dd, 1H), 6.65 (dd, 1H), 6.39 (m, 1H), 6.15 (d, 1H), 4.63 (m, 1H), 3.64 (m, 1H), 3.37 (m, 2H), 3.20 (m, 1H), 3.03 (m, 4H), 2.73 (m, 2H), 2.57 (m, 1H), 2.28 (m, 1H), 2.15 (m, 6H), 1.95 (m, 2H), 1.38 (t, 2H), 0.91 (s, 6H).

EXAMPLE 277

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl]sulfonyl}benzamide

EXAMPLE 277A

4-((tetrahydro-2H-pyran-4-yl)methylamino)-3-(trifluoromethyl)benzenesulfonamide

A mixture of 4-fluoro-3-(trifluoromethyl)benzenesulfonamide (1.056 g), (tetrahydro-2H-pyran-4-yl)methanamine (0.5 g) and N,N-diisopropylethylamine (1.68 g) in anhydrous dimethylsulfoxide (15 mL) solution was heated at 90°C overnight. The reaction mixture was cooled to room temperature and diluted with ethyl acetate. The organic phase was washed with water, brine, dried over anhydrous sodium sulfate, filtered and concentrated to afford the title compound.

EXAMPLE 277B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl]sulfonyl}benzamide

The title compound was prepared by substituting EXAMPLE 277A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11. 22 (s, 1H), 11.20 (s, 1H), 7.91 (d, 1H), 7.76 (dd, 1H), 7.55 (d, 1H), 7.41 (m, 4H), 7.20 (m, 1H), 7.08 (d, 2H), 6.88 (m, 2H), 6.70 (dd, 1H), 6.58 (m, 1H), 6.42 (m, 1H), 6.19 (m, 1H), 3.83 (m, 2H), 3.56 (m, 4H), 3.25 (m, 4H), 3.15 (m, 2H), 2.99 (m, 2H), 2.74 (m, 2H), 2.18 (m, 2H), 2.02 (m, 2H), 1.84 (m, 1H), 1.57 (m, 2H), 1.44 (m, 2H), 1.19 (m, 2H), 0.93 (s, 6H).

EXAMPLE 278

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[2-(1,3-dioxolan-2-yl)ethyl]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

A mixture of EXAMPLE 187A (0.079 g), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (0.016 g), and palladium acetate (0.0045 g) in tetrahydrofuran (1 mL) was stirred at room temperature for 5 minutes. To this mixture was added (2-(1,3-dioxolan-2-yl)ethyl)zinc(II) bromide (0.6 mL). The reaction mixture was stirred overnight. The solvent was removed, and the residue was purified by reverse phase Prep HPLC. The desired fractions were combined, and the organic solvent was partially removed. The resulting mixture was treated with saturated aqueous $NaHCO_3$, extracted with ethyl acetate, dried over $MgSO_4$, filtered, and concentrated to give the title compound. ^1H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.14 (s, 1H), 8.37 (s, 1H), 8.00 (s, 1H), 7.55 (br s., 1H), 7.52 (d, 1H), 7.33-7.39 (m, 4H), 7.08 (br s, 1H), 7.04 (d, 2H), 6.83 (dd, 1H), 6.62 (d, 1H), 6.38 (s, 1H), 6.15 (d, 1H), 4.85 (t, 1H), 3.87-3.89 (m, 2H), 3.76-3.79 (m, 2H), 3.04 (s, 4H), 2.91-2.94 (m, 2H), 2.11-2.15 (m, 4H), 1.88-1.91 (s, 4H), 1.39 (t, 2H), 0.92 (s, 6H).

EXAMPLE 279

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}benzamide

EXAMPLE 279A

3-nitro-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

(Tetrahydro-2H-pyran-4-yl)methanol (2.0 g) in tetrahydrofuran (20 mL) was treated with 60% NaH (1.377 g). The mixture was stirred for 20 minutes at the room temperature. To this mixture was added 4-fluoro-3-nitrobenzenesulfonamide (2.84 g) portion-wise. The reaction was stirred for another 2 hours. The mixture was poured into water, neutralized with 10 % HCl, and extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel eluting with 20%-60% ethyl acetate in hexanes.

EXAMPLE 279B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}benzamide

The title compound was prepared by substituting EXAMPLE 279A for EXAMPLE 1F in EXAMPLE 177. ^1H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.16 (s,

1H), 8.38 (d, 1H), 8.05 (dd, 1H), 7.51 (d, 1H), 7.38-7.41 (m, 3H), 7.34 (d, 1H), 7.15 (d, 1H), 7.04 (d, 2H), 6.85 (dd, 1H), 6.65 (dd, 1H), 6.39 (s, 1H), 6.15 (d, 1H), 4.08 (d, 2H), 3.88 (dd, 2H), 3.04 (s, 4H), 2.77 (s, 2H), 2.12-2.22 (m, 4H), 1.95 (br s, 2H), 1.64 (dd, 2H), 1.36-1.39 (m, 2H), 0.92 (s, 6H).

EXAMPLE 280

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(3-nitro-4-{[2-(3-oxopiperazin-1-yl)ethyl]amino}phenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 1E and EXAMPLE 273A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.24 (br s, 1H), 8.72 (t, 1H), 8.51 (d, 1H), 7.76 (br s, 1H), 7.72 (dd, 1H), 7.53 (d, 1H), 7.34 (d, 2H), 7.28 (t, 1H), 7.18 (d, 1H), 7.04 (d, 2H), 6.97 (t, 2H), 6.70 (dd, 1H), 6.43 (d, 1H), 6.28-6.23 (m, 2H), 3.48 (q, 2H), 3.17 (m, 2H), 3.04 (m, 6H), 2.70 (br s, 2H), 2.68-2.63 (m, 2H), 2.16 (m, 8H), 1.95 (br s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 281

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methyl-5-oxopyrrolidin-3-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 187A for 4-chloro-3-nitrobenzenesulfonamide and 4-amino-1-methylpyrrolidin-2-one hydrochloride for 1-(2-methoxy-ethyl)-piperidin-4-ylamine in EXAMPLE 189A, except the crude was purified by preparative HPLC using a C18 column, 250 x 50 mm, 10μ, and eluting with a gradient of 20-100% CH_3CN vs. 0.1% trifluoroacetic acid in water, giving the product as a trifluoroacetate salt. The salt was dissolved in dichloromethane (6 mL) and washed with 50% aqueous $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to give the title compound. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.14 (s, 1H), 8.56 (d, 1H), 8.34 (br d, 1H), 7.82 (dd, 1H), 7.53 (d, 1H), 7.39 (m, 2H), 7.33 (d, 2H), 7.11 (s, 1H), 7.04 (m, 3H), 6.83 (dd, 1H), 6.64 (dd, 1H), 6.38 (s, 1H), 6.15 (s, 1H), 4.45 (m, 1H), 3.80 (dd, 1H), 3.35 (m, 1H), 3.02 (br s, 4H), 2.81 (dd, 1H), 2.75 (s, 3H), 2.71 (s, 2H), 2.40 (dd, 1H), 2.15 (m, 6H), 1.94 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 282

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methyl-6-oxopiperidin-3-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 187A for 4-chloro-3-nitrobenzenesulfonamide and 5-amino-1-methylpiperidin-2-one hydrochloride for 1-(2-methoxy-ethyl)-piperidin-4-ylamine in EXAMPLE 189A, except the crude was purified by preparative HPLC using a C18 column, 250 x 50 mm, 10μ, and eluting with a gradient of 20-100% CH_3CN vs. 0.1% trifluoroacetic acid in water, giving the product as a trifluoroacetate salt. The salt was dissolved in dichloromethane (6 mL) and washed with 50% aqueous $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give the title compound. ^1H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.16 (s, 1H), 8.58 (d, 1H), 8.31 (br d, 1H), 7.85 (dd, 1H), 7.53 (d, 1H), 7.39 (m, 2H), 7.33 (d, 2H), 7.25 (d, 1H), 7.14 (s, 1H), 7.03 (d, 2H), 6.85 (dd, 1H), 6.64 (dd, 1H), 6.39 (s, 1H), 6.14 (s, 1H), 4.22 (m, 1H), 3.57 (dd, 1H), 3.02 (br s, 4H), 2.84 (m, 1H), 2.83 (s, 3H), 2.72 (s, 2H), 2.36 (m, 2H), 2.16 (m, 6H), 2.05 (m, 2H), 1.94 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 283

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[3-nitro-4-(piperidin-1-ylamino)phenyl]sulfonyl}benzamide

EXAMPLE 283A

3-nitro-4-(piperidin-1-ylamino)benzenesulfonamide

The title compound was prepared by substituting piperidin-1-amine for (tetrahydro-2H-pyran-4-yl)methanamine in EXAMPLE 1F.

EXAMPLE 283B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[3-nitro-4-(piperidin-1-ylamino)phenyl]sulfonyl}benzamide

The title compound was prepared by substituting EXAMPLE 283A for EXAMPLE 1F and EXAMPLE 55B for EXAMPLE 26C in EXAMPLE 177. ^1H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.27 (brs, 1H), 11.33 (s, 1H), 9.14 (s, 1H), 8.48 (d, 1H), 7.66 (dd, 1H), 7.52 (t, 2H), 7.34 (d, 2H), 7.29 (t, 1H), 7.19 (d, 1H), 7.04 (d, 2H), 6.97 (t, 1H), 6.71

(dd, 1H), 6.41 (d, 1H), 6.28 (m, 2H), 3.05 (m, 4H), 2.78 (m, 6H), 2.17 (m, 6H), 1.95 (s, 2H), 1.67 (m, 6H), 1.38 (t, 2H), 0.93 (s, 6H).

EXAMPLE 284

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(piperidin-1-ylamino)phenyl]sulfonyl}benzamide

The title compound was prepared by substituting EXAMPLE 283A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500 MHz, dimethylsulfoxide-d $_6$) δ 11.28 (s, 1H), 11.11 (s, 1H), 9.02 (s, 1H), 8.50 (s, 1H), 7.79 (dd, 1H), 7.52 (m, 2H), 7.35 (m, 4H), 7.07 (m, 3H), 6.82 (m, 1H), 6.60 (m, 1H), 6.36 (m, 1H), 6.14 (m, 1H), 2.99 (m, 4H), 2.75 (m, 6H), 2.16 (m, 6H), 1.99 (m, 2H), 1.94 (m, 2H), 1.64 (m, 4H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 285

4-(4-{[4-(4-chlorophenyl)-1-methyl-1H-pyrazol-5-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 285A

4-(4-chlorophenyl)-1-methyl-1H-pyrazole-5-carbaldehyde

4-Bromo-1-methyl-1H-pyrazole-5-carbaldehyde (0.500 g), 4-chlorophenylboronic acid (0.455 g), tetrabutylammonium bromide (0.853 g), potassium carbonate (0.914 g) and palladium acetate (0.030 g) were stirred together in 5 mL of water and heated to 45°C. After stirring for 2.5 hours, the reaction was diluted with ethyl acetate (75 mL) and washed with water (25 mL), brine (50 mL), dried over magnesium sulfate, filtered and concentrated to give the crude material. The solid was chromatographed over silica gel (SF40-80) eluted using a gradient of 5% to 25% ethyl acetate/hexanes over 30 minutes.

EXAMPLE 285B

methyl 2-(1H-indol-5-yloxy)-4-(4-((4-(4-chlorophenyl)-1-methyl-1H-pyrazol-5-yl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 285A for 4'-chlorobiphenyl-2 carboxaldehyde and methyl 2-(1H-indol-5-yloxy)-4-(piperazin-1-yl)benzoate for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 285C

2-(1H-indol-5-yloxy)-4-(4-((4-(4-chlorophenyl)-1-methyl-1H-pyrazol-5-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 285B for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 285D

2-(1H-indol-5-yloxy)-4-(4-((4-(4-chlorophenyl)-1-methyl-1H-pyrazol-5-yl)methyl)piperazin-1-yl)-N-(3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)phenylsulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 285C for EXAMPLE 1E in EXAMPLE 1G. ^{1}H NMR (300 MHz, CDCL3) δ 10.30 (s, 1H), 8.85 (d, 1H), 8.50 (s, 1H), 8.30 (s, 1H), 8.12 (dd, 1H), 7.95 (d, 1H), 7.49 (s, 1H), 7.43 (d, 1H), 7.36 – 7.22 (m, 6H), 6.97 (dd, 1H), 6.87 (d, 1H), 6.53 (d, 2H), 6.08 (s, 1H), 4.08 – 3.98 (m, 2H), 3.92 (s, 3H), 3.55 (s, 2H), 3.42 (s, 2H), 3.33 – 3.19 (m, 2H), 3.08 (s, 4H), 2.38 (s, 4H), 1.98 (d, 1H), 1.72 (s, 2H), 1.52 – 1.33 (m, 2H).

EXAMPLE 286

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(3-methyloxetan-3-yl)methoxy]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 286A

4-((3-methyloxetan-3-yl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting (3-methyloxetan-3-yl)methanol for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 279A.

EXAMPLE 286B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(3-methyloxetan-3-yl)methoxy]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 286A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.08 (s, 1H), 8.26 (d, 1H), 8.18 (d, 1H), 7.92 (m, 1H), 7.53 (m, 1H), 7.34 (m, 3H), 7.25 (m, 1H), 7.04 (m, 3H), 6.91 (m, 1H), 6.76 (m, 1H), 6.59 (m, 1H), 6.35 (m, 1H), 6.15 (d, 1H), 4.47 (d, 1H),

4.29 (d, 1H), 3.40 (m, 2H), 3.13 (m, 2H), 2.98 (m, 4H), 2.72 (m, 2H), 2.16 (m, 6H), 1.94 (m, 2H), 1.36 (m, 5H), 0.93 (s, 6H).

EXAMPLE 287

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(1-oxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}phenyl)sulfonyl]benzamide

EXAMPLE 287A

3-nitro-4-((tetrahydro-2H-thiopyran-4-yl)methylamino)benzenesulfonamide

The title compound was prepared by substituting (tetrahydro-2H-thiopyran-4-yl)methanamine, hydrochloride for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 287B

3-nitro-4-((1-oxidotetrahydro-2H-thiopyran-4-yl)methylamino)benzenesulfonamide

EXAMPLE 287A (150 mg) was suspended in methanol (5 mL). The reaction mixture was cooled to 0°C, followed by the addition of Oxone® (220 mg) in water (3 mL). The reaction mixture was stirred at room temperature for 2 hours. The precipitate was filtered and washed with $Na_2S_2O_3$ solution and water. The solid was dried in a vacuum oven overnight, and used in the next step without further purification.

EXAMPLE 287C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(1-oxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}phenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 287B for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.17 (s, 1H), 8.69 (t, 1H), 8.58 (d, 1H), 7.81 (dd, 1H), 7.51 (d, 1H), 7.40 (m, 2H), 7.33 (d, 2H), 7.15 (m, 2H), 7.03 (d, 2H), 6.86 (dd, 1H), 6.65 (dd, 1H), 6.40 (m, 1H), 6.13 (m, 1H), 3.38 (m, 4H), 3.05 (m, 6H), 2.73 (m, 2H), 2.11 (m, 8H), 1.95 (m, 3H), 1.67 (m, 2H), 1.38 (t, 2H), 0.90 (s, 6H).

EXAMPLE 288

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1,3-thiazol-5-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting thiazol-5-ylmethanamine, hydrochloric acid for (3S,4R)-4-amino-1-benzylpiperidin-3-ol, hydrochloric acid in EXAMPLE 187B. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.18 (s, 2H), 9.13 (t, 1H), 8.99 (s, 1H), 8.60 (d, 1H), 7.95 (s, 1H), 7.82 (dd, 1H), 7.50 (d, 1H), 7.39-7.42 (, 2H), 7.33 (d, 2H), 7.17 (d, 1H), 7.14 (d, 1H), 7.03 (d, 2H), 6.85 (dd, 1H), 6.64 (dd, 1H), 6.40 (s, 1H), 6.13 (d, 1H), 4.91 (d, 2H), 3.03 (s, 4H), 2.73 (s, 2H), 2.12-2.18 (m, 6H), 1.94 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 289

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}benzamide

The title compound was prepared by substituting EXAMPLE 279A for EXAMPLE 1F and EXAMPLE 55B for EXAMPLE 26C in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.25 (s, 1H), 8.21 (d, J = 2.14 Hz, 1H), 7.95 (dd, 1H), 7.54 (d, 1H), 7.33-7.38 (m, 3H), 7.28 (t, 1H), 7.17 (d, 1H), 7.04 (d, 2H), 6.97 (t, 1H), 6.70 (dd, 1H), 6.41 (d, 1H), 6.27-6.29 (m, 2H), 4.08 (d, 2H), 3.88 (dd, 2H), 3.07 (s, 4H), 2.80 (s, 2H), 2.24 (br s, 2H), 2.12-2.16 (m, 2H), 1.96 (s, 2H), 1.65 (dd, 2H), 1.37-1.40 (m, 2H), 0.92 (s, 6H).

EXAMPLE 290

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 290A

2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-enecarbaldehyde

The title compound was prepared as described in EXAMPLE 253B by replacing EXAMPLE 253A with EXAMPLE 19C.

EXAMPLE 290B

tert-butyl 4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-enyl)methyl)piperazine-1-carboxylate

The title compound was prepared as described in EXAMPLE 1A by replacing EXAMPLE 27C with EXAMPLE 290A.

EXAMPLE 290C

1-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-enyl)methyl)piperazine

The title compound was prepared as described in EXAMPLE 1B by replacing EXAMPLE 1A with EXAMPLE 290B.

EXAMPLE 290D

ethyl 2-(1H-indol-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

The title compound was prepared as described in EXAMPLE 20D by replacing EXAMPLE 20A and EXAMPLE 20C with EXAMPLE 26A and EXAMPLE 290C, respectively.

EXAMPLE 290E

2-(1H-indol-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared as described in EXAMPLE 1E by replacing EXAMPLE 1D with EXAMPLE 290D.

EXAMPLE 290F

2-(1H-indol-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)phenylsulfonyl)benzamide

The title compound was prepared as described in EXAMPLE 175F by replacing EXAMPLE 175E with EXAMPLE 290E. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.17 (s, 2H), 8.62 (t, 1H), 8.58 (d, 1H), 7.80 (dd, 1H), 7.51 (d, 1H), 7.38 - 7.43 (m, 2H), 7.33 (d, 2H), 7.16 (d, 1H), 7.10 (d, 1H), 7.07 (d, 3H), 6.86 (dd, 1H), 6.65 (dd, 1H), 6.39 (s, 1H),

6.14 (d, 1H), 3.85 (dd, 2H), 3.23 - 3.31 (m, 4H), 3.02 (s, 4H), 2.68 (s, 2H), 2.17 (d, 6H), 1.85 - 1.95 (m, 3H), 1.61 (d, 2H), 1.39 (t, 2H), 1.20 - 1.30 (m, 2H), 0.92 (s, 6H).

EXAMPLE 291

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(2-tetrahydro-2H-pyran-4-ylethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 291A

3-nitro-4-(2-(tetrahydro-2H-pyran-4-yl)ethylamino)benzenesulfonamide

The title compound was prepared as described in EXAMPLE 1F by replacing (tetrahydropyran-4-yl)methylamine with 2-(tetrahydro-2H-pyran-4-yl)ethanamine.

EXAMPLE 291B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(2-tetrahydro-2H-pyran-4-ylethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared as described in EXAMPLE 175F by replacing EXAMPLE 175E and EXAMPLE 1F with EXAMPLE 26C and EXAMPLE 291A, respectively. ^{1}H NMR (500 MHz, dimethylsulfoxide-d$_6$) δ 11.16 (s, 2H), 8.57 (d, 1H), 8.53 (t, 1H), 7.80 (dd, 1H), 7.51 (d, 1H), 7.37 - 7.42 (m, 2H), 7.33 (d, 2H), 7.14 (d, 1H), 7.01 - 7.05 (m, 3H), 6.85 (dd, 1H), 6.64 (dd, 1H), 6.39 (s, 1H), 6.14 (d, 1H), 3.83 (dd, 2H), 3.41 (q, 2H), 3.23 - 3.30 (m, 2H), 3.02 (s, 4H), 2.71 (s, 2H), 2.08 - 2.21 (m, 6H), 1.94 (s, 2H), 1.52 - 1.67 (m, 5H), 1.37 (t, 2H), 1.14 - 1.25 (m, 2H), 0.92 (s, 6H).

EXAMPLE 292

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(3-nitro-4-{[2-(trifluoromethoxy)ethyl]amino}phenyl)sulfonyl]benzamide

EXAMPLE 292A

3-nitro-4-(2-(trifluoromethoxy)ethylamino)benzenesulfonamide

The title compound was prepared by substituting piperidin-1-amine for (tetrahydro-2H-pyran-4-yl)methanamine in EXAMPLE 1F.

EXAMPLE 292B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(3-nitro-4-{[2-(trifluoromethoxy)ethyl]amino}phenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 292A for EXAMPLE 1F and EXAMPLE 55B for EXAMPLE 26C in EXAMPLE 177. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.07 (s, 1H), 8.36 (m, 2H), 7.72 (dd, 1H), 7.58 (d, 1H), 7.34 (d, 2H), 7.19 (m, 1H), 7.05 (m, 3H), 6.91 (m, 2H), 6.59 (d, 1H), 6.21 (m, 3H), 4.28 (t, 2H), 3.72 (q, 2H), 2.94 (m, 4H), 2.71 (s, 2H), 2.15 (m, 6H), 1.95 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

EXAMPLE 293

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[2-(2-methoxyethoxy)ethyl]amino}-3-nitrophenyl)sulfonyl]benzamide

EXAMPLE 293A

4-(2-(2-methoxyethoxy)ethylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 2-(2-methoxyethoxy)ethanamine for (tetrahydro-2H-pyran-4-yl)methanamine in EXAMPLE 1F.

EXAMPLE 293B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[2-(2-methoxyethoxy)ethyl]amino}-3-nitrophenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 293A for EXAMPLE 1F and EXAMPLE 55B for EXAMPLE 26C in EXAMPLE 177. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.28 (s, 1H), 11.23 (s, 1H), 8.59 (m, 1H), 8.50 (d, 1H), 7.70 (dd, 1H), 7.52 (d, 1H), 7.34 (d, 2H), 7.28 (t, 1H), 7.17 (d, 1H), 7.05 (m, 3H), 6.96 (t, 1H), 6.71 (dd, 1H), 6.42 (d, 1H), 6.26 (m, 2H), 3.67 (t, 2H), 3.56 (m, 4H), 3.45 (m, 2H), 3.22 (s, 3H), 3.04 (m, 4H), 2.74 (s, 2H), 2.16 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.93 (s, 6H).

EXAMPLE 294

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[3-(methylsulfonyl)propyl]amino}-3-nitrophenyl)sulfonyl]benzamide

EXAMPLE 294A

4-(3-(methylthio)propylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 3-(methylthio)propan-1-amine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 294B

4-(3-(methylsulfonyl)propylamino)-3-nitrobenzenesulfonamide

EXAMPLE 294A (150 mg) was suspended in anhydrous dichloromethane (5mL) and meta-chloroperoxybenzoic acid (848 mg) was added at 0°C. The reaction mixture was stirred at room temperature overnight. The cloudy suspension was filtered. The solid was washed with aqueous $Na_2S_2O_3$ solution, saturated aqueous $NaHCO_3$ solution and water. The solid was dried and used in the next step without further purification.

EXAMPLE 294C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[3-(methylsulfonyl)propyl]amino}-3-nitrophenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 26C and EXAMPLE 294B for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.25 (m, 1H), 8.65 (t, 1H), 8.51 (d, 1H), 7.69 (dd, 1H), 7.52 (d, 1H), 7.34 (d, 2H), 7.28 (m, 1H), 7.18 (m, 1H), 7.05 (m, 3H), 6.97 (m, 1H), 6.70 (dd, 1H), 6.42 (d, 1H), 6.26 (m, 2H), 3.55 (m, 2H), 3.23 (t, 2H), 3.05 (t, 4H), 2.98 (s , 3H), 2.76 (m, 2H), 2.18 (m, 6H), 2.02 (m, 2H), 1.96 (m, 2H), 1.38 (t, 2H), 0.93 (s, 6H).

EXAMPLE 295

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(1,1-dioxidothiomorpholin-4-yl)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 337A for 4-chloro-3-nitrobenzene sulfonamide and 4-(3-aminopropyl)thiomorpholine-1,1-dioxide for 1-(2-methoxy-ethyl)-piperidin-4-ylamine in EXAMPLE 189A. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.23 (s, 1H), 8.79 (s, 1H), 8.48 (d, 1H), 7.72 (dd, 1H), 7.54 (d, 1H), 7.34 (d, 2H), 7.26 (t, 1H), 7.15 (d, 1H), 6.99 (m, 4H), 6.67 (dd, 1H), 6.40 (d, 1H), 6.24 (m, 2H), 3.42 (q, 2H), 3.11 (m, 4H), 3.01 (m, 4H), 2.90 (m, 4H), 2.72 (m, 2H), 2.56 (t, 2H), 2.16 (m, 6H), 1.95 (m, 2H), 1.78 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 296

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(2-tetrahydro-2H-pyran-4-ylethyl)phenyl]sulfonyl}benzamide

EXAMPLE 296A

(2-(tetrahydro-2H-pyran-4-yl)ethyl)zinc(II) bromide

A 25 mL round bottom flask was dried at 120 °C for 6 hours. It was cooled by a stream of dry N_2. To this flask was charged with zinc (0.508 g). The flask was heated at 70 °C under high vacuum for 30 minutes. After back-filling with N_2, iodine (0.033 g) and N,N-dimethylacetamide (5.2 mL) were added, and the resulting mixture was stirred until the red color of iodine had faded. Then, 4-(2-bromoethyl)tetrahydro-2H-pyran (1.0 g) was added to the above mixture via a syringe. The reaction mixture was allowed to stir for 12 hours at 70 °C. After cooling, the reaction mixture was used directly for next step.

EXAMPLE 296B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(2-tetrahydro-2H-pyran-4-ylethyl)phenyl]sulfonyl}benzamide

The title compound was prepared by substituting EXAMPLE 296A for (2-(1,3-dioxolan-2-yl)ethyl)zinc(II) bromide in EXAMPLE 278. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.15 (s, 2H), 8.38 (d, 1H), 8.01 (d, 1H), 7.57 (d, 1H), 7.51 (d, 1H), 7.38-7.40 (m, 2H), 7.34 (d, 2H), 7.12 (d, 1H), 7.04 (d, 2H), 6.82 (dd, 1H), 6.64 (dd, 1H), 6.38 (s, 1H), 6.16 (d, 1H), 3.83 (dd, 2H), 3.24-3.29 (m, 4H), 3.06 (s, 4H), 2.83-2.86 (m, 3H), 2.27 (br s, 2H), 2.12-2.14 (m, 4H), 1.96 (s, 2H), 1.95 (s, 2H), 1.46-1.62 (m, 6H), 1.37-1.40 (m, 2H), 0.92 (s, 6H).

EXAMPLE 297

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide

EXAMPLE 297A

4-((1,4-dioxan-2-yl)methoxy)-3-nitrobenzenesulfonamide

(1,4-Dioxan-2-yl)methanol (380 mg) in tetrahydrofuran (30 ml) was treated with sodium hydride (60%) (245 mg) at room temperature for 30 minutes. The reaction mixture was cooled in an ice bath and 4-fluoro-3-nitrobenzenesulfonamide (675 mg) was added. The resulting mixture was stirred at room temperature for 2 hours and another portion of sodium hydride (60%, 245 mg) was added. The reaction mixture was stirred overnight and quenched with ice water (3 ml). The cloudy mixture was filtered and the filtrate was concentrated. The residue was triturated with methanol to give the title compound.

EXAMPLE 297B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 175F by replacing EXAMPLE 175E and EXAMPLE 1F with EXAMPLE 26C and EXAMPLE 297A, respectively. ^{1}H NMR (500 MHz, dimethylsulfoxide-d$_6$) δ 11.16 (s, 2H), 8.39 (d, 1H), 8.06 (dd, 1H), 7.51 (d, 1H), 7.38 - 7.43 (m, 3H), 7.34 (d, 2H), 7.15 (d, 1H), 7.04 (d, 2H), 6.85 (dd, 1H), 6.64 (dd, 1H), 6.39 (s, 1H), 6.15 (d, 1H), 4.20 - 4.28 (m, 2H), 3.85 - 3.91 (m, 1H), 3.82 (dd, 1H), 3.74 - 3.78 (m, 1H), 3.59 - 3.69 (m, 2H), 3.40 - 3.51 (m, 2H), 3.05 (s, 4H), 2.78 (s, 2H), 2.23 (s, 4H), 2.14 (s, 2H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 298

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[2-(2-methoxyethoxy)ethyl]amino}-3-nitrophenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 293A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500 MHz, dimethylsulfoxide-d$_6$) δ 11.17 (s, 1H), 11.15 (s, 1H), 8.59 (m, 2H), 7.80 (dd, 1H), 7.50 (d, 1H), 7.36 (m, 4H), 7.15 (d, 1H), 7.09 (d, 1H), 7.03 (d, 2H), 6.85 (dd, 1H), 6.65 (dd, 1H), 6.39 (m, 1H), 6.14 (d, 1H), 3.67 (t, 2H), 3.56 (m, 4H), 3.44 (m, 2H), 3.22 (s, 3H), 3.03 (m, 4H), 2.72 (s, 2H), 2.16 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 299

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 337A for 4-chloro-3-nitrobenzene sulfonamide and 1,1-dioxidotetrahydrothiene-3ylamine for 1-(2-methoxy-ethyl)-piperidin-4-ylamine in EXAMPLE 189A. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.35 (s, 1H), 11.23 (s, 1H), 8.49 (m, 2H), 7.78 (dd, 1H), 7.52 (d, 1H), 7.34 (d, 2H), 7.27 (m, 1H), 7.16 (m, 2H), 7.04 (d, 1H), 6.97 (m, 1H), 6.70 (dd, 1H), 6.42 (d, 1H), 6.26 (m, 2H), 4.63 (m, 1H), 3.64 (dd, 1H), 3.37 (m, 2H), 3.20 (m, 1H), 3.05 (m, 4H), 2.74 (m, 2H), 2.58 (m, 1H), 2.28 (m, 1H), 2.16 (m, 6H), 1.95 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 300

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[2-(trifluoromethoxy)ethyl]amino}phenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 292A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.17 (m, 2H), 8.64 (t, 1H), 8.59 (d, 1H), 7.84 (dd, 1H), 7.51 (d, 1H), 7.40 (m, 2H), 7.33 (d, 2H), 7.16 (m, 2H), 7.04 (d, 2H), 6.85 (dd, 1H), 6.64 (dd, 1H), 6.39 (m, 1H), 6.14 (d, 1H), 4.31 (t, 2H), 3.78 (q, 2H), 3.04 (m, 4H), 2.74 (s, 2H), 2.17 (m, 6H), 1.94 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6 H).

EXAMPLE 301

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide

EXAMPLE 301A

3-nitro-4-((1-dioxidotetrahydro-2H-thiopyran-4-yl)methylamino)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 287A for EXAMPLE 294A in EXAMPLE 294B.

EXAMPLE 301B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 26C and EXAMPLE 301A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.26 (s, 1H), 8.68 (t, 1H), 8.51 (d, 1H), 7.73 (dd, 1H), 7.53 (d, 1H), 7.34 (d, 2H), 7.29 (m, 1H), 7.19 (d, 1H), 7.12 (d, 1H), 7.04 (d, 2H), 6.99 (m, 1H), 6.70 (dd, 1H), 6.46 (d, 1H), 6.26 (m, 2H), 3.38 (t, 2H), 3.09 (m, 8H), 2.75 (m, 2H), 2.16 (m, 6H), 2.07 (m, 2H), 1.95 (m, 3H), 1.70 (m, 2H), 1.38 (t, 2H), 0.91 (s, 6H).

EXAMPLE 302

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2,2-difluoroethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

EXAMPLE 302A

4-(2,2-difluoroethylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 2,2-difluoroethanamine for (tetrahydro-2H-pyran-4-yl)methanamine in EXAMPLE 1F.

EXAMPLE 302B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2,2-difluoroethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 302A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.22 (s, 1H), 11.05 (s, 1H), 8.46 (m, 2H), 7.76 (m, 1H), 7.53 (d, 1H), 7.33 (m, 4H), 7.05 (m, 4H), 6.76 (m, 1H), 6.57 (d, 1H), 6.34 (m, 1H), 6.14 (m, 1H), 3.89 (m, 2H), 2.97 (m, 4H), 2.71 (s, 2H), 2.16 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 303

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 26C and EXAMPLE 163A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.28 (m, 1H), 8.13 (d, 1H), 7.78 (dd, 1H), 7.52 (d, 1H), 7.34 (d, 2H), 7.29 (m, 2H), 7.20 (d, 1H), 7.01 (m, 4H), 6.70 (dd, 1H), 6.45 (d, 1H), 6.27 (m,

2H), 3.85 (dd, 2H), 3.26 (t, 4H), 3.05 (m, 4H), 2.75 (m, 2H), 2.16 (m, 6H), 1.95 (m, 2H), 1.84 (m, 1H), 1.55 (m, 2H), 1.38 (t, 2H), 1.23 (m, 2H), 0.92 (s, 6H).

EXAMPLE 304

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 163A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.46 (s, 1H), 11.20 (s, 1H), 9.23 (s, 1H), 8.19 (d, 1H), 7.90 (dd, 1H), 7.53 (d, 1H), 7.41 (m, 4H), 7.33 (m, 1H), 7.17 (d, 1H), 6.86 (dd, 1H), 6.70 (dd, 1H), 6.41 (m, 1H), 6.21 (d, 1H), 3.84 (dd, 2H), 3.57 (m, 4H), 3.26 (m, 6H), 3.00 (m, 2H), 2.74 (s, 2H), 2.18 (s, 2H), 2.01 (s, 2H), 1.83 (m, 1H), 1.54 (m, 2H), 1.45 (t, 2H), 1.23 (m, 2H), 0.94 (s, 6H).

EXAMPLE 305

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4,4-difluorocyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting 4,4-difluorocyclohexanamine, hydrochloric Acid for (3S,4R)-4-amino-1-benzylpiperidin-3-ol, hydrochloric acid in EXAMPLE 187B. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.16 (s, 2H), 8.59 (d, 1H), 8.25 (d, 1H), 7.84 (dd, 1H), 7.50 (d, 2H), 7.39-7.41 (m, 2H), 7.33 (d, 2H), 7.15-7.18 (m, 2H), 7.03 (d, 2H), 6.85 (dd, 1H), 6.65 (dd, 1H), 6.39 (s, 1H), 6.14 (d, 1H), 3.86 (d, 1H), 3.04 (s, 4H), 2.74 (s, 2H), 1.95-2.18 (m, 14H), 1.69-1.73 (m, 2H), 1.38 (d, 2H), 0.92 (s, 6H).

EXAMPLE 306

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-4-yloxy)benzamide

EXAMPLE 306A

1,6-dioxaspiro[2.5]octane-2-carbonitrile

A mixture of dihydro-2H-pyran-4(3H)-one (10.0g) and 2-chloroacetonitrile (7.55 g) in tert-butanol (10 mL) was treated with 1.0 N potassium tert-butoxide (100 mL)

drop-wise over 20 minutes. The reaction mixture was stirred at room temperature for 16 hours. It was diluted with water (10 mL) and 10% HCl (20 mL). The reaction mixture was concentrated to one-third of its original volume, and extracted with diethyl ether four times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel eluting with 20-40% ethyl acetate in hexanes to give the title compound.

EXAMPLE 306B

2-(4-fluorotetrahydro-2H-pyran-4-yl)-2-hydroxyacetonitrile

EXAMPLE 306A (11.5 g) was dissolved in dichloromethane (40 mL) in a polypropylene bottle. The bottle was cooled to 0 °C. To this mixture was added 70% hydrogen fluoride-pyridine (10.31 mL) slowly. The mixture was allowed to warm to room temperature over 3 hours, and stirred for 24 hours. The reaction mixture was diluted with ethyl acetate (200 mL) and poured into saturated aqueous $NaHCO_3$. Additional solid $NaHCO_3$ was used to neutralize the mixture carefully until bubbling ceased. The organic layer was isolated, and the aqueous layer was extracted with additional ethyl acetate three times (150 mL each).The combined organic layers were washed with 1% HCl, brine, dried ($MgSO_4$), filtered and concentrated to give the desired compound which was used directly in the next reaction.

EXAMPLE 306C

(4-fluorotetrahydro-2H-pyran-4-yl)methanol

EXAMPLE 306B (11.78 g) in 2-propanol (150 mL) and water (37.5 mL) was cooled to 0 °C. To this mixture was added sodium borohydride (4.2 g). The mixture was stirred and allowed to warm to room temperature over 3 hours. The reaction was quenched with acetone, and stirred for another 1 hour. The clear liquid was separated from solid by decanting. Additional ethyl acetate was used to wash the solid, and was decanted. The combined organic solution was concentrated. The residue was purified with flash column chromatography on silica gel eluting with 20-40% ethyl acetate in hexanes to give the title compound.

EXAMPLE 306D

4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 306C for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 279A.

EXAMPLE 306E

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 306D for EXAMPLE 1F and EXAMPLE 55B for EXAMPLE 26C in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.24 (s, 1H), 8.28 (d, 1H), 7.98 (dd, 1H), 7.54 (d, 1H), 7.42 (d, 1H), 7.34 (d, 2H), 7.28 (t, 1H), 7.17 (d, 1H), 7.04 (d, 2H), 6.97 (t, 1H), 6.70 (dd, 1H), 6.41 (d, 1H), 6.26-6.28 (m, 2H), 4.38 (d, 2H), 3.76-3.80 (m, 2H), 3.57-3.62 (m, 2H), 3.06 (s, 4H), 2.80 (s, 2H), 2.24 (br s, 2H), 2.15-2.25 (m, 2H), 1.96 (s, 2H), 1.82-1.89 (m, 4H), 1.39 (t, 2H), 0.93 (s, 6H).

EXAMPLE 307

4-(4-{[4-(4-chlorophenyl)-1-isopropyl-6-oxo-1,6-dihydropyridin-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 307A

4-(4-chlorophenyl)-2-fluoro-5-methylpyridine

A mixture of 2-fluoro-4-iodo-5-methylpyridine (1.9 g), 4-chlorophenylboronic acid (1.504 g), tetrakis(triphenylphosphine)palladium(0) (0.463 g), and sodium carbonate (2.55 g) in ethanol (20 mL), water (10 mL) and toluene (10 mL) was heated under reflux for 6 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was separated, and the aqueous layers were extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel using 5% ethyl acetate in hexanes to give the title compound.

EXAMPLE 307B

5-(bromomethyl)-4-(4-chlorophenyl)-2-fluoropyridine

A mixture of EXAMPLE 307A (1.2 g), *N*-bromosuccinimide (1.06 g) and AIBN (azobisisobutyronitrile) (0.178 g) in CCl_4 (30 mL) was heated under reflux for 6 hours. After cooling, the solid was filtered off. The filtrate was concentrated and loaded onto a silica gel column eluting with 3% ethyl acetate in hexanes to give the title compound.

EXAMPLE 307C

tert-butyl 4-((4-(4-chlorophenyl)-6-fluoropyridin-3-yl)methyl)piperazine-1-carboxylate

A mixture of EXAMPLE 307B (1.24 g), tert-butyl piperazine-1-carboxylate (0.768 g), and potassium carbonate (0.570) in N,N-dimethylformamide (20 mL) was stirred at room temperature for 2 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was separated, and the aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel using 10% ethyl acetate in hexanes to give the title compound.

EXAMPLE 307D

tert-butyl 4-((4-(4-chlorophenyl)-6-oxo-1,6-dihydropyridin-3-yl)methyl)piperazine-1-carboxylate

A mixture of EXAMPLE 307C (1.6 g) and 5% HCl (20 mL) in tetrahydrofuran (20 mL) was heated at 80 °C overnight. The solvent was removed to dryness. This solid was re-dissolved and added to tetrahydrofuran (50 mL). To this mixture were added BOC_2O (di-t-butyl-dicarbonate) (1.118 g), triethylamine (0.72 mL), and 4-dimethylamionpyridine (1.4 g). The solvent was removed, and the residue was partitioned between water and ethyl acetate. The reaction mixture was stirred overnight. The organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by Prep HPLC eluting with 20-100% acetonitrile/water with 0.1% trifluoroacetic acid to give the title compound.

EXAMPLE 307E

tert-butyl 4-((4-(4-chlorophenyl)-1-isopropyl-6-oxo-1,6-dihydropyridin-3-yl)methyl)piperazine-1-carboxylate

EXAMPLE 307D (0.404 g) in N,N-dimethylformamide (5 mL) was treated with 60% sodium hydride (0.24 g) at room temperature. To this mixture was added 2-iodopropane (0.204 g). The mixture was stirred overnight. The reaction mixture was

partitioned between ethyl acetate and water. The organic layer was separated, and the aqueous layers were extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel using 10% ethyl acetate in hexanes to give EXAMPLE 307E and EXAMPLE 307F.

EXAMPLE 307F

tert-butyl 4-((4-(4-chlorophenyl)-6-isopropoxypyridin-3-yl)methyl)piperazine-1-carboxylate

This compound was isolated as a by-product during the preparation of EXAMPLE 307E.

EXAMPLE 307G

4-(4-chlorophenyl)-1-isopropyl-5-(piperazin-1-ylmethyl)pyridin-2(1H)-one

The title compound was prepared by substituting EXAMPLE 307E for EXAMPLE 1A in EXAMPLE 1B.

EXAMPLE 307H

ethyl 2-(1H-indol-5-yloxy)-4-(4-((4-(4-chlorophenyl)-1-isopropyl-6-oxo-1,6-dihydropyridin-3-yl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 307G for EXAMPLE 20C and EXAMPLE 26A for EXAMPLE 20A in EXAMPLE 20D.

EXAMPLE 307I

2-(1H-indol-5-yloxy)-4-(4-((4-(4-chlorophenyl)-1-isopropyl-6-oxo-1,6-dihydropyridin-3-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 307H for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 307J

4-(4-{[4-(4-chlorophenyl)-1-isopropyl-6-oxo-1,6-dihydropyridin-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 307I for EXAMPLE 26C in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.07 (s,

1H), 8.62 (t, 1H), 8.59 (d, 1H), 7.79 (dd, 1H), 7.59 (s, 1H), 7.52-7.53 (m, J 3H), 7.38-7.45 (m, 4H), 7.15 (d, 1H), 7.10 (d, 1H), 6.87 (dd, 1H), 6.68 (dd, 1H), 6.39 (s, 1H), 6.22 (s, 1H), 6.17 (d, 1H), 5.01-5.06 (m, 1H), 3.85 (dd, 2H), 3.24-3.31 (m, 6H), 3.09 (s, 2H), 3.00 (s, 4H), 2.26 (m, 4H), 2.09 (m, 2H), 1.60-1.63 (m, 2H), 1.30 (d, 6H).

EXAMPLE 308

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(tetrahydro-2H-pyran-4-ylmethyl)amino]carbonyl}phenyl)sulfonyl]benzamide

EXAMPLE 308A

4-sulfamoyl-N-((tetrahydro-2H-pyran-4-yl)methyl)benzamide

4-Sulfamoylbenzoic acid (201 mg), (tetrahydro-2H-pyran-4-yl)methanamine (144 mg), 1-hydroxybenzotriazole hydrate (230 mg), and 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (288 mg) were combined in acetonitrile. The mixture was stirred at room temperature overnight. The solids were filtered off and reaction mixture was concentrated. The crude material was purified by flash chromatography eluting with a gradient of 2% methanol/dichloromethane to 10% methanol/dichloromethane.

EXAMPLE 308B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(tetrahydro-2H-pyran-4-ylmethyl)amino]carbonyl}phenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 308A for EXAMPLE 1F and EXAMPLE 26C for EXAMPLE 1E in EXAMPLE 1G. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.19 (s, 1H), 8.57 (t, 1H), 7.94 (m, 4H), 7.48 (d, 1H), 7.43 (d, 1H), 7.40 (t, 1H), 7.33 (d, 2H), 7.21 (d, 1H), 7.03 (d, 2H), 6.88 (dd, 1H), 6.63 (dd, 1H), 6.42 (t, 1H), 6.13 (d, 1H), 3.84 (dd, 2H), 3.26 (m, 2H), 3.16 (t, 2H), 3.03 (br s, 4H), 2.74 (br s, 2H), 2.15 (m, 6H), 1.95 (s, 2H), 1.79 (m, 1H), 1.59 (d, 2H), 1.38 (t, 2H), 1.19 (m, 2H), 0.92 (s, 6H).

EXAMPLE 309

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(2-methoxyethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

EXAMPLE 309A

4-(2-methoxyethylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 159C for 4-fluoro-3-nitrobenzenesulfonamide and 2-methoxyethylamine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 309B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(2-methoxyethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 26C and EXAMPLE 309A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.26 (s, 1H), 8.13 (d, 1H), 7.79 (dd, 1H), 7.51 (d, 1H), 7.34 (d, 2H), 7.29 (t, 1H), 7.24 (m, 1H), 7.19 (d, 1H), 7.04 (d, 2H), 6.99 (m, 3H), 6.70 (dd, 1H), 6.44 (d, , 1H), 6.27 (m, 2H), 3.52 (m, 4H), 3.28 (s, 3H), 3.05 (m, 4H), 2.75 (s, 2H), 2.17 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 310

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide

EXAMPLE 310A

4-(aminomethyl)cyclohexanol

The title compound was prepared as described in EXAMPLE 311A by replacing (4-methoxyphenyl)methanamine with (4-hydroxyphenyl)methanamine.

EXAMPLE 310B

2-(1H-indol-5-yloxy)-N-(4-chloro-3-nitrophenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzamide

The title compound was prepared as described in EXAMPLE 1G by replacing EXAMPLE 1E and EXAMPLE 1F with EXAMPLE 26C and 4-chloro-3-nitrobenzenesulfonamide.

EXAMPLE 310C

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide

A mixture of EXAMPLE 310B (100 mg), triethylamine (0.2 ml) and EXAMPLE 310A (35 mg) in dioxane (5 ml) was heated at 100°C for 20 hours and concentrated. The residue was purified by RP-HPLC (10-70% acetonitrile in 0.1% trifluoroacetic aicd water / 70 minutes) to provide the title compound as a trifluroacetic acid salt. ^{1}H NMR (500 MHz, dimethylsulfoxide-d$_6$) δ 11.40 (s, 1H), 11.18 (s, 1H), 9.20 (s, 1H), 8.60 (t, 1H), 8.58 (d, 1H), 7.77 (dd, 1H), 7.54 (d, 1H), 7.42 (s, 1H), 7.37 - 7.41 (m, 3H), 7.14 (d, 1H), 7.04 - 7.09 (m, 3H), 6.86 (dd, 1H), 6.69 (dd, 1H), 6.39 (s, 1H), 6.21 (s, 1H), 3.50 - 3.68 (m, 3H), 3.20 - 3.27 (m, 3H), 2.93 - 3.07 (m, 2H), 2.66 - 2.82 (m, 2H), 2.13 - 2.22 (m, 2H), 2.01 (s, 2H), 1.83 (d, 2H), 1.67 - 1.77 (m, 3H), 1.50 - 1.60 (m, 1H), 1.44 (s, 2H), 0.96 - 1.17 (m, 4H), 0.94 (s, 6H).

EXAMPLE 311

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide

EXAMPLE 311A

(4-methoxycyclohexyl)methanamine

(4-Methoxyphenyl)methanamine (1 g) in ethanol (10 ml) was treated with 5% dry Rh-Al_2O_3 (0.5 g) under H_2 (500 psi) at 60 °C for 6 hours and then at 125°C for 26 hours. The insoluble material was filtered off and the filtrate was concentrated to provide the title compound.

EXAMPLE 311B

4-(((Trans-4-methoxycyclohexyl)methylamino)-3-nitrobenzenesulfonamide

4-fluoro-3-nitrobenzenesulfonamide (15 g) and EXAMPLE 311A (11.71 g) in tetrahydrofuran (200 ml) was treated with triethylamine (28.5 ml) overnight. The reaction was concentrated and the residue was loaded onto a C18 column, and eluted with 40-55% acetonitrile in water to provide the title compound.

EXAMPLE 311C

4-(((Cis-4-methoxycyclohexyl)methylamino)-3-nitrobenzenesulfonamide

This compound was made from the same procedure that also producted EXAMPLE 311B.

EXAMPLE 311D

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide

The title compound was prepared as described in EXAMPLE 175F by replacing EXAMPLE 175E and EXAMPLE 1F with EXAMPLE 26C and EXAMPLE 311B, respectively. ^{1}H NMR (500 MHz, dimethylsulfoxide-d$_6$) δ 11.17 (s, 2H), 8.55 - 8.62 (m, 2H), 7.78 (dd, 1H), 7.51 (d, 1H), 7.37 - 7.43 (m, 2H), 7.33 (d, 2H), 7.15 (d, 1H), 7.01 - 7.08 (m, 3H), 6.86 (dd, 1H), 6.65 (dd, 1H), 6.39 (s, 1H), 6.14 (d, 1H), 3.25 (t, 2H), 3.22 (s, 3H), 3.00 - 3.10 (m, 5H), 2.72 (s, 2H), 2.15 (d, 6H), 2.00 (d, 2H), 1.94 (s, 2H), 1.78 (d, 2H), 1.53 - 1.65 (m, 1H), 1.38 (t, 2H), 0.96 - 1.12 (m, 4H), 0.92 (s, 6H).

EXAMPLE 312

Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide

The title compound (trifluroacetic acid salt) was obtained during the purification of EXAMPLE 310C. ^{1}H NMR (500 MHz, dimethylsulfoxide-d$_6$) δ 11.39 (s, 1H), 11.18 (s, 1H), 9.17 (s, 1H), 8.61 (t, 1H), 8.58 (d, 1H), 7.78 (dd, 1H), 7.54 (d, 1H), 7.34 - 7.43 (m, 5H), 7.14 (d, 1H), 7.07 (t, 3H), 6.85 (dd, 1H), 6.69 (d, 1H), 6.39 (s, 1H), 6.21 (s, 1H), 3.77 (s, 1H), 3.58 (s, 2H), 3.24 - 3.29 (m, 2H), 2.91 - 3.07 (m, 2H), 2.60 - 2.81 (m, 2H), 2.17 (s, 2H), 2.00 (s, 2H), 1.57 - 1.72 (m, 4H), 1.43 (t, 7H), 0.94 (s, 6H).

EXAMPLE 313

Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide

The title compound was prepared as described in EXAMPLE 175F by replacing EXAMPLE 175E and EXAMPLE 1F with EXAMPLE 26C and EXAMPLE 311C, respectively. ^{1}H NMR (500 MHz, dimethylsulfoxide-d $_6$) δ 11.17 (s, 2H), 8.60 (t, 1H), 8.58 (d, 1H), 7.78 (dd, 1H), 7.51 (d, 1H), 7.37 - 7.44 (m, 2H), 7.33 (d, 2H), 7.16 (d, 1H), 7.07 (d, 1H), 7.03 (d, 2H), 6.86 (dd, 1H), 6.65 (dd, 1H), 6.39 (s, 1H), 6.14 (d, 1H), 3.36 - 3.39 (m, 1H), 3.26 (t, 2H), 3.20 (s, 3H), 3.03 (s, 4H), 2.72 (s, 2H), 2.15 (d, 6H), 1.94 (s, 2H), 1.81 (dd, 2H), 1.63 - 1.73 (m, 1H), 1.48 (dd, 2H), 1.23 - 1.41 (m, 6H), 0.92 (s, 6H).

EXAMPLE 314

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[3-nitro-4-(2-tetrahydro-2H-pyran-4-ylethoxy)phenyl]sulfonyl}benzamide

EXAMPLE 314A

3-nitro-4-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)benzenesulfonamide

The title compound was prepared by substituting 2-(tetrahydro-2H-pyran-4-yl)ethanol for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 279A.

EXAMPLE 314B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[3-nitro-4-(2-tetrahydro-2H-pyran-4-ylethoxy)phenyl]sulfonyl}benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 26C and EXAMPLE 314A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.25 (s, 1H), 8.25 (d, 1H), 7.95 (dd, 1H), 7.54 (d, 1H), 7.39 (d, 1H), 7.34 (d, 2H), 7.29 (m, 1H), 7.17 (m, 1H), 7.04 (d, 2H), 6.97 (m, 1H), 6.70 (dd, 1H), 6.41 (d, 1H), 6.28 (m, 2H), 4.26 (t, 2H), 3.83 (m, 2H), 3.27 (m, 2H), 3.07 (m, 4H), 2.80 (m, 2H), 2.15 (m, 6H), 1.96 (s, 2H), 1.70 (m, 3H), 1.60 (m, 2H), 1.39 (t, 2H), 1.22 (m, 2H), 0.93 (s, 6H).

EXAMPLE 315

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(2-methoxyethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 309A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.17 (s, 1H), 8.18 (d, 1H), 7.92 (dd, 1H), 7.49 (d, 1H), 7.40 (m, 2H), 7.33 (d, 2H), 7.26 (m, 1H), 7.17 (d, 1H), 7.04 (m, 3H), 6.86 (dd, 1H), 6.65 (dd, 1H), 6.40 (m, 1H), 6.14 (d, 1H), 3.51 (m, 4H), 3.28 (s, 3H), 3.03 (s, 4H), 2.74 (m, 2H), 2.16 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 316

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[3-(methylsulfonyl)propoxy]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 316A

4-(3-(methylthio)propoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 3-(methylthio)propan-1-ol for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 279A.

EXAMPLE 316B

4-(3-(methylsulfonyl)propoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 316A for EXAMPLE 294A in EXAMPLE 294B.

EXAMPLE 316C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[3-(methylsulfonyl)propoxy]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 26C and EXAMPLE 316B for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.24 (s, 1H), 8.28 (d, 1H), 7.96 (dd, 1H), 7.54 (d, 1H), 7.35 (m, 3H), 7.29 (t, 1H), 7.17 (d, 1H), 7.04 (d, 2H), 6.96 (m, 1H), 6.71 (dd, 1H), 6.39 (d, 1H), 6.29 (m, 2H), 4.34 (t, 2H), 3.27 (m, 4H), 3.07 (m, 4H), 3.03 (s, 3H), 2.81 (s, 2H), 2.21 (m, 6H), 1.96 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

EXAMPLE 317

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(3-methoxypropyl)amino]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 317A

4-(3-methoxypropylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 3-methoxypropan-1-amine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 317B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(3-methoxypropyl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 26C for EXAMPLE 1E and EXAMPLE 317A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (500 MHz, pyridine-d5) δ 12.24 (s, 1H), 9.30 (d, 1H), 8.88 (t, 1H), 8.28 (dd, 1H), 8.19 (d, 1H), 7.51 - 7.56 (m, 2H), 7.41 - 7.46 (m, 3H), 7.04 - 7.12 (m, 3H), 6.78 (d, 1H), 6.73 (dd, 1H), 6.60 (s, 1H), 6.55 (d, 1H), 3.40 (t, 2H), 3.29 - 3.36 (m, 2H), 3.27 (s, 3H), 3.01 - 3.08 (m, 4H), 2.76 (s, 2H), 2.25 (t, 2H), 2.06 - 2.15 (m, 4H), 1.97 (s, 2H), 1.78 - 1.86 (m, 2H), 1.38 (t, 2H), 0.93 (s, 6H).

EXAMPLE 318

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(3-methoxypropyl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 1E and EXAMPLE 317A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (500 MHz, pyridine-d_5) δ 12.39 (s, 1H), 9.21 (d, 1H), 8.86 (t, 1H), 8.15 - 8.24 (m, 2H), 7.42 - 7.50 (m, 3H), 7.38 (d, 1H), 7.04 - 7.13 (m, 3H), 6.73 - 6.81 (m, 4H), 6.67 (d, 1H), 3.39 (t, 2H), 3.32 (q, 2H), 3.27 (s, 3H), 2.96 - 3.07 (m, 4H), 2.76 (s, 2H), 2.25 (t, 2H), 2.07 - 2.16 (m, 4H), 1.97 (s, 2H), 1.77 - 1.87 (m, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

EXAMPLE 319

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-cyanoethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

EXAMPLE 319A

4-(2-cyanoethylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 3-aminopropanenitrile for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 319B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-cyanoethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 26C for EXAMPLE 1E and EXAMPLE 319A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (500 MHz, pyridine-d_5) δ 9.26 (d, 1H), 9.06 (t, 1H), 8.34 (dd, 1H), 8.18 (d, 1H), 7.51 - 7.57 (m, 2H), 7.39 - 7.47 (m, 3H), 7.04 - 7.11 (m, 3H), 7.00 (d, 1H), 6.74 (dd, 1H), 6.60 (s, 1H), 6.54 (d, 1H), 3.83 (q, *J*=6.7 Hz, 2H), 3.01 - 3.08 (m, 4H), 2.98 (t, 2H), 2.76 (s, 2H), 2.25 (t, 2H), 2.07 - 2.15 (m, 4H), 1.97 (s, 2H), 1.38 (t, 2H), 0.93 (s, 6H).

EXAMPLE 320

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-cyanoethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 1E and EXAMPLE 319A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (500 MHz, pyridine-d_5) δ 12.41 (s, 1H), 9.16 (d, 1H), 9.05 (t, 1H), 8.31 (dd, 1H), 8.17 (d, 1H), 7.39 (d, 1H), 7.05 - 7.13 (m, 3H), 6.99 (d, 1H), 6.78 (dd, 1H), 6.72 - 6.76 (m, 2H), 6.66 (d, 1H), 3.83 (q, 2H), 3.01 - 3.07 (m, 4H), 2.98 (t, 2H), 2.76 (s, 2H), 2.25 (t, 2H), 2.08 - 2.16 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

EXAMPLE 321

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(3R)-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 310C by replacing EXAMPLE 310A with 5-aminomethyl-admantan-2-ol. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.17 (s, 2H), 8.57 (d, 1H), 8.51 (t, 1H), 7.76 (dd, 1H), 7.50 (d, 1H), 7.38 - 7.42 (m, 2H), 7.33 (d, 2H), 7.11 - 7.16 (m, 2H), 7.03 (d, 2H), 6.86 (dd, 1H), 6.65 (dd, 1H), 6.39 (s, 1H), 6.14 (d, 1H), 4.61 (d, 1H), 3.63 (d, 1H), 3.13 (d, 2H), 3.03 (s, 4H), 2.73 (s, 2H), 2.11 - 2.21 (m, 6H), 2.04 (d, 2H), 1.95 (s, 2H), 1.78 - 1.86 (m, 3H), 1.49 - 1.60 (m, 6H), 1.38 (t, 2H), 1.29 (d, 2H), 0.92 (s, 6H).

EXAMPLE 322

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[Cis-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 310C by replacing EXAMPLE 310A with 5-aminomethyl-admantan-2-ol. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.16 (s, 2H), 8.57 (d, 1H), 8.52 (t, 1H), 7.71 - 7.80 (m, 1H), 7.51 (d, 1H), 7.37 - 7.42 (m, 2H), 7.33 (d, 2H), 7.09 - 7.17 (m, 2H), 7.03 (d, 2H), 6.85 (dd, 1H), 6.65 (dd, 1H), 6.39 (s, 1H), 6.14 (d, 1H), 4.61 (d, 1H), 3.61 (d, 1H), 3.08 (d, 2H), 3.03 (s, 4H), 2.72 (s, 2H), 2.09 - 2.21 (m, 6H), 1.82 - 1.96 (m, 7H), 1.55 - 1.69 (m, 4H), 1.49 (s, 2H), 1.38 (t, 2H), 1.19 - 1.27 (m, 3H), 0.92 (s, 6H).

EXAMPLE 323

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(3,3,3-trifluoropropyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 323A

3-nitro-4-(3,3,3-trifluoropropylamino)benzenesulfonamide

The title compound was prepared by substituting 3,3,3-trifluoropropan-1-amine for (tetrahydro-2H-pyran-4-yl)methanamine in EXAMPLE 1F.

EXAMPLE 323B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(3,3,3-trifluoropropyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 323A for EXAMPLE 1F and EXAMPLE 55B for EXAMPLE 26C in EXAMPLE 177. ^{1}H NMR (500 MHz, dimethylsulfoxide-d $_6$) δ 11.34 (s, 1H), 11.19 (s, 1H), 8.53 (m, 1H), 8.47 (s, 1H), 7.74 (dd, 1H), 7.54 (d, 1H), 7.34 (d, 2H), 7.25 (m, 1H), 7.13 (d, 1H), 6.99 (m, 4H), 6.67 (d, 1H), 6.36 (d, 1H), 6.24 (m, 2H), 3.65 (q, 2H), 3.01 (m, 4H), 2.68 (m, 4H), 2.16 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.93 (s, 6H).

EXAMPLE 324

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(3,3,3-trifluoropropyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 323A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500 MHz, dimethylsulfoxide-d $_6$) δ 11.06 (s, 1H), 8.44 (m, 2H), 7.75 (dd, 1H), 7.54 (d, 1H), 7.33 (m, 4H), 7.02 (m, 3H), 6.90 (d, 1H), 6.76 (dd, 1H), 6.58 (dd, 1H), 6.33 (m, 1H), 6.15 (d, 1H), 3.63 (q, 2H), 2.97 (m, 4H), 2.68 (m, 4H), 2.16 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 325

N-({5-bromo-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)benzamide

EXAMPLE 325A

5-bromo-6-((tetrahydro-2H-pyran-4-yl)methylamino)pyridine-3-sulfonamide

The mixture of EXAMPLE 329A (93 mg), (tetrahydro-2H-pyran-4-yl)methanamine (40 mg) and triethylamine (0.144 mL) in anhydrous dixoane (4 mL) was heated at 110°C overnight. The organic solvent was removed under vacuum. The residue was suspended in dichloromethane. The solid was filtered and dried to afford the title compound.

EXAMPLE 325B

N-({5-bromo-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 26C and EXAMPLE 325A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.28 (s, 1H), 11.10 (s, 1H), 8.38 (d, 1H), 7.93 (d, 1H), 7.57 (d, 1H), 7.32 (m, 4H), 7.22 (d, 1H), 7.02 (m, 3H), 6.71 (dd, 1H), 6.51 (d, 1H), 6.27 (m, 2H), 3.82 (dd, 2H), 3.31 (m, 2H), 3.23 (m, 2H), 3.05 (m, 4H), 2.74 (s, 2H), 2.16 (m, 6H), 1.95 (s, 2H), 1.88 (m, 1H), 1.55 (m, 2H), 1.37 (m, 2H), 1.18 (m, 2H), 0.92 (s, 6H).

EXAMPLE 326

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1,1-dioxidotetrahydrothien-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 337A for 4-chloro-3-nitrobenzene sulfonamide and (1,1-dioxidotetrahydrothien-3-yl)methylamine hydrochloride for 1-(2-methoxy-ethyl)-piperidin-4-ylamine in EXAMPLE 189A. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.25 (s, 1H), 8.71 (m, 1H), 8.51 (d, 1H), 7.72 (dd, 1H), 7.53 (d, 1H), 7.34 (d, 2H), 7.29 (m, 1H), 7.18 (d, 1H), 7.12 (d, 1H), 7.04 (d, 2H), 6.98 (m, 1H), 6.70 (dd, 1H), 6.44 (d, 1H), 6.26 (dd, 2H), 3.55 (t, 2H), 3.27 (m, 2H), 3.04 (m, 5H), 2.91 (m, 1H), 2.74 (s, 3H), 2.28 (m, 1H), 2.16 (m, 6H), 1.95 (s, 2H), 1.85 (m, 1H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 327

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 306D for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.16 (s, 2H), 8.41 (d, 1H), 8.10 (dd, 1H), 7.51 (d, 1H), 7.39-7.46 (m, 3H), 7.34 (d, 2H), 7.16 (s, 1H), 7.04 (d2H), 6.85 (dd, 1H), 6.64 (dd, 1H), 6.40 (d, 1H), 6.15 (d, 1H), 4.38 (d, 2H), 3.76-3.80 (m, 2H), 3.56-3.61 (m, 2H), 3.05 (s, 4H), 2.78 (s, 2H), 2.12-2.23 (m, 6H), 1.95 (s, 2H), 1.80-1.89 (m, 4H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 328

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-(methylamino)-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

EXAMPLE 328A

4-(methylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 159C for 4-fluoro-3-nitrobenzenesulfonamide and methylamine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 328B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-(methylamino)-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 328A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.17 (s, 1H), 8.17 (d, 1H), 7.91 (dd, 1H), 7.49 (d, 1H), 7.40 (m, 3H), 7.33 (d, 2H), 7.16 (m, 1H), 7.04 (d, 2H), 6.87 (m, 2H), 6.65 (dd, 1H), 6.40 (m, 1H), 6.14 (d, 1H), 3.03 (m, 4H), 2.91 (d, 3H), 2.73 (s, 2H), 2.15 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 329

N-{[5-bromo-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide

EXAMPLE 329A

5-bromo-6-chloropyridine-3-sulfonamide

5-Bromo-6-chloropyridine-3-sulfonyl chloride (8.2 g) in methanol (20 mL) was cooled to 0 °C. To this mixture was added 7N NH_3 in methanol (80 mL). The reaction mixture was stirred overnight. The solvent was removed at low temperature, and the residue was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried ($MgSO_4$),

filtered, and concentrated. The solid was purified by flash column chromatography on silica gel using 10-50% ethyl acetate in hexanes to give the title compound.

EXAMPLE 329B

5-bromo-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

(Tetrahydro-2H-pyran-4-yl)methanol (0.65 g) in tetrahydrofuran (20 mL) was treated with 60% sodium hydride (0.895 g). The reaction mixture was stirred for 10 minutes. To this mixture was added EXAMPLE 329A (1.519 g). The reaction mixture was stirred overnight. It was poured into water, neutralized with 10 % aqueous HCl, and extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel eluting with 20%-60% ethyl acetate in hexanes to give the title compound.

EXAMPLE 329C

N-{[5-bromo-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 329B for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.15 (s, 1H), 8.60 s, 1H), 8.38 (d, 1H), 7.54 (d, 1H), 7.38-7.42 (m, 2H), 7.34 (d, 2H), 7.17 (s, 1H), 7.04 (d, 2H), 6.85 (dd, 1H), 6.64 (dd, 1H), 6.39 (s, 1H), 6.14 (d, 1H), 4.25 (d, 2H), 3.87 (dd, 2H), 3.05 (s, 4H), 2.80 (s, 2H), 2.25 (s, 4H), 2.12-2.14 (m, 4H), 1.95 (s, 2H), 1.63-1.66 (m, 2H), 1.37-1.40 (m, 2H), 0.92 (s, 6H).

EXAMPLE 330

4-(4-{[4-(4-chlorophenyl)-6-isopropoxypyridin-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 330A

1-((4-(4-chlorophenyl)-6-isopropoxypyridin-3-yl)methyl)piperazine

The title compound was prepared by substituting EXAMPLE 307F for EXAMPLE 1A in EXAMPLE 1B.

EXAMPLE 330B

ethyl 2-(1H-indol-5-yloxy)-4-(4-((4-(4-chlorophenyl)-6-isopropoxypyridin-3-yl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 330A for EXAMPLE 20C and EXAMPLE 26A for EXAMPLE 20A in EXAMPLE 20D.

EXAMPLE 330C

2-(1H-indol-5-yloxy)-4-(4-((4-(4-chlorophenyl)-6-isopropoxypyridin-3-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 330B for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 330D

4-(4-{[4-(4-chlorophenyl)-6-isopropoxypyridin-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 330C for EXAMPLE 26C in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.21, (s, 1H), 11.17 (s, 1H), 8.63 (t, 1H), 8.59 (d, 1H), 8.08 (s, 1H), 7.79 (dd1H), 7.54-7.56 (m, 3H), 7.47 (d, 2H), 7.38-7.42 (m, 2H), 7.15 (d, 1H), 7.10 (d, 1H), 6.87 (dd, 1H), 6.68 (dd, 1H), 6.59 (s, 1H), 6.39 (s, 1H), 6.17 (d, 1H), 5.23-5.28 (m, 1H), 3.85 (dd, 2H), 3.24-3.31 (m, 4H), 3.02 (s, 4H), 2.29 (s, 4H), 1.86-1.91 (m, 1H), 1.61-1.63 (m, 2H), 1.28 (d, 6H).

EXAMPLE 331

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[6-(tetrahydro-2H-pyran-4-ylmethoxy)-5-(1,3-thiazol-2-yl)pyridin-3-yl]sulfonyl}benzamide

EXAMPLE 331A

6-((tetrahydro-2H-pyran-4-yl)methoxy)-5-(thiazol-2-yl)pyridine-3-sulfonamide

A mixture of EXAMPLE 329B (0.070 g), 2-(tributylstannyl)thiazole (0.090 g), and tetrakis(triphenylphosphine)palladium(0) (0.069 g) in dioxane (2 mL) was heated at 90 °C for 4 hours. After cooling, the mixture was loaded onto a silica gel column and eluting with 1:3 ethyl acetate:hexanes to give the title compound.

EXAMPLE 331B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[6-(tetrahydro-2H-pyran-4-ylmethoxy)-5-(1,3-thiazol-2-yl)pyridin-3-yl]sulfonyl}benzamide

The title compound was prepared by substituting EXAMPLE 331A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.14 (s, 1H), 9.09 (s, 1H), 8.73 (s, 1H), 8.06 (d, 1H), 7.98 (d, 1H), 7.50 (d, 1H), 7.37-7.38 (m, 2H), 7.33 (d, 2H), 7.17 (d, 1H), 7.03 (d, 2H), 6.84 (dd, 1H), 6.62 (dd, 1H), 6.37 (s, 1H), 6.11 (d, 1H), 4.46 (d, 2H), 3.91 (dd, 2H), 3.36-3.39 (m, 4H), 3.02 (s, 4H), 2.76 (s, 2H), 2.12-2.20 (s, 8H), 1.94 (s, 2H), 1.45-1.47 (m, 2H), 1.37 (t, 2H), 0.91 (s, 6H).

EXAMPLE 332

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(2-methoxyethyl)amino]carbonyl}phenyl)sulfonyl]benzamide

EXAMPLE 332A

N-(2-methoxyethyl)-4-sulfamoylbenzamide

The title compound was prepared by substituting 2-methoxyethanamine for (tetrahydro-2H-pyran-4-yl)methanamine in EXAMPLE 308A.

EXAMPLE 332B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(2-methoxyethyl)amino]carbonyl}phenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 332A for EXAMPLE 1F and EXAMPLE 26C for EXAMPLE 1E in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.28 (br s, 1H), 11.17 (s, 1H), 8.71 (m, 1H), 7.94 (m, 4H), 7.48 (d, 1H), 7.41 (m, 2H), 7.33 (d, 2H), 7.21 (d, 1H), 7.03 (d, 2H), 6.88 (dd, 1H), 6.63 (dd, 1H), 6.42 (t, 1H), 6.13 (d, 1H), 3.45 (m, 4H), 3.27 (s, 3H), 3.03 (m, 4H), 2.73 (br s, 2H), 2.16 (m, 6H), 1.95 (br s, 2H), 1.38 (m, 2H), 0.92 (s, 6H).

EXAMPLE 333

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide

EXAMPLE 333A

5-cyano-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

A mixture of EXAMPLE 329B (0.702 g), dicyanozinc (0.129 g), and tetrakis(triphenylphosphine)palladium(0) (0.231 g) in N,N-dimethylformamide (2 mL) was degassed via vacuum/nitrogen cycle three times. The reaction mixture was heated at 120 °C for 3 hours. After cooling, it was poured into water and extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel eluting with 20%-60% ethyl acetate in hexanes to give the title compound.

EXAMPLE 333B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 333A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.17 (s, 1H), 8.84 (d, 1H), 8.64 (d, 1H), 7.57 (d, 1H), 7.38-7.41 (m, 4H), 7.12 (d, 1H), 7.08 (d, 2H), 6.87 (dd, 1H), 6.71 (dd, 1H), 6.38 (s, 1H), 6.23 (d, 1H), 4.31 (d, 2H), 3.88 (dd, 2H), 3.54 (br s, 2H), 3.02 (br s, 4H), 2.76 (br s, 2H), 2.18(s, 4H), 2.01 (s, 2H), 1.63-1.66 (m, 2H), 1.49 (t, 2H), 0.94 (s, 6H).

EXAMPLE 334

N-({4-[(1-acetylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting 1-acetylpiperidin-4-amine for 1-(2-methoxy-ethyl)-piperidin-4-ylamine and EXAMPLE 310B for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 189A. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.16 (br s, 1H), 8.58 (d, 1H), 8.25 (d, 1H), 7.81 (dd, 1H), 7.51 (d, 1H), 7.43-7.37 (m, 2H),

7.34 (d, 2H), 7.19 (d, 1H), 7.15 (d, 1H), 7.04 (d, 2H), 6.85 (dd, 1H), 6.65 (dd, 1H), 6.39 (t, 1H), 6.15 (d, 1H), 4.32-4.23 (m, 1H), 3.96-3.77 (m, 2H), 3.21 (m, 2H), 3.03 (m, 4H), 2.80 (m, 2H), 2.73 (br s, 2H), 2.16 (m, 6H), 2.02 (s, 3H), 1.95 (br s, 2H), 1.65-1.44 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 335

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[1-(methylsulfonyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]benzamide

The title compound was prepared by substituting 1-(methylsulfonyl)piperidin-4-amine for 1-(2-methoxy-ethyl)-piperidin-4-ylamine and EXAMPLE 187A for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 189A. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.15 (br s, 1H), 8.59 (d, 1H), 8.25 (d, 1H), 7.82 (dd, 1H), 7.51 (d, 1H), 7.43-7.38 (m, 2H), 7.34 (d, 2H), 7.14 (m, 2H), 7.04 (d, 2H), 6.85 (dd, 1H), 6.65 (dd, 1H), 6.39 (t, 1H), 6.15 (d, 1H), 3.80 (m, 1H), 3.57 (m, 2H), 3.04 (m, 4H), 2.95 (m, 2H), 2.92 (br s, 3H), 2.73 (m, 2H), 2.15 (m, 6H), 2.06-1.98 (m, 2H), 1.95 (br s, 2H), 1.70 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 336

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

EXAMPLE 336A

4-((1,4-dioxan-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared as described in EXAMPLE 1F by replacing (tetrahydro-2H-pyran-4-yl)methanamine with (1,4-dioxan-2-yl)methanamine.

EXAMPLE 336B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 175F by replacing EXAMPLE 175E and EXAMPLE 1F with EXAMPLE 26C and EXAMPLE 336A, respectively. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.16 (s, 2H), 8.54 - 8.63 (m, 2H), 7.82 (dd, 1H), 7.50 (d, 1H), 7.38 - 7.42 (m, 2H), 7.33 (d, 2H), 7.16 (d, 1H), 7.10 (d, 1H),

7.03 (d, 2H), 6.86 (dd, 1H), 6.65 (dd, 1H), 6.39 (s, 1H), 6.14 (d, 1H), 3.76 - 3.82 (m, 3H), 3.57 - 3.68 (m, 2H), 3.45 - 3.52 (m, 2H), 3.36 - 3.42 (m, 1H), 3.03 (s, 4H), 2.73 (d, 2H), 2.10 - 2.22 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 337

N-({4-[(1-acetylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)benzamide

EXAMPLE 337A

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 1E and 4-chloro-3-nitrobenzenesulfonamide for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 337B

N-({4-[(1-acetylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)benzamide

The title compound was prepared by substituting 1-acetylpiperidin-4-amine for 1-(2-methoxy-ethyl)-piperidin-4-ylamine and EXAMPLE 337A for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 189A. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.24 (br s, 1H), 8.50 (d, 1H), 8.24 (d, 1H), 7.73 (dd, 1H), 7.52 (d, 1H), 7.34 (d, 2H), 7.27 (t, 1H), 7.19-7.13 (m, 2H), 7.04 (t, 2H), 6.97 (t, 1H), 6.70 (dd, 1H), 6.42 (d, 1H), 6.27 (dd, 1H), 6.24 (t, 1H), 4.29 (m, 1H), 3.97-3.78 (m, 2H), 3.22 (m, 2H), 3.05 (m, 4H), 2.81 (m, 2H), 2.72 (br s, 2H), 2.15 (m, 6H), 2.03 (s, 3H), 1.95 (br s, 2H), 1.66-1.44 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 338

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[1-(methylsulfonyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]benzamide

The title compound was prepared by substituting 1-(methylsulfonyl)piperidin-4-amine for 1-(2-methoxy-ethyl)-piperidin-4-ylamine and EXAMPLE 337A for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 189A. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.24 (br s, 1H), 8.50 (d, 1H), 8.25 (d, 1H), 7.74 (dd, 1H), 7.52 (d, 1H), 7.34 (d, 2H), 7.27 (t,

1H), 7.17 (d, 1H), 7.12 (d, 1H), 7.04 (d, 2H), 6.97 (t, 1H), 6.70 (dd, 1H), 6.42 (d, 1H), 6.27 (d, 1H), 6.24 (t, 1H), 3.81 (m, 1H), 3.58 (m, 2H), 3.05 (m, 4H), 2.96 (m, 2H), 2.92 (s, 3H), 2.74 (m, 2H), 2.16 (m, 6H), 2.06-1.98 (m, 2H), 1.95 (br s, 2H), 1.70 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 339

4-(4-{[4'-chloro-5-(trifluoromethyl)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 339A

methyl 2-(1H-indol-5-yloxy)-4-(4-(2-bromo-4-(trifluoromethyl)benzyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting 4-trifluoromethyl-2-bromobenzaldehyde for EXAMPLE 27C and EXAMPLE 150A for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 339B

methyl 2-(1H-indol-5-yloxy)-4-(4-((4'-chloro-5-(trifluoromethyl)biphenyl-2-yl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 339A for 2-fluoro-4-iodo-5-methylpyridine in EXAMPLE 307A.

EXAMPLE 339C

2-(1H-indol-5-yloxy)-4-(4-((4'-chloro-5-(trifluoromethyl)biphenyl-2-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 339B for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 339D

4-(4-{[4'-chloro-5-(trifluoromethyl)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 339C for EXAMPLE 26C in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.24, (s,

1H), 11.17 (s, 1H), 8.63 (t, 1H), 7.79 (dd, 1H), 7.72 (m, 2H), 7.38-7.53 (m, 8H), 7.15 (d, 1H), 7.10 (d, 1H), 6.87 (dd, 1H), 6.67 (dd, 1H), 6.39 (s, 1H), 6.16 (d, 1H), 3.85 (dd, 2H), 3.41 (s, 2H), 3.24-3.31 (m, 6H), 3.04 (s, 4H), 2.29 (s, 4H), 1.60-1.63 (m, 2H), 1.24-1.28 (m, 2H).

EXAMPLE 340

4-(4-{[4'-chloro-5-(trifluoromethyl)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}benzamide

The title compound was prepared by substituting EXAMPLE 339C for EXAMPLE 26C and EXAMPLE 279A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.40, (s, 1H), 11.17 (s, 1H), 8.41 (d, 1H), 8.07 (dd, 1H), 7.70-7.74 (m, 2H), 7.38-7.53 (m, 8H), 7.16 (d, 1H), 6.87 (dd, 1H), 6.67 (dd, 1H), 6.40 (s, 1H), 6.17 (d, 1H), 4.09 (d, 2H), 3.88 (dd, 2H), 3.42 (s, 2H), 3.05 (s, 4H), 2.30 (s, 4H), 2.00-2.05 (m, 1H), 1.63-1.66 (m, 2H), 1.31-1.37 (m, 2H).

EXAMPLE 341

4-{4-[(5-tert-butyl-4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 341A

methyl 2-(1H-indol-5-yloxy)-4-(4-(2-bromo-4-tert-butylbenzyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting 4-tert-butyl-2-bromobenzaldehyde for EXAMPLE 27C and EXAMPLE 150A for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 341B

methyl 2-(1H-indol-5-yloxy)-4-(4-((5-tert-butyl-4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 341A for 2-fluoro-4-iodo-5-methylpyridine in EXAMPLE 307A.

EXAMPLE 341C

2-(1H-indol-5-yloxy)-4-(4-((5-tert-butyl-4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 341B for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 341D

4-{4-[(5-tert-butyl-4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 341C for EXAMPLE 26C in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.22, (s, 1H), 11.16 (s, 1H), 8.62 (t, 1H), 8.58 (d, 1H), 7.79 (dd, 1H), 7.53 (d, 1H), 7.34-7.44 (m, 8H), 7.18 (s, 1H), 7.14 (d, 1H), 7.09 (d, 1H), 6.86 (dd, 1H), 6.67 (dd, 1H), 6.39 (s, 1H), 6.17 (d, 1H), 3.85 (dd, 2H), 3.24-3.30 (m, 6H), 3.04 (s, 4H), 2.29 (s, 4H), 1.86-1.91 (m, 1H), 1.60-1.63 (m, 2H), 1.28 (s, 9H).

EXAMPLE 342

4-{4-[(5-tert-butyl-4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}benzamide

The title compound was prepared by substituting EXAMPLE 341C for EXAMPLE 26C and EXAMPLE 279A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.25, (br s, 1H), 11.16 (s, 1H), 8.40 (d, 1H), 8.06 (dd, 1H), 7.52 (d, 1H), 7.35-7.46 (m, 8H), 7.19 (s, 1H), 7.15 (d, 1H), 6.85 (dd, 1H), 6.66 (dd, 1H), 6.39 (s, 1H), 6.17 (d, 1H), 4.08 (d, 2H), 3.88 (dd, 2H), 3.05 (s, 4H), 2.32 (s, 4H), 1.64 (dd, 2H), 1.32-1.37 (m, 2H), 1.28 (s, 9H).

EXAMPLE 343

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 343A

3-nitro-4-(2,2,2-trifluoroethylamino)benzenesulfonamide

The title compound was prepared by substituting 2,2,2-trifluoroethanamine for (tetrahydro-2H-pyran-4-yl)methanamine in EXAMPLE 1F.

EXAMPLE 343B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 343A for EXAMPLE 1F and EXAMPLE 55B for EXAMPLE 26C in EXAMPLE 177. ^{1}H NMR (500 MHz, dimethylsulfoxide-d$_6$) δ 10.98 (s, 1H), 8.41 (m, 2H), 7.75 (dd, 1H), 7.54 (d, 1H), 7.34 (d, 2H), 7.28 (m, 2H), 7.06 (m, 3H), 6.93 (m, 1H), 6.70 (dd, 1H), 6.53 (dd, 1H), 6.30 (m, 1H), 6.14 (d, 1H), 4.32 (m, 2H), 2.93 (m, 4H), 2.71 (s, 2H), 2.16 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 344

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 343A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500 MHz, dimethylsulfoxide-d$_6$) δ 11.05 (s, 1H), 8.40 (m, 2H), 7.77 (dd, 1H), 7.60 (d, 1H), 7.34 (d, 2H), 7.18 (m, 1H), 7.12 (d, 1H), 7.04 (m, 3H), 6.88 (t, 1H), 6.58 (dd, 1H), 6.22 (m, 3H), 4.33 (m, 2H), 2.93 (m, 4H), 2.71 (s, 2H), 2.16 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.93 (s, 6H).

EXAMPLE 345

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-{[(tetrahydro-2H-pyran-4-ylmethyl)amino]carbonyl}phenyl)sulfonyl]benzamide

EXAMPLE 345A

3-sulfamoyl-N-((tetrahydro-2H-pyran-4-yl)methyl)benzamide

The title compound was prepared by substituting 3-sulfamoylbenzoic acid for 4-sulfamoylbenzoic acid in EXAMPLE 308A.

EXAMPLE 345B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-{[(tetrahydro-2H-pyran-4-ylmethyl)amino]carbonyl}phenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 345A for EXAMPLE 1F and EXAMPLE 26C for EXAMPLE 1E in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.28 (br s, 1H), 11.18 (s, 1H), 8.75 (t, 1H), 8.41 (m, 1H), 8.10 (d, 1H), 8.01 (d, 1H), 7.60 (t, 1H), 7.48 (d, 1H), 7.41 (m, 2H), 7.33 (d, 2H), 7.23 (d, 1H), 7.03 (d, 2H), 6.88 (dd, 1H), 6.83 (dd, 1H), 6.42 (t, 1H), 6.11 (d, 1H), 3.83 (dd, 2H), 3.19 (m, 4H), 3.02 (m, 4H), 2.73 (m, 2H), 2.16 (m, 6H), 1.94 (br s, 2H), 1.80 (m, 1H), 1.58 (dd, 2H), 1.37 (t, 2H), 1.24 (m, 2H), 0.92 (s, 6H).

EXAMPLE 346

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2R)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

EXAMPLE 346A

(R)-4-((1,4-dioxan-2-yl)methoxy)-3-nitrobenzenesulfonamide

The racemic mixture of EXAMPLE 297A was resolved on a SFC chiral AD column to provide the title compound.

EXAMPLE 346B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2R)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 175F by replacing EXAMPLE 175E and EXAMPLE 1F with EXAMPLE 26C and EXAMPLE 346A, respectively. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.16 (s, 2H), 8.39 (d, 1H), 8.06 (dd, 1H), 7.51 (d, 1H), 7.38 - 7.43 (m, 3H), 7.34 (d, 2H), 7.15 (d, 1H), 7.04 (d, 2H), 6.85 (dd, 1H), 6.64 (dd, 1H), 6.39 (s, 1H), 6.15 (d, 1H), 4.20 - 4.28 (m, 2H), 3.85 - 3.91 (m, 1H), 3.82 (dd, 1H), 3.74 - 3.78 (m, 1H), 3.59 - 3.69 (m, 2H), 3.40 - 3.51 (m, 2H), 3.05 (s, 4H), 2.78 (s, 2H), 2.23 (s, 4H), 2.14 (s, 2H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 347

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2S)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

EXAMPLE 347A

(S)-4-((1,4-dioxan-2-yl)methoxy)-3-nitrobenzenesulfonamide

The racemic mixture of EXAMPLE 297A was resolved on a SFC chiral AD column to provide the title compound.

EXAMPLE 347B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2S)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 175F by replacing EXAMPLE 175E and EXAMPLE 1F with EXAMPLE 26C and EXAMPLE 347A, respectively. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.16 (s, 2H), 8.39 (d, 1H), 8.06 (dd, 1H), 7.51 (d, 1H), 7.38 - 7.43 (m, 3H), 7.34 (d, 2H), 7.15 (d, 1H), 7.04 (d, 2H), 6.85 (dd, 1H), 6.64 (dd, 1H), 6.39 (s, 1H), 6.15 (d, 1H), 4.20 - 4.28 (m, 2H), 3.85 - 3.91 (m, 1H), 3.82 (dd, 1H), 3.74 - 3.78 (m, 1H), 3.59 - 3.69 (m, 2H), 3.40 - 3.51 (m, 2H), 3.05 (s, 4H), 2.78 (s, 2H), 2.23 (s, 4H), 2.14 (s, 2H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 348

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

EXAMPLE 348A

4-(3-morpholinopropylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 159C for 4-fluoro-3-nitrobenzenesulfonamide and 3-morpholinopropan-1-amine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 348B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

5-yloxy)-N-({4-(methylamino)-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 348A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.17 (s, 1H), 8.17 (d, 1H), 7.91 (dd, 1H), 7.49 (d, 1H), 7.40 (m, 3H), 7.33 (d, 2H), 7.15 (d, 1H), 7.03 (m, 3H), 6.85 (dd, 1H), 6.64 (dd, 1H), 6.40 (s, 1H), 6.13 (d, 1H), 3.59 (m, 4H), 3.38 (m, 4H), 3.02 (m, 4H), 2.72 (s, 2H), 2.40 (m, 6H), 2.15 (m, 6H), 1.95 (s, 2H), 1.73 (m, 2H), 0.92 (s, 6H).

EXAMPLE 349

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 26C and EXAMPLE 348A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.25 (s, 1H), 11.08 (m, 1H), 8.12 (d, 1H), 7.81 (dd, 1H), 7.52 (d, 1H), 7.36 (m, 3H), 7.28 (m, 1H), 7.19 (d, 1H), 7.04 (d, 2H), 6.98 (m, 2H), 6.69 (dd, 1H), 6.44 (d, 1H), 6.25 (m, 2H), 3.60 (m, 4H), 3.38 (m, 2H), 3.03 (m, 4H), 2.73 (s, 2H), 2.43 (m, 6H), 2.16 (m, 6H), 1.95 (s, 2H), 1.73 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 350

N-({5-bromo-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 325A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.19 (s, 1H), 11.02(s, 1H), 8.47 (d, 1H), 8.07 (d, 1H), 7.55 (d, 1H), 7.39 (m, 5H), 7.25 (d, 1H), 7.03 (d, 2H), 6.89 (dd, 1H), 6.65 (dd, 1H), 6.42 (s, 1H), 6.11 (d, 1H), 3.82 (dd, 2H), 3.31 (m, 2H), 3.24 (m, 2H), 3.03 (m, 4H), 2.72 (s, 2H), 2.15 (m, 6H), 1.94 (s, 2H), 1.89 (m, 1H), 1.54 (m, 2H), 1.38 (t, 2H), 1.17 (m, 2H), 0.92 (s, 6H).

EXAMPLE 351

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(2-morpholin-4-ylethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

EXAMPLE 351A

4-(2-morpholinoethylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 159C for 4-fluoro-3-nitrobenzenesulfonamide and 2-morpholinoethanamine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 351B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(2-morpholin-4-ylethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 351A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.22 (s, 1H), 11.17 (s, 1H), 8.17 (d, 1H), 7.92 (dd, 1H), 7.61 (s, 1H), 7.48 (d, 1H), 7.40 (m, 2H), 7.33 (d, 2H), 7.15 (d, 1H), 7.03 (d, 2H), 6.93 (d, 1H), 6.85 (dd, 1H), 6.64 (dd, 1H), 6.40 (s, 1H), 6.13 (m, 1H), 3.57 (m, 4H), 3.35 (m, 2H), 3.02 (m, 4H), 2.72 (s, 2H), 2.58 (t, 2H), 2.42 (m, 4H), 2.15 (m, 6H), 1.95 (s, 2H), 1.37 (m, 2H), 0.92 (s, 6H).

EXAMPLE 352

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

EXAMPLE 352A

5-cyano-6-((tetrahydro-2H-pyran-4-yl)methylamino)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 325A for EXAMPLE 329B in EXAMPLE 333A.

EXAMPLE 352B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 352A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.18 (s, 1H), 8.65 (d, 1H), 8.27 (d, 1H), 8.15 (s, 1H), 7.56 (d, 1H), 7.41 (m, 2H), 7.34 (d, 2H), 7.22 (d, 1H), 7.04 (d, 2H), 6.88 (dd, 1H), 6.65 (dd, 1H), 6.41 (m, 1H), 6.12 (d, 1H), 3.82 (dd, 2H), 3.33 (m, 2H), 3.24 (t, 2H), 3.04 (m, 4H), 2.75 (s, 2H), 2.16 (m, 6H), 1.95 (s, 2H), 1.89 (m, 1H), 1.55 (m, 2H), 1.38 (t, 2H), 1.19 (m, 2H), 0.91 (s, 6H).

EXAMPLE 353

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)oxy]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 353A

4-(1-methylpiperidin-4-yloxy)-3-nitrobenzenesulfonamide

To a mixture of 1-methylpiperidin-4-ol (0.542 g) in tetrahydrofuran (10 mL) at 0°C was added NaH (60% in mineral oil) (0.753 g). After stirring for 15 minutes, 4-fluoro-3-nitrobenzenesulfonamide (1.036 g) was added as a solution in tetrahydrofuran (10 mL). The reaction was removed from the ice bath and allowed to warm to room temperature. After 1 hour, the reaction was poured into water and the pH adjusted to ~7 with 1N aqueous HCl. The reaction was extracted with dichloromethane (3 x 100 mL), washed with brine, dried over magnesium sulfate, filtered, and concentrated. The product was suspended in dichloromethane (mL), sonicated and then filtered to give the title compound.

EXAMPLE 353B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)oxy]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 26C for EXAMPLE 1E and EXAMPLE 353A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide) δ 11.03 (s, 1H), 8.21 (d, 1H), 7.87 (dd, 1H), 7.55 (d, 1H), 7.33 (dd, 4H), 7.25 (d, 1H), 7.04 (d, 2H), 6.98 (d, 1H), 6.73 (dd, 1H), 6.56 (d, 1H), 6.33 (s, 1H), 6.14 (d, 1H), 4.79 (s, 1H), 2.96 (s, 6H), 2.72 (s, 2H), 2.57 (s, 3H), 2.18 (s, 6H), 1.94 (m, 6H), 1.39 (m, 2H), 0.92 (s, 6H).

EXAMPLE 354

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 354A

4-((1-methylpiperidin-4-yl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting (1-methylpiperidin-4-yl)methanol for 1-methylpiperidin-4-ol in EXAMPLE 353A.

EXAMPLE 354B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 26C for EXAMPLE 1E and EXAMPLE 354A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide) δ 11.01 (s, 1H), 8.19 (d, 1H), 7.87 (dd, 1H), 7.55 (d, 1H), 7.39 - 7.26 (m, 4H), 7.16 (d, 1H), 7.08 - 7.01 (m, 2H), 6.96 (d, 1H), 6.72 (dd, 1H), 6.54 (d, 1H), 6.32 (s, 1H), 6.14 (d, 1H), 4.05 (d, 2H), 2.95 (s, 4H), 2.89 - 2.59 (m, 7H), 2.17 (s, 6H), 2.00 - 1.78 (m, 5H), 1.53 (s, 2H), 1.37 (m, 2H), 0.92 (s, 6H).

EXAMPLE 355

4-(4-{[4-(4-chlorophenyl)-1-(3-hydroxypropyl)-1,2,5,6-tetrahydropyridin-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 355A

tert-butyl 4-chloro-3-formyl-5,6-dihydropyridine-1(2H)-carboxylate

To N,N-dimethylformamide (3.87 mL) at 0°C, phosphorus oxychloride (3.73 mL) was added dropwise, maintaining the temperature below 5°C. The resulting mixture was diluted with dichloromethane (15 mL) and stirred at room temperature for 1.5 hours. The reaction was then cooled in an ice bath. tert-Butyl 4-oxopiperidine-1-carboxylate (4.98 g) was added as a solution in dichloromethane (20 mL) and the reaction was stirred at room temperature for 1 hour. The reaction mixture was poured over ice and solid sodium acetate, stirred for 15 minutes, and extracted with dichloromethane. The extracts were washed

thoroughly with water and with brine, dried over $MgSO_4$, filtered, and concentrated to obtain the title compound.

EXAMPLE 355B

tert-butyl 4-(4-chlorophenyl)-3-formyl-5,6-dihydropyridine-1(2H)-carboxylate

EXAMPLE 355A (6.14 g), 4-chlorophenylboronic acid (4.10 g) and palladium(II) acetate (0.112 g) were combined in water to give a suspension. Potassium carbonate (8.98 g) and tetrabutylammonium bromide (4.03 g) were added. The resulting mixture was stirred at 45 °C overnight, cooled, and the reaction mixture was diluted with ethyl acetate (200 mL) in order to dissolve any insoluble material, then washed thoroughly with water, dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by flash chromatography eluting with a gradient of 10% ethyl acetate/hexanes to 40% ethyl acetate /hexanes.

EXAMPLE 355C

tert-butyl 3-((4-(3-(1H-indol-4-yloxy)-4-(methoxycarbonyl)phenyl)piperazin-1-yl)methyl)-4-(4-chlorophenyl)-5,6-dihydropyridine-1(2H)-carboxylate

The title compound was prepared by substituting EXAMPLE 355B for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 68B for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 355D

methyl 2-(1H-indol-4-yloxy)-4-(4-((4-(4-chlorophenyl)-1,2,5,6-tetrahydropyridin-3-yl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 355C for EXAMPLE 1A in EXAMPLE 1B.

EXAMPLE 355E

methyl 2-(1H-indol-4-yloxy)-4-(4-((4-(4-chlorophenyl)-1-(3-hydroxypropyl)-1,2,5,6-tetrahydropyridin-3-yl)methyl)piperazin-1-yl)benzoate

EXAMPLE 355D (539 mg), 3-bromopropan-1-ol (83 mg) and triethylamine (0.42 mL) were combined in acetonitrile. The mixture was heated to 60°C overnight, concentrated and then triturated with ether and filtered to give the title compound.

EXAMPLE 355F

2-(1H-indol-4-yloxy)-4-(4-((4-(4-chlorophenyl)-1-(3-hydroxypropyl)-1,2,5,6-tetrahydropyridin-3-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 355E for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 355G

4-(4-{[4-(4-chlorophenyl)-1-(3-hydroxypropyl)-1,2,5,6-tetrahydropyridin-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 355F for EXAMPLE 1E in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.17 (s, 1H), 8.49 (br s, 1H), 8.44 (s, 1H), 7.69 (dd, 1H), 7.56 (d, 1H), 7.40 (d, 1H), 7.24 (m, 1H), 7.13 (m, 3H), 6.98 (m, 1H), 6.94 (t, 1H), 6.86 (dd, 1H), 6.36 (m, 1H), 6.24 (m, 2H), 3.84 (dd, 2H), 3.47 (t, 2H), 3.26 (m, 4H), 2.99 (br s, 4H), 2.80 (m, 3H), 2.44 (m, 2H), 2.21 (m, 4H), 1.86 (m, 1H), 1.73 (m, 2H), 1.62 (m, 2H), 1.26 (m, 5H), 1.17 (m, 2H).

EXAMPLE 356

benzyl 4-({[4-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzoyl]amino}sulfonyl)-2-nitrophenyl]amino}methyl)piperidine-1-carboxylate

EXAMPLE 356A

benzyl 4-((2-nitro-4-sulfamoylphenylamino)methyl)piperidine-1-carboxylate

The title compound was prepared as described in EXAMPLE 1F by replacing (tetrahydro-2H-pyran-4-yl)methanamine with benzyl 4-(aminomethyl)piperidine-1-carboxylate.

EXAMPLE 356B

benzyl 4-({[4-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzoyl]amino}sulfonyl)-2-nitrophenyl]amino}methyl)piperidine-1-carboxylate

The title compound was prepared as described in EXAMPLE 175F by replacing EXAMPLE 175E and EXAMPLE 1F with EXAMPLE 26C and EXAMPLE 356A,

respectively. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.17 (s, 2H), 8.63 (t, 1H), 8.58 (d, 1H), 7.79 (dd, 1H), 7.51 (d, 1H), 7.30 - 7.42 (m, 8H), 7.16 (d, 1H), 7.10 (d, 1H), 7.03 (d, 2H), 6.86 (dd, 1H), 6.65 (dd, 1H), 6.39 (s, 1H), 6.14 (d, 1H), 5.07 (s, 2H), 4.02 (d, 2H), 3.29 - 3.34 (m, 2H), 3.03 (s, 4H), 2.70 - 2.88 (m, 4H), 2.08 - 2.23 (m, 6H), 1.94 (s, 2H), 1.81 - 1.89 (m, 1H), 1.71 (d, 2H), 1.37 (t, 2H), 1.07 - 1.16 (m, 2H), 0.92 (s, 6H).

EXAMPLE 357

N-{[3-(aminocarbonyl)-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide

EXAMPLE 357A

3-cyano-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

To (tetrahydro-2H-pyran-4-yl)methanol (0.206 g) in tetrahydrofuran (5 mL) was added sodium hydride (0.284 g) and the reaction stirred at room temperature for 20 minutes. The reaction was cooled to 0°C and 3-cyano-4-fluorobenzenesulfonamide (0.355 g) in tetrahydrofuran (2 mL) was added dropwise and the reaction was allowed to warm to room temperature. After 3 hours, the reaction was poured into water, made acidic (pH=1) with 1N HCl and extracted with dichloromethane (2 x 75 mL). The organics were combined, washed with brine (50 mL), dried over magnesium sulfate, filtered and concentrated to give the title compound.

EXAMPLE 357B

5-sulfamoyl-2-((tetrahydro-2H-pyran-4-yl)methoxy)benzamide

A mixture of EXAMPLE 357A (0.455 g) in ethanol (3 mL) and tetrahydrofuran (1 mL) was added to hydrogen peroxide (30%, 2 mL) followed by NaOH (1.024 ml) and heated to 35°C for 3 hours. The mixture was poured into dichloromethane (50 mL) and 1N aqueous HCl (25 mL), upon which a precipitate formed. The title compound was extracted into dichloromethane (3 x 50 mL). The organic layer contained a solid which was collected by filtration and dried to give the title compound.

EXAMPLE 357C

N-{[3-(aminocarbonyl)-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 26C for EXAMPLE 1E and EXAMPLE 357B for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300 MHz, CDCL3) δ 10.35 (s, 1H), 8.80 (d, 1H), 8.35 (dd, 2H), 7.91 (d, 1H), 7.44 (d, 2H), 7.39 (d, 1H), 7.34 - 7.29 (m, 1H), 7.22 (d, 2H), 7.07 (d, 1H), 6.99 (dd, 1H), 6.93 - 6.87 (m, 2H), 6.58 (s, 1H), 6.48 (dd, 1H), 6.06 (d, 1H), 5.80 (s, 1H), 4.05 (dd, 4H), 3.46 (dd, 2H), 3.03 (s, 4H), 2.73 (s, 2H), 2.19 (m, 7H), 1.96 (s, 2H), 1.74 (m, 2H), 1.43 (m, 4H), 0.93 (s, 6H).

EXAMPLE 358

4-(4-{[4'-chloro-5-(trifluoromethyl)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 339C for EXAMPLE 26C and EXAMPLE 173C for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.11 (s, 1H), 8.54 (d, 1H), 8.19 (d, 1H), 7.78 (dd, 1H), 7.71-7.74 (m, 2H), 7.44-7.54 (m, 7H), 7.36-7.38 (m, 2H), 7.04-7.07 (m, 2H), 6.87 (dd, 1H), 6.63 (dd, J = 8.7, 1.68 Hz, 1H), 6.36 (s, 1H), 6.16 (d, 1H), 3.93 (dd, 2H), 3.75 (br s, 2H), 3.41 (s, 2H), 3.01-3.07 (m, 6H), 2.66-2.68 (m, 2H), 2.30 (s, 4H), 1.77-1.80 (m, 2H), 1.47-1.53 (m, 2H).

EXAMPLE 359

4-{4-[(5-tert-butyl-4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 341C for EXAMPLE 26C and EXAMPLE 173C for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.11, (s, 1H), 8.53 (t, 1H), 8.19 (d, 1H), 7.76 (dd, 1H), 7.53 (d, 1H), 7.36-7.44 (m, 8H), 7.19 (s, 1H), 7.04-7.07 (m, 2H), 6.81 (dd, 1H), 6.63 (dd, 1H), 6.36 (s, 1H), 6.17 (d, 1H), 3.93 (dd, 2H), 3.74-3.75 (m, 2H), 3.01-3.07 (m, 6H), 2.64-2.67 (m, 2H), 2.29 (s, 4H), 1.99-2.03 (m, 4H), 1.77-1.80 (m, 2H), 1.65-1.67 (m, 2H), 1.28 (s, 9H).

EXAMPLE 360

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(1-methyl-1H-imidazol-5-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide

The title compound was prepared by substituting (1-methyl-1H-imidazol-5-yl)methanamine for (3S,4R)-4-amino-1-benzylpiperidin-3-ol, hydrochloric acid in EXAMPLE 187B. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.17 (s, 1H), 8.81 (t, 1H), 8.59 (d, 1H), 7.83 (dd, 1H), 7.64 (s, 1H), 7.50 (d, 1H), 7.39-7.42 (m, 2H), 7.33 (d, 2H), 7.16-7.17 (m, 2H), 7.03 (d, 2H), 6.98 (s, 1H), 6.85 (dd, 1H), 6.63 (dd, 1H), 6.40 (s, 1H), 6.13 (d, 1H), 4.66 (d, 2H), 3.64 (s, 3H), 3.02 (s, 4H), 2.72 (s, 2H), 2.12-2.16 (m, 6H), 1.94 (s, 2H), 1.37 (t, 2H), 0.92 (s, 6H).

EXAMPLE 361

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(morpholin-4-ylsulfonyl)phenyl]sulfonyl}benzamide

EXAMPLE 361A

4-(morpholinosulfonyl)benzenesulfonamide

The title compound was prepared by substituting 4-(morpholinosulfonyl)benzene-1-sulfonyl chloride for EXAMPLE 66D in EXAMPLE 66E.

EXAMPLE 361B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(morpholin-4-ylsulfonyl)phenyl]sulfonyl}benzamide

The title compound was prepared by substituting EXAMPLE 361A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 10.99 (s, 1H), 7.76 (d, 2H), 7.57 (d, 1H), 7.46 (d, 2H), 7.35 (d, 2H), 7.28 (m, 2H), 7.05 (d, 2H), 6.89 (d, 1H), 6.70 (dd, 1H), 6.57 (dd, 1H), 6.31 (m, 1H), 6.21 (m, 1H), 3.60 (m, 4H), 2.97 (m, 4H), 2.79 (m, 4H), 2.72 (s, 2H), 2.18 (m, 6H), 1.96 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

EXAMPLE 362

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidothiomorpholin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

EXAMPLE 362A

4-[(1,1-dioxidothiomorpholin-4-yl)amino]-3-nitrophenyl}sulfonamide

The title compound was prepared by substituting 4-aminothiomorpholine-1,1-dioxide for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 362B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidothiomorpholin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 362A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.19 (s, 1H), 11.17 (s, 1H), 9.64 (s, 1H), 8.55 (d, 1H), 7.86 (m, 1H), 7.78 (m, 1H), 7.51 (d, 1H), 7.40 (m, 2H), 7.33 (d, 2H), 7.16 (s, 1H), 7.03 (d, 2H), 6.86 (dd, 1H), 6.64 (dd, 1H), 6.39 (s, 1H), 6.13 (d, 1H), 3.50 (m, 4H), 3.17 (m, 4H), 3.02 (m, 4H), 2.72 (s, 2H), 2.15 (m, 6H), 1.94 (s, 2H), 1.37 (t, 2H), 0.91 (s, 6H).

EXAMPLE 363

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 363A

tert-butyl cis-4-morpholinocyclohexylcarbamate

To a mixture of morpholine (4.08 ml) and tert-butyl 4-oxocyclohexylcarbamate (10 g) stirred for 24 hours at room temperature in titanium(IV) isopropoxide (27.5 ml), methanol (10 ml) was added followed by careful addition of sodium borohydride (3.55 g). The reaction mixture was quenched with water, extracted with ether (2 x 100 mL), dried over magnesium sulfate, filtered and concentrated. The crude product was purified by FC (silica

gel 200g, 30% - 100% acetone / hexanes) providing two products, the title compound and trans 4-morpholinocyclohexylcarbamate.

EXAMPLE 363B

cis-4-morpholinocyclohexanamine bis(2,2,2-trifluoroacetate)

The title compound was prepared by substituting EXAMPLE 363A for EXAMPLE 1A in EXAMPLE 1B.

EXAMPLE 363C

4-(cis-4-morpholinocyclohexylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 363B for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 363D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[cis-(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 26C for EXAMPLE 1E and EXAMPLE 363C for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (500 MHz, pyridine-d_5) δ 12.28 (s, 1H), 9.31 (d, 1H), 8.65 (d, 1H), 8.34 (dd, 1H), 8.17 (d, 1H), 7.53 - 7.57 (m, 2H), 7.40 - 7.47 (m, 3H), 7.03 - 7.12 (m, 3H), 6.89 (d, 1H), 6.72 (dd, 1H), 6.62 (s, 1H), 6.54 (d, 1H), 3.69 - 3.75 (m, 4H), 3.67 (s, 1H), 3.00 - 3.07 (m, 4H), 2.75 (s, 2H), 2.41 - 2.47 (m, 4H), 2.24 (t, 2H), 2.07 - 2.16 (m, 5H), 1.97 (s, 2H), 1.76 - 1.85 (m, 2H), 1.54 - 1.65 (m, 6H), 1.38 (t, 2H), 0.93 (s, 6H).

EXAMPLE 364

N-{[5-bromo-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 26C and EXAMPLE 329B for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.17 (s, 1H), 8.65 (d, 1H), 8.33 (s, 1H), 7.58 (d, 1H), 7.35 (d, 2H), 7.24 (t, 1H), 7.07 (m, 3H), 6.89 (m, 1H), 6.67 (dd, 1H), 6.27 (m, 3H), 4.29 (d,

2H), 3.88 (dd, 2H), 3.35 (m, 4H), 3.09 (m, 4H), 2.88 (m, 2H), 2.34 (m, 2H), 2.17 (s, 2H), 2.06 (m, 1H), 1.98 (m, 2H), 1.65 (m, 2H), 1.36 (m, 4H), 0.93 (s, 6H).

EXAMPLE 365

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-5-(1,3-thiazol-2-yl)pyridin-3-yl]sulfonyl}benzamide

The title compound was prepared by substituting EXAMPLE 325B for EXAMPLE 329B in EXAMPLE 331A. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.22 (s, 1H), 9.76 (t, 1H), 9.12 (m, 1H), 8.50 (d, 1H), 8.26 (d, 1H), 8.02 (d, 1H), 7.87 (d, 1H), 7.58 (d, 1H), 7.38 (d, 2H), 7.23 (t, 1H), 7.15 (d, 1H), 7.08 (d, 2H), 6.96 (m, 1H), 6.74 (dd, 1H), 6.47 (d, 1H), 6.33 (s, 1H), 6.22 (s, 1H), 3.86 (dd, 2H), 3.52 (t, 6H), 3.29 (m, 4H), 2.99 (m, 2H), 2.74 (m, 2H), 2.18 (s, 2H), 2.01 (s, 2H), 1.88 (m, 1H), 1.62 (m, 2H), 1.45 (t, 2H), 1.28 (m, 2H), 0.94 (s, 6H).

EXAMPLE 366

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-indol-4-yloxy)benzamide

EXAMPLE 366A

3-cyano-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

3-Cyano-4-fluorobenzenesulfonamide (500 mg), (tetrahydropyran-4-yl)methylamine (288 mg), and N,N-diisopropylethylamine (1.3 mL) were heated at 80°C in tetrahydrofuran (15 mL) overnight. The mixture was diluted with ethyl acetate, washed with $NaHCO_3$ solution and brine, and dried (Na_2SO_4), filtered and concentrated. The product was triturated from ethyl acetate.

EXAMPLE 366B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-indol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 26C and EXAMPLE 366A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.30 (s, 1H), 11.08 (m, 1H), 7.81 (d, 1H), 7.63 (dd, 1H), 7.55 (d, 1H), 7.32 (m, 3H), 7.22 (d, 1H), 7.17 (m, 1H), 7.02 (m, 3H), 6.79 (d, 1H), 6.71 (dd, 1H), 6.47 (d, 1H), 6.28 (m, 2H), 3.84 (dd, 2H), 3.25 (t, 2H), 3.13 (t, 2H), 3.05 (m, 4H), 2.73 (s, 2H), 2.15 (m, 6H), 1.95 (s, 2H), 1.82 (m, 1H), 1.59 (m, 2H), 1.38 (t, 2H), 1.20 (m, 2H), 0.92 (s, 6H).

EXAMPLE 367

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 366A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.20 (s, 1H), 10.99 (s, 1H), 7.94 (d, 1H), 7.74 (dd, 1H), 7.53 (d, 1H), 7.44 (d, 1H), 7.41 (m, 1H), 7.33 (d, 2H), 7.21 (m, 2H), 7.04 (d, 2H), 6.89 (dd, 1H), 6.82 (d, 1H), 6.66 (dd, 1H), 6.42 (s, 1H), 3.83 (dd, 2H), 3.25 (t, 2H), 3.13 (t, 2H), 3.03 (m, 4H), 2.72 (s, 2H), 2.14 (m, 6H), 1.94 (s, 2H), 1.83 (m, 1H), 1.57 (m, 2H), 1.37 (m, 2H), 1.21 (m, 2H), 0.92 (s, 6H).

EXAMPLE 368

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3,3-dimethylbutyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting 3,3-dimethylbutylamine for 1-(2-methoxy-ethyl)-piperidin-4-ylamine and EXAMPLE 187A for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 189A.

EXAMPLE 369

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1S)-1-(hydroxymethyl)-3-methylbutyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting L-leucinol for 1-(2-methoxy-ethyl)-piperidin-4-ylamine and EXAMPLE 187A for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 189A.

EXAMPLE 370

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(2R)-tetrahydrofuran-2-ylmethyl]amino}phenyl)sulfonyl]benzamide

The title compound was prepared by substituting (R)-(-)-tetrahydrofurfurylamine for 1-(2-methoxy-ethyl)-piperidin-4-ylamine and EXAMPLE 187A for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 189A.

EXAMPLE 371

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1R)-1-(hydroxymethyl)-2-methylpropyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting D-valinol for 1-(2-methoxy-ethyl)-piperidin-4-ylamine and EXAMPLE 187A for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 189A.

EXAMPLE 372

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methoxyphenyl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting 4-anisidine for 1-(2-methoxy-ethyl)-piperidin-4-ylamine and EXAMPLE 187A for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 189A.

EXAMPLE 373

N-[(4-{[2-(1,3-benzodioxol-5-yl)ethyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting 2-benzo[1,3]dioxol-5-yl-ethylamine for 1-(2-methoxy-ethyl)-piperidin-4-ylamine and EXAMPLE 187A for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 189A.

EXAMPLE 374

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}phenyl)sulfonyl]benzamide

The title compound was prepared by substituting 1-(3-amino-propyl)-pyrrolidin-2-one for 1-(2-methoxy-ethyl)-piperidin-4-ylamine and EXAMPLE 187A for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 189A.

EXAMPLE 375

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-hydroxyphenyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting 4-aminophenol for 1-(2-methoxy-ethyl)-piperidin-4-ylamine and EXAMPLE 187A for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 189A.

EXAMPLE 376

N-{[4-({2-[4-(aminosulfonyl)phenyl]ethyl}amino)-3-nitrophenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting 4-(2-aminoethyl)benzenesulfonamide for 1-(2-methoxy-ethyl)-piperidin-4-ylamine and EXAMPLE 187A for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 189A.

EXAMPLE 377

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(1H-imidazol-1-yl)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting 1-(3-aminopropyl)imidazole for 1-(2-methoxy-ethyl)-piperidin-4-ylamine and EXAMPLE 187A for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 189A.

EXAMPLE 378

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(1S)-1-phenylethyl]amino}phenyl)sulfonyl]benzamide

The title compound was prepared by substituting (S)-(-)-1-phenylethylamine for 1-(2-methoxy-ethyl)-piperidin-4-ylamine and EXAMPLE 187A for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 189A.

EXAMPLE 379

N-({2-chloro-5-fluoro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide

EXAMPLE 379A

2-chloro-5-fluoro-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

2-Chloro-4,5-difluorobenzenesulfonamide (0.683 g), (tetrahydro-2H-pyran-4-yl)methanamine (0.346 g), N,N-diisopropylethylamine (0.681 ml) and dioxane (10 ml) were heated at 65 °C for 2.5 days. Additional (tetrahydro-2H-pyran-4-yl)methanamine (0.346 g) and N,N-diisopropylethylamine (0.681 ml) were added and heating was continued at 70 °C for 1.5 days. The reaction mixture was concentrated and column chromatographed on silica gel with 0-3% methanol in dichloromethane as eluent. The obtained solid was triturated with dichloromethane to give the title compound.

EXAMPLE 379B

N-({2-chloro-5-fluoro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 26C for EXAMPLE 1E and EXAMPLE 379A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ ppm 11.23 (s, 1H), 11.02 (s, 1H), 7.61 (m, 2H), 7.44 (m, 2H), 7.33 (d, 2H), 7.30 (m, 1H), 7.03 (d, 2H), 6.95 (m, 1H), 6.88 (m, 2H), 6.67 (dd, 1H), 6.44 (m, 1H), 6.09 (d, 1H), 3.82 (dd, 2H), 3.22 (m, 2H), 3.03 (m, 6H), 2.72 (m, 2H), 2.14 (m, 6H), 1.94 (m, 2H), 1.81 (m, 1H), 1.61 (m, 2H), 1.37 (t, 2H), 1.18 (m, 2H), 0.91 (s, 6H).

EXAMPLE 380

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[2-(2-methoxyethoxy)ethyl]thio}-3-nitrophenyl)sulfonyl]benzamide

EXAMPLE 380A

4-(2-(2-methoxyethoxy)ethylthio)-3-nitrobenzenesulfonamide

In a 100 mL round-bottomed flask was added sodium hydride (0.6 g) in tetrahydrofuran (10 ml) to give a suspension. 2-(2-Methoxyethoxy)ethanethiol (1 g) was added slowly. After the mixture stirred for 30 minutes, 4-fluoro-3-nitrobenzenesulfonamide (1.616 g) in 10 ml tetrahydrofuran was added slowly. After the mixture stirred overnight, water was added slowly, and ethyl acetate (20 ml x 3) was used to extract the product. The combined organic layers were dried over Na_2SO_4. After the mixture was filtered and concentrated, the crude product was added to a silica gel column and purified eluting with 0-10% methanol in dichloromethane.

EXAMPLE 380B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[2-(2-methoxyethoxy)ethyl]thio}-3-nitrophenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 380A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 10.99 (s, 1H), 8.42 (s, 1H), 7.75 (d, 1H), 7.56 (d, 1H), 7.34 (m, 5H), 7.05 (d, 2H), 6.90 (d, 1H), 6.69 (dd, 1H), 6.55 (dd, 1H), 6.30 (m, 1H), 6.17 (d, 1H), 3.67 (t, 2H), 3.54 (m, 2H), 3.43 (m, 2H), 3.21 (m, 5H), 2.95 (m, 4H), 2.71 (s, 2H), 2.17 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 381

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[2-(2-methoxyethoxy)ethyl]thio}-3-nitrophenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 380A for EXAMPLE 1F and EXAMPLE 55B for EXAMPLE 26C in EXAMPLE 177. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.06 (s, 1H), 8.37 (d, 1H), 7.80 (dd, 1H), 7.61 (d, 1H), 7.45 (d, 1H), 7.34 (d, 2H), 7.18 (t, 1H), 7.04 (m, 3H), 6.87 (t, 1H), 6.60 (dd, 1H), 6.22 (m, 3H), 3.68 (t, 2H), 3.55 (m, 2H), 3.43 (m, 2H), 3.22 (m, 5H), 2.94 (m, 4H), 2.72 (s, 2H), 2.16 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 382

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(methylsulfonyl)phenyl]sulfonyl}benzamide

The title compound was prepared by substituting 4-(methylamino)-3-nitrobenzenesulfonamide for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.17 (s, 1H), 8.05 (m, 4H), 7.51 (d, 1H), 7.38 (m, 4H), 7.14 (m, 1H), 7.04 (d, 2H), 6.85 (d, 1H), 6.64 (dd, 1H), 6.40 (m, 1H), 6.17 (d, 1H), 3.27 (s, 3H), 3.05 (m, 4H), 2.79 (m, 2H), 2.21 (m, 6H), 1.96 (s, 2H), 1.39 (t, 2H), 0.92 (s, 6H).

EXAMPLE 383

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[4-(methylsulfonyl)phenyl]sulfonyl}benzamide

The title compound was prepared by substituting 4-(methylamino)-3-nitrobenzenesulfonamide for EXAMPLE 1F and EXAMPLE 55B for EXAMPLE 26C in EXAMPLE 177. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 11.26 (s, 1H), 7.96 (m, 4H), 7.54 (d, 1H), 7.35 (d, 2H), 7.30 (m, 1H), 7.18 (d, 1H), 7.05 (d, 2H), 6.97 (t, 1H), 6.70 (dd, 1H), 6.37 (d, 1H), 6.30 (m, 2H), 3.25 (s, 3H), 3.08 (m, 4H), 2.84 (m, 2H), 2.26 (m, 6H), 1.97 (s, 2H), 1.40 (t, 2H), 0.93 (s, 6H).

EXAMPLE 384

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2,2-dimethyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

EXAMPLE 384A

The title compound was prepared as described in EXAMPLE 297A by replacing (1,4-dioxan-2-yl)methanol with (2,2-dimethyltetrahydro-2H-pyran-4-yl)methanol.

EXAMPLE 384B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2,2-dimethyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 175F by replacing EXAMPLE 175E and EXAMPLE 1F with EXAMPLE 26C and EXAMPLE 384A, respectively. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 11.17 (s, 2H), 8.38 (d, 1H), 8.05 (dd, 1H), 7.51 (d, 1H), 7.31 - 7.43 (m, 5H), 7.15 (d, 1H), 7.04 (d, 2H), 6.85 (dd, 1H), 6.65 (dd, 1H), 6.40 (s, 1H), 6.15 (d, 1H), 3.98 - 4.07 (m, 2H), 3.54 - 3.67 (m, 2H), 3.05 (s, 4H), 2.78 (s, 2H), 2.09 - 2.31 (m, 7H), 1.95 (s, 2H), 1.56 - 1.68 (m, 2H), 1.38 (t, 2H), 1.08 - 1.27 (m, 8H), 0.92 (s, 6H).

EXAMPLE 385

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

EXAMPLE 385A

5-bromo-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 306C for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 329B.

EXAMPLE 385B

5-cyano-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 385A for EXAMPLE 329B in EXAMPLE 333A.

EXAMPLE 385C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 385B for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.10 (s, 1H), 8.79 (s, 1H), 8.59 (s, 1H), 7.54 (d, 1H), 7.34-7.38 (m, 4H), 7.04-7.06 (m, 3H), 6.79 (dd, 1H), 6.62 (dd, 1H), 6.35 (s, 1H), 6.17 (d, 1H), 4.28 (d, 2H), 3.76-3.79 (m, 2H), 3.56-3.62 (m, 2H), 3.07 (br s, 4H), 2.12-2.17(m, 4H), 1.96 (s, 2H), 1.80-1.84 (m, 2H), 1.40 (t, 2H), 0.94 (s, 6H).

EXAMPLE 386

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 26C and EXAMPLE 335A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.20 (s, 1H), 8.67 (d, 1H), 8.35 (d, 1H), 7.57 (d, 1H), 7.36 (d, 2H), 7.26 (t, 1H), 7.11 (d, 1H), 7.05 (d, 2H), 6.90 (t, 1H), 6.70 (dd, 1H), 6.31 (d, 1H), 6.30 (d, 1H), 6.27 (s, 1H), 4.30 (d, 2H), 3.88 (dd, 2H), 3.35 (m, 2H), 3.12 (br s, 4H), 2.96 (br s, 2H), 2.40 (br s, 4H), 2.16 (br m, 2H), 2.06 (m, 1H), 1.98 (s, 2H), 1.65 (d, 2H), 1.41 (t, 2H), 1.36 (m, 2H), 0.93 (s, 6H).

EXAMPLE 387

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-4-yloxy)benzamide

EXAMPLE 387A

5,6-dichloropyridine-3-sulfonamide

The title compound was prepared by substituting 5,6-dichloropyridine-3-sulfonyl chloride for 5-bromo-6-chloropyridine-3-sulfonyl chloride in EXAMPLE 329A.

EXAMPLE 387B

5-chloro-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 387A for EXAMPLE 329A in EXAMPLE 329B.

EXAMPLE 387C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 26C and EXAMPLE 387B for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR

(500MHz, dimethylsulfoxide-d_6) δ 11.24 (s, 1H), 8.45 (d, 1H), 8.05 (d, 1H), 7.56 (d, 1H), 7.36 (d, 2H), 7.28 (t, 1H), 7.15 (d, 1H), 7.05 (d, 2H), 6.95 (t, 1H), 6.71 (dd, 1H), 6.39 (d, 1H), 6.30 (d, 1H), 6.27 (s, 1H), 4.26 (d, 2H), 3.88 (dd, 2H), 3.35 (m, 2H), 3.09 (br s, 4H), 2.85 (br s, 2H), 2.30 (br s, 4H), 2.15 (br m, 2H), 2.07 (m, 1H), 1.96 (s, 2H), 1.65 (d, 2H), 1.41 (t, 2H), 1.35 (m, 2H), 0.93 (s, 6H).

EXAMPLE 388

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(2-morpholin-4-ylethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide

EXAMPLE 388A

5-bromo-6-(2-morpholinoethoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting 2-morpholinoethanol for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 329B.

EXAMPLE 388B

5-cyano-6-(2-morpholinoethoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 388A for EXAMPLE 329B in EXAMPLE 335A.

EXAMPLE 388C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(2-morpholin-4-ylethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 388B for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.09 (s, 1H), 8.77 (s, 1H), 8.55 (s, 1H), 7.55 (d, 1H), 7.34-7.36 (m, 4H), 7.04-7.06 (m, 3H), 6.78 (dd, 1H), 6.63 (d, 1H), 6.35 (s, 1H), 6.16 (s, 1H), 4.61 (t, 2H), 3.58 (m, 4H), 3.05 (br s, 4H), 2.89 (br s, 4H), 2.65 (br s, 4H), 2.32-2 (br s, 2H), 2.15 (br s, 2H), 1.96 (s, 2H), 1.39 (t, 2H), 0.92 (s, 6H).

EXAMPLE 389

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)oxy]phenyl}sulfonyl)benzamide

EXAMPLE 389A

1-(tetrahydro-2H-pyran-4-yl)piperidin-4-ol

Piperidin-4-ol (7.8 g) and dihydro-2H-pyran-4(3H)-one (5.0 g) were dissolved in titanium(IV) isopropoxide (30 mL) and the reaction was stirred at room temperature overnight. Methanol (40 mL) was added and the reaction was cooled to 0°. $NaBH_4$ (3.8 g) was added in several portions over one hour. After two hours 1*N* aqueous NaOH was added, followed by ethyl acetate addition. After filtration through celite, the layers were seperated, the aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried over Na_2SO_4. The crude material was purified by column chromatography using CH_2Cl_2 with 5-10% 7*N* NH_3 in methanol.

EXAMPLE 389B

3-nitro-4-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yloxy)benzenesulfonamide

EXAMPLE 389A (370 mg) was dissolved in tetrahydrofuran (10 mL), and 95% NaH (200 mg) was added. After stirring for 10 minutes, 4-fluoro-3-nitrobenzenesulfonamide (420 mg) was added and the reaction was stirred at room temperature overnight. The reaction was purified by column chromatography using CH_2Cl_2 with 6-10% 7*N* NH_3 in methanol, followed by slurrying in diethyl ether and filtering off the solid product.

EXAMPLE 389C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)oxy]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 26C for EXAMPLE 1E and EXAMPLE 389B for EXAMPLE 1F in EXAMPLE 1G, except here 5-7% methanol in CH_2Cl_2 was used for the chromatography. ^1H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.07 (br s, 1H), 8.27 (s, 1H), 7.92 (d, 1H), 7.55 (d, 1H), 7.33 (m, 5H), 7.04 (m, 3H), 6.77 (dd, 1H), 6.58 (d, 1H), 6.35 (s, 1H), 6.14 (s, 1H), 4.85 (s, 1H), 3.93 (dd, 2H), 3.27 (m, 4H), 2.98 (br m, 7H), 2.72 (s, 2H), 2.16 (m, 6H), 2.04 (m, 2H), 1.95 (s, 2H), 1.84 (m, 4H), 1.55 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 390

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-morpholin-4-ylbut-2-ynyl)oxy]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 390A

4-morpholinobut-2-yn-1-ol

To a mixture of morpholine (4.36 g) in toluene (15 mL) was added 4-chlorobut-2-yn-1-ol (2.09 g) in toluene (5 mL). The mixture was stirred at 85 °C for three hours. After cooling, the solid was filtered off. The filtrate was subjected to vacuum distillation to give the title compound.

EXAMPLE 390B

4-(4-morpholinobut-2-ynyloxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 390A for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 279A.

EXAMPLE 390C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-morpholin-4-ylbut-2-ynyl)oxy]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 390B for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.17 (s, 1H), 8.40 (d, 1H), 8.11 (dd, 1H), 7.49-7.53 (m, 2H), 7.39-7.42 (m, 4H), 7.34 (d, 2H), 7.17 (d, 1H), 7.04 (d, J = 8.54 Hz, 2H), 6.85 (dd, 1H), 6.64 (dd, 1H), 6.40 (s, 1H), 6.14 (d, 1H), 5.15 (s, 2H), 3.52-3.54 (m, 4H), 3.04 (br s, 4H), 2.78 (br s, 2H), 2.37-2.39 (m, 4H), 2.12-2.20 (br s, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 391

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-ethynyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-4-yloxy)benzamide

EXAMPLE 391A

6-((tetrahydro-2H-pyran-4-yl)methoxy)-5-((triisopropylsilyl)ethynyl)pyridine-3-sulfonamide

EXAMPLE 329B (0.176 g), bis(triphenylphosphine)palladium(II) chloride (0.176 g), copper(I) iodide (0.010 g), dimethylacetamide (2.5 ml) and triethylamine (0.105 ml) were combined, flushed with nitrogen and stirred for 2 minutes. (Triisopropyl)acetylene (0.135 ml) was added and the reaction mixture was flushed with nitrogen again, heated at 60 °C overnight, diluted with ethyl acetate, washed with water and brine, dried ($MgSO_4$), filtered, concentrated and chromatographed on silica gel with10-30% ethyl acetate in hexanes as the eluent to give the title compound.

EXAMPLE 391B

5-ethynyl-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

EXAMPLE 391A (0.205 g) in tetrahydrofuran (3 ml) at ambient temperature was treated with tetrabutyl ammonium fluoride (1 M in tetrahydrofuran) (0.906 ml) and stirred at ambient temperature for 4 hours. Additional tetrabutyl ammonium fluoride (1 M in tetrahydrofuran) (1.8 mL) was added and the mixture was heated at 40 °C for 45 minutes. Solid tetrabutyl ammonium fluoride (0.253 g) was added and heating was continued for 30 minutes. The reaction mixture was concentrated and then chromatographed on silica gel using 0-2% methanol in dichloromethane as the eluent to give the title compound.

EXAMPLE 391C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-ethynyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 26C and EXAMPLE 391B for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ ppm 11.23 (s, 1H), 8.50 (d, 1H), 8.09 (d, 1H), 7.56 (d, 1H), 7.34 (m, 2H), 7.28 (m, 1H), 7.18 (d, 1H), 7.04 (m, 2H), 6.98 (t, 1H), 6.70 (dd, 1H), 6.44 (d, 1H), 6.27 (m, 2H), 4.55 (s, 1H), 4.25 (d, 2H), 3.87 (dd, 2H), 3.34 (m, 2H), 3.06 (m, 4H), 2.81 (m, 1H), 2.20 (m, 6H), 2.04 (m, 1H), 1.96 (m, 2H), 1.65 (dd, 2H), 1.35 (m, 5H), 0.92 (m, 6H).

EXAMPLE 392

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(2-morpholin-4-ylethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 26C and EXAMPLE 388B for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.15 (s, 1H), 10.99 (s, 1H), 8.64 (d, 1H), 8.33 (d, 1H), 7.58 (d, 1H), 7.35 (d, 2H), 7.24 (m, 1H), 7.07 (m, 3H), 6.89 (m, 1H), 6.66 (dd, 1H), 6.26 (m, 3H), 4.59 (t, 2H), 3.58 (m, 4H), 3.05 (m, 4H), 2.87 (m, 4H), 2.62 (m, 4H), 2.24 (m, 6H), 1.98 (m, 2H), 1.40 (t, 2H), 0.93 (s, 6H).

EXAMPLE 393

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-indol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 55B for EXAMPLE 26C and EXAMPLE 385B for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.17 (s, 1H), 8.66 (s, 1H), 8.36 (s, 1H), 7.58 (d, 1H), 7.36 (d, 2H), 7.25 (s, 1H), 7.07 (m, 3H), 6.89 (m, 1H), 6.68 (m, 1H), 6.27 (m, 3H), 4.60 (s, 1H), 4.54 (s, 1H), 3.78 (m, 2H), 3.60 (m, 2H), 3.33 (m, 2H), 3.09 (m, 4H), 2.92 (m, 2H), 2.36 (m, 2H), 2.16 (m, 2H), 1.97 (s, 2H), 1.87 (m, 4H), 1.40 (t, 2H), 0.93 (s, 6H).

EXAMPLE 394

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-hydroxy-4-methoxyphenyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared by substituting 5-amino-2-methoxyphenol for 1-(2-methoxy-ethyl)-piperidin-4-ylamine and EXAMPLE 187A for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 189A.

EXAMPLE 395

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(2,3-dihydro-1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 103 (676 mg) and $NaCNBH_3$ (49 mg) were combined in acetic acid (10 mL) and stirred at room temperature overnight. The reaction was diluted with water and extracted with 95/5 CH_2Cl_2/methanol. The organic layer was concentrated and the crude

material was purified by preparative HPLC using a C18 column, 250 x 50 mm, 10μ, and eluting with a gradient of 20-100% CH_3CN vs. 0.1% trifluoroacetic acid in water, giving the title compound as a bistrifluoroacetate salt. ^1H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.57 (br s, 1H), 9.70, 9.50 (both v br s, total 2H), 8.57 (d, 1H), 8.20 (br d, 1H), 7.85 (dd, 1H), 7.50 (d, 1H), 7.40 (d, 2H), 7.26 (d, 1H), 7.10 (d, 2H), 6.82 (dd, 1H), 6.75 (dd, 1H), 6.40 (d, 1H), 6.27 (d, 1H), 5.94 (d, 1H), 4.00, 3.70 (both v br m, total 8H),3.55 (v br m, 3H), 3.42 (t, 2H), 3.37 (v br m, 1H), 3.10 (br m, 2H), 2.80 (m, 6H), 2.20 (br m, 4H), 2.03 (s, 2H), 1.82 (br m, 2H), 1.46 (t, 2H), 0.96 (s, 6H).

EXAMPLE 396

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(pyridin-3-ylamino)benzamide

EXAMPLE 396A

Methyl 4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(pyridin-3-ylamino)benzoate

A soution of EXAMPLE 18E (500 mg), cesium carbonate (429 mg), palladium (II) acetate (21 mg), rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (58.5 mg) and toluene (6.4 mL) was degassed with N_2. The mixture was stirred at 115°C for 5 minutes. After cooling to room temperature, pyridin-3-amine (106 mg) was added and the reaction mixture was degassed again with N_2 and was stirred at 115°C for 45 minutes. The mixture was cooled to room temperature, diluted with ethyl acetate and was washed with H_2O, brine, dried ($MgSO_4$), filtered and concentrated. The crude product was purified by flash chromatography on silica gel, eluting with CH_2Cl_2 / 1% methanol to afford the title compound.

EXAMPLE 396B

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(pyridin-3-ylamino)benzoic acid, 2 Hydrochloric Acid

The title compound was prepared by substituting EXAMPLE 396A for EXAMPLE 224C in EXAMPLE 224D.

EXAMPLE 396C

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(4-(1-methylpiperidin-4-ylamino)-3-nitrophenylsulfonyl)-2-(pyridin-3-ylamino)benzamide

The title compound was prepared by substituting EXAMPLE 396B for EXAMPLE 26C and EXAMPLE 21A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 11.32 - 11.40 (br s, 1H), 9.21 - 9.39 (br s, 1H), 8.51 (d, 1H), 8.33 (d, 1H), 8.09 (dd, 1H), 7.98 - 8.07 (m, 1H), 7.94 (dd, 1H), 7.81 (d, 1H), 7.52 - 7.58 (m, 1H), 7.36 (d, 2H), 7.24 - 7.30 (m, 1H), 7.15 (d, 1H), 7.08 (d, 2H), 6.53 (d, 1H), 6.33 (dd, 1H), 3.81 - 3.96 (br s, 2H), 3.02 - 3.12 (br s, 6H), 2.67 - 2.80 (m, 5H), 2.07 - 2.32 (m, 8H), 1.98 (s, 3H), 1.70 - 1.85 (br s, 1H), 1.41 (t, 3H), 0.95 (s, 6H).

EXAMPLE 397

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)-2-(pyridin-3-ylamino)benzamide

The title compound was prepared by substituting EXAMPLE 396B for EXAMPLE 26C and EXAMPLE 173C for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 9.10 - 9.33 (br s, 1H), 8.53 (d, 1H), 8.36 (d, 1H), 8.12 (dd, 1H), 8.00 - 8.07 (m, 1H), 7.96 (dd, 1H), 7.80 (d, 1H), 7.53 - 7.59 (m, 1H), 7.38 (d, 2H), 7.25 - 7.31 (m, 1H), 7.20 (d, 1H), 7.09 (d, 2H), 6.53 (s, 1H), 6.36 (m, 1H), 4.28 - 4.75 (br s, 1H), 3.90 - 4.09 (m, 8H), 3.51 - 3.61 (m, 2H), 3.35 (m, 8H), 3.01 - 3.18 (br s, 4H), 2.15 - 2.26 (m, 1H), 1.88 - 2.09 (m, 5H), 1.56 - 1.86 (m, 4H), 1.44 (t, 2H), 0.96 (s, 6 H).

EXAMPLE 398

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)-2-(pyridin-3-yloxy)benzamide

EXAMPLE 398A

4-Fluoro-2-(pyridin-3-yloxy)-benzoic acid methyl ester

The title compound was prepared by substituting methyl 2,4-difluorobenzoate for ethyl 2,4-difluorobenzote and 3-hydroxypyridine for 5-hydroxyindazole in EXAMPLE 20A.

EXAMPLE 398B

4-{4-[2-(4-Chloro-phenyl)-4,4-dimethyl-cyclohex-1-enylmethyl]-piperazin-1-yl}-2-(pyridin-3-yloxy)-benzoic acid methyl ester

The title compound was prepared by substituting EXAMPLE 398A for EXAMPLE 20A in EXAMPLE 20D.

EXAMPLE 398C

4-{4-[2-(4-Chloro-phenyl)-4,4-dimethyl-cyclohex-1-enylmethyl]-piperazin-1-yl}-2-(pyridin-3-yloxy)-benzoic acid

The title compound was prepared by substituting EXAMPLE 398B for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 398D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(pyridin-3-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 398C for EXAMPLE 1E and EXAMPLE 173C for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 8.36 (d, 1H), 8.11 (t, 1H), 8.08 (t, 2H), 7.70 (dd, 1H), 7.60 (d, 1H), 7.37 (d, 2H), 7.15 (dd, 1H), 7.10-7.03 (m, 3H), 7.00 (dd, 1H), 6.73 (dd, 1H), 6.43 (d, 1H), 3.99-3.93 (m, 3H), 3.86 (m, 1H), 3.13 (m, 6H), 2.78 (br s, 2H), 2.30-2.05 (m, 10H), 1.98 (br s, 2H), 1.92-1.67 (m, 6H), 1.57 (m, 2H), 1.41 (t, 2H), 0.94 (s, 6H).

EXAMPLE 399

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1,2,3,4-tetrahydroisoquinolin-5-yloxy)benzamide

EXAMPLE 399A

tert-butyl 5-hydroxy-3,4-dihydroisoquinoline-2(1H)-carboxylate

A mixture of 1,2,3,4-tetrahydroisoquinolin-5-ol hydrochloric acid (1.0 g), di-tert-butyl dicarbonate (1.27 g) and 1.0 N NaOH (14.5 mL) in dioxane (20 mL) was stirred at room

temperature for 16 hours. The reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was neutralized with 5% HCl. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography on silica gel to give the title compound.

EXAMPLE 399B

tert-butyl 5-(2-(ethoxycarbonyl)-5-fluorophenoxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate

The title compound was prepared by substituting EXAMPLE 399A for 5-hydroxyindazole in EXAMPLE 20A.

EXAMPLE 399C

tert-butyl 5-(5-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(ethoxycarbonyl)phenoxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate

The title compound was prepared by substituting EXAMPLE 399B for EXAMPLE 20A in EXAMPLE 20D.

EXAMPLE 399D

2-(2-(tert-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 399C for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 399E

2-(2-(tert-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic 3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonic anhydride

The title compound was prepared by substituting EXAMPLE 399D for EXAMPLE 26C in EXAMPLE 177.

EXAMPLE 399F

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1,2,3,4-tetrahydroisoquinolin-5-yloxy)benzamide

A mixture of EXAMPLE 399E (0.058 g) and trifluoroacetic acid (1 mL) in dichloromethane (10 mL) was stirred for 2 hours. The solvent was removed, and the residue was taken into ethyl acetate. It was then washed with saturated $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated to give the title compound. ^1H NMR (500MHz, dimethylsulfoxide-d_6) δ 8.36 (t, 1H), 8.27 (d, 1H), 7.65 (d, 1H), 7.36 (d, 2H), 7.07 (d, 2H) 6.93-6.97 (m, 2H), 6.73 (d 1H), 6.69 (dd, 1H), 6.33(d, 1H), 6.26 (d, 1H), 4.19 (s, 2H), 3.85 (dd, 2H), 3.05-3.09 (m, 6H), 2.77 (s, 2H), 2.17-2.24 (m, 6H), 1.98-1.99 (m, 2H), 1.60-1.63 (m, 2H0, 1.41 (t, 2H), 0.94 (s, 6H).

EXAMPLE 400

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 400A

4-Hydroxy-indazole-1-carboxylic acid tert-butyl ester and4-hydroxy-indazole-2-carboxylic acid tert-butyl ester

4-Hydroxyindazole (3.94 g) was added to tetrahydrofuran (250 mL) and cooled to 0°C using an ice bath. Sodium hydride (60% dispersion in mineral oil, 1.23 g) was added, and the mixture was stirred at 0°C for five minutes. The mixture was allowed to warm to room temperature and stirred for an additional 20 minutes. The mixture was again cooled to 0°C using an ice bath, and tert-butyldimethylchlorosilane (4.65 g) was added. The mixture was allowed to warm to room temperature and stirred for 16 hours. Solvent volume was reduced under vacuum, the residue vacuum filtered over a pad of silica gel and washed with ethyl acetate, and the solvent was removed under vacuum. To the residue was added acetonitrile (200 mL), di-tert-butyl dicarbonate (7.06 g), and 4-(dimethylamino)pyridine (0.359 g). The mixture was stirred at room temperature for three hours, and the solvent was removed under vacuum. To the residue was added tetrahydrofuran (200 mL) and tetrabutylammonium fluoride (1M in tetrahyrdofuran, 82 mL). The mixture was stirred at room temperature for four days, the solvent removed under vacuum, and the residue taken up in ethyl acetate. The mixture was extracted with saturated aqueous ammonium chloride, extracted with brine, and dried on anhydrous sodium sulfate. The mixture was vacuum

filtered over silica gel, and the solvent removed under vacuum to give a mixture of the two products, which was used in the next step without further purification.

EXAMPLE 400B

4-Fluoro-2-(1H-indazol-4-yloxy)-benzoic acid methyl ester

EXAMPLE 400A (5.56 g) was added to diglyme (200 mL), and potassium tert-butoxide (1M in tetrahydrofuran, 30.8 mL) was added. The mixture was mixed at room temperature for 15 minutes, methyl 2,4-difluorobenzoate was added, and the mixture was heated at 115°C for 16 hours. The mixture was cooled, the solvent was removed under vacuum, the residue was taken up in dichloromethane (100 mL), and trifluoroacetic acid (22.6 mL) was added. The mixture was stirred at room temperature for 16 hours, the solvent was removed under vacuum, the residue was taken up in ethyl acetate and washed with a saturated aqueous sodium bicarbonate mixture, and the organic layer was dried with anhydrous sodium sulfate. The material was purified by flash column chromatography on silica gel using 30% ethyl acetate (in hexanes) increasing to 40% ethyl acetate (in hexanes).

EXAMPLE 400C

2-(1H-Indazol-4-yloxy)-4-piperazin-1-yl-benzoic acid methyl ester

EXAMPLE 400B (2.00 g) and piperazine (2.71 g) were added to dimethylsulfoxide (60 mL) and heated to 100°C for one hour. The mixture was cooled, addded to dichloromethane, washed with water twice, washed with a saturated aqueous sodium bicarbonate mixture, and dried on anhydrous sodium sulfate. After filtration, the solvent was removed under vacuum.

EXAMPLE 400D

4-{4-[2-(4-Chloro-phenyl)-4,4-dimethyl-cyclohex-1-enylmethyl]-piperazin-1-yl}-2-(1H-indazol-4-yloxy)-benzoic acid methyl ester

The title compound was prepared by substituting EXAMPLE 218A for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 400C for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 400E

4-{4-[2-(4-Chloro-phenyl)-4,4-dimethyl-cyclohex-1-enylmethyl]-piperazin-1-yl}-2-(1H-indazol-4-yloxy)-benzoic acid

The title compound was prepared by substituting EXAMPLE 400D for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 400F

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 400E for EXAMPLE 1E in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 13.09 (s, 1H), 8.56 (t, 1H), 8.38 (d, 1H), 7.80 (s, 1H), 7.56 (dd, 1H), 7.53 (d, 1H), 7.36 (d, 2H), 7.16-7.05 (m, 4H), 6.99 (d, 1H), 6.80 (dd, 1H), 6.52 (d, 1H), 6.19 (dd, 1H), 3.87 (dd, 2H), 3.25-3.12 (m, 6H), 2.78 (m, 2H), 2.30-2.16 (m, 6H), 1.97 (br s, 2H), 1.90 (m, 1H), 1.63 (m, 2H), 1.53 (m, 1H), 1.40 (t, 2H), 1.29 (m, 3H), 0.94 (s, 6H).

EXAMPLE 401

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 401A

N-[(4-chloro-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 400E for EXAMPLE 1E and 4-chloro-3-nitrobenzenesulfonamide for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 13.04 (s, 1H), 8.17 (br s, 1H), 7.75 (s, 1H), 7.73 (d, 1H), 7.66-7.61 (m, 2H), 7.38 (d, 2H), 7.11-7.01 (m, 4H), 6.79 (dd, 1H), 6.54 (d, 1H), 6.10 (dd, 1H), 3.38-3.05 (m, 8H), 2.73 (br s, 2 H), 2.19 (m, 2H), 2.00 (br s, 2H), 1.44 (t, 2H), 0.95 (s, 6H).

EXAMPLE 401B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 173B for 1-(2-methoxy-ethyl)-piperidin-4-ylamine and EXAMPLE 401A for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 189A. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 13.05 (br s, 1H), 8.35 (d, 1H), 8.13 (d, 1H), 7.78 (s, 1H), 7.61-7.52 (m, 2H), 7.35 (d, 2H), 7.11-7.03 (m, 4H), 6.98 (d, 1H), 6.77 (dd, 1H), 6.48 (d, 1H), 6.18 (m, 1H), 3.69-3.52 (m, 4H), 3.12 (m, 6H), 2.76 (br s, 2H), 2.67 (m, 4H), 2.28-2.16 (m, 6H), 2.09-2.01 (m, 2H), 1.97 (br s, 2H), 1.95 (m, 2H), 1.50-1.38 (m, 6H), 0.93 (s, 6H).

EXAMPLE 402

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting trans-4-morpholin-4-yl-cyclohexylamine for 1-(2-methoxy-ethyl)-piperidin-4-ylamine and EXAMPLE 401A for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 189A. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 13.02 (br s, 1H), 8.35 (d, 1H), 8.12 (m, 1H), 7.75 (s, 1H), 7.65-7.55 (m, 2H), 7.35 (d, 2H), 7.10-7.03 (m, 4H), 6.97 (m, 1H), 6.76 (dd, 1H), 6.44 (m, 1H), 6.17 (t, 1H), 3.95 (m, 2H), 3.77 (m, 1H), 3.62 (m, 1H), 3.10 (m, 6H), 2.75 (br s, 2H), 2.28-2.14 (m, 8H), 2.06 (m, 2H), 1.97 (br s, 2H), 1.85 (m, 2H), 1.71 (m, 2H), 1.55 (m, 4H), 1.40 (t, 2H), 0.93 (s, 6H).

EXAMPLE 403

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 403A

methy 4-fluoro-2-(3-fluoro-2-nitophenoxy)benzoate

To a solution of methyl 4-fluoro-2-hydroxybenzoate (3.0 g) in tetrahydrofuran (65 mL) was added potassium t-butoxide (1.979 g) portion wise. The resulting solution was stirred at ambient temperature for 30 minutes and a solution of 1,3-difluoro-2-nitrobenzene (2.338 g) in tetrahydrofuran (15 mL) was added dropwise. After 1 hour, the reaction was heated at reflux for 18 hours. The reaction was quenched with water (10 mL), diluted with

brine (75 mL) and extracted with methylene chloride (2x 75 mL). The crude product was isolated by concentration and purified on silica gel, eluted with a 10, 20, 50 % ethyl acetate in hexane step gradient to provide the title compound.

EXAMPLE 403B

methyl 2(3-(bis(4-methoxyphenyl)methylamino)-2-mitrophenoxy)-4-fluorobenzoate

To a solution of EXAMPLE 403A (3.82 g) and bis(4-methoxyphenyl)methanamine (4.51 g) in N-methyl-2-pyrrolidinone (65 mL) was added N-ethyl-N-isopropylpropan-2-amine (4.30 mL) and the mixture was heated at 100 ° C for 24 hours. The crude product, isolated by concentration, was purified on silica gel, and was eluted with a 10, 25, and 65 % ethyl acetate in hexane step gradient to provide the title compound.

EXAMPLE 403C

methyl 2-(2-amino-3-(bis(4-methoxyphenyl)methylamino)phenoxy)-4-fluorobenzoate

To a solution of EXAMPLE 403B (2.76 g) in tetrahydrofuran (125 mL) in a stainless steel pressure bottle was added nickel catalyst (2.76 g). The mixture was stirred for 1 hour under hydrogen at 30 psi and ambient temperature. The mixture was filtered though a nylon membrane to remove the catalyst, and concentrated to give the product.

EXAMPLE 403D

methyl 2-(1-(bis(4-methoxyphenyl)methyl)-1*H*-benzo[*d*]imidazol-4-yloxy)-4-fluorobenzoate

To a solution EXAMPLE 403C (1.25 g) in triethyl orthoformate (30 mL) was added concentrated hydrochloric acid (0.75 mL). The mixture was stirred for 18 hours, quenched by the slow addition of 50% saturated aqueous sodium carbonate solution (100 mL) and extracted with ethyl acetate (2 x 100 mL). The crude product was isolated by concentration and purified on silica gel, and was eluted with a 25, 50, and 70% ethyl acetate in hexane step gradient to provide title compound.

EXAMPLE 403E

methyl 2-(1-(bis(4-methoxyphenyl)methyl)-1*H*-benzo[*d*]imidazol-4-yloxy)-4-(piperazin-1-yl)benzoate

A solution of EXAMPLE 403D (500 mg), and piperazine (420 mg) in dimethylsulfoxide (9 mL) was heated at 100 °C for 3 hours. The crude product was isolated by concentration and, following an aqueous work up, it was purified on silica gel, and was

eluted with a 5 and 10% methanol in methylene chloride step gradient to provide the title compound.

EXAMPLE 403F

methyl 2-(1-(bis(4-methoxyphenyl)methyl)-1*H*-benzo[*d*]imidazol-4-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

To a solution of EXAMPLE 403E (430 mg) and EXAMPLE 218A (259 mg) in dichloromethane (13 mL) was added sodium triacetoxyborohydride (323 mg) portionwise. After stirring 42 hours, the reaction was quenched slowly with saturated aqueous sodium bicarbonate solution (80 mL) and extracted with methylene chloride (2 X 70 mL). The crude product was isolated by concentration and purified on silica gel, and was eluted with a 0, 2, 10% methanol in methylene chloride step gradient to provide the title compound.

EXAMPLE 403G

2-(1-(bis(4-methoxyphenyl)methyl)-1*H*-benzo[*d*]imidazol-4-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

To a solution of EXAMPLE 403F (545 mg) in a mixture of methanol (7.50 mL) and tetrahydrofuran (7.50 mL) was added a solution of sodium hydroxide (269 mg) in water (3.0 mL). The reaction mixture was heated at 50° C for 18 hours and then concentrated. The residue was mixed with water (100 mL) and the pH was adjusted to ca. 7 with 1M aqueous hydrochloric acid. The mixture was extracted with 10 % methanol in methylene chloride (10 X 50 mL), and the combined organic layers were concentrated to provide the title compound.

EXAMPLE 403H

2-(1-(bis(4-methoxyphenyl)methyl)-1*H*-benzo[*d*]imidazol-4-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-*N*-(3-nitro-4-((tetrahydro-2*H*-pyran-4-yl)methylamino)phenylsulfonyl)benzamide

To a solution of EXAMPLE 403G (200 mg), EXAMPLE 1F (99 mg), triethylamine (0.122 mL), N,N-dimethylpyridin-4-amine (77 mg) in a mixture of dichloromethane (8 mL) and N, N-dimethylformamide (1 mL) was added N^1-((ethylimino)methylene)-N^3,N^3-dimethylpropane-1,3-diamine hydrochloric acid (96 mg). The reaction mixture was stirred 18 hours and then concentrated. The crude product was purified on silica gel eluted with an 80 and 100 % ethyl acetate in hexane step gradient to provide the title compound.

EXAMPLE 403I

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

A solution of EXAMPLE 403H (174 mg) and dichloromethane (25 mL) was cooled in an ice bath and 2,2,2-trifluoroacetic acid (25 mL) was added slowly dropwise. The reaction mixture was stirred 30 minutes under nitrogen and the ice bath was removed. The reaction was stirred 18 hours and then concentrated. The crude product was purified by reverse phase chomatography with ammonium acetate buffer in acetonitrile to give the title compound. ^{1}H NMR (400 MHz, pyridine-d_5) δ 9.30 (d, 1H), 8.69 (t, 1H), 8.59 (s, 1H), 8.42 (dd, 1H), 7.99 (d, 1H), 7.53 (d, 1H), 7.43 (d, 2H), 7.26 (m, 1H), 7.18 (m, 1H), 7.06 (d, 2H), 6.94 (d, 1H), 6.72 - 6.66 (m, 2H), 5.53 (m, 2H), 3.98 (m, 2H), 3.32 (m, 2H), 3.18 (t, 2H), 2.03 (m, 4H), 2.76 (s, 2H), 2.25 (m, 2H), 2.13 (m, 4H), 1.97 (s, 2H), 1.83 (m, 1H), 1.60 (m, 2H), 1.40 - 1.29 (m, 4H), 0.94 (s, 6H).

EXAMPLE 404

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 404A

5-chloro-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 387A for EXAMPLE 329A and EXAMPLE 306C for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 329B.

EXAMPLE 404B

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 404A for EXAMPLE 1F and EXAMPLE 400E for EXAMPLE 26C in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 13.09 (s, 1H), 8.27 (d, 1H), 7.88 (d, 1H), 7.80 (s, 1H), 7.60 (d, 1H), 7.37 (d, 2H), 7.03-7.10 (m, 4H), 6.79 (dd, 1H), 6.53 (d, 1H), 6.13 (d, 1H), 4.50

(d, 2H), 3.76-3.81 (m, 2H), 3.57-3.63 (m, 2H), 3.04 (br s, 4H), 2.84 (br s, 2H), 2.18 (m, 2H), 1.82-1.92 (m, 4H), 1.42 (t, 2H), 0.94 (s, 6H).

EXAMPLE 405

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 404A for EXAMPLE 1F and EXAMPLE 55B for EXAMPLE 26C in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 11.21 (s, 1H), 8.43 (d, 1H), 8.06 (d, 1H), 7.55 (d, 1H), 7.34 (d, 2H), 7.27 (t, 1H), 7.13 (d, 1H), 7.04 (d, 2H), 6.93 (t, 1H), 6.69 (dd, 1H), 6.36 (d, 1H), 6.28 (d, 1H), 6.26 (d, 1H), 4.51 (d, 2H), 3.73-3.79 (m, 2H), 3.55-3.61 (m, 2H), 3.08 (br s, 4H), 2.86 (br s, 2H), 2.31 (br s, 2H), 2.18 (m, 2H), 1.95 (s, 2H), 1.79-1.90 (m, 4H), 1.36 (t, 2H), 0.92 (s, 6H).

EXAMPLE 406

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 385B for EXAMPLE 1F and EXAMPLE 400E for EXAMPLE 26C in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 13.03 (s, 1H), 8.48 (d, 1H), 8.17 (s, 1H), 7.74 (s, 1H), 7.63 (d, 1H), 7.37 (d, 2H), 7.00-7.08 (m, 4H), 6.77 (dd, 1H), 6.51 (s, 1H), 6.07 (d, 1H), 4.55 (d, 2H), 3.77-3.81 (m, 2H), 3.58-3.63 (m, 2H), 3.20 (br s, 4H), 2.19 (br s, 2H), 1.99 (s, 2H), 1.85-1.92 (m, 4H), 1.42 (t, 2H), 0.94 (s, 6H).

EXAMPLE 407

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide

EXAMPLE 407A

(*R*)-*tert*-butyl 1-(2, 2-difluoroethyl)pyrrolidin-3-ylcarbamate

To a solution of (R)-tert-butyl pyrrolidin-3-ylcarbamate (500 mg), 1,1-difluoro-2-iodoethane (618 mg) in N,N-dimethylformamide (6 mL) was added N-ethyl-N-isopropylpropan-2-amine (1.403 mL) and the reaction stirred for 72 hours at 70 °C. The reaction mixture was concentrated and the crude product was purified on a silica gel and was eluted with a 0, 2, and 5 % methanol in methylene chloride step gradient to provide the title compound.

EXAMPLE 407B

(*R*)-1-(2, 2-difluoroethyl)pyrrolidin-3-amine

To a solution of EXAMPLE 407A (525 mg) in a mixture of dichloromethane (3 mL) and methanol (2.0 mL) was added hydrogen chloride, 4M in dioxane (5.24 mL). The reaction was stirred for 3 hours, and concentrated to provide the title compound.

EXAMPLE 407C

(*R*)-4-(1-(2, 2-difluoroethyl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

To a solution of EXAMPLE 407B (468 mg) in tetrahydrofuran (20 mL), N-ethyl-N-isopropylpropan-2-amine (2.193 mL) and N,N-dimethylformamide (2 mL) was added 4-fluoro-3-nitrobenzenesulfonamide (473 mg) and the reaction mixture was stirred 72 hours. The crude product was isolated by concentration and was purified on silica gel, and was eluted with a 0.5, 2.5, and 5 % methanol in methylene chloride step gradient to obtain the title compound.

EXAMPLE 407D

(*R*)-2-(1-(bis(4-methoxyphenyl)methyl)-1*H*-benzo[*d*]imidazol-4-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-nitrophenylsulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 407C for EXAMPLE 1F in EXAMPLE 403H.

EXAMPLE 407E

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 407D for EXAMPLE 403H in EXAMPLE 403I. ^{1}H NMR (400 MHz, pyridine-d_5) δ 9.26 (d, 1H), 8.60 - 8.55 (m, 2H), 8.39 (m, 1H), 7.99 (d, 1H), 7.53 (d, 1H), 7.43 (d, 2H), 7.25 (m, 1H), 7.17 (m, 1H), 7.06 (d, 2H), 6.86 (d, 1H), 6.72 - 6.69 (m, 2H), 6.00 - 6.33 (m, 1H), 5.27 (m, 2H), 4.09 (m, 1H), 3.03 (m, 4H), 2.96 - 2.86 (m, 4H), 2.81 - 2.74 (m, 3H), 2.48 (m, 1H), 2.26 (m, 3H), 2.13 (m, 4H), 1.97 (s, 2H), 1.67 (m, 1H), 1.38 (t, 2H), 0.94 (s, 6H).

EXAMPLE 408

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 408A

2-(1-(bis(4-methoxyphenyl)methyl)-1*H*-benzo[*d*]imidazol-4-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-*N*-(4-((4-fluorotetrahydro-2*H*-pyran-4-yl)methoxy)-3-nitorophenylsulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 306D for EXAMPLE 1F in EXAMPLE 403H.

EXAMPLE 408B

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 408A for EXAMPLE 403H in EXAMPLE 403I. ^{1}H NMR (400 MHz, pyridine-d_5) δ 9.01 (d, 1H), 8.57 (m, 2H), 7.99 (d, 1H), 7.53 (d, 1H), 7.44 (d, 2H), 7.25 (m, 1H), 7.21 (m, 1H), 7.12 (d, 1H), 7.07 (d, 2H), 6.73 - 6.70 (m, 2H), 5.35 (m, 2H), 4.36 (s, 1H), 4.31 (s, 1H), 3.88 (m, 2H), 3.78 (m, 2H), 3.05 (m, 4H), 2.77 (s, 2H), 2.26 (m, 2H), 2.15 (m, 4H), 2.07 – 192 (m, 6H), 1.39 (t, 2H), 0.94 (s, 6H).

EXAMPLE 409

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 409A

(4-fluorotetrahydro-2H-pyran-4-yl)methyl methanesulfonate

A mixture of EXAMPLE 306C (1.4 g), methanesulfonyl chloride (1.054 mL), triethylamine (2.99 mL), and 4-(dimethylamino)pyridine (0.051 g) in CH_2Cl_2 (20 mL) was stirred at 0 °C for 2 hours, concentrated and chromatographed on silica gel with 30% ethyl acetate in hexanes as eluent to give the product.

EXAMPLE 409B

2-((4-fluorotetrahydro-2H-pyran-4-yl)methyl)isoindoline-1,3-dione

A mixture of EXAMPLE 409A (1.8 g) and potassium phthalimide (2.356 g) in N,N-dimethylformamide (30 mL) was heated at 150 °C overnight, diluted with ethyl acetate, washed with water and brine, dried ($MgSO_4$), filtered, concentrated and chromatographed on silica gel with 30% ethyl acetate in hexanes as eluent to give the product.

EXAMPLE 409C

(4-fluorotetrahydro-2H-pyran-4-yl)methanamine

A mixture of EXAMPLE 409B (1.4 g) and hydrazine (1.548 mL) in ethanol (40 mL) was heated at 70 °C overnight, cooled to room temperature, slurried with CH_2Cl_2 (200 mL) and the solid removed by filtration. The filtrate was concentrated and chromatographed on silica gel with 100:5:1 ethyl acetate/methanol/NH_4OH as eluent to give the product.

EXAMPLE 409D

4-((4-fluorotetrahydro-2H-pyran-4-yl)methylamino)-3-nitrobenzenesulfonamide

A mixture of 4-fluoro-3-nitrobenzenesulfonamide (0.44 g), EXAMPLE 409C (0.266 g), and triethylamine (1.11 mL) in tetrahydrofuran (10 mL) was heated at 70 °C overnight, diluted with ethyl acetate, washed with water and brine, dried ($MgSO_4$), filtered, concentrated and chromatographed on silica gel with 50% ethyl acetate in hexanes as eluent to give the product.

EXAMPLE 409E

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 409D for EXAMPLE 1F and EXAMPLE 400E for EXAMPLE 26C in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 13.09 (s, 1H), 8.59 (t, 1H), 8.37 (d, 1H), 7.80 (s, 1H), 7.59 (dd, 1H), 7.37 (d, 2H), 7.04-7.13 (m, 5H), 6.79 (dd, 1H), 6.51 (d, 1H), 6.18 (d, 1H), 3.70-3.79 (m, 4H), 3.50-3.56 (m, 2H), 3.15 (br s, 4H), 2.78 (br s, 2H), 2.32 (br s, 4H), 2.17 (br s, 2H), 1.97 (s, 2H), 1.75-1.83 (m, 4H), 1.40 (t, 2H), 0.93 (s, 6H).

EXAMPLE 410

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-5-(trifluoromethyl)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 410A

5-nitro-3-(trifluoromethyl)pyridin-2-ol

3-(Trifluoromethyl)pyridin-2-ol (2.3 g) was added to concentrated sulfuric acid (15 mL) at 0 °C. The mixture was stirred at 0 °C for 5 minutes. To this solution was added nitric acid (fuming) (6 mL) dropwise over 5 minutes. The reaction mixture was stirred at room temperature for 2 hours, and was heated at 50 °C for 3 hours. After cooling, the reaction mixture was poured into ice (200 g), and the mixture was extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the title compound.

EXAMPLE 410B

2-chloro-5-nitro-3-(trifluoromethyl)pyridine

A mixture of EXAMPLE 410A (1.69 g), phosphorus pentachloride (2.03 g), and phosphoryl trichloride (0.97 mL) was heated at 90 °C for 3 hours. After cooling, the reaction mixture was poured into ice, and extracted with ethyl acetate three times. The extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with 1:9 ethyl acetate\hexanes to give the title compound.

EXAMPLE 410C

A mixture of iron (1.5 g) and ammonium chloride (2.38 g) in water (40 mL) was stirred at room temperature for 5 minutes. To this suspension was added EXAMPLE 410B in methanol (40 mL). The reaction mixture was stirred at room temperature for 1 hour. Additional iron (1.8 g) was added to the reaction mixture, and it was stirred for another 3 hours. The solid from the reaction mixture was filtered off, and the filtrate was partitioned between water and ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with 1:4 ethyl acetate\hexanes to give the title compound.

EXAMPLE 410D

6-chloro-5-(trifluoromethyl)pyridine-3-sulfonyl chloride

Under ice-cooling, thionyl chloride (4 mL) was added dropwise over 20 minutes to water (27 mL). The mixture was stirred overnight for 12 hours to give a SO_2 containing solution. Separately, EXAMPLE 410C (1.14 g) in dioxane (5 mL) was added to concentrated HCl (20 mL) at 0 °C. The solution was stirred for 5 minutes. To this mixture was added sodium nitrite (0.44 g) in water (6 mL) dropwise at 0 °C. The solution stirred at 0 °C for three hours. During this time, any solids formed were crushed with a glass rod to make sure that EXAMPLE 410C was completely reacted. To the SO_2 containing solution was added copper(I) chloride (0.115 g). Then, to this solution was added the diazotized EXAMPLE 410C at 0 °C. The solution was stirred for 30 minutes. The reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with 1:20 ethyl acetate\hexanes to give the title compound.

EXAMPLE 410E

6-chloro-5-(trifluoromethyl)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 410D for 5-bromo-6-chloropyridine-3-sulfonyl chloride in EXAMPLE 329A.

EXAMPLE 410F

The title compound was prepared by substituting EXAMPLE 410E for EXAMPLE 329A and EXAMPLE 306C for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 329B.

EXAMPLE 410G

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-5-(trifluoromethyl)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 410F for EXAMPLE 1F and EXAMPLE 400E for EXAMPLE 26C in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 13.05 (s, 1H), 8.59 (s, 1H), 8.17 (d, 1H), 7.76 (s, 1H), 7.62 (d, 1H), 7.37 (d, 2H), 7.00-7.08 (m, 4H), 6.78 (dd, 1H), 6.51 (s, 1H), 6.11 (d, 1H), 4.56 (d, 2H), 3.77-3.80 (m, 2H), 3.57-3.62 (m, 2H), 3.18 (br s, 2H), 2.32 (br s, 4H), 2.18 (br s, 2H), 1.99 (s, 2H), 1.81-1.90 (m, 4H), 1.42 (t, 2H), 0.94 (s, 6H).

EXAMPLE 411

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyclopropylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 400E for EXAMPLE 1E and EXAMPLE 432A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 13.09 (s, 1H), 8.57 (m, 1H), 8.37 (d, 1H), 7.81 (s, 1H), 7.56 (dd, 1H), 7.52 (d, 1H), 7.38-7.31 (m, 3H), 7.11-7.07 (m, 3H), 6.97 (d, 1H), 6.80 (dd, 1H), 6.52 (d, 1H), 6.17 (d, 1H), 3.84 (d, 1H), 3.24-3.10 (m, 6H), 2.93 (d, 2H), 2.76 (m, 2H), 2.73 (s, 2H), 2.34-2.10 (m, 8H), 1.97 (bs, 2H), 1.67 (m, 1H), 1.40 (t, 2H), 0.93 (s, 6H), 0.47-0.26 (m, 4H).

EXAMPLE 412

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4,4-difluorocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 412A

tert-butyl (4,4-difluorocyclohexyl)methylcarbamate

Tert-butyl (4-oxocyclohexyl)methylcarbamate (5 g) and diethylaminosulfur trifluoride (7.45 g) were stirred in dichloromethane (100 mL) for 24 hours. The mixture was quenched with pH 7 buffer (100 mL), and poured into ether (400 mL). The resulting solution was separated, and the organic layer was washed twice with water, and once with brine, and then concentrated to give the crude product and fluoroolefin in a 3:2 ratio. The crude product was taken up in tetrahydrofuran (70 mL) and water (30 mL), and N-methylmorpholine-N-oxide (1.75 g), and OsO_4 (2.5 wt % solution in t-butanol) were added, and the mixture was stirred for 24 hours. $Na_2S_2O_3$ (10 g) was then added, and the mixture was stirred for 30 minutes. The mixture was then diluted with ether (300 mL), and the resulting solution was separated, and rinsed twice with water, and once with brine, and concentrated. The crude product was chromatographed on silica gel using 5-10% ethyl acetate in hexanes to give the title compound.

EXAMPLE 412B

(4,4-difluorocyclohexyl)methanamine

A solution of EXAMPLE 412A (3 g) in dichloromethane (35 mL), trifluroacetic acid (15 mL), and triethylsilane (1 mL) was stirred for 2 hours. The solution was concentrated, then concentrated from toluene, and left on high vacuum for 24 hours. The semi-solid was taken up in ether/hexane and filtered to give the product as its trifluroacetic acid salt.

EXAMPLE 412C

4-((4,4-difluorocyclohexyl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 412B for 1-(2-methoxy-ethyl)-piperidin-4-ylamine in EXAMPLE 189A.

EXAMPLE 412D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4,4-difluorocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 400E for EXAMPLE 1E and EXAMPLE 412C for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 13.16 (s, 1H), 11.70 (br s, 1H), 8.65 (m, 1H), 8.44 (d, 1H), 7.87 (d, 1H), 7.61 (dd, 2H), 7.41 (d, 2H), 7.02-7.20 (m, 4H), 6.88 (dd, 1H), 6.58 (d, 1H), 6.26 (dd,

1H), 3.22 (m, 4H), 2.86 (m, 2H), 2.20-2.35 (m, 7H), 2.14 (s, 2H), 2.10 (m, 2H), 2.03 (m, 2H), 1.91 (m, 2H), 1.87 (m, 2H), 1.46 (m, 2H), 1.27-1.39 (m, 3H), 1.00 (s, 6H).

EXAMPLE 413

N-[(5-chloro-6-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 413A

The title compound was prepared by substituting EXAMPLE 387A for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 409C for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 413B

N-[(5-chloro-6-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 413A for EXAMPLE 1F and EXAMPLE 400E for EXAMPLE 26C in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 13.14 (s, 1H), 8.19 (d, 1H), 7.87 (s, 1H), 7.60 (d, 1H), 7.56 (d, 1H), 7.36 (d, 2H), 7.31 (br s, 1H), 7.08-7.17 (m, 2H), 7.06 (d, 2H), 6.80 (dd, 1H), 6.53 (d, 1H), 6.20 (d, 1H), 3.70-3.78 (m, 4H), 3.43-3.54 (m, 2H), 3.18 (br s, 4H), 2.81 (s, 2H), 2.26 (br s, 4H), 2.17 (br s, 2H), 1.97 (s, 2H), 1.64-1.80 (m, 4H), 1.40 (t, 2H), 0.94 (s, 6H).

EXAMPLE 414

Trans-N-({5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 414A

Cis-(4-methoxycyclohexyl)methanol and Trans-(4-methoxycyclohexyl)methanol

Ethyl 4-methoxycyclohexanecarboxylate (1 g) in tetrahydrofuran (10 mL) was treated with 1.0 N $LiAlH_4$ in THF (2 mL) at 0°C. The mixture was stirred for 2 hours. The reaction was quenched with water (0.6 mL) followed by 2.0 N aqueous NaOH (0.2 mL). The mixture was stirred for another 20 minutes, and the solid was filtered off. The filtrate was taken up in ethyl acetate, washed with brine, dried over $MgSO_4$, filtered, and concentrated to give the title compound as a mixture of cis and trans isomers.

EXAMPLE 414B

5-chloro-6-((trans-4-methoxycyclohexyl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 387A for EXAMPLE 329A and EXAMPLE 414A for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 329B. The trans isomer was isolated by flash column chromatography on silica gel.

EXAMPLE 414C

Trans-N-({5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 414B for EXAMPLE 1F and EXAMPLE 400E for EXAMPLE 26C in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 13.10 (s, 1H), 8.27 (d, 1H), 7.85 (d, 1H), 7.80 (s, 1H), 7.59 (d, 1H), 7.36 (d, 2H), 7.03-7.10 (m, 4H), 6.79 (dd, 1H), 6.53 (d, 1H), 6.14 (d, 1H), 4.19 (d, 2H), 3.24 (s, 3H), 3.20 (m, 4H), 3.07-3.10 (m, 2H), 2.93 (br s, 2H), 2.39 (s, 4H), 2.18 (s, 2H), 1.98-2.02 (m, 4H), 1.70-1.86 (m, 3H), 1.42 (t, 2H), 1.08-1.17 (m, 4H), 0.94 (s, 6H).

EXAMPLE 415

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(2,2-difluoroethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide

EXAMPLE 415A

tert-Butyl 2-((2-nitro-4-sulfamoylphenylamino)methyl)morpholine-4-carboxylate

This EXAMPLE was prepared by substituting *tert*-butyl 2-(aminomethyl)morpholine-4-carboxylate for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 415B

4-(morpholin-2-ylmethylamino)-3-nitrobenzenesulfonamide

A solution of EXAMPLE 415A (0.8 g) in methylene chloride (10 mL) and trifluoroacetic acid (10 mL) was stirred at room temperature for 2 hours. The solvents were evaporated and the residue was triturated with diethyl ether. The resulting solid was dissolved in 5% aqueous sodium carbonate solution (20 mL). The solution was evaporated to dryness and the resulting solid was triturated with a solution of 10% methanol in dichloromethane several times. Evaporation of the organic solution gave the title compound.

EXAMPLE 415C

4-((4-(2, 2-difluoroethyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

To a solution of EXAMPLE 415B (633 mg) in anhydrous *N,N*-dimethylformamide (10 mL) was added sodium carbonate (254 mg) and 2, 2-difluoroethyl iodide (422 mg). After stirring at 110 °C for 48 hours, the mixture was concentrated. The residue was mixed with water (20 mL) and extracted with ethyl acetate. The crude product was purified on a silica gel column eluting with 10% methanol in methylene chloride to give the title compound.

EXAMPLE 415D

2-(1*H*-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-*N*-{[4-({[4-(2,2-difluoroethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide

This EXAMPLE was prepared by substituting EXAMPLE 415C for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (500MHz, pyridine-d_5) δ 9.26 (d, 1H), 8.87 (t, 1H), 8.57 (s, 1H), 8.37 (dd, 1H), 7.99 (d, 1H), 7.53 (d, 1H), 7.43 (d, 2H), 7.25 (m, 2H), 7.17 (d, 1H), 7.06 (d, 2H), 6.96 (d, 1H), 6.72-6.69 (m, 2H), 6.31, 6.20, 6.09 (tt, 1H), 3.90 (m, 1H), 3.86 (d, 1H), 3.68 (dt, 1H), 3.54-3.41 (m, 2H), 3.03 (m, 4H), 2.97 (d, 1H), 2.83-2.75 (m, 4H), 2.69 (d, 1H), 2.35 (dt, 1H), 2.27-2.23 (m, 3H), 2.14 (m, 4H), 1.97 (s, 2H), 1.38 (t, 2H), 0.94 (s, 6H).

EXAMPLE 416

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-fluoro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 416A

5-bromo-3-fluoro-2-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine

The title compound was prepared by substituting EXAMPLE 306C for (tetrahydro-2H-pyran-4-yl)methanol and 5-bromo-2,3-difluoropyridine for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 279A.

EXAMPLE 416B

tert-butyl 5-fluoro-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridin-3-ylcarbamate

EXAMPLE 416A (0.658 g), tert-butyl carbamate (0.300 g), palladium(II) acetate (0.024 g), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.093 g) and cesium carbonate (1.044 g) were combined in a 20-mL vial with dioxane (10.7 ml). The vial was flushed with nitrogen, capped and stirred at 100 °C overnight. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried ($MgSO_4$), filtered, concentrated and chromatographed on silica gel with 20% ethyl aceate in hexanes as eluent.

EXAMPLE 416C

5-fluoro-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonyl chloride

Under ice-cooling, thionyl chloride (1.563 mL) was added dropwise over 20 minutes to water (9 mL). The mixture was stirred for 12 hours to give a SO_2-containing solution. Separately, EXAMPLE 416B (0.295 g) was added to a mixture of dioxane (3.2 mL) and concentrated HCl (8 ml) at 0 °C. The solution was stirred for 15 minutes, treated with a solution of sodium nitrite (0.065 g) in water (2 mL) dropwise at 0 °C and stirred at 0 °C for three hours. The SO_2-containing solution was cooled to 0 °C, treated sequentially with copper(I) chloride (0.042 g) and the diazotized mixture, and stirred for 30 minutes. The reaction mixture was then extracted with ethyl acetate and the organic layer was dried ($MgSO_4$), filtered and concentrated. The concentrate was chromatographed on silica gel with 5-10% ethyl aceate in hexanes as eluent.

EXAMPLE 416D

5-fluoro-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

EXAMPLE 416C (0.08 g,) in isopropanol (2 mL) at 0 °C was treated with ammonium hydroxide (1.70 mL) and stirred overnight. The reaction mixture was concentrated to dryness, slurried in water, filtered, rinsed with water and dried under vacuum to provide the title compound.

EXAMPLE 416E

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-fluoro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 400E for EXAMPLE 26C and EXAMPLE 416D for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (400 MHz, PYRIDINE-d_5) δ 14.67 (s, 1H), 8.84 (d, 1H), 8.38 (d, 1H), 8.06 (d, 1H), 8.00 (dd, 1H), 7.46 (m, 2H), 7.35 (d, 1H), 7.12 (m, 3H), 6.87 (m, 2H), 6.47 (d, 1H), 4.56 (d, 2H), 3.80 (m, 4H), 3.18 (m, 4H), 2.83 (s, 2H), 2.31 (t, 2H), 2.24 (m, 4H), 1.99 (s, 2H), 1.86 (m, 4H), 1.41 (t, 2H), 0.96 (s, 6H).

EXAMPLE 417

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 417A

2-(1-(bis(4-methoxyphenyl)methyl)-1*H*-benzo[*d*]imidazol-4-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-*N*-(3-nitro-4-(1-(tetrahydro-2*H*-pyran-4-yl)piperidin-4-ylamino)phenylsulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 173C for EXAMPLE 1F in EXAMPLE 403H.

EXAMPLE 417B

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 417A for EXAMPLE 403H in EXAMPLE 403I. ^{1}H NMR (500 MHz, pyridine-d_5) δ 9.27 (m, 1H), 8.59 (s, 1H), 8.47 (d, 1H), 8.43 (d, 1H), 8.01 (d, 1H), 7.53 (d, 1H), 7.43 (d, 2H), 7.24 (m, 1H), 7.18 (m, 1H), 7.07 (d, 2H), 6.96 (d, 1H), 6.70 (m, 2H), 5.34 (m, 2H), 4.03 (m, 2H), 3.53 (m, 1H), 3.31 (m, 2H), 3.03 (m, 4H), 2.82 (m, 2H), 2.76 (s, 2H), 2.42 (m, 1H), 2.32 (m, 2H), 2.26 - 2.19 (m, 2H), 2.14 (m, 4H), 1.98 (m, 4H), 1.67 - 1.52 (m, 6H), 1.38 (m, 2H), 0.94 (s, 6H).

EXAMPLE 418

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 418A

2-(1-(bis(4-methoxyphenyl)methyl)-1*H*-benzo[*d*]imidazol-4-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-*N*-(4-(1-methylpiperidin-4-ylamino)-3-nitrophenylsulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 21A for EXAMPLE 1F in EXAMPLE 403H.

EXAMPLE 418B

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 418A for EXAMPLE 403H in EXAMPLE 403I. ^{1}H NMR (500 MHz, pyridine-d_5) δ 9.25 (m, 1H), 8.58 (s, 1H), 8.42 (m, 2H), 8.02 (d, 1H), 7.52 (d, 1H), 7.43 (d, 2H), 7.23 (m, 1H), 7.14 (d, 1H), 7.07 (d, 2H), 6.92 (d, 1H), 6.70 (m, 2H), 5.52 (m, 2H), 3.50 (m, 1H), 3.03 (m, 4H), 2.77 (s, 2H), 2.68 (m, 2H), 2.25 (m, 2H), 2.20 (s, 3H), 2.14 (m, 6H), 1.97 - 1.90 (m, 4H), 1.67 (m, 2H), 1.38 (t, 2H), 0.94 (s, 6H).

EXAMPLE 419

N-[(5-chloro-6-{[1-(cyanomethyl)-4-fluoropiperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 419A

tert-butyl 4-fluoro-4-(hydroxymethyl)piperidine-1-carboxylate

1-Tert-butyl 4-ethyl 4-fluoropiperidine-1,4-dicarboxylate (1.0 g) in tetrahydrofuran (10 mL) at 0 °C was treated with a 1 N solution of $LiAlH_4$ in tetrahydrofuran (2.54 mL), stirred for 2 hours at room temperature, treated sequentially dropwise with water (0.2 mL) and a 2 N aqueous solution of NaOH (0.6 mL), and stirred for 1 hour. The solid was removed by filtration through a pad of diatomaceous earth rinsing with ethyl acetate. The filtrate was washed with water and brine, dried ($MgSO_4$), filtered and concentrated to give the title compound.

EXAMPLE 419B

tert-butyl 4-((3-chloro-5-sulfamoylpyridin-2-yloxy)methyl)-4-fluoropiperidine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 419A for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 387A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 279A.

EXAMPLE 419C

5-chloro-6-((4-fluoropiperidin-4-yl)methoxy)pyridine-3-sulfonamide, 2•trifluoroacetic acid salt

The title compound was prepared by substituting EXAMPLE 419B for EXAMPLE 1A in EXAMPLE 1B.

EXAMPLE 419D

5-chloro-6-((1-(cyanomethyl)-4-fluoropiperidin-4-yl)methoxy)pyridine-3-sulfonamide

EXAMPLE 419C (0.166 g) in acetonitrile (3.00 mL) was treated with 2-chloroacetonitrile (0.027 g) and sodium carbonate (0.064 g), heated at 60 °C overnight, cooled to room temperature and chromatographed on silica gel with 0 to 3% methanol in

CH_2Cl_2 as eluent. The obtained solid was slurried in water, filtered, rinsed with water and diethyl ether, and dried in a vacuum oven at 80 °C to provide the title compound

EXAMPLE 419E

N-[(5-chloro-6-{[1-(cyanomethyl)-4-fluoropiperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 400E for EXAMPLE 26C and EXAMPLE 419D for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (400 MHz, PYRIDINE-d_5) δ 14.70 (s, 1H), 8.91 (d, 1H), 8.39 (d, 2H), 8.10 (d, 1H), 7.46 (m, 2H), 7.35 (d, 1H), 7.11 (m, 3H), 6.87 (m, 2H), 6.50 (d, 1H), 4.49 (d, 2H), 3.72 (s, 2H), 3.17 (m, 4H), 2.82 (s, 2H), 2.72 (m, 4H), 2.31 (m, 2H), 2.23 (m, 4H), 2.06 (m, 2H), 1.99 (s, 2H), 1.89 (m, 2H), 1.41 (t, 2H), 0.96 (s, 6H).

EXAMPLE 420

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydrofuran-3-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 420A

5-chloro-6-((tetrahydrofuran-3-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 387A for EXAMPLE 329A and (tetrahydrofuran-3-yl)methanol for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 329B.

EXAMPLE 420B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydrofuran-3-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 420B for EXAMPLE 1F and EXAMPLE 400E for EXAMPLE 26C in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 13.07 (s, 1H), 8.25 (d, 1H), 7.85 (d, 1H), 7.79 (s, 1H), 7.60 (d, 1H), 7.36 (d, 2H), 7.03-7.09 (m, 4H), 6.78 (dd, 1H), 6.51 (d, 1H), 6.13 (dd, 1H),

4.25-4.37 (m, 2H), 3.77-3.81 (m, 2H), 3.64-3.70 (m, 2H), 3.54-3.57 (m, 2H), 3.17 (br s, 4H), 2.89 (br s, 2H), 2.68-2.71 (m, 1H), 2.33 (m, 3H), 2.16-2.18 (m, 2H), 1.98-2.01 (m, 3H), 1.66-1.71 (m, 1H), 1.41 (t, 2H), 0.94 (s, 6H).

EXAMPLE 421

Trans-N-({5-chloro-6-[(4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 421A

6-((trans-4-(tert-butyldimethylsilyloxy)cyclohexyl)methoxy)-5-chloropyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 387A for EXAMPLE 329A and trans-4-(tert-butyldimethylsilyloxy)cyclohexylmethanol, synthesized according to the procedure reported in WO 2008/124878 (Page 100), for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 329B.

EXAMPLE 421B

Trans-N-({5-chloro-6-[(4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 421A for EXAMPLE 1F and EXAMPLE 400E for EXAMPLE 26C in EXAMPLE 177, after removal of the *tert*-butyldimethylsilyl group with trifluoroacetic acid. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 13.12 (s, 1H), 8.29 (d, 1H), 7.88 (d, 1H), 7.84 (s, 1H), 7.40 (d, 2H), 7.07-7.13 (m, 4H), 6.83 (dd, 1H), 6.56 (s, 1H), 6.17 (d, 1H), 4.58 (d, 1H), 4.21 (d, 2H), 3.22 (br s, 4H), 2.36-2.40 (m, 3H), 2.20-2.24 (m, 2H), 2.02-2.03 (m, 2H), 1.75-1.89 (m, 5H), 1.45 (t, 2H), 1.11-1.21 (m, 4H), 0.98 (s, 6H).

EXAMPLE 422

N-[(5-chloro-6-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]oxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 422A

(R)-tert-butyl 3-(3-chloro-5-sulfamoylpyridin-2-yloxy)pyrrolidine-1-carboxylate

The title compound was prepared by substituting (R)-tert-butyl 3-hydroxypyrrolidine-1-carboxylate for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 387B.

EXAMPLE 422B

(R)-5-chloro-6-(pyrrolidin-3-yloxy)pyridine-3-sulfonamideHydrochloride salt

EXAMPLE 422A (480 mg) was dissolved in anhydrous tetrahydrofuran (10 mL) followed by addition of hydrogen chloride in dioxane solution (4M, 2.5 mL). The reaction mixture was stirred at room temperature overnight. The solvent was removed under vacuum to provide the title compound.

EXAMPLE 422C

(R)-5-chloro-6-(1-(2,2-difluoroethyl)pyrrolidin-3-yloxy)pyridine-3-sulfonamide

A reaction mixture of EXAMPLE 422B (353 mg), 1,1-difluoro-2-iodoethane (268 mg) and Na_2CO_3 (283 mg) in N,N-dimethylformamide (10 mL) was heated at 80°C overnight. The reaction mixture was cooled to room temperature and diluted with ethyl acetate. The organic phase was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated. The crude material was purified with 2.5-3% methanol/dichloromethane to afford the title compound.

EXAMPLE 422D

N-[(5-chloro-6-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]oxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 400E for EXAMPLE 26C and EXAMPLE 422C for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 12.98 (s, 1H), 8.17 (d, 1H), 7.80 (d, 1H), 7.73 (s, 1H), 7.66 (d, 1H), 7.35 (d, 2H), 7.05 (m, 4H), 6.73 (m, 1H), 6.41 (d, 1H), 6.10 (m, 2H), 5.37 (m, 1H), 2.92 (m, 11H), 2.56 (m, 2H), 2.24 (m, 7H), 1.99 (m, 2H), 1.82 (m, 1H), 1.39 (m, 2H), 0.93 (s, 6H).

EXAMPLE 423

2-(1H-benzimidazol-4-yloxy)-N-[(5-chloro-6-{[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide

EXAMPLE 423A

(*S*)-*tert*-Butyl 2-((3-chloro-5-sulfamoylpyridin-2-yloxy)methyl)morpholine-4-carboxylate

This EXAMPLE was prepared by substituting (*S*)-*tert*-butyl 2-(hydroxymethyl)morpholine-4-carboxylate for 4-hydroxymethyl-tetrahydropyran in EXAMPLE 387B.

EXAMPLE 423B

(*S*)-5-chloro-6-(morpholin-2-ylmethoxy)pyridine-3-sulfonamide

This EXAMPLE was prepared by substituting EXAMPLE 423A for EXAMPLE 415A in EXAMPLE 415B.

EXAMPLE 423C

(*S*)-5-chloro-6-((4-(2-(dimethylamino)acetyl)morpholin-2-yl)methoxy)pyridine-3-sulfonamide

To a solution of EXAMPLE 423B (0.32 g) in anhydrous N,N-dimethylformamide (10 mL) was added sodium carbonate (0.165 g) and 2-(dimethylamino)acetyl chloride hydrochloride (0.40 g). After stirred at ambient temperature overnight, the mixture was concentrated to dryness. The residue was mixed with 5% aqueous Na_2CO_3 (20 mL) and extracted with ethyl acetate. The crude product was purified on a silica gel column eluting with 10% methanol in dichloromethane saturated with ammonia to give the title compound.

EXAMPLE 423D

2-(1*H*-benzimidazol-4-yloxy)-*N*-[(5-chloro-6-{[(2*S*)-4-(*N*,*N*-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 423C for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (500MHz, pyridine-d_5) δ 9.08 (d, 1H), 8.60 (t, 1H), 8.57 (s, 1H), 8.01 (d, 1H), 7.53 (d, 1H), 7.43 (d, 2H), 7.25 (m, 2H), 7.15 (m, 1H), 7.07 (d, 2H), 6.73-6.69

(m, 2H), 4.86-4.36 (m, 4H), 4.05-3.90 (m, 1H), 3.88 (d, 1H), 3.62-3.18 (m, 4H), 3.04 (m, 4H), 2.87 (t, 1H), 2.77 (s, 2H), 2.33 (m, 6H), 2.26 (m, 2H), 2.15 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

EXAMPLE 424

2-(1H-benzimidazol-4-yloxy)-N-[(5-chloro-6-{[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide

EXAMPLE 424A

(*R*)-*tert*-butyl 2-((3-chloro-5-sulfamoylpyridin-2-yloxy)methyl)morpholine-4-carboxylate

This EXAMPLE was prepared by substituting (*R*)-tert-butyl 2-(hydroxymethyl)morpholine-4-carboxylate for 4-hydroxymethyl-tetrahydropyran in EXAMPLE 387B.

EXAMPLE 424B

(R)-5-chloro-6-(morpholin-2-ylmethoxy)pyridine-3-sulfonamide

This EXAMPLE was prepared by substituting EXAMPLE 424A for EXAMPLE 415A in EXAMPLE 415B.

EXAMPLE 424C

(*R*)-5-chloro-6-((4-(2-(dimethylamino)acetyl)morpholin-2-yl)methoxy)pyridine-3-sulfonamide

This EXAMPLE was prepared by substituting EXAMPLE 424B for EXAMPLE 423B in EXAMPLE 423C.

EXAMPLE 424D

2-(1*H*-benzimidazol-4-yloxy)-*N*-[(5-chloro-6-{[(2*R*)-4-(*N*,*N*-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 424C for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (500MHz, pyridine-d_5) δ 9.08 (d, 1H), 8.60 (t, 1H), 8.57 (s, 1H), 8.01 (d, 1H), 7.53 (d, 1H), 7.43 (d, 2H), 7.25 (m, 2H), 7.15 (m, 1H), 7.07 (d,

2H), 6.73-6.69 (m, 2H), 4.86-4.36 (m, 4H), 4.05-3.90 (m, 1H), 3.88 (d, 1H), 3.62-3.18 (m, 4H), 3.04 (m, 4H), 2.87 (t, 1H), 2.77 (s, 2H), 2.33 (m, 6H), 2.26 (m, 2H), 2.15 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

EXAMPLE 425

N-[(5-chloro-6-{[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 400E for EXAMPLE 1E and EXAMPLE 423C for EXAMPLE 1F in EXAMPLE 1G, and was purified by reverse-phase HPLC using a Waters Preparative LC4000 system with Phenomenex Luna C18 column and a water-acetonitrile mobile phase buffered with ammonium acetate. ^{1}H NMR (500MHz, pyridine-d_5) δ 8.87 (dd, 1H), 8.40 (t, 2H), 8.13 (dd, 1H), 7.46 (d, 2H), 7.35 (d, 1H), 7.15-7.10 (m, 3H), 6.87 (d, 1H), 6.85 (s, 1H), 6.50 (dd, 1H), 4.84-4.46 (m, 4H), 4.02-3.90 (m, 1H), 3.88 (m, 1H), 3.60-3.33 (m, 2H), 3.25-3.15 (m, 6H), 2.89-2.84 (m, 1H), 2.83 (s, 2H), 2.32-2.23 (m, 12H), 1.99 (s, 2H), 1.41 (t, 2H), 0.96 (s, 6H).

1250969 EXAMPLE 426 Gary Wang

N-[(5-chloro-6-{[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 400E for EXAMPLE 1E and EXAMPLE 424C for EXAMPLE 1F in EXAMPLE 1G, and was purified by reverse-phase HPLC using a Waters Preparative LC4000 system with Phenomenex Luna C18 column and a water-acetonitrile mobile phase buffered with ammonium acetate. ^{1}H NMR (500MHz, pyridine-d_5) δ 8.87 (dd, 1H), 8.40 (t, 2H), 8.13 (dd, 1H), 7.46 (d, 2H), 7.35 (d, 1H), 7.15-7.10 (m, 3H), 6.87 (d, 1H), 6.85 (s, 1H), 6.50 (dd, 1H), 4.84-4.46 (m, 4H), 4.02-3.90 (m, 1H), 3.88 (m, 1H), 3.60-3.33 (m, 2H), 3.25-3.15 (m, 6H), 2.89-2.84 (m, 1H), 2.83 (s, 2H), 2.32-2.23 (m, 12H), 1.99 (s, 2H), 1.41 (t, 2H), 0.96 (s, 6H).

EXAMPLE 427

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 387B for EXAMPLE 1F and EXAMPLE 400E for EXAMPLE 26C in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 13.09 (s, 1H), 8.27 (d, 1H), 7.85 (d, 1H), 7.80 (s, 1H), 7.59 (d, 1H), 7.36 (d, 2H), 7.03-7.10 (m, 4H), 6.79 (dd, 1H), 6.52 (d, 1H), 6.13 (d, 1H), 4.27 (d, 2H), 3.88 (dd, 2H), 3.19 (br s, 4H), 2.91 (br s, 2H), 2.36-2.40 (br, 3H), 2.18 (m, 2H), 2.05 (m, 1H), 1.98 (s, 2H), 1.64-1.68 (m, 2H), 1.34-1.43 (m, 4H), 1.11-1.21 (m, 4H), 0.94 (s, 6H).

EXAMPLE 428

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(cyanomethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide

EXAMPLE 428A

8-{4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enylmethyl]piperazin-1-yl}-6-oxa-2,11a-diazadibenzo[c,d,g]azulen-11-one

A solution of EXAMPLE 403G (4.5 g) in anhydrous dichloromethane (100 mL) was cooled in an ice bath and catalytic N,N-dimethylformamide was added. This was followed by the dropwise addition of a solution of oxalyl dichloride (1.231 mL) in anhydrous methylene chloride (5 mL). The ice bath was removed and the reaction stirred for 1 hour while warming to ambient temperature. The reaction was quenched by the addition of ice (150 mL) and saturated sodium bicarbonate solution (100 mL). The mixture was further diluted with saturated sodium bicarbonate solution (200 mL) and methylene chloride (200 mL). The organic layer was purified on silica gel, and was eluted with a 0, 10, 25, and 100 % ethyl acetate in methylene chloride step gradient to provide the title compound.

EXAMPLE 428B

(*R*)-*tert*-butyl 3-(2-nitro-4-sulfamoylphenylamino)pyrrolidine-1-carboxylate

To a solution of (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate (1.0 g), tetrahydrofuran (50 ml), N-ethyl-N-isopropylpropan-2-amine (5.61 mL) and N,N-

dimethylformamide (10 mL) was added 4-fluoro-3-nitrobenzenesulfonamide (1.212 g) and the mixture was stirred for 18 hours. The crude product was isolated by concentration and was the material was purified on silica gel, and was eluted with a 30, 50, and 75 % ethyl acetate in hexane step gradient to provide the title compound.

EXAMPLE 428C

(*R*)-3-nitro-4-(pyrrolidin-3-ylamino)benzenesulfonamide

A suspension of EXAMPLE 428B (2.018 g) in anhydrous dichloromethane (25 mL) was cooled in an ice bath and 2,2,2-trifluoroacetic acid (20 mL) was added. After stirring 15 minutes, the ice bath was removed and the reaction was allowed to come to ambient temperature over 2 hours. The reaction mixture was concentrated and the residue was dissolved in water and basified with aqueous sodium carbonate solution. The mixture was extracted repeatedly with 10 % methanol in methylene chloride and the organics were concentrated to provide the title compound.

EXAMPLE 428D

(*R*)-4-(1-(cyanomethyl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

To a solution of EXAMPLE 428C (440 mg) in anhydrous N, N-dimethylformamide (10 mL) was added sodium carbonate (132 mg). To the resulting suspension was added 2-bromoacetonitrile (0.077 mL) and the mixture was heated at 60° C for 18 hours. The crude material was isolated by concentration and was purified on silica gel, and was eluted with a 0.5, 2.5, and 5% methanol in methylene chloride step gradient to provide the title compound.

EXAMPLE 428E

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(cyanomethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide

To a solution of EXAMPLE 428D (82.6 mg) in tetrahydrofuran (7 mL) was added 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepine (0.063 mL). This mixture was stirred at ambient temperature for 45 minutes and a solution of EXAMPLE 428A (117 mg) in tetrahydrofuran (3 mL) was added. After stirring 18 hours, the crude product was isolated by concentration and was purified by reverse phase chromatography with ammonium acetate buffer in acetonitrile to give the title compound. ^{1}H NMR (400 MHz, pyridine-d_5) δ 9.27 (d,

1H), 8.59 (s, 1H), 8.55 (d, 1H), 8.40 (dd, 1H), 7.99 (d, 1H), 7.54 (m, 1H), 7.43 (d, 2H), 7.25 (m, 1H), 7.16 (m, 1H), 7.07 (d, 2H), 6.86 (d, 1H), 6.69 (m, 2H), 5.73 (m, 2H), 4.15 (m, 1H), 3.90 (s, 2H), 3.03 (m, 4H), 2.96 - 287. (m, 2H), 2.81 - 2.76 (m, 3H), 2.58 (m, 1H), 2.32 - 2.23 (m, 3H), 2.14 (m, 4H), 1.97 (s, 2H), 1.73 (m, 1H), 1.38 (t, 2H), 0.94 (s, 6H).

EXAMPLE 429

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({(3R)-1-[2-(2-methoxyethoxy)ethyl]pyrrolidin-3-yl}amino)-3-nitrophenyl]sulfonyl}benzamide

EXAMPLE 429A

(*R*)-4-(1-(2-(2-methoxyethoxy)ethyl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 1-bromo-2-(2-methoxyethoxy)ethane for 2-bromoacetonitrile in EXAMPLE 428D.

EXAMPLE 429B

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({(3R)-1-[2-(2-methoxyethoxy)ethyl]pyrrolidin-3-yl}amino)-3-nitrophenyl]sulfonyl}benzamide

The title compound was prepared by substituting EXAMPLE 429A for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (400 MHz, pyridine-d_5) δ 9.26 (d, 1H), 8.58 (m, 2H), 8.38 (dd, 1H), 8.01 (d, 1H), 7.53 (d, 1H), 7.43 (d, 2H), 7.25 (d, 1H), 7.16 (d, 1H), 7.07 (d, 2H), 6.85 (d, 1H), 6.71 - 6.69 (m, 2H), 5.33 (m, 2H), 4.05 (m, 1H), 3.63 (m, 4H), 3.54 (m, 2H), 3.29 (s, 3H), 3.03 (m, 4H), 2.86 (m, 1H), 2.77 (m, 4H), 2.70 (t, 2H), 2.38 (m, 1H), 2.27 - 2.18 (m, 3H), 2.14 (m, 4H), 1.97 (s, 2H), 1.64 (m, 1H), 1.38 (t, 2H), 0.94 (s, 6H).

EXAMPLE 430

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(N,N-dimethylglycyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide

EXAMPLE 430A

R)-4-(1-(2-(dimethylamino)acetyl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 2-(dimethylamino)acetyl chloride for 2-bromoacetonitrile in EXAMPLE 428D.

EXAMPLE 430B

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(N,N-dimethylglycyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 430A for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (400 MHz, pyridine-d_5) δ 9.25 (m, 1H), 8.59 (d, 1H), 8.47 - 8.35 (m, 2H), 8.01 (d, 1H), 7.54 (d, 1H), 7.44 (d, 2H), 7.25 - 7.20 (m, 2H), 7.16 – 6.92 (m, 4H), 6.71 (m, 2H), 5.55 (m, 1H), 4.34 - 4.18 (m, 1H), 4.03 (m, 1H), 3.84 - 3.63 (m, 3H), 3.44 - 3.34 (m, 2H), 3.03 (m, 4H), 2.77 (s, 2H), 2.43 (m, 6H), 2.25 (m, 3H), 2.14 (m, 4H), 2.03 – 1.83 (m, 3H), 1.38 (t, 2H), 0.94 (s, 6H).

EXAMPLE 431

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(cyanomethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide

EXAMPLE 431A

4-((4-(cyanomethyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

This EXAMPLE was prepared by substituting 2-bromo-acetonitrile for 2, 2-difluoroethyl iodide in EXAMPLE 415C at ambient temperature.

EXAMPLE 431B

2-(1*H*-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-*N*-{[4-({[4-(cyanomethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide

This EXAMPLE was prepared by substituting EXAMPLE 431A for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (500MHz, pyridine-d_5) δ 9.25 (d, 1H), 8.87 (t, 1H), 8.58 (s, 1H), 8.38 (dd, 1H), 8.00 (d, 1H), 7.53 (d, 1H), 7.43 (d, 2H), 7.25 (m, 2H), 7.16 (d, 1H), 7.07 (d, 2H), 6.97 (d, 1H), 6.73-6.68 (m, 2H), 3.96-3.85 (m, 2H), 3.78 (s, 2H), 3.66 (dt,

1H), 3.53-3.42 (m, 2H), 3.03 (m, 4H), 2.90 (d, 1H), 2.76 (s, 2H), 2.61 (d, 1H), 2.51 (dt, 1H), 2.40 (t, 1H), 2.25 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.38 (t, 2H), 0.94 (s, 6H).

EXAMPLE 432

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyclopropylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide

EXAMPLE 432A

4-((4-cyclopropylmorpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

A solution of EXAMPLE 415B (0.633 g) and (1-ethoxycyclopropoxy)trimethylsilane (1.601 ml) in anhydrous methanol (15 mL) and acetic acid (1.7 ml) was refluxed for 30 minutes and allowed to cool to room temperature. Sodium cyanoborohydride (0.377 g) was then added and the mixture was stirred at ambient temperature overnight. The reaction mixture was concentrated to dryness. The residue was mixed with 5% aqueous Na_2CO_3 solution (25 mL) and extracted with ethyl acetate. The crude product was purified on a silica gel column eluting with 5% and 10% methanol in dichloromethane to provide the title compound.

EXAMPLE 432B

2-(1*H*-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-*N*-[(4-{[(4-cyclopropylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide

This EXAMPLE was prepared by substituting EXAMPLE 432A for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (500MHz, pyridine-d_5) δ 9.25 (d, 1H), 8.89 (t, 1H), 8.57 (s, 1H), 8.38 (dd, 1H), 8.00 (d, 1H), 7.53 (d, 1H), 7.43 (d, 2H), 7.25 (m, 2H), 7.16 (d, 1H), 7.07 (d, 2H), 6.98 (d, 1H), 6.73-6.68 (m, 2H), 3.90-3.83 (m, 2H), 3.60 (dt, 1H), 3.55-3.41 (m, 2H), 3.03 (m, 4H), 2.96 (d, 1H), 2.76 (s, 2H), 2.69 (d, 1H), 2.35 (dt, 1H), 2.26-2.20 (m, 3H), 2.14 (m, 4H), 1.97 (s, 2H), 1.59 (m, 1H), 1.38 (t, 2H), 0.94 (s, 6H), 0.47-0.37 (m, 4H).

EXAMPLE 433

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(4-oxetan-3-ylmorpholin-2-yl)methyl]amino}phenyl)sulfonyl]benzamide

EXAMPLE 433A

3-nitro-4-((4-(oxetan-3-yl)morpholin-2-yl)methylamino)benzenesulfonamide

This EXAMPLE was prepared by substituting oxetan-3-one for (1-ethoxycyclopropoxy)-trimethylsilane in EXAMPLE 432A.

EXAMPLE 433B

2-(1*H*-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-*N*-[(3-nitro-4-{[(4-oxetan-3-ylmorpholin-2-yl)methyl]amino}phenyl)sulfonyl]benzamide

This EXAMPLE was prepared by substituting EXAMPLE 433A for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (500MHz, pyridine-d_5) δ 9.25 (d, 1H), 8.87 (t, 1H), 8.57 (s, 1H), 8.38 (dd, 1H), 8.02 (d, 1H), 7.53 (d, 1H), 7.44 (d, 2H), 7.24 (m, 2H), 7.13 (d, 1H), 7.07 (d, 2H), 6.98 (d, 1H), 6.73-6.68 (m, 2H), 4.69-4.62 (m, 4H), 3.98-3.88 (m, 2H), 3.69 (dt, 1H), 3.55-3.35 (m, 3H), 3.03 (m, 4H), 2.77 (s, 2H), 2.74 (d, 1H), 2.44 (d, 1H), 2.25 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.94 (m, 1H), 1.87 (t, 1H), 1.38 (t, 2H), 0.94 (s, 6H).

EXAMPLE 434

N-{[5-chloro-6-({(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl}oxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 434A

(R)-5-chloro-6-(1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yloxy)pyridine-3-sulfonamide

EXAMPLE 422B (278 mg) and 1,3-difluoropropan-2-one (94 mg) were suspended in dichloroethane (10 ml). N,N-dimethylformamide (1.5 mL) was added drop wise until a white milky suspension formed. The reaction mixture was stirred at room temperature for 15 minutes followed by the addition of sodium triacetoxyborohydride (424 mg). The reaction mixture was stirred at room temperature overnight. The solvent was removed under vacuum,

and the crude material was purified with 2.5-5% methanol/dichloromethane to afford the title compound.

EXAMPLE 434B

N-{[5-chloro-6-({(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl}oxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 400E for EXAMPLE 26C and EXAMPLE 434A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 12.96 (s, 1H), 8.16 (d, 1H), 7.79 (m, 1H), 7.69 (m, 2H), 7.35 (d, 2H), 7.05 (m, 4H), 6.72 (m, 1H), 6.39 (d, 1H), 6.09 (dd, 3.05Hz, 1H), 5.37 (m, 1H), 4.66 (t, 2H), 4.54 (t, 2H), 2.91 (m, 12H), 2.23 (m, 7H), 1.97 (s, 2H), 1.82 (m, 1H), 1.40 (t, 2H), 0.93 (s, 6H).

EXAMPLE 435

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 435A

(R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-amine

To a solution of (R)-tert-butyl pyrrolidin-3-ylcarbamate (0.500 g) and 1,3-difluoropropan-2-one (0.278 g) in dichloromethane (5 mL) was added sodium triacetoxyborohydride (0.853 g). After stirring for one hour, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (5 mL). The mixture was extracted with dichloromethane (25 mL), and the organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. The resulting residue was treated with HCl (4.0M in 1,4-dioxane, 4 mL) and methanol (1 mL) and stirred for one hour. The mixture was concentrated to give the title compound.

EXAMPLE 435B

(R)-4-(1-(1,3-difluoropropan-2-yl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

To 4-fluoro-3-nitrobenzenesulfonamide (0.272 g) and EXAMPLE 435A (0.195 g) in tetrahydrofuran (3.0 mL) was added N-ethyl-N-isopropylpropan-2-amine (0.512 mL) and the reaction stirred at room temperature. After stirring for six hours, the reaction was concentrated, loaded onto silica gel (Reveleris 40 g) and the product eluted using a gradient of 25-100% ethyl acetate/hexanes over 30 minutes to give the title compound.

EXAMPLE 435C

4-{4-[2-(4-Chloro-phenyl)-4,4-dimethyl-cyclohex-1-enylmethyl]-piperazin-1-yl}-2-[1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazol-4-yloxy]-benzoic acid methyl ester

EXAMPLE 400D (1000 mg) was dissolved in N,N-dimethylformamide (12 mL) and sodium hydride (60% in mineral oil, 45 mg) was added. The solution was stirred at room temperature for 15 minutes, 2-(trimethylsilyl)ethoxymethyl chloride (299 mg) was added, and the solution was stirred at room temperature for 45 minutes. The solution was added to water and extracted with ethyl acetate. The extract was washed with brine, dried on anhydrous sodium sulfate, filtered, concentrated and purified by flash column chromatography on silica gel using 30-50% ethyl acetate in hexanes.

EXAMPLE 435D

4-{4-[2-(4-Chloro-phenyl)-4,4-dimethyl-cyclohex-1-enylmethyl]-piperazin-1-yl}-2-[1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazol-4-yloxy]-benzoic acid

The title compound was prepared by substituting EXAMPLE 435C for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 435E

N-{4-{4-[2-(4-Chloro-phenyl)-4,4-dimethyl-cyclohex-1-enylmethyl]-piperazin-1-yl}-2-[1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazol-4-yloxy]-benzoyl}-4-[(R)-1-(2-fluoro-1-fluoromethyl-ethyl)-pyrrolidin-3-ylamino]-3-nitro-benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 435D for EXAMPLE 1E and EXAMPLE 435B for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 435F

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 435E (103 mg) was dissolved in trifluoroacetic acid (1.8 mL) and water (0.2 mL) and stirred at room temperature for 90 minutes. The solvents were removed under vacuum, the residue dissolved in 1,4-dioxane (2 mL) and treated with 1M sodium hydroxide (1 mL), and the solution stirred at room temperature for 30 minutes. The solution was added to a saturated aqueous sodium bicarbonate solution and extracted with dichloromethane. The extract was washed with brine, dried on anhydrous sodium sulfate, filtered, and the solvent removed under vacuum. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 13.09 (bs, 1H), 8.37 (m, 2H), 7.84 (d, 1H), 7.58-7.45 (m, 2H), 7.36 (d, 2H), 7.17-7.03 (m, 4H), 6.95 (dd, 1H), 6.84-6.76 (m, 1H), 6.53 (dd, 1H), 6.17 (t, 1H), 4.72 (d, 2H), 4.56 (d, 2H), 4.23 (m, 1H), 3.17 (m, 4H), 3.12-3.03 (m, 2H), 3.02-2.91 (m, 2H), 2.86-2.73 (m, 4H), 2.40-2.14 (m, 6H), 1.97 (bs, 2H), 1.70 (m, 1H), 1.40 (t, 2H), 0.94 (s, 6H).

EXAMPLE 436

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 436A

4-(1-cyclopropyl-piperidin-4-ylamino)-3-nitro-benzenesulfonamide

The title compound was prepared by substituting 1-cyclopropyl-piperidin-4-ylamine for 1-(2-methoxy-ethyl)-piperidin-4-ylamine in EXAMPLE 189A.

EXAMPLE 436B

N-{4-{4-[2-(4-chlorophenyl)-4,4-dimethyl-cyclohex-1-enylmethyl]-piperazin-1-yl}-2-[1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazol-4-yloxy]-benzoyl}-4-(1-cyclopropyl-piperidin-4-ylamino)-3-nitro-benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 435D for EXAMPLE 1E and EXAMPLE 436A for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 436C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 436B for EXAMPLE 435E in EXAMPLE 435F. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 13.05 (bs, 1H), 8.35 (d, 1H), 8.17 (d, 1H), 7.77 (bs, 1H), 7.57 (td, 2H), 7.35 (d, 2H), 7.09-7.03 (m, 4H), 6.98 (d, 1H), 6.77 (dd, 1H), 6.48 (bs, 1H), 6.17 (m, 1H), 3.66 (m, 1H), 3.12 (bs, 4H), 2.92 (m, 2H), 2.76 (bs, 2H), 2.21 (m, 8H), 1.97 (bs, 2H), 1.94 (m, 2H), 1.73 (m, 1H), 1.55 (m, 2H), 1.40 (t, 2H), 0.93 (s, 6H), 0.46 (d, 2H), 0.35 (bs, 2H).

EXAMPLE 437

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide

EXAMPLE 437A

(*R*)-*tert*-butyl 2-((2-nitro-4-sulfamoylphenylamino)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting (*R*)-*tert*-butyl 2-(aminomethyl)morpholine-4-carboxylate for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 437B

(*S*)-4-(morpholin-2-ylmethylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 437A for EXAMPLE 415A in EXAMPLE 415B.

EXAMPLE 437C

(*R*)-4-((4-(2-(dimethylamino)acetyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 437B for EXAMPLE 423B in EXAMPLE 423C.

EXAMPLE 437D

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide

The title compound was prepared by substituting EXAMPLE 437C for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (500MHz, pyridine-d_5) δ 9.25 (s, 1H), 8.86 (t, 1H), 8.57 (s, 1H), 8.38 (t, 1H), 8.02 (d, 1H), 7.53 (d, 1H), 7.44 (d, 2H), 7.24 (m, 2H), 7.13 (d, 1H), 7.07 (d, 2H), 6.97 (dd, 1H), 6.73-6.68 (m, 2H), 4.75, 4.50 (dd, 1H), 4.33,4.02 (dd, 1H), 3.93 (m, 1H), 3.85-3.70 (m, 1H), 3.65-3.40 (m, 3H), 3.33 (dd, 1H), 3.25-3.10 (m, 2H), 3.03 (m, 4H), 2.90 (m, 1H), 2.77 (s, 2H), 2.27-2.25 (m, 8H), 2.14 (m, 4H), 1.97 (s, 2H), 1.38 (t, 2H), 0.94 (s, 6H).

EXAMPLE 438

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide

EXAMPLE 438A

(*S*)-*tert*-butyl 2-((2-nitro-4-sulfamoylphenylamino)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting (*S*)-*tert*-butyl 2-(aminomethyl)morpholine-4-carboxylate for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 438B

(*R*)-4-(morpholin-2-ylmethylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 438A for EXAMPLE 415A in EXAMPLE 415B.

EXAMPLE 438C

(*S*)-4-((4-(2-(dimethylamino)acetyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 438B for EXAMPLE 423B in EXAMPLE 423C.

EXAMPLE 438D

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide

The title compound was prepared by substituting EXAMPLE 438C for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (500MHz, pyridine-d_5) δ 9.25 (s, 1H), 8.86 (t, 1H), 8.57 (s, 1H), 8.38 (t, 1H), 8.02 (d, 1H), 7.53 (d, 1H), 7.44 (d, 2H), 7.24 (m, 2H), 7.13 (d, 1H), 7.07 (d, 2H), 6.97 (dd, 1H), 6.73-6.68 (m, 2H), 4.75, 4.50 (dd, 1H), 4.33,4.02 (dd, 1H), 3.93 (m, 1H), 3.85-3.70 (m, 1H), 3.65-3.40 (m, 3H), 3.33 (dd, 1H), 3.25-3.10 (m, 2H), 3.03 (m, 4H), 2.90 (m, 1H), 2.77 (s, 2H), 2.27-2.25 (m, 8H), 2.14 (m, 4H), 1.97 (s, 2H), 1.38 (t, 2H), 0.94 (s, 6H).

EXAMPLE 439

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydrofuran-3-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 439A

3-nitro-4-((tetrahydrofuran-3-yl)methylamino)benzenesulfonamide

The title compound was prepared by substituting (tetrahydrofuran-3-yl)methylamine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 439B

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydrofuran-3-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 439A for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (500MHz, pyridine-d_5) δ 9.26 (d, 1H), 8.70 (t, 1H), 8.57 (s, 1H), 8.40 (dd, 1H), 8.01 (d, 1H), 7.51 (d, 1H), 7.44 (d, 2H), 7.24 (m, 2H), 7.14 (d, 1H), 7.07 (d, 2H), 6.89 (d, 1H), 6.73-6.68 (m, 2H), 3.93-3.89 (m, 1H), 3.83 (dd, 1H), 3.83-3.68 (m, 2H), 3.33-3.23 (m, 2H), 3.03 (m, 4H), 2.77 (s, 2H), 2.55-2.50 (m, 1H), 2.25 (m, 2H), 2.14 (m, 4H), 2.00-1.93 (m, 3H), 1.65-1.58 (m, 1H), 1.38 (t, 2H), 0.94 (s, 6H).

EXAMPLE 440

Trans-2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 311B for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (500 MHz, pyridine-d_5) δ 9.29 (d, 1H), 8.67 (t, 1H), 8.59 (s, 1H), 8.41 (dd, 1H), 7.99 (d, 1H), 7.52 (d, 1H), 7.43 (d, 2H), 7.24 (m, 1H), 7.17 (m, 1H), 7.07 (d, 2H), 6.90 (d, 1H), 6.72 - 6.68 (m, 2H), 5.97 (m, 2H), 3.29 (s, 3H), 3.14 (t, 2H), 3.02 (m, 5H), 2.76 (s, 2H), 2.25 (m, 2H), 2.13 (m, 4H), 2.07 (m, 2H), 1.97 (s, 2H), 1.82 (m, 2H), 1.57 (m, 1H), 1.38 (t, 2H), 1.22 (m, 2H), 1.01 (m, 2H), 0.94(s, 6H).

EXAMPLE 441

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 409D for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (500 MHz, pyridine-d_5) δ 9.27 (d, 1H), 8.84 (t, 1H), 8.57 (s, 1H), 8.41 (dd, 1H), 7.99 (d, 1H), 7.52 (d, 1H), 7.43 (d, 2H), 7.23 (m, 1H), 7.15 (m, 1H), 7.14 - 7.02 (m, 3H), 6.70 (m, 2H), 6.49 (m, 2H), 3.86 (m, 2H), 3.76 - 3.69 (m, 3H), 3.65 (d, 1H), 3.03 (m, 4H), 2.76 (s, 2H), 2.25 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.92 - 1.76 (m, 4H), 1.38 (t, 2H), 0.94 (s, 6H).

EXAMPLE 442

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-fluoro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 416D for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (500 MHz, pyridine-d_5) δ 9.02 (d, 1H), 8.59 (s, 1H), 8.35 (m, 1H), 8.01 (d, 1H), 7.51 (d, 1H), 7.44 (d, 2H), 7.22 (m, 2H), 7.12 (d, 1H), 7.07 (d, 2H), 6.84 (m, 1H), 6.73 (m, 2H), 4.59 (s, 1H), 4.54 (s, 1H), 3.89 - 3.74 (m, 4H), 3.05 (m, 4H), 2.78 (s, 2H), 2.26 (m, 2H), 2.16 (m, 4H), 2.02 – 1.81 (m, 6H), 1.39 (t, 2H), 0.94 (s, 6H).

EXAMPLE 443

2-(1H-benzimidazol-4-yloxy)-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide

The title compound was prepared by substituting EXAMPLE 404A for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (500 MHz, pyridine-d_5) δ 9.12 (d, 1H), 8.68 (d, 1H), 8.59 (s, 1H), 7.99 (d, 1H), 7.52 (d, 1H), 7.44 (d, 2H), 7.24 (d, 1H), 7.15 (d, 1H), 7.07 (d, 2H), 6.73 - 6.69 (m, 3H), 6.56 (m, 1H), 4.56 (s, 1H), 4.51 (s, 1H), 3.91 - 3.76 (m, 4H), 3.04 (m, 4H), 2.77 (s, 2H), 2.26 (m, 2H), 2.15 (m, 4H), 1.99 - 1.85 (m, 6H), 1.39 (t, 2H), 0.94 (s, 6H).

EXAMPLE 444

N-{[5-chloro-6-({(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl}methoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 444A

(R)-5-chloro-6-((1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 445B for EXAMPLE 422B in EXAMPLE 434A.

EXAMPLE 444B

N-{[5-chloro-6-({(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl}methoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 400E for EXAMPLE 26C and EXAMPLE 444A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 12.98 (s, 1H), 8.19 (d, 1H), 7.81 (d, 1H), 7.73 (s, 1H), 7.66 (d, 1H), 7.35 (d, 2H), 7.05 (m, 4H), 6.73 (dd, 1H), 6.42 (d, 1H), 6.10 (m, 1H), 4.64 (s, 2H), 4.54 (d, 2H), 4.24 (m, 2H), 3.07 (s, 4H), 2.89 (s, 2H), 2.74 (m, 4H), 2.56 (m, 2H), 2.20 (m, 6H), 1.98 (m, 4H), 1.54 (m, 1H), 1.40 (t, 2H), 0.91 (s, 6H).

EXAMPLE 445

N-[(5-chloro-6-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 445A

(R)-tert-butyl 3-((3-chloro-5-sulfamoylpyridin-2-yloxy)methyl)pyrrolidine-1-carboxylate

The title compound was prepared by substituting (R)-tert-butyl 3-(hydroxymethyl)pyrrolidine-1-carboxylate for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 387B.

EXAMPLE 445B

(R)-5-chloro-6-(pyrrolidin-3-ylmethoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 445A for EXAMPLE 422A in EXAMPLE 422B.

EXAMPLE 445C

(R)-5-chloro-6-((1-(2,2-difluoroethyl)pyrrolidin-3-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 445B for EXAMPLE 422B in EXAMPLE 422C.

EXAMPLE 445D

N-[(5-chloro-6-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 400E for EXAMPLE 26C and EXAMPLE 445C for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 12.98 (s, 1H), 8.19 (d, 1H), 7.81 (d, 1H), 7.73 (s, 1H), 7.66 (d, 1H), 7.35 (d, 2H), 7.05 (m, 4H), 6.72 (dd, 1H), 6.41 (d, 1H), 6.10 (m, 2H), 4.23 (m, 2H), 3.07 (s, 4H), 2.82 (m, 5H), 2.62 (m, 3H), 2.24 (s, 4H), 2.17 (s, 2H), 1.94 (m, 3H), 1.53 (m, 1H), 1.40 (t, 2H), 0.93 (s, 6H).

EXAMPLE 446

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide

EXAMPLE 446A

2-[1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazol-4-yloxy]-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(4-((trans-4-methoxycyclohexyl)methylamino)-3-nitrophenylsulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 435D for EXAMPLE 1E and EXAMPLE 311B for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 446B

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 446A for EXAMPLE 435E in EXAMPLE 435F. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 13.08 (bs, 1H), 8.53 (t, 1H), 8.37 (d, 1H), 7.84 (d, 1H), 7.53 (m, 2H), 7.35 (d, 2H), 7.09 (d, 2H), 7.05 (d, 2H), 6.94 (d, 1H), 6.79 (m, 1H), 6.51 (dd, 1H), 6.18 (m, 1H), 3.23 (s, 3H), 3.17-3.00 (m, 5H), 2.78 (bs, 2H), 2.30-2.13 (m, 8H), 2.02 (m, 2H), 1.97, (bs, 2H), 1.80 (m, 2H), 1.60 (m, 1H), 1.40 (t, 2H), 1.07 (m, 4H), 0.93 (s, 6H).

EXAMPLE 447

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 447A

N-{4-{4-[2-(4-Chloro-phenyl)-4,4-dimethyl-cyclohex-1-enylmethyl]-piperazin-1-yl}-2-[1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazol-4-yloxy]-benzoyl}-4-([1,4]dioxan-2-ylmethoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 435D for EXAMPLE 1E and EXAMPLE 297A for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 447B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 447A for EXAMPLE 435E in EXAMPLE 435F. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 13.04 (bs, 1H), 8.07 (bs, 1H), 7.78 (t, 2H), 7.59 (d, 1H), 7.36 (d, 2H), 7.25 (d, 1H), 7.08 (d, 2H), 7.06 (d, 2H), 6.77 (d, 1H), 6.48 (bs, 1H), 6.15 (m, 1H), 4.20 (t, 2H), 3.92-3.76 (m, 3H), 3.65 (m, 2H), 3.48 (td, 2H), 3.14 (bs, 4H), 2.80 (m, 2H), 2.38-2.13 (m, 6H), 1.97 (bs, 2H), 1.40 (t, 2H), 0.94 (s, 6H).

EXAMPLE 448

N-({5-chloro-6-[(1-cyclopropylpiperidin-4-yl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 448A

5-chloro-6-(1-cyclopropyl-piperidin-4-ylamino)-pyridine-3-sulfonic acid amide

The title compound was prepared by substituting 1-cyclopropyl-piperidin-4-ylamine for 1-(2-methoxy-ethyl)-piperidin-4-ylamine and EXAMPLE 387A for 4-chloro-3-nitrobenzenesulfonamide in EXAMPLE 189A.

EXAMPLE 448B

5-Chloro-6-(1-cyclopropyl-piperidin-4-ylamino)-pyridine-3-sulfonic acid 4-{4-[2-(4-chloro-phenyl)-4,4-dimethyl-cyclohex-1-enylmethyl]-piperazin-1-yl}-2-[1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazol-4-yloxy]-benzoylamide

The title compound was prepared by substituting EXAMPLE 435D for EXAMPLE 1E and EXAMPLE 448A for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 448C

N-({5-chloro-6-[(1-cyclopropylpiperidin-4-yl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 448B for EXAMPLE 435E in EXAMPLE 435F. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 13.03 (bs, 1H), 8.18 (d, 1H), 7.79 (bs, 1H), 7.65-7.58 (m, 2H), 7.36 (d, 2H), 7.33 (m, 1H), 7.10 (d, 2H), 7.06 (d, 2H), 6.74 (dd, 1H), 6.43 (bs, 1H), 6.19 (m, 1H), 3.95 (m, 1H), 3.08 (m, 4H), 2.96 (m, 2H), 2.75 (bs, 2H), 2.37-2.10 (m, 9H), 1.97 (bs, 2H), 1.78 (m, 2H), 1.56 (m, 2H), 1.40 (t, 2H), 0.93 (s, 6H), 0.42 (d, 2H), 0.33 (bs, 2H).

EXAMPLE 449

2-(1H-benzimidazol-4-yloxy)-N-({5-chloro-6-[(1-cyclopropylpiperidin-4-yl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide

EXAMPLE 449A

5-chloro-6-(1-cyclopropylpiperidin-4-ylamino)pyridine-3-sulfonamide

A mixture of EXAMPLE 387A (0.4 g), 1-cyclopropylpiperidin-4-amine (0.3 g) and N,N-diisopropylethylamine (0.37 mL) in dioxane (3 mL) was heated at 100° C for 18 hours. The crude product was isolated by concentration and was purified on silica gel, which was eluted with ethyl acetate to give the title compound.

EXAMPLE 449B

2-(1H-benzimidazol-4-yloxy)-N-({5-chloro-6-[(1-cyclopropylpiperidin-4-yl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide

The title compound was prepared by substituting EXAMPLE 449A for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (500 MHz, pyridine-d_5) δ 9.22 (m, 1H), 8.55 (s, 1H), 8.47 (s, 1H), 8.00 (d, 1H), 7.54 (d, 1H), 7.44 (d, 2H), 7.25 (m, 1H), 7.19 (m, 1H), 7.07 (d, 2H), 7.01 (m, 1H), 6.68 (m, 2H), 5.35 (m, 2H), 4.22 (m, 1H), 3.04 – 2.95 (m, 6H), 2.77 (s, 2H), 2.29 - 2.24 (m, 4H), 2.14 (m, 4H), 2.03 (m, 2H), 1.97 (s, 2H), 1.70 (m, 2H), 1.52 (m, 1H), 1.38 (t, 2H), 0.94 (s, 6H), 0.35 (m, 4H).

EXAMPLE 450

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 336A for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (500 MHz, pyridine-$d_5$5) δ 9.24 (m, 1H), 8.81 (m, 1H), 8.56 (s, 1H), 8.37 (dd, 1H), 8.03 (d, 1H), 7.52 (d, 1H), 7.44 (d, 2H), 7.21 (m, 1H), 7.11 (m, 1H), 7.07 (d, 2H), 6.92 (d, 1H), 6.71 (m, 2H), 5.33 (m, 2H), 3.94 (m, 2H), 3.78 (m, 1H), 3.73 - 3.66 (m, 2H), 3.58 (m, 1H), 3.51 - 3.36 (m, 3H), 3.03 (m, 4H), 2.77 (s, 2H), 2.26 (m, 2H), 2.15 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

EXAMPLE 451

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 451A

4-(1-cyclopropylpiperidin-4-ylamino)-3-nitrobenzenesulfonamide

To a solution of 4-fluoro-3-nitrobenzenesulfonamide (1.26 g) and 1-cyclopropylpiperidin-4-amine (0.802 g) in tetrahydrofuran (20 mL) was added N,N-diisopropylethylamine (2.22 g) and 4-dimethylaminopyridine (35 mg). The mixture was heated at reflux for 18 hours and upon cooling was diluted with ethyl acetate (200 mL) and aqueous $NaHCO_3$. The crude product was isolated by concentration of the organic layer and was purified on silica gel, which was eluted with 5% methanolic ammonia in methylene chloride to give the title compound.

EXAMPLE 451B

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 451 A for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (500 MHz, pyridine-d_5) δ 9.26 (m, 1H), 8.59 (s, 1H),

8.46 (d, 1H), 8.42 (dd, 1H), 8.01 (d, 1H), 7.53 (d, 1H), 7.43 (d, 2H), 7.25 (d, 1H), 7.17 (d, 1H), 7.07 (d, 2H), 6.96 (d, 1H), 6.72 - 6.67 (m, 2H), 5.48 (m, 2H), 3.54 (m, 1H), 3.03 (m, 4H), 2.90 (m, 2H), 2.76 (s, 2H), 2.37 (m, 2H), 2.25 (m, 2H), 2.14 (m, 4H), 1.98 - 1.91 (m, 4H), 1.56 (m, 3H), 1.38 (t, 2H), 0.94 (s, 6H), 0.42 (m, 4H).

EXAMPLE 452

Trans-2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 204A for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (500 MHz, pyridine-d_5) δ 9.27 (m, 1 H), 8.59 (s, 1 H), 8.42 (dd, 1 H), 8.36 (d, 1 H), 8.01 (d, 1 H), 7.53 (d, 1 H), 7.43 (d, 2 H), 7.25 (m, 1 H), 7.17 (m, 1 H), 7.07 (d, 2 H), 6.95 (d, 1 H), 6.71 (d, 2 H), 6.33 (m, 2 H), 3.76 (m, 4 H), 3.40 (m, 1 H), 3.03 (m, 4 H), 2.76 (s, 2 H), 2.52 (m, 4 H), 2.25 (m, 3 H), 2.14 (m, 4 H), 2.07 (m, 2 H), 1.97 (m, 2 H), 1.89 (m, 2 H), 1.42 - 1.21 (m, 6 H), 0.94 (s, 6 H).

EXAMPLE 453

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 174A for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (500 MHz, pyridine-d_5) δ 9.25 (m, 2H), 8.59 (s, 1H), 8.44 (m, 1H), 8.00 (d, 1H), 7.68 (d, 1H), 7.53 (d, 1H), 7.43 (d, 2H), 7.25 (m, 1H), 7.17 (m, 1H), 7.06 (d, 2H), 6.72 - 6.67 (m, 2H), 6.36 (m, 1H), 2.02 (m, 4H), 2.93 (m, 4H), 2.76 (s, 2H), 2.74 - 2.61 (m, 2H), 2.35 - 2.22 (m, 5H), 2.19 (s, 3H), 2.16 - 2.10 (m, 4H), 1.97 (m, 2H), 1.38 (t, 2H), 0.94 (s, 6H).

EXAMPLE 454

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-methylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 88A for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (500 MHz, pyridine-d_5) δ 9.28 (m, 1H), 8.66 (m, 1H),

8.58 (s, 1H), 8.40 (dd, 1H), 8.02 (d, 1H), 7.53 (d, 1H), 7.44 (d, 2H), 7.24 (m, 1H), 7.15 (m, 1H), 7.07 (d, 2H), 6.89 (d, 1H), 6.73 - 6.69 (m, 2H), 5.86 (m, 2H), 3.17 (t, 2H), 3.01 - 3.04 (m, 4H), 2.86 (m, 2H), 2.77 (s, 2H), 2.25 (m, 5H), 2.14 (m, 4H), 1.96 - 1.97 (s, 2H), 1.92 (m, 2H), 1.70 (m, 2H), 1.60 (m, 1H), 1.48 – 1.37 (m, 4H), 0.94 (s, 6H).

EXAMPLE 455

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[({(2R)-4-[2-(2-methoxyethoxy)ethyl]morpholin-2-yl}methyl)amino]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 455A

(*R*)-4-((4-(2-(2-methoxyethoxy)ethyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 437B for EXAMPLE 415B and 2-(2-methoxyethoxy)ethyl bromide for 2,2-difluoroethyl iodide in EXAMPLE 415C.

EXAMPLE 455B

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[({(2R)-4-[2-(2-methoxyethoxy)ethyl]morpholin-2-yl}methyl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 455A for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (500MHz, pyridine-d_5) δ 9.24 (d, 1H), 8.85 (t, 1H), 8.56 (s, 1H), 8.36 (dd, 1H), 8.03 (d, 1H), 7.51 (d, 1H), 7.44 (d, 2H), 7.24 (m, 2H), 7.12 (d, 1H), 7.07 (d, 2H), 6.91 (d, 1H), 6.73-6.68 (m, 2H), 3.93-3.86 (m, 2H), 3.72-3.61 (m, 5H), 3.53 (m, 2H), 3.48-3.40 (m, 2H), 3.28 (s, 3H), 3.03 (m, 4H), 2.95 (d, 1H), 2.77 (s, 2H), 2.70 (d, 1H), 2.69 (t, 2H), 2.27-2.10 (m, 8H), 1.97 (s, 2H), 1.38 (t, 2H), 0.94 (s, 6H).

EXAMPLE 456

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4,4-difluorocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 412C for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (500MHz, pyridine-d_5) δ 9.29 (d, 1H), 8.73 (t, 1H), 8.58 (s, 1H), 8.42 (dd, 1H), 7.99 (d, 1H), 7.52 (d, 1H), 7.43 (d, 2H), 7.24 (m, 2H), 7.17 (d, 1H), 7.07 (d, 2H), 6.94 (d, 1H), 6.72 (d, 1H), 6.69 (dd, 1H), 3.22 (t, 2H), 3.03 (m, 4H), 2.76 (s, 2H), 2.25 (m, 2H), 2.13 (m, 6H), 1.97 (s, 2H), 1.85-1.70 (m, 5H), 1.38 (t, 2H), 1.36-1.33 (m, 2H), 0.94 (s, 6H).

EXAMPLE 457

N-[(4-{[(4-acetylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide

EXAMPLE 457A

4-((4-acetylmorpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

A solution of EXAMPLE 415B (145 mg) and *N*-ethyl-*N*-isopropylpropan-2-amine (120 µl) in anhydrous dichloromethane (5 mL) and N,N-dimethylformamide (2 mL) was cooled with an ice bath and acetic anhydride (56 µl) was added dropwise. The mixture was stirred at room temperature for 3 hours and concentrated to dryness. The residue was triturated with water. The resulting solid was dried under vacuum to give the title compound.

EXAMPLE 457B

N-[(4-{[(4-acetylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide

The title compound was prepared by substituting EXAMPLE 457A for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (500MHz, pyridine-d_5) δ 9.24 (d, 1H), 8.83 (t, 1H), 8.56 (s, 1H), 8.38 (dd, 1H), 8.03 (d, 1H), 7.51 (d, 1H), 7.43 (d, 2H), 7.24 (m, 2H), 7.09 (d, 1H), 7.07 (d, 2H), 6.91 (dd, 1H), 6.72 (m, 2H), 3.89 (m, 1H), 3.80-3.70 (m, 1H), 3.60-3.40 (m, 4H), 3.06 (m, 1H), 3.03 (m, 4H), 2.77 (s, 2H), 2.70 (m, 1H), 2.26 (m, 2H), 2.18-2.13 (m, 5H), 2.09 (s, 3H), 1.97 (s, 2H), 1.38 (t, 2H), 0.94 (s, 6H).

EXAMPLE 458

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(methylsulfonyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide

EXAMPLE 458A

4-((4-(methylsulfonyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting methanesulfonyl chloride for acetic anhydride in EXAMPLE 457A.

EXAMPLE 458B

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(methylsulfonyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide

The title compound was prepared by substituting EXAMPLE 458A for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (500MHz, pyridine-d_5) δ 9.23 (d, 1H), 8.85 (t, 1H), 8.57 (s, 1H), 8.37 (dd, 1H), 8.01 (d, 1H), 7.52 (d, 1H), 7.43 (d, 2H), 7.24 (m, 2H), 7.15 (d, 1H), 7.07 (d, 2H), 6.97 (d, 1H), 6.72 (m, 2H), 4.00-3.90 (m, 3H), 3.68-3.59 (m, 3H), 3.58-3.48 (m, 1H), 3.06-3.02 (m, 7H), 2.98-2.89 (m, 2H), 2.77 (s, 2H), 2.25 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.38 (t, 2H), 0.94 (s, 6H).

EXAMPLE 459

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[6-({4-fluoro-1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl}methoxy)-5-(trifluoromethyl)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 459A

tert-butyl 4-fluoro-4-((5-sulfamoyl-3-(trifluoromethyl)pyridin-2-yloxy)methyl)piperidine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 410E for EXAMPLE 329A and EXAMPLE 419A for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 329B.

EXAMPLE 459B

6-((4-fluoropiperidin-4-yl)methoxy)-5-(trifluoromethyl)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 459A for EXAMPLE 422A in EXAMPLE 422B.

EXAMPLE 459C

6-((1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl)methoxy)-5-(trifluoromethyl)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 459B for EXAMPLE 422B in EXAMPLE 434A.

EXAMPLE 459D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[6-({4-fluoro-1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl}methoxy)-5-(trifluoromethyl)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 400E for EXAMPLE 26C and EXAMPLE 459C for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 12.94 (d, 1H), 8.40 (d, 1H), 8.11 (d, 1H), 7.68 (m, 2H), 7.35 (d, 2H), 7.06 (d, 2H), 6.99 (d, 2H), 6.71 (dd, 1H), 6.39 (d, 1H), 6.06 (t, 1H), 4.67 (d, 2H), 4.55 (d, 2H), 4.47 (d, 2H), 3.07 (m, 5H), 2.74 (m, 6H), 2.19 (m, 6H), 1.90 (m, 6H), 1.40 (t, 2H), 0.93 (s, 6H).

EXAMPLE 460

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

The title compound was prepared as described in EXAMPLE 177 by replacing EXAMPLE 26C with EXAMPLE 18G. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 12.87 (s, 1H), 11.60 (s, 1H), 8.58 (s, 1H), 8.47 (d, 1H), 8.11 (s, 1H), 7.81 - 7.91 (m, 1H), 7.76 (dd, 1H), 7.59 - 7.66 (m, 1H), 7.48 (d, 1H), 7.34 (d, 2H), 7.00 - 7.11 (m, 5H), 6.73 (dd, 1H), 6.67 (dd, 1H), 6.08 (d, 1H), 3.85 (dd, 2H), 3.20 - 3.30 (m, 4H), 3.04 (s, 4H), 2.77 (s, 2H), 2.17 (d, 6H), 1.96 (s, 2H), 1.81 - 1.92 (m, 1H), 1.55 - 1.66 (m, 2H), 1.39 (t, 2H), 1.17 - 1.32 (m, 2H), 0.93 (s, 6H).

EXAMPLE 461

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(2-tetrahydrofuran-2-ylethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 461A

5-chloro-6-(2-(tetrahydrofuran-2-yl)ethoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 387A for EXAMPLE 329A and 2-(tetrahydrofuran-2-yl)ethanol for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 329B.

EXAMPLE 461B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(2-tetrahydrofuran-2-ylethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 461A for EXAMPLE 1F and EXAMPLE 400E for EXAMPLE 26C in EXAMPLE 177C. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 13.08 (s, 1H), 8.27 (d, J = 2.17 Hz, 1H), 7.83 (d, J = 1.83 Hz, 1H), 7.80 (s, 1H), 7.58 (d, J = 8.85 Hz, 1H), 7.36 (d, J = 8.54 Hz, 2H), 7.03-7.10 (m, 4H), 6.79 (dd, J = 9, 2.29 Hz, 1H), 6.54 (d, J = 1.53 Hz, 1H), 6.13 (d, J = 7.02 Hz, 1H), 4.41-4.47 (m, 2H), 3.91-3.94 (m, 1H), 3.71-3.80 (m, 1H), 3.56-3.63 (m, 2H), 3.25 (br s, 2H), 2.33 (br s, 2H), 2.16-2.18 (m, 2H), 1.92-2.01 (m, 5H), 1.80-1.86 (m, 2H), 1.47-1.53 (m, 1H), 1.42 (t, J = 6.26 Hz, 2H), 0.94 (s, 6H).

EXAMPLE 462

Trans-2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyanocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide

EXAMPLE 462A

2-(trans-4-(aminomethyl)cyclohexyl)acetonitrile

To a solution of tert-butyl (trans-4-(cyanomethyl)cyclohexyl)methylcarbamate (500 mg) in dichloromethane (5 mL) was slowly added trifluoroacetic acid (3 mL) at 0°C. The

mixture was warmed to room temperature, stirred for 1 hour. The title compound was obtained by concentration.

EXAMPLE 462B

4-((trans-4-cyanocyclohexyl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 462A for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 462C

Trans-2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyanocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 462B for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (500 MHz, pyridine-d_5) δ 9.29 (d, 1H), 8.67 (t, 1H), 8.59 (s, 1H), 8.41 (dd, 1H), 7.98 (d, 1H), 7.53 (d, 1H), 7.43 (d, 2H), 7.25 (m, 1H), 7.19 (m, 1H), 7.07 (d, 2H), 6.91 (d, 1H), 6.73 - 6.68 (m, 2H), 5.24 (m, 2H), 3.13 (t, 2H), 3.03 (m, 4H), 2.76 (s, 2H), 2.43 (m, 1H), 2.25 (m, 2H), 2.13 (m, 4H), 1.99 – 1.94 (m, 4H), 1.77 (m, H), 1.59 (m, 1H), 1.46 (m, 2H), 1.38 (t, 2H), 0.99 - 0.90 (m, 8H).

EXAMPLE 463

2-(1H-benzimidazol-4-yloxy)-N-({5-chloro-6-[(4,4-difluorocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide

EXAMPLE 463A

(4,4-difluorocyclohexyl)methanol

To a slurry of lithium aluminum hydride (0.24 g) in diethyl ether (15 mL) was added dropwise ethyl 4,4-difluorocyclohexanecarboxylate (1.0 g) in diethyl ether (2 mL). The reaction heated at reflux under nitrogen for 4 hours. The reaction was cooled to 0° C, followed by the careful addition of water (0.24 mL), 4*N* aqueous NaOH (0.24 mL), and water (0.72 mL). The reaction was diluted with diethyl ether (40 mL) and stirred with sodium sulfate for 30 minutes. The mixture was filtered though diatomaceous earth and the filtrate was concentrated to provide the title compound.

EXAMPLE 463B

5-chloro-6-((4,4-difluorocyclohexyl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 463A for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 387A for EXAMPLE 329A in EXAMPLE 329B.

EXAMPLE 463C

2-(1H-benzimidazol-4-yloxy)-N-({5-chloro-6-[(4,4-difluorocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide

The title compound was prepared by substituting EXAMPLE 463B for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (500 MHz, pyridine-d_5) δ 9.15 (d, 1H), 8.69 (m, 1H), 8.59 (s, 1H), 7.99 (d, 1H), 7.53 (d, 1H), 7.44 (d, 2H), 7.24 (m, 1H), 7.16 (m, 1H), 7.07 (d, 2H), 6.70 (m, 2H), 5.45(m, 2H), 4.22 (d, 2H), 3.04 (m, 4H), 2.77 (s, 2H), 2.26 (m, 2H), 2.16 - 2.08 (m, 6H), 1.97 (s, 2H), 1.86 - 1.68 (m, 5H), 1.47 - 1.36 (m, 4H), 0.94 (m, 6H).

EXAMPLE 464

N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 464A

3-chloro-4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

The title compound was prepared by substituting 3,4-dichlorobenzenesulfonamide for EXAMPLE 329A and EXAMPLE 306C for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 329B.

EXAMPLE 464B

N-(3-chloro-4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)phenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 435D for EXAMPLE 1E and EXAMPLE 464A for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 464C

N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 464B for EXAMPLE 435E in EXAMPLE 435F. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 13.15 (s, 1H), 11.74 - 11.31 (m, 1H), 7.85 (s, 1H), 7.67 (d, 1H), 7.62 - 7.49 (m, 2H), 7.35 (d, 2H), 7.22 - 7.09 (m, 3H), 7.05 (d, 2H), 6.80 (d, 1H), 6.53 (s, 1H), 6.23 (d, 1H), 4.26 (d, 2H), 3.79 (d, 2H), 3.62 (dd, 2H), 3.17 (s, 4H), 2.77 (d, 2H), 2.22 (d, 6H), 1.88 (dd, 6H), 1.40 (t, 2H), 0.94 (s, 6H).

EXAMPLE 465

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 465A

methyl 2-(1H-indazol-4-yloxy)-4-(4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 400C for tert-butyl piperazine-1-carboxylate and EXAMPLE 145E for EXAMPLE 27C in EXAMPLE 1A.

EXAMPLE 465B

methyl 4-(4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-4-yloxy)benzoate

The title compound was prepared by substituting EXAMPLE 465A for EXAMPLE 400D in EXAMPLE 435C.

EXAMPLE 465C

4-(4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-4-yloxy)benzoic acid

The title compound was prepared by substituting EXAMPLE 465B for EXAMPLE 175D in EXAMPLE 175E.

EXAMPLE 465D

N-(5-chloro-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridin-3-ylsulfonyl)-4-(4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 465C for EXAMPLE 27G and EXAMPLE 404A for EXAMPLE 1F in EXAMPLE 27H.

EXAMPLE 465E

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 465D for EXAMPLE 435E in EXAMPLE 435F, except here the final compound was purified by preparative HPLC using a C18 column, 250 x 50 mm, 10μ, and eluting with a gradient of 20-100% CH_3CN vs. 0.1% trifluoroacetic aicd in water, followed by column chromatography eluting with 98/2 dichloromethane/methanol. ^1H NMR (400 MHz, dimethylsulfoxide-d_6) δ 13.13 (s, 1H), 8.28 (d, 1H), 7.90 (d, 1H), 7.83 (s, 1H), 7.58 (d, 1H), 7.39 (d, 2H), 7.17 (d, 2H), 7.08 (m, 2H), 6.82 (dd, 1H), 6.57 (d, 1H), 6.14 (d, 1H), 4.52 (d, 2H), 4.15 (s, 2H), 3.80 (m, 2H), 3.60 (m, 2H), 3.20 (v br m, 4H), 2.98 (v br s, 2H), 2.35 (v br m, 4H), 2.18 (s, 2H), 1.87 (m, 4H), 1.20 (s, 6H).

Example 466

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-*N*-{[5-cyano-6-(2-tetrahydro-2*H*-pyran-4-ylethoxy)pyridin-3-yl]sulfonyl}-2-(1*H*-indazol-4-yloxy)benzamide

EXAMPLE 466A

5-bromo-6-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting 2-(tetrahydro-2H-pyran-4-yl)ethanol for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 329B.

EXAMPLE 466B

5-cyano-6-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 466A for EXAMPLE 329A in EXAMPLE 333A.

EXAMPLE 466C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-*N*-{[5-cyano-6-(2-tetrahydro-2*H*-pyran-4-ylethoxy)pyridin-3-yl]sulfonyl}-2-(1*H*-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 466B for EXAMPLE 1F and EXAMPLE 400E for EXAMPLE 26C in EXAMPLE 177C. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 13.04 (s, 1H), 8.48 (d, 1H), 8.13 (s, 1H), 7.75 (s, 1H), 7.62 (d, 1H), 7.37 (d, 2H), 7.01-7.08 (m, 4H), 6.76 (dd, 1H), 6.51 (d, 1H), 6.08 (d, 1H), 4.47 (t, 2H), 3.81-3.85 (m, 2H), 3.71-3.80 (m, 1H), 2.18 (m, 2H), 1.99 (m, 2H), 1.62-1.72 (m, 5H), 1.42 (t, 2H), 1.23 (m, 2H), 0.94 (s, 6H).

EXAMPLE 467

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(1R,5S)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide

EXAMPLE 467A

4-((1R,3R,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-ylamino)-3-nitrobenzenesulfonamide

This EXAMPLE was prepared by substituting (1R,3R,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-amine for 1-(2-methoxy-ethyl)-piperidin-4-ylamine in EXAMPLE 189A.

EXAMPLE 467B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(1R,5S)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide

This EXAMPLE was prepared by substituting EXAMPLE 26C for EXAMPLE 1E and EXAMPLE 467A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (500MHz, dimethylsulfoxide -d_6) δ 11.47 (br s, 1H), 11.17 (s, 1H), 9.43 (br s, 1H), 8.69 (d, 1H), 8.62 (d, 1H), 7.90 (dd, 1H), 7.52 (d, 1H), 7.40 (m, 3H), 7.15 (d, 1H), 7.06 (m, 3H), 6.85 (dd, 1H),

6.68 (m, 1H), 6.39 (t, 1H), 6.19 (br s, 1H), 4.01 (m, 1H), 3.91 (m, 2H), 3.58 (m, 3H), 3.01 (m, 3H), 2.73 (m, 5H), 2.32 (m, 6H), 2.16 (m, 6H), 2.0 (m, 2H), 1.45 (m, 2H), 0.94 (s, 6H).

EXAMPLE 468

N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxy-4-(4-{(3-phenylpropanoyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamide

EXAMPLE 468A

methyl 2-phenoxy-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)benzoate

1,4-dioxa-8-azaspiro[4.5]decane (1.18 g), methyl 4-fluoro-2-phenoxybenzoate (1.85 g), and K_2CO_3 (1.14 g) was stirred at 125°C in dimethylsulfoxide (25 mL) for 24 hours. The mixture was cooled, poured into 300 mL water, extracted three times with ether, and the ether extracts were combined, rinsed three times with water, and brine, and concentrated. The residue was chromatographed on silica gel using 10-30% ethyl acetate in hexanes as eluent to give the title compound.

EXAMPLE 468B

methyl 4-(4-oxopiperidin-1-yl)-2-phenoxybenzoate

EXAMPLE 468A (23.7 g) was heated to 80°C in a mixture of acetic acid (30 mL), tetrahydrofuran (40 mL) and water (30 mL) for 24 hours. The mixture was cooled and concentrated. The crude product was chromatographed on silica gel using 25% ethyl acetate in hexanes as the eluent to give the title compound.

EXAMPLE 468C

methyl 2-phenoxy-4-(4-((1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylamino)piperidin-1-yl)benzoate

EXAMPLE 468B (0.99 g) and (1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-amine (0.51 mL) were refluxed in 200 mL methanol under a Dean-Stark trap for 24 hours. The solvent was boiled off to a volume of 75 mL, and the mixture was cooled to room temperature. $NaBH_4$ (0.115 g) was added and the mixture was stirred for 30 minutes. The reaction was quenched with 10 mL water, partially concentrated, and chromatographed on silica gel using 1% triethylamine in ethyl acetate as eluent to give the title compound.

EXAMPLE 468D

methyl 2-phenoxy-4-(4-(3-phenyl-N-((1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)propanamido)piperidin-1-yl)benzoate

EXAMPLE 468C (320 mg), 3-phenylpropanoyl chloride (0.113 mL), and triethylamine (0.116 mL) were stirred in dichloromethane (15 mL) for 24 hours. The reaction mixture was partially concentrated and the residue was chromatographed on silica gel using 20% ethyl acetate in hexanes as eluent to give the title compound.

EXAMPLE 468E

2-phenoxy-4-(4-(3-phenyl-N-((1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)propanamido)piperidin-1-yl)benzoic acid

This EXAMPLE was prepared by substituting EXAMPLE 468D for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 468F

N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxy-4-(4-{(3-phenylpropanoyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 468E for EXAMPLE 1E in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 8.32 (m, 2H), 7.64 (m, 2H), 7.11-7.29 (m, 6H), 6.95 (dd, 1H), 6.89 (dd, 1H), 6.70 (m, 3H), 6.32 (m, 1H), 3.85 (m, 3H), 3.70 (m, 3H), 2.91 (m, 6H), 2.65-2.80 (m, 6H), 1.91 (s, 6H), 1.61 (m, 4H), 1.16-1.36 (m, 4H), 1.11 (m, 6H), 0.95 (m, 4H), 0.87 (d, 2H).

EXAMPLE 469

N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-phenoxy-4-(4-{(3-phenylpropanoyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 468E for EXAMPLE 1E and EXAMPLE 7A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 8.72 (m, 1H), 8.44 (d, 1H), 7.73 (dd, 1H), 7.54 (m, 1H), 7.12-7.28 (m, 6H), 7.05 (dd, 1H), 6.95 (dd, 1H), 6.82 (d, 1H), 6.74 (m, 2H), 6.34 (m, 1H),

3.77 (m, 2H), 3.63 (m, 4H), 3.10 (m, 4H), 3.05 (m, 4H), 2.78 (m, 6H), 1.75-2.10 (m, 8H), 1.55 (m, 2H), 1.40 (m, 2H), 1.19 (m, 6H), 1.01 (m, 2H), 0.95 (m, 2H), 0.88 (d, 2H).

EXAMPLE 470

N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxy-4-(4-{(3-phenylpropyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamide

EXAMPLE 470A

methyl 2-phenoxy-4-(4-((3-phenylpropyl)((1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)amino)piperidin-1-yl)benzoate

EXAMPLE 468C (320 mg), 3-phenylpropanal (111 mg), and $NaBH(OAc)_3$ (205 mg) were stirred in dichloromethane (15 mL) for 24 hours. The reaction mixture was chromatographed on silica gel using 20% ethyl acetate in hexanes as eluent to give the title compound.

EXAMPLE 470B

2-phenoxy-4-(4-((3-phenylpropyl)((1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)amino)piperidin-1-yl)benzoic acid

This EXAMPLE was prepared by substituting EXAMPLE 470A for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 470C

N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxy-4-(4-{(3-phenylpropyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 470B for EXAMPLE 1E in EXAMPLE 1G. ^1H NMR (300MHz, dimethylsulfoxide-d_6) δ 8.57 (m, 1H), 8.47 (d, 1H), 7.50 (m, 1H), 7.32 (m, 1H), 7.12-7.31 (m, 7H), 6.99 (dd, 1H), 6.81 (m, 3H), 6.37 (d, 1H), 4.44 (t, 1H), 3.84 (m, 4H), 3.37 (m, 2H), 3.25 (m, 2H), 3.06 (m, 2H), 2.70 (m, 4H), 2.57 (m, 4H), 1.82 (m, 2H), 1.77 (m, 4H), 1.52-1.71 (m, 8H), 1.25 (m, 3H), 1.15 (s, 3H), 0.95 (d, 2H), 0.93 (s, 3H), 0.74 (d, 2H).

EXAMPLE 471

N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-phenoxy-4-(4-{(3-phenylpropyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 470B for EXAMPLE 1E and EXAMPLE 7A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 8.68 (m, 1H), 8.40 (d, 1H), 7.70 (dd, 1H), 7.55 (d, 1H), 7.11-7.29 (m, 7H), 7.01 (dd, 1H), 6.95 (dd, 1H), 6.76 (d, 2H), 6.34 (m, 1H), 3.75 (m, 2H), 3.61 (m, 4H), 3.43 (m, 4H), 3.05 (m, 6H), 2.75 (m, 2H), 2.60 (m, 2H), 2.41 (m, 4H), 2.15 (m, 1H), 1.82 (m, 4H), 1.69 (m, 2H), 1.51 (m, 1H), 1.18 (m, 8H), 0.96 (m, 1H), 0.94 (s, 3H).

EXAMPLE 472

4-[4-(2-{[(1R,5S)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]amino}benzyl)piperazin-1-yl]-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-phenoxybenzamide

EXAMPLE 472A

Ethyl 4-fluoro-2-phenoxybenzoate (600 mg) and piperazine (596 mg) were dissolved in anhydrous dimethyl sulfoxide and heated at 130°C overnight. The reaction mixture was cooled to room temperature and diluted with ethyl acetate. The organic phase was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated to afford the title compound.

EXAMPLE 472B

EXAMPLE 472A (400 mg), 1-(bromomethyl)-2-nitrobenzene (277 mg) and sodium carbonate (408 mg) were suspended in anhydrous N,N-dimethylformamide (20 mL). The reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was diluted with ethyl acetate. The organic phase was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Flash column purification with 10-40% ethyl acetate/hexane to afford the title compound.

EXAMPLE 472C

A solution of EXAMPLE 472B (0.6 g) in methanol (20 ml) was added to Ra-Ni, solvent washed (0.480 g) in a 250 mL pressure bottle and stirred for 3 hours at 30 psi at room temperature. The mixture was filtered through a nylon membrane and concentrated to afford the product.

EXAMPLE 472D

This EXAMPLE was prepared by substituting (1R,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-one for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 472C for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 472E

This EXAMPLE was prepared by substituting EXAMPLE 472D for EXAMPLE 175D in EXAMPLE 175E.

EXAMPLE 472F

4-[4-(2-{[(1R,5S)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]amino}benzyl)piperazin-1-yl]-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-phenoxybenzamide

This EXAMPLE was prepared by substituting EXAMPLE 472E for EXAMPLE 27G and EXAMPLE 7A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.66 (bs, 1H), 9.90 (bs, 1H), 9.56 (s, 1H), 8.69 (t, 1H), 8.50 (d, 1H), 7.81 (dd, 1H), 7.54 (d, 1H), 7.22 (m, 5H), 7.01 (m, 1H), 6.83 (m, 3H), 6.47 (s, 1H), 3.84 (m, 4H), 3.65 (d, 6H), 3.54 (m, 4H), 3.43 (m, 2H), 3.19 (m, 8H), 2.68 (d, 3H), 2.34 (m, 2H), 2.25 (m, 4H), 1.99 (m, 4H).

EXAMPLE 473

4-[4-(2-{[(1R,5S)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]amino}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

This EXAMPLE was prepared by substituting EXAMPLE 472E for EXAMPLE 27G in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.61 (bs, 1H), 9.38 (bs, 1H), 8.64 (s, 1H), 8.47 (d, 1H), 7.75 (dd, 1H), 7.55 (d, 1H), 7.23 (t, 3H), 7.15 (d, 2H), 6.98 (t, 1H), 6.82 (d, 3H), 6.47 (s, 2H), 3.85 (m, 6H), 3.31 (m, 12H), 2.68 (d, 3H), 2.06 (m, 9H), 1.62 (m, 2H), 1.29 (m, 2H).

EXAMPLE 474

4-{4-[2-(3-azabicyclo[3.2.2]non-3-yl)benzyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

EXAMPLE 474A

2-Fluorobenzaldehyde (264 mg), (1S,5S)-3-azabicyclo[3.2.2]nonane (500 mg) and sodium carbonate (846 mg) were suspended in anhydrous dimethylsulfoxide (3mL). The reaction mixture was heated at 135°C overnight. The reaction mixture was cooled to room temperature and diluted with ethyl acetate. The organic phase was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Flash column purification with 0-10% ethyl acetate/hexane provided the title compound.

EXAMPLE 474B

This EXAMPLE was prepared by substituting EXAMPLE 474A for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 113A for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 474C

This EXAMPLE was prepared by substituting EXAMPLE 474B for EXAMPLE 175D in EXAMPLE 175E.

EXAMPLE 474D

4-{4-[2-(3-azabicyclo[3.2.2]non-3-yl)benzyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

This EXAMPLE was prepared by substituting EXAMPLE 474C for EXAMPLE 27G in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.74 (bs, 1H), 8.64 (t, 1H), 8.47 (d, 1H), 7.76 (dd, 1H), 7.54 (m, 2H), 7.43 (d, 2H), 7.23 (m, 3H), 7.15 (d, 1H), 6.98 (t, 1H), 6.83 (m, 3H), 6.53 (d, 1H), 4.45(bs, 2H), 3.87 (m, 4H), 3.30 (m, 6H), 3.06 (m, 8H), 1.89 (m, 7H), 1.64 (m, 6H), 1.29 (m, 2H).

EXAMPLE 475

4-{4-[2-(3-azabicyclo[3.2.2]non-3-yl)benzyl]piperazin-1-yl}-2-phenoxy-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 474C for EXAMPLE 27G and EXAMPLE 163A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.78 (bs, 1H), 8.11 (d, 1H), 7.86 (dd, 1H), 7.54 (d, 2H), 7.44 (d, 2H), 7.28 (m, 4H), 7.11 (d, 1H), 7.04 (m, 1H), 6.85 (m, 3H), 6.53 (d, 1H), 4.46 (m, 2H), 3.86 (m, 4H), 3.28 (m, 6H), 3.10 (m, 4H), 2.98 (d, 4H), 1.97 (s, 2H), 1.84 (m, 5H), 1.64 (m, 6H), 1.26 (m, 2H).

EXAMPLE 476

4-{4-[2-(3-azabicyclo[3.2.2]non-3-yl)benzyl]piperazin-1-yl}-2-phenoxy-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 474C for EXAMPLE 27G and EXAMPLE 2A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.19 (bs, 1H), 9.83 (bs, 1H), 7.52 (m, 6H), 7.33 (m, 3H), 7.12 (t, 1H), 6.93 (d, 2H), 6.83 (m, 1H), 6.56 (d, 2H), 6.47 (d, 1H), 4.47 (s, 2H), 3.85 (m, 4H), 3.26 (m, 2H), 3.11 (m, 4H), 2.96 (m, 6H), 1.97 (s, 2H), 1.81 (m, 6H), 1.64 (m, 7H), 1.22 (m, 2H).

EXAMPLE 477

4-{4-[2-(3-azabicyclo[3.2.2]non-3-yl)benzyl]piperazin-1-yl}-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-phenoxybenzamide

This EXAMPLE was prepared by substituting EXAMPLE 474C for EXAMPLE 27G and EXAMPLE 7A for EXAMPLE 1F in EXAMPLE 27H. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 11.77 (bs, 1H), 10.04 (bs, 1H), 8.69 (t, 1H), 8.50 (d, 1H), 7.81 (dd, 1H), 7.55 (d, 2H), 7.43 (d, 2H), 7.24 (m, 3H), 7.15 (d, 1H), 7.01 (t, 1H), 6.84 (m, 3H), 6.52 (d, 1H), 4.44 (s, 2H), 3.97 (s, 2H), 3.54 (m, 6H), 3.39 (m, 4H), 3.19 (m, 8H), 2.97 (d, 4H), 1.99 (m, 4H), 1.83 (m, 4H), 1.64 (m, 4H).

EXAMPLE 478

4-(4-{2-[(4R,7S)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-5-yl]benzyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

EXAMPLE 478A

4-(4-Methoxycarbonyl-3-phenoxy-phenyl)-piperazine-1-carboxylic acid tert-butyl ester

This EXAMPLE was prepared by substituting piperazine-1-carboxylic acid tert-butyl ester for EXAMPLE 1B in EXAMPLE 1D.

EXAMPLE 478B

4-(4-Carboxy-3-phenoxy-phenyl)-piperazine-1-carboxylic acid tert-butyl ester

This EXAMPLE was prepared by substituting EXAMPLE 478A for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 478C

4-(4-{3-Nitro-4-[(tetrahydro-pyran-4-ylmethyl)-amino]-benzenesulfonylaminocarbonyl}-3-phenoxy-phenyl)-piperazine-1-carboxylic acid tert-butyl ester

This EXAMPLE was prepared by substituting EXAMPLE 478B for EXAMPLE 1E in EXAMPLE 1G.

EXAMPLE 478D

3-Nitro-N-(2-phenoxy-4-piperazin-1-yl-benzoyl)-4-[(tetrahydro-pyran-4-ylmethyl)-amino]-benzenesulfonamide

This EXAMPLE was prepared by substituting EXAMPLE 478C for EXAMPLE 1A in EXAMPLE 1B to isolate the title compound as the mono trifluoroacetic acid salt.

EXAMPLE 478E

Trifluoromethanesulfonic acid (4R,7S)-(2,3,3a,4,7,7a-hexahydro-1H-4,7-methano-inden-5-yl) ester

(4R,7R)-octahydro-4,7-methano-inden-5-one (2.00 g) was dissolved in tetrahydrofuran (25 mL) and cooled to -78°C using an isopropyl alcohol / dry ice bath. Sodium bis(trimethylsilyl)-amide (1M in tetrahydrofuran, 14.65 mL) was added slowly. The solution was allowed to warm to room temperature, stirred for one hour, cooled to -78°C using an isopropyl alcohol / dry ice bath, and N-phenyltrifluoromethanesulfonimide (5.23 g) was added. The solution was allowed to warm to room temperature and stir for 16 hours. Hexane was added and the solution was stirred at room temperature for one hour, filtered, and the solvent removed under vacuum.

EXAMPLE 478F

(4R,7S)-2-(2,3,3a,4,7,7a-Hexahydro-1H-4,7-methano-inden-5-yl)-benzaldehyde

EXAMPLE 478E (941 mg), 2-formylphenylboronic acid (600 mg), and potassium phosphate tribasic (1416 mg) were added to tetrahydrofuran (20 mL). The solution was degasses and flushed with nitrogen three times. Tetrakis(triphenylphospine)palladium(0) (244 mg) was added and the solution was heated at 60°C for 16 hours. The solution was cooled, added to water, and extracted with 50% ethyl acetate (hexanes). The extract was washed with brine, dried on anhydrous sodium sulfate, concentrated and purified by flash column chromatography on silica gel using 10% ethyl acetate (hexanes).

EXAMPLE 478G

4-(4-{2-[(4R,7S)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-5-yl]benzyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

EXAMPLE 478D (200 mg), EXAMPLE 478F (74 mg), and sodium cyanoborohydride resin (2.15 mmol/g, 144 mg) were added to tetrahydrofuran (3 mL) and acetic acid (0.7 mL) and stirred at room temperature for 16 hours. The solution was concentrated on vacuum and purified by flash column chromatography on silica gel using 5% methanol (dichloromethane) to provide the title compound as the mono acetic acid salt. ^{1}H NMR (300MHz, dimethylsulfoxide-d_6) δ 11.94 (bs, 1H), 8.64 (t, 1H), 8.48 (d, 1H), 7.76 (dd, 1H), 7.51 (d, 1H), 7.40 (m, 1H), 7.27-7.18 (m, 5H), 7.16 (d, 1H), 6.99 (tt, 1H), 6.83 (dt, 2H), 6.78 (dd, 1H), 6.41 (d, 1H), 6.23 (d, 1H), 3.87 (dd, 2H), 3.50 (m, 2H), 3.34 (t, 2H), 3.21 (bs, 4H), 2.73 (bs, 1H), 2.63 (bs, 1H), 2.46 (m, 4H), 2.11 (m, 2H), 1.95-1.75 (m, 4H), 1.91 (s, 3H), 1.66-1.52 (m, 6H), 1.28 (m, 2H), 1.02 (m, 2H), 0.85 (m, 1H).

EXAMPLE 479

4-[4-(2-{5-[(1R,5S)-8-azabicyclo[3.2.1]oct-8-ylmethyl]thien-2-yl}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

EXAMPLE 479A

tert-butyl 4-(4-(methoxycarbonyl)-3-phenoxyphenyl)piperazine-1-carboxylate

This EXAMPLE was prepared by substituting tert-butyl piperazine-1-carboxylate for EXAMPLE 1B in EXAMPLE 1D.

EXAMPLE 479B

4-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2-phenoxybenzoic acid

This EXAMPLE was prepared by substituting EXAMPLE 479A for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 479C

tert-butyl 4-(4-(3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)phenylsulfonylcarbamoyl)-3-phenoxyphenyl)piperazine-1-carboxylate

This EXAMPLE was prepared by substituting EXAMPLE 479B for EXAMPLE 1E in EXAMPLE 1G.

EXAMPLE 479D

N-(3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)phenylsulfonyl)-2-phenoxy-4-(piperazin-1-yl)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 479C for EXAMPLE 1A in EXAMPLE 1B.

EXAMPLE 479E

2-((4-(4-(3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)phenylsulfonylcarbamoyl)-3-phenoxyphenyl)piperazin-1-yl)methyl)phenylboronic acid

EXAMPLE 479D (213 mg), 2-formylphenylboronic acid (54 mg), and sodium cyanoborohydride resin (2.38 mmol/g, 252 mg) were added to tetrahydrofuran (3.5 mL) and acetic acid (1.1 mL), and the solution was stirred at room temperature for 16 hours. The solution was purified by flash column chromatography on silica gel with 1% acetic acid and 10% methanol in dichloromethane.

EXAMPLE 479F

8-((5-bromothiophen-2-yl)methyl)-8-azabicyclo[3.2.1]octane hydrochloride

This EXAMPLE was prepared by substituting 5-bromothiophene-2-carbaldehyde for 4'-chlorobiphenyl-2-carboxaldehyde and 8-azabicyclo[3.2.1]octane hydrochloride for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 479G

4-(4-(2-(5-(8-azabicyclo[3.2.1]octan-8-ylmethyl)thiophen-2-yl)benzyl)piperazin-1-yl)-N-(3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)phenylsulfonyl)-2-phenoxybenzamide

EXAMPLE 479E (80 mg), EXAMPLE 479F (42.5 mg), bis(triphenylphosphine)palladium(II) dichloride (7.7 mg), and lithium hydroxide (10.5 mg) were combined in a mixture of dimethoxyethane (1.6 mL), methanol (0.5 mL) and water (0.7 mL) in a microwave vial. The reaction mixture was heated in a CEM Discover microwave reactor at 150°C for 15 minutes. The crude material was purified by flash chromatography eluting with a gradient of 1% methanol/dichloromethane to 5% methanol/dichloromethane. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 8.33 (m, 2H), 7.64 (m, 2H), 7.44 (m, 1H), 7.39 (m, 1H), 7.32 (m, 2H), 7.12 (m, 3H), 6.90 (m, 2H), 6.85 (t, 1H), 6.68 (m, 3H), 6.30 (d, 1H), 3.83 (dd, 2H), 3.65 (s, 2H), 3.51 (s, 2H), 3.17 (m, 4H), 3.08 (m, 4H), 2.45 (m, 6H), 1.92 (m, 2H), 1.62 (m, 4H), 1.54 (m, 3H), 1.28 (m, 6H).

EXAMPLE 480

4-[4-(2-{5-[(1R,5S)-8-azabicyclo[3.2.1]oct-8-ylmethyl]thien-2-yl}benzylidene)piperidin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

EXAMPLE 480A

methyl 2-phenoxy-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)benzoate

Methyl 4-fluoro-2-phenoxybenzoate (2 g) and 1,4-dioxa-8-azaspiro[4.5]decane (1.279 g) were combined in dimethylsulfoxideO (12 mL) in a 250 mL round-bottom flask. Sodium carbonate (1.291 g) was added. The reaction flask was sealed and heated to 130 °C overnight. The reaction mixture was diluted with ethyl acetate, washed thoroughly with water and with brine, and dried over $MgSO_4$, filtered and concentrated to obtain the desired product.

EXAMPLE 480B

methyl 4-(4-oxopiperidin-1-yl)-2-phenoxybenzoate

EXAMPLE 480A was taken up in acetic acid (30%, 20 mL) and tetrahydrofuran (10 mL). The reaction mixture was heated to 75°C overnight. The volume was reduced under vacuum and the residue was neutralized with sodium hydroxide solution, and extracted with

ethyl acetate. The extracts were washed with water and with brine, dried over $MgSO_4$, filtered and concentrated under vacuum to obtain the desired product.

EXAMPLE 480C

methyl 4-(4-(2-bromobenzylidene)piperidin-1-yl)-2-phenoxybenzoate

Dimethylsulfoxide (22.88 mL) with sodium hydride (0.332 g) was heated to 70 °C for 1 hour, then cooled to room temperature and (2-bromobenzyl)triphenylphosphonium bromide (3.40 g) was added in several portions, and then stirred at room temperature for 1 hour. A solution of methyl 4-(4-oxopiperidin-1-yl)-2-phenoxybenzoate (1.8 g) in dimethylsulfoxide (5.20 mL) was then added and the reaction was heated to 70 °C over the weekend. The reaction was acidified with 1M aqueous HCl solution and extracted with ether. The combined extracts were washed thoroughly with water and brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by flash chromatography eluting with 0-20% ethyl acetate in hexanes.

EXAMPLE 480D

methyl 2-phenoxy-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzylidene)piperidin-1-yl)benzoate

EXAMPLE 480C (259 mg), bis(pinacolato)diboron (206 mg), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane (22 mg), and potassium acetate (159 mg) were combined in dimethyl sulfoxide (2.7 mL). The reaction was heated to 90°C for 36 hours. The reaction mixture was diluted with ethyl acetate, washed thoroughly with water and with brine, and dried over $MgSO_4$, filtered and concentrated under vacuum. The crude solid was washed with hexanes and with hexanes/ether (2:1) to obtain the desired product.

EXAMPLE 480E

4-(4-(2-(5-(8-azabicyclo[3.2.1]octan-8-ylmethyl)thiophen-2-yl)benzylidene)piperidin-1-yl)-2-phenoxybenzoic acid

This EXAMPLE was prepared by substituting EXAMPLE 480D for EXAMPLE 479E in EXAMPLE 479G.

EXAMPLE 480F

4-(4-(2-(5-(8-azabicyclo[3.2.1]octan-8-ylmethyl)thiophen-2-yl)benzylidene)piperidin-1-yl)-N-(3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)phenylsulfonyl)-2-phenoxybenzamide

This EXAMPLE was prepared by substituting EXAMPLE 480E for EXAMPLE 1E in EXAMPLE 1G. ^{1}H NMR (500MHz, dimethylsulfoxide -d_6) δ 11.54 (s, 1H), 9.36 (br s, 1H), 8.48 (d, 1H), 7.76 (dd, 1H), 7.53 (m, 2H), 7.34 (m, 3H), 7.25 (m, 4H), 7.16 (d, 1H), 7.00 (t, 1H), 6.84 (d, 2H), 6.81 (dd, 1H), 6.44 (d, 1H), 6.37 (br s, 1H), 4.36 (d, 2H), 3.85 (m, 3H), 3.44 (m, 2H), 3.28 (m, 6H), 2.36 (m, 3H), 2.23 (m, 4H), 1.90 (m, 3H), 1.81 (m, 2H), 1.62 (m, 5H), 1.47 (m, 1H), 1.29 (m, 2H).

EXAMPLE 481

4-[4-(3-{5-[(1R,5S)-8-azabicyclo[3.2.1]oct-8-ylmethyl]thien-2-yl}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide

EXAMPLE 481A

3-((4-(4-(3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)phenylsulfonylcarbamoyl)-3-phenoxyphenyl)piperazin-1-yl)methyl)phenylboronic acid

This EXAMPLE was prepared by substituting 3-formylphenylboronic acid for 2-formylphenylboronic acid in EXAMPLE 479E.

EXAMPLE 481B

4-(4-(3-(5-(8-azabicyclo[3.2.1]octan-8-ylmethyl)thiophen-2-yl)benzyl)piperazin-1-yl)-N-(3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)phenylsulfonyl)-2-phenoxybenzamide

This EXAMPLE was prepared by substituting EXAMPLE 481A for EXAMPLE 479E in EXAMPLE 479G. ^{1}H NMR (500MHz, dimethylsulfoxide -d_6) δ 11.76 (br s, 1H), 9.55 (br s, 1H), 8.55 (t, 1H), 8.46 (d, 1H), 7.75 (m, 2H), 7.54 (m, 2H), 7.40 (m, 1H), 7.20 (m, 4H), 6.97 (m, 1H), 6.86 (m, 1H), 6.82 (m, 3H), 6.55 (m, 1H), 4.41 (d, 2H), 3.88 (m, 6H), 3.43 (m, 3H), 3.30 (m, 6H), 3.06 (m, 6H), 1.90 (m, 4H), 1.65 (m, 5H), 1.30 (m, 3H).

EXAMPLE 482

N-({5-chloro-6-[(4,4-difluorocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 482A

(4,4-difluorocyclohexyl)methanol

Lithium aluminum hydride (0.24 g) was slurried in diethyl ether (15 mL), ethyl 4,4-difluorocyclohexanecarboxylate (1.0 g) in diethyl ether (2 mL) was added dropwise, and the reaction was stirred under reflux under nitrogen for 4 hours. The reaction was cooled to 0° C, followed by the careful addition of water (0.24 mL), 4*N* aqueous NaOH (0.24 mL), and water (0.72 mL). Na_2SO_4 and diethyl ether (40 mL) were added and the mixture was stirred at room temperature for 30 minutes. Filtration through diatomaceous earth and concentration of the filtrate provided the title compound which was used without purification.

EXAMPLE 482B

5-chloro-6-((4,4-difluorocyclohexyl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 482A for (tetrahydro-2H-pyran-4-yl)methanol and 5,6-dichloropyridine-3-sulfonamide for EXAMPLE 329A in EXAMPLE 329B.

EXAMPLE 482C

N-(5-chloro-6-((4,4-difluorocyclohexyl)methoxy)pyridin-3-ylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 482B for EXAMPLE 1F and EXAMPLE 435D for EXAMPLE 27G in EXAMPLE 27H.

EXAMPLE 482D

N-({5-chloro-6-[(4,4-difluorocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 482C for EXAMPLE 435E in EXAMPLE 435F. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 13.12 (br s, 1H), 8.28 (d, 1H), 7.87 (d, 1H), 7.80 (s, 1H), 7.59 (d, 1H), 7.37 (d, 2H), 7.08 (m, 4H), 6.80 (dd, 1H), 6.55 (d, 1H), 6.14 (d, 1H), 4.25 (d, 2H), 3.24 (br s, 4H), 3.00 (v br s, 2H), 2.45 (v br s, 4H), 2.20 (br m, 2H), 2.05 (m, 2H), 1.98 (s, 2H), 1.97 (m, 1H), 1.90 (m, 4H), 1.42 (t, 2H), 1.38 (m, 2H), 0.94 (s, 6H).

EXAMPLE 483

N-({6-[(trans-4-carbamoylcyclohexyl)methoxy]-5-chloropyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 483A

Trans-N-(bis(4-methoxyphenyl)methyl)-4-(hydroxymethyl)cyclohexanecarboxamide

To a solution of bis(4-methoxyphenyl)methanamine (846 mg), trans-4-(hydroxymethyl)cyclohexanecarboxylic acid (500 mg), and triethylamine (1.322 mL) in N,N-dimethylformamide (30 mL) was added benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate reagent (1.677g). The resulting mixture was stirred for 3 hours, diluted with ethyl acetate, washed with water, aqueous NaOH and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in dichloromethane and loaded into a silica cartridge, eluted with 0 - 100% ethyl acetate in hexane to provide the title compound.

EXAMPLE 483B

(1r,4r)-N-(bis(4-methoxyphenyl)methyl)-4-((3-chloro-5-sulfamoylpyridin-2-yloxy)methyl)cyclohexanecarboxamide

EXAMPLE 483A (1.2 g) and EXAMPLE 387A (0.711 g) in tetrahydrofuran (30 mL) was treated with NaH (60%, 0.51 g) overnight. The reaction was quenched with aqueous NH_4Cl and the pH value of the mixture was adjusted to 4-5 with diluted aqueous HCl. The resulting mixture was extracted with dichloromethane. The dichloromethane layer was washed with brine and concentrated. The residue was purified by silica gel chromatography, and was eluted with 20% - 30% ethyl acetate in hexane to provide the title compound.

EXAMPLE 483C

N-(6-((trans-4-(bis(4-methoxyphenyl)methylcarbamoyl)cyclohexyl)methoxy)-5-chloropyridin-3-ylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-4-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 177 by replacing EXAMPLE 26C and EXAMPLE 1F with EXAMPLE 435D and EXAMPLE 483B, respectively.

EXAMPLE 483D

N-({6-[(trans-4-carbamoylcyclohexyl)methoxy]-5-chloropyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 483C (500 mg) in dichloromethane (10 mL) was treated with water (1 mL) and trifluoroacetic acid (5 mL) for 2 hours. The reaction mixture was concentrated and the residue was purified by reverse phase Gilson HPLC, eluted with 40% - 70% acetonitrile in 0.1% trifluoroacetic acid water over 40 minutes. The desired fractions were concentrated to remove the acetonitrile, neutralized with $NaHCO_3$ and extracted with dichloromethane. The dichloromethane layer was dried over Na_2SO_4, filtered, and concentrated to provide the title compound. ^1H NMR (500 MHz, dimethylsulfoxide-d_6) δ 13.11 (s, 1H), 8.28 (d, 1H), 7.86 (d, 1H), 7.81 (s, 1H), 7.59 (d, 1H), 7.36 (d, 2H), 7.19 (s, 1H), 7.03 - 7.12 (m, 4H), 6.80 (dd, 1H), 6.66 (s, 1H), 6.54 (d, 1H), 6.14 (d, 1H), 4.20 (d, 2H), 3.14 - 3.26 (m, 4H), 2.96 (s, 2H), 2.30 - 2.47 (m, 3H), 2.18 (s, 2H), 2.02 - 2.09 (m, 1H), 1.98 (s, 2H), 1.71 - 1.89 (m, 5H), 1.31 - 1.46 (m, 4H), 1.03 - 1.16 (m, 2H), 0.94 (s, 6H).

EXAMPLE 484

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-cyanocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 484A

trans-4-(aminomethyl)cyclohexanecarbonitrile

To a solution of tert-butyl (trans-4-cyanocyclohexyl)methylcarbamate (500 mg) in dichloromethane (10 mL) was slowly added trifluoroacetic acid (2 mL) at 0°C. The reaction mixture was warmed to room temperature, stirred for 1 hour and concentrated to provide the title compound.

EXAMPLE 484B

4-((trans-4-cyanocyclohexyl)methylamino)-3-nitrobenzenesulfonamide

A mixture of 4-fluoro-3-nitrobenzenesulfonamide (347 mg) and EXAMPLE 484A (300 mg) in tetrahydrofuran (20 mL) was treated with triethylamine (1.4 mL) overnight and concentrated. The residue was triturated with ethyl acetate to provide the title compound.

EXAMPLE 484C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-cyanocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide

A mixture of 4-dimethylaminopyridine (115.0 mg), 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (51.4 mg), EXAMPLE 435D (165 mg) and EXAMPLE 484B (96 mg) in dichloromethane (6 mL) was stirred overnight. To this mixture was added trifluoroacetic acid (5 mL) and the resulting mixture was stirred for 2 hours and concentrated. The residue was purified by reverse phase Gilson HPLC, eluted with 40% - 70% acetonitrile in 0.1% trifluoroacetic acid water over 40 minutes. The desired fractions were concentrated to remove acetonitrile, neutralized with $NaHCO_3$ and extracted with dichloromethane. The dichloromethane layer was dried over Na_2SO_4, filtered, and concentrated to provide the title compound. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 13.10 (s, 1H), 11.54 (s, 1H), 8.56 (t, 1H), 8.37 (d, 1H), 7.81 (s, 1H), 7.49 - 7.59 (m, 2H), 7.35 (d, 2H), 7.02 - 7.14 (m, 4H), 6.95 (d, 1H), 6.80 (dd, 1H), 6.52 (d, 1H), 6.19 (d, 1H), 3.25 (t, 2H), 3.16 (s, 4H), 2.80 (s, 2H), 2.60 - 2.70 (m, 1H), 2.21 (d, 6H), 1.94 - 2.08 (m, 4H), 1.74 - 1.84 (m, 2H), 1.58 - 1.71 (m, 1H), 1.36 - 1.54 (m, 4H), 0.98 - 1.12 (m, 2H), 0.93 (s, 6H).

EXAMPLE 485

N-({5-chloro-6-[2-(1H-imidazol-1-yl)ethoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 485A

The title compound was prepared by substituting 2-(1H-imidazol-1-yl)ethanol for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 387A for EXAMPLE 329A in EXAMPLE 329B.

EXAMPLE 485B

N-(6-(2-(1H-imidazol-1-yl)ethoxy)-5-chloropyridin-3-ylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 485A for EXAMPLE 1F and EXAMPLE 435D for EXAMPLE 1E in EXAMPLE 1G.

EXAMPLE 485C

N-({5-chloro-6-[2-(1H-imidazol-1-yl)ethoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 485B for EXAMPLE 435E in EXAMPLE 435F. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 13.03 (s, 1H), 8.28 (m, 2H), 7.85 (d, 1H), 7.77 (s, 1H), 7.61 (d, 1H), 7.44 (s, 1H), 7.36 (d, 2H), 7.06 (d, 2H), 7.01-7.03 (m, 2H), 6.76 (dd, 1H), 6.49 (d, 1H), 6.10 (dd, 1H), 4.65 (t, 2H), 4.50 (t, 2H), 3.11 (s, 4H), 2.88 (bs, 2H), 2.32-2.36 (m, 4H), 2.17-2.19 (m, 2H), 1.97-1.99 (m, 2H), 1.41 (t, 2H), 1.14-1.23 (m, 4H), 0.94 (s, 6H).

EXAMPLE 486

N-({5-chloro-6-[(1-methyl-1H-imidazol-5-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 486A

5-chloro-6-((1-methyl-1H-imidazol-5-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting (1-methyl-1H-imidazol-5-yl)methanol for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 387A for EXAMPLE 329A in EXAMPLE 329B.

EXAMPLE 486B

N-(5-chloro-6-((1-methyl-1H-imidazol-5-yl)methoxy)pyridin-3-ylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 486A for EXAMPLE 1F and EXAMPLE 435D for EXAMPLE 1E in EXAMPLE 1G.

EXAMPLE486C

N-({5-chloro-6-[(1-methyl-1H-imidazol-5-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 486B for EXAMPLE 435E in EXAMPLE 435F. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 13.05 (s, 1H), 8.29 (s, 1H), 7.86 (d, 1H), 7.78 (s, 1H), 7.62 (d, 1H), 7.36 (d, 2H), 7.04-7.07 (m, 4H), 6.77 (dd, 1H), 6.49 (d, 1H), 6.12 (dd, 1H), 5.46 (s, 2H), 3.70 (s, 3H), 3.15 (s, 54H), 2.87 (bs, 2H), 2.32-2.36 (m, 4H), 2.17-2.19 (m, 2H), 1.98 (s, 2H), 1.41 (t, 2H), 0.94 (s, 6H).

EXAMPLE 487

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-fluoro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 487A

5-bromo-3-fluoro-2-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine

The title compound was prepared by substituting 5-bromo-2,3-difluoropyridine for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 279A.

EXAMPLE 487B

tert-butyl 5-fluoro-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridin-3-ylcarbamate

The title compound was prepared by substituting EXAMPLE 487A for EXAMPLE 416A in EXAMPLE 416B.

EXAMPLE 487C

5-fluoro-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonyl chloride

The title compound was prepared by substituting EXAMPLE 487B for EXAMPLE 416B in EXAMPLE 416C.

EXAMPLE 487D

5-fluoro-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 487C for EXAMPLE 416C in EXAMPLE 416D.

EXAMPLE 487E

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(5-fluoro-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridin-3-ylsulfonyl)-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 435D for EXAMPLE 1E and EXAMPLE 487D for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 487F

EXAMPLE 487E (0.195 g) was treated with trifluoroacetic acid (2.311 mL) and stirred at ambient temperature for 3 hours. The reaction mixture was concentrated, dissolved in dioxane (3.0 mL), treated with 1N NaOH (2.0 mL), and stirred for 3 days. 4N NaOH (1.0 mL) was added and stirring was continued for 4 hours. Saturated $NaHCO_3$ solution was added and the mixture was extracted with CH_2Cl_2. The organic layers were combined, washed with saturated NH_4Cl solution, dried ($MgSO_4$), filtered, concentrated and chromatographed on silica gel with 0 to 4% methanol in CH_2Cl_2 as the eluent. The product was dissolved in CH_3CN, concentrated and dried in a vacuum oven at 80 °C. ^1H NMR (400 MHz, pyridine-d_5) δ 14.70 (s, 1H), 8.86 (d, 1H), 8.39 (d, 1H), 8.06 (d, 1H), 8.00 (dd, 1H), 7.47 (m, 2H), 7.35 (d, 1H), 7.12 (m, 3H), 6.88 (m, 2H), 6.48 (d, 1H), 4.21 (d, 2H), 3.96 (dd, 2H), 3.30 (m, 2H), 3.18 (m, 4H), 2.83 (s, 2H), 2.31 (t, 2H), 2.24 (m, 4H), 1.95 (m, 3H), 1.57 (dd, 2H), 1.38 (m, 4H), 0.96 (s, 6H).

EXAMPLE 488

N-{[5-chloro-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 488A

6-((1,4-dioxan-2-yl)methoxy)-5-chloropyridine-3-sulfonamide

The title compound was prepared by substituting (1,4-dioxan-2-yl)methanol for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 387A for EXAMPLE 329A in EXAMPLE 329B.

EXAMPLE 488B

N-(6-((1,4-dioxan-2-yl)methoxy)-5-chloropyridin-3-ylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 488A for EXAMPLE 1F and EXAMPLE 435D for EXAMPLE 1E in EXAMPLE 1G.

EXAMPLE488C

N-{[5-chloro-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 488B for EXAMPLE 435E in EXAMPLE 435F. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 13.06 (s, 1H), 8.23 (s, 1H), 7.85 (d, 1H), 7.79 (s, 1H), 7.60 (d, 1H), 7.36 (d, 2H), 7.02-7.09 (m, 4H), 6.76-6.79 (m, 1H), 6.51 (s, 1H), 6.11 (d, 1H), 4.35-4.37 (m, 2H), 3.75-3.92 (m, 4H), 3.59-3.68 (m, 2H), 3.41-3.54 (m, 4H), 3.17 (s, 54H), 2.89 (s, 2H), 2.34 (bs, 4H), 2.17-2.19 (m, 2H), 1.98 (s, 2H), 1.41 (t, 2H), 0.94 (s, 6H).

EXAMPLE 490

N-({5-chloro-6-[(4,4-difluoro-1-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 490A

1,1-difluoro4-methylenecyclohexane

Butyllithium (12.32 mL, 2.5 M solution in hexanes) was added to a solution of methyltriphenylphosphonium chloride (9.63 g) in tetrahydrofuran (50 mL) at 0°C, and the reaction was stirred for 5 minutes. 4,4-Difluorocycleohexanone (3.76 g) in dioxane (150 mL)was then added, and the reaction was stirred for 30 minutes. Water (3 mL) was added, and then hexane (150 mL) was slowly added, the reaction was filtered, and the solution carried on in the next step.

EXAMPLE 490B

4,4-difluoro-1-(hydroxymethyl)cyclohexanol

To the solution from EXAMPLE 490A was added water (75 mL), then N-metthylmorpholine-N-oxide (6.4 mL, 50% solution in water) and OsO_4 (14.2 g, 2.5 wt % solution in tert-butanol) were added, and the reaction was stirred for 96 hours at 50°C. The solution was cooled to room temperature, treated with saturated aqueous $Na_2S_2O_3$ solution (100 mL) for 30 minutes, and then acidified with concentrated aqueous HCl. The solution was then extracted three times with ethyl acetate, and the organic layers were combined, washed with 1M aqueous HCl, and brine, and concentrated. The crude mixture was chromatographed on silica gel using 10-100% ethyl acetate in hexanes, and then 5% methanol in ethyl acetate to give the product.

EXAMPLE 490C

5-chloro-6-((4,4-difluoro-1-hydroxycyclohexyl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 490B for tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 387A for EXAMPLE 329A in EXAMPLE 329B.

EXAMPLE 490D

N-({5-chloro-6-[(4,4-difluoro-1-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

A mixture of 4-dimethylaminopyridine (28 mg), 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (62 mg), EXAMPLE 435D (108 mg) and EXAMPLE 490C (55 mg) in dichloromethane (4 mL) was stirred overnight. The mixture was chromatographed on silica gel using 50-100% ethyl acetate in hexanes, and then

5% methanol in ethyl acetate as eluent to give the protected product. This material was taken up in 1M tetrabutyl ammonium fluoride (8 mL) and the resulting mixture was stirred for 4 days at 50°C and concentrated. The residue was neutralized with $NaHCO_3$ and extracted with dichloromethane. The dichloromethane layer was concentrated and chromatographed on silica gel using 50-100% ethyl acetate in hexanes, and then 5% methanol in ethyl acetate as eluent to give the product. ^1H NMR (300MHz, dimethylsulfoxide-d_6) δ 13.05 (br s, 1H), 8.24 (s, 1H), 7.83 (d, 1H), 7.60 (m, 3H), 7.35 (d, 2H), 7.06 (d, 2H), 7.05 (d, 1H), 6.75 (d, 1H), 6.47 (s, 1H), 6.12 (dd, 1H), 4.87 (s, 1H), 4.23 (s, 2H), 3.13 (m, 2H), 3.02 (m, 2H), 2.77 (m, 1H), 2.27 (m, 2H), 2.17 (m, 4H), 1.97 (s, 2H), 1.91 (m, 2H), 1.74 (m, 4H), 1.60 (m, 2H), 1.40 (m, 2H), 1.31 (m, 1H), 0.94 (s, 3H), 0.91 (m, 2H).

EXAMPLE 491

N-({5-chloro-6-[(2,2-difluorocyclopropyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 491A

5-chloro-6-((2,2-difluorocyclopropyl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting (2,2-difluorocyclopropyl)methanol for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 387A for EXAMPLE 329A in EXAMPLE 329B.

EXAMPLE 491B

N-(5-chloro-6-((2,2-difluorocyclopropyl)methoxy)pyridin-3-ylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 435D for EXAMPLE 1E and EXAMPLE 491A for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 491C

N-({5-chloro-6-[(2,2-difluorocyclopropyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 491B (0.196 g) was treated with tetrabutyl ammonium fluoride (1M in tetrahydrofuran) (2.000 mL), heated at 50 °C overnight, cooled to room temperature and then treated with 1N aqueous NaOH solution (2.0 mL). The mixture was stirred for 5 hours at ambient temperature and then extracted with CH_2Cl_2. The extracts were combined, washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by reverse phase HPLC on a C18 column using a gradient of 20-80% acetonitrile/0.1% trifluoroacetic acid in water to give the title compound as the trifluoroacetate salt. The trifluoroacetic acid salt was dissolved in dichloromethane, washed with saturated aqueous $NaHCO_3$ solution and brine, dried (Na_2SO_4), filtered, concentrated, slurried in CH_3CN, concentrated again and dried overnight in a vacuum oven at 80 °C to give the title compound. ^{1}H NMR (400 MHz, pyridine-d_5) δ 14.62 (s, 1H), 8.88 (d, 1H), 8.37 (m, 2H), 8.06 (d, 1H), 7.46 (d, 2H), 7.34 (d, 1H), 7.11 (m, 3H), 6.87 (m, 2H), 6.48 (d, 1H), 4.53 (m, 1H), 4.43 (m, 1H), 3.17 (m, 4H), 2.82 (s, 2H), 2.27 (m, 7H), 1.99 (s, 2H), 1.56 (m, 1H), 1.38 (m, 3H), 0.96 (s, 6H).

EXAMPLE 492

N-({5-chloro-6-[(trans-4-cyanocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

A solution of EXAMPLE 483D (50 mg) in dioxane (12 mL) and pyridine (1.2 mL) was cooled in an ice-water bath. The mixture was slightly warmed by removing the ice bath and then trifluoroacetic acid (0.3 mL) was added. The reaction was stirred for 1 hour and quenched with methanol and aqueous NaOH. The resulting mixture was stirred for 1 hour and concentrated. The residue was purified by reverse phase HPLC, and eluted with 40% - 70% acetonitrile in 0.1% trifluoroacetic acid water over 40 minutes. The desired fractions were concentrated to remove acetonitrile, neutralized with $NaHCO_3$ and extracted with dichloromethane. The dichloromethane layer was dried over Na_2SO_4, filtered, concentrated and dried to provide the title compound. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 13.10 (s, 1H), 8.27 (d, 1H), 7.85 (d, 1H), 7.80 (s, 1H), 7.58 (d, 1H), 7.37 (d, 2H), 7.02 - 7.11 (m, 4H), 6.80 (dd, 1H), 6.54 (d, 1H), 6.14 (d, 1H), 4.19 (d, 2H), 3.22 (s, 4H), 2.97 (s, 2H), 2.59 - 2.71 (m, 1H), 2.41 (s, 2H), 2.18 (s, 2H), 2.05 (dd, 2H), 1.98 (s, 2H), 1.79 - 1.90 (m, 3H), 1.47 - 1.62 (m, 2H), 1.42 (t, 2H), 1.04 - 1.19 (m, 2H), 0.94 (s, 6H).

EXAMPLE 493

N-({5-chloro-6-[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 493A

4-(hydroxymethyl)-1-methylcyclohexanol

4-(Hydroxymethyl)cyclohexanone (800 mg) in tetrahydrofuran (15 mL) was treated with 3 M methylmagnesium chloride in tetrahydrofuran (6.24 mL) at 0°C. The reaction was warmed to room temperature over 2 hours and quenched with methanol and water. The resulting mixture was concentrated and the residue was suspended in ethyl acetate. The precipitates were filtered off and the filtrate was concentrated. The residue was purified by chromatography, eluting with 0-100% ethyl acetate in hexane to provide the title compound.

EXAMPLE 493B

5-chloro-6-((trans-4-hydroxy-4-methylcyclohexyl)methoxy)pyridine-3-sulfonamide

EXAMPLE 493A (970 mg) and EXAMPLE 387A (1.6 g) in N,N-dimethylformamide (8 mL) were treated with sodium hydride (1.8 g, 60%) at room temperature for 2 days. The reaction was quenched with water. The resulting mixture was neutralized with diluted aqueous HCl, and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by a reverse phase chromatography, and was eluting with 30-45% acetonitrile in 0.1% trifluoroacetic acid water to provide the title compound.

EXAMPLE 493C

5-chloro-6-((cis-4-hydroxy-4-methylcyclohexyl)methoxy)pyridine-3-sulfonamide

EXAMPLE 493A (970 mg) and EXAMPLE 387A (1.6 g) in N,N-dimethylformamide (8 mL) were treated with sodium hydride (1.8 g, 60%) at room temperature for 2 days. The reaction was quenched with water. The resulting mixture was neutralized with diluted aqueous HCl, and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by a reverse phase chromatography, and was eluting with 30-45% acetonitrile in 0.1% trifluoroacetic acid water to provide the title compound.

EXAMPLE 493D

N-({5-chloro-6-[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

A mixture of 4-dimethylaminopyridine (175.0 mg), 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (82 mg), EXAMPLE 435D (251 mg) and EXAMPLE 493C (120 mg) in dichloromethane (6 mL) was stirred overnight and concentrated. The residue was dissolved in a 1 M tetrabutyl ammonium fluoride monohydrate tetrahydrofuran solution (11 mL) and the resulting solution was refluxed for 9 hours and concentrated. The residue was purified by reverse phase HPLC, eluted with 40% - 70% acetonitrile in 0.1% trifluoroacetic acid water over 40 minutes. The desired fractions were concentrated to remove acetonitrile, neutralized with $NaHCO_3$ and extracted with dichloromethane. The dichloromethane layer was dried over Na_2SO_4, filtered, concentrated and dried to provide the title compound. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 13.11 (s, 1H), 8.27 (d, 1H), 7.85 (d, 1H), 7.81 (s, 1H), 7.59 (d, 1H), 7.36 (d, 2H), 7.03 - 7.11 (m, 4H), 6.80 (dd, 1H), 6.54 (d, 1H), 6.14 (d, 1H), 4.20 (d, 2H), 3.96 (s, 1H), 3.21 (s, 4H), 2.86 - 3.05 (m, 1H), 2.40 (s, 2H), 2.18 (s, 2H), 1.98 (s, 2H), 1.63 - 1.78 (m, 1H), 1.50 - 1.62 (m, 4H), 1.36 - 1.49 (m, 4H), 1.20 - 1.34 (m, 2H), 1.10 (s, 3H), 0.94 (s, 6H).

EXAMPLE 494

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 494A

4-Hydroxy-indazole-1-carboxylic acid tert-butyl ester and 4-hydroxy-indazole-2-carboxylic acid tert-butyl ester

4-Hydroxyindazole (3.94 g) was added to tetrahydrofuran (250 mL) and cooled to 0°C using an ice bath. Sodium hydride (60% dispersion in mineral oil, 1.23 g) was added, and the mixture was stirred at 0°C for five minutes. The mixture was allowed to warm to room temperature and stirred for an additional 20 minutes. The mixture was again cooled to 0°C using an ice bath, and tert-butyldimethylchlorosilane (4.65 g) was added. The mixture was allowed to warm to room temperature and stirred for 16 hours. The solvent volume was

reduced under vacuum, the residue vacuum filtered over a pad of silica gel and washed with ethyl acetate, and the solvent was removed under vacuum. To the residue was added acetonitrile (200 mL), di-tert-butyl dicarbonate (7.06 g), and 4-(dimethylamino)pyridine (0.359 g). The mixture was stirred at room temperature for three hours, and the solvent was removed under vacuum. To the residue was added tetrahydrofuran (200 mL) and tetrabutylammonium fluoride (1M in tetrahyrdofuran, 82 mL). The mixture was stirred at room temperature for four days, the solvent removed under vacuum, and the residue taken up in ethyl acetate. The mixture was extracted with saturated aqueous ammonium chloride, extracted with brine, and dried on anhydrous sodium sulfate. The mixture was vacuum filtered over silica gel, and the solvent removed under vacuum to give a mixture of the two products, which was used in the next step without further purification.

EXAMPLE 494B

4-Fluoro-2-(1H-indazol-4-yloxy)-benzoic acid methyl ester

EXAMPLE 494A (5.56 g) was added to diglyme (200 mL), and potassium tert-butoxide (1M in tetrahydrofuran, 30.8 mL) was added. The mixture was stirred at room temperature for 15 minutes, methyl 2,4-difluorobenzoate was added, and the mixture was heated at 115°C for 16 hours. The mixture was cooled, the solvent was removed under vacuum, the residue was taken up in dichloromethane (100 mL), and trifluoroacetic acid (22.6 mL) was added. The mixture was stirred at room temperature for 16 hours, the solvent was removed under vacuum, the residue was taken up in ethyl acetate and washed with a saturated aqueous sodium bicarbonate mixture, and the organic layer was dried with anhydrous sodium sulfate. The material was purified by flash column chromatography on silica gel using 30% ethyl acetate (in hexanes) increasing to 40% ethyl acetate (in hexanes).

EXAMPLE 494C

2-(1H-Indazol-4-yloxy)-4-piperazin-1-yl-benzoic acid methyl ester

EXAMPLE 494B (2.00 g) and piperazine (2.71 g) were added to dimethylsulfoxide (60 mL) and heated to 100°C for one hour. The mixture was cooled, added to dichloromethane, washed with water twice, washed with a saturated aqueous sodium bicarbonate mixture, and dried on anhydrous sodium sulfate. After filtration, the solvent was removed under vacuum.

EXAMPLE 494D

methyl 4,4-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

To a suspension of hexane washed NaH (17 g) in dichloromethane (700 mL), 5,5-dimethyl-2-methoxycarbonylcyclohexanone (38.5 g) was added dropwise at 0°C. After stirring for 30 minutes, the mixture was cooled to –78°C and trifluoromethanesulfonic anhydride (40 mL) was added. The reaction mixture was warmed to room temperature and stirred for 24 hours. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated to give the product.

EXAMPLE 494E

methyl 2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enecarboxylate

EXAMPLE 494D (62.15g), 4-chlorophenylboronic acid (32.24 g), CsF (64 g) and tetrakis(triphenylphosphine)palladium(0) (2g) in 2:1 1,2-dimethoxyethane/methanol (600 mL) were heated to 70°C for 24 hours. The mixture was concentrated. Ether (4x 200 mL) was added and the mixture was filtered. The combined ether solution was concentrated to give the product.

EXAMPLE 494F

(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methanol

To a mixture of $LiBH_4$ (13g), EXAMPLE 494E (53.8 g) and ether (400 mL), methanol (25 mL) was added slowly by syringe. The mixture was stirred at room temperature for 24 hours. The reaction was quenched with 1N aqueous HCl with ice-cooling. The mixture was diluted with water and extracted with ether (3x 100mL). The extracts were dried (Na_2SO_4), and concentrated. The crude product was chromatographed on silica gel with 0-30% ethyl acetate/hexanes.

EXAMPLE 494G

2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enecarbaldehyde

To a solution of EXAMPLE 494F in dichloromethane (120 mL) at 0°C was added Dess-Martin periodinane (17.7 g) and the reaction was allowed to warm to room temperature. The reaction was diluted with dichloromethane (200 mL), washed twice with saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was filtered through a silica gel plug to give the title compound.

EXAMPLE 494H

4-{4-[2-(4-Chloro-phenyl)-4,4-dimethyl-cyclohex-1-enylmethyl]-piperazin-1-yl}-2-(1H-indazol-4-yloxy)-benzoic acid methyl ester

To dichloromethane (60 mL) was added EXAMPLE 494C (2.500 g) and EXAMPLE 494G (2.029 g). The solution was stirred at room temperature for 30 minutes, sodium triacetoxyborohydride (1.804 g) was added, and the solution stirred at room temperature for 16 hours. The solution was diluted with ethyl acetate, washed with a saturated aqueous solution of sodium bicarbonate, washed with brine, and the organic layer dried on anhydrous sodium sulfate. After filtration, the solution was concentrated and purified by flash column chromatography on silica gel using 20-50% ethyl acetate in hexanes.

EXAMPLE 494I

methyl 4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-trityl-1H-indazol-4-yloxy)benzoate

EXAMPLE 494H (300 mg) was dissolved in dichloromethane (1.5 mL), cooled to 0 °C, then triethylamine (0.22 mL) and trityl chloride (145 mg) were added. The reaction was allowed to warm to room temperature overnight. The reaction mixture was directly put on a silica gel column and eluted with 10-30% ethyl acetate in hexanes to give the title compound.

EXAMPLE 494J

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-trityl-1H-indazol-4-yloxy)benzoic acid

EXAMPLE 494I (0.591 g) was dissolved in tetrahydrofuran (6 mL) and methanol (2 mL) and to the resulting solution was added 1M aqueous LiOH solution (2.14 mL) and the reaction was heated to 60°C for 5 hours. The reaction was cooled and diluted with dichloromethane (100 mL) and water (10 mL), and then quenched with 1N aqueous HCl (2 mL). The organic layer was separated, washed with brine (25 mL) and concentrated. Silica gel chromatography (Reveleris 40 g) eluting with a gradient of 1% to 4% methanol/dichloromethane over 30 minutes gave the title compound.

EXAMPLE 494K

4-(hydroxymethyl)-1-methylcyclohexanol

4-(Hydroxymethyl)cyclohexanone (800 mg) in tetrahydrofuran (15 mL) was treated with 3 M methylmagnesium chloride in tetrahydrofuran (6.24 mL) at 0°C. The reaction was

warmed to room temperature over 2 hours and was quenched with methanol and water. The resulting mixture was concentrated and the residue was suspended in ethyl acetate. The precipitates were filtered off and the filtrate was concentrated. The residue was purified by chromatography, eluting with 0-100% ethyl acetate in hexane to provide the title compound.

EXAMPLE 494L

5,6-dichloropyridine-3-sulfonamide

To a solution of 5,6-dichloropyridine-3-sulfonyl chloride (32.16 g) in isopropyl alcohol (300 mL) at 0 °C was added a 30% aqueous solution of NH_4OH (50.8 mL). After stirring overnight, the solvent was reduced to 1/3 of the original volume. It was then partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed on silica gel. The material was then slurried in 1:9 ethyl acetate/hexanes, filtered and dried under vacuum to give the title compound.

EXAMPLE 494M

5-chloro-6-((trans-4-hydroxy-4-methylcyclohexyl)methoxy)pyridine-3-sulfonamide

EXAMPLE 494K (970 mg) and EXAMPLE 494L (1.6 g) in N,N-dimethylformamide (8 mL) were treated with sodium hydride (1.8 g, 60%) at room temperature for 2 days. The reaction was quenched with water. The resulting mixture was neutralized with diluted aqueous HCl, and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by a reverse phase chromatography, and was eluting with 30-45% acetonitrile in 0.1% trifluoroacetic acid/water to provide the title compound.

EXAMPLE 494N

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

A mixture of EXAMPLE 494J (3.4 g), EXAMPLE 494M (1.539 g), N, N-dimethylpyridin-4-amine (2.043 g) and N^1-((ethylimino)methylene)-N^3,N^3-dimethylpropane-1,3-diamine hydrochloride (1.042 g) in dichloromethane (65 mL) was stirred overnight.

Water (5 mL) was added. The resulting mixture was cooled in an ice bath and then trifluoroacetic acid (5 mL) was slowly added. The mixture was stirred while warmed from 0°C to room temperature and then stirred at room temperature for 2 hours. The reaction mixture was concentrated without heating and the residue was suspended in a mixture of dimethylsulfoxide and methanol (1:1, 40 mL). The precipitates were filtered off. The filtrate was loaded onto a C18 column, eluted with 40%-70% acetonitrile in 0.1% trifluoroacetic acid water. The desired fractions were concentrated to remove acetonitrile, neutralized with $NaHCO_3$ and extracted with dichloromethane. The organic layer was dried over Na_2SO_4, filtered, concentrated and dried to provide the title compound. ^{1}H NMR (500 MHz, dimethylsulfoxide-d_6) δ 13.11 (s, 1H), 8.28 (d, 1H), 7.85 (d, 1H), 7.81 (s, 1H), 7.59 (d, 1H), 7.37 (d, 2H), 7.03 - 7.12 (m, 4H), 6.80 (dd, 1H), 6.54 (d, 1H), 6.14 (d, 1H), 4.18 - 4.31 (m, 3H), 3.15 - 3.26 (m, 4H), 2.96 (s, 2H), 2.28 - 2.48 (m, 3H), 2.18 (s, 2H), 1.98 (s, 2H), 1.69 - 1.82 (m, 3H), 1.56 (d, 2H), 1.34 - 1.45 (m, 4H), 1.16 - 1.27 (m, 2H), 1.11 (s, 3H), 0.94 (s, 6H).

EXAMPLE 496

N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 496A

3-chloro-4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 306C for (tetrahydro-2H-pyran-4-yl)methanol and 3-chloro-4-fluorobenzenesulfonamide for EXAMPLE 329A in EXAMPLE 329B.

EXAMPLE 496B

N-(3-chloro-4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)phenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 496A for EXAMPLE 1F and EXAMPLE 435D for EXAMPLE 27G in EXAMPLE 27H.

EXAMPLE 496C

N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 496B for EXAMPLE 435E in EXAMPLE 435F. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 13.16 (s, 1H), 11.62 (v br s, 1H), 7.86 (s, 1H), 7.67 (d, 1H), 7.59 (dd, 1H), 7.55 (d, 1H), 7.39 (d, 2H), 7.15 (m, 5H), 6.80 (dd, 1H), 6.52 (d, 1H), 6.22 (d, 1H), 4.25 (d, 2H), 4.14 (s, 2H), 3.80 (m, 2H), 3.60 (m, 2H), 3.17 (br m, 4H), 2.88 (s, 2H), 2.25 (br m, 4H), 2.16 (s, 2H), 1.90 (m, 4H), 1.20 (s, 6H).

EXAMPLE 497

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-(trifluoromethyl)phenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 497A

4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-3-(trifluoromethyl)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 306C for (tetrahydro-2H-pyran-4-yl)methanol and 4-fluoro-3-(trifluoromethyl)benzenesulfonamide for EXAMPLE 329A in EXAMPLE 329B.

EXAMPLE 497B

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-3-(trifluoromethyl)phenylsulfonyl)-2-(1-trityl-1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 498C for EXAMPLE 1E and EXAMPLE 497A for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 497C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-(trifluoromethyl)phenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 497B (0.1557 g) in dichloromethane (1.5 mL) at 0 °C was treated dropwise with trifluoroacetic acid (1.041 mL), stirred for 1 hour, diluted with CH_2Cl_2 and basified with saturated $NaHCO_3$ solution. The layers were separated and the organic layer was washed with water and brine, dried (Na_2SO_4), filtered and concentrated. The concentrate was chromatographed on silica gel with 0 to 4% methanol in CH_2Cl_2 as the eluent. ^1H NMR (500 MHz, pyridine -d_5) δ 14.59 (s, 1H), 8.58 (d, 1H), 8.39 (dd, 1H), 8.36 (s, 1H), 8.07 (d, 1H), 7.46 (m, 2H), 7.37 (d, 1H), 7.17 (t, 1H), 7.09 (m, 3H), 6.85 (dd, 1H), 6.82 (d, 1H), 6.55 (d, 1H), 4.21 (d, 2H), 3.86 (m, 2H), 3.78 (td, 2H), 3.15 (m, 4H), 2.81 (s, 2H), 2.29 (t, 2H), 2.21 (m, 4H), 1.95 (m, 6H), 1.41 (t, 2H), 0.95 (s, 6H).

EXAMPLE 498

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-chloro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 498A

3-chloro-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

The title compound was prepared by substituting 3-chloro-4-fluorobenzenesulfonamide for EXAMPLE 329A in EXAMPLE 329B.

EXAMPLE 498B

methyl 4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-trityl-1H-indazol-4-yloxy)benzoate

EXAMPLE 400D (300 mg) was dissolved in dichloromethane (1.5 mL), cooled to 0° C, then triethylamine (0.22 mL) and trityl chloride (145 mg) were added. The reaction was allowed to come to room temperature overnight. The reaction mixture was directly put on a silica gel column and eluted with 10-30% ethyl acetate in hexanes to give the title compound.

EXAMPLE 498C

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-trityl-1H-indazol-4-yloxy)benzoic acid

The title compound was prepared by substituting EXAMPLE 498B for EXAMPLE 175D in EXAMPLE 175E.

EXAMPLE 498D

N-(3-chloro-4-((tetrahydro-2H-pyran-4-yl)methoxy)phenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-trityl-1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 498C for EXAMPLE 1E and EXAMPLE 498A for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 498E

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-chloro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 498D (150 mg) was dissolved in dichloromethane (3.5 mL) and trifluoroacetic acid (3.5 mL). After stirring at room temperature for 30 minutes, the reaction was poured into saturated aqueous $NaHCO_3$ and extracted with dichloromethane. The organic layer was washed with brine and dried over Na_2SO_4. After filtration and concentration the residue was purified by reverse phase HPLC on a C18 column using a gradient of 40-60% acetonitrile/0.1% trifluoroacetic acid in water to give the title compound as the trifluoroacetate salt. The trifluoroacetic acid salt was dissolved in dichloromethane (6 mL) and washed with 50% aqueous $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to give the title compound. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 13.16 (s, 1H), 7.85 (s, 1H), 7.64 (d, 1H), 7.57 (dd, 1H), 7.55 (d, 1H), 7.35 (d, 2H), 7.35 (m, 3H), 7.04 (d, 2H), 6.80 (dd, 1H), 6.53 (d, 1H), 6.22 (d, 1H), 3.97 (d, 2H), 3.88 (m, 2H), 3.35 (m, 2H), 3.18 (br m, 4H), 2.80 (s, 2H), 2.27 (br m, 4H), 2.18 (br m, 2H), 2.04 (m, 1H), 1.97 (s, 2H), 1.69 (m, 2H), 1.40 (m, 4H) 0.93 (s, 6H).

EXAMPLE 499

2-(1H-benzimidazol-4-yloxy)-N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide

The title compound was prepared by substituting EXAMPLE 496A for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (500MHz, pyridine-d_5) δ 8.58 (s, 1H), 8.53 (d, 1H), 8.33 (dd, 1H), 7.96 (d, 1H), 7.54 (d, 1H), 7.43 (d, 2H), 7.26 (t, 1H), 7.20 (m, 2H), 7.07 (d,

2H), 7.04 (d, 1H), 6.72-6.68 (m, 2H), 4.17 (d, 2H), 3.89 (m, 2H), 3.83 (m, 2H), 3.03 (m, 4H), 2.76 (s, 2H), 2.26 (m, 2H), 2.14 (m, 4H), 2.03-1.95 (m, 6H), 1.38 (t, 2H), 0.94 (s, 6H).

EXAMPLE 500

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}benzamide

The title compound was prepared by substituting EXAMPLE 387B for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (500MHz, pyridine-d_5) δ 9.16 (d, 1H), 8.72 (d, 1H), 8.59 (s, 1H), 7.97 (d, 1H), 7.53 (d, 1H), 7.43 (d, 2H), 7.25 (t, 1H), 7.20 (m, 2H), 7.07 (d, 2H), 6.73-6.68 (m, 2H), 4.21 (d, 2H), 3.99 (dd, 2H), 3.33 (dt, 2H), 3.03 (m, 4H), 2.77 (s, 2H), 2.25 (m, 2H), 2.14 (m, 4H), 1.98 (m, 1H), 1.97 (s, 2H), 1.60 (d, 2H), 1.43 (m, 2H), 1.38 (t, 2H), 0.94 (s, 6H).

EXAMPLE 501

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 501A

3-cyano-4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

The title compound was prepared by substituting (4-fluorotetrahydro-2H-pyran-4-yl)methanol for (tetrahydro-2H-pyran-4-yl)methanol and 3-cyano-4-fluorobenzenesulfonamide for EXAMPLE 329A in EXAMPLE 329B.

EXAMPLE 501B

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-cyano-4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)phenylsulfonyl)-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 501A for EXAMPLE 1F and EXAMPLE 435D for EXAMPLE 1E in EXAMPLE 1G.

EXAMPLE 501C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 501B for EXAMPLE 435E in EXAMPLE 435F. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 13.09 (s, 1H), 7.85 (m, 2H), 7.79 (s, 1H), 7.57 (d, 1H), 7.35 (d, 2H), 7.22 (m, 1H), 7.13 (m, 2H), 7.05 (d, 2H), 6.78 (dd, 1H), 6.50 (d, 1H), 6.17 (dd, 1H), 4.34 (d, 2H), 3.79 (m, 2H), 3.63 (m, 2H), 3.16 (m, 4H), 2.82 (m, 2H), 2.27 (m, 4H), 2.17 (m, 3H), 1.97 (m, 2H), 1.91 (m, 2H), 1.85 (m, 2H), 1.40 (t, 2H), 0.94 (s, 6H).

EXAMPLE 502

N-{[3-chloro-4-(1,4-dioxan-2-ylmethoxy)phenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 502A

4-((1,4-dioxan-2-yl)methoxy)-3-chlorobenzenesulfonamide

The title compound was prepared by substituting (1,4-dioxan-2-yl)methanol for (tetrahydro-2H-pyran-4-yl)methanol and 3-chloro-4-fluorobenzenesulfonamide for EXAMPLE 329A in EXAMPLE 329B.

EXAMPLE 502B

N-(4-((1,4-dioxan-2-yl)methoxy)-3-chlorophenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 502A for EXAMPLE 1F and EXAMPLE 435D for EXAMPLE 1E in EXAMPLE 1G.

EXAMPLE 502C

N-{[3-chloro-4-(1,4-dioxan-2-ylmethoxy)phenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 502B for EXAMPLE 435E in EXAMPLE 435F. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 13.02 (s, 1H), 7.78

(m, 1H), 7.63 (m, 1H), 7.58 (m, 1H), 7.42 (m, 1H), 7.35 (d, 2H), 7.11 (d, 2H), 7.06 (d, 2H), 6.99 (m, 1H), 6.74 (m, 1H), 6.42 (m, 1H), 6.15 (m, 1H), 4.06 (m, 2H), 3.83 (m, 2H), 3.65 (m, 2H), 3.47 (m, 2H), 3.07 (m, 4H), 2.75 (m, 2H), 2.21 (m, 6H), 1.97 (m, 2H), 1.40 (t, 2H), 1.23 (m, 1H), 0.93 (s, 6H).

EXAMPLE 503

2-(1H-benzimidazol-4-yloxy)-N-[(5-chloro-6-{[(2S)-4-cyclopropylmorpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide

EXAMPLE 503A

(S)-5-chloro-6-((4-cyclopropylmorpholin-2-yl)methoxy)pyridine-3-sulfonaminde

The title compound was prepared by substituting EXAMPLE 423B for EXAMPLE 415B in EXAMPLE 432A.

EXAMPLE 503B

2-(1H-benzimidazol-4-yloxy)-N-[(5-chloro-6-{[(2S)-4-cyclopropylmorpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide

The title compound was prepared by substituting EXAMPLE 503A for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (400 MHz, pyridine-d_5) δ 9.08 (d, 1H), 8.64 (m, 1H), 8.56 (s, 1H), 7.99 (d, 1H), 7.51 (d, 1H), 7.43 (d, 2H), 7.23 (d, 1H), 7.13 (m, 1H), 7.07 (d, 2H), 6.71 (m, 2H), 6.51 (m, 1H), 5.86 (m, 1H), 4.62 - 4.57 (m, 1H), 4.52 - 4.48 (m, 1H), 3.99 (m, 1 H), 3.84 (m, 1H), 3.57 (m, 1H), 3.04 (m, 5H), 2.77 (s, 2H), 2.69 (m, 1H), 2.40 - 2.32 (m, 2H), 2.29 - 2.23 (m, 2H), 2.15 (m, 4H), 1.97 (s, 2H), 1.59 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H), 0.48 - 0.36 (m, 4H).

EXAMPLE 504

N-[(5-chloro-6-{[(2S)-4-cyclopropylmorpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 503A for EXAMPLE 1F and EXAMPLE 400E for EXAMPLE 26C in EXAMPLE 177. ^{1}H NMR (400 MHz,

pyridine-d_5) δ 8.86 (d, 1H), 8.38 (d, 2H), 8.14 (d, 1H), 7.47 (d, 2H), 7.34 (d, 1H), 7.13 - 7.10 (m, 3H), 6.88 - 6.85 (m, 2H), 6.49 (d, 1H), 5.41 (m, 2H), 4.62 - 4.57 (m, 1H), 4.51 - 4.47 (m, 1H), 3.98 (m, 1H), 3.84 (m, 1H), 3.57 (m, 1H), 3.16 (m, 4H), 3.02 (m, 1H), 2.83 (s, 2H), 2.69 (m, 1H), 2.38 - 2.27 (m, 4H), 2.24 (m, 4H), 1.99 (s, 2H), 1.58 (m, 1H), 1.41 (t, 2H), 0.96 (m, 6H), 0.48 - 0.36 (m, 4H).

EXAMPLE 505

methyl 2-{[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}morpholine-4-carboxylate

EXAMPLE 505A

methyl 2-((2-nitro-4-sulfamoylphenylamino)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting methyl chloroformate for acetyl chloride in EXAMPLE 457A.

EXAMPLE 505B

methyl 2-{[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}morpholine-4-carboxylate

The title compound was prepared by substituting EXAMPLE 400E for EXAMPLE 26C and EXAMPLE 505A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500MHz, pyridine-d_5) δ 14.58 (bs, 1H), 9.05 (d, 1H), 8.82 (t, 1H), 8.36 (s, 1H), 8.18 (d, 1H), 8.12 (d, 1H), 7.45 (d, 2H), 7.34 (d, 1H), 7.15 (t, 1H), 7.10 (d, 2H), 6.87-6.82 (m, 3H), 6.53 (d, 1H), 4.29, 4.03 (bd, 1H), 3.86 (m, 1H), 3.73 (m, 2H), 3.71 (s, 3H), 3.54-3.40 (m, 3H), 3.14 (m, 4H), 2.96 (dt, 1H), 2.85 (m, 1H), 2.82 (s, 2H), 2.30 (m, 2H), 2.22 (m, 4H), 1.99 (s, 2H), 1.41 (t, 2H), 0.96 (s, 6H).

EXAMPLE 506

2-{[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide

EXAMPLE 506A

N-ethyl-N-methyl-2-((2-nitro-4-sulfamoylphenylamino)methyl)morpholine-4-carboxamide

The title compound was prepared by substituting *N*-ethyl-*N*-methyl-carbamoyl chloride for acetyl chloride in EXAMPLE 457A.

EXAMPLE 506B

2-{[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide

The title compound was prepared by substituting EXAMPLE 400E for EXAMPLE 26C and EXAMPLE 506A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500MHz, pyridine-d_5) δ 14.58 (bs, 1H), 9.07 (d, 1H), 8.82 (t, 1H), 8.37 (s, 1H), 8.13 (m, 2H), 7.45 (d, 2H), 7.34 (d, 1H), 7.15 (t, 1H), 7.11 (d, 2H), 6.87 (d, 1H), 6.83-6.79 (m, 2H), 6.54 (d, 1H), 3.92-3.85 (m, 2H), 3.75 (m, 1H), 3.62 (dt, 1H), 3.50 (m, 1H), 3.40 (m, 2H), 3.21 (q, 2H), 3.14 (m, 4H), 3.00 (dt, 1H), 2.82 (s, 2H), 2.76 (s, 3H), 2.30 (m, 2H), 2.23 (m, 4H), 1.99 (s, 2H), 1.41 (t, 2H), 1.06 (t, 3H), 0.96 (s, 6H).

EXAMPLE 507

2-{[(4-{[2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide

The title compound was prepared by substituting EXAMPLE 506A for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (500MHz, pyridine-d_5) δ 9.25 (d, 1H), 8.86 (t, 1H), 8.56 (s, 1H), 8.35 (dd, 1H), 8.01 (d, 1H), 7.52 (d, 1H), 7.43 (d, 2H), 7.25 (m, 1H), 7.13 (d, 1H), 7.07 (d, 2H), 6.94 (d, 1H), 6.73-6.68 (m, 2H), 3.96-3.85 (m, 2H), 3.87 (m, 1H), 3.64 (dt, 1H), 3.53 (m, 1H), 3.48-3.41 (m, 2H), 3.21 (q, 2H), 3.03 (m, 5H), 2.92 (dd, 1H), 2.90 (d, 1H), 2.76 (s, 5H), 2.25 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.38 (t, 2H), 1.06 (t, 3H), 0.94 (s, 6H).

EXAMPLE 508

N-({5-chloro-6-[(trans-4-ethyl-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 508A

1-ethyl-4-(hydroxymethyl)cyclohexanol

4-(Hydroxymethyl)cyclohexanone (1.22 g) in tetrahydrofuran (20 mL) was treated with 1M ethylmagnesium bromide in tetrahydrofuran (28.6 mL) at 0°C. The reaction was warmed to room temperature over 4 hours and quenched with methanol (2 mL) and water (2 mL). The resulting mixture was concentrated and the residue was suspended in ethyl acetate. The precipitates were filtered off and the filtrate was concentrated and purified by flash chromatography, eluted with 0-100% ethyl acetate in hexane to provide the title compound.

EXAMPLE 508B

5-chloro-6-((trans-4-ethyl-4-hydroxycyclohexyl)methoxy)pyridine-3-sulfonamide

The title compound was prepared as described in EXAMPLE 493B by replacing EXAMPLE 493A with EXAMPLE 508A.

EXAMPLE 508C

5-chloro-6-((cis-4-ethyl-4-hydroxycyclohexyl)methoxy)pyridine-3-sulfonamide

The title compound was prepared as described in EXAMPLE 493B by replacing EXAMPLE 493A with EXAMPLE 508A.

EXAMPLE 508D

N-({5-chloro-6-[(trans-4-ethyl-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 177 by replacing EXAMPLE 26C and EXAMPLE 1F with EXAMPLE 400E and EXAMPLE 508B, respectively. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 13.20 (s, 1H), 8.37 (d, 1H), 7.95 (d, 1H), 7.91 (s, 1H), 7.70 (d, 1H), 7.47 (d, 2H), 7.14 - 7.21 (m, 4H), 6.89 (dd, 1H), 6.63 (d, 1H), 6.25 (dd, 1H), 4.34 (d, 2H), 4.11 (s, 1H), 3.24 - 3.33 (m, 4H), 3.02 (d, 2H), 2.46 (s, 4H), 2.28 (s, 2H), 2.09 (s, 2H), 1.77 - 1.96 (m, 3H), 1.61 - 1.76 (m, 3H), 1.48 - 1.60 (m, 4H), 1.21 - 1.47 (m, 5H), 1.04 (s, 6H), 0.91 (t, 3H).

EXAMPLE 509

N-({5-chloro-6-[(cis-4-ethyl-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 177 by replacing EXAMPLE 26C and EXAMPLE 1F with EXAMPLE 400E and EXAMPLE 508C, respectively. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 13.10 (s, 1H), 8.26 (d, 1H), 7.84 (d, 1H), 7.80 (s, 1H), 7.59 (d, 1H), 7.36 (d, 2H), 7.03 - 7.11 (m, 4H), 6.79 (dd, 1H), 6.53 (s, 1H), 6.12 - 6.15 (m, 1H), 4.20 (d, 2H), 3.77 (s, 1H), 3.11 - 3.24 (m, 4H), 2.88 (s, 2H), 2.24 - 2.41 (m, 3H), 2.18 (s, 2H), 1.98 (s, 2H), 1.71 (s, 1H), 1.55 (d, 5H), 1.18 - 1.49 (m, 9H), 0.94 (s, 6H), 0.83 (t, 3H).

EXAMPLE 510

5-chloro-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 510A

methyl 2-(1H-indazol-4-yloxy)-5-chloro-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

A mixture of EXAMPLE 400D (0.5 g) and 1-chloropyrrolidine-2,5-dione (0.126 g) in acetonitrile (10 mL) was stirred at room temperature for 4 hours. The solvent was removed, and the residue was purified by flash column chromatography on silica gel to give the title compound.

EXAMPLE 510B

2-(1H-indazol-4-yloxy)-5-chloro-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 435C for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 510C

5-chloro-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 404A for EXAMPLE 1F and EXAMPLE 510B for EXAMPLE 26C in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 13.22 (s, 1H), 8.38 (d, 1H), 8.03 (d, 1H), 7.54 (d, 2H), 7.19-7.26 (m, 4H), 6.83 (s, 1H), 6.34 (d, 1H), 4.60 (d, 2H), 3.88-3.93 (m, 2H), 3.70-3.73 (m, 2H), 3.15 (br s, 4H), 2.86 (br s, 2H), 2.30 (bs, 2H), 2.13 (s, 2H), 1.94-2.05 (m, 4H), 1.55 (t, 2H), 1.06 (s, 6H).

EXAMPLE 511

5-chloro-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 409D for EXAMPLE 1F and EXAMPLE 510B for EXAMPLE 26C in EXAMPLE 177. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 13.07 (s, 1H), 8.46 (s, 1H), 8.33 (s, 1H), 8.03 (d, 1H), 7.75 (s, 1H), 7.68 (s, 1H), 7.60-7.62 (m, 1H), 7.38 (d, 2H), 7.06-7.11 (m, 5H), 6.69 (d, 1H), 6.20 (d, 1H), 3.67-3.77 (m, 4H), 3.50-3.55 (m, 2H), 2.89 (br s, 6H), 2.14 (bs, 2H), 1.97 (s, 2H), 1.76-1.82 (m, 4H), 1.39 (t, 2H), 0.92 (s, 6H).

EXAMPLE 512

N-({5-chloro-6-[(cis-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 512A

A dimethylsulfoxide (40 mL) solution of 1,4-dioxaspiro[4.5]decan-8-one (6.25 g) was added dropwise to a solution of trimethylsulfoxonium iodide (8.8 g) and potassium t-butoxide (4.5 g) in dimethylsulfoxide (50 mL). The mixture was stirred at room temperature overnight. The mixture was then poured over ice-water and extracted with ethyl ether (3x 200 mL). The

combined organic extracts were washed with water and brine, dried over Na_2SO_4. Filtration and evaporation of solvent gave the crude product.

EXAMPLE 512B

(8-fluoro-1,4-dioxaspiro[4.5]decan-8-yl)methanol

A solution of pyridine hydrofluoride (4 g) in dichloromethane (10 mL) was added dropwise to a solution of EXAMPLE 512A (1.7 g) in dichloromethane (20 mL) in a polyethylene bottle at 0°C. The mixture was stirred at room temperature overnight. TLC showed the reaction was complete. The mixture was carefully poured over a mixture of ice-water and Na_2CO_3 and extracted with ethyl acetate (2x 300mL). After washing with water and brine, the organic layer was dried over Na_2SO_4. Filtration and evaporation of the solvent gave the crude product.

EXAMPLE 512C

5-chloro-6-((8-fluoro-1,4-dioxaspiro[4.5]decan-8-yl)methoxy)pyridine-3-sulfonamide

To a solution of EXAMPLE 512B (500 mg) in N,N-dimethylformamide (5 mL) was added NaH (65% in mineral oil, 252 mg) at room temperature. The mixture was stirred for 30 minutes, and then 5,6-dichloropyridine-3-sulfonamide (0.6 g) was added. The mixture was stirred at room temperature overnight. The mixture was poured over aqueous NH_4Cl and extracted with ethyl acetate (3x 100 mL). The combined organic layers were washed with water, brine and dried over Na_2SO_4. After filtration and evaporation of the solvent, the residue was loaded on a silica gel cartridge and eluted with 30% ethyl acetate in hexane to give the pure product.

EXAMPLE 512D

5-chloro-6-((1-fluoro-4-oxocyclohexyl)methoxy)pyridine-3-sulfonamide

To a solution of EXAMPLE 512C (1.6 g) and pyridinium p-toluenesulfonate (1.2 g) in acetone (10 mL) was added water (2 mL) and the mixture was stirred in a CEM Discover microwave reactor at 100°C for 10 minutes. The mixture was diluted with dichloromethane (300 mL) and washed with aqueous $NaHCO_3$, water, brine and dried over Na_2SO_4. Filtration and evaporation of the solvent gave the crude product.

EXAMPLE 512E

5-chloro-6-((cis-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy)pyridine-3-sulfonamide

To a solution of EXAMPLE 512D (1.2 g) in tetrahydrofuran (30 mL) was added dropwise a solution of methylmagnesium bromide (5 mL, 3.0M in ether) at 0°C. Upon the addition, the reaction mixture solidified. More tetrahydrofuran (10 mL) was added to the mixture and stirring was continued for 1 hour. The mixture was poured over aqueous NH_4Cl and extracted with ethyl acetate (3x 300mL). The combined organic layers were washed with water, brine and dried over Na_2SO_4. The mixture was filtered and the solvent was evaporated, and the crude residue was dissolved in dimehtylsulfoxide/methanol (20 mL, 1:1) and loaded on HPLC (Gilson, C18 (100A) 250 x 121.2 mm (10 micron), conditions: 20% acetonitrile to 45% acetonitrile in 40 minutes) to separate the two isomers, of which EXAMPLE 512E is the cis isomer.

EXAMPLE 512F

N-({5-chloro-6-[(cis-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 512E for EXAMPLE 493C in EXAMPLE 493D. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 13.04 (s, 1H), 8.26 (d, 1H), 7.87 (d, 1H), 7.78 (s, 1H), 7.61 (d, 1H), 7.36 (d, 2H), 7.06 (m, 5H), 6.77 (dd, 1H), 6.49 (s, 1H), 4.49 (d, 2H), 4.35 (s, 1H), 3.16 (m, 5H), 2.88 (m, 2H), 2.26 (m, 4H), 1.95 (m, 4H), 1.68 (m, 4H), 1.43 (m, 4H), 1.12 (s, 3H), 0.94 (s, 6H).

EXAMPLE 513

N-({5-chloro-6-[(trans-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 513A

5-chloro-6-((trans-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy)pyridine-3-sulfonamide

This compound was also isolated as a product of EXAMPLE 512E.

EXAMPLE 513B

N-({5-chloro-6-[(trans-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 400E for EXAMPLE 1E and EXAMPLE 513A for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 13.06 (s, 1H), 8.24 (d, 1H), 7.87 (d, 1H), 7.79 (s, 1H), 7.60 (d, 1H), 7.36 (d, 2H), 7.06 (m, 5H), 6.78 (dd, 1H), 6.51 (d, 1H), 6.13 (dd, 1H), 4.45 (d, 2H), 4.15 (s, 1H), 3.18 (m, 4H), 2.86 (m, 2H), 2.27 (m, 4H), 1.85 (m, 6H), 1.48 (m, 7H), 1.15 (s, 3H), 0.94 (s, 6H).

EXAMPLE 514

2-(1H-benzotriazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide

EXAMPLE 514A

4-(tert-butyldimethylsilyloxy)-1H-benzo[d][1,2,3]triazole

1H-benzo[d][1,2,3]triazol-4-ol (2.0 g) in tetrahydrofuran (30 mL) was treated with 60% sodium hydride (0.622 g). After 10 minutes, tert-butylchlorodimethylsilane (2.454 g) was added. The solution was stirred for 16 hours. The solvent was removed, and the residue was purified by flash column chromatography on silica gel using 10-50% ethyl acetate in hexanes as eluent to give the title compound.

EXAMPLE 514B

4-(tert-butyldimethylsilyloxy)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d][1,2,3]triazole

EXAMPLE 514A (1.5 g) in tetrahydrofuran (30 mL) was treated with 60% sodium hydride (0.253 g). After 10 minutes, (2-(chloromethoxy)ethyl)trimethylsilane (1.1 g) was added. The solution was stirred for 2 hours. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with additional ethyl acetate. The combined organic layers were washed with brine, dried

over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel using 5% ethyl acetate in hexanes as eluent to give the desired product.

EXAMPLE 514C

1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d][1,2,3]triazol-4-ol

A mixture of EXAMPLE 514B (1.32 g) and 1.0 N tetrabutyl ammonium fluoride (10.4 mL) in tetrahydrofuran (15 mL) was stirred for 2 hours. The solvent was removed, and the residue was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with additional ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel using 10% ethyl acetate in hexanes as eluent to give the title compound.

EXAMPLE 514D

methyl 4-fluoro-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d][1,2,3]triazol-4-yloxy)benzoate

The title compound was prepared by substituting EXAMPLE 514C for 1H-indazol-5-ol and methyl 2,4-difluorobenzoate for ethyl 2,4-difluorobenzoate in EXAMPLE 20A.

EXAMPLE 514E

methyl 4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d][1,2,3]triazol-4-yloxy)benzoate

The title compound was prepared by substituting EXAMPLE 514D for EXAMPLE 20A in EXAMPLE 20D.

EXAMPLE 514F

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d][1,2,3]triazol-4-yloxy)benzoic acid

The title compound was prepared by substituting EXAMPLE 514E for EXAMPLE 1D in EXAMPLE 1E.

EXAMPLE 514G

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(4-((4-fluorotetrahydro-2H-pyran-4-yl)methylamino)-3-nitrophenylsulfonyl)-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d][1,2,3]triazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 514F for EXAMPLE 1E and EXAMPLE 409D for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 514H

2-(1H-benzotriazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 514G for EXAMPLE 498D in EXAMPLE 498E. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 8.58 (s, 1H), 8.33 (d, 1H), 7.62 (d, 1H), 7.56 (d, 1H), 7.34-7.38 (m, 3H), 7.04-7.10 (m, 4H), 6.80 (dd, 1H), 6.53 (s, 1H), 6.41 (d, 1H), 3.70-3.80 (m, 3H), 3.52-3.58 (m, 2H), 3.17 (br s, 4H), 2.81 (br s, 6H), 2.17-2.32 (m, 6H), 1.97 (s, 2H), 1.78-1.87 (m, 4H), 1.40 (t, 2H), 0.94 (s, 6H).

EXAMPLE 515

2-(1H-benzotriazol-4-yloxy)-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide

EXAMPLE 515A

N-(5-chloro-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridin-3-ylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d][1,2,3]triazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 514F for EXAMPLE 1E and EXAMPLE 404A for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 515B

2-(1H-benzotriazol-4-yloxy)-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide

The title compound was prepared by substituting EXAMPLE 515A for EXAMPLE 498D in EXAMPLE 498E. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 8.21 (s, 1H), 7.86 (d, 1H), 7.65 (d, 1H), 7.36-7.38 (m, 3H), 7.06-7.10 (m, 3H), 6.79 (dd, 1H), 6.56 (s, 1H), 6.30 (s, 1H), 4.48 (d, 2H), 3.77-3.81 (m, 3H), 3.59-3.64 (m, 3H), 3.23 (br s, 4H), 2.19 (s, 2H), 1.87-1.99 (m, 6H), 1.42 (t, 2H), 0.94 (s, 6H).

EXAMPLE 516

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-chloro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}benzamide

The title compound was prepared by substituting EXAMPLE 498A for EXAMPLE 428D and in EXAMPLE 428E. ^{1}H NMR (500 MHz, pyridine-d_5) δ 9.27 (d, 1H), 8.59 (s, 1H), 8.55 (d, 1H), 8.40 (dd, 1H), 7.99 (d, 1H), 7.54 (m, 1H), 7.43 (d, 2H), 7.25 (m, 1H), 7.16 (m, 1H), 7.07 (d, 2H), 6.86 (d, 1H), 6.69 (m, 2H), 5.73 (m, 2H), 4.15 (m, 1H), 3.90 (s, 2H), 3.03 (m, 4H), 2.96 - 287. (m, 2H), 2.81 - 2.76 (m, 3H), 2.58 (m, 1H), 2.32 - 2.23 (m, 3H), 2.14 (m, 4H), 1.97 (s, 2H), 1.73 (m, 1H), 1.38 (t, 2H), 0.94 (s, 6H).

EXAMPLE 517

N-[(3-chloro-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 517A

ethyl 4-fluoro-1-(oxetan-3-yl)piperidine-4-carboxylate

To 1-*tert*-butyl 4-ethyl 4-fluoropiperidine-1,4-dicarboxylate (1.0 g) was added HCl (4.0M in dioxane, 4.5 mL). After 1 hour the reaction was concentrated and dried under high vacuum. The resulting solid was dissolved in dichloromethane (5 mL) and treated with sodium triacetoxyborohydride (1.2 g) and oxetan-3-one (0.26 g) and stirred overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) and extracted into dichloromethane (2 x 25 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (Reveleris 80 g) eluting with a gradient of 0.5% to 3.75% methanol/dichloromethane over 40 minutes (flow = 30 mL/minutes) gave the title compound.

EXAMPLE 517B

(4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methanol

To a solution of EXAMPLE 517A (0.59 g) in tetrahydrofuran (5 mL) was added lithium aluminum hydride (1.8 mL) at 0°C. The reaction was removed from the ice bath and allowed to warm to room temperature. The reaction was quenched by the dropwise addition of 0.6 mL of water followed by 0.2 ml of 2N aqueous NaOH. The reaction was filtered through diatomaceous earth, rinsed with ethyl acetate (50 mL) and concentrated. Silica gel chromatography over silica gel (Reveleris 40 g) eluting with a gradient of 0.75% to 7.5% methanol/dichloromethane over 30 minutes (flow = 40 ml/minutes) gave the title compound.

EXAMPLE 517C

3-chloro-N,N-bis(2,4-dimethoxybenzyl)-4-fluorobenzenesulfonamide

To a solution of bis(2,4-dimethoxybenzyl)amine (12 g) and 3-chloro-4-fluorobenzene-1-sulfonyl chloride (8.66 g) in dichloromethane (120 mL) was added N,N-diisopropylethylamine (13.5 mL) and catalytic amount of 4-dimethylaminopyridine. The mixture was stirred at room temperature overnight. The mixture was diluted with ethyl acetate (600 mL) and washed with 5% aqueous HCl, water and brine. After drying over Na_2SO_4, the mixture was filtered and the filtrate was concentrated under vacuum to give crude product which was loaded on a 400 g silica gel column and eluted with 30% ethyl acetate in hexane to give the title compound.

EXAMPLE 517D

3-chloro-N,N-bis(2,4-dimethoxybenzyl)-4-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)benzenesulfonamide

To a solution of EXAMPLE 517B (0.100 g) in tetrahydrofuran (3 mL) was added sodium hydride (0.042 g). After stirring for 15 minutes, EXAMPLE 517C (0.270 g) was added in one portion and the reaction stirred at room temperature for 16 hours then heated to 50°C for 2 hours. The reaction was cooled and quenched with water (20 mL) and extracted into dichloromethane (2 x 30 mL). The organics were combined, washed with brine (25 mL), dried over magnesium sulfate, filtered and concentrated. The resulting oil was loaded onto silica gel (Reveleris 40 g) and eluted using a gradient of 0.5% to 5% methanol/dichloromethane over 30 minutes (flow = 40 ml/minute) to give the title compound.

EXAMPLE 517E

3-chloro-4-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)benzenesulfonamide

To a solution of EXAMPLE 517D (0.258 g) in dichloromethane (3 mL) was added trifluoroacetic acid (2 mL) dropwise. The reaction was stirred for 1 hour then quenched by the addition of saturated $NaHCO_3$ solution (20 mL). The reaction was extracted with dichloromethane (2 x 50 mL), the dichloromethane layer was concentrated, ethyl acetate (20 mL) was added and the resulting solid was filtered. The organic layer was diluted to 50 ml, washed with brine (25 mL), dried over magnesium sulfate, filtered and concentrated. The resulting oil was treated with dichloromethane and concentrated,and the solid was triturated with ethyl acetate and filtered to give the title compound.

EXAMPLE 517F

The title compound was prepared by substituting EXAMPLE 498C for EXAMPLE 1E and EXAMPLE 517E for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 517G

N-[(3-chloro-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 517F for EXAMPLE 497B in EXAMPLE 497C. ^1H NMR (300 MHz, dimethylsulfoxide-d_6) δ 13.14 (d, 1H), 11.61 – 11.29 (m, 1H), 7.84 (d, 1H), 7.67 (d, 1H), 7.61 – 7.56 (m, 1H), 7.54 (d, 1H), 7.38 – 7.31 (m, 2H), 7.21 – 7.09 (m, 3H), 7.08 – 7.01 (m, 2H), 6.87 – 6.72 (m, 1H), 6.52 (d, 1H), 6.23 (dd, 1H), 4.55 (t, 2H), 4.45 (t, 2H), 4.24 (d, 2H), 3.55 – 3.41 (m, 1H), 3.16 (s, 4H), 2.80 (s, 2H), 2.69 – 2.54 (m, 2H), 2.38 – 1.67 (m, 14H), 1.40 (s, 2H), 0.93 (s, 6H).

EXAMPLE 518

N-({5-chloro-6-[(cis-1-fluoro-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 518A

5-chloro-6-((cis-1-fluoro-4-hydroxycyclohexyl)methoxy)pyridine-3-sulfonamide

To a solution of EXAMPLE 512D (336 mg) in tetrahydrofuran (10 mL) was added $NaBH_4$ (75 mg). The mixture was stirred at room temperature for 45 minutes. The mixture was diluted with ethyl acetate (300 mL) and washed with 2N aqueous NaOH, water, and brine. After drying over Na_2SO_4, the mixture was filtered, and the solvent was evaporated to give the crude product.

EXAMPLE 518B

N-({5-chloro-6-[(cis-1-fluoro-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 518A for EXAMPLE 493C in EXAMPLE 493D. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 12.94 (s, 1H), 8.17 (d, 1H), 7.82 (d, 1H), 7.71 (s, 1H), 7.66 (d, 1H), 7.35 (d, 2H), 7.04 (m, 5H), 6.71 (dd, 1H), 6.40 (d, 1H), 6.09 (m, 1H), 4.61 (d, 1H), 4.38 (d, 2H), 3.47 (m, 1H), 3.17 (d, 1H), 3.06 (m, 4H), 2.74 (m, 2H), 2.24 (m, 5H), 1.99 (m, 5H), 1.56 (m, 7H), 0.92 (m, 6H)

EXAMPLE 519

2-(1H-benzotriazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)benzamide

EXAMPLE 519A

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-3-nitrophenylsulfonyl)-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d][1,2,3]triazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 514F for EXAMPLE 1E and EXAMPLE 306D for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE519B

2-(1H-benzotriazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 519A for EXAMPLE 498D in EXAMPLE 498E. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 8.04 (d, 1H), 7.73 (d, 1H), 7.65 (d, 1H), 7.35-7.38 (m, 3H), 7.18-7.19 (m, 1H), 7.05-7.09 (m, 3H), 6.78 (dd, 1H), 6.52 (s, 1H), 6.32 (s, 1H), 4.34 (d, 2H), 3.78-3.82 (m, 2H), 3.59-3.64 (m, 2H), 3.23 (br s, 4H), 2.83 (br s, 2H), 2.18-2.30 (m, 6H), 1.82-1.98 (m, 6H), 1.41 (t, 2H), 0.94 (s, 6H).

EXAMPLE 520

N-[(5-chloro-6-{[(1R,2R,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 520A

(1R,4S)-methyl spiro[bicyclo[2.2.1]heptane-2,2'-[1,3]dioxolane]-5-carboxylate

A mixture of 1,4-dioxaspiro[4.4]non-6-ene (5 g), methyl acrylate (10.24 g), and hydroquinone (0.13 g) was heated in an autoclave at 100 °C in acetonitrile (12 mL) for three days. After cooling, the solvent was removed, and residue was purified by flash chromatography on silica gel eluting with 4:1 hexane/ethyl acetate to give the title compound as a mixture of two 5-isomers.

EXAMPLE 520B

(1R,4S)-spiro[bicyclo[2.2.1]heptane-2,2'-[1,3]dioxolane]-5-ylmethanol

EXAMPLE 520A (1.0 g) in tetrahydrofuran was cooled to 0 °C. To this solution was added 1.0 N lithium aluminum hydride (2.8 mL) dropwise. The reaction mixture was stirred for 2 hours. Water (0.4 mL) was added followed by 2 N aqueous NaOH (0.2 mL). The solid was filtered off, and the filtrate was concentrated. Toluene was added, and it was then distilled off to move trace amounts of water. The title compound was used for the next reaction without further purification.

EXAMPLE 520C

5-chloro-6-(((1S,2R,4R)-5-oxobicyclo[2.2.1]heptan-2-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 520B for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 387A for EXAMPLE 329A in EXAMPLE 329B.

The two isomers were isolated by reverse phase Prep HPLC. The desired fractions were collected, and the solvents were removed under reduced vacuum at 60°C. During this process, a lot of solid formed. It was then partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with additional ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated to give the desired ketone.

EXAMPLE 520D

5-chloro-6-(((1S,2R,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]heptan-2-yl)methoxy)pyridine-3-sulfonamide

EXAMPLE 520C (0.44 g) in tetrahydrofuran (15 mL) was treated with 3.0 M methylmagnesium bromide (5.3 mL) at 0 °C. The mixture was stirred for 16 hours. The reaction mixture was then partitioned between ethyl acetate and 0.05 N aqueous HCl (20 mL). The organic layer was separated, and the aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel using 10-50% ethyl acetate in hexanes as eluent to give the title compound.

EXAMPLE 520E

N-[(5-chloro-6-{[(1R,2R,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 400E for EXAMPLE 1E and EXAMPLE 520D for EXAMPLE 1F in EXAMPLE 1G. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 13.10 (s, 1H), 8.28 (d, 1H), 7.84 (d, 1H), 7.82 (s, 1H), 7.59 (d, 1H), 7.36 (d, 2H), 7.04-7.11 (m, 4H), 6.80 (dd, 1H), 6.54 (d, 1H), 6.14 (d, 1H), 4.41-4.46 (m, 2H), 4.35 (s, 1H), 3.20 (br s, 4H), 2.93 (br s, 2H), 2.31-2.37 (m, 4H), 2.17-2.02 (m, 4H), 1.98-1.99 (m, 2H), 1.89 (d, 1H), 1.68-1.71 (m, 1H), 1.56 (d, 1H), 1.31-1.48 (m, 7H), 1.20 (s, 6H), 0.94 (s, 6H).

EXAMPLE 521

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 521A

ethyl 5,5-difluoro-2-oxocyclohexanecarboxylate

To a solution of diethyl 4,4-difluoroheptanedioate (4.3 g) in toluene (50 mL) was added potassium 2-methylpropan-2-olate (2.87 g) and the reaction stirred overnight at room temperature. The reaction was quenched with 1N aqueous HCl (100 mL) and extracted with diethyl ether (150 mL). The ether layer was washed with brine (50 mL), dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (Reveleris 40 g) eluting with a gradient of 1% to 5% ethyl acetate/hexanes gave the title compound.

EXAMPLE 521B

ethyl 5,5-difluoro-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

To a solution of EXAMPLE 521A (2.37 g) in dichloromethane (40 mL) at 0°C was added N,N-diisopropylethylamine (5.02 mL) followed by trifluoromethanesulfonic anhydride (2.33 mL) and the reaction was allowed to slowly warm to room temperature. After stirring overnight the reaction was quenched with 10 ml of water then 1N aqueous HCl (100 mL). The reaction was extracted with dichloromethane (3 x 75 mL), the combined organics were washed with brine (50 mL) and concentrated. Silica gel chromatography (Reveleris 40 g) eluting with a gradient of 1% to 25% ethyl acetate/hexanes gave the title compound.

EXAMPLE 521C

ethyl 2-(4-chlorophenyl)-5,5-difluorocyclohex-1-enecarboxylate

A solution of EXAMPLE 521B (3.47 g), 4-chlorophenylboronic acid (1.925 g) and cesium fluoride (3.43 g) in 30 ml of dimethoxyethane and 15 ml of ethanol was degassed with nitrogen for 5 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.237 g) was added and the reaction was heated to 70°C. The reaction was diluted with ether (200 mL) and washed with 1N aqueous HCl (100 mL), brine (100 mL), dried over magnesium sulfate, filtered and concentrated. Silica gel chromatography (Reveleris 40 g) eluting with a gradient of 1% to 8% ethyl acetate/hexanes over 40 minutes gave the title compound.

EXAMPLE 521D

(2-(4-chlorophenyl)-5,5-difluorocyclohex-1-enyl)methanol

To a solution of EXAMPLE 521C (1.84 g) in diethyl ether (25 mL) at 0°C was added lithium aluminum hydride (1.0M, 4.28 mL). The reaction was quenched with the dropwise addition of water, then 1N aqueous HCl (50 mL) was added and the reaction was diluted with diethyl ether (100 mL). The organic layer was separated, washed with brine (50 mL) dried over magnesium sulfate, filtered, and concentrated to give the title compound.

EXAMPLE 521E

2-(4-chlorophenyl)-5,5-difluorocyclohex-1-enecarbaldehyde

To a solution of EXAMPLE 521D (1.38 g) in dichloromethane (25 mL) was added Dess-Martin periodinane (2.489 g) and the reaction stirred for 1 hour at room temperature. The reaction was quenched with 1N aqueous NaOH solution (75 mL) and the product extracted into dichloromethane (2 x 100 mL). The combined organics were washed with brine (75 mL), dried over magnesium sulfate, filtered and concentrated. Silica gel chromatography (Reveris 80 g) eluting with a gradient of 1% to 10% ethyl acetate/hexanes over 40 minutes gave the title compound.

EXAMPLE 521F

methyl 2-(1H-indazol-4-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-difluorocyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

To a solution of EXAMPLE 521E (1.05 g) in dichloromethane (10 mL) was added EXAMPLE 400C (1.31 g) followed by sodium triacetoxyhydroborate (1.18 g) and the reaction was stirred overnight at room temperature. The reaction was quenched with saturated $NaHCO_3$ (50 mL) and extracted with dichloromethane (2 x 100 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (Reveleris 80 g) eluting with a gradient of 0.5% to 5% methanol/dichloromethane over 40 minutes gave the title compound.

EXAMPLE 521G

methyl 4-(4-((2-(4-chlorophenyl)-5,5-difluorocyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-trityl-1H-indazol-4-yloxy)benzoate

To a solution of EXAMPLE 521F (1.81 g) and triethylamine (0.85 mL) in dichloromethane (10 mL) was added trityl-chloride (1.06 g) and the reaction stirred at room

temperature. After stirring for 16 hours the reaction was loaded onto silica gel (Reveleris 80 g) and eluted using a gradient of 0.1% to 1.5% methanol/dichloromethane over 40 minutes (flow = 40 ml/min) to give the title compound.

EXAMPLE 521H

4-(4-((2-(4-chlorophenyl)-5,5-difluorocyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-trityl-1H-indazol-4-yloxy)benzoic acid

To a solution of EXAMPLE 521G (2.51 g) in tetrahydrofuran (30 mL) and methanol (10 mL) was added lithium hydroxide (1.0M, 10 mL) and the solution heated to 60°C. After 4 hours the reaction was cooled, diluted with dichloromethane (150 mL) and quenched with 1N aqueous HCl (10 mL) and water (30 mL). The organic layer was washed with brine (50 mL), dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (Reveleris 120 g) eluting with a gradient of 0.25% to 2.5% methanol/dichloromethane over 40 minutes gave the title compound.

EXAMPLE 521I

N-(5-chloro-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridin-3-ylsulfonyl)-4-(4-((2-(4-chlorophenyl)-5,5-difluorocyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-trityl-1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 521H for EXAMPLE 1E and EXAMPLE 404A for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 521J

2-(1H-indazol-4-yloxy)-N-(5-chloro-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridin-3-ylsulfonyl)-4-(4-((2-(4-chlorophenyl)-5,5-difluorocyclohex-1-enyl)methyl)piperazin-1-yl)benzamide

To a solution of EXAMPLE 521I (0.24 g) dichloromethane (1 mL) was added trifluoroacetic acid (0.5 mL). After stirring for 1 hour, the reaction was concentrated, dissolved in dichloromethane (5 mL) and quenched with saturated $NaHCO_3$ (5 mL). The reaction was diluted with water (10 mL) and saturated $NaHCO_3$ (15 mL) and the product extracted into dichloromethane (2 x 25 mL). The combined organics were washed with brine (25 mL), dried over magnesium sulfate, filtered, and concentrated. The residue was loaded onto silica gel (Reveleris 40 g) and eluted using a gradient of 0.5% to 3% methanol/dichloromethane over 30 minutes (flow = 40 ml/minutes). The product was

collected, concentrated, dissolved in acetonitrile and concentrated, and dried in vacuum oven at 75°C overnight to give the title compound. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 13.12 (s, 1H), 12.24 - 11.44 (m, 1H), 8.31 (d, 1H), 7.91 (d, 1H), 7.83 (s, 1H), 7.57 (d, 1H), 7.40 (d, 2H), 7.13 (d, 4H), 6.81 (dd, 1H), 6.56 (d, 1H), 6.16 (dd, 1H), 4.52 (d, 2H), 3.79 (dt, 2H), 3.70 - 3.51 (m, 2H), 3.20 (s, 4H), 2.76 (dd, 4H), 2.49 (m, 8H), 2.02 - 1.71 (m, 4H).

EXAMPLE 522

N-[(5-chloro-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 522A

5-chloro-6-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 387A for EXAMPLE 329A and EXAMPLE 517B for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 329B.

EXAMPLE 522B

N-(5-chloro-6-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)pyridin-3-ylsulfonyl)-4-(4-((2-(4-chlorophenyl)-5,5-difluorocyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-trityl-1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 521H for EXAMPLE 1E and EXAMPLE 522A for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 522C

2-(1H-indazol-4-yloxy)-N-(5-chloro-6-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)pyridin-3-ylsulfonyl)-4-(4-((2-(4-chlorophenyl)-5,5-difluorocyclohex-1-enyl)methyl)piperazin-1-yl)benzamide

The title compound was prepared by substituting EXAMPLE 522B for EXAMPLE 521I in EXAMPLE 521J. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 13.10 (s, 1H), 11.54 (s, 1H), 8.29 (d, 1H), 7.90 (d, 1H), 7.81 (s, 1H), 7.58 (d, 1H), 7.40 (d, 2H), 7.13 (d, 4H), 6.80 (dd, 1H), 6.53 (d, 1H), 6.15 (dd, 1H), 4.53 (d, 6H), 3.60 (s, 1H), 3.18 (s, 4H), 2.74 (dd, 8H), 2.41 - 1.70 (m, 12H).

EXAMPLE 523

2-(1H-benzotriazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 523A

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)phenylsulfonyl)-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d][1,2,3]triazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 514F for EXAMPLE 1E in EXAMPLE 1G.

EXAMPLE 523B

2-(1H-benzotriazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 523A for EXAMPLE 498D in EXAMPLE 498E. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 8.51 (s, 1H), 8.30 (d, 1H), 7.57-7.59 (m, 2H), 7.33-7.38 (m, 3H), 7.04-7.10 (m, 3H), 6.90 (d, 1H), 6.79 (dd, 1H), 6.52 (d, 1H), 6.39 (d, 1H), 3.87 (dd, 2H), 3.143 (br s, 4H), 2.78 (br s, 2H), 2.17-2.23 (m, 6H), 1.88-1.97 (m, 3H), 1.63-1.66 (m, 2H), 1.40 (t, 2H), 1.23-1.32 (m, 2H), 0.93 (s, 6H).

EXAMPLE 524

4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 524A

4-(4-((2-(4-chlorophenyl)-5,5-difluorocyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)phenylsulfonyl)-2-(1-trityl-1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 521H for EXAMPLE 1E in EXAMPLE 1G.

EXAMPLE 524B

2-(1H-indazol-4-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-difluorocyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)phenylsulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 524A for EXAMPLE 521I in EXAMPLE 521J. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 13.10 (d, 1H), 11.63 (s, 1H), 8.57 (t, 1H), 8.38 (d, 1H), 7.81 (d, 1H), 7.52 (d, 2H), 7.39 (d, 2H), 7.11 (dd, 4H), 7.00 (d, 1H), 6.80 (dd, 1H), 6.52 (d, 1H), 6.20 (dd, 1H), 3.86 (dd, 2H), 3.29 (d, 4H), 3.16 (s, 4H), 2.83 - 2.60 (m, 4H), 2.49 (s, 2H), 2.34 - 2.01 (m, 6H), 1.89 (dd, 1H), 1.63 (d, 2H), 1.27 (qd, 2H).

EXAMPLE 525

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 525A

tert-butyl (4-hydroxy-4-methylcyclohexyl)methylcarbamate

To a vigorous stirring solution of tert-butyl (4-oxocyclohexyl)methylcarbamate (1.7 g) in tetrahydrofuran (40 mL) at -78°C was dropwise added 1.6 M methyllithium (14.02 mL) in ether. After completion of the addition, the mixture was stirred at -78°C for 1.2 hours and poured into a cold aqueous NH_4Cl solution. The resulting mixture was extracted with dichloromethane (3x 100 mL) and the organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in dichloromethane and loaded onto an Analogix purification system, and was eluted with 0 - 50% ethyl acetate in dichloromethane to provide the title compound.

EXAMPLE 525B

4-(aminomethyl)-1-methylcyclohexanol

EXAMPLE 525A (1.3 g) in dichloromethane (5 mL) at 0°C was treated with trifluoroacetic acid (2.1 mL) and a few drops of water for 1 hours. The reaction mixture was concentrated and the residue was directly used for next step.

EXAMPLE 525C

4-((trans-4-hydroxy-4-methylcyclohexyl)methylamino)-3-nitrobenzenesulfonamide

EXAMPLE 525B (732 mg) and 4-fluoro-3-nitrobenzenesulfonamide (1.1 g) in tetrahydrofuran (15 mL) were treated with triethylamine overnight. The reaction mixture was concentrated and the residue was purified by a reverse phase chromatography, eluting with 30% - 50% acetonitrile in 0.1% trifluoroacetic acid water solution to provide the title compound.

EXAMPLE 525D

4-((cis-4-hydroxy-4-methylcyclohexyl)methylamino)-3-nitrobenzenesulfonamide

EXAMPLE 525B (732 mg) and 4-fluoro-3-nitrobenzenesulfonamide (1.1 g) in tetrahydrofuran (15 mL) were treated with triethylamine overnight. The reaction mixture was concentrated and the residue was purified by a reverse phase chromatography, eluting with 30% - 50% acetonitrile in 0.1% trifluoroacetic acid water solution to provide the title compound.

EXAMPLE 525E

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 177 by replacing EXAMPLE 26C and EXAMPLE 1F with EXAMPLE 400E and EXAMPLE 525C, respectively. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 13.10 (s, 1H), 11.54 (s, 1H), 8.53 (t, 1H), 8.37 (d, 1H), 7.82 (s, 1H), 7.48 - 7.58 (m, 2H), 7.32 - 7.39 (m, 2H), 7.02 - 7.11 (m, 4H), 6.95 (d, 1H), 6.80 (dd, 1H), 6.52 (d, 1H), 6.17 (dd, 1H), 4.25 (s, 1H), 3.26 - 3.31 (m, 2H), 3.17 (s, 4H), 2.80 (s, 2H), 2.21 (d, 6H), 1.97 (s, 2H), 1.60 - 1.75 (m, 3H), 1.56 (d, 2H), 1.30 - 1.43 (m, 4H), 1.08 - 1.19 (m, 5H), 0.93 (s, 6H).

EXAMPLE 526

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 177 by replacing EXAMPLE 26C and EXAMPLE 1F with EXAMPLE 400E and EXAMPLE 525D, respectively. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 13.11 (d, 1H), 11.55 (s, 1H), 8.56 (t, 1H), 8.37 (d, 1H), 7.81 (s, 1H), 7.50 - 7.55 (m, 2H), 7.33 - 7.38 (m, 2H), 7.04 - 7.13 (m, 4H), 6.95 (d, 1H), 6.80 (dd, 1H), 6.52 (d, 1H), 6.17 (d, 1H), 3.97 (s, 1H), 3.26 (t, 2H), 3.16 (s, 4H), 2.79 (s, 2H), 2.20 (d, 6H), 1.97 (s, 2H), 1.46 - 1.61 (m, 5H), 1.35 - 1.45 (m, 4H), 1.19 - 1.30 (m, 2H), 1.09 (s, 3H), 0.93 (s, 6H).

EXAMPLE 527

2-(1H-benzotriazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S)-4-cyclopropylmorpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide

EXAMPLE 527A

(S)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(4-((4-cyclopropylmorpholin-2-yl)methylamino)-3-nitrophenylsulfonyl)-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d][1,2,3]triazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 514F for EXAMPLE 1E and EXAMPLE 529A for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 527B

2-(1H-benzotriazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S)-4-cyclopropylmorpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide

The title compound was prepared by substituting EXAMPLE 527A for EXAMPLE 498D in EXAMPLE 498E. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 8.56 (s, 1H), 8.31 (s, 1H), 7.55-7.60 (m, 2H), 7.34-7.38 (m, 3H), 7.04-7.10 (m, 3H), 6.92 (d, 1H), 6.80 (dd, 1H), 6.53 (d, 1H), 6.38 (d, 1H), 3.84 (d, 1H), 3.55 (m, 1H), 3.41-3.54 (m, 6H), 3.17 (m, 4H), 2.74-2.94 (m, 6H), 2.15-2.36 (m, 10H), 1.97 (s, 2H), 1.69 (t, 2H), 1.40 (t, 2H), 0.94 (s, 6H), 0.35-0.44 (m, 4H).

EXAMPLE 528

N-[(5-chloro-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 528A

N-(5-chloro-6-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)pyridin-3-ylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-trityl-1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 522A for EXAMPLE 1F and EXAMPLE 498C for EXAMPLE 1E in EXAMPLE 1G.

EXAMPLE 528B

N-[(5-chloro-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 528A for EXAMPLE 542E in EXAMPLE 542F. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 13.08 (s, 1H), 8.26 (d, 1H), 7.88 (d, 1H), 7.79 (m, 1H), 7.60 (d, 1H), 7.37 (d, 2H), 7.07 (m, 4H), 6.79 (dd, 1H), 6.53 (d, 1H), 6.13 (d, 1H), 4.57 (t, 2H), 4.52 (s, 1H), 4.47 (m, 3H), 3.55 (m, 2H), 3.18 (m, 4H), 2.94 (m, 2H), 2.67 (m, 2H), 2.38 (m, 3H), 2.18 (m, 4H), 1.97 (m, 5H), 1.80 (m, 1H), 1.41 (t, 2H), 0.94 (s, 6H).

EXAMPLE 529

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S)-4-cyclopropylmorpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 529A

(S)-4-((4-cyclopropylmorpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 438B for EXAMPLE 415B in EXAMPLE 432A.

EXAMPLE 529B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S)-4-cyclopropylmorpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 400E for EXAMPLE 26C and EXAMPLE 529A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500MHz, pyridine-d_5) δ 14.58 (bs, 1H), 9.05 (d, 1H), 8.87 (t, 1H), 8.37 (s, 1H), 8.16 (dd, 1H), 8.08 (d, 1H), 7.45 (d, 2H), 7.34 (d, 1H), 7.15 (t, 1H), 7.10 (d, 2H), 6.90-6.80 (m, 3H), 6.52 (d, 1H), 3.90-3.81 (m, 2H), 3.57 (dt, 1H), 3.50-3.42 (m, 2H), 3.15 (m, 4H), 2.93 (m, 1H), 2.82 (s, 2H), 2.71 (m, 1H), 2.31 (dt, 1H), 2.30 (m, 2H), 2.22 (m, 4H), 2.21 (m, 1H), 1.99 (s, 2H), 1.58 (m, 1H), 1.41 (t, 2H), 0.96 (s, 6H), 0.40 (m, 4H).

EXAMPLE 530

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S)-4-cyclopropylmorpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide

The title compound was prepared by substituting EXAMPLE 529A for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (500MHz, pyridine-d_5) δ 9.25 (d, 1H), 8.90 (t, 1H), 8.57 (s, 1H), 8.37 (dd, 1H), 7.99 (d, 1H), 7.53 (d, 1H), 7.43 (d, 2H), 7.24 (d, 1H), 7.17 (d, 1H), 7.07 (d, 2H), 6.97 (d, 1H), 6.73-6.68 (m, 2H), 3.92-3.85 (m, 2H), 3.59 (dt, 1H), 3.50-3.40 (m, 2H), 3.02 (m, 4H), 2.95 (d, 1H), 2.76 (s, 2H), 2.69 (d, 1H), 2.36 (dt, 1H), 2.20-2.20 (m, 3H), 2.14 (m, 4H), 1.97 (s, 2H), 1.59 (m, 1H), 1.38 (t, 2H), 0.93 (s, 6H), 0.41 (m, 4H).

EXAMPLE 531

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 531A

ethyl 1,4-dioxaspiro[4.5]decane-8-carboxylate

To a solution of ethyl 4-oxocyclohexanecarboxylate (31.8 g) in toluene (100 mL) was added ethylene glycol (36.5 mL) and p-toluenesulfonic acid monohydrate (0.426 g). The two phase mixture was stirred rapidly at ambient temperature for 72 hours. The reaction was

diluted with water (900 mL) and extracted with ether (900 mL). The organic layer was washed with saturated sodium bicarbonate solution and brine, and then dried over anhydrous sodium sulfate. After filtration, the title compound was obtained by concentration of the filtrate under high vacuum.

EXAMPLE 531B

1,4-dioxaspiro[4.5]decan-8-ylmethanol

To a suspension of lithium aluminum hydride (8.19 g) in tetrahydrofuran (400 mL) was added slowly dropwise a solution of EXAMPLE 531A (37.8 g) in tetrahydrofuran (75 mL). The mixture was then heated at reflux for 2 hours. The reaction mixture was cooled in an ice bath and quenched very slowly with water (8 mL). Then added sequentially were 4N aqueous sodium hydroxide (8 mL), ether (200 mL), water (24 mL), ether (500 mL) and anhydrous sodium sulfate (250 g). The resulting mixture was stirred rapidly for 2 hours and then filtered. The title compound was isolated by concentration of the filtrate.

EXAMPLE 531C

8-(benzyloxymethyl)-1,4-dioxaspiro[4.5]decane

To a suspension of sodium hydride (60% oil dispersion) (8.86 g) in tetrahydrofuran (170 mL) was added a solution of EXAMPLE 531B (30.52 g) in tetrahydrofuran (100 mL). This mixture was stirred for 30 minutes and benzyl bromide (24 mL) was added. After stirring for 72 hours, the reaction was quenched with saturated aqueous ammonium chloride solution (400 mL) and diluted with ether (500 mL). The layers were separated and the aqueous layer was extracted with ether (2 X 150 mL). The combined organics were dried over sodium sulfate, filtered and concentrated. The crude product was purified on silica gel eluting with a 0, 10, 15, 75 % ethyl acetate in hexanes step gradient to give the title compound.

EXAMPLE 531D

4-(benzyloxymethyl)cyclohexanone

To a solution of EXAMPLE 531C (43.02 g) in dioxane (500 mL) was added water (125 mL) and 2M hydrochloric acid (90 mL). The mixture was heated at 85 °C for 18 hours. Upon cooling, the reaction mixture was diluted with brine (1500 mL), saturated sodium bicarbonate solution (300 mL) and ether (1000 mL). The organic layer was dried over sodium sulfate, filtered and concentrated. The crude product was purified on silica gel

eluting with a 5, 15, 25, 50% ethyl acetate in hexanes step gradient to give the title compound.

EXAMPLE 531E

trans-4-(benzyloxymethyl)-1-methylcyclohexanol

To 2,6-di-t-butyl-4-methylphenol (83.4 g) in toluene (1100 mL) was added 2.0M (in hexanes) $(CH_3)_3Al$ (95 mL) somewhat carefully to control methane evolution and a small exotherm. The reaction mixture was stirred at ambient temperature under N_2 for 75 minutes and was then cooled to -77° C. A solution of EXAMPLE 531D (14 g) in toluene (15 mL) was added dropwise, keeping the temperature below -74 °C. Methyllithium (1.6M in diethyl ether) (120 mL) was then added dropwise, keeping the temperature below -65 °C. The resulting mixture was stirred at -77 °C under N_2 for 2 hours. The reaction mixture was then poured into 1N aqueous HCl (1600 mL), rinsing the flask with toluene. The organic layer was washed with brine and the combined aqueous layers were extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The concentrate was chromatographed on 650 g of spherical silica gel using 2.5 L of 80/20 hexanes/ethyl acetate, then 3.0 L of 75/25 hexanes/ethyl acetate, and finally 4.0 L of 70/30 hexanes/ethyl acetate as the eluents to give the title compound.

EXAMPLE 531F

trans-4-(hydroxymethyl)-1-methylcyclohexanol

EXAMPLE 531E (12.6 g) and ethanol (120 mL) were added to wet 20% $Pd(OH)_2/C$ (1.26 g) in a 500 mL SS pressure bottle. The reaction mixture was stirred at ambient temperature under 30 psi hydrogen gas. Hydrogen uptake ceased at 5 minutes. The mixture was filtered through a nylon membrane rinsing with ethanol. The filtrate was concentrated and then azeotroped with toluene (100 mL) to remove any remaining ethanol. The concentrate was dried under high vacuum for 40 minutes to give the title compound.

EXAMPLE 531G

5-chloro-6-((trans-4-hydroxy-4-methylcyclohexyl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 387A for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 531F for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 279A.

EXAMPLE 531H

N-(5-chloro-6-((trans-4-hydroxy-4-methylcyclohexyl)methoxy)pyridin-3-ylsulfonyl)-4-(4-((2-(4-chlorophenyl)-5,5-difluorocyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-trityl-1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 521H for EXAMPLE 1E and EXAMPLE 531G for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 531I

2-(1H-indazol-4-yloxy)-N-(5-chloro-6-((trans-4-hydroxy-4-methylcyclohexyl)methoxy)pyridin-3-ylsulfonyl)-4-(4-((2-(4-chlorophenyl)-5,5-difluorocyclohex-1-enyl)methyl)piperazin-1-yl)benzamide

The title compound was prepared by substituting EXAMPLE 531H for EXAMPLE 521I in EXAMPLE 521J. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 13.13 (s, 1H), 12.05 - 11.55 (m, 1H), 8.29 (d, 1H), 7.92 - 7.78 (m, 2H), 7.56 (d, 1H), 7.47 - 7.33 (m, 2H), 7.19 - 6.98 (m, 4H), 6.82 (dd, 1H), 6.56 (d, 1H), 6.16 (dd, 1H), 4.25 (d, 3H), 3.20 (s, 4H), 2.72 (s, 4H), 2.48 - 2.40 (m, 2H), 2.41 - 2.03 (m, 6H), 1.76 (s, 3H), 1.54 (s, 2H), 1.38 (m, 2H), 1.21 (m, 2H), 1.11 (s, 3H).

EXAMPLE 532

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 532A

4-((cis-4-hydroxy-4-methylcyclohexyl)methoxy)-3-nitrobenzenesulfonamide

EXAMPLE 493A (732 mg) and 4-fluoro-3-nitrobenzenesulfonamide (1.2 g) in tetrahydrofuran (40 mL) were treated with 60% sodium hydride (1.6 g) for 3 days. The reaction was quenched with water. The resulting mixture was neutralized with diluted aqueous HCl, and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by a reverse phase chromatography, eluting with 30-50% acetonitrile in 0.1% trifluoroacetic acid water to provide the title compound.

EXAMPLE 532B

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(4-((cis-4-hydroxy-4-methylcyclohexyl)methoxy)-3-nitrophenylsulfonyl)-2-(1-trityl-1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 532A for EXAMPLE 1F and EXAMPLE 498C for EXAMPLE 1E in EXAMPLE 1G.

EXAMPLE 532C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 532B for EXAMPLE 542E in EXAMPLE 542F. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 13.09 (s, 1H), 8.10 (m, 1H), 7.81 (s, 1H), 7.78 (dd, 1H), 7.56 (d, 1H), 7.36 (d, 2H), 7.28 (d, 1H), 7.11 (m, 2H), 7.06 (d, 2H), 6.80 (dd, 1H), 6.52 (d, 1H), 6.17 (dd, 1H), 4.02 (d, 2H), 3.96 (s, 1H), 3.18 (m, 4H), 2.86 (m, 2H), 2.17 (m, 2H), 1.98 (m, 3H), 1.69 (m, 2H), 1.55 (m, 4H), 1.41 (m, 5H), 1.29 (m, 3H), 1.11 (s, 3H), 0.94 (m, 6H).

EXAMPLE 533

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 533A

4-((trans-4-hydroxy-4-methylcyclohexyl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 531F for (tetrahydro-2H-pyran-4-yl)methanol and 4-fluoro-3-nitrobenzenesulfonamide for EXAMPLE 329A in EXAMPLE 329B.

EXAMPLE 533B

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(4-((trans-4-hydroxy-4-methylcyclohexyl)methoxy)-3-nitrophenylsulfonyl)-2-(1-trityl-1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 533A for EXAMPLE 1F and EXAMPLE 498C for EXAMPLE 1E in EXAMPLE 1G.

EXAMPLE 533C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 533B for EXAMPLE 542E in EXAMPLE 542F. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 13.11 (s, 1H), 8.11 (m, 1H), 7.81 (m, 2H), 7.57 (dd, 1H), 7.36 (d, 2H), 7.28 (m, 1H), 7.11 (m, 2H), 7.06 (d, 2H), 6.80 (dd, 1H), 6.52 (d, 1H), 6.18 (d, 1H), 4.27 (s, 1H), 4.06 (d, 2H), 3.16 (m, 4H), 2.81 (m, 2H), 2.20 (m, 4H), 1.98 (m, 2H), 1.74 (m, 3H), 1.57 (m, 2H), 1.40 (m, 4H), 1.24 (m, 3H), 1.11 (s, 3H), 0.94 (s, 6H).

EXAMPLE 534

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-cyano-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 534A

3-cyano-4-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)benzenesulfonamide

To a solution of EXAMPLE 517B (0.185 g) in tetrahydrofuran (5 mL) was added sodium hydride (0.090 g). After 30 minutes, 3-cyano-4-fluorobenzenesulfonamide (0.178 g) was added in one portion. The reaction was stirred at room temperature for 2 hours. The reaction was quenched with 1N aqueous HCl (4 mL), diluted with dichloromethane (30 mL) and saturated aqueous $NaHCO_3$ (25 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. The resulting solid material was triturated with dichloromethane and filtered to give the title compound.

EXAMPLE 534B

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-cyano-4-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)phenylsulfonyl)-2-(1-trityl-1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 521H for EXAMPLE 1E and EXAMPLE 534A for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 534C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-cyano-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 534B for EXAMPLE 521I in EXAMPLE 521J. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 13.11 (s, 1H), 11.64 - 11.28 (m, 1H), 7.95 - 7.75 (m, 3H), 7.56 (d, 1H), 7.44 - 7.26 (m, 2H), 7.22 (d, 1H), 7.09 (ddd, 4H), 6.81 (s, 1H), 6.52 (d, 1H), 6.18 (dd, 1H), 4.51 (dt, 4H), 4.33 (d, 2H), 3.50 (s, 1H), 3.18 (s, 8H), 2.49 - 1.68 (m, 14H), 1.42 (d, 2H), 0.94 (s, 6H).

EXAMPLE 535

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-{[3-nitro-4-(2-oxaspiro[3.5]non-7-ylmethoxy)phenyl]sulfonyl}benzamide

EXAMPLE 535A

diethyl 1,4-dioxaspiro[4.5]decane-8,8-dicarboxylate

A 500 mL round-bottomed flask was charged with diisopropylamine (16 mL) and tetrahydrofuran (311 mL). The solution was cooled to -78°C under N_2 and n-BuLi (2.5 M in hexanes, 44.8 mL) was added. The reaction was stirred for 30 minutes at -78 °C and ethyl 1,4-dioxaspiro[4.5]decane-8-carboxylate (20 g) was added as a tetrahydrofuran solution (ca. 10 mL). The solution was stirred at -78 °C for 1 hour and ethyl chloroformate (9 mL) was added neat. After stirring at -78 °C for 10 minutes, the reaction was warmed to room temperature over 2 hours. The reaction was quenched with saturated aqueous NH_4Cl and diluted with diethyl ether. The layers were separated, the aqueous layer was extracted with diethyl ether and the combined organics were dried (Na_2SO_4), filtered and concentrated by rotary evaporation. The residue was purified by regular phase flash column chromatography (Analogix, 0-65% hexanes / ethyl acetate).

EXAMPLE 535B

1,4-dioxaspiro[4.5]decane-8,8-diyldimethanol

To a 1 L round-bottomed flask was added EXAMPLE 535A (26.6 g) and tetrahydrofuran (310 mL). The solution was cooled to 0°C and lithium aluminum hydride (2M in tetrahydrofuran, 62 mL) was added via syringe. The reaction was allowed to warm to room temperature and stirred overnight. The mixture was cooled back down to 0°C, quenched slowly with 4.7 mL water, 4.7 ml 10% aqueous NaOH and 14 mL water, and allowed to stir until salts were formed and then the mixture was filtered through a Supelco 90 mm silica gel Buchner funnel. The filtrate was concentrated by rotary evaporation and the residue was purified by regular phase flash column chromatography (Analogix, 0-80% hexanes / ethyl acetate).

EXAMPLE 535C

2,8,11-trioxadispiro[3.2.4.2]tridecane

To a 1 L round-bottomed flask was added EXAMPLE 535B (13 g) in tetrahydrofuran (321 mL). The solution was cooled to -78°C under N_2 and n-butyllithium (25.7 mL) was added dropwise via syringe. After the addition was complete, the reaction was stirred for 30 minutes and a tetrahydrofuran solution of toluene-2-sulfonyl chloride (12.25 g) was added via addition funnel. The reaction was allowed to stir overnight, gradually warming to room temperature. The reaction was recooled to -78 °C and n-butyllithium (25.7mL) was added. The reaction was allowed to warm to room temperature and stirred for 3 hours. The reaction was quenched with saturated aqueous NH_4Cl and diluted with diethyl ether. The layers were separated, the aqueous layer was extracted with diethyl ether and the combined organics were dried (Na_2SO_4), filtered and concentrated by rotary evaporation. The residue was purified by regular phase flash column chromatography (Analogix, 0-20% acetone / hexanes).

EXAMPLE 535D

2-oxaspiro[3.5]nonan-7-one

To a 500 mL round-bottomed flask was added EXAMPLE 535C (11 g) in 80 % acetic acid (200 mL). The reaction was heated to 65°C and stirred for about 4 hours. Most of the acetic acid and water were removed by rotary evaporation and the residue was purified by regular phase flash column chromatography (Analogix, 0-65% hexanes/ethyl acetate).

EXAMPLE 535E

7-methylene-2-oxaspiro[3.5]nonane

To a 250 mL round-bottomed flask was added methyltriphenylphosphonium iodide (4.33 g) in tetrahydrofuran (35.7 mL). The suspension was cooled to -15°C. n-Butyllithium (2.5 M in hexanes, 4.28 mL) was added dropwise. The mixture was stirred at -15°C for 40 minutes and EXAMPLE 535D (1 g) was added as a tetrahydrofuran (ca. 5 mL) solution. The mixture was stirred at -15°C for about 15 minutes and warmed to room temperature. After 1.5 hours the reaction was complete and was quenched with saturated aqueous NH_4Cl and diluted with diethyl ether. The layers were separated and the aqueous layer was extracted (2x) with diethyl ether. The combined organics were washed with brine, dried (Na_2SO_4), filtered and concentrated by rotary evaporation. The residue was purified by regular phase chromatography (Analogix, 0-50% hexanes/ethyl acetate).

EXAMPLE 535F

2-oxaspiro[3.5]nonan-7-ylmethanol

To a 25 mL round-bottomed flask was added EXAMPLE 535E (568 mg) and tetrahydrofuran (4.11 mL). 9-Borabicyclo[3.3.1]nonane (0.5 M in tetrahydrofuran, 24.7 mL) was added and the reaction was allowed to stir for 2 hours at room temperature. Ethanol (11 mL) was added followed by aqueous NaOH (5M, 4.11 mL) and then 30% hydrogen peroxide (2.1 mL) was added. The reaction was heated at 50°C for 2 hours. Most of the ethanol and tetrahydrofuran was removed by rotary evaporation and the residue was diluted with water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (3x) and the combined organics were dried (Na_2SO_4), filtered and concentrated by rotary evaporation. The residue was purified by regular phase flash column chromatography (Analogix, 0-70 % hexanes / ethyl acetate).

EXAMPLE 535G

4-(2-oxaspiro[3.5]nonan-7-ylmethoxy)-3-nitrobenzenesulfonamide

EXAMPLE 535G was prepared by substituting EXAMPLE 535F for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 279A.

EXAMPLE 535H

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-{[3-nitro-4-(2-oxaspiro[3.5]non-7-ylmethoxy)phenyl]sulfonyl}benzamide

In a 4 mL vial was added EXAMPLE 498C (171 mg) and EXAMPLE 535G (75 mg) in dichloromethane (1052 µl) to give a colorless solution. 1-Ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (64.5 mg) and 4-dimethylaminopyridine (77 mg) were added and the solution was stirred overnight at room temperature. The reaction was loaded directly onto silica gel and chromatographed by regular phase flash column chromatography (Analogix, 0-100% hexanes / ethyl acetate). The fractions were combined, concentrated, treated with 50% trifluoroacetic acid in dichloromethane (2 mL) and stirred for 2 hours. The volatiles were removed by a stream of nitrogen, the residue was taken up in dichloromethane, loaded directly onto silica gel and purified by flash column column chromatography (Analogix, 0.4 - 4% dichloromethane / methanol). ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 13.10 (s, 1H) 8.11 (d, 1H) 7.76 - 7.84 (m, 2H) 7.55 (d, 1H) 7.36 (d, 2H) 7.27 (d, 1H) 7.02 - 7.15 (m, 4H) 6.79 (dd, 1H) 6.52 (d, 1H) 6.18 (dd, 1H) 4.30 (s, 2H) 4.21 (s, 2H) 4.00 (d , 2H) 3.11 - 3.26 (m, 4H) 2.85 (s, 3H) 2.70 - 2.75 (m, 1H) 2.22 - 2.46 (m, 3H) 2.13 - 2.22 (m, 3H) 2.07 (d, 2H) 1.98 (s, 2H) 1.66 - 1.77 (m, 3H) 1.36 - 1.50 (m, 4H) 0.98 - 1.16 (m, 2H) 0.94 (s, 6H).

EXAMPLE 536

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 536A

methyl 5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-6-carboxylate

To a 50 ml pressure bottle were placed methyl imidazo[1,2-a]pyridine-6-carboxylate (0.26 g), acetic acid (10 mL), and wet 5% palladium on carbon (0.052 g). The reaction mixture was stirred for 16 hours at 30 psi and 50 °C. The solid was filtered off, and the filtrate was concentrated. The residue was dissolved in ethyl acetate. It was then washed with saturated sodium bicarbonate, brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel to give the title compound.

EXAMPLE 536B

(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-yl)methanol

The title compound was prepared by substituting EXAMPLE 536A for EXAMPLE 339A in EXAMPLE 339B.

EXAMPLE 536C

5-chloro-6-((5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 536B for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 387A for EXAMPLE 329A in EXAMPLE 329B.

EXAMPLE 536D

N-(5-chloro-6-((5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-yl)methoxy)pyridin-3-ylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 435D for EXAMPLE 1E and EXAMPLE 536C for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 536E

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 536D for EXAMPLE 435E in EXAMPLE 435F. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 12.97 (s, 1H), 8.20 (d, 1H), 7.84 (d, 1H), 7.72 (s, 1H), 7.66 (d, 1H), 7.35 (d, 2H), 7.29 (s, 1H), 7.15 (s, 1H), 7.03-7.07 (m, 4H), 6.72 (dd, 1H), 6.40 (d, 1H), 6.09 (dd, 1H), 4.35-4.48 (m, 2H), 4.24-4.28 (m, 1H), 3.84-3.90 (m, 1H), 3.06 (br s, 4H), 2.83-2.92 (m, 2H), 2.76 (s, 2H), 2.09-2.23 (m, 8H), 1.97 (s, 2H), 1.76 (m, 1H), 1.40 (t, 2H), 0.93 (s, 6H).

EXAMPLE 537

2-(1H-benzimidazol-4-yloxy)-N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide

The title compound was prepared by substituting EXAMPLE 493B for EXAMPLE 428D and in EXAMPLE 428E. ^{1}H NMR (500 MHz, pyridine-d_5) δ 9.17 (d, 1H), 8.70 (d, 1H), 8.57 - 8.58 (s, 1H), 7.98 (d, 1H), 7.53 (d, 1H), 7.43 (d, 2H), 7.24 (t, 1H), 7.16 (d, 1H),

7.07 (d, 2H), 6.70 (m, 2H), 5.94 (m, 3H), 4.30 (d, 2H), 3.03 (m, 4H), 2.77 (s, 2H), 2.25 (m, 2H), 2.13 (m, 4H), 1.97 (s, 2H), 1.94 - 1.87 (m, 5H), 1.76 (m, 2H), 1.43 - 1.28 (m, 7H), 0.94 (m, 6H).

EXAMPLE 538

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-cyano-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 538A

5-bromo-6-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 517B for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 329B.

EXAMPLE 538B

5-cyano-6-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 538A for EXAMPLE 329B in EXAMPLE 333A.

EXAMPLE 538C

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(5-cyano-6-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)pyridin-3-ylsulfonyl)-2-(1-trityl-1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 498C for EXAMPLE 1E and EXAMPLE 538B for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 538D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-cyano-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 538C for EXAMPLE 521I in EXAMPLE 521J. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 13.03 (s, 1H), 8.49 (d, 1H), 8.19 (s, 1H), 7.74 (s, 1H), 7.62 (d, 1H), 7.37 (d, 2H), 7.14 - 6.94 (m, 3H), 6.77 (dd, 1H),

6.51 (s, 1H), 6.09 (dd, 1H), 4.53 (dt, 6H), 3.60 (s, 3H), 2.84 (dd, 8H), 2.46 - 1.71 (m, 12H), 1.44 (d, 2H), 0.94 (s, 6H).

EXAMPLE 539

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 539A

ethyl 8-methyl-1,4-dioxaspiro[4.5]decane-8-carboxylate

To a 500 mL round-bottomed flask was added diisopropylamine (7.98 mL) in tetrahydrofuran (233 mL). The mixture was cooled to -78°C under N_2 and n-butyllithium (2.5 M in hexanes, 22.40 mL) was added. The reaction was stirred for 30 minutes and ethyl 1,4-dioxaspiro[4.5]decane-8-carboxylate (10 g) was added. The reaction was allowed to stir for 1.5 hours upon which time CH_3I (4.38 mL) was added. The reaction was allowed to warm to room temperature overnight with stirring. Water was added and the aqueous layer was extracted with ethyl acetate. The combined organics were dried (Na_2SO_4), filtered and concentrated by rotary evaporation. The residue was purified by normal phase flash column chromatography (Analogix, 0-50% hexanes / ethyl acetate).

EXAMPLE 539B

(8-methyl-1,4-dioxaspiro[4.5]decan-8-yl)methanol

To a 500 mL round-bottomed flask was added lithium aluminum hydride (1.772 g) in tetrahydrofuran (234 mL). The mixture was cooled to 0°C and EXAMPLE 539A (10.66 g) was added via addition funnel. The reaction was stirred overnight at room temperature and then cooled back down to 0°C. The excess lithium aluminum hydride was slowly quenched with 1.8 mL water, 1.8 mL aqueous NaOH (5N) and 5.6 mL water. The suspension was stirred until the salts turned white and then filtered through a plug of silica gel. The filtrate was concentrated by rotary evaporation and the residue was purified by regular phase flash column chromatography (Analogix, 0-75% hexanes / ethyl acetate).

EXAMPLE 539C

8-(methoxymethyl)-8-methyl-1,4-dioxaspiro[4.5]decane

To a 250 mL round-bottomed flask was added NaH (0.902 g) and tetrahydrofuran (37.6 mL). EXAMPLE 539B (3.8 g) was added as a tetrahydrofuran solution at room temperature. The suspension was stirred for 30 minutes and then CH_3I (0.611 mL) was added. The reaction was stirred under N_2 overnight, carefully quenched with brine and diluted with water and ether. The aqueous layer was extracted with ether (2x) and the combined organics were dried (Na_2SO_4), filtered and concentrated by rotary evaporation. The residue was purified by flash column chromatography (Analogix, 0-60% hexanes / ethyl acetate).

EXAMPLE 539D

4-(methoxymethyl)-4-methylcyclohexanone

The title compound was prepared by substituting EXAMPLE 539C for EXAMPLE 535C in EXAMPLE 535D.

EXAMPLE 539E

2-chloro-5-(methoxymethyl)-5-methylcyclohex-1-enecarbaldehyde

To a 25 mL round-bottomed flask was added N,N-dimethylformamide (0.70 mL) and dichloromethane (3.31 mL). The solution was cooled to 0°C and $POCl_3$ (0.772 mL) was added dropwise under nitrogen. After the addition was complete, the solution was warmed to room temperature and stirred for 35 minutes. EXAMPLE 539D (1.035 g) was then added as a dichloromethane solution and the mixture was allowed to stir overnight at room temperature. The reaction was poured into ice and $NaHCO_3$, warmed to room temperature, and extracted with dichloromethane (2x). The combined aqueous was extracted with diethyl ether and then the combined organics were dried (Na_2SO_4), filtered and concentrated by rotary evaporation. The residue was purified by regular phase flash column chromatography (Analogix, 0-45% hexanes / ethyl acetate).

EXAMPLE 539F

2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-enecarbaldehyde

To a 20 mL vial was added EXAMPLE 539E (700 mg) and 4-chlorophenylboronic acid (648 mg) in water (3.8 mL). Tetrabutylammonium bromide (1.1 g) and potassium carbonate (1.2 g) were added followed by palladium (II) acetate (23.3mg). The mixture was degassed with nitrogen for 2 minutes, the vial was capped and the reaction was heated at 45°C overnight. The reaction mixture was diluted with ethyl acetate and water and the

aqueous layer was extracted with ethyl acetate (3x). The combined organics were dried ($NaSO_4$), filtered and concentrated by rotary evaporation. The residue was purified by regular phase flash column chromatography (Analogix, 0-60% hexanes / ethyl acetate).

EXAMPLE 539G

methyl 2-(1H-indazol-4-yloxy)-4-(4-((2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

To a 20 mL vial was added EXAMPLE 400C (531 mg) and EXAMPLE 539F (420 mg) in dichloromethane (8 mL). Sodium triacetoxyborohydride (415 mg) was added. The reaction was stirred for 2 days at room temperature and then quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with dichloromethane (3x), dried ($MgSO_4$), filtered and concentrated by rotary evaporation. The residue was purified by regular phase flash column chromatography (Analogix, 0.4% - 4% dichloromethane/methanol).

EXAMPLE 539H

methyl 4-(4-((2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-trityl-1H-indazol-4-yloxy)benzoate

To a 25 mL round-bottomed flask was added EXAMPLE 539G (704 mg) in dichloromethane (5 mL). Triethylamine (319 µl) was added followed by trityl-chloride (399 mg). The reaction was stirred overnight and diluted with water and dichloromethane. The aqueous layer was extracted with dichloromethane (2x) and the combined organics were dried ($MgSO_4$), filtered and concentrated by rotary evaporation. The residue was taken up in dichloromethane and passed over a pre-packed Supelco silica gel buchner funnel and the non-polar impurities were rinsed off with dichloromethane. The product was eluted with 5% methanol in dichloromethane. The residue was concentrated by rotary evaporation and the residue was used in the next step without further purification.

EXAMPLE 539I

4-(4-((2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-trityl-1H-indazol-4-yloxy)benzoic acid

The title compound was prepared by substituting EXAMPLE 539H for EXAMPLE 175D in EXAMPLE 175E.

EXAMPLE 539J

N-(5-chloro-6-((trans-4-hydroxy-4-methylcyclohexyl)methoxy)pyridin-3-ylsulfonyl)-4-(4-((2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-trityl-1H-indazol-4-yloxy)benzamide

The title compound was prepared substituting EXAMPLE 539I for EXAMPLE 1E and EXAMPLE 493B for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 539K

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared substituting EXAMPLE 539J for EXAMPLE 542E in EXAMPLE 542F. 1H NMR (300 MHz, dimethylsulfoxide-d_6) δ 13.10 (s, 1H) 8.28 (d, 1H) 7.77 - 7.91 (m, 2H) 7.58 (d, 1H) 7.37 (d, 2H) 6.99 - 7.19 (m, 4H) 6.80 (dd, 1H) 6.54 (s, 1H) 6.15 (dd, 1H) 4.10 - 4.34 (m, 3H) 3.26 (s, 3H) 3.05 - 3.21 (m, 6H) 2.12 - 2.29 (m, 4H) 2.09 (s, 1H) 1.85 - 1.98 (m, 1H) 1.68 - 1.81 (m, 4H) 1.50 - 1.63 (m, 4H) 1.31 - 1.45 (m, 3H) 1.13 - 1.30 (m, 2H) 1.11 (s, 3H) 0.94 (s, 3H).

EXAMPLE 540

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-{[3-nitro-4-({[(2S)-4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)phenyl]sulfonyl}benzamide

EXAMPLE 540A

(S)-3-nitro-4-((4-(oxetan-3-yl)morpholin-2-yl)methylamino)benzenesulfonamide

A round-bottom flask was charged with EXAMPLE 438B (1.012 g), anhydrous methanol (15 mL) and acetic acid (2.75 mL). Oxetan-3-one (0.461 g) was added and the mixture was stirred at room temperature for 30 minutes. Sodium cyanoborohydride (0.603 g) was then added and the mixture was stirred at room temperature overnight. The mixture was concentrated and the residue taken up in 5% aqueous Na_2CO_3 solution (15 mL). The mixture was extracted with ethyl acetate, and the combined organic layers were concentrated. The crude product was purified on a silica gel column eluting with 5% and 10% methanol in CH_2Cl_2 giving the title compound.

EXAMPLE 540B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-{[3-nitro-4-({[(2S)-4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)phenyl]sulfonyl}benzamide

The title compound was prepared by substituting EXAMPLE 400E for EXAMPLE 26C and EXAMPLE 540A for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500MHz, pyridine-d_5) δ 14.58 (bs, 1H), 9.05 (d, 1H), 8.85 (t, 1H), 8.37 (s, 1H), 8.17 (dd, 1H), 8.02 (d, 1H), 7.45 (d, 2H), 7.34 (d, 1H), 7.15 (t, 1H), 7.10 (d, 2H), 6.90-6.80 (m, 3H), 6.53 (d, 1H), 4.67-4.61 (m, 4H), 3.94-3.90 (m, 2H), 3.68 (dt, 1H), 3.47 (m, 1H), 3.44-3.34 (m, 2H), 3.14 (m, 4H), 2.82 (s, 2H), 2.71 (d, 1H), 2.44 (d, 1H), 2.30 (m, 2H), 2.22 (m, 4H), 1.99 (s, 2H), 1.95 (dt, 1H), 1.84 (t, 1H), 1.41 (t, 2H), 0.96 (s, 6H).

EXAMPLE 541

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-({[(2S)-4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)phenyl]sulfonyl}benzamide

The title compound was prepared by substituting EXAMPLE 540A for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (500MHz, pyridine-d_5) δ 9.25 (d, 1H), 8.87 (t, 1H), 8.57 (s, 1H), 8.38 (dd, 1H), 8.01 (d, 1H), 7.52 (d, 1H), 7.43 (d, 2H), 7.24 (d, 1H), 7.14 (d, 1H), 7.07 (d, 2H), 6.97 (d, 1H), 6.73-6.68 (m, 2H), 4.69-4.62 (m, 4H), 3.97-3.89 (m, 2H), 3.69 (dt, 1H), 3.51 (m, 1H), 3.47-3.35 (m, 2H), 3.03 (m, 4H), 2.77 (s, 2H), 2.74 (d, 1H), 2.43 (d, 1H), 2.25 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.95 (m, 1H), 1.86 (t, 1H), 1.38 (t, 2H), 0.94 (s, 6H).

EXAMPLE 542

N-[(5-chloro-6-{[trans-4-(2-hydroxypropan-2-yl)cyclohexyl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 542A

trans-methyl 4-((tert-butyldimethylsilyloxy)methyl) cyclohexanecarboxylate

Trans-methyl 4-(hydroxymethyl)cyclohexanecarboxylate was dissolved in dichloromethane (30 mL), then imidazole (1.0 g) and tert-butylchlorodimethylsilane (1.6 g) were added. The reaction was stirred at room temperature overnight. The reaction mixture was then concentrated, dissolved in ethyl acetate and washed with 1*N* aqueous HCl, water, and brine. The organic layer was dried over Na_2SO_4. The title compound was obtained after filtration and concentration.

EXAMPLE 542B

2-(trans-4-((tert-butyldimethylsilyloxy)methyl)cyclohexyl)propan-2-ol

EXAMPLE 542A (1.4 g) was dissolved in tetrahydrofuran (15 mL), then a solution of 3.0*M* methylmagnesium chloride in tetrahydrofuran (3.4 mL) was carefully added and the reaction allowed to stir at room temperature under nitrogen overnight. The reaction was then poured into saturated aqueous NH_4Cl and extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. After filtration and concentration the product was purified by column chromatography on silica gel using 9/1 hexanes/ethyl acetate.

EXAMPLE 542C

2-(trans-4-(hydroxymethyl)cyclohexyl)propan-2-ol

EXAMPLE 542B was dissolved in tetrahydrofuran (10 mL), then a solution of 1.0*M* tetrabutylammonium fluoride in tetrahydrofuran (17.5 mL) was added and the reaction was stirred at room temperature overnight. The reaction was concentrated and the residue was purified by column chromatography on silica gel using 50-70% ethyl acetate in hexanes.

EXAMPLE 542D

5-chloro-6-((trans-4-(2-hydroxypropan-2-yl)cyclohexyl)methoxy) pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 542C for (tetrahydro-2H-pyran-4-yl)methanol and 5,6-dichloropyridine-3-sulfonamide for EXAMPLE 329A in EXAMPLE 329B, except here dimethylformamide was used in place of tetrahydrofuran.

EXAMPLE 542E

N-(5-chloro-6-((trans-4-(2-hydroxypropan-2-yl)cyclohexyl)methoxy)pyridin-3-ylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(2-trityl-2H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 498C for EXAMPLE 1E and EXAMPLE 542D for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 542F

N-[(5-chloro-6-{[trans-4-(2-hydroxypropan-2-yl)cyclohexyl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 542E (310 mg) was dissolved in dichloromethane (2.5 mL), and p-toluenesulfonic acid monohydrate (27 mg) was added. After stirring at room temperature for 30 minutes, the reaction was poured into saturated aqueous $NaHCO_3$ and extracted with dichloromethane. The organic layer was washed with brine and dried over Na_2SO_4. After filtration and concentration the residue was purified by column chromatography on silica gel using 2-10% methanol in dichloromethane. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 13.10 (s, 1H), 8.27 (d, 1H), 7.85 (d, 1H), 7.81 (s, 1H), 7.58 (d, 1H), 7.37 (d, 2H), 7.06 (m, 4H), 6.80 (dd, 1H), 6.54 (d, 1H), 6.13 (d, 1H), 4.19 (d, 2H), 4.00 (s, 1H), 3.21 (br s, 4H), 2.96 (v br s, 2H), 2.40 (br s, 4H), 2.19 (br m, 2H), 1.98 (s, 2H), 1.83 (br m, 4H), 1.70 (br m, 1H), 1.42 (t, 2H), 1.18 (br m, 1H), 1.02 (br m, 4H), 1.02 (s, 6H), 0.93 (s, 6H).

EXAMPLE 543

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]phenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 543A

3-cyano-4-((trans-4-hydroxy-4-methylcyclohexyl)methoxy)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 531F for EXAMPLE 517B in EXAMPLE 534A.

EXAMPLE 543B

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-cyano-4-((trans-4-hydroxy-4-methylcyclohexyl)methoxy)phenylsulfonyl)-2-(1-trityl-1H-indazol-4-yloxy)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 498C for EXAMPLE 1E and EXAMPLE 543A for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 543C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]phenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 543B for EXAMPLE 521I in EXAMPLE 521J. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 13.12 (s, 1H), 11.70 - 11.35 (m, 1H), 7.87 (d, 1H), 7.81 (t, 2H), 7.55 (d, 1H), 7.39 - 7.33 (m, 2H), 7.20 - 7.10 (m, 3H), 7.09 - 7.03 (m, 2H), 6.80 (dd, 1H), 6.53 (d, J = 2.1 Hz, 1H), 6.18 (dd, 1H), 4.26 (s, 1H), 4.05 (d, 2H), 3.19 (s, 4H), 2.86 (s, 2H), 2.17 (m, 6H), 1.98 (s, 2H), 1.77 (m, 3H), 1.56 (m, 2H), 1.42 (m, 6H), 1.12 (s, 3H), 0.94 (s, 6H).

EXAMPLE 544

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 544A

5-bromo-6-((trans-4-hydroxy-4-methylcyclohexyl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 531F for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 329B.

EXAMPLE 544B

5-cyano-6-((trans-4-hydroxy-4-methylcyclohexyl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 544A for EXAMPLE 329B in EXAMPLE 333A.

EXAMPLE 544C

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(5-cyano-6-((trans-4-hydroxy-4-methylcyclohexyl)methoxy)pyridin-3-ylsulfonyl)-2-(1-trityl-1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 498C for EXAMPLE 1E and EXAMPLE 544B for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 544D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 544C for EXAMPLE 521I in EXAMPLE 521J. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 13.07 (s, 1H), 8.50 (d, 1H), 8.23 - 8.12 (m, 1H), 7.76 (s, 1H), 7.60 (d, 1H), 7.37 (d, 2H), 7.07 (dd, 4H), 6.87 - 6.72 (m, 1H), 6.54 (d, 1H), 6.17 - 6.03 (m, 1H), 4.29 (d, 3H), 3.25 - 3.11 (m, 4H), 2.19 (s, 4H), 2.00 (s, 2H), 1.76 (s, 4H), 1.55 (s, 3H), 1.48 - 1.31 (m, 4H), 1.31 - 1.14 (m, 4H), 1.12 (s, 3H), 0.94 (s, 6H).

EXAMPLE 545

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-({5-nitro-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)benzamide

EXAMPLE 545A

6-amino-5-nitropyridine-3-sulfonic acid

6-Aminopyridine-3-sulfonic acid (20 g) in concentrated H_2SO_4 (80 mL) was heated at 50 °C until it was completely dissolved. To this solution was added fuming HNO_3 dropwise over 20 minutes. The rate of addition was kept slow so that the internal temperature did not exceeded 55 °C. After the addition was complete, the reaction mixture was heated at 50 °C for 1 hour. After the mixture cooled to room temperature, it was poured into 150 g of ice. The mixture was stirred for another 1 hour. The whole flask was cooled to 0 °C, and was kept at 0 °C for another 2 hours. The solid was collected by filtration, and was washed with cold 1:1 water/ethanol (20 mL), followed by diethyl ether (10 mL). The solid was dried in a vacuum oven overnight to give the title compound.

EXAMPLE 545B

6-hydroxy-5-nitropyridine-3-sulfonic acid

EXAMPLE 545A (4.0 g) in HCl (37%, 12 mL) and water (50 mL) was treated with sodium nitrite (1.19 g) in water (8 mL) dropwise at 0 °C. After the addition was complete, the reaction mixture was stirred at 0 °C for 1 hour. The mixture was then heated under reflux for 2 hours. Water was distilled off to give a near dry residue. After it cooled to room temperature, a solution of 1:1 ethanol/water (20 mL) was added. The resulting suspension was cooled to 0 °C, and kept at 0 °C for 1 hour. The solid was collected by filtration to give the title compound.

EXAMPLE 545C

6-chloro-5-nitropyridine-3-sulfonyl chloride

A mixture of EXAMPLE 545B (2.6 g), PCl_5 (5.91 g), and $POCl_3$ (10 mL) was heated at 120 °C for 4 hours. The initial suspension became a clear solution. The excess of $POCl_3$ was distilled off. After it was cooled to room temperature, the residue was poured into 50 g of crushed ice. The solid was extracted into ethyl acetate. The aqueous layer was extracted with additional ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give the crude product that was used for the next reaction without further purification.

EXAMPLE 545D

6-chloro-5-nitropyridine-3-sulfonamide

EXAMPLE 545C in tetrahydrofuran (10 mL) was cooled to -10 °C. To this solution was added concentrated ammonium hydroxide (0.82 mL) dropwise. The solution was stirred at -10 °C for 10 minutes. The solvent was removed under pressure at room temperature. The residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel to give the title compound.

EXAMPLE 545E

5-nitro-6-((tetrahydro-2H-pyran-4-yl)methylamino)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 545D for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 1F.

EXAMPLE 545F

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(5-nitro-6-((tetrahydro-2H-pyran-4-yl)methylamino)pyridin-3-ylsulfonyl)-2-(1-trityl-1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 498C for EXAMPLE 1E and EXAMPLE 545E for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 545G

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-({5-nitro-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 545F for EXAMPLE 542E EXAMPLE 542F. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 13.03 (s, 1H), 8.66 (br s, 1H), 8.49 (d, 1H), 8.45 (d, 1H), 7.78 (s, 1H), 7.57 (d, 1H), 7.36 (d, 2H), 7.01-7.07 (m, 4H), 6.79 (dd, 1H), 6.52 (s, 1H), 6.11 (dd, 1H), 3.84 (dd, 2H), 3.51 (t, 1H), 3.23-3.29 (m, 2H), 3.17 (br s, 4H), 2.84 (br s, 2H), 2.16-2.34 (m, 6H), 1.98 (s, 2H), 1.58-1.61 (m, 2H), 1.41 (t, 2H), 0.94 (s, 6H).

EXAMPLE 546

2-(1H-benzotriazol-4-yloxy)-N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide

EXAMPLE 546A

N-(5-chloro-6-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methoxy)pyridin-3-ylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d][1,2,3]triazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 514F for EXAMPLE 1E and EXAMPLE 493B for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 546B

2-(1H-benzotriazol-4-yloxy)-N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide

EXAMPLE 546A (0.22 g) in tetrahydrofuran (10 mL) was treated with 1.0 N tetrabutyl ammonium fluoride (4.3 M). The reaction mixture was heated at 50 °C for 3 hours. The solvent was removed, and the residue was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by reverse phase Gilson Prep HPLC system with a Phenomenex prep column (Luna, 5 μ, C18(2), 250X21.20 mm, 5 Å) eluting with 20-80% acetonitrile in water with 0.1% trifluoroacetic acid to give the title compound. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 8.24 (s, 1H), 7.86 (d, 1H), 7.63 (d, 1H), 7.36-7.38 (m, 3H), 7.06-7.09 (m, 3H), 6.81 (dd, 1H), 6.57 (d, 1H), 6.33 (d, 1H), 4.32 (s, 1H), 4.22 (d, 2H), 3.00 (br s, 4H), 2.41 (br s, 2H), 2.19 (s, 2H), 1.99 (s, 2H), 1.73-1.77 (m, 2H), 1.56-1.59 (m, 2H), 1.36-1.43 (m, 4H), 1.12-1.27 (m, 6H), 0.94 (s, 6H).

EXAMPLE 547

N-({3-chloro-4-[(cis-4-cyano-1-fluorocyclohexyl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 547A

1-oxaspiro[2.5]octane-6-carbonitrile

A solution of 4-oxocyclohexanecarbonitrile (1.90 g) in dimethylsulfoxide (8 mL) was added dropwise to a solution of potassium t-butoxide (2.60 g) and trimethylsulfoxonium iodide (5.09 g) in dimethylsulfoxide (30 mL) at room temperature. The mixture was stirred overnight, diluted with 20% brine, and extracted with 3x ethyl acetate. The combined organic layers were washed with 20% brine, dried over Na_2SO_4, and concentrated. The crude was purified on a 40 g column using an ISCO Companion flash system eluting with hexane/ethyl acetate (6:4 to 5:5) to give the desired product.

EXAMPLE 547B

cis-4-fluoro-4-(hydroxymethyl)cyclohexanecarbonitrile

A solution of pyridine hydrofluoride (2.25 g) in dichloromethane (8 mL) was added dropwise to a solution of EXAMPLE 547A (0.780 g) in dichloromethane (8 mL) in a polyethlene bottle at 0°C. The reaction was slowly warmed to room temperature and stirred for 43 hours. The reaction mixture was slowly added to ice-cold saturated aqueous Na_2CO_3 until pH=8-9 and extracted twice with ethyl acetate. The combined organic layers were dried over Na_2SO_4, concentrated, and purified on an 80g silica column using an ISCO Companion flash system eluting with hexane/ethyl acetate (65:35 to 55:45) to give the desired product. EXAMPLE 548A was also isolated from this reaction.

EXAMPLE 547C

3-chloro-4-((cis-4-cyano-1-fluorocyclohexyl)methoxy)-N,N-bis(2,4-dimethoxybenzyl)benzenesulfonamide

The title compound was prepared as described in EXAMPLE 329B by replacing EXAMPLE 329A with EXAMPLE 517C and (tetrahydro-2H-pyran-4-yl)methanol with EXAMPLE 547B.

EXAMPLE 547D

3-chloro-4-((cis-4-cyano-1-fluorocyclohexyl)methoxy)benzenesulfonamide

The title compound was prepared as described in EXAMPLE 517E by replacing EXAMPLE 517D with EXAMPLE 547C.

EXAMPLE 547E

N-(3-chloro-4-((cis-4-cyano-1-fluorocyclohexyl)methoxy)phenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-trityl-1H-indazol-4-yloxy)benzamide.

The title compound was prepared as described in EXAMPLE 1G by replacing EXAMPLE 1E with EXAMPLE 498C and EXAMPLE 1F with EXAMPLE 547D.

EXAMPLE 547F

2-(1H-indazol-4-yloxy)-N-(3-chloro-4-((cis-4-cyano-1-fluorocyclohexyl)methoxy)phenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzamide.

The title compound was prepared as described in EXAMPLE 497C by replacing EXAMPLE 497B with EXAMPLE 547E. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 13.14 (s, 1H), 11.18-12.10 (bs, 1H), 7.84 (s, 1H), 7.66 (d, 1H), 7.48-7.63 (m, 2H), 7.28-7.42 (m, 2H), 7.09-7.24 (m, 3H), 7.05 (m, 2H), 6.80 (dd, 1H), 6.52 (d, 1H), 6.14-6.31 (m, 1H), 4.20 (d, 2H), 3.05-3.26 (m, 4H), 2.69-2.93 (m, 3H), 2.10-2.37 (m, 6H), 1.89-2.11 (m, 7H), 1.50-1.85 (m, 4H), 1.40 (t, 1H), 0.94 (s, 6H).

EXAMPLE 548

N-({3-chloro-4-[(trans-4-cyano-1-fluorocyclohexyl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 548A

trans-4-fluoro-4-(hydroxymethyl)cyclohexanecarbonitrile

The title compound was prepared and isolated as described in EXAMPLE 547B.

EXAMPLE 548B

3-chloro-4-((trans-4-cyano-1-fluorocyclohexyl)methoxy)-N,N-bis(2,4-dimethoxybenzyl)benzenesulfonamide

The title compound was prepared as described in EXAMPLE 329B by replacing EXAMPLE 329A with EXAMPLE 517C and (tetrahydro-2H-pyran-4-yl) methanol with EXAMPLE 548A.

EXAMPLE 548C

3-chloro-4-((trans-4-cyano-1-fluorocyclohexyl)methoxy)benzenesulfonamide

The title compound was prepared as described in EXAMPLE 517E by replacing EXAMPLE 517D with EXAMPLE 548B.

EXAMPLE 548D

N-(3-chloro-4-((trans-4-cyano-1-fluorocyclohexyl)methoxy)phenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-trityl-1H-indazol-4-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 1G by replacing EXAMPLE 1E with EXAMPLE 498C and EXAMPLE 1F with EXAMPLE 548C.

EXAMPLE 548E

N-(3-chloro-4-((trans-4-cyano-1-fluorocyclohexyl)methoxy)phenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-trityl-1H-indazol-4-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 497C by replacing EXAMPLE 497B with EXAMPLE 548D. ^{1}H NMR (300 MHz, dimethylsulfoxide-d_6) δ 13.15 (s, 1H), 11.50 (s, 1H), 7.85 (s, 1H), 7.67 (d, 1H), 7.46-7.64 (m, 2H), 7.35 (d, 2H), 7.11-7.23 (m, 3H), 7.05 (d, 2H), 6.80 (dd, 1H), 6.52 (d, 1H), 6.23 (d, 1H), 4.30 (d, 2H), 3.10-3.25 (m, 5H), 2.81 (s, 2H), 2.09-2.35 (m, 6H), 1.70-2.07 (m, 10H), 1.40 (t, 2H), 0.83-1.02 (m, 6H).

EXAMPLE 549

N-({5-chloro-6-[(cis-4-cyano-1-fluorocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 549A

5-chloro-6-((cis-4-cyano-1-fluorocyclohexyl)methoxy)pyridine-3-sulfonamide

The title compound was prepared as described in EXAMPLE 329B by replacing EXAMPLE 329A with EXAMPLE 387A and (tetrahydro-2H-pyran-4-yl)methanol with EXAMPLE 547B.

EXAMPLE 549B

N-(5-chloro-6-((cis-4-cyano-1-fluorocyclohexyl)methoxy)pyridin-3-ylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-trityl-1H-indazol-4-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 1G by replacing EXAMPLE 1E with EXAMPLE 498C and EXAMPLE 1F with EXAMPLE 549A.

EXAMPLE 549C

2-(1H-indazol-4-yloxy)-N-(5-chloro-6-((cis-4-cyano-1-fluorocyclohexyl)methoxy)pyridin-3-ylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzamide

The title compound was prepared as described in EXAMPLE 497C by replacing EXAMPLE 497B with EXAMPLE 549B. ^{1}H NMR (400 MHz, pyridine-d_5) δ 8.92 (d, 1H), 8.39 (bs, 2H), 8.07 (d, 1H), 7.46 (d, 2H), 7.36 (d, 1H), 7.13 (m, 2H), 6.86 (m, 3H), 6.50 (d, 1H), 4.50 (m, 2H), 3.17 (m, 3H), 3.01 (m, 1H), 2.82 (s, 2H), 2.30 (m, 2H), 2.24 (m, 3H), 2.23 (m, 4H), 1.97-2.04 (m, 4H), 1.83-1.90 (m, 2H), 1.77 (m, 2H), 1.41 (t, 2H), 0.96 (s, 6H).

EXAMPLE 550

N-({5-chloro-6-[(trans-4-cyano-1-fluorocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 550A

5-chloro-6-((trans-4-cyano-1-fluorocyclohexyl)methoxy)pyridine-3-sulfonamide

The title compound was prepared as described in EXAMPLE 329B by replacing EXAMPLE 329A with EXAMPLE 387A and (tetrahydro-2H-pyran-4-yl)methanol with EXAMPLE 548A.

EXAMPLE 550B

N-(5-chloro-6-((trans-4-cyano-1-fluorocyclohexyl)methoxy)pyridin-3-ylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-trityl-1H-indazol-4-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 1G by replacing EXAMPLE 1E with EXAMPLE 498C and EXAMPLE 1F with EXAMPLE 550A.

EXAMPLE 550C

2-(1H-indazol-4-yloxy)-N-(5-chloro-6-((trans-4-cyano-1-fluorocyclohexyl)methoxy)pyridin-3-ylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzamide

The title compound was prepared as described in EXAMPLE 497C by replacing EXAMPLE 497B with EXAMPLE 550B. ^{1}H NMR (400 MHz, pyridine-d_5) δ 8.92 (d, 1H),

8.39 (bs, 2H), 8.07 (d, 1H), 7.46 (d, 2H), 7.36 (d, 1H), 7.13 (m, 2H), 6.86 (m, 3H), 6.50 (d, 1H), 4.50 (m, 2H), 3.17 (m, 3H), 3.01 (m, 1H), 2.82 (s, 2H), 2.30 (m, 2H), 2.24 (m, 3H), 2.23 (m, 4H), 1.97-2.04 (m, 4H), 1.83-1.90 (m, 2H), 1.77 (m, 2H), 1.41 (t, 2H), 0.96 (s, 6H).

EXAMPLE 551

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 551A

methyl 4-(4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)-2-(1-trityl-1H-indazol-4-yloxy)benzoate

The title compound was prepared by substituting EXAMPLE 465A for EXAMPLE 400D in EXAMPLE 498B.

EXAMPLE 551B

4-(4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)-2-(1-trityl-1H-indazol-4-yloxy)benzoic acid

The title compound was prepared by substituting EXAMPLE 551A for EXAMPLE 175D in EXAMPLE 175E.

EXAMPLE 551C

N-(5-chloro-6-((trans-4-hydroxy-4-methylcyclohexyl)methoxy)pyridin-3-ylsulfonyl)-4-(4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)-2-(1-trityl-1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 551B for EXAMPLE 1E and EXAMPLE 493B for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 551D

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 551C for EXAMPLE 542E in EXAMPLE 542F. ^{1}H NMR (400MHz, dimethylsulfoxide-d_6) δ 13.13 (s, 1H), 8.27 (d, 1H), 7.85 (d, 1H), 7.81 (s, 1H), 7.57 (d, 1H), 7.38 (d, 2H), 7.15 (d, 2H), 7.08 (m, 2H), 6.80 (dd, 1H), 6.56 (d, 1H), 6.14 (d, 1H), 4.26 (s, 1H), 4.25 (d, 2H), 4.15 (s, 2H), 3.20 (br s, 4H), 2.95 (v br s, 2H), 2.31 (br s, 4H), 1.98 (s, 2H), 1.77 (m, 3H), 1.58 (m, 2H), 1.39 (m, 2H), 1.22 (m, 2H), 1.20 (s, 6H), 1.10 (s, 3H).

EXAMPLE 552

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 525C for EXAMPLE 428D and in EXAMPLE 428E. ^{1}H NMR (500 MHz, pyridine-d_5) δ 9.30 (m, 1H), 8.69 (t, 1H), 8.59 (s, 1H), 8.41 (dd, 1H), 7.99 (d, 1H), 7.53 (d, 1H), 7.43 (d, 2H), 7.25 (t, 1H), 7.18 (d, 1H), 7.07 (d, 2H), 6.94 (d, 1H), 6.72 - 6.68 (m, 2H), 5.85 (m, 3H), 3.22 (t, 2H), 3.02 (m, 4H), 2.76 (s, 2H), 2.25 (m, 2H), 2.13 (m, 4H), 1.97 (s, 2H), 1.92 - 1.85 (m, 4H), 1.78 - 1.71 (m, 3H), 1.43 - 1.36 (m, 5H), 1.33 - 1.21 (m, 2H), 0.94 (s, 6H).

EXAMPLE 553

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 553A

2-chloro-5-methoxy-5-methylcyclohex-1-enecarbaldehyde

N,N-dimethylformamide (1.298 mL) in dichloromethane (2.0 mL) at -10 °C was treated dropwise with $POCl_3$ (1.426 mL). The mixture was stirred for 5 minutes and then warmed to room temperature and stirred 30 minutes. The solution was cooled to -10 °C, treated dropwise with a solution of 4-methoxy-4-methylcyclohexanone (1.74 g) in dichloromethane (2.5 mL) and stirred for 4 hours at ambient temperature. The reaction mixture was poured over a mixture of ice and 25% sodium acetate solution. When the ice had melted, the reaction mixture was poured into a separatory funnel and extracted with diethyl ether (4 x 125 mL). The diethyl ether extracts were washed with aqueous $NaHCO_3$

solution and brine, dried ($MgSO_4$), filtered and concentrated. The concentrate was chromatographed on silica gel with 0 to 5% ethyl acetate in hexanes as the eluent.

EXAMPLE 553B

2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-enecarbaldehyde

EXAMPLE 553A (1.55 g), 4-chlorophenylboronic acid (1.542 g), palladium(II) acetate (0.055 g), K_2CO_3 (2.84 g) and tetrabuylammonium bromide (2.65 g) were combined in a 50-mL round-bottomed flask equipped with a magnetic stir bar. Water (9.13 mL) was added. The vial was flushed with nitrogen, capped and stirred at 45 °C for 14 hours. The reaction mixture was cooled to room temperature and partitioned between brine and diethyl ether. The organic layer was washed with brine, dried ($MgSO_4$), filtered through a plug of diatomaceous earth, concentrated and chromatographed on silica gel with 5 to 20% ethyl acetate in hexanes as the eluent.

EXAMPLE 553C

methyl 2-(1H-indazol-4-yloxy)-4-(4-((2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 553B for 4-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 400C for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A except that a small amount of dimethylsulfoxide was added to the reaction mixture to dissolve the reactants.

EXAMPLE 553D

methyl 4-(4-((2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-trityl-1H-indazol-4-yloxy)benzoate

EXAMPLE 553C (1.46 g) in dichloromethane (11.84 mL) was treated sequentially with trityl chloride (0.667 g) and triethylamine (0.990 mL) and stirred for 7 days at room temperature. The reaction mixture was concentrated and chromatographed on silica gel with 0 to 4% methanol in CH_2Cl_2 as the eluent.

EXAMPLE 553E

4-(4-((2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-trityl-1H-indazol-4-yloxy)benzoic acid

The title compound was prepared by substituting EXAMPLE 553D for EXAMPLE 175D in EXAMPLE 175E.

EXAMPLE 553F

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy)pyridin-3-yl}sulfonyl)-4-(4-((2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-trityl-1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 553E for EXAMPLE 1E and EXAMPLE 531G for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 553G

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 553F for EXAMPLE 542E in EXAMPLE 542F. ^{1}H NMR (500 MHz, pyridine -d_5) δ 14.62 (s, 1H), 8.95 (d, 1H), 8.39 (d, 1H), 8.38 (d, 1H), 8.06 (d, 1H), 7.44 (m, 2H), 7.37 (d, 1H), 7.14 (m, 3H), 6.86 (m, 2H), 6.50 (d, 1H), 4.29 (d, 2H), 3.24 (s, 3H), 3.17 (t, 4H), 2.82 (m, 2H), 2.62 (d, 1H), 2.52 (m, 1H), 2.25 (m, 6H), 1.88 (m, 6H), 1.75 (m, 2H), 1.64 (m, 1H), 1.41 (s, 3H), 1.32 (m, 2H), 1.24 (s, 3H).

EXAMPLE 554

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-chloro-6-{[1-(1,3-thiazol-2-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 554A

methyl 1-(thiazol-2-yl)piperidine-4-carboxylate

A mixture of methyl piperidine-4-carboxylate (2.045 g), 2-bromothiazole (1.64 g), and Cs_2CO_3 (5.86 g) in N,N-dimethylformamide (15 mL) was heated at 100 °C overnight. After the mixture was cooled to room temperature, the reaction mixture was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed

with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel to give the title compound.

EXAMPLE 554B

(1-(thiazol-2-yl)piperidin-4-yl)methanol

The title compound was prepared by substituting EXAMPLE 554A for EXAMPLE 520A in EXAMPLE 520B.

EXAMPLE 554C

5-chloro-6-((1-(thiazol-2-yl)piperidin-4-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 554B for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 387A for EXAMPLE 329A in EXAMPLE 329B.

EXAMPLE 554D

N-(5-chloro-6-((1-(thiazol-2-yl)piperidin-4-yl)methoxy)pyridin-3-ylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-2-(1-trityl-1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 498C for EXAMPLE 1E and EXAMPLE 554C for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 554E

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-chloro-6-{[1-(1,3-thiazol-2-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 554D for EXAMPLE 542E in EXAMPLE 545F. ^1H NMR (500MHz, dimethylsulfoxide-d_6) δ 13.17 (s, 1H), 9.50 (s, 1H), 8.32 (d, 1H), 7.88 (d, 1H), 7.83 (s, 1H), 7.59 (d, 1H), 7.40 (d, 2H), 7.18 (d, 1H), 7.04-7.13 (m, 4H), 6.87 (d, 1H), 6.84 (d, 1H), 6.66 (d, 1H), 6.14 (d, 1H), 4.30 (d, 2H), 3.94-3.99 (m, 2H), 3.80-3.82 (m, 2H), 3.05-3.12 (m, 6H), 2.78 (br s, 2H), 2.25 (s, 2H), 2.04-2.12 (m 4H), 1.86-1.89 (m, 2H), 1.41-1.49 (m, 5H), 0.96 (s, 6H).

EXAMPLE 555

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(6-{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-5-nitropyridin-3-yl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 555A

tert-butyl (4-hydroxy-4-methylcyclohexyl)methylcarbamate

A solution of tert-butyl (4-oxocyclohexyl)methylcarbamate (1.00 g) was dissolved in tetrahydrofuran (20 mL) and cooled to -78°C. Methylmagnesium bromide (4.40 mL) was added dropwise. The reaction was stirred for 2 hours at -78°C then allowed to warm to 0°C and stirred for 30 minutes. The resulting suspension was quenched with water (10 mL), diluted with ether (50 mL) and washed with ammonium chloride (25 mL) and brine (25 mL), dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (Reveleris 80 g) eluting using a gradient of 5% to 50% ethyl acetate/dichloromethane over 30 minutes (flow = 60 ml/min) gave the title compound as a ~2:1 mixture of cis and trans isomers.

EXAMPLE 555B

4-(aminomethyl)-1-methylcyclohexanol trifluoroacetic acid salt

To a solution of EXAMPLE 555A (0.75 g) in dichloromethane (3 mL) was added a few drops of water followed by trifluoroacetic acid (1.19 mL) and the reaction stirred at room temperature. After stirring for 2 hours, additional trifluoroacetic acid (0.5 mL) was added. After an additional 4 hours, the reaction mixture was concentrated and dried under high vacuum. The resulting oily solid was triturated with diethyl ether with sonication. Filtration and washing with diethyl ether gave the title compound as a mixture of cis and trans isomers.

EXAMPLE 555C

6-((cis-4-hydroxy-4-methylcyclohexyl)methylamino)-5-nitropyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 545D for EXAMPLE 387A and EXAMPLE 555B for (4-fluorotetrahydro-2H-pyran-4-yl)methanamine in EXAMPLE 413A. Two isomers were isolated by reverse phase Gilson Prep HPLC system with a Phenomenex prep column (Luna, 5 μ, C18(2), 250X21.20 mm, 5 Å) eluting with 20-80% acetonitrile in water with 0.1% trifluoroacetic acid.

EXAMPLE 555D

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(6-(((1s,4s)-4-hydroxy-4-methylcyclohexyl)methylamino)-5-nitropyridin-3-ylsulfonyl)-2-(1-trityl-1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 498C for EXAMPLE 1E and EXAMPLE 555C for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 555E

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(6-{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-5-nitropyridin-3-yl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 555D for EXAMPLE 542E in EXAMPLE 542F. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 13.04 (s, 1H), 8.85 (s, 1H), 8.48 (d, 1H), 8.44 (d, 1H), 7.79 (s, 1H), 7.57 (d, 1H), 7.36 (d, 2H), 6.96-7.07 (m, 4H), 6.80 (dd, 1H), 6.54 (d, 1H), 6.11 (dd, 1H), 3.95 (s, 1H), 3.48 (t, 2H), 3.19 (s, 4H), 2.87 (br s, 2H), 2.30-2.34 (m, 4H), 2.18 (m 2H), 1.97-1.99 (m, 2H), 1.35-1.55 (m, 10H), 1.20-1.26 (m, 4H), 1.08 (s, 3H), 0.94 (s, 6H).

EXAMPLE 556

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide

EXAMPLE 556A

6-((trans-4-hydroxy-4-methylcyclohexyl)methoxy)-5-(trifluoromethyl)pyridine-3-sulfonamide

This EXAMPLE was prepared by substituting EXAMPLE 493A for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 410E for EXAMPLE 329A in EXAMPLE 329B. The crude reaction products were purified by reverse phase Gilson Prep HPLC system with a Phenomenex prep column (Luna, 5 μ, C18(2), 250X21.20 mm, 5 Å) eluting with 20-80% acetonitrle in water with 0.1% trifluoroacetic acid to give the title compound.

EXAMPLE 556B

The title compound was prepared by substituting EXAMPLE 498C for EXAMPLE 1E and EXAMPLE 556A for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 556C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 556B for EXAMPLE 542E in EXAMPLE 542F. ^{1}H NMR (500MHz, dimethylsulfoxide-d_6) δ 13.06 (s, 1H), 8.49 (s, 1H), 8.13 (d, 1H), 7.77 (s, 1H), 7.61 (d, 1H), 7.37 (d, 2H), 7.01-7.08 (m, 4H), 6.78 (dd, 1H), 6.51 (s, 1H), 6.12 (dd, 1H), 4.26-4.30 (m, 3H), 3.18 (s, 4H), 2.91 (br s, 2H), 2.31-2.35 (m, 2H), 2.16-2.18 (m 2H), 1.97-1.99 (m, 2H), 1.68-1.75 (m, 4H), 1.55-1.58 (m, 2H), 1.26 (m, 2H), 1.10 (s, 3H), 0.94 (s, 6H).

EXAMPLE 557

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 525D for EXAMPLE 428D in EXAMPLE 428E. ^{1}H NMR (500MHz, pyridine-d_5) δ 9.29 (d, 1H), 8.58 (s, 1H), 8.40 (dd, 1H), 8.00 (d, 1H), 7.53 (d, 1H), 7.43 (d, 2H), 7.25 (m, 2H), 7.18 (d, 1H), 7.07 (d, 2H), 6.91 (d, 1H), 6.73-6.68 (m, 2H), 3.21 (t, 2H), 3.02 (m, 4H), 2.76 (s, 2H), 2.25 (m, 2H), 2.13 (m, 4H), 1.97 (s, 2H), 1.90-1.79 (m, 4H), 1.70-1.60 (m, 3H), 1.45-1.30 (m, 8H), 0.94 (s, 6H).

EXAMPLE 558

N-(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)-4-cyanopiperidine-1-carboxamide

EXAMPLE 558A

4-cyanopiperidine-1-carboxamide

A round-bottom flask containing phosgene (20%wt in toluene, 3.16 mL) and dichloromethane (10 mL) was cooled with an ice bath. A solution of N-ethyl-N-

isopropylpropan-2-amine (1.393 mL) and piperidine-4-carbonitrile (0.441 g) in dichloromethane (5 mL) was added via a syringe dropwise. The mixture was stirred at room temperature overnight and then concentrated to dryness. The residue was dissolved in methanol (10 mL) and 2 mL of 7 N NH_3 in methanol. The mixture was stirred at 50 °C overnight. The mixture was concentrated and the residual solid was mixed with brine (5 mL) and extracted with ethyl acetate (8x 25 mL). The organic solution was dried ($MgSO_4$), filtered and concentrated. The crude material was purified on a silica gel column eluting with 5-10% methanol in CH_2Cl_2.

EXAMPLE 558B

4-cyano-N-(2-nitro-4-sulfamoylphenyl)piperidine-1-carboxamide

The title compound was prepared by substituting EXAMPLE 558A for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 279A.

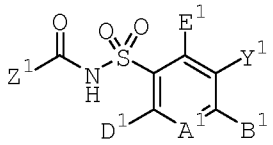
EXAMPLE 558C

N-(4-(N-(2-(1H-indazol-4-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenyl)-4-cyanopiperidine-1-carboxamide

The title compound was prepared by substituting EXAMPLE 400E for EXAMPLE 26C and EXAMPLE 558B for EXAMPLE 1F in EXAMPLE 177. ^{1}H NMR (500MHz, pyridine-d_5) δ 14.58 (bs, 1H), 10.43 (s, 1H), 9.05 (d, 1H), 8.56 (d, 1H), 8.36 (s, 1H), 8.16 (d, 1H), 8.10 (d, 1H), 7.45 (d, 2H), 7.35 (d, 1H), 7.14 (d, 1H), 7.11 (d, 2H), 6.85 (m, 2H), 6.49 (d, 1H), 3.79 (m, 2H), 3.46 (m, 2H), 3.16 (m, 4H), 2.98 (m, 1H), 2.82 (s, 2H), 2.30 (t, 2H), 2.24 (m, 4H), 1.99 (s, 2H), 1.85 (m, 2H), 1.79 (m, 2H), 1.41 (t, 2H), 0.96 (s, 6H).

WHAT IS CLAIMED IS:

1. A compound having formula I



(I),

or a therapeutically acceptable salt, prodrug or salt of prodrug thereof ,

A^1 is N or $C(A^2)$;

one or two or three or each of A^2, B^1, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$; and

Y^1 is H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ or $NHSO_2R^{17}$;

or

B^1 and Y^1, together with the atoms to which they are attached, are imidazole or triazole; and

one or two or each of A^2, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$;

R^1 is R^2, R^3, R^4 or R^5;

R^{1A} is C_1-C_6-alkyl, C_3-C_6-alkenyl or C_3-C_6-alkynyl;

R^2 is phenyl which is unfused or fused with arene, heteroarene or R^{2A}; R^{2A} is cycloalkane or heterocycloalkane;

R^3 is heteroaryl which is unfused or fused with benzene, heteroarene or R^{3A}; R^{3A} is cycloalkane or heterocycloalkane;

R^4 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with arene, heteroarene or R^{4A}; R^{4A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^5 is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^6 is C_2-C_5-spiroalkyl, each of which is unsubstituted or substituted with OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ or $N(CH_3)_2$;

R^{6A} and R^{6B} are independently selected alkyl or, together with the N to which they are attached, R^{6C};

R^{6C} is aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, each having one CH_2 moiety unreplaced or replaced with O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH;

R^7 is R^8, R^9, R^{10} or R^{11};

R^8 is phenyl which is unfused or fused with arene, heteroarene or R^{8A};

R^{8A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^9 is heteroaryl which is unfused or fused with arene, heteroarene or R^{9A}; R^{9A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{10} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{10A}; R^{10A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{11} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{12} is R^{13}, R^{14}, R^{15} or R^{16};

R^{13} is phenyl which is unfused or fused with arene, heteroarene or R^{13A}; R^{13A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{14} is heteroaryl, each of which is unfused or fused with arene, heteroarene or R^{14A}; R^{14A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{15} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene, each of which is unfused or fused with arene, heteroarene or R^{15A}; R^{15A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{16} is alkyl, alkenyl or alkynyl;

R^{17} is R^{18}, R^{19}, R^{20} or R^{21};

R^{18} is phenyl which is unfused or fused with arene, heteroarene or R^{18A}; R^{18A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{19} is heteroaryl which is unfused or fused with arene, heteroarene or R^{19A}; R^{19A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{20} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{20A}; R^{20A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{21} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{22} is R^{23}, R^{24} or R^{25};

R^{23} is phenyl which is unfused or fused with arene, heteroarene or R^{23A}; R^{23A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{24} is heteroarene which is unfused or fused with arene, heteroarene or R^{24A}; R^{24A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{25} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{25A}; R^{25A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

Z^1 is R^{26} or R^{27}, each of which is substituted with R^{28}, R^{29} or R^{30}, each of which is substituted with F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} or $N(R^{32})R^{37}$;

R^{26} is phenyl which is unfused or fused with arene or heteroarene;

R^{27} is heteroarene which is unfused or fused with arene or heteroarene;

R^{28} is phenyl which is unfused or fused with arene, heteroarene or R^{28A}; R^{28A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{29} is heteroaryl or R^{29A}; R^{29A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{30} is cycloalkyl or cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{30A}; R^{30A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{31} and R^{31A} are independently F, Cl, Br or alkyl or are taken together and are C_2-C_5-spiroalkyl;

R^{32} is R^{33}, $C(O)R^{33}$ or $C(O)OR^{33}$;

R^{33} is R^{34} or R^{35};

R^{34} is phenyl which is unfused or fused with aryl, heteroaryl or R^{34A}; R^{34A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{35} is alkyl which is unsubstituted or substituted with R^{36};

R^{36} is phenyl which is unfused or fused with arene, heteroarene or R^{36A}; R^{36A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{37} is R^{38}, R^{39} or R^{40}, each of which is substituted with F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ or SO_2R^{41};

R^{38} is phenyl which is unfused or fused with arene, heteroarene or R^{38A}; R^{38A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{39} is heteroaryl which is unfused or fused with arene, heteroarene or R^{39A}; R^{39A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{40} is C_3-C_8-cycloalkyl or C_4-C_8-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{40A}; R^{40A} cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{41} is R^{42}, R^{43}, R^{44} or R^{45};

R^{42} is phenyl which is unfused or fused with arene, heteroarene or R^{42A}; R^{42A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{43} is heteroaryl which is unfused or fused with arene, heteroarene or R^{43A}; R^{43A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{44} is C_3-C_9-cycloalkyl or C_4-C_7-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2

or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{44A}; R^{44A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{45} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two independently selected R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), $C(O)OH$, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{46} is R^{47}, R^{48} or R^{49};

R^{47} is phenyl which is unfused or fused with arene, heteroarene or R^{47A}; R^{47A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{48} is heteroaryl or R^{48A}; R^{48A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{49} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{49A}; R^{49A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein the moieties represented by R^{26} and R^{27} are further substituted by one or two or three of independently selected R^{50A}, OR^{50A}, SR^{50A}, $S(O)R^{50A}$, SO_2R^{50A} or NHR^{50A};

R^{50A} is R^{51A}, R^{52A}, R^{53A} or R^{54A};

R^{51A} is phenyl which is unfused or fused with benzene, heteroarene or R^{51AA},

wherein R^{51AA} is cycloalkane, cycloalkene or heterocycloalkane heterocycloalkene,

R^{52A} is heteroaryl;

R^{53A} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl; each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{53AA};

wherein R^{53AA} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{54A} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{55AA}, OR^{55AA}, SR^{55AA}, $S(O)R^{55AA}$, SO_2R^{55AA}, NHR^{55AA}, $N(R^{55AA})_2$, $C(O)R^{55AA}$, $C(O)NH_2$, $C(O)NHR^{55AA}$, $NHC(O)R^{55AA}$, $NHSO_2R^{55AA}$, $NHC(O)OR^{55AA}$, SO_2NH_2, SO_2NHR^{55AA}, $SO_2N(R^{55AA})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55AA}$, OH, (O), $C(O)OH$, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{55AA} is alkyl, alkenyl, alkynyl, phenyl or heteroaryl, or R^{56A};

R^{56A} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N;

wherein moieties represented by R^2 R^3 R^4, R^6, R^{6C}, R^8, R^{8A} R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{18}, R^{19}, R^{20}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{34}, R^{36}, R^{38}, R^{39}, R^{40}, R^{42}, R^{43}, R^{44}, R^{47}, R^{48}, and R^{49} are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five independently selected R^{50AA}, R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{50AA} is spirocyclyl;

R^{50} is R^{51}, R^{52}, R^{53} or R^{54};

R^{51} is phenyl which is unfused or fused with arene, heteroarene or R^{51B}; R^{51B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{52} is heteroaryl;

R^{53} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{53B};

wherein R^{53B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

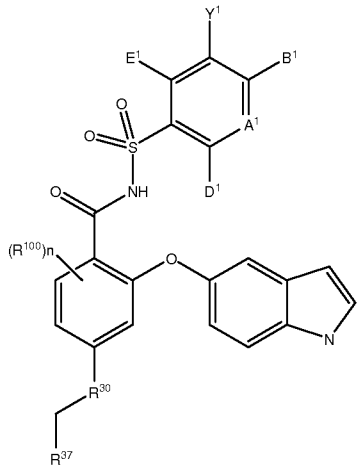
R^{54} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{55} is alkyl, alkenyl, alkynyl, phenyl, heteroaryl or R^{56};

wherein the alkyl, alkenyl, alkynyl are unsubstituted or substituted with OCH_3; and

R^{56} is C_3-C_8-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N.

2. A compound having formula II



(II),

or a therapeutically acceptable salt, prodrug or salt of prodrug thereof ,

wherein

R^{100} is as described for substituents on R^{26};

n is 0, 1, 2, or 3;

A^1 is N or $C(A^2)$;

one or two or three or each of A^2, B^1, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$; and

Y^1 is H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ or $NHSO_2R^{17}$;

or

B^1 and Y^1, together with the atoms to which they are attached, are imidazole or triazole; and

one or two or each of A^2, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$;

R^1 is R^2, R^3, R^4 or R^5;

R^{1A} is C_1-C_6-alkyl, C_3-C_6-alkenyl or C_3-C_6-alkynyl;

R^2 is phenyl which is unfused or fused with arene, heteroarene or R^{2A}; R^{2A} is cycloalkane or heterocycloalkane;

R^3 is heteroaryl which is unfused or fused with benzene, heteroarene or R^{3A}; R^{3A} is cycloalkane or heterocycloalkane;

R^4 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with arene, heteroarene or R^{4A}; R^{4A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^5 is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^6 is C_2-C_5-spiroalkyl, each of which is unsubstituted or substituted with OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ or $N(CH_3)_2$;

R^{6A} and R^{6B} are independently selected alkyl or, together with the N to which they are attached, R^{6C};

R^{6C} is aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, each having one CH_2 moiety unreplaced or replaced with O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH;

R^7 is R^8, R^9, R^{10} or R^{11};

R^8 is phenyl which is unfused or fused with arene, heteroarene or R^{8A};

R^{8A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^9 is heteroaryl which is unfused or fused with arene, heteroarene or R^{9A}; R^{9A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{10} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{10A}; R^{10A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{11} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{12} is R^{13}, R^{14}, R^{15} or R^{16};

R^{13} is phenyl which is unfused or fused with arene, heteroarene or R^{13A}; R^{13A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{14} is heteroaryl, each of which is unfused or fused with arene, heteroarene or R^{14A}; R^{14A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{15} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene, each of which is unfused or fused with arene, heteroarene or R^{15A}; R^{15A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{16} is alkyl, alkenyl or alkynyl;

R^{17} is R^{18}, R^{19}, R^{20} or R^{21};

R^{18} is phenyl which is unfused or fused with arene, heteroarene or R^{18A}; R^{18A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{19} is heteroaryl which is unfused or fused with arene, heteroarene or R^{19A}; R^{19A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{20} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{20A}; R^{20A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{21} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{22} is R^{23}, R^{24} or R^{25};

R^{23} is phenyl which is unfused or fused with arene, heteroarene or R^{23A}; R^{23A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{24} is heteroarene which is unfused or fused with arene, heteroarene or R^{24A}; R^{24A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{25} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{25A}; R^{25A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{30} is cycloalkyl or cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and

one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{30A}; R^{30A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; each of which is substituted with F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} or $N(R^{32})R^{37}$;

R^{31} and R^{31A} are independently F, Cl, Br or alkyl or are taken together and are C_2-C_5-spiroalkyl;

R^{32} is R^{33}, $C(O)R^{33}$ or $C(O)OR^{33}$;

R^{33} is R^{34} or R^{35};

R^{34} is phenyl which is unfused or fused with aryl, heteroaryl or R^{34A}; R^{34A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{35} is alkyl which is unsubstituted or substituted with R^{36};

R^{36} is phenyl which is unfused or fused with arene, heteroarene or R^{36A}; R^{36A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{37} is R^{38}, R^{39} or R^{40}, each of which is substituted with F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ or SO_2R^{41};

R^{38} is phenyl which is unfused or fused with arene, heteroarene or R^{38A}; R^{38A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{39} is heteroaryl which is unfused or fused with arene, heteroarene or R^{39A}; R^{39A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{40} is C_3-C_8-cycloalkyl or C_4-C_8-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{40A}; R^{40A} cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{41} is R^{42}, R^{43}, R^{44} or R^{45};

R^{42} is phenyl which is unfused or fused with arene, heteroarene or R^{42A}; R^{42A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{43} is heteroaryl which is unfused or fused with arene, heteroarene or R^{43A}; R^{43A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{44} is C_3-C_9-cycloalkyl or C_4-C_7-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{44A}; R^{44A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{45} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two independently selected R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{46} is R^{47}, R^{48} or R^{49};

R^{47} is phenyl which is unfused or fused with arene, heteroarene or R^{47A}; R^{47A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{48} is heteroaryl or R^{48A}; R^{48A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{49} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{49A}; R^{49A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein moieties represented by R^2 R^3 R^4, R^6, R^{6C}, R^8, R^{8A} R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{18}, R^{19}, R^{20}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{34}, R^{36}, R^{38}, R^{39}, R^{40}, R^{42}, R^{43}, R^{44}, R^{47}, R^{48}, and R^{49} are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five independently selected R^{50AA}, R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{50AA} is spirocyclyl;

R^{50} is R^{51}, R^{52}, R^{53} or R^{54};

R^{51} is phenyl which is unfused or fused with arene, heteroarene or R^{51B}; R^{51B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{52} is heteroaryl;

R^{53} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{53B};

wherein R^{53B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

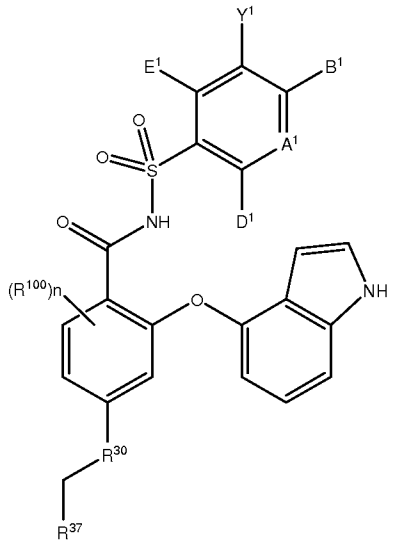
R^{54} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{55} is alkyl, alkenyl, alkynyl, phenyl, heteroaryl or R^{56};

wherein the alkyl, alkenyl, alkynyl are unsubstituted or substituted with OCH_3; and

R^{56} is C_3-C_8-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N.

3. A compound having formula III



(III),

or a therapeutically acceptable salt, prodrug or salt of prodrug thereof ,

wherein

R^{100} is as described for substituents on R^{26};

n is 0, 1, 2, or 3;

A^1 is N or $C(A^2)$;

one or two or three or each of A^2, B^1, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$,

$NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$; and

Y^1 is H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ or $NHSO_2R^{17}$;

or

B^1 and Y^1, together with the atoms to which they are attached, are imidazole or triazole; and

one or two or each of A^2, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$;

R^1 is R^2, R^3, R^4 or R^5;

R^{1A} is C_1-C_6-alkyl, C_3-C_6-alkenyl or C_3-C_6-alkynyl;

R^2 is phenyl which is unfused or fused with arene, heteroarene or R^{2A}; R^{2A} is cycloalkane or heterocycloalkane;

R^3 is heteroaryl which is unfused or fused with benzene, heteroarene or R^{3A}; R^{3A} is cycloalkane or heterocycloalkane;

R^4 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with arene, heteroarene or R^{4A}; R^{4A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^5 is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^6 is C_2-C_5-spiroalkyl, each of which is unsubstituted or substituted with OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ or $N(CH_3)_2$;

R^{6A} and R^{6B} are independently selected alkyl or, together with the N to which they are attached, R^{6C};

R^{6C} is aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, each having one CH_2 moiety unreplaced or replaced with O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH;

R^7 is R^8, R^9, R^{10} or R^{11};

R^8 is phenyl which is unfused or fused with arene, heteroarene or R^{8A};

R^{8A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^9 is heteroaryl which is unfused or fused with arene, heteroarene or R^{9A}; R^{9A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{10} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{10A}; R^{10A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{11} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{12} is R^{13}, R^{14}, R^{15} or R^{16};

R^{13} is phenyl which is unfused or fused with arene, heteroarene or R^{13A}; R^{13A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{14} is heteroaryl, each of which is unfused or fused with arene, heteroarene or R^{14A}; R^{14A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{15} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene, each of which is unfused or fused with arene, heteroarene or R^{15A}; R^{15A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{16} is alkyl, alkenyl or alkynyl;

R^{17} is R^{18}, R^{19}, R^{20} or R^{21};

R^{18} is phenyl which is unfused or fused with arene, heteroarene or R^{18A}; R^{18A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{19} is heteroaryl which is unfused or fused with arene, heteroarene or R^{19A}; R^{19A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{20} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{20A}; R^{20A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{21} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{22} is R^{23}, R^{24} or R^{25};

R^{23} is phenyl which is unfused or fused with arene, heteroarene or R^{23A}; R^{23A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{24} is heteroarene which is unfused or fused with arene, heteroarene or R^{24A}; R^{24A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{25} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{25A}; R^{25A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{30} is cycloalkyl or cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{30A}; R^{30A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; each of which is substituted with F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} or $N(R^{32})R^{37}$;

R^{31} and R^{31A} are independently F, Cl, Br or alkyl or are taken together and are C_2-C_5-spiroalkyl;

R^{32} is R^{33}, $C(O)R^{33}$ or $C(O)OR^{33}$;

R^{33} is R^{34} or R^{35};

R^{34} is phenyl which is unfused or fused with aryl, heteroaryl or R^{34A}; R^{34A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{35} is alkyl which is unsubstituted or substituted with R^{36};

R^{36} is phenyl which is unfused or fused with arene, heteroarene or R^{36A}; R^{36A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{37} is R^{38}, R^{39} or R^{40}, each of which is substituted with F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ or SO_2R^{41};

R^{38} is phenyl which is unfused or fused with arene, heteroarene or R^{38A}; R^{38A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{39} is heteroaryl which is unfused or fused with arene, heteroarene or R^{39A}; R^{39A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{40} is C_3-C_8-cycloalkyl or C_4-C_8-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{40A}; R^{40A} cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{41} is R^{42}, R^{43}, R^{44} or R^{45};

R^{42} is phenyl which is unfused or fused with arene, heteroarene or R^{42A}; R^{42A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{43} is heteroaryl which is unfused or fused with arene, heteroarene or R^{43A}; R^{43A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{44} is C_3-C_9-cycloalkyl or C_4-C_7-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{44A}; R^{44A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{45} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two independently selected R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{46} is R^{47}, R^{48} or R^{49};

R^{47} is phenyl which is unfused or fused with arene, heteroarene or R^{47A}; R^{47A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{48} is heteroaryl or R^{48A}; R^{48A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{49} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{49A}; R^{49A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein moieties represented by R^2 R^3 R^4, R^6, R^{6C}, R^8, R^{8A} R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{18}, R^{19}, R^{20}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{34}, R^{36}, R^{38}, R^{39}, R^{40}, R^{42}, R^{43}, R^{44}, R^{47}, R^{48}, and R^{49} are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five independently selected R^{50AA}, R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50},

$N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{50AA} is spirocyclyl;

R^{50} is R^{51}, R^{52}, R^{53} or R^{54};

R^{51} is phenyl which is unfused or fused with arene, heteroarene or R^{51B}; R^{51B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{52} is heteroaryl;

R^{53} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{53B};

wherein R^{53B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

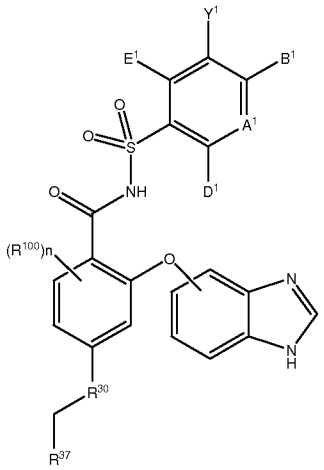
R^{54} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{55} is alkyl, alkenyl, alkynyl, phenyl, heteroaryl or R^{56};

wherein the alkyl, alkenyl, alkynyl are unsubstituted or substituted with OCH_3; and

R^{56} is C_3-C_8-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N.

4. A compound having formula IV



(IV),

or a therapeutically acceptable salt, prodrug or salt of prodrug thereof ,

wherein

R^{100} is as described for substituents on R^{26};

n is 0, 1, 2, or 3;

A^1 is N or $C(A^2)$;

one or two or three or each of A^2, B^1, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$; and

Y^1 is H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ or $NHSO_2R^{17}$;

or

B^1 and Y^1, together with the atoms to which they are attached, are imidazole or triazole; and

one or two or each of A^2, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$;

R^1 is R^2, R^3, R^4 or R^5;

R^{1A} is C_1-C_6-alkyl, C_3-C_6-alkenyl or C_3-C_6-alkynyl;

R^2 is phenyl which is unfused or fused with arene, heteroarene or R^{2A}; R^{2A} is cycloalkane or heterocycloalkane;

R^3 is heteroaryl which is unfused or fused with benzene, heteroarene or R^{3A}; R^{3A} is cycloalkane or heterocycloalkane;

R^4 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with arene, heteroarene or R^{4A}; R^{4A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^5 is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^6 is C_2-C_5-spiroalkyl, each of which is unsubstituted or substituted with OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ or $N(CH_3)_2$;

R^{6A} and R^{6B} are independently selected alkyl or, together with the N to which they are attached, R^{6C};

R^{6C} is aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, each having one CH_2 moiety unreplaced or replaced with O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH;

R^7 is R^8, R^9, R^{10} or R^{11};

R^8 is phenyl which is unfused or fused with arene, heteroarene or R^{8A};

R^{8A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^9 is heteroaryl which is unfused or fused with arene, heteroarene or R^{9A}; R^{9A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{10} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{10A}; R^{10A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{11} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{12} is R^{13}, R^{14}, R^{15} or R^{16};

R^{13} is phenyl which is unfused or fused with arene, heteroarene or R^{13A}; R^{13A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{14} is heteroaryl, each of which is unfused or fused with arene, heteroarene or R^{14A}; R^{14A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{15} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene, each of which is unfused or fused with arene, heteroarene or R^{15A}; R^{15A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{16} is alkyl, alkenyl or alkynyl;

R^{17} is R^{18}, R^{19}, R^{20} or R^{21};

R^{18} is phenyl which is unfused or fused with arene, heteroarene or R^{18A}; R^{18A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{19} is heteroaryl which is unfused or fused with arene, heteroarene or R^{19A}; R^{19A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{20} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{20A}; R^{20A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{21} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{22} is R^{23}, R^{24} or R^{25};

R^{23} is phenyl which is unfused or fused with arene, heteroarene or R^{23A}; R^{23A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{24} is heteroarene which is unfused or fused with arene, heteroarene or R^{24A}; R^{24A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{25} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{25A}; R^{25A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{30} is cycloalkyl or cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and

one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{30A}; R^{30A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; each of which is substituted with F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} or $N(R^{32})R^{37}$;

R^{31} and R^{31A} are independently F, Cl, Br or alkyl or are taken together and are C_2-C_5-spiroalkyl;

R^{32} is R^{33}, $C(O)R^{33}$ or $C(O)OR^{33}$;

R^{33} is R^{34} or R^{35};

R^{34} is phenyl which is unfused or fused with aryl, heteroaryl or R^{34A}; R^{34A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{35} is alkyl which is unsubstituted or substituted with R^{36};

R^{36} is phenyl which is unfused or fused with arene, heteroarene or R^{36A}; R^{36A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{37} is R^{38}, R^{39} or R^{40}, each of which is substituted with F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ or SO_2R^{41};

R^{38} is phenyl which is unfused or fused with arene, heteroarene or R^{38A}; R^{38A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{39} is heteroaryl which is unfused or fused with arene, heteroarene or R^{39A}; R^{39A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{40} is C_3-C_8-cycloalkyl or C_4-C_8-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{40A}; R^{40A} cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{41} is R^{42}, R^{43}, R^{44} or R^{45};

R^{42} is phenyl which is unfused or fused with arene, heteroarene or R^{42A}; R^{42A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{43} is heteroaryl which is unfused or fused with arene, heteroarene or R^{43A}; R^{43A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{44} is C_3-C_9-cycloalkyl or C_4-C_7-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{44A}; R^{44A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{45} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two independently selected R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{46} is R^{47}, R^{48} or R^{49};

R^{47} is phenyl which is unfused or fused with arene, heteroarene or R^{47A}; R^{47A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{48} is heteroaryl or R^{48A}; R^{48A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{49} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{49A}; R^{49A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein moieties represented by R^2 R^3 R^4, R^6, R^{6C}, R^8, R^{8A} R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{18}, R^{19}, R^{20}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{34}, R^{36}, R^{38}, R^{39}, R^{40}, R^{42}, R^{43}, R^{44}, R^{47}, R^{48}, and R^{49} are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five independently selected R^{50AA}, R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{50AA} is spirocyclyl;

R^{50} is R^{51}, R^{52}, R^{53} or R^{54};

R^{51} is phenyl which is unfused or fused with arene, heteroarene or R^{51B}; R^{51B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{52} is heteroaryl;

R^{53} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{53B};

wherein R^{53B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

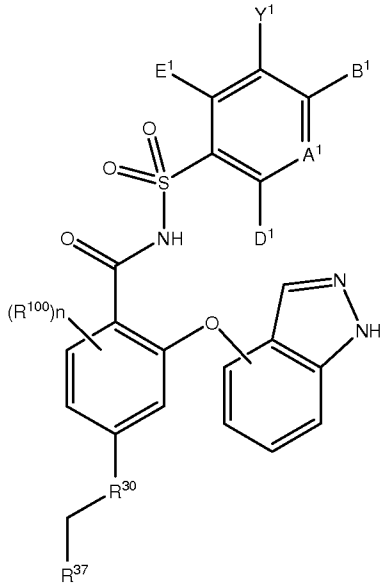
R^{54} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{55} is alkyl, alkenyl, alkynyl, phenyl, heteroaryl or R^{56};

wherein the alkyl, alkenyl, alkynyl are unsubstituted or substituted with OCH_3; and

R^{56} is C_3-C_8-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N.

5. A compound having formula V



(V),

or a therapeutically acceptable salt, prodrug or salt of prodrug thereof ,

wherein

R^{100} is as described for substituents on R^{26};

n is 0, 1, 2, or 3;

A^1 is N or $C(A^2)$;

one or two or three or each of A^2, B^1, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$,

$NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$; and

Y^1 is H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ or $NHSO_2R^{17}$;

or

B^1 and Y^1, together with the atoms to which they are attached, are imidazole or triazole; and

one or two or each of A^2, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$;

R^1 is R^2, R^3, R^4 or R^5;

R^{1A} is C_1-C_6-alkyl, C_3-C_6-alkenyl or C_3-C_6-alkynyl;

R^2 is phenyl which is unfused or fused with arene, heteroarene or R^{2A}; R^{2A} is cycloalkane or heterocycloalkane;

R^3 is heteroaryl which is unfused or fused with benzene, heteroarene or R^{3A}; R^{3A} is cycloalkane or heterocycloalkane;

R^4 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with arene, heteroarene or R^{4A}; R^{4A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^5 is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^6 is C_2-C_5-spiroalkyl, each of which is unsubstituted or substituted with OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ or $N(CH_3)_2$;

R^{6A} and R^{6B} are independently selected alkyl or, together with the N to which they are attached, R^{6C};

R^{6C} is aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, each having one CH_2 moiety unreplaced or replaced with O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH;

R^7 is R^8, R^9, R^{10} or R^{11};

R^8 is phenyl which is unfused or fused with arene, heteroarene or R^{8A};

R^{8A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^9 is heteroaryl which is unfused or fused with arene, heteroarene or R^{9A}; R^{9A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{10} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{10A}; R^{10A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{11} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{12} is R^{13}, R^{14}, R^{15} or R^{16};

R^{13} is phenyl which is unfused or fused with arene, heteroarene or R^{13A}; R^{13A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{14} is heteroaryl, each of which is unfused or fused with arene, heteroarene or R^{14A}; R^{14A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{15} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene, each of which is unfused or fused with arene, heteroarene or R^{15A}; R^{15A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{16} is alkyl, alkenyl or alkynyl;

R^{17} is R^{18}, R^{19}, R^{20} or R^{21};

R^{18} is phenyl which is unfused or fused with arene, heteroarene or R^{18A}; R^{18A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{19} is heteroaryl which is unfused or fused with arene, heteroarene or R^{19A}; R^{19A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{20} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{20A}; R^{20A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{21} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{22} is R^{23}, R^{24} or R^{25};

R^{23} is phenyl which is unfused or fused with arene, heteroarene or R^{23A}; R^{23A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{24} is heteroarene which is unfused or fused with arene, heteroarene or R^{24A}; R^{24A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{25} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{25A}; R^{25A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{30} is cycloalkyl or cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{30A}; R^{30A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; each of which is substituted with F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} or $N(R^{32})R^{37}$;

R^{31} and R^{31A} are independently F, Cl, Br or alkyl or are taken together and are C_2-C_5-spiroalkyl;

R^{32} is R^{33}, $C(O)R^{33}$ or $C(O)OR^{33}$;

R^{33} is R^{34} or R^{35};

R^{34} is phenyl which is unfused or fused with aryl, heteroaryl or R^{34A}; R^{34A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{35} is alkyl which is unsubstituted or substituted with R^{36};

R^{36} is phenyl which is unfused or fused with arene, heteroarene or R^{36A}; R^{36A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{37} is R^{38}, R^{39} or R^{40}, each of which is substituted with F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ or SO_2R^{41};

R^{38} is phenyl which is unfused or fused with arene, heteroarene or R^{38A}; R^{38A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{39} is heteroaryl which is unfused or fused with arene, heteroarene or R^{39A}; R^{39A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{40} is C_3-C_8-cycloalkyl or C_4-C_8-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{40A}; R^{40A} cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{41} is R^{42}, R^{43}, R^{44} or R^{45};

R^{42} is phenyl which is unfused or fused with arene, heteroarene or R^{42A}; R^{42A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{43} is heteroaryl which is unfused or fused with arene, heteroarene or R^{43A}; R^{43A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{44} is C_3-C_9-cycloalkyl or C_4-C_7-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{44A}; R^{44A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{45} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two independently selected R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{46} is R^{47}, R^{48} or R^{49};

R^{47} is phenyl which is unfused or fused with arene, heteroarene or R^{47A}; R^{47A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{48} is heteroaryl or R^{48A}; R^{48A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{49} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{49A}; R^{49A} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein moieties represented by R^2 R^3 R^4, R^6, R^{6C}, R^8, R^{8A} R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{18}, R^{19}, R^{20}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{34}, R^{36}, R^{38}, R^{39}, R^{40}, R^{42}, R^{43}, R^{44}, R^{47}, R^{48}, and R^{49} are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five independently selected R^{50AA}, R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50},

$N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{50AA} is spirocyclyl;

R^{50} is R^{51}, R^{52}, R^{53} or R^{54};

R^{51} is phenyl which is unfused or fused with arene, heteroarene or R^{51B}; R^{51B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{52} is heteroaryl;

R^{53} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with arene, heteroarene or R^{53B};

wherein R^{53B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{54} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{55} is alkyl, alkenyl, alkynyl, phenyl, heteroaryl or R^{56};

wherein the alkyl, alkenyl, alkynyl are unsubstituted or substituted with OCH_3; and

R^{56} is C_3-C_8-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N.

6. The compound of claim 1, claim 2, claim 3, claim 4, or claim 5, wherein

A^1 is $C(A^2)$; and

A^2 is H.

7. The compound of claim 1, claim 2, claim 3, claim 4, or claim 5, wherein

A^1 is $C(A^2)$ or N;

A^2 is H; and

B^1 is NHR^1.

8. The compound of claim 1, claim 2, claim 3, claim 4, or claim 5, wherein
A^1 is $C(A^2)$ or N;
A^2 is H;
B^1 is NHR^1; and
D^1 is H.

9. The compound of claim 1, claim 2, claim 3, claim 4, or claim 5, wherein
A^1 is $C(A^2)$ or N;
A^2 is H;
B^1 is NHR^1;
D^1 is H; and
E^1 is H.

10. The compound of claim 1, claim 2, claim 3, claim 4, or claim 5, wherein
A^1 is $C(A^2)$ or N;
A^2 is H;
B^1 is NHR^1;
D^1 is H;
E^1 is H; and
Y^1 is NO_2.

11. A compound of claim 1, wherein the compound is chosen from:
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;
2-(benzyloxy)-4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(2-phenylethoxy)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(phenylthio)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(phenylthio)-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-(phenylthio)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(phenylsulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(phenylsulfinyl)benzamide;
2-benzyl-4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;
2-benzyl-4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;
2-benzyl-4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(2-phenylethyl)benzamide;
2-(benzylamino)-4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;
2-anilino-4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;
2-anilino-4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-methoxy-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indazol-5-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indazol-5-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-(1,2,3,4-tetrahydroquinolin-6-yloxy)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)-2-(1,2,3,4-tetrahydroquinolin-6-yloxy)benzamide;

4-(4-((4'-chloro-4-(pyrrolidin-1-ylmethyl)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-pyrrolidin-1-ylethyl)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((1-cyclopentylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)-3-isobutylpiperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-(2,4-dioxo-3-azabicyclo(3.2.0)hept-3-yl)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-(3,3-dimethyl-2-oxoazetidin-1-yl)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-(4-nitro-2H-1,2,3-triazol-2-yl)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((2-(2-piperidin-1-ylethoxy)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-((((1-ethylpyrrolidin-2-yl)methyl)amino)carbonyl)-4-methoxyphenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1-naphthyloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(2-naphthyloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-(2-naphthyloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(2-naphthyloxy)-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(quinolin-7-yloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(quinolin-6-yloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(isoquinolin-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(isoquinolin-5-yloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(quinolin-6-yloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-6-yloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(isoquinolin-7-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(isoquinolin-7-yloxy)benzamide;

4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-4-yloxy)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-4-yloxy)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-methoxyphenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-methylphenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
N-((3-((chloro(difluoro)methyl)sulfonyl)-4-((3-(dimethylamino)propyl)amino)phenyl)sulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

2-(1H-indol-4-yloxy)-4-(4-((2-(4-methoxyphenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4,4-dimethyl-2-(4-(trifluoromethyl)phenyl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4,4-dimethyl-2-(4-(trifluoromethoxy)phenyl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4,4-dimethyl-2-(3-(trifluoromethyl)phenyl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(3-fluorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-fluorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

N-((3-((chloro(difluoro)methyl)sulfonyl)-4-((1-methylpiperidin-4-yl)amino)phenyl)sulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-((2-(4-chlorophenyl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(phenoxymethyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(pyridin-3-yloxy)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(pyridin-3-yloxy)-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-(((1R)-3-(dimethylamino)-1-((phenylthio)methyl)propyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(pyridin-4-yloxy)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-(pyridin-3-yloxy)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-(pyridin-4-yloxy)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((2-(4-methylpiperazin-1-yl)ethyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(4-methylpiperazin-1-yl)propyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)(methyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-(((1-methylpiperidin-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-cyano-4-((3-(dimethylamino)propyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-(trifluoromethyl)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(isopropyl(methyl)amino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-(3-(dimethylamino)propoxy)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((2-(4-methylpiperazin-1-yl)ethyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((3-(4-methylpiperazin-1-yl)propyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((3-(4-methylpiperazin-1-yl)propyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-(3-(dimethylamino)propoxy)-3-nitrophenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((2-(4-methylpiperazin-1-yl)ethyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-(((1-methylpiperidin-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-(((1-methylpiperidin-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-(3-(dimethylamino)propoxy)-3-nitrophenyl)sulfonyl)-2-(1H-indol-4-yloxy)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-(4-methylpiperazin-1-yl)-3-nitrophenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((1-(2,2,2-trifluoroethyl)piperidin-4-yl)amino)phenyl)sulfonyl)benzamide;
4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-(((4-(dimethylamino)-1-methylpiperidin-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(2,3-dihydro-1,4-benzodioxin-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;
5-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-1,1'-biphenyl-2-carboxamide;

5-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-1,1'-biphenyl-2-carboxamide;
4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-4-(3-piperidin-1-ylpropoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-4-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-4-(3-(dimethylamino)propoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-4-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-4-(3-piperidin-1-ylpropoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-4-(3-(dimethylamino)propoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-3-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-3-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-3-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-morpholin-4-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((4'-chloro-4-(2-(dimethylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((1-(2,2,2-trifluoroethyl)piperidin-4-yl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-4-(2-pyrrolidin-1-ylethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-4-(2-(diisopropylamino)ethoxy)-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-(2,3-dihydro-1H-indol-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)cyclohept-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)cyclooct-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)cyclopent-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((3-nitro-4-((3-pyrrolidin-1-ylpropyl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclopent-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)cyclooct-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)cyclohept-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)cyclopent-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)cyclohept-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((1-methylpiperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((2-(dimethylamino)ethyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((4-(dimethylamino)butyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((1-(phenylsulfonyl)piperidin-4-yl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((1-(quinolin-8-ylsulfonyl)piperidin-4-yl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((1-(phenylsulfonyl)piperidin-4-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((1-(quinolin-8-ylsulfonyl)piperidin-4-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-(((1S)-3-(dimethylamino)-1-thien-2-ylpropyl)amino)-3-nitrophenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((thien-2-ylmethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-2-phenoxy-N-((4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((2-(1H-1,2,3-triazol-1-yl)ethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((2-(2H-1,2,3-triazol-2-yl)ethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-nitrophenyl)sulfonyl)-2-(2-naphthyloxy)benzamide;
4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((2-(2-oxopyridin-1(2H)-yl)ethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((2-(pyridin-2-yloxy)ethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((4'-chloro-1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((2-pyridin-4-ylethyl)amino)phenyl)sulfonyl)-2-phenoxybenzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((3-(dimethylamino)propyl)amino)-3-(trifluoromethyl)phenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((3-cyano-4-((3-(dimethylamino)propyl)amino)phenyl)sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1*H*-indol-5-yloxy)-*N*-((3-nitro-4-((1-tetrahydro-2*H*-pyran-4-ylpiperidin-4-yl)amino)phenyl)sulfonyl)benzamide;

4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1*H*-indol-5-yloxy)-*N*-((4-((4-methylpiperazin-1-yl)amino)-3-nitrophenyl)sulfonyl)benzamide;

4-(4-(1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl)piperazin-1-yl)-2-(1*H*-indol-4-yloxy)-*N*-((3-nitro-4-((tetrahydro-2*H*-pyran-4-ylmethyl)amino)phenyl)sulfonyl)benzamide;

N-((4-(((4-aminotetrahydro-2*H*-pyran-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1*H*-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(2-methoxyethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(3S)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(3R)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-hydroxy-1-methylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-3-fluoro-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-3-fluoro-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-hydroxy-1-methylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

N-[(4-{[(3S,4R)-1-benzyl-3-hydroxypiperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

N-[(4-{[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[1-(2-methoxyethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(2-hydroxyethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[1-(2-methoxyethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(3-hydroxypropyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-[4-({4'-chloro-3-[3-(dimethylamino)propyl]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(3-hydroxypropyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-{4-[(4'-chloro-4-morpholin-4-yl-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-[4-({4'-chloro-3-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(diethylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(dimethylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(diethylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-[4-({4'-chloro-3-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-{4-[1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(dimethylamino)tetrahydro-2H-pyran-4-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;

N-({4-[(2-aminocyclohexyl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-[4-({4'-chloro-4-[3-(dimethylamino)prop-1-ynyl]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(3-nitro-4-{[1-(4,4,4-trifluorobutyl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[2-(4-hydroxy-1-methylpiperidin-4-yl)ethyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[1-(1,3-thiazol-2-yl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[4'-chloro-4-(2-hydroxyethoxy)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(cyclopropylmethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[1-(4,4,4-trifluorobutyl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide;

4-{4-[1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-(hydroxymethyl)piperazin-1-yl]-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-(hydroxymethyl)piperazin-1-yl]-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-(4-{[4'-chloro-4-(2-hydroxyethoxy)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[3-(3-oxopiperazin-1-yl)propyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(3-nitro-4-{[3-(3-oxopiperazin-1-yl)propyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-5-hydroxycyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-5-hydroxycyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-5-hydroxycyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(2,3-dihydro-1H-inden-2-yl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(2,3-dihydro-1H-inden-2-yl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(1-morpholin-4-ylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[1-(1,3-thiazol-2-ylmethyl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[1-(1,3-thiazol-4-ylmethyl)piperidin-4-yl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(2-hydroxyethyl)piperazin-1-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(3S)-1-methylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(3-fluoropropyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-(hydroxymethyl)piperazin-1-yl]-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

N-[(4-{[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-(hydroxymethyl)piperazin-1-yl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(2-methoxyethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-hydroxy-1-tetrahydro-2H-pyran-4-ylethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-({1-[2-(1H-pyrazol-1-yl)ethyl]piperidin-4-yl}amino)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(methylamino)-3-nitrophenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[4-(methylamino)-3-nitrophenyl]sulfonyl}benzamide;

4-{4-[1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-5-hydroxycyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-5-morpholin-4-ylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

N-[(4-{[(1-aminocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[2-(2-oxopyrrolidin-1-yl)ethyl]amino}phenyl)sulfonyl]benzamide;

4-{4-[1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{1-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]ethyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{1-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]ethyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-{4-[(1R)-1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
4-{4-[(1S)-1-(4'-chloro-1,1'-biphenyl-2-yl)ethyl]piperazin-1-yl}-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{1-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]ethyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide;
4-(4-{1-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]ethyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(cyclohexylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(morpholin-4-ylamino)-3-nitrophenyl]sulfonyl}benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-3-ylmethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[4-(morpholin-4-ylamino)-3-nitrophenyl]sulfonyl}benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylamino)phenyl]sulfonyl}benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(3-methyloxetan-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methoxycyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(1,1-dioxidothiomorpholin-4-yl)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[2-(2-oxopiperidin-1-yl)ethyl]amino}phenyl)sulfonyl]benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[2-(2-oxoimidazolidin-1-yl)ethyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(2-pyridin-4-ylethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-morpholin-4-yl-3-nitrophenyl)sulfonyl]benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(4-methoxypiperidin-1-yl)-3-nitrophenyl]sulfonyl}benzamide;
4-(4-{[2-(4-chlorophenyl)-5-pyrrolidin-1-ylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[2-(3-oxopiperazin-1-yl)ethyl]amino}phenyl)sulfonyl]benzamide;
4-[4-({4'-chloro-4-[2-(dimethylamino)ethoxy]-1,1'-biphenyl-2-yl}methyl)piperazin-1-yl]-2-(1H-indol-4-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1,1-dioxidotetrahydrothien-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl]sulfonyl}benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[2-(1,3-dioxolan-2-yl)ethyl]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(3-nitro-4-{[2-(3-oxopiperazin-1-yl)ethyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methyl-5-oxopyrrolidin-3-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methyl-6-oxopiperidin-3-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[3-nitro-4-(piperidin-1-ylamino)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(piperidin-1-ylamino)phenyl]sulfonyl}benzamide;

4-(4-{[4-(4-chlorophenyl)-1-methyl-1H-pyrazol-5-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(3-methyloxetan-3-yl)methoxy]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(1-oxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1,3-thiazol-5-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(2-tetrahydro-2H-pyran-4-ylethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(3-nitro-4-{[2-(trifluoromethoxy)ethyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[2-(2-methoxyethoxy)ethyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[3-(methylsulfonyl)propyl]amino}-3-nitrophenyl)sulfonyl]benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(1,1-dioxidothiomorpholin-4-yl)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(2-tetrahydro-2H-pyran-4-ylethyl)phenyl]sulfonyl}benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[2-(2-methoxyethoxy)ethyl]amino}-3-nitrophenyl)sulfonyl]benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-4-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[2-(trifluoromethoxy)ethyl]amino}phenyl)sulfonyl]benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2,2-difluoroethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4,4-difluorocyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-1-isopropyl-6-oxo-1,6-dihydropyridin-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(tetrahydro-2H-pyran-4-ylmethyl)amino]carbonyl}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(2-methoxyethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[3-nitro-4-(2-tetrahydro-2H-pyran-4-ylethoxy)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(2-methoxyethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[3-(methylsulfonyl)propoxy]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(3-methoxypropyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(3-methoxypropyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-cyanoethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-cyanoethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-4-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(3R)-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[Cis-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(3,3,3-trifluoropropyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(3,3,3-trifluoropropyl)amino]phenyl}sulfonyl)benzamide;
N-({5-bromo-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1,1-dioxidotetrahydrothien-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-4-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-(methylamino)-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;
N-{[5-bromo-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[4-(4-chlorophenyl)-6-isopropoxypyridin-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[6-(tetrahydro-2H-pyran-4-ylmethoxy)-5-(1,3-thiazol-2-yl)pyridin-3-yl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(2-methoxyethyl)amino]carbonyl}phenyl)sulfonyl]benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;
N-({4-[(1-acetylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[1-(methylsulfonyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
N-({4-[(1-acetylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[1-(methylsulfonyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;
4-(4-{[4'-chloro-5-(trifluoromethyl)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[4'-chloro-5-(trifluoromethyl)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}benzamide;
4-{4-[(5-tert-butyl-4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
4-{4-[(5-tert-butyl-4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-{[(tetrahydro-2H-pyran-4-ylmethyl)amino]carbonyl}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2R)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2S)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;
N-({5-bromo-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(2-morpholin-4-ylethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)oxy]-3-nitrophenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)benzamide;
4-(4-{[4-(4-chlorophenyl)-1-(3-hydroxypropyl)-1,2,5,6-tetrahydropyridin-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;
benzyl 4-({[4-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzoyl]amino}sulfonyl)-2-nitrophenyl]amino}methyl)piperidine-1-carboxylate;
N-{[3-(aminocarbonyl)-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[4'-chloro-5-(trifluoromethyl)-1,1'-biphenyl-2-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-{4-[(5-tert-butyl-4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(1-methyl-1H-imidazol-5-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(morpholin-4-ylsulfonyl)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidothiomorpholin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

N-{[5-bromo-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-5-(1,3-thiazol-2-yl)pyridin-3-yl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3,3-dimethylbutyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1S)-1-(hydroxymethyl)-3-methylbutyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(2R)-tetrahydrofuran-2-ylmethyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1R)-1-(hydroxymethyl)-2-methylpropyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methoxyphenyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

N-[(4-{[2-(1,3-benzodioxol-5-yl)ethyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-hydroxyphenyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

N-{[4-({2-[4-(aminosulfonyl)phenyl]ethyl}amino)-3-nitrophenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(1H-imidazol-1-yl)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(1S)-1-phenylethyl]amino}phenyl)sulfonyl]benzamide;

N-({2-chloro-5-fluoro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[2-(2-methoxyethoxy)ethyl]thio}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-[(4-{[2-(2-methoxyethoxy)ethyl]thio}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-{[4-(methylsulfonyl)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)-N-{[4-(methylsulfonyl)phenyl]sulfonyl}benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2,2-dimethyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-4-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-4-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(2-morpholin-4-ylethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)oxy]phenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-morpholin-4-ylbut-2-ynyl)oxy]-3-nitrophenyl}sulfonyl)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-ethynyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-4-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(2-morpholin-4-ylethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indol-4-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-indol-4-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-hydroxy-4-methoxyphenyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(2,3-dihydro-1H-indol-4-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(pyridin-3-ylamino)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)-2-(pyridin-3-ylamino)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)-2-(pyridin-3-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1,2,3,4-tetrahydroisoquinolin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-5-(trifluoromethyl)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyclopropylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4,4-difluorocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

N-[(5-chloro-6-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

Trans-N-({5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(2,2-difluoroethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-fluoro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

N-[(5-chloro-6-{[1-(cyanomethyl)-4-fluoropiperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydrofuran-3-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

Trans-N-({5-chloro-6-[(4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-[(5-chloro-6-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]oxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-N-[(5-chloro-6-{[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

2-(1H-benzimidazol-4-yloxy)-N-[(5-chloro-6-{[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

N-[(5-chloro-6-{[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-[(5-chloro-6-{[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(cyanomethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({(3R)-1-[2-(2-methoxyethoxy)ethyl]pyrrolidin-3-yl}amino)-3-nitrophenyl]sulfonyl}benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(N,N-dimethylglycyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(cyanomethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyclopropylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(4-oxetan-3-ylmorpholin-2-yl)methyl]amino}phenyl)sulfonyl]benzamide;

N-{[5-chloro-6-({(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl}oxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydrofuran-3-ylmethyl)amino]phenyl}sulfonyl)benzamide;

Trans-2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-fluoro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

N-{[5-chloro-6-({(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl}methoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-[(5-chloro-6-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(1-cyclopropylpiperidin-4-yl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-N-({5-chloro-6-[(1-cyclopropylpiperidin-4-yl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

Trans-2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-methylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[({(2R)-4-[2-(2-methoxyethoxy)ethyl]morpholin-2-yl}methyl)amino]-3-nitrophenyl}sulfonyl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4,4-difluorocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

N-[(4-{[(4-acetylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(methylsulfonyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[6-({4-fluoro-1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl}methoxy)-5-(trifluoromethyl)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(2-tetrahydrofuran-2-ylethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

Trans-2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyanocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzimidazol-4-yloxy)-N-({5-chloro-6-[(4,4-difluorocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-*N*-{[5-cyano-6-(2-tetrahydro-2*H*-pyran-4-ylethoxy)pyridin-3-yl]sulfonyl}-2-(1*H*-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(4-{[(1R,5S)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]amino}-3-nitrophenyl)sulfonyl]benzamide;

N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxy-4-(4-{(3-phenylpropanoyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamide;

N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-phenoxy-4-(4-{(3-phenylpropanoyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamide;

N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxy-4-(4-{(3-phenylpropyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamide;

N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-phenoxy-4-(4-{(3-phenylpropyl)[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino}piperidin-1-yl)benzamide;

4-[4-(2-{[(1R,5S)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]amino}benzyl)piperazin-1-yl]-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-phenoxybenzamide;

4-[4-(2-{[(1R,5S)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]amino}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide;

4-{4-[2-(3-azabicyclo[3.2.2]non-3-yl)benzyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide;

4-{4-[2-(3-azabicyclo[3.2.2]non-3-yl)benzyl]piperazin-1-yl}-2-phenoxy-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-{4-[2-(3-azabicyclo[3.2.2]non-3-yl)benzyl]piperazin-1-yl}-2-phenoxy-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-{4-[2-(3-azabicyclo[3.2.2]non-3-yl)benzyl]piperazin-1-yl}-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-phenoxybenzamide;

4-(4-{2-[(4R,7S)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-5-yl]benzyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide;

4-[4-(2-{5-[(1R,5S)-8-azabicyclo[3.2.1]oct-8-ylmethyl]thien-2-yl}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide;

4-[4-(2-{5-[(1R,5S)-8-azabicyclo[3.2.1]oct-8-ylmethyl]thien-2-yl}benzylidene)piperidin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide;

4-[4-(3-{5-[(1R,5S)-8-azabicyclo[3.2.1]oct-8-ylmethyl]thien-2-yl}benzyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-phenoxybenzamide;

N-({5-chloro-6-[(4,4-difluorocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({6-[(trans-4-carbamoylcyclohexyl)methoxy]-5-chloropyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-cyanocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[2-(1H-imidazol-1-yl)ethoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(1-methyl-1H-imidazol-5-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-fluoro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

N-{[5-chloro-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(4,4-difluoro-1-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(2,2-difluorocyclopropyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(trans-4-cyanocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-(trifluoromethyl)phenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-chloro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

N-{[3-chloro-4-(1,4-dioxan-2-ylmethoxy)phenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-N-[(5-chloro-6-{[(2S)-4-cyclopropylmorpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

N-[(5-chloro-6-{[(2S)-4-cyclopropylmorpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

methyl 2-{[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}morpholine-4-carboxylate;

2-{[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide;

2-{[(4-{[2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}-N-ethyl-N-methylmorpholine-4-carboxam
ide;

N-({5-chloro-6-[(trans-4-ethyl-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(cis-4-ethyl-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

5-chloro-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamid
e;

5-chloro-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(cis-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamid
e;

N-({5-chloro-6-[(trans-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzam
ide;

2-(1H-benzotriazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

2-(1H-benzotriazol-4-yloxy)-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-chloro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}benzamide;

N-[(3-chloro-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(cis-1-fluoro-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzotriazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)benzamide;

N-[(5-chloro-6-{[(1R,2R,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-[(5-chloro-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzotriazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzotriazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S)-4-cyclopropylmorpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

N-[(5-chloro-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S)-4-cyclopropylmorpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S)-4-cyclopropylmorpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}benzamide;

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-cyano-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-{[3-nitro-4-(2-oxaspiro[3.5]non-7-ylmethoxy)phenyl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzami
de;

2-(1H-benzimidazol-4-yloxy)-N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-cyano-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)b
enzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-{[3-nitro-4-({[(2S)-4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)phenyl]sulfonyl}benzamide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-({[(2S)-4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)phenyl]sulfonyl}benzamide;

N-[(5-chloro-6-{[trans-4-(2-hydroxypropan-2-yl)cyclohexyl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]phenyl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)-N-({5-nitro-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)benzamide;

2-(1H-benzotriazol-4-yloxy)-N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzamide;

N-({3-chloro-4-[(cis-4-cyano-1-fluorocyclohexyl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({3-chloro-4-[(trans-4-cyano-1-fluorocyclohexyl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(cis-4-cyano-1-fluorocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(trans-4-cyano-1-fluorocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzami

de;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-chloro-6-{[1-(1,3-thiazol-2-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(6-{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-5-nitropyridin-3-yl)sulfonyl]-2-(1H-indazol-4-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-indazol-4-yloxy)benz
amide;

2-(1H-benzimidazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]benzamide;

N-(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indazol-4-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)-4-cyanopiperidine-1-carboxamide; and therapeutically acceptable salts, prodrugs, salts of prodrugs and metabolites thereof.

12. A composition for treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer, said composition comprising an excipient and a therapeutically effective amount of the compound of claim 1.

13. A method of treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies

of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer in a patient, said method comprising administering to the patient a therapeutically effective amount of a compound of claim 1.

14. A method of treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer in a patient, said method comprising administering to the patient therapeutically effective amount of the compound of claim 1 and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/036919

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D405/12 A61K31/404 A61P35/00 C07D209/32 C07D211/96
C07D213/64 C07D215/20 C07D217/16 C07D235/26 C07D249/04
C07D295/14 C07D309/14 C07D401/12 C07D295/125 C07D231/56

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2010/065865 A2 (ABBOTT LAB [US]; BRUNCKO MILAN [US]; DING HONG [US]; DOHERTY GEORGE A) 10 June 2010 (2010-06-10) claims examples 1-481	1-14
E	WO 2010/083441 A2 (ABBOTT LAB [US]; HEXAMER LAURA [US]; DING HONG [US]; ELMORE STEVEN W [) 22 July 2010 (2010-07-22) claims examples	1-14
X	US 2007/072860 A1 (BRUNCKO MILAN [US] ET AL) 29 March 2007 (2007-03-29) the whole document	1-14

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 August 2010	19/08/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Fax: (+31–70) 340–3016	Kollmannsberger, M

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/036919

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/030836 A2 (ABBOTT LAB [US]; ELMORE STEVEN W [US]; ROSENBERG SAUL [US]; GORDON GAR) 13 March 2008 (2008-03-13) page 8, line 11 - page 15, line 24	1-14
Y	CHEOL-MIN PARK ET AL: "Discovery of an orally bioavailable small molecule inhibitor of prosurvival B-cell lymphoma 2 proteins" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US LNKD-DOI:10.1021/JM800669S, vol. 51, no. 21, 13 November 2008 (2008-11-13), pages 6902-6915, XP002574160 ISSN: 0022-2623 [retrieved on 2008-10-08] page 6905, column 2 - page 6907, column 1 compounds 1-34	1-14
Y	BRUNCKO M ET AL: "Studies leading to potent, dual inhibitors of Bcl-2 and Bcl-xL" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US LNKD-DOI:10.1021/JM061152T, vol. 50, no. 4, 22 February 2007 (2007-02-22), pages 641-662, XP002574161 ISSN: 0022-2623 [retrieved on 2007-01-26] * abstract compounds 1-2, 23i-23z, 43a, 43b, 8a-8n, 10a-10k,	1-14
X	US 2005/159427 A1 (BRUNCKO MILAN [US] ET AL) 21 July 2005 (2005-07-21) the whole document	1-14
X	US 2007/015787 A1 (BRUNCKO MILAN [US] ET AL) 18 January 2007 (2007-01-18) the whole document	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2010/036919

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010065865 A2	10-06-2010	US 2010152183 A1	17-06-2010
WO 2010083441 A2	22-07-2010	US 2010184750 A1	22-07-2010
US 2007072860 A1	29-03-2007	NONE	
WO 2008030836 A2	13-03-2008	CA 2662320 A1	13-03-2008
		CN 101534904 A	16-09-2009
		EP 2061560 A2	27-05-2009
		JP 2010502727 T	28-01-2010
		US 2008076779 A1	27-03-2008
US 2005159427 A1	21-07-2005	US 2006128706 A1	15-06-2006
US 2007015787 A1	18-01-2007	NONE	

DERIVADOS DE SULFONAMIDA COMO AGENTES INDUCTORES DE APOPTOSIS CON SELECTIVIDAD POR Bcl-2 PARA EL TRATAMIENTO DE CÁNCER Y ENFERMEDADES INMUNES

La presente solicitud es una continuación parcial de la solicitud de patente estadounidense No. 12/631,404, presentada el 4 de diciembre de 2009, que invoca prioridad sobre las solicitudes estadounidense No. 61/120,275, presentada el 5 de diciembre de 2008, y la solicitud provisional de patente estadounidense No. 61/181,180, presentada el 26 de mayo 2009, las cuales están incorporadas en la presente en su totalidad.

CAMPO DE LA INVENCIÓN

La presente invención se refiere a compuestos que inhiben de manera selectiva la actividad de familia de proteínas anti-apoptóticas Bcl-2, composiciones que contienen dichos compuestos, y métodos para tratar enfermedades durante las cuales se expresan las proteínas anti-apoptóticas Bcl-2.

ANTECEDENTES DE LA INVENCIÓN

Las proteínas anti-apoptóticas de la familia Bcl-2 se asocian con diversas enfermedades y están siendo investigadas como potenciales objetivos para fármacos terapéuticas. Dichos objetivos para la terapia intervencionista incluyen, por ejemplo, a la familia de proteínas Bcl-2 Bcl-2, Bcl-X_L y Bcl-w. Recientemente, los inhibidores de la familia de proteínas Bcl-2 han sido informados en PCT/US/2004/36770, publicada como WO 2005/049593 y PCT/US/2004/367911, publicada como WO 2005/049594, de propiedad conjunta. Aunque en dicho arte se describen inhibidores con alto grado de unión a la proteína objetivo, la afinidad de unión del compuesto es solo uno de muchos parámetros que se deben tomar en consideración. Una meta consiste en producir compuestos que se unan a una proteína con preferencia sobre otra proteína, es decir, que se unan con selectividad por la primera. Para mostrar dicha selectividad, se sabe bien que un compuesto no solo muestra una alta afinidad de unión por una proteína en particular sino además una menor afinidad de unión por otros miembros.

Una medida típica de la afinidad de unión de un inhibidor de proteína anti-apoptótica es el equilibrio entre los procesos de unión y de disociación entre la proteína y el inhibidor (K_i). La constante de inhibición (K_i) es la constante de disociación de un complejo enzima-inhibidor o un complejo de proteína/moléculas pequeñas, donde las moléculas pequeñas inhiben la unión de una proteína a otra proteína. Por lo tanto, un valor K_i grande indica una baja afinidad de unión, y un valor K_i pequeño indica una alta afinidad de unión.

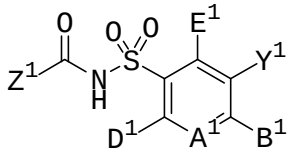
Una medida típica de la actividad celular de un inhibidor de proteína anti-apoptótica es la concentración que causa un 50% del efecto en la célula (EC_{50}).

Por lo tanto, los inventores han descubierto que aunque los compuestos divulgados en el arte son útiles para el tratamiento de diversos tipos de cáncer y enfermedades inmunes, los mismos no poseen selectividad por las proteínas anti-apoptóticas Bcl-2 sobre las proteínas anti-apoptóticas Bcl-X_L y que por lo tanto presentan una mayor probabilidad de causar efectos secundarios caracterizados por la inhibición de proteínas anti-apoptóticas Bcl-X_L tales como trombocitopenia.

Por lo tanto, la presente invención comprende una serie de compuestos que muestran propiedades inesperadas con respecto a su selectividad por unirse a la proteína anti-apoptótica Bcl-2, e inhibir su actividad, respecto de la proteína anti-apoptótica Bcl-X_L que es significativamente mayor que las de los compuestos divulgados en PCT/US/2004/36770 y PCT/US/2004/367911.

SÍNTESIS DE LA INVENCIÓN

Una realización de esta invención, por lo tanto, se refiere a compuestos o sus sales, profármacos, o sales de profármacos terapéuticamente aceptables, que son útiles como inhibidores selectivos de uno o más miembros de la familia de proteínas anti-apoptóticas, donde los compuestos tienen la Fórmula (I)



(I),

en donde A^1 es N o $C(A^2)$;

uno o dos o tres o cada uno de A^2, B^1, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1,

$SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes se seleccionan en forma independiente entre H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$; y

Y^1 es H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ o $NHSO_2R^{17}$;

o

B^1 y Y^1, junto con los átomos a los cuales están unidos , son imidazol o triazol; y

uno o dos o cada uno de A^2, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes se seleccionan en forma independiente entre H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$;

R^1 es R^2, R^3, R^4 o R^5;

R^{1A} es C_1-C_6-alquilo, C_3-C_6-alquenilo o C_3-C_6-alquinilo;

R^2 es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{2A}; R^{2A} es cicloalcano o heterocicloalcano;

R^3 es heteroarilo que no está fusionado o está fusionado con benceno, heteroareno o R^{3A}; R^{3A} es cicloalcano o heterocicloalcano;

R^4 es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{4A}; R^{4A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^5 es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I;

R^6 es C_2-C_5-espiroalquilo, cada uno de los cuales no esta sustituido o está sustituido con OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ o $N(CH_3)_2$;

R^{6A} y R^{6B} se seleccionan en forma independiente entre alquilo o, junto con el N al cual están unidos, R^{6C};

R^{6C} es aziridin-1–ilo, azetidin-1–ilo, pirrolidin-1–ilo o piperidin-1–ilo, teniendo cada uno una unidad CH_2 no reemplazada o reemplazada con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH;

R^7 es R^8, R^9, R^{10} o R^{11};

R^8 es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{8A};

R^{8A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^9 es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{9A}; R^{9A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{10} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{10A}; R^{10A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{11} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I;

R^{12} es R^{13}, R^{14}, R^{15} o R^{16};

R^{13} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{13A}; R^{13A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{14} es heteroarilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{14A}; R^{14A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{15} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{15A}; R^{15A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{16} es alquilo, alquenilo o alquinilo;

R^{17} es R^{18}, R^{19}, R^{20} o R^{21};

R^{18} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{18A}; R^{18A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{19} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{19A}; R^{19A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{20} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH,

$CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{20A}; R^{20A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{21} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I;

R^{22} es R^{23}, R^{24} o R^{25};

R^{23} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{23A}; R^{23A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{24} es heteroareno que no está fusionado o está fusionado con areno, heteroareno o R^{24A}; R^{24A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{25} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{25A}; R^{25A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

Z^1 es R^{26} o R^{27}, cada uno de los cuales está sustituido con R^{28}, R^{29} o R^{30}, cada uno de los cuales está sustituido con F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} o $N(R^{32})R^{37}$;

R^{26} es fenilo que no está fusionado o está fusionado con areno o heteroareno;

R^{27} es heteroareno que no está fusionado o está fusionado con areno o heteroareno;

R^{28} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{28A}; R^{28A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{29} es heteroarilo o R^{29A}; R^{29A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{30} es cicloalquilo o cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{30A}; R^{30A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{31} y R^{31A} son en forma independiente F, Cl, Br o alquilo o se toman juntos y son C_2-C_5-espiroalquilo;

R^{32} es R^{33}, $C(O)R^{33}$ o $C(O)OR^{33}$;

R^{33} es R^{34} o R^{35};

R^{34} es fenilo que no está fusionado o está fusionado con arilo, heteroarilo o R^{34A}; R^{34A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{35} es alquilo que no está sustituido o está sustituido con R^{36};

R^{36} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{36A}; R^{36A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{37} es R^{38}, R^{39} o R^{40}, cada uno de los cuales está sustituido con F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ o SO_2R^{41};

R^{38} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{38A}; R^{38A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{39} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{39A}; R^{39A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{40} es C_3-C_8-cicloalquilo o C_4-C_8-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{40A}; R^{40A} cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{41} es R^{42}, R^{43}, R^{44} o R^{45};

R^{42} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{42A}; R^{42A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{43} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{43A}; R^{43A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{44} es C_3-C_9-cicloalquilo o C_4-C_7-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{44A}; R^{44A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{45} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos sustituyentes seleccionados en forma independiente entre: R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{46} es R^{47}, R^{48} o R^{49};

R^{47} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{47A}; R^{47A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{48} es heteroarilo o R^{48A}; R^{48A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{49} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{49A}; R^{49A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

en donde las unidades representadas por R^{26} y R^{27} se sustituyen adicionalmente con uno o dos o tres sustituyentes seleccionados en forma independiente entre: R^{50A}, OR^{50A}, SR^{50A}, $S(O)R^{50A}$, SO_2R^{50A} o NHR^{50A};

R^{50A} es R^{51A}, R^{52A}, R^{53A} o R^{54A};

R^{51A} es fenilo que no está fusionado o está fusionado con benceno, heteroareno o R^{51AA},

en donde R^{51AA} es cicloalcano, cicloalqueno o heterocicloalcano heterocicloalqueno,

R^{52A} es heteroarilo;

R^{53A} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo; donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{53AA};

en donde R^{53AA} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{54A} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre: R^{55AA}, OR^{55AA}, SR^{55AA}, $S(O)R^{55AA}$, SO_2R^{55AA}, NHR^{55AA}, $N(R^{55AA})_2$, $C(O)R^{55AA}$, $C(O)NH_2$, $C(O)NHR^{55AA}$, $NHC(O)R^{55AA}$, $NHSO_2R^{55AA}$, $NHC(O)OR^{55AA}$, SO_2NH_2, SO_2NHR^{55AA}, $SO_2N(R^{55AA})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55AA}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{55AA} es alquilo, alquenilo, alquinilo, fenilo o heteroarilo, o R^{56A};

R^{56A} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N;

en donde las unidades representadas por R^2 R^3 R^4, R^6, R^{6C}, R^8, R^{8A}, R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{18}, R^{19} R^{20}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{34}, R^{36}, R^{38}, R^{39}, R^{40}, R^{42}, R^{43}, R^{44}, R^{47},

R^{48}, y R^{49} son en forma independiente no sustituidas, adicionalmente no sustituidas, sustituidas o adicionalmente sustituidas con uno o dos o tres o cuatro o cinco sustituyentes seleccionados en forma independiente entre R^{50AA}, R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{50AA} es espirociclilo;

R^{50} es R^{51}, R^{52}, R^{53} o R^{54};

R^{51} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{51B};

R^{51B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{52} es heteroarilo;

R^{53} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{53B};

en donde R^{53B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

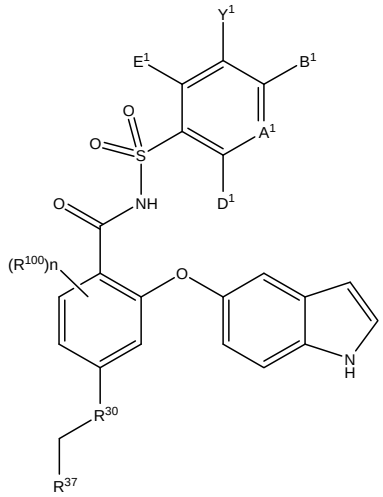
R^{54} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{55} es alquilo, alquenilo, alquinilo, fenilo, heteroarilo o R^{56};

en donde el alquilo, alquenilo, alquinilo no están sustituidos o están sustituidos con OCH_3; y

R^{56} es C_3-C_8-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N.

Otra forma de realización de esta invención se refiere a compuestos o sus sales, profármacos, o sales de profármacos terapéuticamente aceptables, que son útiles como inhibidores selectivos de proteínas antiapoptóticas Bd-2, donde los compuestos tienen la Fórmula (II)



(II),

en donde

R^{100} tiene los valores que se definen para los sustituyentes de R^{26};

n es 0, 1, 2, o 3;

A^1 es N o $C(A^2)$;

uno o dos o tres o cada uno de A^2, B^1, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes se seleccionan en forma independiente entre H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$; y

Y^1 es H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ o $NHSO_2R^{17}$;

o

B^1 y Y^1, junto con los átomos a los cuales están unidos , son imidazol o triazol; y

uno o dos o cada uno de A^2, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes se seleccionan en forma independiente entre H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$;

R^1 es R^2, R^3, R^4 o R^5;

R^{1A} es C_1-C_6-alquilo, C_3-C_6-alquenilo o C_3-C_6-alquinilo;

R^2 es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{2A}; R^{2A} es cicloalcano o heterocicloalcano;

R^3 es heteroarilo que no está fusionado o está fusionado con benceno, heteroareno o R^{3A}; R^{3A} es cicloalcano o heterocicloalcano;

R^4 es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{4A}; R^{4A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^5 es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I

R^6 es C_2-C_5-espiroalquilo, cada uno de los cuales no esta sustituido o está sustituido con OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ o $N(CH_3)_2$;

R^{6A} y R^{6B} se seleccionan en forma independiente entre alquilo o, junto con el N al cual están unidos, R^{6C};

R^{6C} es aziridin-1–ilo, azetidin-1–ilo, pirrolidin-1–ilo o piperidin-1–ilo, teniendo cada uno una unidad CH_2 no reemplazada o reemplazada con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH;

R^7 es R^8, R^9, R^{10} o R^{11};

R^8 es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{8A};

R^{8A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^9 es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{9A}; R^{9A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{10} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{10A}; R^{10A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{11} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{12} es R^{13}, R^{14}, R^{15} o R^{16};

R^{13} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{13A}; R^{13A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{14} es heteroarilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{14A}; R^{14A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{15} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{15A}; R^{15A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{16} es alquilo, alquenilo o alquinilo;

R^{17} es R^{18}, R^{19}, R^{20} o R^{21};

R^{18} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{18A}; R^{18A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{19} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{19A}; R^{19A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{20} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{20A}; R^{20A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{21} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{22} es R^{23}, R^{24} o R^{25};

R^{23} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{23A}; R^{23A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{24} es heteroareno que no está fusionado o está fusionado con areno, heteroareno o R^{24A}; R^{24A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{25} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{25A}; R^{25A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{30} es cicloalquilo o cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{30A}; R^{30A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; cada uno de los cuales está sustituido con F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} o $N(R^{32})R^{37}$;

R^{31} y R^{31A} son en forma independiente F, Cl, Br o alquilo o se toman juntos y son C_2-C_5-espiroalquilo;

R^{32} es R^{33}, $C(O)R^{33}$ o $C(O)OR^{33}$;

R^{33} es R^{34} o R^{35};

R^{34} es fenilo que no está fusionado o está fusionado con arilo, heteroarilo o R^{34A}; R^{34A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{35} es alquilo que no está sustituido o está sustituido con R^{36};

R^{36} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{36A}; R^{36A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{37} es R^{38}, R^{39} o R^{40}, cada uno de los cuales está sustituido con F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ o SO_2R^{41};

R^{38} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{38A}; R^{38A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{39} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{39A}; R^{39A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{40} es C_3-C_8-cicloalquilo o C_4-C_8-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{40A}; R^{40A} cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{41} es R^{42}, R^{43}, R^{44} o R^{45};

R^{42} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{42A}; R^{42A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{43} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{43A}; R^{43A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{44} es C_3-C_9-cicloalquilo o C_4-C_7-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH,

$CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{44A}; R^{44A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{45} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos sustituyentes seleccionados en forma independiente entre: R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{46} es R^{47}, R^{48} o R^{49};

R^{47} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{47A}; R^{47A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{48} es heteroarilo o R^{48A}; R^{48A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{49} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{49A}; R^{49A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

en donde las unidades representadas por R^2 R^3 R^4, R^6, R^{6C}, R^8, R^{8A} R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{18}, R^{19}, R^{20}, R^{23} R^2, R^{2A}, R^3, R^{3A}, R^4, R^{4A}, R^6, R^{6C}, R^8, R^{8A}, R^9, R^{10}, R^{10A}, R^{13}, R^{13A}, R^{14}, R^{14A}, R^{15}, R^{15A}, R^{18}, R^{18A}, R^{19}, R^{19A}, R^{20}, R^{20A}, R^{23}, R^{23A}, R^{24}, R^{24A}, R^{25}, R^{25A}, R^{26}, R^{27}, R^{28}, R^{28A}, R^{29}, R^{29A}, R^{30}, R^{30A}, R^{34}, R^{34A}, R^{36}, R^{36A}, R^{38}, R^{38A}, R^{39}, R^{39A}, R^{40}, R^{40A}, R^{42}, R^{42A}, R^{43}, R^{43A}, R^{44}, R^{44A}, R^{47}, R^{47A}, R^{48}, R^{48A}, R^{49}, y R^{49A} son en forma independiente no sustituidas, adicionalmente no sustituidas, sustituidas o adicionalmente sustituidas con uno o dos o tres o cuatro o cinco sustituyentes seleccionados en forma independiente entre R^{50AA}, R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{50AA} es espirociclilo;

R^{50} es R^{51}, R^{52}, R^{53} o R^{54};

R^{51} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{51B}; R^{51B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{52} es heteroarilo;

R^{53} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{53B};

en donde R^{53B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

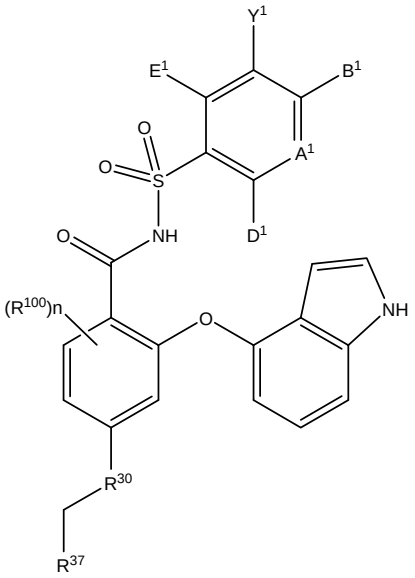
R^{54} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{55} es alquilo, alquenilo, alquinilo, fenilo, heteroarilo o R^{56};

en donde el alquilo, alquenilo, alquinilo no están sustituidos o están sustituidos con OCH_3; y

R^{56} es C_3-C_8-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N.

Otra forma de realización de esta invención se refiere a compuestos o sus sales, profármacos, o sales de profármacos terapéuticamente aceptables, que son útiles como inhibidores selectivos de proteínas antiapoptóticas Bd-2, donde los compuestos tienen la Fórmula (III)



(III),

en donde

R^{100} tiene los valores que se definen para los sustituyentes de R^{26};
n es 0, 1, 2, o 3;
A^1 es N o $C(A^2)$;

uno o dos o tres o cada uno de A^2, B^1, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes se seleccionan en forma independiente entre H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$; y

Y^1 es H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ o $NHSO_2R^{17}$;

o

B^1 y Y^1, junto con los átomos a los cuales están unidos , son imidazol o triazol; y

uno o dos o cada uno de A^2, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes se seleccionan en forma independiente entre H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$;

R^1 es R^2, R^3, R^4 o R^5;

R^{1A} es C_1-C_6-alquilo, C_3-C_6-alquenilo o C_3-C_6-alquinilo;

R^2 es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{2A}; R^{2A} es cicloalcano o heterocicloalcano;

R^3 es heteroarilo que no está fusionado o está fusionado con benceno, heteroareno o R^{3A}; R^{3A} es cicloalcano o heterocicloalcano;

R^4 es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{4A}; R^{4A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^5 es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$,

$NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^6 es C_2-C_5-espiroalquilo, cada uno de los cuales no esta sustituido o está sustituido con OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ o $N(CH_3)_2$;

R^{6A} y R^{6B} se seleccionan en forma independiente entre alquilo o, junto con el N al cual están unidos, R^{6C};

R^{6C} es aziridin-1–ilo, azetidin-1–ilo, pirrolidin-1–ilo o piperidin-1–ilo, teniendo cada uno una unidad CH_2 no reemplazada o reemplazada con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH;

R^7 es R^8, R^9, R^{10} o R^{11};

R^8 es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{8A};

R^{8A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^9 es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{9A}; R^{9A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{10} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{10A}; R^{10A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{11} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{12} es R^{13}, R^{14}, R^{15} o R^{16};

R^{13} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{13A}; R^{13A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{14} es heteroarilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{14A}; R^{14A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{15} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{15A}; R^{15A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{16} es alquilo, alquenilo o alquinilo;

R^{17} es R^{18}, R^{19}, R^{20} o R^{21};

R^{18} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{18A}; R^{18A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{19} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{19A}; R^{19A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{20} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{20A}; R^{20A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{21} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{22} es R^{23}, R^{24} o R^{25};

R^{23} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{23A}; R^{23A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{24} es heteroareno que no está fusionado o está fusionado con areno, heteroareno o R^{24A}; R^{24A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{25} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{25A}; R^{25A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{30} es cicloalquilo o cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{30A}; R^{30A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; cada uno de los cuales está sustituido con F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} o $N(R^{32})R^{37}$;

R^{31} y R^{31A} son en forma independiente F, Cl, Br o alquilo o se toman juntos y son C_2-C_5-espiroalquilo;

R^{32} es R^{33}, $C(O)R^{33}$ o $C(O)OR^{33}$;

R^{33} es R^{34} o R^{35};

R^{34} es fenilo que no está fusionado o está fusionado con arilo, heteroarilo o R^{34A}; R^{34A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{35} es alquilo que no está sustituido o está sustituido con R^{36};

R^{36} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{36A}; R^{36A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{37} es R^{38}, R^{39} o R^{40}, cada uno de los cuales está sustituido con F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ o SO_2R^{41};

R^{38} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{38A}; R^{38A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{39} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{39A}; R^{39A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{40} es C_3-C_8-cicloalquilo o C_4-C_8-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{40A}; R^{40A} cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{41} es R^{42}, R^{43}, R^{44} o R^{45};

R^{42} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{42A}; R^{42A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{43} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{43A}; R^{43A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{44} es C_3-C_9-cicloalquilo o C_4-C_7-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{44A}; R^{44A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{45} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos sustituyentes seleccionados en forma independiente entre: R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{46} es R^{47}, R^{48} o R^{49};

R^{47} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{47A}; R^{47A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{48} es heteroarilo o R^{48A}; R^{48A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{49} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{49A}; R^{49A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

en donde las unidades representadas por R^2, R^{2A}, R^3, R^{3A}, R^4, R^{4A}, R^6, R^{6C}, R^8, R^{8A}, R^9, R^{10}, R^{10A}, R^{13}, R^{13A}, R^{14}, R^{14A}, R^{15}, R^{15A}, R^{18}, R^{18A}, R^{19}, R^{19A}, R^{20}, R^{20A}, R^{23}, R^{23A}, R^{24}, R^{24A}, R^{25}, R^{25A}, R^{26}, R^{27}, R^{28}, R^{28A}, R^{29}, R^{29A}, R^{30}, R^{30A}, R^{34}, R^{34A}, R^{36}, R^{36A}, R^{38}, R^{38A}, R^{39}, R^{39A}, R^{40}, R^{40A}, R^{42}, R^{42A}, R^{43}, R^{43A}, R^{44}, R^{44A}, R^{47}, R^{47A}, R^{48}, R^{48A}, R^{49}, y R^{49A} son en forma independiente no sustituidas, adicionalmente no sustituidas, sustituidas o adicionalmente sustituidas con uno o dos o tres o cuatro o cinco sustituyentes seleccionados en forma independiente entre R^{50AA}, R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br o I;

R^{50AA} es espirociclilo;

R^{50} es R^{51}, R^{52}, R^{53} o R^{54};

R^{51} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{51B}; R^{51B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{52} es heteroarilo;

R^{53} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{53B};

en donde R^{53B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

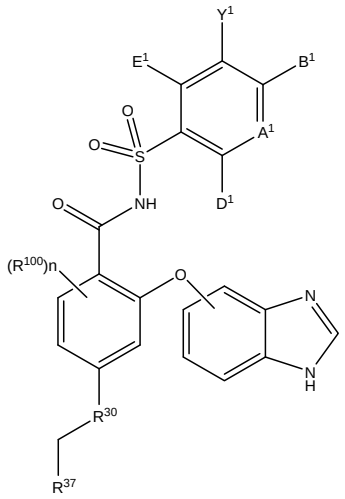
R^{54} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br o I;

R^{55} es alquilo, alquenilo, alquinilo, fenilo, heteroarilo o R^{56};

en donde el alquilo, alquenilo, alquinilo no están sustituidos o están sustituidos con OCH_3; y

R^{56} es C_3-C_8-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N.

Otra forma de realización de esta invención se refiere a compuestos o sus sales, profármacos, o sales de profármacos terapéuticamente aceptables, que son útiles como inhibidores selectivos de proteínas antiapoptóticas Bd-2, donde los compuestos tienen la Fórmula (IV)



(IV),

en donde

R^{100} tiene los valores que se definen para los sustituyentes de R^{26};

n es 0, 1, 2, o 3;

A^1 es N o $C(A^2)$;

uno o dos o tres o cada uno de A^2, B^1, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes se seleccionan en forma independiente entre H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$; y

Y^1 es H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ o $NHSO_2R^{17}$;

o

B^1 y Y^1, junto con los átomos a los cuales están unidos , son imidazol o triazol; y

uno o dos o cada uno de A^2, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes se seleccionan en forma independiente entre H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$;

R^1 es R^2, R^3, R^4 o R^5;

R^{1A} es C_1-C_6-alquilo, C_3-C_6-alquenilo o C_3-C_6-alquinilo;

R^2 es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{2A}; R^{2A} es cicloalcano o heterocicloalcano;

R^3 es heteroarilo que no está fusionado o está fusionado con benceno, heteroareno o R^{3A}; R^{3A} es cicloalcano o heterocicloalcano;

R^4 es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{4A}; R^{4A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^5 es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^6 es C_2-C_5-espiroalquilo, cada uno de los cuales no esta sustituido o está sustituido con OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ o $N(CH_3)_2$;

R^{6A} y R^{6B} se seleccionan en forma independiente entre alquilo o, junto con el N al cual están unidos, R^{6C};

R^{6C} es aziridin-1–ilo, azetidin-1–ilo, pirrolidin-1–ilo o piperidin-1–ilo, teniendo cada uno una unidad CH_2 no reemplazada o reemplazada con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH;

R^7 es R^8, R^9, R^{10} o R^{11};

R^8 es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{8A};

R^{8A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^9 es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{9A}; R^{9A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{10} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{10A}; R^{10A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{11} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{12} es R^{13}, R^{14}, R^{15} o R^{16};

R^{13} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{13A}; R^{13A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{14} es heteroarilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{14A}; R^{14A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{15} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{15A}; R^{15A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{16} es alquilo, alquenilo o alquinilo;

R^{17} es R^{18}, R^{19}, R^{20} o R^{21};

R^{18} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{18A}; R^{18A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{19} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{19A}; R^{19A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{20} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{20A}; R^{20A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{21} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma

independiente: R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{22} es R^{23}, R^{24} o R^{25};

R^{23} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{23A}; R^{23A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{24} es heteroareno que no está fusionado o está fusionado con areno, heteroareno o R^{24A}; R^{24A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{25} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{25A}; R^{25A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{30} es cicloalquilo o cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{30A}; R^{30A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; cada uno de los cuales está sustituido con F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} o $N(R^{32})R^{37}$;

R^{31} y R^{31A} son en forma independiente F, Cl, Br o alquilo o se toman juntos y son C_2-C_5-espiroalquilo;

R^{32} es R^{33}, $C(O)R^{33}$ o $C(O)OR^{33}$;

R^{33} es R^{34} o R^{35};

R^{34} es fenilo que no está fusionado o está fusionado con arilo, heteroarilo o R^{34A}; R^{34A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{35} es alquilo que no está sustituido o está sustituido con R^{36};

R^{36} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{36A}; R^{36A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{37} es R^{38}, R^{39} o R^{40}, cada uno de los cuales está sustituido con F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ o SO_2R^{41};

R^{38} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{38A}; R^{38A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{39} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{39A}; R^{39A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{40} es C_3-C_8-cicloalquilo o C_4-C_8-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{40A}; R^{40A} cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{41} es R^{42}, R^{43}, R^{44} o R^{45};

R^{42} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{42A}; R^{42A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{43} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{43A}; R^{43A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{44} es C_3-C_9-cicloalquilo o C_4-C_7-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{44A}; R^{44A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{45} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos sustituyentes seleccionados en forma independiente entre: R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{46} es R^{47}, R^{48} o R^{49};

R^{47} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{47A}; R^{47A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{48} es heteroarilo o R^{48A}; R^{48A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{49} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{49A}; R^{49A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

en donde las unidades representadas por R^2, R^{2A}, R^3, R^{3A}, R^4, R^{4A}, R^6, R^{6C}, R^8, R^{8A}, R^9, R^{10}, R^{10A}, R^{13}, R^{13A}, R^{14}, R^{14A}, R^{15}, R^{15A}, R^{18}, R^{18A}, R^{19}, R^{19A}, R^{20}, R^{20A}, R^{23}, R^{23A}, R^{24}, R^{24A}, R^{25}, R^{25A}, R^{26}, R^{27}, R^{28}, R^{28A}, R^{29}, R^{29A}, R^{30}, R^{30A}, R^{34}, R^{34A}, R^{36}, R^{36A}, R^{38}, R^{38A}, R^{39}, R^{39A}, R^{40}, R^{40A}, R^{42}, R^{42A}, R^{43}, R^{43A}, R^{44}, R^{44A}, R^{47}, R^{47A}, R^{48}, R^{48A}, R^{49}, y R^{49A} son en forma independiente no sustituidas, adicionalmente no sustituidas, sustituidas o adicionalmente

sustituidas con uno o dos o tres o cuatro o cinco sustituyentes seleccionados en forma independiente entre R^{50AA}, R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{50AA} es espirociclilo;

R^{50} es R^{51}, R^{52}, R^{53} o R^{54};

R^{51} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{51B};

R^{51B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{52} es heteroarilo;

R^{53} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{53B};

en donde R^{53B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

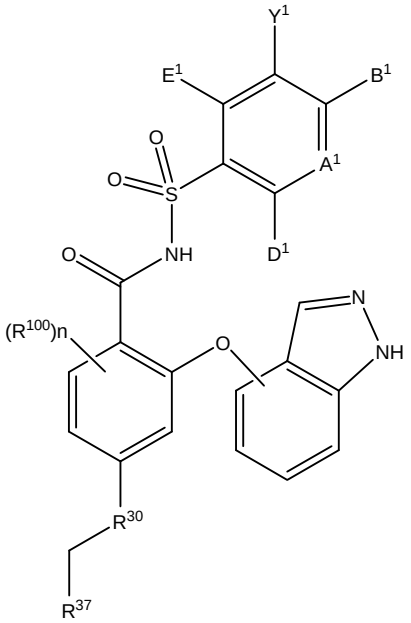
R^{54} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br o I;

R^{55} es alquilo, alquenilo, alquinilo, fenilo, heteroarilo o R^{56};

en donde el alquilo, alquenilo, alquinilo no están sustituidos o están sustituidos con OCH_3; y

R^{56} es C_3-C_8-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N.

Otra forma de realización de esta invención se refiere a compuestos o sus sales, profármacos, o sales de profármacos terapéuticamente aceptables, que son útiles como inhibidores selectivos de proteínas antiapoptóticas Bd-2, donde los compuestos tienen la Fórmula (V)



(V),

en donde

R^{100} tiene los valores que se definen para los sustituyentes de R^{26};

n es 0, 1, 2, o 3;

A^1 es N o $C(A^2)$;

uno o dos o tres o cada uno de A^2, B^1, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes se seleccionan en forma independiente entre H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$; y

Y^1 es H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ o $NHSO_2R^{17}$;

o

B^1 y Y^1, junto con los átomos a los cuales están unidos , son imidazol o triazol; y

uno o dos o cada uno de A^2, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes se seleccionan en forma independiente entre H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$;

R^1 es R^2, R^3, R^4 o R^5;

R^{1A} es C_1-C_6-alquilo, C_3-C_6-alquenilo o C_3-C_6-alquinilo;

R^2 es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{2A}; R^{2A} es cicloalcano o heterocicloalcano;

R^3 es heteroarilo que no está fusionado o está fusionado con benceno, heteroareno o R^{3A}; R^{3A} es cicloalcano o heterocicloalcano;

R^4 es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{4A}; R^{4A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^5 es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I;

R^6 es C_2-C_5-espiroalquilo, cada uno de los cuales no esta sustituido o está sustituido con OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ o $N(CH_3)_2$;

R^{6A} y R^{6B} se seleccionan en forma independiente entre alquilo o, junto con el N al cual están unidos, R^{6C};

R^{6C} es aziridin-1–ilo, azetidin-1–ilo, pirrolidin-1–ilo o piperidin-1–ilo, teniendo cada uno una unidad CH_2 no reemplazada o reemplazada con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH;

R^7 es R^8, R^9, R^{10} o R^{11};

R^8 es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{8A};

R^{8A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^9 es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{9A}; R^{9A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{10} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{10A}; R^{10A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{11} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma

independiente: R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I;

R^{12} es R^{13}, R^{14}, R^{15} o R^{16};

R^{13} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{13A}; R^{13A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{14} es heteroarilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{14A}; R^{14A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{15} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{15A}; R^{15A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{16} es alquilo, alquenilo o alquinilo;

R^{17} es R^{18}, R^{19}, R^{20} o R^{21};

R^{18} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{18A}; R^{18A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{19} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{19A}; R^{19A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{20} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{20A}; R^{20A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{21} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{22} es R^{23}, R^{24} o R^{25};

R^{23} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{23A}; R^{23A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{24} es heteroareno que no está fusionado o está fusionado con areno, heteroareno o R^{24A}; R^{24A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{25} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con

N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{25A}; R^{25A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{30} es cicloalquilo o cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{30A}; R^{30A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; cada uno de los cuales está sustituido con F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} o $N(R^{32})R^{37}$;

R^{31} y R^{31A} son en forma independiente F, Cl, Br o alquilo o se toman juntos y son C_2-C_5-espiroalquilo;

R^{32} es R^{33}, $C(O)R^{33}$ o $C(O)OR^{33}$;

R^{33} es R^{34} o R^{35};

R^{34} es fenilo que no está fusionado o está fusionado con arilo, heteroarilo o R^{34A}; R^{34A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{35} es alquilo que no está sustituido o está sustituido con R^{36};

R^{36} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{36A}; R^{36A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{37} es R^{38}, R^{39} o R^{40}, cada uno de los cuales está sustituido con F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ o SO_2R^{41};

R^{38} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{38A}; R^{38A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{39} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{39A}; R^{39A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{40} es C_3-C_8-cicloalquilo o C_4-C_8-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{40A}; R^{40A} cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{41} es R^{42}, R^{43}, R^{44} o R^{45};

R^{42} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{42A}; R^{42A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{43} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{43A}; R^{43A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{44} es C_3-C_9-cicloalquilo o C_4-C_7-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{44A}; R^{44A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{45} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos sustituyentes seleccionados en forma independiente entre: R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{46} es R^{47}, R^{48} o R^{49};

R^{47} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{47A}; R^{47A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{48} es heteroarilo o R^{48A}; R^{48A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{49} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{49A}; R^{49A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

en donde las unidades representadas por R^2, R^{2A}, R^3, R^{3A}, R^4, R^{4A}, R^6, R^{6C}, R^8, R^{8A}, R^9, R^{10}, R^{10A}, R^{13}, R^{13A}, R^{14}, R^{14A}, R^{15}, R^{15A}, R^{18}, R^{18A}, R^{19}, R^{19A}, R^{20}, R^{20A}, R^{23}, R^{23A}, R^{24}, R^{24A}, R^{25}, R^{25A}, R^{26}, R^{27}, R^{28}, R^{28A}, R^{29}, R^{29A}, R^{30}, R^{30A}, R^{34}, R^{34A}, R^{36}, R^{36A}, R^{38}, R^{38A}, R^{39}, R^{39A}, R^{40}, R^{40A}, R^{42}, R^{42A}, R^{43}, R^{43A}, R^{44}, R^{44A}, R^{47}, R^{47A}, R^{48}, R^{48A}, R^{49}, y R^{49A} son en forma independiente no sustituidas, adicionalmente no sustituidas, sustituidas o adicionalmente sustituidas con uno o dos o tres o cuatro o cinco sustituyentes seleccionados en forma independiente entre R^{50AA}, R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, $C(O)NHOH$, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{50AA} es espirociclilo;

R^{50} es R^{51}, R^{52}, R^{53} o R^{54};

R^{51} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{51B}; R^{51B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{52} es heteroarilo;

R^{53} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{53B};

en donde R^{53B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{54} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{55} es alquilo, alquenilo, alquinilo, fenilo, heteroarilo o R^{56};

en donde el alquilo, alquenilo, alquinilo no están sustituidos o están sustituidos con OCH_3; y

R^{56} es C_3-C_8-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N.

Otra forma de realización se refiere a compuestos de Fórmula (I), Fórmula (II), Fórmula (III), Fórmula (IV), o Fórmula (V) en donde A^1 es $C(A^2)$; y A^2 es H.

Otra forma de realización se refiere a compuestos de Fórmula (I), Fórmula (II), Fórmula (III), Fórmula (IV), o Fórmula (V) en donde A^1 es $C(A^2)$o N; A^2 es H; y B^1 es NHR^1.

Otra forma de realización se refiere a compuestos de Fórmula (I), Fórmula (II), Fórmula (III), Fórmula (IV), o Fórmula (V) en donde A^1 es $C(A^2)$ o N; A^2 es H; B^1 es NHR^1; y D^1 es H.

Otra forma de realización se refiere a compuestos de Fórmula (I), Fórmula (II), Fórmula (III), Fórmula (IV), o Fórmula (V) en donde A^1 es $C(A^2)$ o N; A^2 es H; B^1 es NHR^1;D^1 es H; y E^1 es H.

Otra forma de realización se refiere a compuestos de Fórmula (I), Fórmula (II), Fórmula (III), Fórmula (IV), o Fórmula (V) en donde A^1 es $C(A^2)$ o N; A^2 es H; B^1 es NHR^1;D^1 es H; E^1 es H; y Y^1 es NO_2.

Aún otra forma de realización se refiere a compuestos que tienen la Fórmula I que son

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;
benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
2-(benciloxi)-4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(2-feniletoxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(feniltio)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(feniltio)-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)-2-(feniltio)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(fenilsulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(fenilsulfinil)benzamida;
2-bencil-4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
2-bencil-4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
2-bencil-4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(2-feniletil)benzamida;
2-(bencilamino)-4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
2-anilino-4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
2-anilino-4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-metoxi-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indazol-5–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indazol-5–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)-2-(1,2,3,4-tetrahidroquinolin-6–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)-2-(1,2,3,4-tetrahidroquinolin-6–iloxi)benzamida;
4-(4-((4'-cloro-4-(pirrolidin-1–ilmetil)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(2-pirrolidin-1–iletil)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((1-ciclopentilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)-3-isobutilpiperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-(2,4-dioxo-3-azabiciclo(3.2.0)hept-3–il)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-(4-metil-6-oxo-1,4,5,6-tetrahidropiridazin-3–il)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-(3,3-dimetil-2-oxoazetidin-1–il)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-(4-nitro-2H-1,2,3-triazol-2–il)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((2-(2-piperidin-1–iletoxi)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-((((1-etilpirrolidin-2–il)metil)amino)carbonil)-4-metoxifenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1-naftiloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(2-naftiloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)-2-(2-naftiloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(2-naftiloxi)-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(quinolin-7–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(quinolin-6–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(isoquinolin-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(isoquinolin-5–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(quinolin-6–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-4–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-6–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(isoquinolin-7–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(isoquinolin-7–iloxi)benzamida;

4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-4–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-4–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-metoxifenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-metilfenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;

N-((3-((cloro(difluoro)metil)sulfonil)-4-((3-(dimetilamino)propil)amino)fenil)sulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

2-(1H-indol-4–iloxi)-4-(4-((2-(4-metoxifenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;

4-(4-((4,4-dimetil-2-(4-(trifluorometil)fenil)ciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;

4-(4-((4,4-dimetil-2-(4-(trifluorometoxi)fenil)ciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;

4-(4-((4,4-dimetil-2-(3-(trifluorometil)fenil)ciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;

4-(4-((2-(3-fluorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;

4-(4-((2-(4-fluorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;

N-((3-((cloro(difluoro)metil)sulfonil)-4-((1-metilpiperidin-4–il)amino)fenil)sulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

4-(4-((2-(4-clorofenil)ciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(fenoximetil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(piridin-3–iloxi)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(piridin-3–iloxi)-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-(((1R)-3-(dimetilamino)-1-((feniltio)metil)propil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(piridin-4–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)-2-(piridin-3–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)-2-(piridin-4–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((2-(4-metilpiperazin-1–il)etil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(4-metilpiperazin-1–il)propil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)(metil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-(((1-metilpiperidin-4–il)metil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-ciano-4-((3-(dimetilamino)propil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-(trifluorometil)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(isopropil(metil)amino)propil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-(3-(dimetilamino)propoxi)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((2-(4-metilpiperazin-1–il)etil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((3-(4-metilpiperazin-1–il)propil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((3-(4-metilpiperazin-1–il)propil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-(3-(dimetilamino)propoxi)-3-nitrofenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((2-(4-metilpiperazin-1–il)etil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-(((1-metilpiperidin-4–il)metil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-(((1-metilpiperidin-4–il)metil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-(3-(dimetilamino)propoxi)-3-nitrofenil)sulfonil)-2-(1H-indol-4–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-(4-metilpiperazin-1–il)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((1-(2,2,2-trifluoroetil)piperidin-4–il)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-(((4-(dimetilamino)-1-metilpiperidin-4–il)metil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(2,3-dihidro-1,4-benzodioxin-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
5-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-1,1'-bifenil-2-carboxamida;
5-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-1,1'-bifenil-2-carboxamida;
4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-4-(3-piperidin-1–ilpropoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-4-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-4-(3-(dimetilamino)propoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-4-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(3-piperidin-1–ilpropoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(3-(dimetilamino)propoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-3-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-3-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((1-(2,2,2-trifluoroetil)piperidin-4–il)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-4-(2-pirrolidin-1–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-4-(2-(diisopropilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(2,3-dihidro-1H-indol-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)ciclohept-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)ciclooct-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)ciclopent-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclopent-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)ciclooct-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)ciclohept-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)ciclopent-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)ciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)ciclohept-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((2-(dimetilamino)etil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((4-(dimetilamino)butil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((1-(fenilsulfonil)piperidin-4–il)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((1-(quinolin-8–ilsulfonil)piperidin-4–il)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((1-(fenilsulfonil)piperidin-4–il)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((1-(quinolin-8–ilsulfonil)piperidin-4–il)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-(((1S)-3-(dimetilamino)-1-tien-2–ilpropil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tien-2–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((2-(1H-1,2,3-triazol-1–il)etil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((2-(2H-1,2,3-triazol-2–il)etil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(2-naftiloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((2-(2-oxopiridin-1(2H)–il)etil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((2-(piridin-2–iloxi)etil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((2-piridin-4–iletil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-(trifluorometil)fenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((3-ciano-4-((3-(dimetilamino)propil)amino)fenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1*H*-indol-5–iloxi)-*N*-((3-nitro-4-((1-tetrahidro-2*H*-piran-4–ilpiperidin-4–il)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1*H*-indol-5–iloxi)-*N*-((4-((4-metilpiperazin-1–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-(1-(4'-cloro-1,1'-bifenil-2–il)etil)piperazin-1–il)-2-(1*H*-indol-4–iloxi)-*N*-((3-nitro-4-((tetrahidro-2*H*-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
N-((4-(((4-aminotetrahidro-2*H*-piran-4–il)metil)amino)-3-nitrofenil)sulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1*H*-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-morfolin-4–ilciclohexil)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(2-metoxietil)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[(3S)-tetrahidro-2H-piran-3–ilmetil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[(3R)-tetrahidro-2H-piran-3–ilmetil]amino}fenil)sulfonil]benzamida;
4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-hidroxi-1-metilpiperidin-4–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-3-fluoro-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-3-fluoro-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-hidroxi-1-metilpiperidin-4–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;
N-[(4-{[(3S,4R)-1-bencil-3-hidroxipiperidin-4–il]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;
N-[(4-{[(4-aminotetrahidro-2H-piran-4–il)metil]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[1-(2-metoxietil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(2-hidroxietil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[1-(2-metoxietil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(3-hidroxipropil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;
4-[4-({4'-cloro-3-[3-(dimetilamino)propil]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(3-hidroxipropil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-{4-[(4'-cloro-4-morfolin-4–il-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-[4-({4'-cloro-3-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(dietilamino)ciclohexil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(dimetilamino)ciclohexil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(dietilamino)ciclohexil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(4-morfolin-4–ilciclohexil)amino]-3-nitrofenil}sulfonil)benzamida;
4-[4-({4'-cloro-3-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;
4-{4-[1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[4-(dimetilamino)tetrahidro-2H-piran-4–il]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida;
N-({4-[(2-aminociclohexil)amino]-3-nitrofenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;
4-[4-({4'-cloro-4-[3-(dimetilamino)prop-1-ynil]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(3-nitro-4-{[1-(4,4,4-trifluorobutil)piperidin-4–il]amino}fenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[2-(4-hidroxi-1-metilpiperidin-4–il)etil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[1-(1,3-tiazol-2–il)piperidin-4–il]amino}fenil)sulfonil]benzamida;

4-(4-{[4'-cloro-4-(2-hidroxietoxi)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(ciclopropilmetil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[1-(4,4,4-trifluorobutil)piperidin-4–il]amino}fenil)sulfonil]benzamida;

4-{4-[1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-[4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}-3-(hidroximetil)piperazin-1–il]-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-[4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}-3-(hidroximetil)piperazin-1–il]-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;

4-(4-{[4'-cloro-4-(2-hidroxietoxi)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[3-(3-oxopiperazin-1–il)propil]amino}fenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(3-nitro-4-{[3-(3-oxopiperazin-1–il)propil]amino}fenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-5-hidroxiciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-5-hidroxiciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-5-hidroxiciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(2,3-dihidro-1H-inden-2–il)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(2,3-dihidro-1H-inden-2–il)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(1-morfolin-4–ilciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[1-(1,3-tiazol-2–ilmetil)piperidin-4–il]amino}fenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[1-(1,3-tiazol-4–ilmetil)piperidin-4–il]amino}fenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[4-(hidroximetil)tetrahidro-2H-piran-4–il]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(2-hidroxietil)piperazin-1–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(3S)-1-metilpirrolidin-3–il]amino}-3-nitrofenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(3-fluoropropil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-[4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}-3-(hidroximetil)piperazin-1–il]-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

N-[(4-{[(4-aminotetrahidro-2H-piran-4–il)metil]amino}-3-nitrofenil)sulfonil]-4-[4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}-3-(hidroximetil)piperazin-1–il]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1-hidroxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(2-metoxietil)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(hidroximetil)tetrahidro-2H-piran-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(hidroximetil)tetrahidro-2H-piran-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2-hidroxi-1-tetrahidro-2H-piran-4–iletil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-({1-[2-(1H-pirazol-1–il)etil]piperidin-4–il}amino)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(metilamino)-3-nitrofenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[4-(metilamino)-3-nitrofenil]sulfonil}benzamida;
4-{4-[1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-5-hidroxiciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-5-morfolin-4–ilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
N-[(4-{[(1-aminociclohexil)metil]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[2-(2-oxopirrolidin-1–il)etil]amino}fenil)sulfonil]benzamida;
4-{4-[1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{1-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]etil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{1-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]etil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida;
4-{4-[(1R)-1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-{4-[(1S)-1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{1-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]etil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{1-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]etil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(ciclohexilmetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(morfolin-4–ilamino)-3-nitrofenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-3–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[4-(morfolin-4–ilamino)-3-nitrofenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(tetrahidro-2H-piran-4–ilamino)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(3-metiloxetan-3–il)metil]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-metoxiciclohexil)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[3-(1,1-dioxidotiomorfolin-4–il)propil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[2-(2-oxopiperidin-1–il)etil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[2-(2-oxoimidazolidin-1–il)etil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(2-piridin-4–iletil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-morfolin-4–il-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(4-metoxipiperidin-1–il)-3-nitrofenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-5-pirrolidin-1–ilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[2-(3-oxopiperazin-1–il)etil]amino}fenil)sulfonil]benzamida;
4-[4-({4'-cloro-4-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1,1-dioxidotetrahidrotien-3–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1,1-dioxidotetrahidrotien-3–il)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-[(tetrahidro-2H-piran-4–ilmetil)amino]-3-(trifluorometil)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[2-(1,3-dioxolan-2–il)etil]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(tetrahidro-2H-piran-4–ilmetoxi)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(3-nitro-4-{[2-(3-oxopiperazin-1–il)etil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metil-5-oxopirrolidin-3–il)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metil-6-oxopiperidin-3–il)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[3-nitro-4-(piperidin-1–ilamino)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(piperidin-1–ilamino)fenil]sulfonil}benzamida;
4-(4-{[4-(4-clorofenil)-1-metil-1H-pirazol-5–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(3-metiloxetan-3–il)metoxi]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[(1-oxidotetrahidro-2H-tiopiran-4–il)metil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1,3-tiazol-5–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[3-nitro-4-(tetrahidro-2H-piran-4–ilmetoxi)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(2-tetrahidro-2H-piran-4–iletil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(3-nitro-4-{[2-(trifluorometoxi)etil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[2-(2-metoxietoxi)etil]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[3-(metilsulfonil)propil]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[3-(1,1-dioxidotiomorfolin-4–il)propil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(2-tetrahidro-2H-piran-4–iletil)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-(1,4-dioxan-2–ilmetoxi)-3-nitrofenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[2-(2-metoxietoxi)etil]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1,1-dioxidotetrahidrotien-3–il)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[2-(trifluorometoxi)etil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1,1-dioxidotetrahidro-2H-tiopiran-4–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2,2-difluoroetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4,4-difluorociclohexil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[4-(4-clorofenil)-1-isopropil-6-oxo-1,6-dihidropiridin-3–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(tetrahidro-2H-piran-4–ilmetil)amino]carbonil}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(2-metoxietil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-hidroxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(4-metoxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-hidroxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(4-metoxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[3-nitro-4-(2-tetrahidro-2H-piran-4–iletoxi)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(2-metoxietil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[3-(metilsulfonil)propoxi]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(3-metoxipropil)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(3-metoxipropil)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2-cianoetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2-cianoetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[(3R)-4-hidroxi-1-adamantil]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[Cis-4-hidroxi-1-adamantil]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(3,3,3-trifluoropropil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(3,3,3-trifluoropropil)amino]fenil}sulfonil)benzamida;
N-({5-bromo-6-[(tetrahidro-2H-piran-4–ilmetil)amino]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1,1-dioxidotetrahidrotien-3–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-(metilamino)-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
N-{[5-bromo-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[4-(4-clorofenil)-6-isopropoxipiridin-3–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[6-(tetrahidro-2H-piran-4–ilmetoxi)-5-(1,3-tiazol-2–il)piridin-3–il]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(2-metoxietil)amino]carbonil}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-ciano-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indol-5–iloxi)benzamida;
N-({4-[(1-acetilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[1-(metilsulfonil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1,4-dioxan-2–ilmetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
N-({4-[(1-acetilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[1-(metilsulfonil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[4'-cloro-5-(trifluorometil)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[4'-cloro-5-(trifluorometil)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(tetrahidro-2H-piran-4–ilmetoxi)fenil]sulfonil}benzamida;
4-{4-[(5-tert-butil-4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-{4-[(5-tert-butil-4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(tetrahidro-2H-piran-4–ilmetoxi)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(2,2,2-trifluoroetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(2,2,2-trifluoroetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-{[(tetrahidro-2H-piran-4–ilmetil)amino]carbonil}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2R)-1,4-dioxan-2–ilmetoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2S)-1,4-dioxan-2–ilmetoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
N-({5-bromo-6-[(tetrahidro-2H-piran-4–ilmetil)amino]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(2-morfolin-4–iletil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-ciano-6-[(tetrahidro-2H-piran-4–ilmetil)amino]piridin-3–il}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)oxi]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)metoxi]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[4-(4-clorofenil)-1-(3-hidroxipropil)-1,2,5,6-tetrahidropiridin-3–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-({[4-({[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzoil]amino}sulfonil)-2-nitrofenil]amino}metil)piperidin-1-carboxilato de bencilo;
N-{[3-(aminocarbonil)-4-(tetrahidro-2H-piran-4–ilmetoxi)fenil]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[4'-cloro-5-(trifluorometil)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;
4-{4-[(5-tert-butil-4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(1-metil-1H-imidazol-5–il)metil]amino}-3-nitrofenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(morfolin-4–ilsulfonil)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1,1-dioxidotiomorfolin-4–il)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-morfolin-4–ilciclohexil)amino]-3-nitrofenil}sulfonil)benzamida;
N-{[5-bromo-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[6-[(tetrahidro-2H-piran-4–ilmetil)amino]-5-(1,3-tiazol-2–il)piridin-3–il]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-ciano-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-ciano-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(3,3-dimetilbutil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1S)-1-(hidroximetil)-3-metilbutil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[(2R)-tetrahidrofuran-2–ilmetil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1R)-1-(hidroximetil)-2-metilpropil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-metoxifenil)amino]-3-nitrofenil}sulfonil)benzamida;
N-[(4-{[2-(1,3-benzodioxol-5–il)etil]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[3-(2-oxopirrolidin-1–il)propil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-hidroxifenil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
N-{[4-({2-[4-(aminosulfonil)fenil]etil}amino)-3-nitrofenil]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[3-(1H-imidazol-1–il)propil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[(1S)-1-feniletil]amino}fenil)sulfonil]benzamida;
N-({2-cloro-5-fluoro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[2-(2-metoxietoxi)etil]tio}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[2-(2-metoxietoxi)etil]tio}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(metilsulfonil)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[4-(metilsulfonil)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2,2-dimetiltetrahidro-2H-piran-4–il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-ciano-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-ciano-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-cloro-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-ciano-6-(2-morfolin-4–iletoxi)piridin-3–il]sulfonil}-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)oxi]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-morfolin-4–ilbut-2-ynil)oxi]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-etinil-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-ciano-6-(2-morfolin-4–iletoxi)piridin-3–il]sulfonil}-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-ciano-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(3-hidroxi-4-metoxifenil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(2,3-dihidro-1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)-2-(piridin-3–ilamino)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)-2-(piridin-3–ilamino)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)-2-(piridin-3–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(1,2,3,4-tetrahidroisoquinolin-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;
Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)-N-({4-[(4-morfolin-4–ilciclohexil)amino]-3-nitrofenil}sulfonil)benzamida;
2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;
N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-ciano-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-2-(1H-indazol-4–iloxi)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(3R)-1-(2,2-difluoroetil)pirrolidin-3–il]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-fluorotetrahidro-2H-piran-4–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]-5-(trifluorometil)piridin-3–il]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-ciclopropilmorfolin-2–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4,4-difluorociclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4–iloxi)benzamida;

N-[(5-cloro-6-{[(4-fluorotetrahidro-2H-piran-4–il)metil]amino}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

Trans-N-({5-cloro-6-[(4-metoxiciclohexil)metoxi]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[4-(2,2-difluoroetil)morfolin-2–il]metil}amino)-3-nitrofenil]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-fluoro-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-2-(1H-indazol-4–iloxi)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;

N-[(5-cloro-6-{[1-(cianometil)-4-fluoropiperidin-4–il]metoxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-cloro-6-(tetrahidrofuran-3–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;

Trans-N-({5-cloro-6-[(4-hidroxiciclohexil)metoxi]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

N-[(5-cloro-6-{[(3R)-1-(2,2-difluoroetil)pirrolidin-3–il]oxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

2-(1H-benzimidazol-4–iloxi)-N-[(5-cloro-6-{[(2S)-4-(N,N-dimetilglicil)morfolin-2–il]metoxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)benzamida;

2-(1H-benzimidazol-4–iloxi)-N-[(5-cloro-6-{[(2R)-4-(N,N-dimetilglicil)morfolin-2–il]metoxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)benzamida;

N-[(5-cloro-6-{[(2S)-4-(N,N-dimetilglicil)morfolin-2–il]metoxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

N-[(5-cloro-6-{[(2R)-4-(N,N-dimetilglicil)morfolin-2–il]metoxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-cloro-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(3R)-1-(cianometil)pirrolidin-3–il]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({(3R)-1-[2-(2-metoxietoxi)etil]pirrolidin-3–il}amino)-3-nitrofenil]sulfonil}benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(3R)-1-(N,N-dimetilglicil)pirrolidin-3–il]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[4-(cianometil)morfolin-2–il]metil}amino)-3-nitrofenil]sulfonil}benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-ciclopropilmorfolin-2–il)metil]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(3-nitro-4-{[(4-oxetan-3–ilmorfolin-2–il)metil]amino}fenil)sulfonil]benzamida;

N-{[5-cloro-6-({(3R)-1-[2-fluoro-1-(fluorometil)etil]pirrolidin-3–il}oxi)piridin-3–il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({(3R)-1-[2-fluoro-1-(fluorometil)etil]pirrolidin-3–il}amino)-3-nitrofenil]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1-ciclopropilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)-2-(1H-indazol-4–iloxi)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[(2R)-4-(N,N-dimetilglicil)morfolin-2–il]metil}amino)-3-nitrofenil]sulfonil}benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[(2S)-4-(N,N-dimetilglicil)morfolin-2–il]metil}amino)-3-nitrofenil]sulfonil}benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(tetrahidrofuran-3–ilmetil)amino]fenil}sulfonil)benzamida;

Trans-2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-metoxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-fluorotetrahidro-2H-piran-4–il)metil]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-fluoro-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)benzamida;

N-{[5-cloro-6-({(3R)-1-[2-fluoro-1-(fluorometil)etil]pirrolidin-3–il}metoxi)piridin-3–il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

N-[(5-cloro-6-{[(3R)-1-(2,2-difluoroetil)pirrolidin-3–il]metoxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)-N-[(4-{[(4-metoxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-(1,4-dioxan-2–ilmetoxi)-3-nitrofenil]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;

N-({5-cloro-6-[(1-ciclopropilpiperidin-4–il)amino]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

2-(1H-benzimidazol-4–iloxi)-N-({5-cloro-6-[(1-ciclopropilpiperidin-4–il)amino]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1,4-dioxan-2–ilmetil)amino]-3-nitrofenil}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1-ciclopropilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;

Trans-2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-morfolin-4–ilciclohexil)amino]-3-nitrofenil}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1-metilpiperidin-4–il)metil]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[({(2R)-4-[2-(2-metoxietoxi)etil]morfolin-2–il}metil)amino]-3-nitrofenil}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4,4-difluorociclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;

N-[(4-{[(4-acetilmorfolin-2–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[4-(metilsulfonil)morfolin-2–il]metil}amino)-3-nitrofenil]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[6-({4-fluoro-1-[2-fluoro-1-(fluorometil)etil]piperidin-4–il}metoxi)-5-(trifluorometil)piridin-3–il]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-cloro-6-(2-tetrahidrofuran-2–iletoxi)piridin-3–il]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;

Trans-2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-cianociclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-N-({5-cloro-6-[(4,4-difluorociclohexil)metoxi]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)benzamida;

N-({3-cloro-4-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-*N*-{[5-ciano-6-(2-tetrahidro-2*H*-piran-4–iletoxi)piridin-3–il]sulfonil}-2-(1*H*-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(1R,5S)-8-metil-8-azabiciclo[3.2.1]oct-3–il]amino}-3-nitrofenil)sulfonil]benzamida;

N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxi-4-(4-{(3-fenilpropanoil)[(1S,2S,3S,5R)-2,6,6-trimetilbiciclo[3.1.1]hept-3–il]amino}piperidin-1–il)benzamida;

N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)-2-fenoxi-4-(4-{(3-fenilpropanoil)[(1S,2S,3S,5R)-2,6,6-trimetilbiciclo[3.1.1]hept-3–il]amino}piperidin-1–il)benzamida;

N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxi-4-(4-{(3-fenilpropil)[(1S,2S,3S,5R)-2,6,6-trimetilbiciclo[3.1.1]hept-3–il]amino}piperidin-1–il)benzamida;

N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)-2-fenoxi-4-(4-{(3-fenilpropil)[(1S,2S,3S,5R)-2,6,6-trimetilbiciclo[3.1.1]hept-3–il]amino}piperidin-1–il)benzamida;

4-[4-(2-{[(1R,5S)-8-metil-8-azabiciclo[3.2.1]oct-3–il]amino}bencil)piperazin-1–il]-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)-2-fenoxibenzamida;

4-[4-(2-{[(1R,5S)-8-metil-8-azabiciclo[3.2.1]oct-3–il]amino}bencil)piperazin-1–il]-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida;

4-{4-[2-(3-azabiciclo[3.2.2]non-3–il)bencil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida;

4-{4-[2-(3-azabiciclo[3.2.2]non-3–il)bencil]piperazin-1–il}-2-fenoxi-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;

4-{4-[2-(3-azabiciclo[3.2.2]non-3–il)bencil]piperazin-1–il}-2-fenoxi-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-{4-[2-(3-azabiciclo[3.2.2]non-3–il)bencil]piperazin-1–il}-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)-2-fenoxibenzamida;
4-(4-{2-[(4R,7S)-2,3,3a,4,7,7a-hexahidro-1H-4,7-metanoinden-5–il]bencil}piperazin-1–il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida;
4-[4-(2-{5-[(1R,5S)-8-azabiciclo[3.2.1]oct-8–ilmetil]tien-2–il}bencil)piperazin-1–il]-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida;
4-[4-(2-{5-[(1R,5S)-8-azabiciclo[3.2.1]oct-8–ilmetil]tien-2–il}benciliden)piperidin-1–il]-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida;
4-[4-(3-{5-[(1R,5S)-8-azabiciclo[3.2.1]oct-8–ilmetil]tien-2–il}bencil)piperazin-1–il]-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida;
N-({5-cloro-6-[(4,4-difluorociclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
N-({6-[(trans-4-carbamoilciclohexil)metoxi]-5-cloropiridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(trans-4-cianociclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;
N-({5-cloro-6-[2-(1H-imidazol-1-il)etoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
N-({5-cloro-6-[(1-metil-1H-imidazol-5-il)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[5-fluoro-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil}-2-(1H-indazol-4-iloxi)benzamida;
N-{[5-cloro-6-(1,4-dioxan-2-ilmetoxi)piridin-3-il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
N-({5-cloro-6-[(4,4-difluoro-1-hidroxiciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
N-({5-cloro-6-[(2,2-difluorociclopropil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
N-({5-cloro-6-[(trans-4-cianociclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(cis-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
N-({3-cloro-4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]fenil}sulfonil)-4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]-3-(trifluorometil)fenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-cloro-4-(tetrahidro-2H-piran-4-ilmetoxi)fenil]sulfonil}-2-(1H-indazol-4-iloxi)benzamida;
2-(1H-benzimidazol-4-iloxi)-N-({3-cloro-4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida;
2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[5-cloro-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-ciano-4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]fenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida;
N-{[3-cloro-4-(1,4-dioxan-2-ilmetoxi)fenil]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
2-(1H-benzimidazol-4-iloxi)-N-[(5-cloro-6-{[(2S)-4-ciclopropilmorfolin-2-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida;
N-[(5-cloro-6-{[(2S)-4-ciclopropilmorfolin-2-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
2-{[(4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzoil]sulfamoil}-2-nitrofenil)amino]metil}morfolin-4-carboxilato de metilo

2-{[(4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzoil]sulfamoil}-2-nitrofenil)amino]metil}-N-etil-N-metilmorfolin-4-carboxamida;

2-{[(4-{[2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzoil]sulfamoil}-2-nitrofenil)amino]metil}-N-etil-N-metilmorfolin-4-carboxamida;

N-({5-cloro-6-[(trans-4-etil-4-hidroxiciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(cis-4-etil-4-hidroxiciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

5-cloro-N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

5-cloro-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4-fluorotetrahidro-2H-piran-4-il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(cis-1-fluoro-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(trans-1-fluoro-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

2-(1H-benzotriazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4-fluorotetrahidro-2H-piran-4-il)metil]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzotriazol-4-iloxi)-N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida;

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-cloro-4-(tetrahidro-2H-piran-4-ilmetoxi)fenil]sulfonil}benzamida;

N-[(3-cloro-4-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}fenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(cis-1-fluoro-4-hidroxiciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

2-(1H-benzotriazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]-3-nitrofenil}sulfonil)benzamida;

N-[(5-cloro-6-{[(1R,2R,4R,5R)-5-hidroxi-5-metilbiciclo[2.2.1]hept-2-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-[(5-cloro-6-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

2-(1H-benzotriazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(trans-4-hidroxi-4-metilciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(cis-4-hidroxi-4-metilciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;

2-(1H-benzotriazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({[(2S)-4-ciclopropilmorfolin-2-il]metil}amino)-3-nitrofenil]sulfonil}benzamida;

N-[(5-cloro-6-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({[(2S)-4-ciclopropilmorfolin-2-il]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-indazol-4-iloxi)benzamida;

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({[(2S)-4-ciclopropilmorfolin-2-il]metil}amino)-3-nitrofenil]sulfonil}benzamida;

N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(cis-4-hidroxi-4-metilciclohexil)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(trans-4-hidroxi-4-metilciclohexil)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-ciano-4-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}fenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-{[3-nitro-4-(2-oxaspiro[3.5]non-7-ilmetoxi)fenil]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[5-cloro-6-(5,6,7,8-tetrahidroimidazo[1,2-a]piridin-6-ilmetoxi)piridin-3-il]sulfonil}-2-(1H-indazol-4-iloxi)benzamida;

2-(1H-benzimidazol-4-iloxi)-N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(5-ciano-6-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}piridin-3-il)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-5-(metoximetil)-5-metilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-{[3-nitro-4-({[(2S)-4-(oxetan-3-il)morfolin-2-il]metil}amino)fenil]sulfonil}benzamida;

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-nitro-4-({[(2S)-4-(oxetan-3-il)morfolin-2-il]metil}amino)fenil]sulfonil}benzamida;

N-[(5-cloro-6-{[trans-4-(2-hidroxipropan-2-il)ciclohexil]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-ciano-4-[(trans-4-hidroxi-4-metilciclohexil)metoxi]fenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({5-ciano-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-({5-nitro-6-[(tetrahidro-2H-piran-4-ilmetil)amino]piridin-3-il}sulfonil)benzamida;

2-(1H-benzotriazol-4-iloxi)-N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida;

N-({3-cloro-4-[(cis-4-ciano-1-fluorociclohexil)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({3-cloro-4-[(trans-4-ciano-1-fluorociclohexil)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(cis-4-ciano-1-fluorociclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(trans-4-ciano-1-fluorociclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(trans-4-hidroxi-4-metilciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;
N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-5-metoxi-5-metilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(5-cloro-6-{[1-(1,3-tiazol-2-il)piperidin-4-il]metoxi}piridin-3-il)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(6-{[(cis-4-hidroxi-4-metilciclohexil)metil]amino}-5-nitropiridin-3-il)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]-5-(trifluorometil)piridin-3-il}sulfonil)-2-(1H-indazol-4-iloxi)benzamida;
2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(cis-4-hidroxi-4-metilciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;
N-(4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzoil]sulfamoil}-2-nitrofenil)-4-cianopiperidin-1-carboxamida; y sus sales, profármacos, sales de profármacos y metabolitos terapéuticamente aceptables.

Otra forma de realización se refiere a una composición para tratar cáncer de vejiga, cáncer de cerebro, cáncer de mamas, cáncer de médula ósea, cáncer cervical, leucemia linfocítica crónica, cáncer colorrectal, cáncer de esófago, cáncer hepatocelular, leucemia linfoblástica, linfoma folicular, malignidades linfoides originadas en células T o células B, melanoma, leucemia mielógena, mieloma, cáncer oral, cáncer de ovarios, cáncer de pulmón de células no pequeñas, leucemia linfocítica crónica, mieloma, cáncer de próstata, cáncer de pulmón o cáncer de bazo de células pequeñas, donde dicha composición comprende un excipiente y una cantidad terapéuticamente efectiva del compuesto de fórmula (I).

Otra forma de realización se refiere a un método para tratar cáncer de vejiga, cáncer de cerebro, cáncer de mamas, cáncer de médula ósea, cáncer cervical, leucemia linfocítica crónica, cáncer colorrectal, cáncer de esófago, cáncer hepatocelular, leucemia linfoblástica, linfoma folicular, malignidades linfoides originadas en células T o células B, melanoma, leucemia mielógena, mieloma, cáncer oral, cáncer de ovarios, cáncer de pulmón de células no pequeñas, leucemia linfocítica crónica, mieloma, cáncer de próstata, cáncer de pulmón o

cáncer de bazo de células pequeñas en un paciente, donde dicho método comprende administrar al paciente una cantidad terapéuticamente efectiva de la fórmula (I).

Otra forma de realización se refiere a un método para tratar cáncer de vejiga, cáncer de cerebro, cáncer de mamas, cáncer de médula ósea, cáncer cervical, leucemia linfocítica crónica, cáncer colorrectal, cáncer de esófago, cáncer hepatocelular, leucemia linfoblástica, linfoma folicular, malignidades linfoides originadas en células T o células B, melanoma, leucemia mielógena, mieloma, cáncer oral, cáncer de ovarios, cáncer de pulmón de células no pequeñas, leucemia linfocítica crónica, mieloma, cáncer de próstata, cáncer de pulmón o cáncer de bazo de células pequeñas en un paciente, donde dicho método comprende administrar al paciente una cantidad terapéuticamente efectiva del compuesto de fórmula (I) y una cantidad terapéuticamente efectiva de un agente terapéutico adicional o más de un agente terapéutico adicional.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Los grupos variables en la presente están representados por identificadores (letras en mayúscula con valores numéricos y/o alfabéticos en superíndice) y se pueden realizar específicamente.

Se desea aclarar que las valencias correctas se mantienen para todas las unidades y sus combinaciones, que las unidades monovalentes con más de un átomo se han dibujado de izquierda a derecha y están unidas a través de sus extremos izquierdos, y que las unidades divalentes también se han dibujado de izquierda a derecha.

También se podrá comprender que una realización específica de un grupo variable en la presente puede ser igual o diferente de otra realización específica que tiene al mismo identificador.

El término "alquenilo" como se lo utiliza en la presente, significa una cadena hidrocarbonada lineal o ramificada que contiene entre 2 y 10 carbonos y que contiene al menos un doble enlace carbono-carbono. El término "C_x-C_y alquilo" significa una cadena de hidrocarburo lineal o ramificada que contiene por lo menos una unión doble carbono-carbono que contiene entre x e y átomos de carbono. El término "C3-C6 alquenilo" significa un grupo alquenilo que contiene 3-6 átomos de carbono. Los ejemplos representativos de alquenilos incluyen, sin limitaciones, buta-2,3-dienilo, etenilo, 2-propenilo, 2-metil-2-propenilo, 3-butenilo, 4-pentenilo, 5-hexenilo, 2-heptenilo, 2-metil-1-heptenilo y 3-decenilo.

El término "alquenileno" hace referencia a un grupo divalente derivado de un hidrocarburo de cadena lineal o ramificada de entre 2 y 4 átomos de carbono que contiene al

menos un enlace doble carbono-carbono. El término "C_x-C_y alquileno" significa un grupo divalente derivado de una cadena de hidrocarburo lineal o ramificada que contiene por lo menos una unión doble carbono-carbono y que contiene entre x e y átomos de carbono. Los ejemplos representativos de alquenileno incluyen, sin que esto constituya limitación alguna, -CH=CH- y -CH_2CH=CH-.

El término "alquilo" como se lo utiliza en la presente, significa una cadena hidrocarbonada saturada lineal o ramificada que contiene entre 1 y 10 átomos de carbono. El término "C_x-C_y alquilo" significa un hidrocarburo saturado de cadena lineal o ramificada, que contiene entre x e y átomos de carbono. Por ejemplo "C_1-C_6 alquilo" significa un hidrocarburo saturado de cadena lineal o ramificada, que contiene entre 2 y 6 átomos de carbono. Los ejemplos representativos de alquilo incluyen, sin limitaciones, metilo, etilo, n-propilo, iso-propilo, n-butilo, sec-butilo, iso-butilo, ter-butilo, n-pentilo, isopentilo, neopentilo, n-hexilo, 3-metilhexilo, 2,2-dimetilpentilo, 2,3-dimetilpentilo, n-heptilo, n-octilo, n-nonilo y n-decilo.

El término "alquileno" significa un grupo divalente derivado de una cadena de hidrocarburo saturado lineal o ramificada, de entre 1 y 10 átomos de carbono, por ejemplo, de entre 1 y 4 átomos de carbono. El término "C_x-C_y alquileno" significa un grupo divalente derivado de un hidrocarburo saturado de cadena lineal o ramificada, que contiene entre x e y átomos de carbono. Por ejemplo "C_2-C_6 alquileno" significa un hidrocarburo saturado de cadena lineal o ramificada, que contiene entre 2 y 6 átomos de carbono. Los ejemplos representativos de alquilenos incluyen, pero de manera no taxativa, -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2$-, y -$CH_2CH(CH_3)CH_2$-.

El término "alquinilo" como se lo usa en la presente documentación, hace referencia a un grupo hidrocarburo de cadena recta o ramificada que contiene entre 2 y 10 átomos de carbono y que contiene al menos un enlace triple carbono-carbono. El término "C_x-C_y alquinilo" significa un grupo hidrocarburo de cadena lineal o ramificada que contiene entre x e y átomos de carbono. Por ejemplo "C_3-C_6 alquinilo" significa un grupo hidrocarburo de cadena lineal o ramificada que contiene entre 3 y 6 átomos de carbono y que contiene por lo menos una unión triple carbono-carbono. Los ejemplos representativos de alquinilo incluyen, sin limitaciones, acetilenilo, 1-propinilo, 2-propinilo, 3-butinilo, 2-pentinilo y 1-butinilo.

El término "alquinileno", según se usa aquí, significa un radical divalente derivado de un grupo hidrocarburo de cadena lineal o ramificada que contiene entre 2 y 10 átomos de carbono y que contiene por lo menos una unión triple carbono-carbono.

El término "arilo" según se usa aquí, significa fenilo.

El término “unidad cíclica”, según se usa aquí, significa benceno, fenilo, fenileno, cicloalcano, cicloalquilo, cicloalquileno, cicloalqueno, cicloalquenilo, cicloalquenileno, cicloalquino, cicloalquinilo, cicloalquinileno, heteroareno, heteroarilo, heterocicloalcano, heterocicloalquilo, heterocicloalqueno, heterocicloalquenilo y espiroalquilo.

El término “cicloalquileno” o “cicloalquilo” o “cicloalcano” según se usa aquí, significa un sistema de anillo hidrocarburo monocíclico o con puente. El cicloalquilo monocíclico es un sistema de anillos carbocíclico que contiene entre tres y diez átomos de carbono, cero heteroátomos y cero dobles enlaces. Los ejemplos de sistemas de anillos monocíclicos incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo y ciclooctilo. El anillo cicloalquenilo monocíclico puede contener 1 o 2 puentes alquileno, donde cada uno consiste en 1, 2 ó 3 átomos de carbono, cada uno uniendo dos átomos de carbono no adyacentes del sistema de anillos. Los ejemplos representativos de dichos sistemas de anillos cicloalquilo con puente incluyen, pero de manera no taxativa, biciclo[3.1.1]heptano, biciclo[2.2.1]heptano, biciclo[2.2.2]octano, biciclo[3.2.1]octano, biciclo[3.2.2]nonano, biciclo[3.3.1]nonano, biciclo[4.2.1]nonano, triciclo[3.3.1.$0^{3,7}$]nonano (octahidro-2,5-metanopentaleno o noradamantano), y triciclo[3.3.1.$1^{3,7}$]decano (adamantano). El cicloalquilo monocíclico y con puente puede estar unido a la unidad molecular principal a través de cualquier átomo que pueda ser sustituido contenido dentro del sistema de anillos.

El término “cicloalquenileno”, o “cicloalquenilo” o “cicloalqueno” según se usa aquí, significa un sistema de anillo hidrocarburo monocíclico o con puente. El cicloalquenilo monocíclico tiene entre cuatro y diez átomos de carbono y cero heteroátomos. Los sistemas de anillos de cuatro miembros tienen una unión doble, los sistemas de anillos de cinco o de seis miembros tienen una o dos uniones dobles, los sistemas de anillos siete o de ocho miembros tienen una, dos, o tres uniones dobles, y los anillos de nueve o de diez miembros tienen una, dos, tres, o cuatro uniones dobles. Los ejemplos representativos de grupos cicloalquenilo monocíclicos incluyen, sin que esto constituya limitación alguna, ciclobutenilo, ciclopentenilo, ciclohexenilo, cicloheptenilo y ciclooctenilo. El anillo cicloalquenilo monocíclico puede contener 1 o 2 puentes alquileno, donde cada uno consiste en 1, 2 ó 3 átomos de carbono, cada uno uniendo dos átomos de carbono no adyacentes del sistema de anillos. Los ejemplos representativos de los grupos cicloalquenilo con puente incluyen, pero de manera no taxativa, biciclo[2.2.1]hept-2-eno, 4,5,6,7-tetrahidro-3aH-indeno, octahidronaftalenilo, y 1,6-dihidro-pentaleno. El cicloalquenilo monocíclico y con puente puede estar unido a la unidad molecular principal a través de cualquier átomo que pueda ser sustituido contenido dentro del sistema de anillos.

El término “cicloalquino”, o “cicloalquinilo”, o “cicloalquinileno”, según se usa aquí, significa un sistema de anillo hidrocarburo monocíclico o con puente. El cicloalquinilo monocíclico tiene ocho o más átomos de carbono, cero heteroátomos, y una o más uniones triples. El anillo cicloalquinilo monocíclico puede contener 1 o 2 puentes alquileno, donde cada uno consiste en 1, 2 ó 3 átomos de carbono, cada uno uniendo dos átomos de carbono no adyacentes del sistema de anillos. El cicloalquinilo monocíclico y con puente puede estar unido a la unidad molecular principal a través de cualquier átomo que pueda ser sustituido contenido dentro del sistema de anillos.

El término “heteroareno”, o “heteroarilo”, o “heteroarileno”, según se usa aquí, significa un anillo aromático de cinco miembros o de seis miembros que tiene por lo menos un átomo de carbono y uno o más de uno que se seleccionan independientemente entre átomos de nitrógeno, oxígeno o azufre. Los heteroarenos de la presente invención están conectados a través de cualquiera de los átomos del anillo adyacentes, con la condición de que se deben mantener las valencias correctas. Los ejemplos representativos de heteroarilo incluyen, pero de manera no taxativa, furanilo (que incluye, pero de manera no taxativa, a: furan-2-ilo), imidazolilo (que incluye, pero de manera no taxativa, a: 1H-imidazol-1-ilo), isoxazolilo, isotiazolilo, oxadiazolilo, 1,3-oxazolilo, piridinilo (por ejemplo Piridin-4-ilo, piridin-2-ilo, piridin-3-ilo), piridazinilo, pirimidinilo, pirazinilo, pirazolilo, pirrolilo, tetrazolilo, tiadiazolilo, 1,3-tiazolilo, tienilo (que incluye, pero de manera no taxativa, a: tien-2-ilo, tien-3-ilo), triazolilo, y triazinilo.

El término “heterocicloalcano”, o “heterocicloalquilo”, o “heterocicloalquileno”, según se usa aquí, significa anillo monocíclico o con puente de tres, cuatro, cinco, seis, siete, u ocho miembros, que contiene por lo menos un heteroátomo que se selecciona independientemente entre el grupo que consiste en O, N, y S y cero uniones dobles. El heterocicloalcano monocíclico y con puente está conectado a la unidad molecular principal a través de cualquier átomo de carbono que pueda ser sustituido o cualquier átomo de nitrógeno que pueda ser sustituido contenidos dentro de los anillos. Los heteroátomos nitrógeno y azufre en los anillos heterocíclicos pueden estar opcionalmente oxidados y los átomos de nitrógeno opcionalmente pueden ser cuaternarios. Los ejemplos representativos de grupos heterocicloalcanos incluyen, pero de manera no taxativa, 8-azabiciclo[3.2.1]octano, 3-azabiciclo[3.2.2]nonano, morfolinilo, tetrahidropiranilo, pirrolidinilo, piperidinilo, dioxolanilo, tetrahidrofuranilo, tiomorfolinilo, 1,4-dioxanilo, tetrahidrotienilo, tetrahidrotiopiranilo, oxetanilo, piperazinilo, imidazolidinilo, azetidina, azepanilo, aziridinilo, diazepanilo, ditiolanilo, ditianilo, isoxazolidinilo, isotiazolidinilo, oxadiazolidinilo,

oxazolidinilo, pirazolidinilo, tetrahidrotienilo, tiadiazolidinilo, tiazolidinilo, tiomorfolinilo, tritianilo, y tritianilo.

El término “heterocicloalqueno”, o “heterocicloalquenilo”, o “heterocicloalquenileno”, según se usa aquí, significa anillo monocíclico o con puente de tres, cuatro, cinco, seis, siete, u ocho miembros que contiene por lo menos un heteroátomo que se selecciona independientemente entre el grupo que consiste en O, N, y S y una o más uniones dobles. El heterocicloalqueno monocíclico y con puente está conectado a la unidad molecular principal a través de cualquier átomo de carbono que pueda ser sustituido o cualquier átomo de nitrógeno que pueda ser sustituido contenidos dentro de los anillos. Los heteroátomos nitrógeno y azufre en los anillos heterocíclicos pueden estar opcionalmente oxidados y los átomos de nitrógeno opcionalmente pueden ser cuaternarios. Los ejemplos representativos de grupos heterocicloalqueno incluyen, pero de manera no taxativa, 1,4,5,6-tetrahidropiridazinilo, 1,2,3,6-tetrahidropiridinilo, dihidropiranilo, imidazolinilo, isotiazolinilo, oxadiazolinilo, isoxazolinilo, oxazolinilo, piranilo, pirazolinilo, pirrolinilo, tiadiazolinilo, tiazolinilo, y tiopiranilo.

El término “fenileno”, según se usa aquí, significa un radical divalente formado al suprimir un átomo de hidrógeno del fenilo.

El término “espiroalquilo”, según se usa aquí, significa un alquileno, del cual ambos extremos están unidas al mismo átomo de carbono y pueden ser ejemplificados por C_2-espiroalquilo, C_3-espiroalquilo, C_4-espiroalquilo, C_5-espiroalquilo, C_6-espiroalquilo, C_7-espiroalquilo, C_8-espiroalquilo, C_9-espiroalquilo y semejantes.

El término “espiroheteroalquilo”, según se usa aquí, significa espiroalquilo donde una o dos unidades CH_2 han sido reemplazadas por una unidad que se selecciona independientemente entre: O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y donde una o dos unidades CH no han sido reemplazadas o han sido reemplazadas por N.

El término “espiroheteroalquenilo”, según se usa aquí, significa espiroalquenilo donde una o dos unidades CH_2 han sido reemplazadas por una unidad que se selecciona independientemente entre: O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no han sido reemplazadas o han sido reemplazadas por N y también significa espiroalquenilo con una o dos unidades CH_2 que no han sido reemplazadas o han sido reemplazadas por una unidad que se selecciona independientemente entre: O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH han sido reemplazadas por N.

El término, “espirociclo”, según se usa aquí, significa dos sustituyentes sobre el mismo átomo de carbono, que, junto con el átomo de carbono al cual están unidos, forman un anillo cicloalcano, heterocicloalcano, cicloalqueno, o heterocicloalqueno.

El término “C_2-C_5-espiroalquilo”, según se usa aquí, significa C_2-espiroalquilo, C_3-espiroalquilo, C_4-espiroalquilo, y C_5-espiroalquilo.

El término “C_2-espiroalquilo”, según se usa aquí, significa et-1,2-ileno, del cual ambos extremos remplazan átomos de hidrógeno de la misma unidad CH_2.

El término “C_3-espiroalquilo”, según se usa aquí, significa prop-1,3-ileno, del cual ambos extremos remplazan átomos de hidrógeno de la misma unidad CH_2.

El término “C_4-espiroalquilo”, según se usa aquí, significa but-1,4-ileno, del cual ambos extremos remplazan átomos de hidrógeno de la misma unidad CH_2.

El término “C_5-espiroalquilo”, según se usa aquí, significa pent-1,5-ileno, del cual ambos extremos remplazan átomos de hidrógeno de la misma unidad CH_2.

El término “C_6-espiroalquilo”, según se usa aquí, significa hex-1,6-ileno, del cual ambos extremos remplazan átomos de hidrógeno de la misma unidad CH_2.

El término “grupo protector de NH”, según se usa aquí, significa tricloroetoxicarbonilo, tribromoetoxicarbonilo, benciloxicarbonilo, para-nitrobencilcarbonilo, orto-bromobenciloxicarbonilo, cloroacetilo, dicloroacetilo, tricloroacetilo, trifluoroacetilo, fenilacetilo, formilo, acetilo, benzoílo, tert-amiloxicarbonilo, tert-butoxicarbonilo, para-metoxibenciloxicarbonilo, 3,4-dimetoxibencil-oxicarbonilo, 4-(fenilazo)benciloxicarbonilo, 2-furfuril-oxicarbonilo, difenilmetoxicarbonilo, 1,1-dimetilpropoxi-carbonilo, isopropoxicarbonilo, ftaloílo, succinilo, alanilo, leucilo, 1-adamantiloxicarbonilo, 8-quinoliloxicarbonilo, bencilo, difenilmetilo, trifenilmetilo, 2-nitrofeniltio, metanosulfonilo, para-toluensulfonilo, N,N-dimetilaminometileno, bencilideno, 2-hidroxibencilideno, 2-hidroxi-5-clorobencilideno, 2-hidroxi-1-naftil-metileno, 3-hidroxi-4-piridilmetileno, ciclohexilideno, 2-etoxicarbonilciclohexilideno, 2-etoxicarbonilciclopentilideno, 2-acetilciclohexilideno, 3,3-dimetil-5-oxiciclo-hexilideno, difenilfosforilo, dibencilfosforilo, 5-metil-2-oxo-2H-1,3-dioxol-4-il-metilo, trimetilsililo, trietilsililo, y trifenilsililo.

El término “grupo protector de C(O)OH”, según se usa aquí, significa metilo, etilo, n-propilo, isopropilo, 1,1-dimetilpropilo, n-butilo, tert-butilo, fenilo, naftilo, bencilo, difenilmetilo, trifenilmetilo, para-nitrobencilo, para-metoxibencilo, bis(para-metoxifenil)metilo, acetilmetilo, benzoilmetilo, para-nitrobenzoilmetilo, para-bromobenzoilmetilo, para-metanosulfonilbenzoilmetilo, 2-tetrahidropiranilo 2-tetrahidrofuranilo, 2,2,2-tricloro-etilo, 2-(trimetilsilil)etilo, acetoximetilo, propioniloximetilo,

pivaloiloximetilo, ftalimidometilo, succinimidometilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, metoximetilo, metoxietoximetilo, 2-(trimetilsilil)etoximetilo, benciloximetilo, metiltiometilo, 2-metiltioetilo, feniltiometilo, 1,1-dimetil-2-propenilo, 3-metil-3-butenilo, alilo, trimetilsililo, trietilsililo, triisopropilsililo, dietilisopropilsililo, tert-butildimetilsililo, tert-butildifenilsililo, difenilmetilsililo, y tert-butilmetoxifenilsililo.

El término "grupo protector de OH o SH", según se usa aquí, significa benciloxicarbonilo, 4-nitrobenciloxicarbonilo, 4-bromobenciloxicarbonilo, 4-metoxibenciloxicarbonilo, 3,4-dimetoxibenciloxicarbonilo, metoxicarbonilo, etoxicarbonilo, tert-butoxicarbonilo, 1,1-dimetilpropoxicarbonilo, isopropoxicarbonilo, isobutiloxicarbonilo, difenilmetoxicarbonilo, 2,2,2-tricloroetoxicarbonilo, 2,2,2-tribromoetoxicarbonilo, 2-(trimetilsilil)etoxicarbonilo, 2-(fenilsulfonil)etoxicarbonilo, 2-(trifenilfosfonio)etoxicarbonilo, 2-furfuriloxicarbonilo, 1-adamantiloxicarbonilo, viniloxicarbonilo, aliloxicarbonilo, S-benciltiocarbonilo, 4-etoxi-1-naftiloxicarbonilo, 8-quinoliloxicarbonilo, acetilo, formilo, cloroacetilo, dicloroacetilo, tricloroacetilo, trifluoroacetilo, metoxiacetilo, fenoxiacetilo, pivaloílo, benzoílo, metilo, tert-butilo, 2,2,2-tricloroetilo, 2-trimetilsililetilo, 1,1-dimetil-2-propenilo, 3-metil-3-butenilo, alilo, bencilo (fenilmetilo), para-metoxibencilo, 3,4-dimetoxibencilo, difenilmetilo, trifenilmetilo, tetrahidrofurilo, tetrahidropiranilo, tetrahidrotiopiranilo, metoximetilo, metiltiometilo, benciloximetilo, 2-metoxietoximetilo, 2,2,2-tricloro-etoximetilo, 2-(trimetilsilil)etoximetilo, 1-etoxietilo, metanosulfonilo, para-toluensulfonilo, trimetilsililo, trietilsililo, triisopropilsililo, dietilisopropilsililo, tert-butildimetilsililo, tert-butildifenilsililo, difenilmetilsililo, y tert-butilmetoxifenilsililo.

Compuestos

Los compuestos de la presente pueden presentarse como isómeros geométricos. Los Compuestos de la presente invención pueden contener uniones dobles carbono-carbono o uniones dobles carbono-nitrógeno con la configuración E o Z, donde el término "E" significa que los sustituyentes de mayor orden se encuentran sobre lados opuestos de la unión doble carbono-carbono o carbono-nitrógeno y el término "Z" significa que los sustituyentes de mayor orden se encuentran del mismo lado de la unión doble carbono-carbono o carbono-nitrógeno según se determina siguiendo las reglas de prioridad de Cahn-Ingold-Prelog. Los compuestos de esta invención también pueden existir como una mezcla de isómeros "E" y "Z". Los sustituyentes alrededor de un cicloalquilo o heterocicloalquilo se designan con la configuración cis o trans. Además, la invención contempla a los diversos isómeros y mezclas

de los mismos que son el resultado de la disposición de los sustituyentes alrededor de un sistema de anillo adamantano. Si hay dos sustituyentes alrededor de un único anillo dentro de un sistema de anillo adamantano se designan con una configuración relativa Z o E. Para ver ejemplos, véase C. D. Jones, M. Kaselj, R. N. Salvatore, W. J. le Noble *J. Org. Chem*. **1998**, 63, 2758-2760 y E. L. Eliel, y S.H. Wilen. (1994) *Stereochemistry of Organic Compounds*. New York, NY: John Wiley & Sons, Inc.

Los compuestos de la presente invención contienen átomos de carbono sustituidos de manera asimétrica en la configuración R o S, donde los términos "R" y "S" son según se los define en la IUPAC 1974 Recomendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem. (1976) 45, 13-10. Los compuestos con átomos de carbono sustituidos de manera asimétrica con cantidades iguales de las configuraciones R y S son racémicos en dichos átomos de carbono. A los átomos con más de una configuración que de la otra se les asigna la configuración que se presenta en mayor cantidad, preferiblemente en más de aproximadamente 85%-90%, más preferiblemente en más de aproximadamente 95%-99%, y aún más preferiblemente en un exceso mayor de aproximadamente 99%. Por lo tanto, la presente invención incluye a las mezclas racémicas, a los estereoisómeros relativos y absolutos, y a las mezclas de estereoisómeros relativos y absolutos.

Los compuestos de esta invención que contienen grupos NH, C(O)OH, OH o SH pueden estar unidos a grupos formadores de profármacos. Los grupos formadores de profármacos son eliminados por los procesos metabólicos y liberan *in vivo* a los compuestos con el grupo hidroxilo, amino o ácido carboxílico libre. Los profármacos son de utilidad para ajustar propiedades farmacocinéticas de los compuestos tales como solubilidad y/o carácter hidrofóbico, absorción en el tracto gastrointestinal, biodisponibilidad, penetración en tejidos y velocidad de depuración.

Compuestos Enriquecidos en un Isótopo o Marcados

Los compuestos de la invención pueden existir en una forma marcada con isótopos o en una forma enriquecida que contiene uno o más átomos que tienen una masa atómica o un número másico diferente de la masa atómica o del número másico más abundante en la naturaleza. Los isótopos pueden ser isótopos radioactivos o no radioactivos. Los isótopos de átomos tales como hidrógeno, carbono, fósforo, azufre, flúor, cloro y iodo incluyen, pero en un sentido no limitativo, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl y ^{125}I. Los compuestos que contienen otros isótopos de estos y/u otros átomos se encuentran dentro del alcance de esta invención.

En otra forma de realización, los compuestos marcados con isótopos contienen deuterio (^{2}H), tritio (^{3}H) o isótopos de ^{14}C. Los compuestos marcados con isótopos de esta invención se pueden preparar mediante los métodos generales bien conocidos por los especialistas en la técnica. Dichos compuestos marcados con isótopos se pueden preparar convenientemente utilizando los procedimientos divulgados en los Ejemplos y Esquemas por sustitución de un reactivo marcado con isótopos de fácil acceso por un reactivo no marcado. En algunos casos, los compuestos pueden ser tratados con un reactivo marcado con isótopos para intercambiar un átomo normal por su isótopo, por ejemplo, se puede intercambiar hidrógeno por deuterio por acción de un ácido deutérico, tal como D_2SO_4/D_2O. Además de lo anterior, los procedimientos e intermediarios relevantes se divulgan, por ejemplo, en Lizondo, J et al., *Drugs Fut*, 21(11), 1116 (1996); Brickner, S J *et al., J Med Chem*, 39(3), 673 (1996); Mallesham, B et al., *Org Lett*, 5(7), 963 (2003); publicaciones de PCT WO1997010223, WO2005099353, WO1995007271, WO2006008754; Patentes de los EE.UU. Nº: 7538189; 7534814; 7531685; 7528131; 7521421; 7514068; 7511013; y las publicaciones de Solicitudes de Patente de los EE.UU. Nº: 20090137457; 20090131485; 20090131363; 20090118238; 20090111840; 20090105338; 20090105307; 20090105147; 20090093422; 20090088416; y 20090082471, los métodos se incorporan en la presente a modo de referencia.

Los compuestos marcados con un isótopo de la invención se pueden utilizar como estándares para determinar la efectividad de los inhibidores de Bcl-2 en ensayos de unión. Los compuestos que contienen isótopos se han utilizado en la investigación farmacéutica para conocer el destino metabólico in vivo de los compuestos por evaluación del mecanismo de acción y de la vía metabólica del compuesto progenitor no marcado con isótopos (Blake et al. *J. Pharm. Sci.* 64, 3, 367-391 (1975)). Dichos estudios metabólicos son importantes en el diseño del fármacos terapéuticas seguras y efectivas, ya sea porque el compuesto activo administrado *in vivo* al paciente o porque los metabolitos producidos a partir del compuesto progenitor han demostrado ser tóxicos o carcinogénicos (Foster et al., *Advances in Drug Research*, Vol. 14. 2-36, Academic press, Londres, 1985; Kato et al., J. *Labelled Comp. Radiopharmaceut.*, 36(10):927-932 (1995); Kushner et al., *Can. J. Physiol. Pharmacol.*, 77, 79-88 (1999).

Además, los fármacos que contienen isótopos no radioactivos, tales como los fármacos deuteradas denominadas “fármacos pesados”, se pueden usar para el tratamiento de enfermedades y condiciones relacionadas con la actividad Bcl-2. El incremento de la cantidad de un isótopo presente en un compuesto por encima de su abundancia natural se denomina

enriquecimiento. Los ejemplos de cantidad de enriquecimiento incluyen entre aproximadamente 0,5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 21, 25, 29, 33, 37, 42, 46, 50, 54, 58, 63, 67, 71, 75, 79, 84, 88, 92, 96, hasta aproximadamente 100% mol. Se ha realizado y mantenido el reemplazo de hasta un 15% aproximadamente de átomos normales por un isótopo pesado por un período de días a semanas en mamíferos, incluyendo roedores y perros, con mínimos efectos secundarios (Czajka D M y Finkel A *J, Ann. N.Y. Acad. Sci*., 1960 84.770:770; Thomson J F, *Ann. New York Acad. Sci*., 1960 84.736:736; Czakja D M et al., *Am. J. Physiol*., 1961 201:357). Se encontró que un reemplazo agudo de tanto como un 15%-23% en fluidos humanos con deuterio no causaba toxicidad (Blagojevic N et al., en "Dosimetry & Treatment Planning for Neutron Capture Therapy", Zamenhof R, Solares G y Harling O Eds., 1994; *Advanced Medical Publishing*, Madison Wis. Págs.125-134; *Diabetes Metab*., 23:251 (1997)). 23: 251 (1997)).

Una marcación estable con isótopos de un fármaco altera sus propiedades fisicoquímicas tales como pKa y solubilidad de lípidos. Estos efectos y alteraciones pueden afectar la respuesta farmacodinámica de la molécula del fármaco si la sustitución isotópica afecta una región comprometida en una interacción de ligando-receptor. Aunque algunas de las propiedades físicas de una molécula marcada con isótopos estable son diferentes de las propiedades de una molécula no marcada, las propiedades químicas y biológicas son las mismas, con una excepción importante: dado el incremento en la masa del isótopo pesado, cualquier enlace que comprenda al isótopo pesado y otro átomo será más fuerte que el mismo enlace entre el isótopo liviano y dicho átomo. Por lo tanto, la incorporación de un isótopo en un sitio de transformación enzimática o del metabolismo va a demorar tales reacciones alterando potencialmente el perfil farmacocinético o la eficacia con relación al compuesto no isotópico.

Amidas, Ésteres y Profármacos

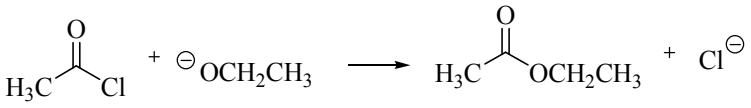
Las profármacos son derivados de una fármaco activa diseñada para mejorar alguna propiedad física o biológica identificada, que no es deseable. Las propiedades físicas usualmente son la solubilidad (una solubilidad excesiva o insuficiente en lípidos o en agua) o la estabilidad relacionada, mientras que las propiedades biológicas problemáticas incluyen un metabolismo demasiado rápido o una biodisponibilidad insatisfactoria, la que en sí misma puede estar relacionada con una propiedad fisicoquímica.

Las profármacos usualmente se preparan por: a) formación de ésteres, hemi ésteres, ésteres carbonato, ésteres nitrato, amidas, ácidos hidroxámicos, carbamatos, iminas, bases de Mannich, fosfatos, ésteres de fosfatos y enaminas de la fármaco activa, b) funcionalización de

la fármaco con grupos funcionales azo, glucósido, péptido, y éter, c) uso de aminales, hemi-aminales, polímeros, sales, complejos, fosforamidas, las formas de acetales, hemiacetales, y cetales de la fármaco. Por ejemplo, véase "Essentials of Medicinal Chemistry" de Andrejus Korolkovas, John Wiley-Interscience Publications, John Wiley y Sons, New York (1988), pp. 97-118, que se incorpora aquí en su totalidad como referencia.

Los ésteres se pueden preparar a partir de sustratos de fórmula (I) que contienen ya sea un grupo hidroxilo o un grupo carboxi usando métodos generales conocidos por las personas con experiencia en el arte. Las reacciones típicas de dichos compuestos son sustituciones donde se reemplaza uno de los heteroátomos por otro átomo, por ejemplo:

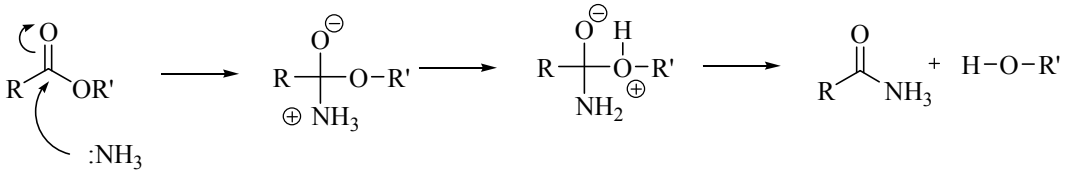
Esquema 1



Cloruro de acilo Alcóxido Éster

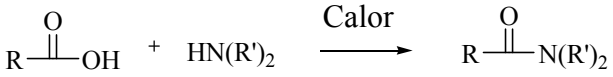
Las amidas se pueden preparar a partir de sustratos de fórmula (I) que contienen ya sea un grupo amino o un grupo carboxi de una manera similar. Los ésteres también pueden reaccionar con aminas o amoníaco para formar amidas.

Esquema 2



Otra manera de hacer amidas a partir de compuestos de fórmula (I) consiste en calentar juntos ácidos carboxílicos y aminas.

Esquema 3

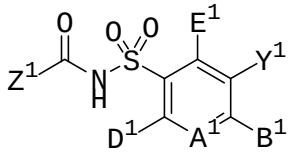


En los anteriores Esquemas 2 y 3, R y R' son independientemente sustratos de fórmula (I), alquilo o hidrógeno.

Los grupos apropiados para A^1, B^1, D^1, E^1, Y^1, y Z^1 en los compuestos de fórmula (I) se seleccionan independientemente. Las formas de realización descritas de la presente invención se pueden combinar. Dicha combinación se contempla y se encuentra dentro del alcance de la presente invención. Por ejemplo, se contempla que las formas de realización

para cualquiera de A^1, B^1, D^1, E^1, Y^1, y Z^1 se puedan combinar con las formas de realización definidas para otro cualesquiera de A^1, B^1, D^1, E^1, Y^1, y Z^1.

Una realización de esta invención, por lo tanto, se refiere a compuestos o sus sales, profármacos, o sales de profármacos terapéuticamente aceptables, que son útiles como inhibidores selectivos de uno o más miembros de la familia de proteínas anti-apoptóticas, donde los compuestos tienen la Fórmula (I)



(I),

en donde A^1 es N o $C(A^2)$;

uno o dos o tres o cada uno de A^2, B^1, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes se seleccionan en forma independiente entre H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$; y

Y^1 es H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ o $NHSO_2R^{17}$;

o

B^1 y Y^1, junto con los átomos a los cuales están unidos , son imidazol o triazol; y

uno o dos o cada uno de A^2, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes se seleccionan en forma independiente entre H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$;

R^1 es R^2, R^3, R^4 o R^5;

R^{1A} es C_1-C_6-alquilo, C_3-C_6-alquenilo o C_3-C_6-alquinilo;

R^2 es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{2A}; R^{2A} es cicloalcano o heterocicloalcano;

R^3 es heteroarilo que no está fusionado o está fusionado con benceno, heteroareno o R^{3A}; R^{3A} es cicloalcano o heterocicloalcano;

R^4 es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{4A}; R^{4A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^5 es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^6 es C_2-C_5-espiroalquilo, cada uno de los cuales no esta sustituido o está sustituido con OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ o $N(CH_3)_2$;

R^{6A} y R^{6B} se seleccionan en forma independiente entre alquilo o, junto con el N al cual están unidos, R^{6C};

R^{6C} es aziridin-1–ilo, azetidin-1–ilo, pirrolidin-1–ilo o piperidin-1–ilo, teniendo cada uno una unidad CH_2 no reemplazada o reemplazada con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH;

R^7 es R^8, R^9, R^{10} o R^{11};

R^8 es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{8A};

R^{8A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^9 es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{9A}; R^{9A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{10} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{10A}; R^{10A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{11} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{12} es R^{13}, R^{14}, R^{15} o R^{16};

R^{13} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{13A}; R^{13A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{14} es heteroarilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{14A}; R^{14A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{15} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{15A}; R^{15A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{16} es alquilo, alquenilo o alquinilo;

R^{17} es R^{18}, R^{19}, R^{20} o R^{21};

R^{18} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{18A}; R^{18A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{19} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{19A}; R^{19A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{20} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{20A}; R^{20A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{21} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I;

R^{22} es R^{23}, R^{24} o R^{25};

R^{23} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{23A}; R^{23A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{24} es heteroareno que no está fusionado o está fusionado con areno, heteroareno o R^{24A}; R^{24A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{25} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{25A}; R^{25A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

Z^1 es R^{26} o R^{27}, cada uno de los cuales está sustituido con R^{28}, R^{29} o R^{30}, cada uno de los cuales está sustituido con F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} o $N(R^{32})R^{37}$;

R^{26} es fenilo que no está fusionado o está fusionado con areno o heteroareno;

R^{27} es heteroareno que no está fusionado o está fusionado con areno o heteroareno;

R^{28} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{28A}; R^{28A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno

R^{29} es heteroarilo o R^{29A}; R^{29A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{30} es cicloalquilo o cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{30A}; R^{30A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{31} y R^{31A} son en forma independiente F, Cl, Br o alquilo o se toman juntos y son C_2-C_5-espiroalquilo;

R^{32} es R^{33}, $C(O)R^{33}$ o $C(O)OR^{33}$;

R^{33} es R^{34} o R^{35};

R^{34} es fenilo que no está fusionado o está fusionado con arilo, heteroarilo o R^{34A}; R^{34A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{35} es alquilo que no está sustituido o está sustituido con R^{36};

R^{36} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{36A}; R^{36A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{37} es R^{38}, R^{39} o R^{40}, cada uno de los cuales está sustituido con F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ o SO_2R^{41};

R^{38} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{38A}; R^{38A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{39} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{39A}; R^{39A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{40} es C_3-C_8-cicloalquilo o C_4-C_8-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{40A}; R^{40A} cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{41} es R^{42}, R^{43}, R^{44} o R^{45};

R^{42} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{42A}; R^{42A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{43} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{43A}; R^{43A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{44} es C_3-C_9-cicloalquilo o C_4-C_7-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{44A}; R^{44A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{45} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos sustituyentes seleccionados en forma independiente entre: R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{46} es R^{47}, R^{48} o R^{49};

R^{47} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{47A}; R^{47A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{48} es heteroarilo o R^{48A}; R^{48A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{49} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{49A}; R^{49A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

en donde las unidades representadas por R^{26} y R^{27} se sustituyen adicionalmente con uno o dos o tres sustituyentes seleccionados en forma independiente entre: R^{50A}, OR^{50A}, SR^{50A}, $S(O)R^{50A}$, SO_2R^{50A} o NHR^{50A},

R^{50A} es R^{51A}, R^{52A}, R^{53A} o R^{54A};

R^{51A} es fenilo que no está fusionado o está fusionado con benceno, heteroareno o R^{51AA},

en donde R^{51AA} es cicloalcano, cicloalqueno o heterocicloalcano heterocicloalqueno,

R^{52A} es heteroarilo;

R^{53A} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo; donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{53AA};

en donde R^{53AA} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{54A} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre: R^{55AA}, OR^{55AA}, SR^{55AA}, $S(O)R^{55AA}$, SO_2R^{55AA}, NHR^{55AA}, $N(R^{55AA})_2$, $C(O)R^{55AA}$, $C(O)NH_2$, $C(O)NHR^{55AA}$, $NHC(O)R^{55AA}$, $NHSO_2R^{55AA}$, $NHC(O)OR^{55AA}$, SO_2NH_2, SO_2NHR^{55AA}, $SO_2N(R^{55AA})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55AA}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{55AA} es alquilo, alquenilo, alquinilo, fenilo o heteroarilo, o R^{56A};

R^{56A} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N;

en donde las unidades representadas por R^2, R^{2A}, R^3, R^{3A}, R^4, R^{4A}, R^6, R^{6C}, R^8, R^{8A}, R^9, R^{10}, R^{10A}, R^{13}, R^{13A}, R^{14}, R^{14A}, R^{15}, R^{15A}, R^{18}, R^{18A}, R^{19}, R^{19A}, R^{20}, R^{20A}, R^{23}, R^{23A}, R^{24}, R^{24A}, R^{25}, R^{25A}, R^{26}, R^{27}, R^{28}, R^{28A}, R^{29}, R^{29A}, R^{30}, R^{30A}, R^{34}, R^{34A}, R^{36}, R^{36A}, R^{38}, R^{38A}, R^{39}, R^{39A}, R^{40}, R^{40A}, R^{42}, R^{42A}, R^{43}, R^{43A}, R^{44}, R^{44A}, R^{47}, R^{47A}, R^{48}, R^{48A}, R^{49}, y R^{49A} son en forma independiente no sustituidas, adicionalmente no sustituidas, sustituidas o adicionalmente sustituidas con uno o dos o tres o cuatro o cinco sustituyentes seleccionados en forma independiente entre R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br o I;

R^{50} es R^{51}, R^{52}, R^{53} o R^{54};

R^{51} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{51B};

R^{51B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{52} es heteroarilo;

R^{53} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{53B};

en donde R^{53B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{54} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma

independiente: R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br o I;

R^{55} es alquilo, alquenilo, alquinilo, fenilo, heteroarilo o R^{56}; y

en donde el alquilo, alquenilo, alquinilo no están sustituidos o están sustituidos con OCH_3; y

R^{56} es C_3-C_8-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N.

Otra forma de realización de esta invención se refiere a compuestos de Fórmula (I), en donde

A^1 es N o $C(A^2)$;

uno o dos o tres o cada uno de A^2, B^1, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes se seleccionan en forma independiente entre H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$; y

Y^1 es H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ o $NHSO_2R^{17}$;

o

B^1 y Y^1, junto con los átomos a los cuales están unidos , son imidazol o triazol; y

uno o dos o cada uno de A^2, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes se seleccionan en forma independiente entre H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$;

R^1 es R^2, R^3, R^4 o R^5;

R^{1A} es C_1-C_6-alquilo, C_3-C_6-alquenilo o C_3-C_6-alquinilo;

R^2 es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{2A}; R^{2A} es cicloalcano o heterocicloalcano;

R^3 es heteroarilo que no está fusionado o está fusionado con benceno, heteroareno o R^{3A}; R^{3A} es cicloalcano o heterocicloalcano;

R^4 es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{4A}; R^{4A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^5 es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^6 es C_2-C_5-espiroalquilo, cada uno de los cuales no esta sustituido o está sustituido con OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ o $N(CH_3)_2$;

R^{6A} y R^{6B} se seleccionan en forma independiente entre alquilo o, junto con el N al cual están unidos, R^{6C};

R^{6C} es aziridin-1–ilo, azetidin-1–ilo, pirrolidin-1–ilo o piperidin-1–ilo, teniendo cada uno una unidad CH_2 no reemplazada o reemplazada con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH;

R^7 es R^8, R^9, R^{10} o R^{11};

R^8 es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{8A};

R^{8A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^9 es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{9A}; R^{9A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{10} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{10A}; R^{10A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{11} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{12} es R^{13}, R^{14}, R^{15} o R^{16};

R^{13} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{13A}; R^{13A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{14} es heteroarilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{14A}; R^{14A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{15} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{15A}; R^{15A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{16} es alquilo, alquenilo o alquinilo;

R^{17} es R^{18}, R^{19}, R^{20} o R^{21};

R^{18} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{18A}; R^{18A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{19} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{19A}; R^{19A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{20} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{20A}; R^{20A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{21} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{22} es R^{23}, R^{24} o R^{25};

R^{23} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{23A}; R^{23A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{24} es heteroareno que no está fusionado o está fusionado con areno, heteroareno o R^{24A}; R^{24A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{25} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{25A}; R^{25A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

Z^1 es R^{26} o R^{27}, cada uno de los cuales está sustituido con R^{28}, R^{29} o R^{30}, cada uno de los cuales está sustituido con F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} o $N(R^{32})R^{37}$;

R^{26} es fenilo que no está fusionado o está fusionado con areno o heteroareno;

R^{27} es heteroareno que no está fusionado o está fusionado con areno o heteroareno;

R^{28} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{28A}; R^{28A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno

R^{29} es heteroarilo o R^{29A}; R^{29A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{30} es cicloalquilo o cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{30A}; R^{30A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{31} y R^{31A} son en forma independiente F, Cl, Br o alquilo o se toman juntos y son C_2-C_5-espiroalquilo;

R^{32} es R^{33}, $C(O)R^{33}$ o $C(O)OR^{33}$;

R^{33} es R^{34} o R^{35};

R^{34} es fenilo que no está fusionado o está fusionado con arilo, heteroarilo o R^{34A}; R^{34A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{35} es alquilo que no está sustituido o está sustituido con R^{36};

R^{36} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{36A}; R^{36A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{37} es R^{38}, R^{39} o R^{40}, cada uno de los cuales está sustituido con F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ o SO_2R^{41};

R^{38} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{38A}; R^{38A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{39} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{39A}; R^{39A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{40} es C_3-C_8-cicloalquilo o C_4-C_8-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{40A}; R^{40A} cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{41} es R^{42}, R^{43}, R^{44} o R^{45};

R^{42} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{42A}; R^{42A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{43} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{43A}; R^{43A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{44} es C_3-C_9-cicloalquilo o C_4-C_7-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{44A}; R^{44A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{45} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos sustituyentes seleccionados en forma independiente entre: R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{46} es R^{47}, R^{48} o R^{49};

R^{47} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{47A}; R^{47A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{48} es heteroarilo o R^{48A}; R^{48A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{49} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{49A}; R^{49A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

en donde las unidades representadas por R^{26} y R^{27} están adicionalmente sustituidos con OR^{50A};

R^{50A} es R^{51A};

R^{51A} es fenilo que está unido con heteroareno;

en donde las unidades representadas por R^2, R^{2A}, R^3, R^{3A}, R^4, R^{4A}, R^6, R^{6C}, R^8, R^{8A}, R^9, R^{10}, R^{10A}, R^{13}, R^{13A}, R^{14}, R^{14A}, R^{15}, R^{15A}, R^{18}, R^{18A}, R^{19}, R^{19A}, R^{20}, R^{20A}, R^{23}, R^{23A}, R^{24}, R^{24A}, R^{25}, R^{25A}, R^{26}, R^{27}, R^{28}, R^{28A}, R^{29}, R^{29A}, R^{30}, R^{30A}, R^{34}, R^{34A}, R^{36}, R^{36A}, R^{38}, R^{38A}, R^{39}, R^{39A}, R^{40}, R^{40A}, R^{42}, R^{42A}, R^{43}, R^{43A}, R^{44}, R^{44A}, R^{47}, R^{47A}, R^{48}, R^{48A}, R^{49}, y R^{49A} son en forma independiente no sustituidas, adicionalmente no sustituidas, sustituidas o adicionalmente sustituidas con uno o dos o tres o cuatro o cinco sustituyentes seleccionados en forma

independiente entre R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{50} es R^{51}, R^{52}, R^{53} o R^{54};

R^{51} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{51B};

R^{51B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{52} es heteroarilo;

R^{53} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{53B};

en donde R^{53B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{54} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{55} es alquilo, alquenilo, alquinilo, fenilo, heteroarilo o R^{56}; y

en donde el alquilo, alquenilo, alquinilo no están sustituidos o están sustituidos con OCH_3; y

R^{56} es C_3-C_8-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N.

A^1 es N o $C(A^2)$;

uno o dos o tres o cada uno de A^2, B^1, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes son sustituyentes seleccionados en forma independiente entre H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$; y

Y^1 es H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ o $NHSO_2R^{17}$;

or

B^1 y Y^1, junto con los átomos a los cuales están unidos, son imidazol o triazol; y

uno o dos o cada uno de A^2, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes son sustituyentes seleccionados en forma independiente entre H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$;

R^1 es R^2, R^3, R^4 o R^5;

R^{1A} es C_1-C_6-alquilo, C_3-C_6-alquenilo o C_3-C_6-alquinilo;

R^2 es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{2A}; R^{2A} es cicloalcano o heterocicloalcano;

R^3 es heteroarilo que no está fusionado o está fusionado con benceno, heteroareno o R^{3A}; R^{3A} es cicloalcano o heterocicloalcano;

R^4 es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{4A}; R^{4A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^5 es alquilo, alquenilo o alquinilo, cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados entre R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^6 es C_2-C_5-espiroalquilo, cada uno de los cuales no está sustituido o está sustituido con OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ o $N(CH_3)_2$;

R^{6A} y R^{6B} se seleccionan en forma independiente entre alquilo o, junto con el N al cual están unidos, R^{6C};

R^{6C} es aziridin-1-ilo, azetidin-1-ilo, pirrolidin-1-il o piperidin-1-ilo, teniendo cada uno una unidad CH_2 no reemplazada o reemplazada con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH;

R^7 es R^8, R^9, R^{10} o R^{11};

R^8 es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{8A};

R^{8A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^9 es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{9A}; R^{9A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{10} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, teniendo cada uno una o dos unidades CH_2 no reemplazadas o reemplazadas con O, C(O), CNOH, CNOCH#3, S, S(O), SO_2 o NH seleccionados en forma independiente y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{10A}; R^{10A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{11} es alquilo, alquenilo o alquinilo, cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados entre R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{12} es R^{13}, R^{14}, R^{15} o R^{16};

R^{13} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{13A}; R^{13A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{14} es heteroarilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{14A}; R^{14A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{15} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{15A}; R^{15A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{16} es alquilo, alquenilo o alquinilo;

R^{17} es R^{18}, R^{19}, R^{20} o R^{21};

R^{18} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{18A}; R^{18A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{19} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{19A}; R^{19A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{20} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, teniendo cada uno una o dos unidades CH_2 no reemplazadas o reemplazadas con O, C(O), CNOH, CNOCH#3, S, S(O), SO_2 o NH seleccionados en forma independiente y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno,

heteroareno o R^{20A}; R^{20A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{21} es alquilo, alquenilo o alquinilo, cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados entre R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{22} es R^{23}, R^{24} o R^{25};

R^{23} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{23A}; R^{23A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{24} es heteroareno que no está fusionado o está fusionado con areno, heteroareno o R^{24A}; R^{24A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{25} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, teniendo cada uno una o dos unidades CH_2 no reemplazadas o reemplazadas con O, C(O), CNOH, CNOCH#3, S, S(O), SO_2 o NH seleccionados en forma independiente y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{25A}; R^{25A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

Z^1 es R^{26} o R^{27}, cada uno de los cuales está sustituido con R^{28}, R^{29} o R^{30}, cada uno de los cuales está sustituido con F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} o $N(R^{32})R^{37}$;

R^{26} es fenilo que no está fusionado o está fusionado con areno o heteroareno;

R^{27} es heteroareno que no está fusionado o está fusionado con areno o heteroareno;

R^{28} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{28A}; R^{28A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{29} es heteroarilo o R^{29A}; R^{29A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{30} es cicloalquilo o cicloalquenilo, teniendo cada uno una o dos unidades CH_2 no reemplazadas o reemplazadas con O, C(O), CNOH, CNOCH#3, S, S(O), SO_2 o NH seleccionados en forma independiente y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{30A}; R^{30A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{31} y R^{31A} son en forma independiente F, Cl, Br o alquilo o se toman juntos y son C_2-C_5-espiroalquilo;

R^{32} es R^{33}, $C(O)R^{33}$ o $C(O)OR^{33}$;

R^{33} es R^{34} o R^{35};

R^{34} es fenilo que no está fusionado o está fusionado con arilo, heteroarilo o R^{34A}; R^{34A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{35} es alquilo which no está sustituido o está sustituido con R^{36};

R^{36} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{36A}; R^{36A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{37} es R^{38}, R^{39} o R^{40}, cada uno de los cuales está sustituido con F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ o SO_2R^{41};

R^{38} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{38A}; R^{38A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{39} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{39A}; R^{39A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{40} es C_3-C_8-cicloalquilo o C_4-C_8-cicloalquenilo, teniendo cada uno una o dos unidades CH_2 no reemplazadas o reemplazadas con O, C(O), CNOH, CNOCH#3, S, S(O), SO_2 o NH seleccionados en forma independiente y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{40A}; R^{40A} cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{41} es R^{42}, R^{43}, R^{44} o R^{45};

R^{42} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{42A}; R^{42A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{43} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{43A}; R^{43A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{44} es C_3-C_9-cicloalquilo o C_4-C_7-cicloalquenilo, teniendo cada uno una o dos unidades CH_2 no reemplazadas o reemplazadas con O, C(O), CNOH, CNOCH#3, S, S(O), SO_2 o NH seleccionados en forma independiente y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{44A}; R^{44A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{45} es alquilo, alquenilo o alquinilo, cada uno de los cuales no está sustituido o está sustituido con uno o dos sustituyentes seleccionados en forma independiente entre R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{46} es R^{47}, R^{48} o R^{49};

R^{47} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{47A}; R^{47A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{48} es heteroarilo o R^{48A}; R^{48A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{49} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, teniendo cada uno una o dos unidades CH_2 no reemplazadas o reemplazadas con O, C(O), CNOH, CNOCH#3, S, S(O), SO_2 o NH seleccionados en forma independiente y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{49A}; R^{49A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

donde las unidades representadas por R^{26} y R^{27} están adicionalmente sustituidas con uno o dos o tres sustituyentes seleccionados en forma independiente entre R^{50A}, OR^{50A}, SR^{50A}, $S(O)R^{50A}$, SO_2R^{50A} o NHR^{50A};

R^{50A} es R^{51A}, R^{52A}, R^{53A} o R^{54A};

R^{51A} es fenilo que no está fusionado o está fusionado con benceno, heteroareno o R^{51AA},

donde R^{51AA} es cicloalcano, cicloalqueno o heterocicloalcano heterocicloalqueno,

R^{52A} es heteroarilo;

R^{53A} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo; teniendo cada uno una o dos unidades CH_2 no reemplazadas o reemplazadas con O, C(O), CNOH, CNOCH#3, S, S(O), SO_2 o NH seleccionados en forma independiente y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{53AA};

donde R^{53AA} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{54A} es alquilo, alquenilo o alquinilo, cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre R^{55AA}, OR^{55AA}, SR^{55AA}, $S(O)R^{55AA}$, SO_2R^{55AA}, NHR^{55AA}, $N(R^{55AA})_2$, $C(O)R^{55AA}$, $C(O)NH_2$, $C(O)NHR^{55AA}$, $NHC(O)R^{55AA}$, $NHSO_2R^{55AA}$, $NHC(O)OR^{55AA}$, SO_2NH_2, SO_2NHR^{55AA}, $SO_2N(R^{55AA})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55AA}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{55AA} es alquilo, alquenilo, alquinilo, fenilo o heteroarilo, o R^{56A};

R^{56A} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquilo, teniendo cada uno una o dos unidades CH_2 no reemplazadas o reemplazadas con O, C(O), CNOH, CNOCH#3, S, S(O), SO_2 o NH

seleccionados en forma independiente y una o dos unidades CH no reemplazadas o reemplazadas con N;

donde las unidades representadas por R^2 R^3 R^4, R^6, R^{6C}, R^8, R^{8A} R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{18}, R^{19}, R^{20}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{34}, R^{36}, R^{38}, R^{39}, R^{40}, R^{42}, R^{43}, R^{44}, R^{47}, R^{48}, y R^{49} en forma independiente no están sustituidas , no están adicionalmente sustituidas, están sustituidas o adicionalmente sustituidas con uno o dos o tres o cuatro o cinco sustituyentes seleccionados en forma independiente entre R^{50AA}, R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{50AA} es espirociclilo;

R^{50} es R^{51}, R^{52}, R^{53} o R^{54};

R^{51} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{51B};

R^{51B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{52} es heteroarilo;

R^{53} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, teniendo cada uno una o dos unidades CH_2 no reemplazadas o reemplazadas con O, C(O), CNOH, CNOCH#3, S, S(O), SO_2 o NH seleccionados en forma independiente y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{53B};

donde R^{53B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{54} es alquilo, alquenilo o alquinilo, cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados entre R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{55} es alquilo, alquenilo, alquinilo, fenilo, heteroarilo o R^{56};

donde el alquilo, alquenilo, alquinilo no están sustituidos o están sustituidos con OCH_3; y

R^{56} es C_3-C_8-cicloalquilo o C_4-C_6-cicloalquenilo, teniendo cada uno una o dos unidades CH_2 no reemplazadas o reemplazadas con O, C(O), CNOH, CNOCH#3, S, S(O),

SO_2 o NH seleccionados en forma independiente y una o dos unidades CH no reemplazadas o reemplazadas con N.

En una forma de realización de la Fórmula (I),

A^1 es N o $C(A^2)$;

uno o dos o tres o cada uno de A^2, B^1, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, SO_2R^1, $NHC(O)R^1$, NHR^1, $N(R^1)_2$, o $C(O)NHR^1$, y los restantes se seleccionan en forma independiente entre H, F, Cl, Br, o I;

Y^1 es H, CN, NO_2, F, Cl, Br, I, CF_3, R^{17}, $NHC(O)R^{17}$, o $C(O)NH_2$;

R^1 es R^2, R^3, R^4 o R^5;

R^2 es fenilo;

R^3 es heteroarilo;

R^4 es cicloalquilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{4A}; R^{4A} es cicloalcano;

R^5 es alquilo, o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^6, R^7, OR^7, SR^7, SO_2R^7, $N(R^7)_2$, OH, CN, CF_3, F, Cl, Br o I ;

R^6 es C_2-C_5-espiroalquilo;

R^7 es R^8, R^9, R^{10} o R^{11};

R^8 es fenilo que no está fusionado o está fusionado con R^{8A};

R^{8A} es heterocicloalcano;

R^9 es heteroarilo;

R^{10} es C_3-C_{10}-cicloalquilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N y cada uno de los cuales no está fusionado o está fusionado con heteroareno;

R^{11} es alquilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: OR^{12}, F, Cl, Br o I ;

R^{12} es R^{16};

R^{16} es alquilo;

R^{17} es R^{19} o R^{21};

R^{19} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{19A}; R^{19A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{21} es alquinilo;

Z^1 es R^{26}, cada uno de los cuales está sustituido con R^{30}, cada uno de los cuales está sustituido con F, Cl, Br, I, CH_2R^{37}, o $CH(R^{31})(R^{37})$;

R^{26} es fenilo;

R^{30} es cicloalquilo, donde cada uno tiene dos CH_2 moieties no reemplazada o reemplazada con NH;

R^{31} y R^{31A} son en forma independiente alquilo;

R^{37} es R^{38}, R^{39} o R^{40}, cada uno de los cuales está sustituido con F, Cl, Br, I, NHR^{41}, o R^{41};

R^{38} es fenilo;

R^{39} es heteroarilo;

R^{40} es C_3-C_8-cicloalquilo o C_4-C_8-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH;

R^{41} es R^{42}, R^{43}, o R^{44};

R^{42} es fenilo;

R^{43} es heteroarilo;

R^{44} es C_3-C_9-cicloalquilo o C_4-C_7-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con R^{44A}; R^{44A} es cicloalcano;

en donde la porción representada por $R^{26\ es}$ está adicionalmente sustituida por uno o dos o tres sustituyentes seleccionados en forma independiente entre: R^{50A}, OR^{50A}, SR^{50A}, $S(O)R^{50A}$, SO_2R^{50A} o NHR^{50A};

R^{50A} es R^{51A}, $R^{52A\ o}$ R^{54A};

R^{51A} es fenilo que no está fusionado o está fusionado con benceno, heteroareno o R^{51AA};

en donde R^{51AA} es heterocicloalcano;

R^{52A} es heteroarilo;

R^{54A} es alquilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre: R^{55AA}, o OR^{55AA};

R^{55AA} es fenilo;

en donde las unidades representadas por R^2 R^3 R^4, R^4, R^6, R^8, R^{8A} R^9, R^{10}, R^{19}, R^{26}, R^{30}, R^{38}, R^{39}, R^{40}, R^{42}, R^{43}, R^{44}, y R^{44A} en forma independiente no están sustituidas, no están adicionalmente sustituidas, están sustituidas o adicionalmente sustituidas con uno o dos

o tres o cuatro o cinco sustituyentes seleccionados en forma independiente entre R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, NH_2, NHR^{50}, $C(O)NH_2$, $C(O)N(R^{50})_2$, SO_2NH_2, OH, (O), CN, CF_3, OCF_3, F, Cl, Br o I ;

R^{50} es R^{51}, R^{52}, o R^{54};

R^{51} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{51B};

R^{51B} es heterocicloalcano;

R^{52} es heteroarilo;

R^{53} es C_3-C_6-cicloalquilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, y una o dos unidades CH no reemplazadas o reemplazadas con N;

R^{54} es alquilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{55}, OR^{55}, $N(R^{55})_2$, OH, CN, F, Cl, Br o I; y

R^{55} es alquilo o fenilo;

en donde el alquilo no esta sustituido o está sustituido con OCH_3; y

R^{56} es C_3-C_8-cicloalquilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con NH y una o dos unidades CH no reemplazadas o reemplazadas con N.

En una realización de Fórmula (I), A^1 es N. En otra forma de realización de Fórmula (I), A^1 es $C(A^2)$. En otra forma de realización de Fórmula (I), A^1 es $C(A^2)$, y A^2 es H.

En una realización de Fórmula (I), B^1 es R^1, OR^1, SR^1, SO_2R^1, $NHC(O)R^1$, NHR^1, $N(R^1)_2$, o $C(O)NHR^1$. En otra forma de realización de Fórmula (I), B^1 es NHR^1. En otra forma de realización de Fórmula (I), B^1 es NHR^1, y A^1 es $C(A^2)$, y A^2 es H. En otra forma de realización de Fórmula (I), B^1 es NHR^1, y A^1 es $C(A^2)$ o N, y A^2 es H. En otra forma de realización de la Fórmula (I), B^1 es OR^1. En otra forma de realización de Fórmula (I), B^1 es OR^1, y A^1 es $C(A^2)$, y A^2 es H. En otra forma de realización de la Fórmula (I), B^1 es OR^1, y A^1 es $C(A^2)$ o N, y A^2 es H.

En una realización de Fórmula (I), D^1 y E^1 son H. En otra forma de realización de Fórmula (I), B^1 es NHR^1, y A^1 es $C(A^2)$, A^2 es H, y D^1 y E^1 son H. En otra forma de realización de Fórmula (I), B^1 es NHR^1, y A^1 es $C(A^2)$ o N, A^2 es H, y D^1 y E^1 son H. En otra forma de realización de la Fórmula (I), B^1 es OR^1, y A^1 es $C(A^2)$, A^2 es H, y D^1 y E^1 son H. En otra forma de realización de la Fórmula (I), B^1 es OR^1, y A^1 es $C(A^2)$ o N, A^2 es H, y D^1 y E^1 son H.

En una realización de Fórmula (I), Y^1 es H, CN, NO_2, F, Cl, Br, I, CF_3, R^{17}, $NHC(O)R^{17}$, o $C(O)NH_2$. En otra forma de realización de Fórmula (I), Y^1 es NO_2. En otra forma de realización de Fórmula (I), Y^1 es Cl. En otra forma de realización de Fórmula (I), B^1 es NHR^1, y A^1 es $C(A^2)$, A^2 es H, D^1 y E^1 son H, y Y^1 es NO_2. En otra forma de realización de Fórmula (I), B^1 es NHR^1, y A^1 es $C(A^2)$ o N, A^2 es H, D^1 y E^1 son H, y Y^1 es NO_2. En otra forma de realización de la Fórmula (I), B^1 es OR^1, y A^1 es $C(A^2)$, A^2 es H, D^1 y E^1 son H, y Y^1 es Cl. En otra forma de realización de la Fórmula (I), B^1 es OR^1, y A^1 es $C(A^2)$ o N, A^2 es H, D^1 y E^1 son H, y Y^1 es Cl.

En una realización de Fórmula (I), R^1 es R^2, R^3, R^4 o R^5. En otra forma de realización de Fórmula (I), R^1 es R^2, y R^2 es fenilo.

En una realización de Fórmula (I), R^1 es R^3, y R^3 es heteroarilo. En otra forma de realización de Fórmula (I), R^3 es triazolilo.

En una realización de Fórmula (I), R^1 es R^4. En otra forma de realización de Fórmula (I), R^1 es R^4, y R^4 es cicloalquilo. En otra forma de realización de Fórmula (I), R^1 es R^4, y R^4 es ciclohexilo. En otra forma de realización de Fórmula (I), R^1 es R^4, y R^4 es heterocicloalquilo. En otra forma de realización de Fórmula (I), R^1 es R^4, y R^4 es 8-azabiciclo[3.2.1]octano, azetidinilo, piperidinilo, piperazinilo, pirrolidinilo, morfolinilo, tetrahidropiranilo, o tetrahidrotiofenilo. En otra forma de realización de Fórmula (I), R^1 es R^4, y R^4 es heterocicloalquenilo. En otra forma de realización de Fórmula (I), R^1 es R^4, y R^4 es tetrahidropiridazinilo.

En una realización de Fórmula (I), R^1 es R^5. En otra forma de realización de Fórmula (I), R^1 es R^5 y R^5 es alquilo o alquinilo. En otra forma de realización de Fórmula (I), R^1 es R^5 y R^5 es alquilo que no está sustituido. En otra forma de realización de Fórmula (I), R^1 es R^5 y R^5 es alquilo que está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^6, R^7, OR^7, SR^7, SO_2R^7, $N(R^7)_2$, OH, CN, CF_3, F, Cl, Br o I . En otra forma de realización de Fórmula (I), R^1 es R^5 y R^5 es alquilo que está sustituido con R^7.

En una realización de Fórmula (I), R^7 es R^8, R^9, R^{10} o R^{11}. En otra forma de realización de Fórmula (I), R^7 es R^8, y R^8 es fenilo que no está fusionado o está fusionado con R^{8A}, y R^{8A} es heterocicloalcano. . En otra forma de realización de Fórmula (I), R^7 es R^8, y R^8 es fenilo que no está fusionado. En otra forma de realización de Fórmula (I), R^7 es R^9, y R^9 es heteroarilo. En otra forma de realización de Fórmula (I), R^7 es R^9, y R^9 es furanilo, imidazolilo, isotiazolilo, isoxazolilo, 1,2,3-oxadiazoilo, 1,2,5-oxadiazolilo, oxazolilo, pirazinilo, pirazolilo, piridazinilo, piridinilo, pirimidinilo, pirrolilo, tetrazolilo, tiazolilo,

tiofenilo, triazinilo o 1,2,3-triazolilo. En otra forma de realización de Fórmula (I), R^7 es R^9, y R^9 es piridinilo, tiazolilo, imidazoilo, y 1,2,3-triazolilo. En otra forma de realización de Fórmula (I), R^7 es R^{10}, y R^{10} es C_3-C_{10}-cicloalquilo. En otra forma de realización de Fórmula (I), R^7 es R^{10}, y R^{10} es C_3, C_6, C_7 o C_{10}-cicloalquilo. En otra forma de realización de Fórmula (I), R^7 es R^{10}, y R^{10} es ciclopropilo, ciclohexilo, biciclo[2.2.1]heptanilo, o adamantanilo. En otra forma de realización de Fórmula (I), R^7 es R^{10}, y R^{10} es morfolinilo, piperazinilo, piperidinilo, tetrahidro-2H-piranilo, 1,2-dihidropiridinilo, piranilo, piridin-1(H)–ilo, pirrolidinilo, oxetanilo, tiomorfolinilo, imidazolidinilo, tetrahidrotiofenilo, dioxolanilo, tetrahidrotiopiranilo, dioxanilo, 5,6,7,8-tetrahidroimidazo[1,2-a]piridinilo, o tetrahidrofuranilo. En otra forma de realización de Fórmula (I), R^7 es R^{10}, y R^{10} es morfolinilo, piperazinilo, piperidinilo, tetrahidro-2H-piranilo, 1,2-dihidropiridinilo, pirrolidinilo, oxetanilo, tiomorfolinilo, imidazolidinilo, tetrahidrotiofenilo, dioxolanilo, tetrahidrotiopiranilo, dioxanilo, 5,6,7,8-tetrahidroimidazo[1,2-a]piridinilo, o tetrahidrofuranilo. En otra forma de realización de Fórmula (I), R^7 es R^{11}, y R^{11} es alquilo que no está sustituido o está sustituido. En otra forma de realización de Fórmula (I), R^7 es R^{11}, y R^{11} es alquilo que no está sustituido. En otra forma de realización de Fórmula (I), R^7 es R^{11}, y R^{11} es alquilo que está sustituido. En otra forma de realización de Fórmula (I), R^7 es R^{11}, y R^{11} es alquilo que está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: OR^{12}, F, Cl, Br o I . En otra forma de realización de Fórmula (I), R^7 es R^{11}, R^{11} es alquilo que está sustituido con OR^{12}, R^{12} es R^{16}, y R^{16} es alquilo.

En una realización de Fórmula (I), R^{17} es R^{19} o R^{21}. En otra forma de realización de Fórmula (I), R^{17} es R^{19}, y R^{19} es heteroarilo. En otra forma de realización de Fórmula (I), R^{17} es R^{19}, y R^{19} es tiazolilo. En otra forma de realización de Fórmula (I), R^{17} es R^{21}, y R^{21} es alquinilo. En otra forma de realización de Fórmula (I), R^{17} es R^{21}, y R^{21} es etinilo.

Aún otra forma de realización se refiere a compuestos que tienen la Fórmula I que son 4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;

benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

2-(benciloxi)-4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(2-feniletoxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(feniltio)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(feniltio)-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)-2-(feniltio)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(fenilsulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(fenilsulfinil)benzamida;
2-bencil-4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
2-bencil-4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
2-bencil-4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(2-feniletil)benzamida;
2-(bencilamino)-4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
2-anilino-4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
2-anilino-4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-metoxi-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indazol-5–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indazol-5–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)-2-(1,2,3,4-tetrahidroquinolin-6–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)-2-(1,2,3,4-tetrahidroquinolin-6–iloxi)benzamida;
4-(4-((4'-cloro-4-(pirrolidin-1–ilmetil)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(2-pirrolidin-1–iletil)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((1-ciclopentilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)-3-isobutilpiperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-(2,4-dioxo-3-azabiciclo(3.2.0)hept-3–il)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-(4-metil-6-oxo-1,4,5,6-tetrahidropiridazin-3–il)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-(3,3-dimetil-2-oxoazetidin-1–il)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-(4-nitro-2H-1,2,3-triazol-2–il)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((2-(2-piperidin-1–iletoxi)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-((((1-etilpirrolidin-2–il)metil)amino)carbonil)-4-metoxifenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1-naftiloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(2-naftiloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)-2-(2-naftiloxi)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(2-naftiloxi)-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(quinolin-7–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(quinolin-6–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(isoquinolin-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(isoquinolin-5–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(quinolin-6–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-4–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-6–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(isoquinolin-7–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(isoquinolin-7–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-4–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-4–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-metoxifenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-metilfenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
N-((3-((cloro(difluoro)metil)sulfonil)-4-((3-(dimetilamino)propil)amino)fenil)sulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;
2-(1H-indol-4–iloxi)-4-(4-((2-(4-metoxifenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((4,4-dimetil-2-(4-(trifluorometil)fenil)ciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((4,4-dimetil-2-(4-(trifluorometoxi)fenil)ciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;

4-(4-((4,4-dimetil-2-(3-(trifluorometil)fenil)ciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((2-(3-fluorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-fluorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
N-((3-((cloro(difluoro)metil)sulfonil)-4-((1-metilpiperidin-4–il)amino)fenil)sulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;
4-(4-((2-(4-clorofenil)ciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(fenoximetil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(piridin-3–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(piridin-3–iloxi)-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-(((1R)-3-(dimetilamino)-1-((feniltio)metil)propil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(piridin-4–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)-2-(piridin-3–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)-2-(piridin-4–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((2-(4-metilpiperazin-1–il)etil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(4-metilpiperazin-1–il)propil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)(metil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-(((1-metilpiperidin-4–il)metil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-ciano-4-((3-(dimetilamino)propil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-(trifluorometil)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(isopropil(metil)amino)propil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-(3-(dimetilamino)propoxi)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((2-(4-metilpiperazin-1–il)etil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((3-(4-metilpiperazin-1–il)propil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((3-(4-metilpiperazin-1–il)propil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-(3-(dimetilamino)propoxi)-3-nitrofenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((2-(4-metilpiperazin-1–il)etil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-(((1-metilpiperidin-4–il)metil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-(((1-metilpiperidin-4–il)metil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-(3-(dimetilamino)propoxi)-3-nitrofenil)sulfonil)-2-(1H-indol-4–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-(4-metilpiperazin-1–il)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((1-(2,2,2-trifluoroetil)piperidin-4–il)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-(((4-(dimetilamino)-1-metilpiperidin-4–il)metil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(2,3-dihidro-1,4-benzodioxin-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
5-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-1,1'-bifenil-2-carboxamida;
5-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-1,1'-bifenil-2-carboxamida;
4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-4-(3-piperidin-1–ilpropoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-4-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-4-(3-(dimetilamino)propoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-4-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(3-piperidin-1–ilpropoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-4-(3-(dimetilamino)propoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-4-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-4-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-3-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-3-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((1-(2,2,2-trifluoroetil)piperidin-4–il)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-4-(2-pirrolidin-1–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-4-(2-(diisopropilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(2,3-dihidro-1H-indol-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)ciclohept-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)ciclooct-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)ciclopent-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclopent-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)ciclooct-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)ciclohept-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)ciclopent-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)ciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)ciclohept-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((2-(dimetilamino)etil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((4-(dimetilamino)butil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((1-(fenilsulfonil)piperidin-4–il)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((1-(quinolin-8–ilsulfonil)piperidin-4–il)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((1-(fenilsulfonil)piperidin-4–il)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((1-(quinolin-8–ilsulfonil)piperidin-4–il)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-(((1S)-3-(dimetilamino)-1-tien-2–ilpropil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tien-2–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((2-(1H-1,2,3-triazol-1–il)etil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((2-(2H-1,2,3-triazol-2–il)etil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(2-naftiloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((2-(2-oxopiridin-1(2H)–il)etil)amino)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((2-(piridin-2–iloxi)etil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((2-piridin-4–iletil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-(trifluorometil)fenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((3-ciano-4-((3-(dimetilamino)propil)amino)fenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1*H*-indol-5–iloxi)-*N*-((3-nitro-4-((1-tetrahidro-2*H*-piran-4–ilpiperidin-4–il)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1*H*-indol-5–iloxi)-*N*-((4-((4-metilpiperazin-1–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-(1-(4'-cloro-1,1'-bifenil-2–il)etil)piperazin-1–il)-2-(1*H*-indol-4–iloxi)-*N*-((3-nitro-4-((tetrahidro-2*H*-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
N-((4-(((4-aminotetrahidro-2*H*-piran-4–il)metil)amino)-3-nitrofenil)sulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1*H*-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-morfolin-4–ilciclohexil)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(2-metoxietil)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[(3S)-tetrahidro-2H-piran-3–ilmetil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[(3R)-tetrahidro-2H-piran-3–ilmetil]amino}fenil)sulfonil]benzamida;
4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-hidroxi-1-metilpiperidin-4–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-3-fluoro-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-3-fluoro-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-hidroxi-1-metilpiperidin-4–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;

N-[(4-{[(3S,4R)-1-bencil-3-hidroxipiperidin-4–il]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

N-[(4-{[(4-aminotetrahidro-2H-piran-4–il)metil]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[1-(2-metoxietil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(2-hidroxietil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[1-(2-metoxietil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(3-hidroxipropil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;

4-[4-({4'-cloro-3-[3-(dimetilamino)propil]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(3-hidroxipropil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-{4-[(4'-cloro-4-morfolin-4–il-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-[4-({4'-cloro-3-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(dietilamino)ciclohexil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(dimetilamino)ciclohexil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(dietilamino)ciclohexil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(4-morfolin-4–ilciclohexil)amino]-3-nitrofenil}sulfonil)benzamida;

4-[4-({4'-cloro-3-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-{4-[1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[4-(dimetilamino)tetrahidro-2H-piran-4–il]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida;

N-({4-[(2-aminociclohexil)amino]-3-nitrofenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

4-[4-({4'-cloro-4-[3-(dimetilamino)prop-1-ynil]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(3-nitro-4-{[1-(4,4,4-trifluorobutil)piperidin-4–il]amino}fenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[2-(4-hidroxi-1-metilpiperidin-4–il)etil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[1-(1,3-tiazol-2–il)piperidin-4–il]amino}fenil)sulfonil]benzamida;

4-(4-{[4'-cloro-4-(2-hidroxietoxi)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(ciclopropilmetil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[1-(4,4,4-trifluorobutil)piperidin-4–il]amino}fenil)sulfonil]benzamida;

4-{4-[1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-[4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}-3-(hidroximetil)piperazin-1–il]-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-[4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}-3-(hidroximetil)piperazin-1–il]-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;

4-(4-{[4'-cloro-4-(2-hidroxietoxi)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[3-(3-oxopiperazin-1–il)propil]amino}fenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(3-nitro-4-{[3-(3-oxopiperazin-1–il)propil]amino}fenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-5-hidroxiciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-5-hidroxiciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-5-hidroxiciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(2,3-dihidro-1H-inden-2–il)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(2,3-dihidro-1H-inden-2–il)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(1-morfolin-4–ilciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[1-(1,3-tiazol-2–ilmetil)piperidin-4–il]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[1-(1,3-tiazol-4–ilmetil)piperidin-4–il]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[4-(hidroximetil)tetrahidro-2H-piran-4–il]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(2-hidroxietil)piperazin-1–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(3S)-1-metilpirrolidin-3–il]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(3-fluoropropil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-[4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}-3-(hidroximetil)piperazin-1–il]-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
N-[(4-{[(4-aminotetrahidro-2H-piran-4–il)metil]amino}-3-nitrofenil)sulfonil]-4-[4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}-3-(hidroximetil)piperazin-1–il]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1-hidroxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(2-metoxietil)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(hidroximetil)tetrahidro-2H-piran-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(hidroximetil)tetrahidro-2H-piran-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2-hidroxi-1-tetrahidro-2H-piran-4–iletil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-({1-[2-(1H-pirazol-1–il)etil]piperidin-4–il}amino)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(metilamino)-3-nitrofenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[4-(metilamino)-3-nitrofenil]sulfonil}benzamida;
4-{4-[1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-5-hidroxiciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-5-morfolin-4–ilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
N-[(4-{[(1-aminociclohexil)metil]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[2-(2-oxopirrolidin-1–il)etil]amino}fenil)sulfonil]benzamida;
4-{4-[1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{1-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]etil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{1-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]etil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida;
4-{4-[(1R)-1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-{4-[(1S)-1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{1-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]etil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{1-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]etil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(ciclohexilmetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(morfolin-4–ilamino)-3-nitrofenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-3–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[4-(morfolin-4–ilamino)-3-nitrofenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(tetrahidro-2H-piran-4–ilamino)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(3-metiloxetan-3–il)metil]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-metoxiciclohexil)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[3-(1,1-dioxidotiomorfolin-4–il)propil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[2-(2-oxopiperidin-1–il)etil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[2-(2-oxoimidazolidin-1–il)etil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(2-piridin-4–iletil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-morfolin-4–il-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(4-metoxipiperidin-1–il)-3-nitrofenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-5-pirrolidin-1–ilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[2-(3-oxopiperazin-1–il)etil]amino}fenil)sulfonil]benzamida;
4-[4-({4'-cloro-4-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1,1-dioxidotetrahidrotien-3–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1,1-dioxidotetrahidrotien-3–il)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-[(tetrahidro-2H-piran-4–ilmetil)amino]-3-(trifluorometil)fenil]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[2-(1,3-dioxolan-2–il)etil]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(tetrahidro-2H-piran-4–ilmetoxi)fenil]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(3-nitro-4-{[2-(3-oxopiperazin-1–il)etil]amino}fenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metil-5-oxopirrolidin-3–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metil-6-oxopiperidin-3–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[3-nitro-4-(piperidin-1–ilamino)fenil]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(piperidin-1–ilamino)fenil]sulfonil}benzamida;

4-(4-{[4-(4-clorofenil)-1-metil-1H-pirazol-5–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(3-metiloxetan-3–il)metoxi]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[(1-oxidotetrahidro-2H-tiopiran-4–il)metil]amino}fenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1,3-tiazol-5–ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[3-nitro-4-(tetrahidro-2H-piran-4–ilmetoxi)fenil]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(2-tetrahidro-2H-piran-4–iletil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(3-nitro-4-{[2-(trifluorometoxi)etil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[2-(2-metoxietoxi)etil]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[3-(metilsulfonil)propil]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[3-(1,1-dioxidotiomorfolin-4–il)propil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(2-tetrahidro-2H-piran-4–iletil)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-(1,4-dioxan-2–ilmetoxi)-3-nitrofenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[2-(2-metoxietoxi)etil]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1,1-dioxidotetrahidrotien-3–il)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[2-(trifluorometoxi)etil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1,1-dioxidotetrahidro-2H-tiopiran-4–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2,2-difluoroetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4,4-difluorociclohexil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[4-(4-clorofenil)-1-isopropil-6-oxo-1,6-dihidropiridin-3–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(tetrahidro-2H-piran-4–ilmetil)amino]carbonil}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(2-metoxietil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-hidroxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(4-metoxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-hidroxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(4-metoxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[3-nitro-4-(2-tetrahidro-2H-piran-4–iletoxi)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(2-metoxietil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[3-(metilsulfonil)propoxi]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(3-metoxipropil)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(3-metoxipropil)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2-cianoetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2-cianoetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[(3R)-4-hidroxi-1-adamantil]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[Cis-4-hidroxi-1-adamantil]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(3,3,3-trifluoropropil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(3,3,3-trifluoropropil)amino]fenil}sulfonil)benzamida;
N-({5-bromo-6-[(tetrahidro-2H-piran-4–ilmetil)amino]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1,1-dioxidotetrahidrotien-3–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-(metilamino)-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
N-{[5-bromo-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[4-(4-clorofenil)-6-isopropoxipiridin-3–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[6-(tetrahidro-2H-piran-4–ilmetoxi)-5-(1,3-tiazol-2–il)piridin-3–il]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(2-metoxietil)amino]carbonil}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-ciano-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indol-5–iloxi)benzamida;
N-({4-[(1-acetilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[1-(metilsulfonil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1,4-dioxan-2–ilmetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
N-({4-[(1-acetilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[1-(metilsulfonil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[4'-cloro-5-(trifluorometil)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[4'-cloro-5-(trifluorometil)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(tetrahidro-2H-piran-4–ilmetoxi)fenil]sulfonil}benzamida;
4-{4-[(5-tert-butil-4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-{4-[(5-tert-butil-4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(tetrahidro-2H-piran-4–ilmetoxi)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(2,2,2-trifluoroetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(2,2,2-trifluoroetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-{[(tetrahidro-2H-piran-4–ilmetil)amino]carbonil}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2R)-1,4-dioxan-2–ilmetoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2S)-1,4-dioxan-2–ilmetoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
N-({5-bromo-6-[(tetrahidro-2H-piran-4–ilmetil)amino]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(2-morfolin-4–iletil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-ciano-6-[(tetrahidro-2H-piran-4–ilmetil)amino]piridin-3–il}sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)oxi]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)metoxi]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[4-(4-clorofenil)-1-(3-hidroxipropil)-1,2,5,6-tetrahidropiridin-3–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-({[4-({[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzoil]amino}sulfonil)-2-nitrofenil]amino}metil)piperidin-1-carboxilato de bencilo ;

N-{[3-(aminocarbonil)-4-(tetrahidro-2H-piran-4–ilmetoxi)fenil]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[4'-cloro-5-(trifluorometil)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;

4-{4-[(5-tert-butil-4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(1-metil-1H-imidazol-5–il)metil]amino}-3-nitrofenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(morfolin-4–ilsulfonil)fenil]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1,1-dioxidotiomorfolin-4–il)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-morfolin-4–ilciclohexil)amino]-3-nitrofenil}sulfonil)benzamida;

N-{[5-bromo-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[6-[(tetrahidro-2H-piran-4–ilmetil)amino]-5-(1,3-tiazol-2–il)piridin-3–il]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-ciano-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-ciano-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(3,3-dimetilbutil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1S)-1-(hidroximetil)-3-metilbutil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[(2R)-tetrahidrofuran-2–ilmetil]amino}fenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1R)-1-(hidroximetil)-2-metilpropil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-metoxifenil)amino]-3-nitrofenil}sulfonil)benzamida;

N-[(4-{[2-(1,3-benzodioxol-5–il)etil]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[3-(2-oxopirrolidin-1–il)propil]amino}fenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-hidroxifenil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;

N-{[4-({2-[4-(aminosulfonil)fenil]etil}amino)-3-nitrofenil]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[3-(1H-imidazol-1–il)propil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[(1S)-1-feniletil]amino}fenil)sulfonil]benzamida;

N-({2-cloro-5-fluoro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[2-(2-metoxietoxi)etil]tio}-3-nitrofenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[2-(2-metoxietoxi)etil]tio}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(metilsulfonil)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[4-(metilsulfonil)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2,2-dimetiltetrahidro-2H-piran-4–il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-ciano-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-ciano-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-cloro-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-ciano-6-(2-morfolin-4–iletoxi)piridin-3–il]sulfonil}-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)oxi]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-morfolin-4–ilbut-2-ynil)oxi]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-etinil-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-ciano-6-(2-morfolin-4–iletoxi)piridin-3–il]sulfonil}-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-ciano-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(3-hidroxi-4-metoxifenil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(2,3-dihidro-1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)-2-(piridin-3–ilamino)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)-2-(piridin-3–ilamino)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)-2-(piridin-3–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(1,2,3,4-tetrahidroisoquinolin-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;
Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)-N-({4-[(4-morfolin-4–ilciclohexil)amino]-3-nitrofenil}sulfonil)benzamida;
2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;
N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-ciano-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-2-(1H-indazol-4–iloxi)benzamida;
2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(3R)-1-(2,2-difluoroetil)pirrolidin-3–il]amino}-3-nitrofenil)sulfonil]benzamida;
2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-fluorotetrahidro-2H-piran-4–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]-5-(trifluorometil)piridin-3–il]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-ciclopropilmorfolin-2–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4,4-difluorociclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4–iloxi)benzamida;

N-[(5-cloro-6-{[(4-fluorotetrahidro-2H-piran-4–il)metil]amino}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

Trans-N-({5-cloro-6-[(4-metoxiciclohexil)metoxi]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[4-(2,2-difluoroetil)morfolin-2–il]metil}amino)-3-nitrofenil]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-fluoro-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-2-(1H-indazol-4–iloxi)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;

N-[(5-cloro-6-{[1-(cianometil)-4-fluoropiperidin-4–il]metoxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-cloro-6-(tetrahidrofuran-3–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;

Trans-N-({5-cloro-6-[(4-hidroxiciclohexil)metoxi]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

N-[(5-cloro-6-{[(3R)-1-(2,2-difluoroetil)pirrolidin-3–il]oxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

2-(1H-benzimidazol-4–iloxi)-N-[(5-cloro-6-{[(2S)-4-(N,N-dimetilglicil)morfolin-2–il]metoxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)benzamida;

2-(1H-benzimidazol-4–iloxi)-N-[(5-cloro-6-{[(2R)-4-(N,N-dimetilglicil)morfolin-2–il]metoxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)benzamida;

N-[(5-cloro-6-{[(2S)-4-(N,N-dimetilglicil)morfolin-2–il]metoxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

N-[(5-cloro-6-{[(2R)-4-(N,N-dimetilglicil)morfolin-2–il]metoxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-cloro-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(3R)-1-(cianometil)pirrolidin-3–il]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({(3R)-1-[2-(2-metoxietoxi)etil]pirrolidin-3–il}amino)-3-nitrofenil]sulfonil}benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(3R)-1-(N,N-dimetilglicil)pirrolidin-3–il]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[4-(cianometil)morfolin-2–il]metil}amino)-3-nitrofenil]sulfonil}benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-ciclopropilmorfolin-2–il)metil]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(3-nitro-4-{[(4-oxetan-3–ilmorfolin-2–il)metil]amino}fenil)sulfonil]benzamida;

N-{[5-cloro-6-({(3R)-1-[2-fluoro-1-(fluorometil)etil]pirrolidin-3–il}oxi)piridin-3–il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({(3R)-1-[2-fluoro-1-(fluorometil)etil]pirrolidin-3–il}amino)-3-nitrofenil]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1-ciclopropilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)-2-(1H-indazol-4–iloxi)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[(2R)-4-(N,N-dimetilglicil)morfolin-2–il]metil}amino)-3-nitrofenil]sulfonil}benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[(2S)-4-(N,N-dimetilglicil)morfolin-2–il]metil}amino)-3-nitrofenil]sulfonil}benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(tetrahidrofuran-3–ilmetil)amino]fenil}sulfonil)benzamida;

Trans-2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-metoxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-fluorotetrahidro-2H-piran-4–il)metil]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-fluoro-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)benzamida;

N-{[5-cloro-6-({(3R)-1-[2-fluoro-1-(fluorometil)etil]pirrolidin-3–il}metoxi)piridin-3–il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

N-[(5-cloro-6-{[(3R)-1-(2,2-difluoroetil)pirrolidin-3–il]metoxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)-N-[(4-{[(4-metoxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-(1,4-dioxan-2–ilmetoxi)-3-nitrofenil]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;

N-({5-cloro-6-[(1-ciclopropilpiperidin-4–il)amino]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

2-(1H-benzimidazol-4–iloxi)-N-({5-cloro-6-[(1-ciclopropilpiperidin-4–il)amino]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1,4-dioxan-2–ilmetil)amino]-3-nitrofenil}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1-ciclopropilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;

Trans-2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-morfolin-4–ilciclohexil)amino]-3-nitrofenil}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1-metilpiperidin-4–il)metil]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[({(2R)-4-[2-(2-metoxietoxi)etil]morfolin-2–il}metil)amino]-3-nitrofenil}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4,4-difluorociclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;

N-[(4-{[(4-acetilmorfolin-2–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[4-(metilsulfonil)morfolin-2–il]metil}amino)-3-nitrofenil]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[6-({4-fluoro-1-[2-fluoro-1-(fluorometil)etil]piperidin-4–il}metoxi)-5-(trifluorometil)piridin-3–il]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-cloro-6-(2-tetrahidrofuran-2–iletoxi)piridin-3–il]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;

Trans-2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-cianociclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-N-({5-cloro-6-[(4,4-difluorociclohexil)metoxi]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)benzamida;

N-({3-cloro-4-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-*N*-{[5-ciano-6-(2-tetrahidro-2*H*-piran-4–iletoxi)piridin-3–il]sulfonil}-2-(1*H*-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(1R,5S)-8-metil-8-azabiciclo[3.2.1]oct-3–il]amino}-3-nitrofenil)sulfonil]benzamida;

N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxi-4-(4-{(3-fenilpropanoil)[(1S,2S,3S,5R)-2,6,6-trimetilbiciclo[3.1.1]hept-3–il]amino}piperidin-1–il)benzamida;

N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)-2-fenoxi-4-(4-{(3-fenilpropanoil)[(1S,2S,3S,5R)-2,6,6-trimetilbiciclo[3.1.1]hept-3–il]amino}piperidin-1–il)benzamida;

N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxi-4-(4-{(3-fenilpropil)[(1S,2S,3S,5R)-2,6,6-trimetilbiciclo[3.1.1]hept-3–il]amino}piperidin-1–il)benzamida;

N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)-2-fenoxi-4-(4-{(3-fenilpropil)[(1S,2S,3S,5R)-2,6,6-trimetilbiciclo[3.1.1]hept-3–il]amino}piperidin-1–il)benzamida;

4-[4-(2-{[(1R,5S)-8-metil-8-azabiciclo[3.2.1]oct-3–il]amino}bencil)piperazin-1–il]-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)-2-fenoxibenzamida;

4-[4-(2-{[(1R,5S)-8-metil-8-azabiciclo[3.2.1]oct-3–il]amino}bencil)piperazin-1–il]-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida;

4-{4-[2-(3-azabiciclo[3.2.2]non-3–il)bencil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida;

4-{4-[2-(3-azabiciclo[3.2.2]non-3–il)bencil]piperazin-1–il}-2-fenoxi-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;

4-{4-[2-(3-azabiciclo[3.2.2]non-3–il)bencil]piperazin-1–il}-2-fenoxi-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-{4-[2-(3-azabiciclo[3.2.2]non-3–il)bencil]piperazin-1–il}-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)-2-fenoxibenzamida;

4-(4-{2-[(4R,7S)-2,3,3a,4,7,7a-hexahidro-1H-4,7-metanoinden-5–il]bencil}piperazin-1–il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida;

4-[4-(2-{5-[(1R,5S)-8-azabiciclo[3.2.1]oct-8–ilmetil]tien-2–il}bencil)piperazin-1–il]-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida;

4-[4-(2-{5-[(1R,5S)-8-azabiciclo[3.2.1]oct-8–ilmetil]tien-2–il}benciliden)piperidin-1–il]-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida;

4-[4-(3-{5-[(1R,5S)-8-azabiciclo[3.2.1]oct-8–ilmetil]tien-2–il}bencil)piperazin-1–il]-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida;
N-({5-cloro-6-[(4,4-difluorociclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
N-({6-[(trans-4-carbamoilciclohexil)metoxi]-5-cloropiridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(trans-4-cianociclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;
N-({5-cloro-6-[2-(1H-imidazol-1-il)etoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
N-({5-cloro-6-[(1-metil-1H-imidazol-5-il)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[5-fluoro-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil}-2-(1H-indazol-4-iloxi)benzamida;
N-{[5-cloro-6-(1,4-dioxan-2-ilmetoxi)piridin-3-il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
N-({5-cloro-6-[(4,4-difluoro-1-hidroxiciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
N-({5-cloro-6-[(2,2-difluorociclopropil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
N-({5-cloro-6-[(trans-4-cianociclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
N-({5-cloro-6-[(cis-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
N-({3-cloro-4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]fenil}sulfonil)-4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]-3-(trifluorometil)fenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-cloro-4-(tetrahidro-2H-piran-4-ilmetoxi)fenil]sulfonil}-2-(1H-indazol-4-iloxi)benzamida;

2-(1H-benzimidazol-4-iloxi)-N-({3-cloro-4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida;

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[5-cloro-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-ciano-4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]fenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida;

N-{[3-cloro-4-(1,4-dioxan-2-ilmetoxi)fenil]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

2-(1H-benzimidazol-4-iloxi)-N-[(5-cloro-6-{[(2S)-4-ciclopropilmorfolin-2-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida;

N-[(5-cloro-6-{[(2S)-4-ciclopropilmorfolin-2-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

2-{[(4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzoil]sulfamoil}-2-nitrofenil)amino]metil}morfolin-4-carboxilato de metilo;

2-{[(4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzoil]sulfamoil}-2-nitrofenil)amino]metil}-N-etil-N-metilmorfolin-4-carboxamida;

2-{[(4-{[2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzoil]sulfamoil}-2-nitrofenil)amino]metil}-N-etil-N-metilmorfolin-4-carboxamida;

N-({5-cloro-6-[(trans-4-etil-4-hidroxiciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(cis-4-etil-4-hidroxiciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

5-cloro-N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

5-cloro-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4-fluorotetrahidro-2H-piran-4-il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(cis-1-fluoro-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(trans-1-fluoro-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

2-(1H-benzotriazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4-fluorotetrahidro-2H-piran-4-il)metil]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzotriazol-4-iloxi)-N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida;

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-cloro-4-(tetrahidro-2H-piran-4-ilmetoxi)fenil]sulfonil}benzamida;

N-[(3-cloro-4-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}fenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(cis-1-fluoro-4-hidroxiciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

2-(1H-benzotriazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]-3-nitrofenil}sulfonil)benzamida;

N-[(5-cloro-6-{[(1R,2R,4R,5R)-5-hidroxi-5-metilbiciclo[2.2.1]hept-2-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-[(5-cloro-6-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

2-(1H-benzotriazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(trans-4-hidroxi-4-metilciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(cis-4-hidroxi-4-metilciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;

2-(1H-benzotriazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({[(2S)-4-ciclopropilmorfolin-2-il]metil}amino)-3-nitrofenil]sulfonil}benzamida;

N-[(5-cloro-6-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({[(2S)-4-ciclopropilmorfolin-2-il]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-indazol-4-iloxi)benzamida;

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({[(2S)-4-ciclopropilmorfolin-2-il]metil}amino)-3-nitrofenil]sulfonil}benzamida;

N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(cis-4-hidroxi-4-metilciclohexil)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(trans-4-hidroxi-4-metilciclohexil)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-ciano-4-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}fenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-{[3-nitro-4-(2-oxaspiro[3.5]non-7-ilmetoxi)fenil]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[5-cloro-6-(5,6,7,8-tetrahidroimidazo[1,2-a]piridin-6-ilmetoxi)piridin-3-il]sulfonil}-2-(1H-indazol-4-iloxi)benzamida;

2-(1H-benzimidazol-4-iloxi)-N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(5-ciano-6-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}piridin-3-il)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-5-(metoximetil)-5-metilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-{[3-nitro-4-({[(2S)-4-(oxetan-3-il)morfolin-2-il]metil}amino)fenil]sulfonil}benzamida;

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-nitro-4-({[(2S)-4-(oxetan-3-il)morfolin-2-il]metil}amino)fenil]sulfonil}benzamida;

N-[(5-cloro-6-{[trans-4-(2-hidroxipropan-2-il)ciclohexil]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-ciano-4-[(trans-4-hidroxi-4-metilciclohexil)metoxi]fenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida;

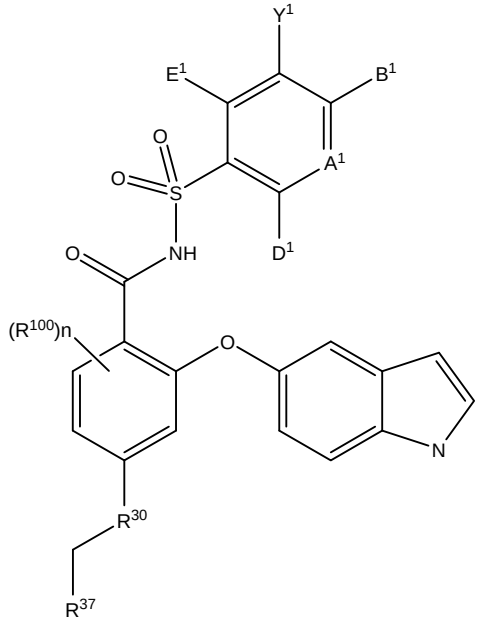
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({5-ciano-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-({5-nitro-6-[(tetrahidro-2H-piran-4-ilmetil)amino]piridin-3-il}sulfonil)benzamida;
2-(1H-benzotriazol-4-iloxi)-N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida;
N-({3-cloro-4-[(cis-4-ciano-1-fluorociclohexil)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
N-({3-cloro-4-[(trans-4-ciano-1-fluorociclohexil)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
N-({5-cloro-6-[(cis-4-ciano-1-fluorociclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
N-({5-cloro-6-[(trans-4-ciano-1-fluorociclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(trans-4-hidroxi-4-metilciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;
N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-5-metoxi-5-metilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(5-cloro-6-{[1-(1,3-tiazol-2-il)piperidin-4-il]metoxi}piridin-3-il)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(6-{[(cis-4-hidroxi-4-metilciclohexil)metil]amino}-5-nitropiridin-3-il)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]-5-(trifluorometil)piridin-3-il}sulfonil)-2-(1H-indazol-4-iloxi)benzamida;

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(cis-4-hidroxi-4-metilciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;

N-(4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzoil]sulfamoil}-2-nitrofenil)-4-cianopiperidin-1-carboxamida; y sus sales, profármacos, sales de profármacos y metabolitos terapéuticamente aceptables.

En otro aspecto, la presente invención provee compuestos de Fórmula (II)



(II)

y sus sales, profármacos, sales de profármacos y metabolitos terapéuticamente aceptables, en donde A^1, B^1, D^1, E^1, Y^1, R^{30}, y R^{37} tienen los valores que se han descrito precedentemente para la Fórmula (I), n es 0, 1, 2, o 3; que indica la cantidad de sustituyentes en R^{26}, y R^{100} tiene los valores que se definen para los sustituyentes de R^{26}.

En una realización de Fórmula (II), A^1 es N. En otra forma de realización de Fórmula (II), A^1 es $C(A^2)$. En otra forma de realización de Fórmula (II), A^1 es $C(A^2)$, y A^2 es H.

En una realización de Fórmula (II), B^1 es R^1, OR^1, SR^1, SO_2R^1, $NHC(O)R^1$, NHR^1, $N(R^1)_2$, o $C(O)NHR^1$. En otra forma de realización de Fórmula (II), B^1 es NHR^1. En otra forma de realización de Fórmula (II), B^1 es NHR^1, y A^1 es $C(A^2)$, y A^2 es H. En otra forma de realización de Fórmula (II), B^1 es NHR^1, y A^1 es $C(A^2)$ o N, y A^2 es H. En otra forma de realización de la Fórmula (II), B^1 es OR^1. En otra forma de realización de Fórmula (II), B^1 es

OR^1, y A^1 es $C(A^2)$, y A^2 es H. En otra forma de realización de la Fórmula (II), B^1 es OR^1. En otra forma de realización de la Fórmula (II), B^1 es OR^1, y A^1 es $C(A^2)$ o N, y A^2 es H.

En una realización de Fórmula (II), D^1 y E^1 son H. En otra forma de realización de Fórmula (II), B^1 es NHR^1, y A^1 es $C(A^2)$, A^2 es H, y D^1 y E^1 son H. En otra forma de realización de Fórmula (II), B^1 es NHR^1, y A^1 es $C(A^2)$ o N, A^2 es H, y D^1 y E^1 son H. En otra forma de realización de la Fórmula (II), B^1 es OR^1, y A^1 es $C(A^2)$, A^2 es H, y D^1 y E^1 son H. En otra forma de realización de la Fórmula (II), B^1 es OR^1, y A^1 es $C(A^2)$ o N,A^2 es H, y D^1 y E^1 son H.

En una realización de Fórmula (II), Y^1 es H, CN, NO_2, F, Cl, Br, I, CF_3, R^{17}, $NHC(O)R^{17}$, o $C(O)NH_2$. En otra forma de realización de Fórmula (II), Y^1 es NO_2. En otra forma de realización de Fórmula (II), Y^1 es Cl. En otra forma de realización de la Fórmula (II), B^1 es NHR^1, y A^1 es $C(A^2)$, A^2 es H, D^1 y E^1 son H, y Y^1 es NO_2. En otra forma de realización de Fórmula (II), B^1 es NHR^1, y A^1 es $C(A^2)$ o N, A^2 es H, D^1 y E^1 son H, y Y^1 es NO_2. En otra forma de realización de la Fórmula (II), B^1 es OR^1, y A^1 es $C(A^2)$, A^2 es H, D^1 y E^1 son H, y Y^1 es Cl. En otra forma de realización de Fórmula (II), B^1 es OR^1, y A^1 es $C(A^2)$ o N, A^2 es H, D^1 y E^1 son H, y Y^1 es Cl.

En una realización de Fórmula (II), R^1 es R^2, R^3, R^4 o R^5. En otra forma de realización de Fórmula (II), R^1 es R^2, y R^2 es fenilo.

En una realización de Fórmula (II), R^1 es R^3, y R^3 es heteroarilo. En otra forma de realización de Fórmula (II), R^3 es triazolilo.

En una realización de Fórmula (II), R^1 es R^4. En otra forma de realización de Fórmula (II), R^1 es R^4, y R^4 es cicloalquilo. En otra forma de realización de Fórmula (II), R^1 es R^4, y R^4 es ciclohexilo. En otra forma de realización de Fórmula (II), R^1 es R^4, y R^4 es heterocicloalquilo. En otra forma de realización de Fórmula (II), R^1 es R^4, y R^4 es 8-azabiciclo[3.2.1]octano, azetidinilo, piperidinilo, piperazinilo, pirrolidinilo, morfolinilo, tetrahidropiranilo, o tetrahidrotiofenilo. En otra forma de realización de Fórmula (II), R^1 es R^4, y R^4 es heterocicloalquenilo. En otra forma de realización de Fórmula (II), R^1 es R^4, y R^4 es tetrahidropiridazinilo.

En una realización de Fórmula (II), R^1 es R^5. En otra forma de realización de Fórmula (II), R^1 es R^5 y R^5 es alquilo o alquinilo. En otra forma de realización de Fórmula (II), R^1 es R^5 y R^5 es alquilo que no está sustituido. En otra forma de realización de Fórmula (II), R^1 es R^5 y R^5 es alquilo que está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^6, R^7, OR^7, SR^7, SO_2R^7, $N(R^7)_2$, OH, CN, CF_3, F, Cl,

Br o I . En otra forma de realización de Fórmula (II), R^1 es R^5 y R^5 es alquilo que está sustituido con R^7.

En una realización de Fórmula (II), R^7 es R^8, R^9, R^{10} o R^{11}. En otra forma de realización de Fórmula (II), R^7 es R^8, y R^8 es fenilo que no está fusionado o está fusionado con R^{8A}, y R^{8A} es heterocicloalcano. . En otra forma de realización de Fórmula (II), R^7 es R^8, y R^8 es fenilo que no está fusionado. En otra forma de realización de Fórmula (II), R^7 es R^9, y R^9 es heteroarilo. En otra forma de realización de Fórmula (II), R^7 es R^9, y R^9 es furanilo, imidazolilo, isotiazolilo, isoxazolilo, 1,2,3-oxadiazoilo, 1,2,5-oxadiazolilo, oxazolilo, pirazinilo, pirazolilo, piridazinilo, piridinilo, pirimidinilo, pirrolilo, tetrazolilo, tiazolilo, tiofenilo, triazinilo o 1,2,3-triazolilo. En otra forma de realización de Fórmula (II), R^7 es R^9, y R^9 es piridinilo, tiazolilo, imidazoilo, y 1,2,3-triazolilo. En otra forma de realización de Fórmula (II), R^7 es R^{10}, y R^{10} es C_3-C_{10}-cicloalquilo. En otra forma de realización de Fórmula (II), R^7 es R^{10}, y R^{10} es C_3, C_6, C_7 o C_{10}-cicloalquilo. En otra forma de realización de Fórmula (II), R^7 es R^{10}, y R^{10} es ciclopropilo, ciclohexilo, biciclo[2.2.1]heptanilo, o adamantanilo. En otra forma de realización de Fórmula (II), R^7 es R^{10}, y R^{10} es morfolinilo, piperazinilo, piperidinilo, tetrahidro-2H-piranilo, 1,2-dihidropiridinilo, piranilo, piridin-1(H)–ilo, pirrolidinilo, oxetanilo, tiomorfolinilo, imidazolidinilo, tetrahidrotiofenilo, dioxolanilo, tetrahidrotiopiranilo, dioxanilo, 5,6,7,8-tetrahidroimidazo[1,2-a]piridinilo, o tetrahidrofuranilo. En otra forma de realización de Fórmula (II), R^7 es R^{10}, y R^{10} es morfolinilo, piperazinilo, piperidinilo, tetrahidro-2H-piranilo, 1,2-dihidropiridinilo, pirrolidinilo, oxetanilo, tiomorfolinilo, imidazolidinilo, tetrahidrotiofenilo, dioxolanilo, tetrahidrotiopiranilo, dioxanilo, 5,6,7,8-tetrahidroimidazo[1,2-a]piridinilo, o tetrahidrofuranilo. En otra forma de realización de Fórmula (II), R^7 es R^{11}, y R^{11} es alquilo que no está sustituido o está sustituido. En otra forma de realización de Fórmula (II), R^7 es R^{11}, y R^{11} es alquilo que no está sustituido. En otra forma de realización de Fórmula (II), R^7 es R^{11}, y R^{11} es alquilo que está sustituido. En otra forma de realización de Fórmula (II), R^7 es R^{11}, y R^{11} es alquilo que está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: OR^{12}, F, Cl, Br o I . En otra forma de realización de Fórmula (II), R^7 es R^{11}, R^{11} es alquilo que está sustituido con OR^{12}, R^{12} es R^{16}, y R^{16} es alquilo.

En una realización de Fórmula (II), R^{17} es R^{19} o R^{21}. En otra forma de realización de Fórmula (II), R^{17} es R^{19}, y R^{19} es heteroarilo. En otra forma de realización de Fórmula (II), R^{17} es R^{19}, y R^{19} es tiazolilo. En otra forma de realización de Fórmula (II), R^{17} es R^{21}, y R^{21} es alquinilo. En otra forma de realización de Fórmula (II), R^{17} es R^{21}, y R^{21} es etinilo.

Aún otra forma de realización se refiere a compuestos que tienen la Fórmula II que son

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((1-ciclopentilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;

N-((3-((cloro(difluoro)metil)sulfonil)-4-((3-(dimetilamino)propil)amino)fenil)sulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

N-((3-((cloro(difluoro)metil)sulfonil)-4-((1-metilpiperidin-4–il)amino)fenil)sulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

4-(4-((2-(4-clorofenil)ciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((2-(4-metilpiperazin-1–il)etil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((3-(4-metilpiperazin-1–il)propil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-(3-(dimetilamino)propoxi)-3-nitrofenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-(((1-metilpiperidin-4–il)metil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-(4-metilpiperazin-1–il)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-(((4-(dimetilamino)-1-metilpiperidin-4–il)metil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-3-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(2,3-dihidro-1H-indol-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)ciclohept-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-(trifluorometil)fenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((3-ciano-4-((3-(dimetilamino)propil)amino)fenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1*H*-indol-5–iloxi)-*N*-((3-nitro-4-((1-tetrahidro-2*H*-piran-4–ilpiperidin-4–il)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1*H*-indol-5–iloxi)-*N*-((4-((4-metilpiperazin-1–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-morfolin-4–ilciclohexil)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(2-metoxietil)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[(3S)-tetrahidro-2H-piran-3–ilmetil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[(3R)-tetrahidro-2H-piran-3–ilmetil]amino}fenil)sulfonil]benzamida;
4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-hidroxi-1-metilpiperidin-4–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-3-fluoro-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-3-fluoro-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;

N-[(4-{[(3S,4R)-1-bencil-3-hidroxipiperidin-4–il]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

N-[(4-{[(4-aminotetrahidro-2H-piran-4–il)metil]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[1-(2-metoxietil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-5-fluoro-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-5-fluoro-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(3-hidroxipropil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(dietilamino)ciclohexil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[4-(dimetilamino)tetrahidro-2H-piran-4–il]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida;

N-({4-[(2-aminociclohexil)amino]-3-nitrofenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[2-(4-hidroxi-1-metilpiperidin-4–il)etil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[1-(1,3-tiazol-2–il)piperidin-4–il]amino}fenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(ciclopropilmetil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[1-(4,4,4-trifluorobutil)piperidin-4–il]amino}fenil)sulfonil]benzamida;
4-[4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}-3-(hidroximetil)piperazin-1–il]-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;
4-[4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}-3-(hidroximetil)piperazin-1–il]-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[3-(3-oxopiperazin-1–il)propil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-5-hidroxiciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-5-hidroxiciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-5-hidroxiciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(2,3-dihidro-1H-inden-2–il)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(1-morfolin-4–ilciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[1-(1,3-tiazol-2–ilmetil)piperidin-4–il]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[1-(1,3-tiazol-4–ilmetil)piperidin-4–il]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[4-(hidroximetil)tetrahidro-2H-piran-4–il]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(2-hidroxietil)piperazin-1–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(3S)-1-metilpirrolidin-3–il]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(3-fluoropropil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-[4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}-3-(hidroximetil)piperazin-1–il]-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
N-[(4-{[(4-aminotetrahidro-2H-piran-4–il)metil]amino}-3-nitrofenil)sulfonil]-4-[4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}-3-(hidroximetil)piperazin-1–il]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1-hidroxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(hidroximetil)tetrahidro-2H-piran-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2-hidroxi-1-tetrahidro-2H-piran-4–iletil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-({1-[2-(1H-pirazol-1–il)etil]piperidin-4–il}amino)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(metilamino)-3-nitrofenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-5-hidroxiciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-5-morfolin-4–ilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
N-[(4-{[(1-aminociclohexil)metil]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[2-(2-oxopirrolidin-1–il)etil]amino}fenil)sulfonil]benzamida;
4-{4-[1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{1-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]etil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{1-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]etil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{1-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]etil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{1-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]etil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(ciclohexilmetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(morfolin-4–ilamino)-3-nitrofenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-3–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(tetrahidro-2H-piran-4–ilamino)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(3-metiloxetan-3–il)metil]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-metoxiciclohexil)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[3-(1,1-dioxidotiomorfolin-4–il)propil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[2-(2-oxopiperidin-1–il)etil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[2-(2-oxoimidazolidin-1–il)etil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(2-piridin-4–iletil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-morfolin-4–il-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(4-metoxipiperidin-1–il)-3-nitrofenil]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-5-pirrolidin-1–ilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[2-(3-oxopiperazin-1–il)etil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1,1-dioxidotetrahidrotien-3–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1,1-dioxidotetrahidrotien-3–il)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-[(tetrahidro-2H-piran-4–ilmetil)amino]-3-(trifluorometil)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[2-(1,3-dioxolan-2–il)etil]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(tetrahidro-2H-piran-4–ilmetoxi)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metil-5-oxopirrolidin-3–il)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metil-6-oxopiperidin-3–il)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(piperidin-1–ilamino)fenil]sulfonil}benzamida;
4-(4-{[4-(4-clorofenil)-1-metil-1H-pirazol-5–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(3-metiloxetan-3–il)metoxi]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[(1-oxidotetrahidro-2H-tiopiran-4–il)metil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1,3-tiazol-5–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(2-tetrahidro-2H-piran-4–iletil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(2-tetrahidro-2H-piran-4–iletil)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-(1,4-dioxan-2–ilmetoxi)-3-nitrofenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[2-(2-metoxietoxi)etil]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[2-(trifluorometoxi)etil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2,2-difluoroetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4,4-difluorociclohexil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[4-(4-clorofenil)-1-isopropil-6-oxo-1,6-dihidropiridin-3–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(tetrahidro-2H-piran-4–ilmetil)amino]carbonil}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-hidroxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(4-metoxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-hidroxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(4-metoxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(2-metoxietil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(3-metoxipropil)amino]-3-nitrofenil}sulfonil)benzamida;

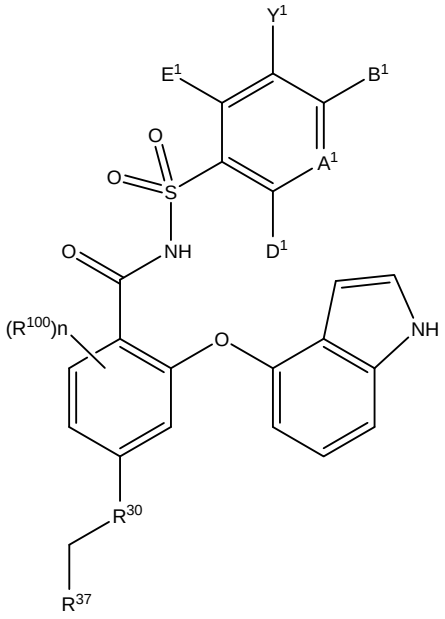
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2-cianoetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[(3R)-4-hidroxi-1-adamantil]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[(3R)-4-hidroxi-1-adamantil]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(3,3,3-trifluoropropil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-(metilamino)-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
N-{[5-bromo-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[4-(4-clorofenil)-6-isopropoxipiridin-3–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[6-(tetrahidro-2H-piran-4–ilmetoxi)-5-(1,3-tiazol-2–il)piridin-3–il]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(2-metoxietil)amino]carbonil}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-ciano-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indol-5–iloxi)benzamida;
N-({4-[(1-acetilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[1-(metilsulfonil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1,4-dioxan-2–ilmetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[4'-cloro-5-(trifluorometil)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[4'-cloro-5-(trifluorometil)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(tetrahidro-2H-piran-4–ilmetoxi)fenil]sulfonil}benzamida;

4-{4-[(5-tert-butil-4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-{4-[(5-tert-butil-4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(tetrahidro-2H-piran-4–ilmetoxi)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(2,2,2-trifluoroetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-{[(tetrahidro-2H-piran-4–ilmetil)amino]carbonil}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2R)-1,4-dioxan-2–ilmetoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2S)-1,4-dioxan-2–ilmetoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
N-({5-bromo-6-[(tetrahidro-2H-piran-4–ilmetil)amino]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(2-morfolin-4–iletil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-ciano-6-[(tetrahidro-2H-piran-4–ilmetil)amino]piridin-3–il}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)oxi]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)metoxi]-3-nitrofenil}sulfonil)benzamida;
4-({[4-({[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzoil]amino}sulfonil)-2-nitrofenil]amino}metil)piperidin-1-carboxilato de bencilo ;
N-{[3-(aminocarbonil)-4-(tetrahidro-2H-piran-4–ilmetoxi)fenil]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[4'-cloro-5-(trifluorometil)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;
4-{4-[(5-tert-butil-4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(1-metil-1H-imidazol-5–il)metil]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(morfolin-4–ilsulfonil)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1,1-dioxidotiomorfolin-4–il)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-morfolin-4–ilciclohexil)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-ciano-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(3,3-dimetilbutil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1S)-1-(hidroximetil)-3-metilbutil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[(2R)-tetrahidrofuran-2–ilmetil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1R)-1-(hidroximetil)-2-metilpropil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-metoxifenil)amino]-3-nitrofenil}sulfonil)benzamida;
N-[(4-{[2-(1,3-benzodioxol-5–il)etil]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[3-(2-oxopirrolidin-1–il)propil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-hidroxifenil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
N-{[4-({2-[4-(aminosulfonil)fenil]etil}amino)-3-nitrofenil]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[3-(1H-imidazol-1–il)propil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[(1S)-1-feniletil]amino}fenil)sulfonil]benzamida;
N-({2-cloro-5-fluoro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[2-(2-metoxietoxi)etil]tio}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(metilsulfonil)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2,2-dimetiltetrahidro-2H-piran-4–il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-ciano-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-ciano-6-(2-morfolin-4–iletoxi)piridin-3–il]sulfonil}-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)oxi]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-morfolin-4–ilbut-2-ynil)oxi]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(3-hidroxi-4-metoxifenil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(1R,5S)-8-metil-8-azabiciclo[3.2.1]oct-3–il]amino}-3-nitrofenil)sulfonil]benzamida;
y sus sales, profármacos, sales de profármacos y metabolitos terapéuticamente aceptables.

En otro aspecto, la presente invención provee compuestos de Fórmula (III)



(III)

y sus sales, profármacos, sales de profármacos y metabolitos terapéuticamente aceptables, en donde A^1, B^1, D^1, E^1, Y^1, R^{30}, y R^{37} tienen los valores que se han descrito precedentemente para la Fórmula (I), n es 0, 1, 2, o 3; que indica la cantidad de sustituyentes en R^{26}, y R^{100} tiene los valores que se definen para los sustituyentes de R^{26}.

En una realización de Fórmula (III), A^1 es N. En otra forma de realización de Fórmula (III), A^1 es $C(A^2)$. En otra forma de realización de Fórmula (III), A^1 es $C(A^2)$, y A^2 es H.

En una realización de Fórmula (III), B^1 es R^1, OR^1, SR^1, SO_2R^1, $NHC(O)R^1$, NHR^1, $N(R^1)_2$, o $C(O)NHR^1$. En otra forma de realización de Fórmula (III), B^1 es NHR^1. En otra forma de realización de Fórmula (III), B^1 es NHR^1, y A^1 es $C(A^2)$, y A^2 es H. En otra forma de realización de Fórmula (III), B^1 es NHR^1, y A^1 es $C(A^2)$ o N, y A^2 es H. En otra forma de realización de la Fórmula (III), B^1 es OR^1. En otra forma de realización de Fórmula (III), B^1 es OR^1, y A^1 es $C(A^2)$, y A^2 es H. En otra forma de realización de la Fórmula (III), B^1 es OR^1, y A^1 es $C(A^2)$ o N, y A^2 es H.

En una realización de Fórmula (III), D^1 y E^1 son H. En otra forma de realización de Fórmula (III), B^1 es NHR^1, y A^1 es $C(A^2)$, A^2 es H, y D^1 y E^1 son H. En otra forma de realización de Fórmula (III), B^1 es NHR^1, y A^1 es $C(A^2)$ o N, A^2 es H, y D^1 y E^1 son H. En otra forma de realización de la Fórmula (III), B^1 es OR^1, y A^1 es $C(A^2)$, A^2 es H, y D^1 y E^1 son H. En otra forma de realización de la Fórmula (III), B^1 es OR^1, y A^1 es $C(A^2)$ o N, A^2 es H, y D^1 y E^1 son H.

En una realización de Fórmula (III), Y^1 es H, CN, NO_2, F, Cl, Br, I, CF_3, R^{17}, $NHC(O)R^{17}$, o $C(O)NH_2$. En otra forma de realización de Fórmula (III), Y^1 es NO_2. En otra forma de realización de Fórmula (III), Y^1 es Cl. En otra forma de realización de la Fórmula

(III), B^1 es NHR^1, y A^1 es $C(A^2)$, A^2 es H, D^1 y E^1 son H, y Y^1 es NO_2. En otra forma de realización de Fórmula (III), B^1 es NHR^1, y A^1 es $C(A^2)$ o N, A^2 es H, D^1 y E^1 son H, y Y^1 es NO_2. En otra forma de realización de la Fórmula (III), B^1 es OR^1, y A^1 es $C(A^2)$, A^2 es H, D^1 y E^1 son H, y Y^1 es Cl. En otra forma de realización de Fórmula (III), B^1 es OR^1, y A^1 es $C(A^2)$ o N, A^2 es H, D^1 y E^1 son H, y Y^1 es Cl.

En una realización de Fórmula (III), R^1 es R^2, R^3, R^4 o R^5. En otra forma de realización de Fórmula (III), R^1 es R^2, y R^2 es fenilo.

En una realización de Fórmula (III), R^1 es R^3, y R^3 es heteroarilo. En otra forma de realización de Fórmula (III), R^3 es triazolilo.

En una realización de Fórmula (III), R^1 es R^4. En otra forma de realización de Fórmula (III), R^1 es R^4, y R^4 es cicloalquilo. En otra forma de realización de Fórmula (III), R^1 es R^4, y R^4 es ciclohexilo. En otra forma de realización de Fórmula (III), R^1 es R^4, y R^4 es heterocicloalquilo. En otra forma de realización de Fórmula (III), R^1 es R^4, y R^4 es 8-azabiciclo[3.2.1]octano, azetidinilo, piperidinilo, piperazinilo, pirrolidinilo, morfolinilo, tetrahidropiranilo, o tetrahidrotiofenilo. En otra forma de realización de Fórmula (III), R^1 es R^4, y R^4 es heterocicloalquenilo. En otra forma de realización de Fórmula (III), R^1 es R^4, y R^4 es tetrahidropiridazinilo.

En una realización de Fórmula (III), R^1 es R^5. En otra forma de realización de Fórmula (III), R^1 es R^5 y R^5 es alquilo o alquinilo. En otra forma de realización de Fórmula (III), R^1 es R^5 y R^5 es alquilo que no está sustituido. En otra forma de realización de Fórmula (III), R^1 es R^5 y R^5 es alquilo que está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^6, R^7, OR^7, SR^7, SO_2R^7, $N(R^7)_2$, OH, CN, CF_3, F, Cl, Br o I . En otra forma de realización de Fórmula (III), R^1 es R^5 y R^5 es alquilo que está sustituido con R^7.

En una realización de Fórmula (III), R^7 es R^8, R^9, R^{10} o R^{11}. En otra forma de realización de Fórmula (III), R^7 es R^8, y R^8 es fenilo que no está fusionado o está fusionado con R^{8A}, y R^{8A} es heterocicloalcano. . En otra forma de realización de Fórmula (III), R^7 es R^8, y R^8 es fenilo que no está fusionado. En otra forma de realización de Fórmula (III), R^7 es R^9, y R^9 es heteroarilo. En otra forma de realización de Fórmula (III), R^7 es R^9, y R^9 es furanilo, imidazolilo, isotiazolilo, isoxazolilo, 1,2,3-oxadiazoilo, 1,2,5-oxadiazolilo, oxazolilo, pirazinilo, pirazolilo, piridazinilo, piridinilo, pirimidinilo, pirrolilo, tetrazolilo, tiazolilo, tiofenilo, triazinilo o 1,2,3-triazolilo. En otra forma de realización de Fórmula (III), R^7 es R^9, y R^9 es piridinilo, tiazolilo, imidazoilo, y 1,2,3-triazolilo. En otra forma de realización de Fórmula (III), R^7 es R^{10}, y R^{10} es C_3-C_{10}-cicloalquilo. En otra forma de realización de

Fórmula (III), R^7 es R^{10}, y R^{10} es C_3, C_6, C_7 o C_{10}-cicloalquilo. En otra forma de realización de Fórmula (III), R^7 es R^{10}, y R^{10} es ciclopropilo, ciclohexilo, biciclo[2.2.1]heptanilo, o adamantanilo. En otra forma de realización de Fórmula (III), R^7 es R^{10}, y R^{10} es morfolinilo, piperazinilo, piperidinilo, tetrahidro-2H-piranilo, 1,2-dihidropiridinilo, piranilo, piridin-1(H)–ilo, pirrolidinilo, oxetanilo, tiomorfolinilo, imidazolidinilo, tetrahidrotiofenilo, dioxolanilo, tetrahidrotiopiranilo, dioxanilo, 5,6,7,8-tetrahidroimidazo[1,2-a]piridinilo, o tetrahidrofuranilo. En otra forma de realización de Fórmula (III), R^7 es R^{10}, y R^{10} es morfolinilo, piperazinilo, piperidinilo, tetrahidro-2H-piranilo, 1,2-dihidropiridinilo, pirrolidinilo, oxetanilo, tiomorfolinilo, imidazolidinilo, tetrahidrotiofenilo, dioxolanilo, tetrahidrotiopiranilo, dioxanilo, 5,6,7,8-tetrahidroimidazo[1,2-a]piridinilo, o tetrahidrofuranilo. En otra forma de realización de Fórmula (III), R^7 es R^{11}, y R^{11} es alquilo que no está sustituido o está sustituido. En otra forma de realización de Fórmula (III), R^7 es R^{11}, y R^{11} es alquilo que no está sustituido. En otra forma de realización de Fórmula (III), R^7 es R^{11}, y R^{11} es alquilo que está sustituido. En otra forma de realización de Fórmula (III), R^7 es R^{11}, y R^{11} es alquilo que está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: OR^{12}, F, Cl, Br o I substituents. En otra forma de realización de Fórmula (III), R^7 es R^{11}, R^{11} es alquilo que está sustituido con OR^{12}, R^{12} es R^{16}, y R^{16} es alquilo.

En una realización de Fórmula (III), R^{17} es R^{19} o R^{21}. En otra forma de realización de Fórmula (III), R^{17} es R^{19}, y R^{19} es heteroarilo. En otra forma de realización de Fórmula (III), R^{17} es R^{19}, y R^{19} es tiazolilo. En otra forma de realización de Fórmula (III), R^{17} es R^{21}, y R^{21} es alquinilo. En otra forma de realización de Fórmula (III), R^{17} es R^{21}, y R^{21} es etinilo.

Aún otra forma de realización se refiere a compuestos que tienen la Fórmula (III) que son

4-(4-((4'-cloro-4-(pirrolidin-1–ilmetil)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-4-(2-pirrolidin-1–iletil)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-4–iloxi)benzamida;

4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-4–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-4–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
2-(1H-indol-4–iloxi)-4-(4-((2-(4-metoxifenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((4,4-dimetil-2-(4-(trifluorometil)fenil)ciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((4,4-dimetil-2-(4-(trifluorometoxi)fenil)ciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((4,4-dimetil-2-(3-(trifluorometil)fenil)ciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((2-(3-fluorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-fluorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((3-(4-metilpiperazin-1–il)propil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((2-(4-metilpiperazin-1–il)etil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-(((1-metilpiperidin-4–il)metil)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-(3-(dimetilamino)propoxi)-3-nitrofenil)sulfonil)-2-(1H-indol-4–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((1-(2,2,2-trifluoroetil)piperidin-4–il)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-3-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)ciclohept-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)ciclooct-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)ciclopent-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclopent-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)ciclooct-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)ciclohept-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)ciclopent-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)ciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-(1-(4'-cloro-1,1'-bifenil-2–il)etil)piperazin-1–il)-2-(1*H*-indol-4–iloxi)-*N*-((3-nitro-4-((tetrahidro-2*H*-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

N-((4-(((4-aminotetrahidro-2*H*-piran-4–il)metil)amino)-3-nitrofenil)sulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1*H*-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-hidroxi-1-metilpiperidin-4–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(2-hidroxietil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[1-(2-metoxietil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(3-hidroxipropil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;

4-[4-({4'-cloro-3-[3-(dimetilamino)propil]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-{4-[(4'-cloro-4-morfolin-4–il-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-[4-({4'-cloro-3-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;

4-{4-[1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(dimetilamino)ciclohexil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(dietilamino)ciclohexil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(4-morfolin-4–ilciclohexil)amino]-3-nitrofenil}sulfonil)benzamida;

4-[4-({4'-cloro-3-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-{4-[1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;

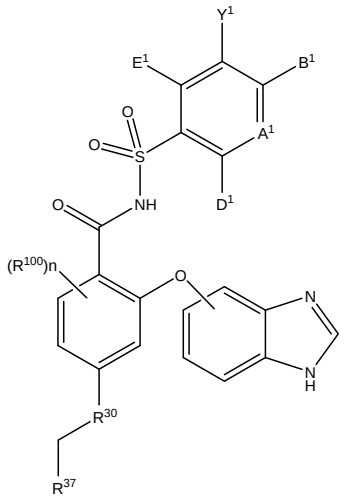
4-[4-({4'-cloro-4-[3-(dimetilamino)prop-1-ynil]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(3-nitro-4-{[1-(4,4,4-trifluorobutil)piperidin-4–il]amino}fenil)sulfonil]benzamida;
4-(4-{[4'-cloro-4-(2-hidroxietoxi)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
4-{4-[1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[4'-cloro-4-(2-hidroxietoxi)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(3-nitro-4-{[3-(3-oxopiperazin-1–il)propil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(2,3-dihidro-1H-inden-2–il)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(2-metoxietil)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(hidroximetil)tetrahidro-2H-piran-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[4-(metilamino)-3-nitrofenil]sulfonil}benzamida;
4-{4-[1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)benzamida;
4-{4-[(1R)-1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-{4-[(1S)-1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[4-(morfolin-4–ilamino)-3-nitrofenil]sulfonil}benzamida;
4-[4-({4'-cloro-4-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(3-nitro-4-{[2-(3-oxopiperazin-1–il)etil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[3-nitro-4-(piperidin-1–ilamino)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[3-nitro-4-(tetrahidro-2H-piran-4–ilmetoxi)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(3-nitro-4-{[2-(trifluorometoxi)etil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[2-(2-metoxietoxi)etil]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[3-(metilsulfonil)propil]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[3-(1,1-dioxidotiomorfolin-4–il)propil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1,1-dioxidotetrahidrotien-3–il)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1,1-dioxidotetrahidro-2H-tiopiran-4–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(2-metoxietil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[3-nitro-4-(2-tetrahidro-2H-piran-4–iletoxi)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[3-(metilsulfonil)propoxi]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(3-metoxipropil)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2-cianoetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(3,3,3-trifluoropropil)amino]fenil}sulfonil)benzamida;
N-({5-bromo-6-[(tetrahidro-2H-piran-4–ilmetil)amino]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1,1-dioxidotetrahidrotien-3–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;
N-({4-[(1-acetilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[1-(metilsulfonil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(2,2,2-trifluoroetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
4-(4-{[4-(4-clorofenil)-1-(3-hidroxipropil)-1,2,5,6-tetrahidropiridin-3–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
N-{[5-bromo-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[6-[(tetrahidro-2H-piran-4–ilmetil)amino]-5-(1,3-tiazol-2–il)piridin-3–il]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-ciano-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[2-(2-metoxietoxi)etil]tio}-3-nitrofenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[4-(metilsulfonil)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-ciano-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-cloro-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-etinil-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-ciano-6-(2-morfolin-4–iletoxi)piridin-3–il]sulfonil}-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-ciano-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-2-(1H-indol-4–iloxi)benzamida;
N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)benzamida;
y sus sales, profármacos, sales de profármacos y metabolitos terapéuticamente aceptables.

En otro aspecto, la presente invención provee compuestos de Fórmula (IV)



(IV)

y sus sales, profármacos, sales de profármacos y metabolitos terapéuticamente aceptables, en donde A^1, B^1, D^1, E^1, Y^1, R^{30}, y R^{37} tienen los valores que se han descrito precedentemente para la Fórmula (I), n es 0, 1, 2, o 3; que indica la cantidad de sustituyentes en R^{26}, y R^{100} tiene los valores que se definen para los sustituyentes de R^{26}.

En una realización de Fórmula (IV), A^1 es N. En otra forma de realización de Fórmula (IV), A^1 es $C(A^2)$. En otra forma de realización de Fórmula (IV), A^1 es $C(A^2)$, y A^2 es H.

En una realización de Fórmula (IV), B^1 es R^1, OR^1, SR^1, SO_2R^1, $NHC(O)R^1$, NHR^1, $N(R^1)_2$, o $C(O)NHR^1$. En otra forma de realización de Fórmula (IV), B^1 es NHR^1. En otra forma de realización de Fórmula (IV), B^1 es NHR^1, y A^1 es $C(A^2)$, y A^2 es H. En otra forma de realización de Fórmula (IV), B^1 es NHR^1, y A^1 es $C(A^2)$ o N, y A^2 es H. En otra forma de realización de la Fórmula (IV), B^1 es OR^1. En otra forma de realización de Fórmula (IV), B^1 es OR^1, y A^1 es $C(A^2)$, y A^2 es H. En otra forma de realización de la Fórmula (IV), B^1 es OR^1, y A^1 es $C(A^2)$ o N, y A^2 es H.

En una realización de Fórmula (IV), D^1 y E^1 son H. En otra forma de realización de Fórmula (IV), B^1 es NHR^1, y A^1 es $C(A^2)$, A^2 es H, y D^1 y E^1 son H. En otra forma de realización de Fórmula (IV), B^1 es NHR^1, y A^1 es $C(A^2)$ o N, A^2 es H, y D^1 y E^1 son H. En otra forma de realización de la Fórmula (IV), B^1 es OR^1, y A^1 es $C(A^2)$, A^2 es H, y D^1 y E^1 son H. En otra forma de realización de la Fórmula (IV), B^1 es OR^1, y A^1 es $C(A^2)$ o N, A^2 es H, y D^1 y E^1 son H.

En una realización de Fórmula (IV), Y^1 es H, CN, NO_2, F, Cl, Br, I, CF_3, R^{17}, $NHC(O)R^{17}$, o $C(O)NH_2$. En otra forma de realización de Fórmula (IV), Y^1 es NO_2. En otra forma de realización de Fórmula (IV), Y^1 es Cl. En otra forma de realización de la Fórmula (IV), B^1 es NHR^1, y A^1 es $C(A^2)$, A^2 es H, D^1 y E^1 son H, y Y^1 es NO_2. En otra forma de realización de Fórmula (IV), B^1 es NHR^1, y A^1 es $C(A^2)$ o N, A^2 es H, D^1 y E^1 son H, y Y^1 es NO_2. En otra forma de realización de la Fórmula (IV), B^1 es OR^1, y A^1 es $C(A^2)$, A^2 es H, D^1 y E^1 son H, y Y^1 es Cl. En otra forma de realización de Fórmula (IV), B^1 es OR^1, y A^1 es $C(A^2)$ o N, A^2 es H, D^1 y E^1 son H, y Y^1 es Cl.

En una realización de Fórmula (IV), R^1 es R^2, R^3, R^4 o R^5. En otra forma de realización de Fórmula (IV), R^1 es R^2, y R^2 es fenilo.

En una realización de Fórmula (IV), R^1 es R^3, y R^3 es heteroarilo. En otra forma de realización de Fórmula (IV), R^3 es triazolilo.

En una realización de Fórmula (IV), R^1 es R^4. En otra forma de realización de Fórmula (IV), R^1 es R^4, y R^4 es cicloalquilo. En otra forma de realización de Fórmula (IV), R^1 es R^4, y R^4 es ciclohexilo. En otra forma de realización de Fórmula (IV), R^1 es R^4, y R^4 es heterocicloalquilo. En otra forma de realización de Fórmula (IV), R^1 es R^4, y R^4 es 8-azabiciclo[3.2.1]octano, azetidinilo, piperidinilo, piperazinilo, pirrolidinilo, morfolinilo, tetrahidropiranilo, o tetrahidrotiofenilo. En otra forma de realización de Fórmula (IV), R^1 es R^4, y R^4 es heterocicloalquenilo. En otra forma de realización de Fórmula (IV), R^1 es R^4, y R^4 es tetrahidropiridazinilo.

En una realización de Fórmula (IV), R^1 es R^5. En otra forma de realización de Fórmula (IV), R^1 es R^5 y R^5 es alquilo o alquinilo. En otra forma de realización de Fórmula (IV), R^1 es R^5 y R^5 es alquilo que no está sustituido. En otra forma de realización de Fórmula (IV), R^1 es R^5 y R^5 es alquilo que está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^6, R^7, OR^7, SR^7, SO_2R^7, $N(R^7)_2$, OH, CN, CF_3, F, Cl, Br o I substituents. En otra forma de realización de Fórmula (IV), R^1 es R^5 y R^5 es alquilo que está sustituido con R^7.

En una realización de Fórmula (IV), R^7 es R^8, R^9, R^{10} o R^{11}. En otra forma de realización de Fórmula (IV), R^7 es R^8, y R^8 es fenilo que no está fusionado o está fusionado con R^{8A}, y R^{8A} es heterocicloalcano. . En otra forma de realización de Fórmula (IV), R^7 es R^8, y R^8 es fenilo que no está fusionado. En otra forma de realización de Fórmula (IV), R^7 es R^9, y R^9 es heteroarilo. En otra forma de realización de Fórmula (IV), R^7 es R^9, y R^9 es furanilo, imidazolilo, isotiazolilo, isoxazolilo, 1,2,3-oxadiazoilo, 1,2,5-oxadiazolilo, oxazolilo, pirazinilo, pirazolilo, piridazinilo, piridinilo, pirimidinilo, pirrolilo, tetrazolilo, tiazolilo, tiofenilo, triazinilo o 1,2,3-triazolilo. En otra forma de realización de Fórmula (IV), R^7 es R^9, y R^9 es piridinilo, tiazolilo, imidazoilo, y 1,2,3-triazolilo. En otra forma de realización de Fórmula (IV), R^7 es R^{10}, y R^{10} es C_3-C_{10}-cicloalquilo. En otra forma de realización de Fórmula (IV), R^7 es R^{10}, y R^{10} es C_3, C_6, C_7 o C_{10}-cicloalquilo. En otra forma de realización de Fórmula (IV), R^7 es R^{10}, y R^{10} es ciclopropilo, ciclohexilo, biciclo[2.2.1]heptanilo, o adamantanilo. En otra forma de realización de Fórmula (IV), R^7 es R^{10}, y R^{10} es morfolinilo, piperazinilo, piperidinilo, tetrahidro-2H-piranilo, 1,2-dihidropiridinilo, piranilo, piridin-1(H)–ilo, pirrolidinilo, oxetanilo, tiomorfolinilo, imidazolidinilo, tetrahidrotiofenilo, dioxolanilo, tetrahidrotiopiranilo, dioxanilo, 5,6,7,8-tetrahidroimidazo[1,2-a]piridinilo, o tetrahidrofuranilo. En otra forma de realización de Fórmula (IV), R^7 es R^{10}, y R^{10} es morfolinilo, piperazinilo, piperidinilo, tetrahidro-2H-piranilo, 1,2-dihidropiridinilo, pirrolidinilo, oxetanilo, tiomorfolinilo, imidazolidinilo, tetrahidrotiofenilo, dioxolanilo, tetrahidrotiopiranilo, dioxanilo, 5,6,7,8-tetrahidroimidazo[1,2-a]piridinilo, o tetrahidrofuranilo. En otra forma de realización de Fórmula (IV), R^7 es R^{11}, y R^{11} es alquilo que no está sustituido o está sustituido. En otra forma de realización de Fórmula (IV), R^7 es R^{11}, y R^{11} es alquilo que no está sustituido. En otra forma de realización de Fórmula (IV), R^7 es R^{11}, y R^{11} es alquilo que está sustituido. En otra forma de realización de Fórmula (IV), R^7 es R^{11}, y R^{11} es alquilo que está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: OR^{12}, F, Cl, Br o I . En otra forma de realización de

Fórmula (IV), R^7 es R^{11}, R^{11} es alquilo que está sustituido con OR^{12}, R^{12} es R^{16}, y R^{16} es alquilo.

En una realización de Fórmula (IV), R^{17} es R^{19} o R^{21}. En otra forma de realización de Fórmula (IV), R^{17} es R^{19}, y R^{19} es heteroarilo. En otra forma de realización de Fórmula (IV), R^{17} es R^{19}, y R^{19} es tiazolilo. En otra forma de realización de Fórmula (IV), R^{17} es R^{21}, y R^{21} es alquinilo. En otra forma de realización de Fórmula (IV), R^{17} es R^{21}, y R^{21} es etinilo.

Aún otra forma de realización se refiere a compuestos que tienen la Fórmula (IV) que son

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(3R)-1-(2,2-difluoroetil)pirrolidin-3–il]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]-3-nitrofenil}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[4-(2,2-difluoroetil)morfolin-2–il]metil}amino)-3-nitrofenil]sulfonil}benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-N-[(5-cloro-6-{[(2S)-4-(N,N-dimetilglicil)morfolin-2–il]metoxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)benzamida;

2-(1H-benzimidazol-4–iloxi)-N-[(5-cloro-6-{[(2R)-4-(N,N-dimetilglicil)morfolin-2–il]metoxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(3R)-1-(cianometil)pirrolidin-3–il]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({(3R)-1-[2-(2-metoxietoxi)etil]pirrolidin-3–il}amino)-3-nitrofenil]sulfonil}benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(3R)-1-(N,N-dimetilglicil)pirrolidin-3–il]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[4-(cianometil)morfolin-2–il]metil}amino)-3-nitrofenil]sulfonil}benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-ciclopropilmorfolin-2–il)metil]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(3-nitro-4-{[(4-oxetan-3–ilmorfolin-2–il)metil]amino}fenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[(2R)-4-(N,N-dimetilglicil)morfolin-2–il]metil}amino)-3-nitrofenil]sulfonil}benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[(2S)-4-(N,N-dimetilglicil)morfolin-2–il]metil}amino)-3-nitrofenil]sulfonil}benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(tetrahidrofuran-3–ilmetil)amino]fenil}sulfonil)benzamida;

Trans-2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-metoxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-fluorotetrahidro-2H-piran-4–il)metil]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-fluoro-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)benzamida;

2-(1H-benzimidazol-4–iloxi)-N-({5-cloro-6-[(1-ciclopropilpiperidin-4–il)amino]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1,4-dioxan-2–ilmetil)amino]-3-nitrofenil}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1-ciclopropilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;

Trans-2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-morfolin-4–ilciclohexil)amino]-3-nitrofenil}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1-metilpiperidin-4–il)metil]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[({(2R)-4-[2-(2-metoxietoxi)etil]morfolin-2–il}metil)amino]-3-nitrofenil}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4,4-difluorociclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;

N-[(4-{[(4-acetilmorfolin-2–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[4-(metilsulfonil)morfolin-2–il]metil}amino)-3-nitrofenil]sulfonil}benzamida;

Trans-2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-cianociclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-N-({5-cloro-6-[(4,4-difluorociclohexil)metoxi]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)benzamida;

2-(1H-benzimidazol-4-iloxi)-N-({3-cloro-4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida;

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[5-cloro-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil}benzamida;

2-(1H-benzimidazol-4-iloxi)-N-[(5-cloro-6-{[(2S)-4-ciclopropilmorfolin-2-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida;

2-{[(4-{[2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzoil]sulfamoil}-2-nitrofenil)amino]metil}-N-etil-N-metilmorfolin-4-carboxamida;

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-cloro-4-(tetrahidro-2H-piran-4-ilmetoxi)fenil]sulfonil}benzamida;

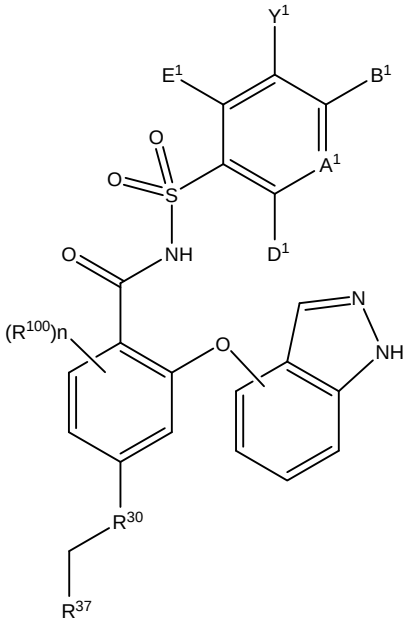
2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({[(2S)-4-ciclopropilmorfolin-2-il]metil}amino)-3-nitrofenil]sulfonil}benzamida;

2-(1H-benzimidazol-4-iloxi)-N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida;

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-nitro-4-({[(2S)-4-(oxetan-3-il)morfolin-2-il]metil}amino)fenil]sulfonil}benzamida;

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(trans-4-hidroxi-4-metilciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;
2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(cis-4-hidroxi-4-metilciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;y sus sales, profármacos, sales de profármacos y metabolitos terapéuticamente aceptables.

En otro aspecto, la presente invención provee compuestos de Fórmula (V)



(V)

y sus sales, profármacos, sales de profármacos y metabolitos terapéuticamente aceptables, en donde A^1, B^1, D^1, E^1, Y^1, R^{30}, y R^{37} tienen los valores que se han descrito precedentemente para la Fórmula (I), n es 0, 1, 2, o 3; que indica la cantidad de sustituyentes en R^{26}, y R^{100} tiene los valores que se definen para los sustituyentes de R^{26}.

En una realización de Fórmula (V), A^1 es N. En otra forma de realización de Fórmula (V), A^1 es $C(A^2)$. En otra forma de realización de Fórmula (V), A^1 es $C(A^2)$, y A^2 es H.

En una realización de Fórmula (V), B^1 es R^1, OR^1, SR^1, SO_2R^1, $NHC(O)R^1$, NHR^1, $N(R^1)_2$, o $C(O)NHR^1$. En otra forma de realización de Fórmula (V), B^1 es NHR^1. En otra forma de realización de Fórmula (V), B^1 es NHR^1, y A^1 es $C(A^2)$, y A^2 es H. En otra forma de realización de Fórmula (V), B^1 es NHR^1, y A^1 es $C(A^2)$ o N, y A^2 es H. En otra forma de realización de la Fórmula (V), B^1 es OR^1. En otra forma de realización de Fórmula (V), B^1 es OR^1, y A^1 es $C(A^2)$, y A^2 es H. En otra forma de realización de la Fórmula (V), B^1 es OR^1, y A^1 es $C(A^2)$ o N, y A^2 es H.

En una realización de Fórmula (V), D^1 y E^1 son H. En otra forma de realización de Fórmula (V), B^1 es NHR^1, y A^1 es $C(A^2)$, A^2 es H, y D^1 y E^1 son H. En otra forma de realización de Fórmula (V), B^1 es NHR^1, y A^1 es $C(A^2)$ o N, A^2 es H, y D^1 y E^1 son H. En otra forma de realización de la Fórmula (V), B^1 es OR^1, y A^1 es $C(A^2)$, A^2 es H, y D^1 y E^1 son H. En otra forma de realización de la Fórmula (V), B^1 es OR^1, y A^1 es $C(A^2)$ o N, A^2 es H, y D^1 y E^1 son H.

En una realización de Fórmula (V), Y^1 es H, CN, NO_2, F, Cl, Br, I, CF_3, R^{17}, $NHC(O)R^{17}$, o $C(O)NH_2$. En otra forma de realización de Fórmula (V), Y^1 es NO_2. En otra forma de realización de Fórmula (V), Y^1 es Cl. En otra forma de realización de la Fórmula (V), B^1 es NHR^1, y A^1 es $C(A^2)$, A^2 es H, D^1 y E^1 son H, y Y^1 es NO_2. En otra forma de realización de Fórmula (V), B^1 es NHR^1, y A^1 es $C(A^2)$ o N, A^2 es H, D^1 y E^1 son H, y Y^1 es NO_2. En otra forma de realización de Fórmula (I), B^1 es OR^1, y A^1 es $C(A^2)$, A^2 es H, D^1 y E^1 son H, y Y^1 es Cl. En otra forma de realización de la Fórmula (V), B^1 es OR^1, y A^1 es $C(A^2)$ o N, A^2 es H, D^1 y E^1 son H, y Y^1 es Cl.

En una realización de Fórmula (V), R^1 es R^2, R^3, R^4 o R^5. En otra forma de realización de Fórmula (V), R^1 es R^2, y R^2 es fenilo.

En una realización de Fórmula (V), R^1 es R^3, y R^3 es heteroarilo. En otra forma de realización de Fórmula (V), R^3 es triazolilo.

En una realización de Fórmula (V), R^1 es R^4. En otra forma de realización de Fórmula (V), R^1 es R^4, y R^4 es cicloalquilo. En otra forma de realización de Fórmula (V), R^1 es R^4, y R^4 es ciclohexilo. En otra forma de realización de Fórmula (V), R^1 es R^4, y R^4 es heterocicloalquilo. En otra forma de realización de Fórmula (V), R^1 es R^4, y R^4 es 8-azabiciclo[3.2.1]octano, azetidinilo, piperidinilo, piperazinilo, pirrolidinilo, morfolinilo, tetrahidropiranilo, o tetrahidrotiofenilo. En otra forma de realización de Fórmula (V), R^1 es R^4, y R^4 es heterocicloalquenilo. En otra forma de realización de Fórmula (V), R^1 es R^4, y R^4 es tetrahidropiridazinilo.

En una realización de Fórmula (V), R^1 es R^5. En otra forma de realización de Fórmula (V), R^1 es R^5 y R^5 es alquilo o alquinilo. En otra forma de realización de Fórmula (V), R^1 es R^5 y R^5 es alquilo que no está sustituido. En otra forma de realización de Fórmula (V), R^1 es R^5 y R^5 es alquilo que está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^6, R^7, OR^7, SR^7, SO_2R^7, $N(R^7)_2$, OH, CN, CF_3, F, Cl, Br o I substituents. En otra forma de realización de Fórmula (V), R^1 es R^5 y R^5 es alquilo que está sustituido con R^7.

En una realización de Fórmula (V), R^7 es R^8, R^9, R^{10} o R^{11}. En otra forma de realización de Fórmula (V), R^7 es R^8, y R^8 es fenilo que no está fusionado o está fusionado con R^{8A}, y R^{8A} es heterocicloalcano. . En otra forma de realización de Fórmula (V), R^7 es R^8, y R^8 es fenilo que no está fusionado. En otra forma de realización de Fórmula (V), R^7 es R^9, y R^9 es heteroarilo. En otra forma de realización de Fórmula (V), R^7 es R^9, y R^9 es furanilo, imidazolilo, isotiazolilo, isoxazolilo, 1,2,3-oxadiazoilo, 1,2,5-oxadiazolilo, oxazolilo, pirazinilo, pirazolilo, piridazinilo, piridinilo, pirimidinilo, pirrolilo, tetrazolilo, tiazolilo, tiofenilo, triazinilo o 1,2,3-triazolilo. En otra forma de realización de Fórmula (V), R^7 es R^9, y R^9 es piridinilo, tiazolilo, imidazoilo, y 1,2,3-triazolilo. En otra forma de realización de Fórmula (V), R^7 es R^{10}, y R^{10} es C_3-C_{10}-cicloalquilo. En otra forma de realización de Fórmula (V), R^7 es R^{10}, y R^{10} es C_3, C_6, C_7 o C_{10}-cicloalquilo. En otra forma de realización de Fórmula (V), R^7 es R^{10}, y R^{10} es ciclopropilo, ciclohexilo, biciclo[2.2.1]heptanil,o adamantanilo. En otra forma de realización de Fórmula (V), R^7 es R^{10}, y R^{10} es morfolinilo, piperazinilo, piperidinilo, tetrahidro-2H-piranilo, 1,2-dihidropiridinilo, piranilo, piridin-1(H)–ilo, pirrolidinilo, oxetanilo, tiomorfolinilo, imidazolidinilo, tetrahidrotiofenilo, dioxolanilo, tetrahidrotiopiranilo, dioxanilo, 5,6,7,8-tetrahidroimidazo[1,2-a]piridinilo, o tetrahidrofuranilo. En otra forma de realización de Fórmula (V), R^7 es R^{10}, y R^{10} es morfolinilo, piperazinilo, piperidinilo, tetrahidro-2H-piranilo, 1,2-dihidropiridinilo, pirrolidinilo, oxetanilo, tiomorfolinilo, imidazolidinilo, tetrahidrotiofenilo, dioxolanilo, tetrahidrotiopiranilo, dioxanilo, 5,6,7,8-tetrahidroimidazo[1,2-a]piridinilo, o tetrahidrofuranilo. En otra forma de realización de Fórmula (V), R^7 es R^{11}, y R^{11} es alquilo que no está sustituido o está sustituido. En otra forma de realización de Fórmula (V), R^7 es R^{11}, y R^{11} es alquilo que no está sustituido. En otra forma de realización de Fórmula (V), R^7 es R^{11}, y R^{11} es alquilo que está sustituido. En otra forma de realización de Fórmula (V), R^7 es R^{11}, y R^{11} es alquilo que está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: OR^{12}, F, Cl, Br o I substituents. En otra forma de realización de Fórmula (V), R^7 es R^{11}, R^{11} es alquilo que está sustituido con OR^{12}, R^{12} es R^{16}, y R^{16} es alquilo.

En una realización de Fórmula (V), R^{17} es R^{19} o R^{21}. En otra forma de realización de Fórmula (V), R^{17} es R^{19}, y R^{19} es heteroarilo. En otra forma de realización de Fórmula (V), R^{17} es R^{19}, y R^{19} es tiazolilo. En otra forma de realización de Fórmula (V), R^{17} es R^{21}, y R^{21} es alquinilo. En otra forma de realización de Fórmula (V), R^{17} es R^{21}, y R^{21} es etinilo.

Aún otra forma de realización se refiere a compuestos que tienen la Fórmula (V) que son

N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-ciano-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-fluorotetrahidro-2H-piran-4–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]-5-(trifluorometil)piridin-3–il]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-ciclopropilmorfolin-2–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4,4-difluorociclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4–iloxi)benzamida;

N-[(5-cloro-6-{[(4-fluorotetrahidro-2H-piran-4–il)metil]amino}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

Trans-N-({5-cloro-6-[(4-metoxiciclohexil)metoxi]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-fluoro-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-2-(1H-indazol-4–iloxi)benzamida;

N-[(5-cloro-6-{[1-(cianometil)-4-fluoropiperidin-4–il]metoxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-cloro-6-(tetrahidrofuran-3–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;

Trans-N-({5-cloro-6-[(4-hidroxiciclohexil)metoxi]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

N-[(5-cloro-6-{[(3R)-1-(2,2-difluoroetil)pirrolidin-3–il]oxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;
N-[(5-cloro-6-{[(2S)-4-(N,N-dimetilglicil)morfolin-2–il]metoxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;
N-[(5-cloro-6-{[(2R)-4-(N,N-dimetilglicil)morfolin-2–il]metoxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-cloro-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;
N-{[5-cloro-6-({(3R)-1-[2-fluoro-1-(fluorometil)etil]pirrolidin-3–il}oxi)piridin-3–il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({(3R)-1-[2-fluoro-1-(fluorometil)etil]pirrolidin-3–il}amino)-3-nitrofenil]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1-ciclopropilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)-2-(1H-indazol-4–iloxi)benzamida;
N-{[5-cloro-6-({(3R)-1-[2-fluoro-1-(fluorometil)etil]pirrolidin-3–il}metoxi)piridin-3–il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;
N-[(5-cloro-6-{[(3R)-1-(2,2-difluoroetil)pirrolidin-3–il]metoxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;
Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)-N-[(4-{[(4-metoxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-(1,4-dioxan-2–ilmetoxi)-3-nitrofenil]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;
N-({5-cloro-6-[(1-ciclopropilpiperidin-4–il)amino]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

2-(1H-benzimidazol-4–iloxi)-N-({5-cloro-6-[(1-ciclopropilpiperidin-4–il)amino]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[6-({4-fluoro-1-[2-fluoro-1-(fluorometil)etil]piperidin-4–il}metoxi)-5-(trifluorometil)piridin-3–il]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-cloro-6-(2-tetrahidrofuran-2–iletoxi)piridin-3–il]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;

N-({3-cloro-4-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-*N*-{[5-ciano-6-(2-tetrahidro-2*H*-piran-4–iletoxi)piridin-3–il]sulfonil}-2-(1*H*-indazol-4–iloxi)benzamida;

N-({5-cloro-6-[(4,4-difluorociclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({6-[(trans-4-carbamoilciclohexil)metoxi]-5-cloropiridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(trans-4-cianociclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[2-(1H-imidazol-1-il)etoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(1-metil-1H-imidazol-5-il)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[5-fluoro-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil}-2-(1H-indazol-4-iloxi)benzamida;

N-{[5-cloro-6-(1,4-dioxan-2-ilmetoxi)piridin-3-il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(4,4-difluoro-1-hidroxiciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(2,2-difluorociclopropil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(trans-4-cianociclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(cis-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({3-cloro-4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]fenil}sulfonil)-4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]-3-(trifluorometil)fenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-cloro-4-(tetrahidro-2H-piran-4-ilmetoxi)fenil]sulfonil}-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-ciano-4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]fenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida;

N-{[3-cloro-4-(1,4-dioxan-2-ilmetoxi)fenil]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-o1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-[(5-cloro-6-{[(2S)-4-ciclopropilmorfolin-2-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

2-{[(4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzoil]sulfamoil}-2-nitrofenil)amino]metil}morfolin-4-carboxilato de metilo;

2-{[(4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzoil]sulfamoil}-2-nitrofenil)amino]metil}-N-etil-N-metilmorfolin-4-carboxamida;

N-({5-cloro-6-[(trans-4-etil-4-hidroxiciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(cis-4-etil-4-hidroxiciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

5-cloro-N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

5-cloro-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4-fluorotetrahidro-2H-piran-4-il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(cis-1-fluoro-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(trans-1-fluoro-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-[(3-cloro-4-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}fenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(cis-1-fluoro-4-hidroxiciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-[(5-cloro-6-{[(1R,2R,4R,5R)-5-hidroxi-5-metilbiciclo[2.2.1]hept-2-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-[(5-cloro-6-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil) benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(trans-4-hidroxi-4-metilciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(cis-4-hidroxi-4-metilciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;
N-[(5-cloro-6-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({[(2S)-4-ciclopropilmorfolin-2-il]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-indazol-4-iloxi)benzamida;
N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(cis-4-hidroxi-4-metilciclohexil)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(trans-4-hidroxi-4-metilciclohexil)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-ciano-4-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}fenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-{[3-nitro-4-(2-oxaspiro[3.5]non-7-ilmetoxi)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[5-cloro-6-(5,6,7,8-tetrahidroimidazo[1,2-a]piridin-6-ilmetoxi)piridin-3-il]sulfonil}-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(5-ciano-6-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}piridin-3-il)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;
N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-5-(metoximetil)-5-metilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-{[3-nitro-4-({[(2S)-4-(oxetan-3-il)morfolin-2-il]metil}amino)fenil]sulfonil}benzamida;

N-[(5-cloro-6-{[trans-4-(2-hidroxipropan-2-il)ciclohexil]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-ciano-4-[(trans-4-hidroxi-4-metilciclohexil)metoxi]fenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({5-ciano-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-({5-nitro-6-[(tetrahidro-2H-piran-4-ilmetil)amino]piridin-3-il}sulfonil)benzamida;

N-({3-cloro-4-[(cis-4-ciano-1-fluorociclohexil)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({3-cloro-4-[(trans-4-ciano-1-fluorociclohexil)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(cis-4-ciano-1-fluorociclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(trans-4-ciano-1-fluorociclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

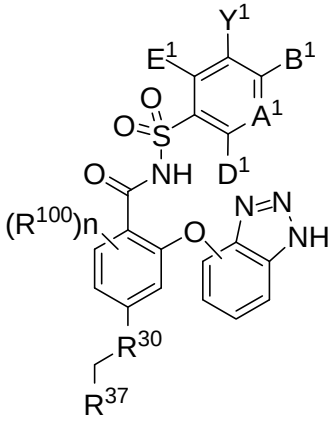
N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-5-metoxi-5-metilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(5-cloro-6-{[1-(1,3-tiazol-2-il)piperidin-4-il]metoxi}piridin-3-il)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(6-{[(cis-4-hidroxi-4-metilciclohexil)metil]amino}-5-nitropiridin-3-il)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]-5-(trifluorometil)piridin-3-il}sulfonil)-2-(1H-indazol-4-iloxi)benzamida ; y therapeutically acceptable salts,
N-(4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzoil]sulfamoil}-2-nitrofenil)-4-cianopiperidin-1-carboxamida; y sus sales, profármacos, sales de profármacos y metabolitos terapéuticamente aceptables.

En otro aspecto, la presente invención provee compuestos de Fórmula (VI)



(VI)

y sus sales farmacéuticamente aceptables, profármacos, sales de profármacos y metabolitos, donde A^1, B^1, D^1, E^1, Y^1, R^{30}, y R^{37} tienen los valores que se describen en la presente para la Fórmula (VI), n es 0, 1, 2, o 3; que describen la cantidad de sustituyentes en R^{26}, y R^{100} tiene los valores descritos para los sustituyentes en R^{26}.

En una forma de realización de la Fórmula (VI), A^1 es N. En otra forma de realización de la Fórmula (VI), A^1 es $C(A^2)$. En otra forma de realización de la Fórmula (VI), A^1 es $C(A^2)$, y A^2 es H.

En una forma de realización de la Fórmula (VI), B^1 es R^1, OR^1, SR^1, SO_2R^1, $NHC(O)R^1$, NHR^1, $N(R^1)_2$, o $C(O)NHR^1$. En otra forma de realización de la Fórmula (VI), B^1 es NHR^1. En otra forma de realización de la Fórmula (VI), B^1 es NHR^1, y A^1 es $C(A^2)$, y A^2 es H. En otra forma de realización de la Fórmula (VI), B^1 es NHR^1, y A^1 es $C(A^2)$ o N, y A^2 es H. En otra forma de realización de la Fórmula (VI), B^1 es OR^1. En otra forma de realización de la Fórmula (VI), B^1 es OR^1, y A^1 es $C(A^2)$, y A^2 es H. En otra forma de realización de la Fórmula (VI), B^1 es OR^1, y A^1 es $C(A^2)$ o N, y A^2 es H.

En una forma de realización de la Fórmula (VI), D^1 y E^1 son H. En otra forma de realización de la Fórmula (VI), B^1 es NHR^1, y A^1 es $C(A^2)$, A^2 es H, y D^1 y E^1 son H. En otra forma de realización de la Fórmula (VI), B^1 es NHR^1, y A^1 es $C(A^2)$ o N, A^2 es H, y D^1 y E^1 son H. En otra forma de realización de la Fórmula (VI), B^1 es OR^1, y A^1 es $C(A^2)$, A^2 es H, y D^1 y E^1 son H. En otra forma de realización de la Fórmula (VI), B^1 es OR^1, y A^1 es $C(A^2)$ o N, A^2 es H, y D^1 y E^1 son H.

En una forma de realización de la Fórmula (VI), Y^1 es H, CN, NO_2, F, Cl, Br, I, CF_3, R^{17}, $NHC(O)R^{17}$, o $C(O)NH_2$. En otra forma de realización de la Fórmula (VI), Y^1 es NO_2. En otra forma de realización de la Fórmula (VI), Y^1 es Cl. En otra forma de realización de la Fórmula (VI), B^1 es NHR^1, y A^1 es $C(A^2)$, A^2 es H, D^1 y E^1 son H, y Y^1 es NO_2. En otra forma de realización de la Fórmula (VI), B^1 es NHR^1, y A^1 es $C(A^2)$ o N, A^2 es H, D^1 y E^1 son H, y Y^1 es NO_2. En otra forma de realización de la Fórmula (VI), B^1 es OR^1, y A^1 es $C(A^2)$, A^2 es H, D^1 y E^1 son H, y Y^1 es Cl. En otra forma de realización de la Fórmula (VI), B^1 es OR^1, y A^1 es $C(A^2)$ o N, A^2 es H, D^1 y E^1 son H, y Y^1 es Cl.

En una forma de realización de la Fórmula (VI), R^1 es R^2, R^3, R^4 o R^5. En otra forma de realización de la Fórmula (VI), R^1 es R^2, y R^2 es fenilo.

En una forma de realización de la Fórmula (VI), R^1 es R^3, y R^3 es heteroarilo. En otra forma de realización de la Fórmula (VI), R^3 es triazolilo.

En una forma de realización de la Fórmula (VI), R^1 es R^4. En otra forma de realización de la Fórmula (VI), R^1 es R^4, y R^4 es cicloalquilo. En otra forma de realización de la Fórmula (VI), R^1 es R^4, y R^4 es ciclohexilo. En otra forma de realización de la Fórmula (VI), R^1 es R^4, y R^4 es heterocicloalquilo. En otra forma de realización de la Fórmula (VI), R^1 es R^4, y R^4 es 8-azabiciclo[3.2.1]octano, azetidinilo, piperidinilo, piperazinilo, pirrolidinilo, morfolinilo, tetrahidropiranilo, o tetrahidrotiofenilo. En otra forma de realización de la Fórmula (VI), R^1 es R^4, y R^4 es heterocicloalquenilo. En otra forma de realización de la Fórmula (VI), R^1 es R^4, y R^4 es tetrahidropiridazinilo.

En una forma de realización de la Fórmula (VI), R^1 es R^5. En otra forma de realización de la Fórmula (VI), R^1 es R^5 y R^5 es alquilo o alquinilo. En otra forma de realización de la Fórmula (VI), R^1 es R^5 y R^5 es alquilo que no está sustituido. En otra forma de realización de la Fórmula (VI), R^1 es R^5 y R^5 es alquilo que está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre R^6, R^7, OR^7, SR^7, SO_2R^7, $N(R^7)_2$, OH, CN, CF_3, F, Cl, Br o I . En otra forma de realización de la Fórmula (VI), R^1 es R^5 y R^5 es alquilo que está sustituido con R^7.

En una forma de realización de la Fórmula (VI), R^7 es R^8, R^9, R^{10} o R^{11}. En otra forma de realización de la Fórmula (VI), R^7 es R^8, y R^8 es fenilo que no está fusionado o está fusionado con R^{8A}, y R^{8A} es heterocicloalcano. En otra forma de realización de la Fórmula (VI), R^7 es R^8, y R^8 es fenilo que no está fusionado. En otra forma de realización de la Fórmula (VI), R^7 es R^9, y R^9 es heteroarilo. En otra forma de realización de la Fórmula (VI), R^7 es R^9, y R^9 es furanilo, imidazolilo, isotiazolilo, isoxazolilo, 1,2,3-oxadiazoilo, 1,2,5-oxadiazolilo, oxazolilo, pirazinilo, pirazolilo, piridazinilo, piridinilo, pirimidinilo, pirrolilo, tetrazolilo, tiazolilo, tiofenilo, triazinil o 1,2,3-triazolilo. En otra forma de realización de la Fórmula (VI), R^7 es R^9, y R^9 es piridinilo, tiazolilo, imidazoilo, y 1,2,3-triazolilo. En otra forma de realización de la Fórmula (VI), R^7 es R^{10}, y R^{10} es C_3-C_{10}-cicloalquilo. En otra forma de realización de la Fórmula (VI), R^7 es R^{10}, y R^{10} es C_3, C_6, C_7 o C_{10}-cicloalquilo. En otra forma de realización de la Fórmula (VI), R^7 es R^{10}, y R^{10} es ciclopropilo, ciclohexilo, biciclo[2.2.1]heptanilo, o adamantanilo. En otra forma de realización de la Fórmula (VI), R^7 es R^{10}, y R^{10} es morfolinilo, piperazinilo, piperidinilo, tetrahidro-2H-piranilo, 1,2-dihidropiridinilo, piranilo, piridin-1(H)-ilo, pirrolidinilo, oxetanilo, tiomorfolinilo, imidazolidinilo, tetrahidrotiofenilo, dioxolanilo, tetrahidrotiopiranilo, dioxanilo, 5,6,7,8-tetrahidroimidazo[1,2-a]piridinilo, o tetrahidrofuranilo. En otra forma de realización de la Fórmula (VI), R^7 es R^{10}, y R^{10} es morfolinilo, piperazinilo, piperidinilo, tetrahidro-2H-piranilo, 1,2-dihidropiridinilo, pirrolidinilo, oxetanilo, tiomorfolinilo, imidazolidinilo, tetrahidrotiofenilo, dioxolanilo, tetrahidrotiopiranilo, dioxanilo, 5,6,7,8-tetrahidroimidazo[1,2-a]piridinilo, o tetrahidrofuranilo. En otra forma de realización de la Fórmula (VI), R^7 es R^{11}, y R^{11} es alquilo que no está sustituido o está sustituido. En otra forma de realización de la Fórmula (VI), R^7 es R^{11}, y R^{11} es alquilo que no está sustituido. En otra forma de realización de la Fórmula (VI), R^7 es R^{11}, y R^{11} es alquilo que está sustituido. En otra forma de realización de la Fórmula (VI), R^7 es R^{11}, y R^{11} es alquilo que está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre OR^{12}, F, Cl, Br o I . En otra forma de realización de la Fórmula (VI), R^7 es R^{11}, R^{11} es alquilo que está sustituido con OR^{12}, R^{12} es R^{16}, y R^{16} es alquilo.

En una forma de realización de la Fórmula (VI), R^{17} es R^{19} o R^{21}. En otra forma de realización de la Fórmula (VI), R^{17} es R^{19}, y R^{19} es heteroarilo. En otra forma de realización de la Fórmula (VI), R^{17} es R^{19}, y R^{19} es tiazolilo. En otra forma de realización de la Fórmula (VI), R^{17} es R^{21}, y R^{21} es alquinilo. En otra forma de realización de la Fórmula (VI), R^{17} es R^{21}, y R^{21} es etinilo.

Aún otra forma de realización se refiere a compuestos que tienen la Fórmula (V) que son
2-(1H-benzotriazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4-fluorotetrahidro-2H-piran-4-il)metil]amino}-3-nitrofenil)sulfonil]benzamida;
2-(1H-benzotriazol-4-iloxi)-N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida;
2-(1H-benzotriazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]-3-nitrofenil}sulfonil)benzamida;
2-(1H-benzotriazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)benzamida;
2-(1H-benzotriazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({[(2S)-4-ciclopropilmorfolin-2-il]metil}amino)-3-nitrofenil]sulfonil}benzamida;
2-(1H-benzotriazol-4-iloxi)-N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida y ; sus sales terapéuticamente aceptables, sales de prodrogas y metabolitos.

Composiciones farmacéuticas, Terapias de combinación, Métodos de Tratamiento, y Administración

Otra forma de realización comprende composiciones farmacéuticas que comprenden un compuesto con Fórmula (I) y un excipiente.

Aún otra realización comprende métodos para tratar cáncer en un mamífero, que comprende administrarle al mismo una cantidad terapéuticamente aceptable de un compuesto de la fórmula (I).

Aún otra forma de realización comprende métodos para tratar una enfermedad autoinmune en un mamífero, que comprende administrarle al mismo una cantidad terapéuticamente aceptable de un compuesto con Fórmula (I).

Aún otra forma de realización se refiere a composiciones para tratar enfermedades durante las cuales se expresan las proteínas anti-apoptóticas Bcl-2, donde dichas

composiciones comprenden un excipiente y una cantidad terapéuticamente efectiva del compuesto de Fórmula (I).

Aún otra forma de realización se refiere a métodos para tratar una enfermedad en un paciente durante la cual se expresan las proteínas anti-apoptóticas Bcl-2, donde dichos métodos comprenden administrar al paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula (I).

Aún otra forma de realización se refiere a composiciones para tratar cáncer de vejiga, cáncer de cerebro, cáncer de mamas, cáncer de médula ósea, cáncer cervical, leucemia linfocítica crónica, cáncer colorrectal, cáncer de esófago, cáncer hepatocelular, leucemia linfoblástica, linfoma folicular, malignidades linfoides originadas en células T o células B, melanoma, leucemia mielógena, mieloma, cáncer oral, cáncer de ovarios, cáncer de pulmón de células no pequeñas, cáncer de próstata, cáncer de pulmón o cáncer de bazo de células pequeñas, donde dichas composiciones comprenden un excipiente y una cantidad terapéuticamente efectiva del compuesto de Fórmula (I).

Aún otra forma de realización se refiere a métodos para tratar cáncer de vejiga, cáncer de cerebro, cáncer de mamas, cáncer de médula ósea, cáncer cervical, leucemia linfocítica crónica, cáncer colorrectal, cáncer de esófago, cáncer hepatocelular, leucemia linfoblástica, linfoma folicular, malignidades linfoides originadas en células T o células B, melanoma, leucemia mielógena, mieloma, cáncer oral, cáncer de ovarios, cáncer de pulmón de células no pequeñas, cáncer de próstata, cáncer de pulmón o cáncer de bazo de células pequeñas en un paciente, donde dichos métodos comprenden administrar al paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula (I).

Aún otra forma de realización se refiere a composiciones para tratar enfermedades durante las cuales se expresan proteínas anti-apoptóticas Bcl-2, donde dichas composiciones comprenden un excipiente y una cantidad terapéuticamente efectiva del compuesto de Fórmula (I) y una cantidad terapéuticamente efectiva de un agente terapéutico adicional o más de un agente terapéutico adicional.

Aún otra forma de realización se refiere a métodos para tratar una enfermedad en un paciente durante la cual se expresan proteínas anti-apoptóticas Bcl-2, donde dichos métodos comprenden administrar al paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula (I) y una cantidad terapéuticamente efectiva de un agente terapéutico adicional o más de un agente terapéutico adicional.

Aún otra forma de realización se refiere a composiciones para tratar cáncer de vejiga, cáncer de cerebro, cáncer de mamas, cáncer de médula ósea, cáncer cervical, leucemia

linfocítica crónica, cáncer colorrectal, cáncer de esófago, cáncer hepatocelular, leucemia linfoblástica, linfoma folicular, malignidades linfoides originadas en células T o células B, melanoma, leucemia mielógena, mieloma, cáncer oral, cáncer de ovarios, cáncer de pulmón de células no pequeñas, leucemia linfocítica crónica, mieloma, cáncer de próstata, cáncer de pulmón o cáncer de bazo de células pequeñas, donde dichas composiciones comprenden un excipiente y una cantidad terapéuticamente efectiva del compuesto de Fórmula (I) y una cantidad terapéuticamente efectiva de un agente terapéutico adicional o más de un agente terapéutico adicional.

Aún otra forma de realización se refiere a métodos para tratar cáncer de vejiga, cáncer de cerebro, cáncer de mamas, cáncer de médula ósea, cáncer cervical, leucemia linfocítica crónica, cáncer colorrectal, cáncer de esófago, cáncer hepatocelular, leucemia linfoblástica, linfoma folicular, malignidades linfoides originadas en células T o células B, melanoma, leucemia mielógena, mieloma, cáncer oral, cáncer de ovarios, cáncer de pulmón de células no pequeñas, leucemia linfocítica crónica, mieloma, cáncer de próstata, cáncer de pulmón o cáncer de bazo de células pequeñas en un paciente, donde dichos métodos comprenden administrar al paciente una cantidad terapéuticamente efectiva del compuesto de Fórmula (I) y una cantidad terapéuticamente efectiva de un agente terapéutico adicional o más de un agente terapéutico adicional.

Los metabolitos de los compuestos con la Fórmula I, producidos por procesos metabólicos in vitro o in vivo, también pueden ser útiles para tratar enfermedades asociadas con la proteína anti-apoptótica Bcl-2.

Ciertos compuestos precursores que se pueden metabolizar in vitro o in vivo para formar compuestos con la Fórmula I también pueden ser útiles para tratar enfermedades asociadas con la expresión de la proteína anti-apoptótica Bcl-2.

Los compuestos de la Fórmula I pueden existir como sales de adición ácida, sales de adición básica o zwiteriones. Las sales de los compuestos se preparan durante la aislación o después de la purificación de los compuestos. Las sales de adición ácida de los compuestos son aquellas derivadas de la reacción de los compuestos con un ácido. Por ejemplo, las sales acetato, adipato, alginato, bicarbonato, citrato, aspartato, benzoato, bencenosulfonato, bisulfato, butirato, alcanforato, alcanforsufonato, digluconato, formiato, fumarato, glicerofosfato, glutamato, hemisulfato, heptanoato, hexanoato, clorhidrato, bromhidrato, yodhidrato, lactobionato, lactato, maleato, mesitilenosulfonato, metanosulfonato, naftilenosulfonato, nicotinato, oxalato, pamoato, pectinato, persulfato, fosfato, picrato, propionato, succinato, tartrato, tiocianato, tricloroacetato, trifluoroacetato, para-

toluensulfonato, y undecanoato de los compuestos y sus profármacos se consideran abarcados por la presente invención. Las sales de adición básica de los compuestos son aquellas que derivan de la reacción de los compuestos con los hidróxidos, carbonatos o bicarbonatos de cationes tales como litio, sodio, potasio, calcio, y magnesio.

Los compuestos de la Fórmula I se pueden administrar, por ejemplo, por vía bucal, oftálmica, oral, osmótica, parenteral (intramuscular, intraperitoneal, intraesternal, intravenosa, subcutánea), rectal, tópica, transdérmica o vaginal.

Las cantidades terapéuticamente efectivas de los compuestos con la Fórmula I dependen de quien reciba el tratamiento, del trastorno que esté siendo tratado y de su gravedad, de la composición que contiene el compuesto, del momento de la administración, de la ruta de administración, de la duración de tratamiento, de la potencia del compuesto, de su velocidad de eliminación y de si se está co-administrando otra fármaco o no. La cantidad de un compuesto de la invención de fórmula I usada para conformarla como una composición que será administrada diariamente a un paciente en una sola dosis o en dosis divididas comprende entre aproximadamente 0,03 y aproximadamente 200 mg/kg peso corporal. Las composiciones de dosis única contienen estas cantidades o una combinación de submúltiplos de las mismas.

Los compuestos de la Fórmula I se pueden administrar con o sin un excipiente. Los excipientes incluyen, por ejemplo, materiales encapsulantes o aditivos tales como aceleradores de la absorción, antioxidantes, aglutinantes, soluciones amortiguadoras, agentes de recubrimiento, agentes colorantes, disolventes, agentes desintegradores, emulsionantes, diluyentes, rellenos, agentes saborizantes, humectantes, lubricantes, perfumes, conservantes, propelentes, agentes de liberación, agentes esterilizantes, edulcorantes, solubilizantes, agentes humectantes y mezclas de los mismos.

Los excipientes para la preparación de composiciones que comprenden un compuesto con Fórmula I para administrar en forma oral en formas de dosificación sólida incluyen, por ejemplo, ágar agar, ácido algínico, hidróxido de aluminio, alcohol bencílico, benzoato de bencilo, 1,3-butilenglicol, Carbomers, aceite de castor, celulosa, acetato de celulosa, manteca de cacao, almidón de maíz, aceite de maíz, aceite de algodón, crospovidona, diglicéridos, etanol, etilcelulosa, laureato de etilo, oleato de etilo, ésteres de ácido graso, gelatina, aceite de germen, glucosa, glicerol, aceite de cacahuete, hidroxipropilmetilcelulosa, isopropanol, solución salina isotónica, lactosa, hidróxido de magnesio, estearato de magnesio, maltosa, manitol, monoglicéridos, aceite de oliva, aceite de maní, sales fosfato de potasio, almidón de papa (patata), povidona, propilenglicol, solución de Ringer, aceite de sasafrás, aceite de

sésamo, carboximetilcelulosa sódica, sales fosfato de sodio, lauril sulfato de sodio, sorbitol sódico, aceite de soja, ácidos esteáricos, fumarato de estearilo, sacarosa, tensioactivos, talco, goma tragacanto, alcohol tetrahidrofurfurílico, triglicéridos, agua, y mezclas de los mismos. Los excipientes para la preparación de composiciones que comprenden un compuesto de la presente invención con la Fórmula I para administrar por vía oftálmica o en forma oral en formas de dosificación líquidas incluyen, por ejemplo, 1,3-butilenglicol, aceite de castor, aceite de maíz, aceite de algodón, etanol, ésteres de ácido graso de sorbitan, aceite de germen, aceite de cacahuete, glicerol, isopropanol, aceite de oliva, polietilenglicoles, propilenglicol, aceite de sésamo, agua y mezclas de los mismos. Los excipientes para la preparación de composiciones que comprenden un compuesto de la invención de la fórmula I que serán administradas osmóticamente incluyen, por ejemplo, clorofluoro-hidrocarburos, etanol, agua y mezclas de los mismos. Los excipientes para la preparación de composiciones que comprenden un compuesto de la invención de la fórmula I que serán administradas por vía parenteral incluyen, por ejemplo, 1,3-butanodiol, aceite de castor, aceite de maíz, aceite de semillas de algodón, dextrosa, aceite de germen, aceite de cacahuete, liposomas, ácido oleico, aceite de oliva, aceite de maní, solución de Ringer, aceite de alazor, aceite de sésamo, aceite de soja, solución de cloruro de sodio grado U.S.P. o isotónica, agua y mezclas de los mismos. Los excipientes para la preparación de composiciones que comprenden un compuesto de la invención de la fórmula I que serán administradas por vía rectal o vaginal incluyen, por ejemplo, manteca de cacao, polietilenglicol, cera y mezclas de los mismos.

Se espera que los compuestos con la Fórmula (I) sean útiles cuando se los utiliza con agentes alquilantes, inhibidores de angiogénesis, anticuerpos, antimetabolitos, antimitóticos, antiproliferativos, antivirales, inhibidores de aurora quinasa, otros inhibidores promotores de la apoptosis (por ejemplo, Bcl-X_L, Bcl-w y Bfl-1), activadores de la vía metabólica de los receptores de muerte (vía extrínseca), inhibidores de Bcr-Abl quinasa, anticuerpos de tipo BiTE (ligador biespecífico de células T), conjugados anticuerpo-fármaco, modificadores de la respuesta biológica, inhibidores de quinasa dependiente de ciclina, inhibidores del ciclo celular, inhibidores de ciclooxigenasa-2, DVDs, inhibidores del receptor del homólogo del oncogen viral de leucemia (ErbB2), inhibidores del factor de crecimiento, inhibidores de la proteína de choque térmico (HSP)-90, inhibidores de histona desacetilasa (HDAC), terapias hormonales, inmunológicas, inhibidores de inhibidores de las proteínas de apoptosis (IAPs), antibióticos intercalantes, inhibidores de quinasa, inhibidores de quinesina, inhibidores de Jak2, inhibidores del objetivo de la rapamicina en mamíferos, microARNs, inhibidores de quinasas reguladas por señal extracelular y activadas por mitógeno, proteínas de unión

multivalente, fármacos antiinflamatorio no esteroides (NSAIDs), inhibidores de poli ADP (adenosina difosfato)-ribosa polimerasa (PARP), quimioterapéuticos de platino, inhibidores de quinasa de tipo Polo (Plk), inhibidores de fosfoinositida-3 quinasa (PI3K), inhibidores de proteosoma, análogos de purina, análogos de pirimidina, inhibidores de receptores tirosina quinasa, alcaloides vegetales etinoides/deltoides, ácidos ribonucleicos inhibidores pequeños (siARNs), inhibidores de topoisomerasa, inhibidores ubiquitina ligasa, etcétera, y en combinación con uno o más de dichos agentes.

Los anticuerpos BiTE son anticuerpos biespecíficos que dirigen a las células T para que ataquen a las células cancerosas uniendo simultáneamente las dos células. Luego, las células T atacan a la célula cancerosa objetivo. Los ejemplos de anticuerpos BiTE incluyen adecatumumab (Micromet MT201), blinatumomab (Micromet MT103) y semejantes. Sin ser limitados por la teoría, uno de los mecanismos por el cual las células T suscitan la apoptosis de la célula cancerosa objetivo es por la exocitosis de componentes granulares citolíticos, que incluyen perforina y granzima B. Con respecto a esto, se ha mostrado que Bcl-2 atenúa la inducción de la apoptosis tanto por perforina como por granzima B. Dichos datos sugieren que la inhibición de Bcl-2 puede intensificar los efectos citotóxicos que suscitan las células T cuando se dirigen hacia células cancerosas (V.R. Sutton, D.L. Vaux y J.A. Trapani, *J. de Immunology* **1997**, 158 (12), 5783).

Los siARNs son moléculas con bases de ARN endógenas o nucleótidos modificados químicamente. Las modificaciones no anulan la actividad celular, sino que impartirán una mayor estabilidad y/o una mayor potencia celular. Los ejemplos de modificaciones químicas incluyen grupos de fosforotioato, 2'-desoxinucleótidos, ribonucleótidos que contienen 2'-OCH_3, 2'-F-ribonucleótidos, 2'-metoxietil-ribonucleótidos o una combinación de los mismos. El siARN puede variar en cuanto a longitudes (10-200 bps) y estructuras (horquillas, cadenas simples/dobles, protuberancias, nicks/huecos, coincidencias erróneas) y se puede procesar en la célula para proporcionar un silenciamiento de genes activos. Un siARN de cadena doble (dsARN) puede tener la misma cantidad de nucleótidos en cada cadena (extremos romos) o extremos asimétricos (proyecciones). La proyección de 1-2 nucleótidos puede estar presente sobre la cadena orientada en el sentido del marco de lectura y/o sobre la cadena antisentido, así como por los extremos 5' y/o 3' de una cadena dada. Por ejemplo, se ha mostrado que los siARNs dirigidos hacia Mcl-1 intensifican la actividad de ABT-263, (es decir, N-(4-(4-((2-(4-clorofenil)-5,5-dimetil-1-ciclohex-1-en-1-il)metil)piperazin-1-il)benzoil)-4-(((1R)-3-(morfolin-4-il)-1-((fenilsulfanil)metil)propil) amino)-3-((trifluorometil)sulfonil)bencenosulfonamida) o ABT-737 (es decir, N-(4-(4-((4'-cloro(1,1'-

bifenil)-2-il)metil)piperazin-1-il)benzoil)-4-(((1R)-3-(dimetilamino)-1-((fenilsulfanil)metil)propil)amino)-3-nitrobencenosulfonamida) en múltiples líneas celulares de tumor (Tse et. al, *Cancer Research* **2008**, 68(9), 3421 y las referencias que figuran allí).

Las proteínas de unión multivalente son proteínas de unión que comprenden dos o más sitios de unión a antígeno. Las proteínas de unión multivalente se diseñan para que tengan tres o más sitios de unión al antígeno y en general no son anticuerpos de origen natural. El término "proteína de unión multiespecífica" significa una proteína de unión con la capacidad de unirse a dos o más blancos relacionados o no relacionados. Las proteínas de unión con dominio variable doble (DVD) son proteínas de unión tetravalentes o multivalentes que comprenden dos o más sitios de unión a antígenos. Dichas DVD pueden ser monoespecíficas, (es decir, con la capacidad de unirse a un antígeno), o multiespecíficas, (es decir, con la capacidad de unirse a dos o más antígenos). Las proteínas de unión DVD que comprenden dos polipéptidos DVD de cadena pesada y dos polipéptidos DVD de cadena liviana se conocen como una Ig DVD. Cada mitad de una Ig DVD comprende un polipéptido DVD de cadena pesada, y un polipéptido DVD de cadena liviana, y dos sitios de unión al antígeno. Cada sitio de unión comprende un dominio variable de la cadena pesada y un dominio variable de la cadena liviana, con la participación de un total de 6 CDR en la unión al antígeno por sitio de unión al antígeno. Los DVD multiespecíficos incluyen Proteínas de unión DVD que se unen a DLL4 y VEGF, o C-met y EFGR o ErbB3 y EGFR.

Los agentes alquilantes incluyen altretamina, AMD-473, AP-5280, apazicuona, bendamustina, brostalicina, busulfano, carbocuona, carmustina (BCNU), clorambucilo, CLORETAZINE™ (laromustina, VNP 40101M), ciclofosfamida, decarbacina, estramustina, fotemustina, glufosfamida, ifosfamida, KW-2170, lomustina (CCNU), mafosfamida, melfalano, mitobronitol, mitolactol, nimustina, N-óxido de mostaza nitrogenada, ranimustina, temozolomida, tiotepa, TREANDA® (bendamustina), treosulfano, rofosfamida y semejantes.

Entre los inhibidores de angiogénesis se incluyen inhibidores del receptor de tirosina quinasa específico de endotelio (Tie-2), inhibidores del receptor del factor de crecimiento epidérmico (EGFR), inhibidores del receptor del factor de crecimiento insulínico-2 (IGFR-2), inhibidores de metalproteinasa de matriz-2 (MMP-2), inhibidores de metalproteinasa de matriz-9 (MMP-9), inhibidores del receptor del factor de crecimiento derivado de plaquetas (PDGFR), análogos de trombospondina, inhibidores del receptor tirosina quinasa del factor de crecimiento de endotelio vascular (VEGFR) y similares.

Los antimetabolitos incluyen ALIMTA® (metrexed disódico, LY231514, MTA), 5-azacitidina, XELODA® (capecitabina), carmofur, LEUSTAT® (cladribina), clofarabina,

citarabina, ocfosfato de citarabina, arabinósido de citosina, decitabina, deferoxamina, doxifluridina, eflornitina, EICAR, (5-etinil-1-β -D-ribofuranosilimidazol-4-carboxamida), enocitabina, etinilcitidina, fludarabina, 5-fluorouracilo sólo o en combinación con leucovorina, GEMZAR® (gemcitabina), hidroxiurea, ALQUERAN® (melfalán), mercaptopurina, 6-mercaptopurina ribósido, metotrexato, ácido micofenólico, nelarabina, nolatrexed, ocfosfato, pelitrexol, pentostatina, raltitrexed, Ribavirina, triapina, trimetrexato, S-1, tiazofurina, tegafur, TS-1, vidarabina, UFT y semejantes.

Los antivirales incluyen ritonavir, hidroxicloroquina y semejantes.

Los inhibidores de aurora quinasa incluyen ABT-348, AZD-1152, MLN-8054, VX-680, Inhibidores específicos de Aurora quinasa A, Inhibidores específicos de Aurora quinasa B y Inhibidores de pan-Aurora quinasa y semejantes.

Los inhibidores de proteínas Bcl-2 incluyen AT-101 ((-)gosipol), GENASENSE® (G3139 u oblimersen (oligonucleótido antisentido dirigido a Bcl-2)), IPI-194, IPI-565, N-(4-(4-((4'-cloro(1,1'-bifenil)-2-il)metil)piperazin-1-il)benzoil)-4-(((1R)-3-(dimetilamino)-1-((fenilsulfanil)metil)propil)amino)-3-nitrobencenosulfonamida) (ABT-737), N-(4-(4-((2-(4-clorofenil)-5,5-dimetil-1-ciclohex-1-en-1-il)metil)piperazin-1-il)benzoil)-4-(((1R)-3-(morfolin-4-il)-1-((fenilsulfanil)metil)propil)amino)-3-((trifluorometil)sulfonil) bencenosulfonamida (ABT-263), GX-070 (obatoclax) y semejantes.

Los inhibidores de la Bcr-Abl quinasa incluyen DASATINIB® (BMS-354825), GLEEVEC® (imatinib) y semejantes.

Entre los inhibidores de CDK se incluyen AZD-5438, BMI-1040, BMS-032, BMS-387, CVT-2584, flavopiridol, GPC-286199, MCS-5A, PD0332991, PHA-690509, seliciclib (CIC-202, R-roscovitina), ZK-304709 y similares.

Entre los inhibidores de la COX-2 se incluyen ABT-963, ARCOXIA® (etoricoxib), BEXTRA® (valdecoxib), BMS347070, CELEBREX® (celecoxib), COX-189 (lumiracoxib), CT-3, DERAMAXX® (deracoxib), JTE-522, 4-metil-2-(3,4-dimetilfenil)-1-(4-sulfamoilfenil-1H-pirrol), MK--663 (etoricoxib), NS-398, parecoxib, RS-57067, SC-58125, SD-8381, SVT-2016, S-2474, T-614, VIOXX® (rofecoxib) y similares.

Los inhibidores de EGFR incluyen ABX-EGF, anti-EGFR inmunoliposomas, vacuna EGF, EMD-7200, ERBITUX® (cetuximab), HR3, anticuerpos IgA, IRESSA® (gefitinib), TARCEVA® (erlotinib o OSI-774), TP-38, proteína de fusión EGFR, TYKERB® (lapatinib) y similares.

Entre los inhibidores de ErbB2 se incluyen CP-724-714, CI-1033 (canertinib), Herceptin® (trastuzumab), TYKERB® (lapatinib), OMNITARG® (2C4, petuzumab), TAK-

165, GW-572016 (ionafarnib), GW-282974, EKB-569, PI-166, dHER2 (vacuna HER2), APC-8024 (vacuna HER-2), anticuerpo biespecífico anti-HER/2neu, B7.her2IgG3, anticuerpos biespecíficos trifuncionales AS HER2, anticuerpo monoclonal AR-209, anticuerpo monoclonal 2B-1 y similares.

Los inhibidores de histona desacetilasa incluyen depsipéptido, LAQ-824, MS-275, trapoxina, ácido hidroxámico suberoilanilida (SAHA), TSA, ácido valproico y semejantes.

Los inhibidores de HSP-90 incluyen 17-AAG-nab, 17-AAG, CNF-101, CNF-1010, CNF-2024, 17-DMAG, geldanamicina, IPI-504, KOS-953, MYCOGRAB®, (anticuerpo recombinante humano para HSP-90), NCS-683664, PU24FCl, PU-3, radicicol, SNX-2112, STA-9090 VER49009 y semejantes.

Los inhibidores de inhibidores de las proteínas de apoptosis incluyen HGS1029, GDC-0145, GDC-0152, LCL-161, LBW-242 y semejantes.

Los conjugados anticuerpo-fármaco incluyen anti-CD22-MC-MMAF, anti-CD22-MC-MMAE, anti-CD22-MCC-DM1, CR-011-vcMMAE, PSMA-ADC, MEDI-547, SGN-19Am SGN-35, SGN-75 y semejantes.

Los activadores de la vía metabólica de los receptores de muerte (vía extrínseca) incluyen TRAIL, anticuerpos u otros agentes dirigidos hacia TRAIL o receptores de muerte (por ejemplo, DR4 y DR5) tales como Apomab, conatumumab, ETR2-ST01, GDC0145, (lexatumumab), HGS-1029, LBY-135, PRO-1762 y trastuzumab.

Los inhibidores de quinesina incluyen inhibidores de Eg5 tales como AZD4877, ARRY-520; inhibidores de CENPE tales como GSK923295A y semejantes.

Los inhibidores de JAK-2 incluyen CEP-701 (lesaurtinib), XL019 y INCB018424 y semejantes.

Entre los inhibidores de MEK se incluyen ARRY-142886, ARRY-438162 PD-325901, PD-98059 y similares.

Los inhibidores de mTOR incluyen AP-23573, CCI-779, everolimus, RAD-001, rapamicina, temsirolimus, inhibidores de TORC1/TORC2 que compiten por el ATP, que incluyen PI-103, PP242, PP30, Torin 1 y semejantes.

Los fármacos antiinflamatorias no esteroides incluyen AMIGESIC® (salsalato), DOLOBID® (diflunisal), MOTRIN® (ibuprofeno), ORUDIS® (ketoprofeno), RELAFEN® (nabumetona), FELDENE® (piroxicam) crema ibuprofeno, ALEVE® y NAPROSYN® (naproxeno), VOLTAREN® (diclofenac), INDOCIN® (indometacina), CLINORIL® (sulindac), TOLECTIN® (tolmetin), LODINE® (etodolac), TORADOL® (ketorolac), DAYPRO® (oxaprozina) y semejantes.

Los inhibidores de PDGFR incluyen C-451, CP-673, CP-868596 y semejantes.

Los quimioterapéuticos de platino incluyen cisplatino, ELOXATIN® (oxaliplatino) eptaplatino, lobaplatino, nedaplatino, PARAPLATIN® (carboplatino), satraplatino, picoplatino y semejantes.

Los inhibidores de quinasa del tipo polo incluyen BI-2536 y semejantes.

Los inhibidores de fosfoinositida-3 quinasa (PI3K) incluyen wortmanina, LY294002, XL-147, CAL-120, ONC-21, AEZS-127, ETP-45658, PX-866, GDC-0941, BGT226, BEZ235, XL765 y semejantes.

Entre los análogos de trombospondina se incluyen ABT-510, ABT-567, ABT-898, TSP-1 y similares.

Los inhibidores de VEGFR incluyen AVASTIN® (bevacizumab), ABT-869, AEE-788, ANGIOZIMA™ (una ribozima que inhibe la angiogénesis (Ribozime Pharmaceuticals (Boulder, CO.) y Chiron, (Emeryville, CA)), axitinib (AG-13736), AZD-2171, CP-547,632, IM-862, MACUGEN (pegaptamib), NEXAVAR® (sorafenib, BAY43-9006), pazopanib (GW-786034), vatalanib (PTK-787, ZK-222584), SUTENT® (sunitinib, SU-11248), trampa de VEGF, ZACTIMA™ (vandetanib, ZD-6474), GA101, ofatumumab, ABT-806 (mAb-806), anticuerpos específicos de ErbB3 , BSG2 anticuerpos específicos de BSG2 , anticuerpos específicos de DLL4 y anticuerpos específicos, de C-met y semejantes.

Los antibióticos incluyen antibióticos intercalantes aclarubicina, actinomicina D, amrubicina, anamicina, adriamicina, BLENOXANE® (bleomicina), daunorubicina, CAELYX® o MYOCET® (doxorubicina liposómica), elsamitrucina, epirbucina, glarbuicina, ZAVEDOS® (idarubicina), mitomicina C, nemorubicina, neocarzinostatina, peplomicina, pirarubicina, rebecamicina, stimalamer, estreptozocina, VALSTAR® (valrubicina), zinostatina y semejantes.

Entre los inhibidores de topoisomerasa se incluyen aclarubicina, 9-aminocamptotecina, amonafida, amsacrina, becatecarina, belotecan, BN-80915, CAMPTOSAR® (clorhidrato de irinotecan), camptotecina, CARDIOXANE® (dexrazoxina), diflomotecan, edotecarina, ELLENCE® o PHARMORUBICIN® (epirubicina), etopósido, exatecan, 10-hidroxicamptotecina, gimatecan, lurtotecan, mitoxantrona, oratecina, pirarbucin, pixantrona, rubitecan, sobuzoxan, SN-38, taflupósido, topotecan y similares.

Los anticuerpos incluyen AVASTIN® (bevacizumab), anticuerpos específicos para CD40, chTNT-1/B, denosumab, ERBITUX® (cetuximab), HUMAX-CD4® (zanolimumab),

anticuerpos específicos para IGF1R, lintuzumab, PANOREX® (edrecolomab), RENCAREX® (WX G250), RITUXAN® (rituximab), ticilimumab, trastuzimab y semejantes.

Las terapias hormonales incluyen ARIMIDEX® (anastrozol), AROMASIN® (exemestano), arzoxifeno, CASODEX® (bicalutamida), CETROTIDE® (cetrorelix), degarelix, deslorelina, DESOPAN® (trilostano), dexametasona, DROGENIL®, (flutamida), EVISTA® (raloxifeno), AFEMA™ (fadrozol), FARESTON® (toremifeno), FASLODEX® (fulvestranto),FEMARA®, (letrozol), formestano, glucocorticoides, HECTOROL® o RENAGEL® (doxercalciferol), lasofoxifeno, acetato de leuprolida, MEGACE® (megesterol), MIFEPREX® (mifepristona), NILANDRON™ (nilutamida), NOLVADEX® (citrato de tamoxifeno), PLENAXIS™ (abarelix), predisona, PROPECIA® (finasterida), rilostano, SUPREFACT® (buserelina), TRELSTAR® (hormona de liberación de la hormona luteinizante (LHRH)), VANTAS® (implante de histrelina), VETORYL®, (trilostano o modrastano), ZOLADEX® (fosrelina, goserelina) y semejantes.

Los deltoides y retinoides incluyen seocalcitol (EB1089, CB1093), lexacalcitrol (KH1060), fenretinida, PANRETIN® (alitretinoina), ATRAGEN® (tretinoína liposómica), TARGRETIN® (bexaroteno), LGD-1550 y semejantes.

Los inhibidores de PARP incluyen ABT-888 (veliparib), olaparib, KU-59436, AZD-2281, AG-014699, BSI-201, BGP-15, INO-1001, ONO-2231 y semejantes.

Los alcaloides vegetales incluyen, pero en un sentido no limitativo, vincristina, vinblastina, vindesina, vinorelbina y semejantes.

Entre los inhibidores de proteosoma se incluyen VELCADE® (bortezomib), MG132, NPI-0052, PR-171 y similares.

Los ejemplos de sustancias inmunológicas incluyen interferones y otros agentes mejoradores del sistema inmune. Los interferones incluyen interferón alfa, interferón alfa-2a, interferón alfa-2b, interferón beta, interferón gamma-1a, ACTIMMUNE® (interferón gamma-1b) o interferón gamma-n1, combinaciones de los mismos y semejantes. Otros agentes incluyen ALFAFERONE®, (IFN-α), BAM-002 (glutatión oxidado), BEROMUN® (tasonermina), BEXXAR® (tositumomab), CAMPATH® (alemtuzumab), CTLA4 (antígeno de linfocitos citotóxico 4), decarbazina, denileuquina, epratuzumab, GRANOCYTE® (lenograstim), lentinan, alpha interferón de leucocitos, imiquimod, MDX-010 (anti-CTLA-4), vacuna contra melanoma, mitumomab, molgramostim, MILOTARG™ (gemtuzumab ozogamicina), NEUPOGEN® (filgrastim), OncoVAC-CL, OVAREX® (oregovomab), pemtumomab (Y-muHMFG1), PROVENGE® (sipuleucel-T), sargaramostima, sizofilán, teceleuquina, THERACYS® (bacilo de Calmette-Guerin), ubenimex, VIRULIZIN®

(inmunoterapéutico, Lorus Pharmaceuticals), Z-100 (sustancia específica de maruyama (SSM)), WF-10 (tetraclorodecaóxido (TCDO)), PROLEUKIN® (aldesleuquina), ZADAXIN® (timalfasin), ZENAPAX® (daclizumab), ZEVALIN® (90Y-Ibritumomab tiuxetano) y semejantes.

Los modificadores de la respuesta biológica son agentes que modifican los mecanismos de defensa de organismos vivientes o respuestas biológicas, tales como sobrevida, crecimiento o diferenciación de células de tejidos para dirigirlas hacia una actividad antitumoral e incluyen crestina, lentinano, sizofirano, picibanilo PF-3512676 (CpG-8954), ubenimex y similares.

Entre los análogos de pirimidina se incluyen citarabina (ara C o Arabinósido C), arabinósido de citosina, doxifluridina, FLUDARA® (fludarabina), 5-FU (5-fluorouracilo), floxuridina, GEMZAR® (gemcitabina), TOMUDEX® (raltitrexed), TROXATYL™ (triacetiluridina troxacitabina) y similares.

Los análogos de purina incluyen LANVIS® (tioguanina) y PURI-NETHOL® (mercaptopurina).

Los agentes antimitóticos incluyen batabulina, epotilona D (KOS-862), N-(2-((4-hidroxifenil)amino)piridin-3-il)-4-metoxibencenosulfonamida, ixabepilona (BMS 247550), paclitaxel, TAXOTERE® (docetaxel), PNU100940 (109881), patupilona, XRP-9881 (larotaxel), vinflunina, ZK-EPO (epotilona sintética) y semejantes.

Los inhibidores de ubiquitina ligasa incluyen inhibidores de MDM2, como por ejemplo nutlinas, inhibidores de NEDD8 tales como MLN4924 y semejantes.

Los compuestos de la presente invención también se pueden utilizar como radiosensibilizantes que incrementan la eficacia de la radioterapia. Los ejemplos de radioterapias incluyen radioterapia con haces externos, teleterapia, braquiterapia y radioterapia con fuentes selladas, fuentes no selladas y semejantes.

Además, los compuestos con la Fórmula (I) se pueden combinar con otro agentes quimioterapéuticos tales como ABRAXANE™ (ABI-007), ABT-100 (inhibidor de farnesil transferasa), ADVEXIN® (vacuna Ad5CMV-p53), ALTOCOR® o MEVACOR® (lovastatina), AMPLIGEN® (poli I:poli C12U, un ARN sintético), APTOSYN® (exisulind), AREDIA® (ácido pamidrónico), arglabina, L-asparaginasa, atamestano (1-metil-3,17-dion-androsta-1,4-dieno), AVAGE® (tazaroteno), AVE-8062 (derivado de combreastatina), BEC2 (mitumomab), caquectina o caquexina (factor de necrosis tumoral), canvaxina (vacuna), CEAVAC™ (vacuna contra cáncer), CELEUK® (celmoleuquina), CEPLENE® (diclorhidrato

de histamina), CERVARIX™ (vacuna contra el papilomavirus humano), CHOP® (C: CYTOXAN® (ciclofosfamida); H: ADRIAMYCIN® (hidroxidoxorubicina); O: Vincristina (ONCOVIN®); P: prednisona), CyPat™ (acetato de ciproterona), combrestatina A4P, DAB(389)EGF (dominios catalítico y de traslocación de la toxina de la difteria fusionados por medio de un ligador His-Ala al factor de crecimiento epidérmico humanó) o TransMID-107R™ (toxinas de la difteria), dacarbazina, dactinomicina, ácido 5,6-dimetilxantenona-4-acético (DMXAA), eniluracilo, EVIZON™ (lactato de esqualamina), DIMERICINE® (loción liposómica T4N5), discodermolida, DX-8951f (mesilato de exatecan), enzastaurina, EPO906 (epotilona B), GARDASIL® (vacuna recombinante tetravalente contra el papilomavirus humano (Tipos 6, 11, 16, 18)), GASTRIMMUNE®, GENASENSE®, GMK (vacuna con gangliósidos conjugados), GVAX® (vacuna contra cáncer de próstata), halofuginona, histerelina, hidroxicarbamida, ácido ibandrónico, IGN-101, IL-13-PE38, IL-13-PE38QQR (cintredequina besudotox), IL-13-exotoxina de pseudomonas, interferón-α, interferón-γ, JUNOVAN™ o MEPACT™ (mifamurtida), lonafarnib, 5,10-metilentetrahidrofolato, miltefosina (hexadecilfosfocolina), NEOVASTAT®(AE-941), NEUTREXIN® (trimetrexato glucuronato), NIPENT® (pentostatina), ONCONASE® (una enzima ribonucleasa), ONCOPHAGE® (tratamiento con vacuna para melanoma), ONCOVAX® (vacuna de IL-2), ORATHECIN™ (rubitecano), OSIDEM® (droga celular en base a anticuerpos), OVAREX® MAb (anticuerpo monoclonal murino), paclitaxel, PANDIMEX™ (saponinas aglicona de ginseng que comprende 20(*S*)protopanaxadiol (aPPD) y 20(*S*)protopanaxatriol (aPPT)), panitumumab, PANVAC®-VF (vacuna contra el cáncer en investigación), pegaspargasa, PEG Interferón A, fenoxodiol, procarbazina, rebimastato, REMOVAB® (catumaxomab), REVLIMID® (lenalidomida), RSR13 (efaproxiral), SOMATULINE® LA (lanreotido), SORIATANE® (acitretina), estaurosporina (*Streptomyces staurospores*), talabostat (PT100), TARGRETIN® (bexaroteno), TAXOPREXIN® (DHA-paclitaxel), TELCYTA™ (canfosfamida, TLK286), temilifeno, TEMODAR® (temozolomida), tesmilifeno, talidomida, THERATOPE® (STn-KLH), timitaq (diclorhidrato de 2-amino-3,4-dihidro-6-metil-4-oxo-5-(4-piridiltio)quinazolina), TNFERADE™ (adenovector: vehículo de ADN que contiene el gen para el factor de necrosis tumoral-α), TRACLEER® o ZAVESCA® (bosentano), tretinoína (Retin-A), tetrandrina, TRISENOX® (trióxido de arsénico), VIRULIZIN®, ukraína (derivado de alcaloides de la planta *Celidonia*), vitaxina (anticuerpo anti-alfavbeta3), XCYTRIN® (motexafin gadolinio), XINLAY™ (atrasentano), XYOTAX™ (paclitaxel

poliglumex), YONDELIS™ (trabectedina), ZD-6126, ZINECARD® (dexrazoxan), ZOMETA® (ácido zolendrónico), zorubicina y similares.

Datos

La determinación de la utilidad de los compuestos con la Fórmula I como ligantes para proteínas anti-apoptóticas Bcl-2 y Bcl-X_L y como inhibidores de las mismas; se llevó a cabo usando el Ensayo de fluorescencia por transferencia de energía de resonancia con resolución en el tiempo (TR-FRET [por las siglas en inglés de: *Time Resolved-Fluorescence Resonance Energy Transfer*]). El anticuerpo Tb-anti-GST se adquirió a Invitrogen (Nº en Catálogo: PV4216).

Síntesis de Sondas

Todos los reactivos se utilizaron tal como se obtuvieron del proveedor a no ser que se especifique otra cosa. Los reactivos de síntesis de péptidos, que incluyeron: diisopropiletilamina (DIEA), diclorometano (DCM), N-metilpirrolidona (NMP), hexafluorofosfato de 2-(1H-benzotriazol-1-il)-1,1,3,3-tetrametiluronio (HBTU), N-hidroxibenzotriazol (HOBt) y piperidina se obtuvieron de Applied Biosystems, Inc. (ABI), Foster City, CA o American Bioanalytical, Natick, MA. Los cartuchos precargados con 9-Fluorenilmetiloxicarbonilo (Fmoc) y aminoácidos (Fmoc-Ala-OH, Fmoc-Cys(Trt)-OH, Fmoc-Asp(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Fe-OH, Fmoc-Gli-OH, Fmoc-His(Trt)-OH, Fmoc-Ile-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Met-OH, Fmoc-Asn(Trt)-OH, Fmoc-Pro-OH, Fmor-Gln(Trt)-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Thr(tBu)-OH, Fmoc-Val-OH, Fmoc-Trp(Boc)-OH, Fmoc-Tyr(tBu)-OH) se obtuvieron de ABI o Anaspec, San José, CA. La resina para síntesis de péptidos (resina Fmoc-Rink amida MBHA) y Fmoc-Lys(Mtt)-OH se obtuvieron de Novabiochem, San Diego, CA. El éster succinimidilo de 6-carboxifluoresceína como un único isómero (6-FAM-NHS) se obtuvo de Anaspec. El ácido trifluoroacético (TFA) se obtuvo de Oakwood Products, West Columbia, SC. El tioanisol, fenol, triisopropilsilano (TIS), 3,6-dioxa-1,8-octanoditiol (DODT) y el isopropanol se obtuvieron de Aldrich Chemical Co., Milwaukee, WI. Los espectros de masas con ionización/desorción por láser asistida por matriz (MALDI-MS) se registraron en un Applied Biosystems Voyager DE-PRO MS. Espectros de masas con electrospray (ESI-MS) se registraron en un Finnigan SSQ7000 (Finnigan Corp., San José, CA) en ambas modalidades de ion positivo y negativo.

Procedimiento general para la síntesis en fase sólida de péptidos (SPPS)

Los péptidos se sintetizaron con, como máximo, 250 µmol de resina Wang precargada/recipiente en un sintetizador de péptidos ABI 433A usando ciclos de

acoplamiento Fastmoc™ en una escala de 250 μmol. Se utilizaron cartuchos precargados que contenían 1 mmol de estándar Fmoc-aminoácidos, excepto para la posición de unión del fluoróforo, donde se puso 1 mmol de Fmoc-Lys(Mtt)-OH en los cartuchos, con monitoreo por retroalimentación de conductividad. La acetilación N-terminal se realizó utilizando 1 mmol de ácido acético en un cartucho en condiciones de acoplamiento estándar.

Eliminación de 4-Metiltritilo (Mtt) de la Lisina

La resina proveniente del sintetizador se lavó tres veces con diclorometano y se mantuvo húmeda. Se hicieron fluir 150 ml de diclorometano:triisopropilsilano:ácido trifluoroacético 95:4:1 a través del lecho de resina durante 30 minutos. La mezcla tomó un color amarillo profundo que luego se desvaneció a un amarillo pálido. Se hicieron fluir 100 ml de DMF a través del lecho durante 15 minutos. Luego se lavó la resina tres veces con DMF y se filtró. Las pruebas con ninhidrina mostraron una fuerte señal para amina primaria.

Marcado de resina con 6-Carboxifluoresceína-NHS (6-FAM-NHS)

La resina se trató con 2 equivalentes de 6-FAM-NHS en 1% de DIEA/DMF y se agitó o sacudió a la temperatura ambiente durante toda la noche. Cuando se completó esta tarea, la resina se drenó, se lavó tres veces con DMF, tres veces con (1% de DCM y 1% de metanol) y se secó para dar una resina de color naranja que dio negativo con la prueba de la ninhidrina.

Procedimiento general para el clivaje y desprotección de péptido unido a resina

Los péptidos se clivaron de la resina sacudiendo durante 3 horas a la temperatura ambiente en un cóctel de clivaje que consistía en 80% de TFA, 5% de agua, 5% de tioanisol, 5% de fenol, 2,5% de TIS, y 2,5% de EDT (1 ml/0,1 g de resina). La resina se retiró por filtración y se enjuagó dos veces con TFA. El TFA se evaporó del filtrado, y el producto se precipitó con éter (10 ml/0,1 g de resina), se recuperó por centrifugación, se lavó dos veces con éter (10 ml/0,1 g de resina) y se secó para dar el péptido en bruto.

Procedimiento general para la purificación de péptidos

Los péptidos en bruto se purificaron en un sistema Gilson de HPLC preparativa corriendo software de análisis Unipoint® (Gilson, Inc., Middleton, WI) en una columna de compresión radial que contenía dos segmentos de 25 × 100 mm rellenos con partículas Delta-Pak™ C18 de 15 μm con tamaño de poro de 100 Å y se eluyeron con uno de los métodos de gradiente que se dan más adelante. Se purificaron entre uno y dos mililitros de solución de péptido en bruto (10 mg/ml en DMSO/agua al 90%) por inyección. Los picos que contenían el(los) producto(s) de cada corrida se combinaron y se liofilizaron. Todas las corridas preparativas se realizaron a 20 ml/min usando como eluyentes solución amortiguadora de pH A: TFA al 0,1% en agua y solución amortiguadora de pH B: acetonitrilo.

Procedimiento general para HPLC analítica

La HPLC analítica se llevó a cabo en un sistema Hewlett-Packard serie 1200 con a detector de matriz de diodos y un detector de fluorescencia Hewlett-Packard 1046A corriendo el software HPLC 3D ChemStation versión A.03.04 (Hewlett-Packard. Palo Alto, CA) en una columna YMC de 4,6 × 250 mm rellena con partículas ODS-AQ de 5 μm con un tamaño de poro de 120 Å y se eluyeron con uno de los métodos de gradiente que se dan más adelante luego de preequilibrar en las condiciones iniciales durante 7 minutos. Los eluyentes fueron solución amortiguadora de pH A: TFA al 0,1% en agua y solución amortiguadora de pH B: acetonitrilo. El caudal para todos los gradientes fue de 1 ml/min.

F-Bak: Sonda de péptido: Acetil--(SEQ ID NO: 1)GQVGRQLAIIGDK(6-FAM)-(SEQ ID NO: 2) INR-NH_2

Se extendió resina Fmoc-Rink amida MBHA usando el procedimiento general de síntesis de péptidos para dar el péptido protegido unido a la resina (1,020 g). Se eliminó el grupo Mtt, se marcó con 6-FAM-NHS y se clivó y desprotegió según se describió aquí anteriormente para dar el producto en bruto como un sólido de color naranja (0,37 g). Este producto se purificó por RP-HPLC. Las fracciones a través del pico principal se analizaron por RP-HPLC analítica, y las fracciones puras se aislaron y se liofilizaron, donde el pico principal dio el compuesto del título (0,0802 g) como un sólido amarillo; MALDI-MS m/z = 2137,1 ($(M+H)^+$).

Síntesis alternativa de sonda de péptido F-Bak: Acetil--(SEQ ID NO: 1)GQVGRQLAIIGDK(6-FAM)- -(SEQ ID NO: 2)INR-NH_2

El péptido protegido se dispuso en 0,25 mmol de resina Fmoc-Rink amida MBHA (Novabiochem) en un sintetizador de péptidos automatizado Applied Biosystems 433A corriendo ciclos de acoplamiento Fastmoc™ usando cartuchos de aminoácidos precargados con 1 mmol, excepto para la lisina marcada con fluoresceína (6-FAM), donde se pesó 1 mmol de Fmoc-Lys(4-metiltritilo) en los cartuchos. El grupo acetilo N-terminal se incorporó poniendo 1 mmol de ácido acético en un cartucho y acoplando según se describió aquí anteriormente. La eliminación selectiva del grupo 4-metiltritilo se realizó con una solución de DCM:TIS:TFA 95:4:1 (v/v/v) que se hizo fluir a través de la resina durante 15 minutos, y luego se detuvo la reacción con un flujo de dimetilformamida. La 6-carboxifluoresceína-NHS en un único isómero se hizo reaccionar con la cadena lateral de lisina en DIEA al 1% en DMF y se confirmó la completitud realizando la prueba de la ninhidrina. El péptido se clivó de la resina y las cadenas laterales se desprotegieron por tratamiento con TFA:agua: fenol: tioanisol:triisopropilsilano:3,6-dioxa-1,8-octanoditiol 80:5:5:5:2,5:2,5 (v/v/v/v/v/v), y el

péptido en bruto se recuperó por precipitación con dietil éter. El péptido en bruto se purificó por cromatografía líquida de alto rendimiento en fase inversa, y su pureza e identidad se confirmaron por cromatografía líquida de alto rendimiento en fase inversa analítica y espectrometría de masas con desorción por láser asistida por matriz (m/z = 2137,1 ($(M+H)^+$)).

Ensayo de fluorescencia por transferencia de energía de resonancia con resolución en el tiempo (TR-FRET)

Los compuestos representativos se diluyeron en series en dimetilsulfóxido (DMSO) comenzando a 50 μM (2× de la concentración inicial; 10% de DMSO) y se transfirieron 10 μL a placas de 384 cavidades. Luego, se agregaron 10 μL de una mezcla de proteína/sonda/anticuerpo a cada cavidad en las concentraciones finales según la lista que se da en la tabla 1.

TABLA 1. Proteína, Sonda y Anticuerpo que se utilizaron para los ensayos TR-FRET

Proteína	Sonda	Proteína (nM)	Sonda (nM)	Anticuerpo	Anticuerpo (nM)
GST-Bcl-2	F-Bak(SEQ. ID. No. 1) (GQVGRQLAIIGDK(6-FAM) (SEQ ID Nº2)INR-amida)	1	100	Tb-anti-GST	1
GST-Bcl-X_L	F-Bak(SEQ. ID. No. 1) (GQVGRQLAIIGDK(6-FAM) (SEQ ID Nº2)INR-amida)	1	100	Tb-anti-GST	1

6-FAM = 6- carboxifluoresceína.; Tb = terbio; GST = glutationa S-transferasa

Luego, las muestras se mezclaron en un aparato para sacudir durante 1 minuto y se incubaron durante otras 3 horas a la temperatura ambiente. Para cada ensayo, se incluyeron la sonda/anticuerpo y la proteína/sonda/anticuerpo en cada placa de ensayo como controles negativo y positivo, respectivamente. La fluorescencia se midió en el Envision (Perkin Elmer) usando un filtro de excitación de 340/35 nm y filtros de emisión de 520/525 (F-Bak péptido) y 495/510 nm (anticuerpo anti-Histidina marcado con Tb).

Las constantes de inhibición (K_i) para los compuestos de acuerdo con la invención y ABT-737, y la relación de la selectividad de unión (Bcl-X_L K_i:Bcl-2 K_i) para cada una se muestran más adelante en la tabla 2. La constante de inhibición (K_i) es la constante de disociación de un complejo enzima-inhibidor o un complejo de proteína/moléculas pequeñas,

donde las moléculas pequeñas inhiben la unión de una proteína a otra proteína o péptido. Donde la K_i para un compuesto se representa como ">" (mayor que) cierto valor numérico, la intención es expresar que el valor de la afinidad de unión (por ejemplo, para Bcl-X_L) es mayor que los límites de detección del ensayo que se utilice. Donde la relación de la selectividad de unión por un compuesto se representa como ">" (mayor que) cierto valor numérico, la intención es expresar que la selectividad de un compuesto en particular por Bcl-2 respecto de Bcl-X_L es por lo menos tan grande como el número que se indica. Donde la K_i para un compuesto se representa como "<" (menor que) cierto valor numérico, la intención es expresar que el valor de la afinidad de unión (por ejemplo, para Bcl-2) es menor que el límite de detección del ensayo que se utilice. Las constantes de inhibición se determinaron usando la ecuación de Wang (Wang Z-X., An Exact Mathematical Expression For Describing Competitive Binding Of Dos Different Ligands To A Protein Molecule. *FEBS Lett.* **1995**, 360:111-4).

TABLA 2. Afinidad de unión TR-FRET

Ejemplo	Bcl-2 K_i , (μM)	Bcl-X_L K_i (μM)	Relación de la selectividad de unión (Bcl-X_L K_i /Bcl-2 K_i)
ABT-737	0,000088	0,00008	0,9
1	0,006773	0,57833	85,4
18	0,000238	0,008131	34,2
19	0,000847	0,020027	23,6
20	0,002365	0,077593	32,8
21	0,005428	0,19038	35,1
22	0,006218	0,1253	20,2
23	0,006639	0,16782	25,3
24	0,000194	>0,66	>3402,1
25	0,00005	0,20519	4103,8
26	0,00014	>0,66	>4714,3
28	0,033705	>0,66	>19,6
29	0,011911	>0,66	>55,4
30	0,10292	>0,66	>6,4

31	0,036614	>0,66	>18,0
32	0,061123	>0,66	>10,8
33	0,006684	0,33339	49,9
34	0,001986	0,088007	44,3
36	0,000796	0,008995	11,3
37	0,000464	0,044422	95,7
40	0,000534	>0,66	>1236,0
42	0,000048	0,003841	80
45	0,000828	>0,66	>797,1
46	0,000159	0,018958	119,2
47	0,00663	0,10428	15,7
50	0,000471	0,090073	191,2
51	0,000252	0,015646	62,1
52	0,000239	0,079805	333,9
53	0,000081	0,004845	59,8
54	0,000757	0,082015	108,3
55	0,000196	0,02488	126,9
56	0,000268	0,012924	48,2
57	0,000068	0,004674	68,7
58	0,001085	0,28807	265,5
59	0,000672	1,255	1867,6
60	0,01893	>0,66	>34,9
61	0,05221	>0,66	>12,6
62	0,003516	0,5711	162,4
64	0,000523	0,040334	77,1
65	0,004558	0,021805	4,8
67	0,28867	>0,66	>2,3
68	0,001227	0,013969	11,4
69	0,001245	0,092074	74
70	0,001192	0,074407	62,4
71	0,006233	>0,66	>105,9
72	0,003022	0,052359	17,3

73	0,001697	0,016885	9,9
74	0,00002	0,025249	1262,5
75	0,000125	0,10653	852,2
76	0,000051	0,003288	64,5
78	0,11251	>0,66	>5,9
79	0,00205	0,0972	47,4
85	0,000236	0,011521	48,8
86	0,000212	0,010522	49,6
87	0,000762	0,40679	533,8
88	0,000069	0,004642	67,3
89	0,000129	0,007453	57,8
90	0,002134	0,28384	133
91	0,000193	0,010191	52,8
92	0,004375	0,34857	79,7
93	0,000231	0,013861	60
94	0,00007	0,002317	33,1
95	0,00006	0,015699	261,7
96	0,000047	0,008781	186,8
97	0,000027	0,002611	96,7
98	0,000013	>0,66	>50769,2
99	0,00004	0,00553	138,3
100	0,000116	0,008288	71,4
101	0,000092	0,011152	121,2
102	0,000035	0,002242	64,1
103	0,000056	0,11738	2096,1
104	0,000077	0,049106	637,7
105	0,00008	0,005016	62,7
107	0,002087	0,13041	62,5
108	0,002342	0,059639	25,5
109	0,000161	>0,66	>4099,4
114	0,000096	0,014325	149,2
115	0,000176	0,027527	156,4

116	0,000036	0,008305	230,7
117	0,002299	>0,66	>287,1
118	0,000769	>0,66	>858,3
119	0,000622	0,23029	370,2
120	0,000443	0,099593	224,8
121	0,000001	0,000388	388
122	0,000058	0,012144	209,4
123	0,000015	0,001372	91,5
124	0,000335	0,073725	220,1
125	0,000003	0,011637	3879
126	0,000012	0,1629	13575
127	0,000459	>0,66	>1437,9
128	0,000051	0,363	7117,6
129	0,000056	>0,66	>11785,7
130	0,00014	>0,66	>4714,3
131	0,000106	0,24297	2292,2
132	0,000553	0,31529	570,1
133	0,000009	0,000281	31,2
134	0,000052	0,01805	347,1
135	0,000008	0,006239	779,9
136	0,000259	0,061863	238,9
137	0,000305	0,015977	52,4
138	0,000009	0,005174	574,9
139	0,000101	0,010416	103,1
140	0,004726	>0,66	>139,7
141	0,000673	0,028642	42,6
142	0,003664	0,10184	27,8
143	0,002232	0,075383	33,8
144	0,053902	>0,66	>12,2
145	0,00003	0,012029	401
146	0,044184	>0,66	>14,9
147	0,000514	>0,66	>1284,0

148	0,00289	>0,66	>228,4
149	0,000265	>0,66	>2490,6
150	0,000014	0,009338	667
151	0,000162	>0,66	>4074,1
152	0,000026	0,000412	15,8
153	0,000265	0,093006	351
154	0,000133	0,005375	40,4
155	0,000484	0,037667	77,8
156	0,000116	0,006155	53,1
157	0,004454	>0,66	>148,2
158	0,06478	>0,66	>10,2
161	0,00171	>0,66	>386,0
162	0,001348	0,16692	123,8
163	0,005616	>0,66	>117,5
164	0,000963	0,13795	143,3
165	0,000823	0,036585	44,5
166	0,000459	0,00327	7,1
169	0,00097	0,088637	91,4
170	0,000126	0,003802	30,2
171	0,002942	0,052053	17,7
172	0,002048	0,06569	32,1
173	0,000108	0,022102	204,6
174	0,000105	0,062087	591,3
175	0,0001	>0,660	>6600
176	0,00018	0,032	177,8
177	0,000165	0,132	799,7
178	0,000226	>0,660	>2915,8
179	0,000181	>0,660	>3642,4
180	0,000192	>0,660	>3438,6
181	0,000291	>0,660	>2271,9
182	0,000087	>0,660	>7595,8
183	0,000039	0,009428	240,5

184	0,000281	>0,660	>2345,3
185	0,000228	0,082582	361,5
186	0,00001	0,011199	1069,2
187	0,000329	>0,660	>2003,9
188	0,000102	0,11529	1135,4
189	0,000144	0,051724	358,6
190	0,000512	0,097064	189,6
191	0,000073	0,009162	125,2
194	0,000151	0,032029	212,4
195	0,000039	0,00671	170,2
196	0,000032	>0,660	>20552,4
197	0,000025	0,004837	193
198	0,003966	>0,660	>166,4
199	0,000014	0,005231	369,8
200	0,0001	>0,660	>6588,8
201	0,000125	0,024585	196,6
202	0,000052	0,005073	97,1
203	0,000031	0,004305	139,5
204	0,000145	0,042341	291,3
205	0,000005	0,003573	658,6
206	0,000083	>0,660	>7916,4
207	0,000218	>0,660	>3021,3
208	0,000589	>0,660	>1120,6
209	0,000267	>0,660	>2476,0
210	0,000624	>0,660	>1057,6
211	0,000009	0,005612	651,1
212	0,000737	>0,660	>895,1
213	< 0,00001	>0,660	>66000
214	0,000082	0,064044	776,6
215	0,000503	0,060768	120,8
216	0,000615	>0,660	>1073,2
217	0,000262	0,044761	171,1

218	0,000131	0,096873	738,2
219	0,000236	0,029861	126,8
220	0,000192	0,031387	163,7
221	0,000057	0,1701	3005,2
222	0,000107	0,13661	1275,3
223	0,000169	0,097266	574,1
224	<0,00001	0,000999	>99,9
225	0,00001	0,003482	>348,2
226	0,000017	0,009928	577,7
227	0,006831	>0,660	>96,6
228	0,004669	>0,660	>141,4
229	0,049413	>0,660	>13,4
230	0,008819	>0,660	>74,8
231	0,000918	>0,660	>718,8
232	0,00046	0,19749	429,1
233	0,000243	>0,660	>2714,3
234	0,000369	0,024503	66,3
235	0,000252	0,058196	231,4
236	0,000369	>0,660	>1787,6
237	0,000401	0,268	668,3
238	0,00043	>0,660	>1534,3
239	0,000252	0,10842	430,9
240	0,00083	>0,660	>795,4
241	0,006091	>0,660	>108,3
242	0,001796	>0,660	>367,6
243	0,00028	>0,660	>2357,6
244	0,00016	>0,660	>4136,9
245	0,001617	>0,660	>408,2
246	0,000783	0,38418	490,9
247	0,000188	0,027265	145,3
248	0,000013	0,15503	12079,6
249	0,00009	>0,660	>7302,0

250	0,000266	0,21547	811
251	0,000328	0,47166	1438,5
252	0,000077	>0,660	>8570,3
253	0,000142	>0,660	>4663,3
254	0,000126	0,053315	421,7
255	0,007834	>0,660	>84,2
256	0,00012	>0,660	>5519,8
257	0,000171	0,017126	100,2
258	0,000048	0,004085	86
259	0,001995	>0,660	>330,9
260	0,001087	>0,660	>607,2
261	0,000088	>0,660	>7530,1
262	0,003001	>0,660	219,9
263	0,000316	>0,660	>2090,0
264	0,000235	>0,660	>2808,4
265	0,001698	>0,660	>388,8
266	0,000183	>0,660	>3607,7
267	0,000454	>0,660	>1453,3
268	0,000092	0,14465	1563,9
269	nd	nd	nd
270	0,003314	>0,660	>199,1
271	0,006156	>0,660	>107,2
272	0,000011	>0,660	>58011,8
273	0,000076	0,18104	2396,1
274	0,000135	0,032908	244,6
275	0,000097	>0,660	>6832,4
276	0,000144	0,38147	2650,8
277	0,029684	>0,660	>22,2
278	0,00071	>0,660	>929,4
279	0,000095	>0,660	>6923,2
280	0,000178	0,19477	1097,2
281	0,000076	0,11925	1558,9

282	0,000164	0,56153	3434,4
283	0,047464	>0,660	>13,9
284	0,001552	>0,660	>425,2
285	0,006994	>0,660	>94,4
286	0,000567	>0,660	>1165,0
287	nd	nd	nd
288	0,000177	>0,660	>3730,9
289	0,000112	>0,660	>5917,7
290	0,000365	>0,660	>1808,5
291	0,00056	>0,660	>1179,1
292	0,000598	>0,660	>1104,2
293	0,000516	0,2604	505,1
294	0,000258	0,065126	252
295	0,000183	0,10971	599,4
296	0,000651	>0,660	>1014,4
297	0,000128	0,28281	2209,5
298	0,000315	0,44593	1415,7
299	0,000425	0,24551	577,7
300	nd	>0,660	nd
301	0,000291	>0,660	>2268,0
302	0,000504	>0,660	>1309,5
303	0,00148	>0,660	>445,9
304	0,000678	>0,660	>973,5
305	0,003684	>0,660	>179,2
306	0,000077	0,047895	622
307	0,003727	>0,660	>177,1
308	0,057376	>0,660	>11,5
309	0,004417	>0,660	>149,4
310	0,000049	>0,660	>13469,4
311	0,00026	>0,660	>2538,5
312	0,00034	>0,660	>1941,2
313	0,000044	0,066	1500

314	0,003066	>0,660	>215,3
315	0,003461	>0,660	>190,7
316	0,000149	0,079528	533,7
317	0,002798	>0,660	>235,9
318	0,001468	0,15067	102,6
319	0,000413	0,20791	503,4
320	0,001243	0,12873	103,6
321	0,000689	>0,660	>957,9
322	0,000184	>0,660	>3591,4
323	0,000949	>0,660	>695,2
324	0,001481	>0,660	>445,7
325	0,002331	>0,660	>283,1
326	0,000116	>0,660	>5708,8
327	0,000031	0,095575	3035,4
328	0,001859	>0,660	>355,0
329	0,000285	>0,660	>2319,5
330	0,074915	>0,660	>8,8
331	0,008266	>0,660	>79,8
332	0,012582	>0,660	>52,5
333	0,000089	>0,660	>7415,7
334	0,000179	>0,660	>3697,5
335	0,000438	>0,660	>1508,2
336	0,000105	0,24152	2301,3
337	0,000535	>0,660	>1233,3
338	0,000403	>0,660	>1637,7
339	0,014136	>0,660	>46,7
340	0,007593	>0,660	>86,9
341	0,012998	>0,660	>50,8
342	0,025752	>0,660	>25,6
343	0,000576	>0,660	>1145,9
344	0,000284	0,44708	1576,9
345	0,001146	>0,660	>575,9

346	0,000018	0,20364	11405,2
347	0,000243	0,30556	1256,7
348	0,000302	0,029266	97,1
349	0,000467	0,024235	51,9
350	0,00597	>0,660	>110,6
351	0,001576	>0,660	>418,7
352	0,006825	>0,660	>96,7
353	0,000292	>0,660	>2260,0
354	0,000036	0,00541	148,8
355	0,00012	>0,660	>5489,5
356	0,005015	>0,660	>131,6
357	0,001336	>0,660	>493,9
358	0,005417	>0,660	>121,8
359	0,013481	>0,660	>49,0
360	0,000228	0,14423	633,9
361	0,007128	>0,660	>92,6
362	0,000082	0,28999	3548,2
363	0,00018	>0,660	>3670,5
364	0,000006	0,07596	12197,3
365	0,001077	>0,660	>612,9
366	0,005457	>0,660	>121,0
367	0,004608	>0,660	>143,2
368	>1,195	>0,660	nd
369	0,8382	>0,660	>0,8
370	0,000904	>0,660	>729,9
371	0,008376	>0,660	>78,8
372	>1,195	>0,660	nd
374	0,002266	>0,660	>291,2
375	0,011254	>0,660	>58,6
376	0,022405	>0,660	>29,5
377	0,00014	0,32457	2317,4
378	0,063003	>0,660	>10,5

379	0,25595	>0,660	>2,6
380	0,000083	0,17491	2107,3
381	0,000054	0,024207	448,3
382	0,00115	>0,660	>573,9
383	0,00217	>0,660	>304,1
384	0,000076	>0,660	>8684,2
385	0,000062	0,12998	2096,5
386	0,000239	0,11818	494,5
387	0,000162	0,27983	1723,4
388	0,000188	0,034845	185,1
389	0,000098	0,067181	685,5
390	0,000341	0,11581	339,6
391	0,00354	>0,660	>186,4
392	0,00038	0,121691	320,2
393	0,000083	0,0921	1109,6
394	0,002507	> 660	> 263262,9
395	0,000798	0,018843	23,6
396	0,11567	> 660	>5705,9
397	0,022972	> 660	>28730,6
398	0,001233	0,083449	67,7
399	0,002923	> 660	> 225764,5
400	< 0,00001	0,036438	> 3643,8
401	< 0,00001	0,001621	> 162,1
402	0,00003	0,004152	137,4
403	0,000003	0,024340	8250,6
404	0,000012	0,030268	2423,5
405	0,000040	0,055325	1394,8
406	0,000035	0,044553	1263,8
407	0,000015	0,074556	4930,6
408	0,000002	0,028131	13701,7
409	< 0,000010	0,017485	1748,5
410	0,000055	0,101630	1838,6

411	0,000003	0,007453	2352,3
412	0,000021	0,135210	6545,5
413	0,000120	0,096802	803,8
414	0,000007	0,095640	13930,5
415	0,000002	0,026900	17326,9
416	0,000023	0,059112	2569,0
417	0,000046	0,003986	87,1
418	0,000004	0,001566	404,7
419	0,000197	0,211240	1070,8
420	0,000063	0,072108	1153,3
421	0,000026	0,054039	2089,5
422	0,000071	0,289500	4073,4
423	< 0,000010	0,007566	756,6
424	< 0,000010	0,007825	782,5
425	0,000003	0,003995	1282,2
426	0,000007	0,004311	604,2
427	0,000002	0,085636	34408,6
428	0,000003	0,015643	5832,2
429	< 0,000010	0,001407	140,7
430	< 0,000010	0,000998	99,8
431	< 0,000010	0,006774	677,4
432	0,000023	0,009298	408,8
433	< 0,000010	0,002286	228,55
434	0,000052	0,075474	1459,4
435	0,000017	0,032896	1935,1
436	0,000011	0,006500	590,9
437	< 0,000010	0,000514	51,4
438	< 0,000010	0,000345	34,5
439	< 0,000010	0,014968	1496,8
440	< 0,000010	0,045491	4549,1
441	< 0,000010	0,024219	2421,9
442	< 0,000010	0,033589	3358,9

443	< 0,000010	0,019357	1935,7
444	0,000112	0,081494	727,6
445	0,000028	0,013557	484,2
446	0,000038	0,019318	508,4
447	0,000028	0,065838	2373,1
448	0,000005	0,014610	3119,3
449	0,000240	0,017841	74,4
450	0,000299	0,032065	107,3
451	< 0,000010	0,003599	359,9
452	< 0,000010	0,006004	600,4
453	< 0,000010	0,003630	363,0
454	0,000026	0,018906	735,2
455	0,000004	0,000619	139,4
456	< 0,000010	0,000540	54,0
457	0,000045	0,330930	7413,6
458	< 0,000010	0,002372	237,2
459	< 0,000010	0,005416	541,6
460	0,000049	0,028982	586,5
461	0,000093	0,003650	39,4
462	0,000026	0,018425	710,8
463	0,000007	0,043884	6042,9
464	0,000081	0,521110	6431,8
465	0,000025	0,037216	1472,4
467	0,000080	0,13291	1653,0
473	0,079276	0,19124	2,4
474	0,0081	nd	nd
475	nd	nd	nd
476	nd	nd	nd
477	0,0085	nd	nd
478	nd	nd	nd
479	nd	nd	nd
480	nd	nd	nd

481	nd	nd	nd
482	0,000064	0,349890	5442,9
483	< 0,000010	0,005630	>563,0
484	< 0,000010	0,034339	>3433,9
485	0,000167	0,054207	324,0
486	0,000328	0,025460	77,6
487	0,000033	0,075419	2287,2
488	< 0,000010	0,023459	>2345,9
490	0,001144	0,106070	92,7
491	0,000017	0,077183	4600,5
492	< 0,000010	0,045096	>4509,6
493	< 0,000010	0,041883	>4188,3
494	< 0,000010	0,015566	>1556,6
496	0,000078	0,043348	558,9
497	0,000082	0,124230	1517,4
498	< 0,000010	0,124910	>12491,0
499	< 0,000010	0,104150	>10415,0
500	< 0,000010	0,147340	>14734,0
501	0,000027	0,162530	6025,7
502	0,000025	0,144860	5754,1
503	0,000062	0,146640	2356,5
504	< 0,000010	0,005499	>549,9
505	< 0,000010	0,004861	>486,1
506	< 0,000010	0,004457	>445,7
507	< 0,000010	0,033347	>3334,7
508	< 0,000010	0,043152	>4315,2
509	0,006300	0,229180	36,4
510	0,000674	0,173870	257,8
511	< 0,000010	0,021592	>2159,2
512	< 0,000010	0,017338	>1733,8
513	< 0,000010	0,006462	>646,2
514	< 0,000010	0,010413	>1041,3

515	< 0,000010	0,139940	>13994,0
516	< 0,000010	0,004823	>482,3
517	< 0,000010	0,006077	>607,7
518	< 0,000010	0,002546	>254,6
519	0,000012	0,310940	25935,4
520	< 0,000010	0,015378	>1537,8
521	< 0,000010	0,004669	>466,9
522	< 0,000010	0,002079	>207,9
523	< 0,000010	0,049444	>4944,4
524	< 0,000010	0,022184	>2218,4
525	< 0,000010	0,018984	>1898,4
526	< 0,000010	0,004679	>467,9
527	< 0,000010	0,004219	>421,9
528	< 0,000010	0,003669	>366,9
529	< 0,000010	0,008284	>828,4
530	< 0,000010	0,076660	>7666,0
531	< 0,000010	0,012578	>1257,8
532	< 0,000010	0,009812	>981,2
533	< 0,000010	0,010443	>1044,3
534	< 0,000010	0,046039	>4603,9
535	< 0,000010	0,002505	>250,5
536	0,000025	0,022152	886,1
538	< 0,000010	0,008001	>800,1
539	< 0,000010	0,040843	>4084,3
540	< 0,000010	0,001247	>124,7
541	< 0,000010	0,001382	>138,2
542	0,000023	0,124230	5359,8
543	< 0,000010	0,150470	>15047,0
544	< 0,000010	0,067003	>6700,3
545	< 0,000010	0,003566	>356,6
546	< 0,000010	0,006699	>669,9
547	0,000015	0,062949	4287,5

548	0,000014	0,028544	2111,7
549	< 0,000010	0,014820	>1482,0
550	0,000016	0,027218	1738,4
551	< 0,000010	0,016246	>1624,6
552	< 0,000010	0,010447	>1044,7
553	< 0,000010	0,013383	>1338,3
554	0,000034	0,057243	1674,6
555	< 0,000010	0,006298	>629,8
556	0,000034	0,091831	2730,2
557	0,000069	0,013166	189,8
538	0,000064	0,349890	5442,9
539	< 0,000010	0,005630	>563,0
540	< 0,000010	0,034339	>3433,9
541	0,000167	0,054207	324,0
542	0,000328	0,025460	77,6
543	0,000033	0,075419	2287,2
544	< 0,000010	0,023459	>2345,9
545	0,0001749	0,13811	789,7
546	0,001144	0,106070	92,7
547	0,000017	0,077183	4600,5
548	< 0,000010	0,045096	>4509,6
549	< 0,000010	0,041883	>4188,3
550	< 0,000010	0,015566	>1556,6
551	0,000078	0,043348	558,9
552	0,000082	0,124230	1517,4
553	< 0,000010	0,124910	>12491,0
554	< 0,000010	0,104150	>10415,0
555	< 0,000010	0,147340	>14734,0
556	0,000027	0,162530	6025,7
557	0,000025	0,144860	5754,1
558	nd	nd	nd

nd = no determinado

La TABLA 2 muestra la utilidad de los compuestos con la Fórmula I para inhibir funcionalmente a la proteína anti-apoptótica Bcl-2. La misma también muestra que sorprendentemente dichos compuestos con una afinidad comparativamente menor por la proteína anti-apoptótica Bcl-X_L, que a su vez da origen a relaciones de unión con un alto grado de selectividad (Bcl-X_L K_i / Bcl-2 K_i) que varían dentro del rango entre >2 y > 250.000. Dicha selectividad por la proteína Bcl-2 es significativamente mayor que la de los compuestos divulgados anteriormente en PCT US 2004/36770 y PCT US 2004/367911, según lo ejemplifica ABT-737 en la tabla 2.

Para algunos compuestos (por ejemplo, 192 y 193), el ensayo no detectó ninguna actividad contra Bcl-2 ni Bcl-X_L en las condiciones especificadas anteriormente en la descripción de los experimentos para el ensayo FRET. Como apreciarán aquellos con experiencia en el arte, sobre los límites de detección superior e inferior en un ensayo influyen las condiciones del ensayo, y para el ensayo FRET específicamente, la concentración de la sonda que se esté utilizando. Como los compuestos representados en los Ejemplos 192 y 193 muestran valores de K_i mayores que los límites de detección en el formato del ensayo que se utilizó, se puede especificar que su afinidad por Bcl-2 y Bcl-X_L es menor que el límite de detección superior de los ensayos. Sin embargo, los mismos aún pueden tener afinidad por una o ambas proteínas, y los inventores esperan que también posean selectividad por Bcl-2.

Ensayo de viabilidad de las células plaquetarias

Se incubó plasma rico en plaquetas (PRP) (preparado en el mismo laboratorio de acuerdo con técnicas convencionales) con ABT-737 (4-(4-((4'-cloro-1,1'-bifenil-2-il)metil)piperazin-1-il)-N-((4-(((1R)-3-(dimetilamino)-1-((feniltio)metil)propil)amino)-3-nitrofenil)sulfonil)benzamida) o compuestos de la invención en diversas concentraciones durante cinco horas a 37°C. Luego de la incubación, las plaquetas se equilibraron a la temperatura ambiente durante 20 minutos y luego se agregó un volumen igual de reactivo Cell Titer Glo (Promega Corporation). Las muestras se mezclaron durante dos minutos y luego se dejaron equilibrar durante otros 10 minutos a la temperatura ambiente. La luminiscencia generada por las muestras se cuantificó usando una lectora de placas LJL Analyst. Los valores IC_{50} son las concentraciones de compuesto necesarias para conseguir una inhibición del 50% de la viabilidad celular.

Ensayo de viabilidad de las células FL5.12/Bcl-2

FL5.12 es una línea celular murina prolinfocítica dependiente de IL-3 que sufre apoptosis al suspender la IL-3 como resultado de la sensibilización de las proteínas pro-

apoptóticas Bcl-2 tales como Bim y Puma. La sobreexpresión estable de la proteína anti-apoptótica Bcl-2 (FL5.12/Bcl-2) protege contra la apoptosis inducida por retiro de IL-3 por secuestro de Bim y Puma. [Refs. Harada, et al. P*NAS* 101, 15313 (2004); Certo, et al. *Cancer Cell* 9, 351 (2006).] La capacidad de los compuestos de matar a las células FL5.12/Bcl-2 suspendiendo la IL-3 es una medida directa de la capacidad de los compuestos de inhibir la función de la proteína anti-apoptótica Bcl-2.

Se cultivaron transfectantes estables de FL5.12 de tipo silvestre que sobreexpresan Bcl-2 en RPMI-1640 suplementado con L-glutamina 2 mM, 10% de FBS, piruvato de sodio 1 mM, HEPES 2 mM, 1% de penicilina/estreptomicina (Invitrogen), β-ME 57 μM, y 10% de medio acondicionado WEHI-3B (fuente de IL-3) y se mantuvo a 37 °C con CO_2 al 5%. Se lavaron $1x10^6$ células/ml con 1 x PBS y se resuspendieron en medio no suplementado con 10% de WEHI-3B durante 48 horas antes de los ensayos de citotoxicidad. Luego, las células se trataron durante otras 24 horas en presencia de diversas concentraciones de los compuestos que se indican. La viabilidad de las células se evaluó usando el ensayo CellTitre Glo (Promega Corp.) de acuerdo con las recomendaciones del fabricante.

El análisis de los datos se llevó a cabo usando GraphPad Prism 4.0 y los resultados se muestran en la tabla 3 más adelante.

TABLA 3. Actividad celular

	FL5,12/Bcl-2	Plaque-tas caninas	Relación de selectividad
	EC_{50} (μM)	EC_{50} (μM)	(plaqueta EC_{50} / FL5,12/Bcl-2 EC_{50})
ABT-737	0,025	0,282	11
18	0,123	29,69	241
21	1,01	>50	>49
22	0,825	>50	>61
23	1,44	>50	>35
24	0,055	>50	>906
25	0,049	>50	>1020
26	0,035	>50	>1429
40	0,165	>50	>303
45	0,139	>50	>360
46	0,041	30	725
52	0,016	>50	>3164

53	0,011	18,325	1697
54	0,064	>50	>785
55	0,022	36	1614
56	0,049	27	554
57	0,016	16,8	1077
68	0,044	>50	>1144
69	0,075	>50	>666
70	0,111	>50	>450
71	0,46	>50	>107
72	0,154	>50	>325
73	0,14	23,22	166
74	0,008	16,71	1989
75	0,022	17,73	821
76	0,039	8,66	221
86	0,074	36,27	489
88	0,032	19,87	613
89	0,065	31,95	495
94	0,04	23,85	590
96	0,011	22,27	2043
97	0,013	14,1	1052
98	0,004	17,94	4849
99	0,009	21,72	2440
100	0,015	31,25	2029
102	0,02	20,21	996
103	0,014	31,35	2305
104	0,021	>50	>2392
105	0,013	30,31	2262
106	0,009	15,24	1657
109	0,036	>50	>1404
120	0,319	>50	>157
121	0,038	0,309	8
122	0,04	>50	>1259
123	0,087	2,81	32
125	0,01	44,83	4719
126	0,031	>50	>1618
128	0,025	>50	>2000
129	0,021	>50	>2415
130	0,197	>50	>254
131	0,031	>50	>1597

132	0,042	>50	>1196
133	0,02	0,095	5
134	0,048	4,72	98
135	0,042	4,55	108
136	0,19	>50	>263
137	0,281	>50	>178
138	0,029	17,75	616
139	0,046	38,5	841
140	2,13	>50	>23
141	0,076	>50	>661
142	0,27	>50	>185
143	0,199	>50	>251
144	0,046	40,02	864
145	0,004	3,21	730
146	0,152	21,97	145
147	0,009	17,62	1895
148	0,071	19,77	278
149	0,013	16,74	1298
150	0,006	2,9	509
151	0,049	31,4	642
152	0,009	2,66	283
154	0,085	29	343
155	0,421	>50	>119
166	0,153	>50	>327
170	0,015	7,35	507
171	0,276	>50	>181
172	0,194	>50	>257
173	0,011	>50	>4587
174	0,011	19,5	1857
175	0,0062	nd	nd
176	0,0585	nd	nd
177	0,01966	nd	nd
178	0,0186	nd	nd
179	0,02346	nd	nd
180	0,02047	nd	nd
181	0,03353	nd	nd
182	0,01242	nd	nd
183	0,03077	nd	nd
184	0,02698	nd	nd

185	0,06335	nd	nd
186	0,02036	nd	nd
187	0,34128	nd	nd
188	0,02466	nd	nd
189	0,01489	nd	nd
190	0,02421	nd	nd
191	0,01172	nd	nd
192	> 0,5	nd	nd
193	> 0,5	nd	nd
194	0,02697	nd	nd
195	0,01124	nd	nd
196	0,01236	nd	nd
197	0,00618	nd	nd
198	nd	nd	nd
199	0,02854	nd	nd
200	0,00629	nd	nd
201	0,0174	nd	nd
202	0,01383	nd	nd
203	0,0223	nd	nd
204	0,02738	nd	nd
205	0,03753	nd	nd
206	0,00501	nd	nd
207	0,1199	nd	nd
208	0,26403	nd	nd
209	0,13896	nd	nd
210	0,25691	nd	nd
211	0,01713	nd	nd
212	> 0,5	nd	nd
213	0,43216	nd	nd
214	0,01569	nd	nd
215	0,11576	nd	nd
216	0,03985	nd	nd
217	0,02083	nd	nd
218	0,033	nd	nd
219	0,02296	nd	nd
220	0,02403	nd	nd
221	0,14872	nd	nd
222	0,02366	nd	nd
223	0,03713	nd	nd

224	0,02116	nd	nd
225	0,02989	nd	nd
226	0,02301	nd	nd
227	> 0,5	nd	nd
228	> 0,5	nd	nd
229	> 0,5	nd	nd
230	0,17755	nd	nd
231	0,0509	nd	nd
232	0,01228	nd	nd
233	nd	nd	nd
234	nd	nd	nd
235	nd	nd	nd
236	nd	nd	nd
237	nd	nd	nd
238	0,05896	nd	nd
239	0,01764	nd	nd
240	0,20943	nd	nd
241	nd	nd	nd
242	0,16457	nd	nd
243	0,028	nd	nd
244	0,02025	nd	nd
245	0,07244	nd	nd
246	0,048	nd	nd
247	0,01607	nd	nd
248	0,04981	nd	nd
249	0,0412	nd	nd
250	0,07951	nd	nd
251	0,07812	nd	nd
252	0,00662	nd	nd
253	0,00758	nd	nd
254	0,01693	nd	nd
255	> 0,5	nd	nd
256	0,00889	nd	nd
257	0,00934	nd	nd
258	0,00911	nd	nd
259	> 0,5	nd	nd
260	0,05944	nd	nd
261	0,01701	nd	nd
262	0,17622	nd	nd

263	0,02835	nd	nd
264	0,02571	nd	nd
265	0,24417	nd	nd
266	0,01148	nd	nd
267	0,05643	nd	nd
268	0,06822	nd	nd
269	nd	nd	nd
270	0,42893	nd	nd
271	> 0,5	nd	nd
272	0,19406	nd	nd
273	0,07001	nd	nd
274	0,15519	nd	nd
275	0,03801	nd	nd
276	0,06218	nd	nd
277	> 0,5	nd	nd
278	0,15272	nd	nd
279	0,01623	nd	nd
280	0,24715	nd	nd
281	0,06022	nd	nd
282	0,09216	nd	nd
283	> 0,5	nd	nd
284	> 0,5	nd	nd
285	> 0,5	nd	nd
286	0,27896	nd	nd
287	nd	nd	nd
288	0,06432	nd	nd
289	0,02736	nd	nd
290	0,04468	nd	nd
291	0,05801	nd	nd
292	0,06916	nd	nd
293	0,06806	nd	nd
294	0,05981	nd	nd
295	0,04634	nd	nd
296	0,18237	nd	nd
297	0,01321	nd	nd
298	0,01948	nd	nd
299	0,07725	nd	nd
300	0,06215	nd	nd
301	0,05945	nd	nd

302	0,03238	nd	nd
303	> 0,5	nd	nd
304	0,41529	nd	nd
305	> 0,5	nd	nd
306	0,00716	nd	nd
307	> 0,5	nd	nd
308	> 0,5	nd	nd
309	> 0,5	nd	nd
310	0,00451	nd	nd
311	0,0334	nd	nd
312	0,01924	nd	nd
313	0,08289	nd	nd
314	0,24014	nd	nd
315	> 0,5	nd	nd
316	0,06749	nd	nd
317	0,08309	nd	nd
318	0,07695	nd	nd
319	0,03141	nd	nd
320	0,04158	nd	nd
321	0,02909	nd	nd
322	0,04445	nd	nd
323	0,09208	nd	nd
324	0,13417	nd	nd
325	0,25639	nd	nd
326	0,03509	nd	nd
327	0,00657	nd	nd
328	> 0,5	nd	nd
329	0,12652	nd	nd
330	> 0,5	nd	nd
331	> 0,5	nd	nd
332	> 0,5	nd	nd
333	0,10932	nd	nd
334	0,06592	nd	nd
335	0,03897	nd	nd
336	0,00749	nd	nd
337	0,12389	nd	nd
338	0,07113	nd	nd
339	> 0,5	nd	nd
340	> 0,5	nd	nd

341	> 0,5	nd	nd
342	> 0,5	nd	nd
343	0,05489	nd	nd
344	0,07147	nd	nd
345	> 0,5	nd	nd
346	0,01747	nd	nd
347	0,04681	nd	nd
348	0,0872	nd	nd
349	0,14571	nd	nd
350	0,31119	nd	nd
351	0,34452	nd	nd
352	0,15632	nd	nd
353	0,05828	nd	nd
354	0,0056	nd	nd
355	> 0,5	nd	nd
356	> 0,5	nd	nd
357	> 0,5	nd	nd
358	> 0,5	nd	nd
359	> 0,5	nd	nd
360	0,10622	nd	nd
361	> 0,5	nd	nd
362	0,17126	nd	nd
363	0,08692	nd	nd
364	0,18474	nd	nd
365	> 0,5	nd	nd
366	> 0,5	nd	nd
367	> 0,5	nd	nd
368	> 0,5	nd	nd
369	> 0,5	nd	nd
370	0,26334	nd	nd
371	> 0,5	nd	nd
372	> 0,5	nd	nd
374	> 0,5	nd	nd
375	> 0,5	nd	nd
376	> 0,5	nd	nd
377	0,08573	nd	nd
378	> 0,5	nd	nd
379	> 0,5	nd	nd
380	0,06849	nd	nd

381	0,07185	nd	nd
382	> 0,5	nd	nd
383	> 0,5	nd	nd
384	0,10121	nd	nd
385	0,05636	nd	nd
386	0,15353	nd	nd
387	0,08652	nd	nd
388	0,08288	nd	nd
389	0,02812	nd	nd
390	0,04118	nd	nd
391	> 0,5	nd	nd
392	nd	nd	nd
393	nd	nd	nd
394	nd	nd	nd
395	nd	nd	nd
396	> 0,5	nd	nd
397	nd	nd	nd
398	0,33382	nd	nd
399	> 0,5	nd	nd
400	0,00847	nd	nd
401	0,00538	nd	nd
402	0,01336	nd	nd
403	0,00292	nd	nd
404	0,00234	nd	nd
405	0,01162	nd	nd
406	0,02046	nd	nd
407	0,0081	nd	nd
408	0,00239	nd	nd
409	0,0012	nd	nd
410	0,01386	nd	nd
411	0,01145	nd	nd
412	0,00948	nd	nd
474	0.0934	nd	nd
475	0.223	nd	nd
477	>1.67	nd	nd
478	>5.0	nd	nd

nd = no determinado

La TABLA 3 muestra la utilidad de los compuestos con la Fórmula I para inhibir funcionalmente a la proteína anti-apoptótica Bcl-2 en un contexto celular. FL5.12 es una línea celular murina prolinfocítica dependiente de IL-3 que sufre apoptosis al suspender la IL-3 como resultado de la sensibilización de la familia de proteínas pro-apoptóticas Bcl-2 tales como Bim y Puma. La sobreexpresión estable de la proteína anti-apoptótica Bcl-2 (FL5.12/Bcl-2) protege contra la apoptosis inducida por retiro de IL-3 por secuestro de Bim y Puma. (Refs. Harada, et al. P*NAS* **2004**, 101, 15313; Certo, et al. *Cancer Cell* **2006,** 9, 351). La capacidad de los compuestos de matar células FL5.12/Bcl-2 al suspender la IL-3 es una medida directa de los compuestos de la capacidad de inhibir la función de la proteína anti-apoptótica Bcl-2. Los compuestos de fórmula I son muy efectivos para matar células FL5.12/Bcl-2 al retirar la IL-3 según lo muestran los bajos valores EC_{50}.

Los compuestos de la presente invención se unen a las proteínas anti-apoptóticas Bcl-2 con alta afinidad e inhiben potentemente la función de la proteína anti-apoptótica Bcl-2 en un contexto celular y por lo tanto se espera que tengan utilidad para el tratamiento de enfermedades durante las cuales se expresa la proteína anti-apoptótica Bcl-2.

La proteína anti-apoptótica Bcl-X_L ha sido divulgada en otros sitios (*Cell* **Marzo 23, 2007**, 128, 1173-1176) como el principal regulador de la sobrevivencia de las células plaquetarias que circulan en animales. Las mutaciones genéticas de la proteína Bcl-X_L que reducen la estabilidad y la vida media de la proteína Bcl-X_L causan una reducción de la sobrevivencia de las células plaquetarias y la duración de la vida en ratones con dichas mutaciones. Un potente inhibidor farmacológico de Bcl-X_L, ABT-737, causa una rápida disminución de las plaquetas en circulación dependiente de la concentración luego de la inyección en ratones C57BL/6 o en perros beagle (*Cell* **Marzo 23, 2007**, 128, 1173-1176.; *Cell Death Differ*. **Mayo 2007**; 14(5), 943-51). Por lo tanto, sin ser limitados por la teoría, se puede esperar que los compuestos de la presente invención que poseen una afinidad reducida por Bcl-X_L muestren menores niveles de apoptosis de células plaquetarias que la informada anteriormente para los compuestos con mayor afinidad por Bcl-X_L.

El efecto de los compuestos sobre la sobrevivencia de las células plaquetarias se puede evaluar directamente ex vivo examinando la viabilidad de las células plaquetarias caninas aisladas en presencia de diversas concentraciones de compuesto. Los datos de la tabla 3 muestran que los compuestos de fórmula I tienen un efecto significativamente menor o ningún efecto sobre la viabilidad de las células plaquetarias caninas aisladas ex vivo (mayores valores EC_{50}) en comparación con los compuestos divulgados anteriormente en PCT US 2004/36770 y PCT US 2004/367911, según lo ejemplifica ABT-737. Además, la

proporción de selectividad funcional (células plaquetarias caninas EC_{50}: FL5.12/Bcl-2 EC_{50}) para los compuestos de fórmula I varía dentro del rango entre 32 y 4849, que es significativamente mayor que para los compuestos divulgados anteriormente en PCT US 2004/36770 y PCT US 2004/367911, según lo ejemplifica ABT-737.

Como los compuestos con la Fórmula I se unen a la proteína anti-apoptótica Bcl-2 con una unión comparativamente baja a la proteína anti-apoptótica Bcl- X_L, los compuestos pueden ser útiles como medicamentos para el tratamiento de cáncer y autoinmune y enfermedades inmunes con reducción de los efectos secundarios de la trombocitopenia (es decir, podrían no atacar a las plaquetas en circulación). La relación de Bcl- X_L con la trombocitopenia se divulga en *Cell* **Marzo 23, 2007**, 128, 1173-1176. Según se describió aquí y en otros lados, un potente inhibidor de Bcl- X_L, ABT-737, causa una reducción de las plaquetas en circulación dependiente de la dosis luego de la inyección en ratones C57BL/6 o en perros (*Cell Death Difer. M***ayo 2007**; 14(5), 943-51). Los compuestos con menor afinidad por Bcl- X_L muestran una reducción sustancialmente menor de las plaquetas en circulación o ninguna reducción. Por lo tanto, sin ser limitados por la teoría, se puede esperar que los compuestos de la presente invención que poseen una afinidad reducida por Bcl- X_L muestren menores niveles de apoptosis de las células plaquetarias que los compuestos con mayor afinidad por Bcl- X_L informados anteriormente. Los datos de EC_{50} de la tabla 2 muestran los efectos de la administración de los compuestos de la presente invención, en comparación con ABT-737, en células plaquetarias caninas.

La relación de la proteína Bcl-2 con el cáncer de vejiga, cáncer de cerebro, cáncer de mamas, cáncer de médula ósea, cáncer cervical, leucemia linfocítica crónica, cáncer colorrectal, cáncer de esófago, cáncer hepatocelular, leucemia linfoblástica, linfoma folicular, malignidades linfoides originadas en células T o células B, melanoma, leucemia mielógena, mieloma, cáncer oral, cáncer de ovarios, cáncer de pulmón de células no pequeñas, cáncer de próstata, cáncer de pulmón de células pequeñas, leucemia linfocítica crónica, mieloma, cáncer de próstata cáncer de bazo, etcétera ha sido descrita en PCT US 2004/36770, de propiedad conjunta, publicada como WO 2005/049593, y PCT US 2004/37911, publicada como WO 2005/024636.

La relación de las proteínas Bcl-2 con las enfermedades inmunes y autoinmunes ha sido descrita en *Current Allergy y Asthma Reports* **2003**, 3, 378-384; *British Journal of Haematology* **2000**, 110(3), 584-90; *Blood* **2000,** 95(4), 1283-92; y *New England Journal of Medicine* **2004**, 351(14), 1409-1418.

La relación de la proteína Bcl-2 con la artritis se divulga en la Solicitud Provisional de

Patente de los EE.UU. Nº de Acta 60/988.479 de propiedad conjunta.

La relación de la proteína Bcl-2 con el rechazo de trasplantes de médula ósea se divulga en la Solicitud de Patente de los EE.UU. Nº de Acta 11/941.196 de propiedad conjunta (ahora Solicitud de EE.UU. Publicada 20080182845A1).

Existe una correlación entre la sobreexpresión de la proteína Bcl-2 y la resistencia a la quimioterapia, los resultados clínicos, el progreso de la enfermedad, prognosis general o una combinación de los mismos en diversos tipos de cáncer y trastornos del sistema inmunitario. Los tipos de cáncer incluyen, pero de manera no taxativa, a los tipos hematológico y de tumor sólido tales como neuroma acústico, leucemia aguda, leucemia linfoblástica aguda, leucemia mielógena aguda (monocítica, mieloblástica, adenocarcinoma, angiosarcoma, astrocitoma, mielomonocítica y promielocítica), leucemia aguda de células T, carcinoma de células basales, carcinoma del conducto biliar, cáncer de vejiga, cáncer de cerebro, cáncer de mamas (que incluye al cáncer de mamas positivo para receptor de estrógenos), carcinoma broncogénico, linfoma de Burkitt, cáncer cervical, condriosarcoma, cordoma, coriocarcinoma, leucemia crónica, leucemia linfocítica crónica, leucemia mielocítica crónica (granulocítica), leucemia mielógena crónica, cáncer de colon, cáncer colorrectal, craniofaringioma, cistadenocarcinoma, cambios disproliferativos (displasias y metaplasias), carcinoma embrionario, cáncer endometrial, endoteliosarcoma, ependimoma, carcinoma epitelial, eritroleucemia, cáncer de esófago, cáncer de mamas positivo para receptor de estrógenos, trombocitemia esencial, tumor de Ewing, fibrosarcoma, carcinoma gástrico, cáncer de testículo de células germinales, enfermedad trofoblástica gestacional, glioblastoma, cáncer de cabeza y cuello, enfermedades de las cadenas pesadas, hemangioblastoma, hepatoma, cáncer hepatocelular, cáncer de próstata insensible a hormonas, leiomiosarcoma, liposarcoma, cáncer de pulmón (que incluye: cáncer de pulmón de células pequeñas y cáncer de pulmón de células no pequeñas), linfangioendotelio-sarcoma, linfangiosarcoma, leucemia linfoblástica, linfoma (linfoma, incluyendo: linfoma de células B grandes difuso, linfoma folicular, linfoma de Hodgkin y linfoma no de Hodgkin), malignidades y trastornos hiperproliferativos de la vejiga, mamas, colon, pulmones, ovarios, páncreas, próstata, piel y útero, malignidades linfoides originadas en células T o células B, leucemia, carcinoma medular, meduloblastoma, melanoma, meningioma, mesotelioma, mieloma múltiple, leucemia mielógena, mieloma, mixosarcoma, neuroblastoma, oligodendroglioma, cáncer oral, sarcoma osteogénico, cáncer de ovarios, cáncer pancreático, adenocarcinomas papilares, carcinoma papilar, linfoma de células T periféricas, pinealoma, policitemia vera, cáncer de próstata (que incluye al cáncer de próstata insensible a hormonas (refractario)), cáncer rectal,

carcinoma de células renales, retinoblastoma, rabdomiosarcoma, sarcoma, carcinoma de glándula sebácea, seminoma, cáncer de piel, carcinoma de pulmón de células pequeñas, tumores sólidos (carcinomas y sarcomas), cáncer de estómago, carcinoma de células escamosas, sinovioma, carcinoma de glándulas sudoríparas, cáncer de testículo (incluyendo al cáncer de testículo de células germinales), cáncer de tiroides, macroglobulinemia de Waldenström, tumores testiculares, cáncer uterino, tumor de Wilms y semejantes.

También se espera que los compuestos con la Fórmula I puedan inhibir el crecimiento de las células que expresan la proteína Bcl-2 derivada de un cáncer pediátrico o neoplasma incluyendo rabdomiosarcoma embrionario, leucemia linfoblástica aguda pediátrica, leucemia mielógena aguda pediátrica, rabdomiosarcoma alveolar pediátrico, ependimoma anaplástico pediátrico, linfoma anaplástico de células grandes pediátrico, meduloblastoma anaplástico pediátrico, tumor teratoide/rabdoide atípico pediátrico del sistema nervioso central, leucemia aguda bifenotípica pediátrica, linfoma de Burkitt pediátrico, tipos de cáncer pediátricos de la familia de tumores de Ewing tales como tumores neuroectodérmicos primitivos, tumor de Wilm anaplástico difuso pediátrico, tumor de Wilm pediátrico con histología favorable, glioblastoma pediátrico, meduloblastoma pediátrico, neuroblastoma pediátrico, mielocitomatosis derivada de neuroblastoma pediátrica, tipos de cáncer pediátricos en estadio pre-células B (tales como leucemia), psteosarcoma pediátrico, tumor rabdoide de riñón pediátrico, rabdomiosarcoma pediátrico, y tipos de cáncer de células T pediátrico tales como linfoma y cáncer de piel y semejantes.

Los trastornos autoinmunes incluyen enfermedad del síndrome de inmunodeficiencia adquirida (SIDA), síndrome linfoproliferativo autoinmune, anemia hemolítica, enfermedades inflamatorias, y trombocitopenia, enfermedad inmune aguda o crónica asociada con trasplante de órganos, enfermedad de Addison, enfermedades alérgicas, alopecía, alopecia areata, enfermedad ateromatosa/arteriosclerosis, aterosclerosis, artritis (que incluye osteoartritis, artritis crónica juvenil, artritis séptica, artritis de Lyme, artritis psoriásica y artritis reactiva), enfermedad ampollosa autoinmune, abetalipoproteinemia, enfermedades relacionadas con la inmunodeficiencia adquirida, enfermedad inmune aguda asociada con trasplante de órganos, acrocianosis adquirida, procesos parasitarios o infecciosos agudos y crónicos, pancreatitis aguda, insuficiencia renal aguda, fiebre reumática aguda, mielitis transversal aguda, adenocarcinomas, latidos ectópicos atriales, síndrome de angustia respiratoria (aguda) en adultos, complejo de demencia por SIDA, cirrosis por alcoholismo, lesión hepática inducida por alcohol, hepatitis inducida por alcohol, conjuntivitis alérgica, dermatitis de contacto alérgica, rinitis alérgica, alergia y asma, rechazo de aloinjerto,

deficiencia de alfa-l- antitripsina, enfermedad de Alzheimer, esclerosis lateral amiotrófica, anemia, angina de pecho, espondilitis anquilosante asociada a enfermedad pulmonar, degeneración celular del cuerno anterior, citotoxicidad mediada por anticuerpos, síndrome antifosfolípido, reacciones de hipersensibilidad anti-receptor, aneurismas aórtica y periférica, disección aórtica, hipertensión arterial, arteriosclerosis, fístula arteriovenosa, artropatía, astenia, asma, ataxia, alergia atópica, fibrilación auricular (sostenida o paroxismal), aleteo auricular, bloqueo aurículoventricular, hipotiroidismo autoinmune atrófico, anemia hemolítica autoinmune, hepatitis autoinmune, hepatitis autoinmune de tipo-1 (hepatitis autoinmune clásica o lupoide), hipoglucemia mediada por procesos autoinmunes, neutropenia autoinmune, trombocitopenia autoinmune, enfermedad de tiroides autoinmune, linfoma de células B, rechazo de injerto de hueso, rechazo en trasplante de médula ósea (BMT), bronquiolitis obliterante, bloqueo completo de ramas, quemaduras, caquexia, arritmias cardíacas, síndrome de "*stun*" cardíaco, tumores cardíacos, cardiomiopatía, respuesta inflamatoria al bypass cardiopulmonar, rechazo al trasplante de cartílago, degeneraciones corticales cerebelosas, trastornos cerebelosos, taquicardia auricular caótica o multifocal, trastornos asociados a la quimioterapia, clamidia, colestasis, alcoholismo crónico, hepatitis activa crónica, síndrome de fatiga crónica, enfermedad inmune crónica asociada con trasplante de órganos, neumonía eosinofílica crónica, patologías inflamatorias crónicas, candidiasis mucocutánea crónica, enfermedad pulmonar obstructiva crónica (COPD), intoxicación crónica con salicilato, inmunodeficiencia colorrectal variada común (hipogammaglobulinemia común variable), conjuntivitis, enfermedad de tejido conectivo asociada con enfermedad pulmonar intersticial, dermatitis de contacto, anemia hemolítica positiva para la prueba de Coombs, cor pulmonale, enfermedad de Creutzfeldt-Jakob, hepatitis autoinmune criptogénica, alveolitis fibrosante criptogénica, sepsis con cultivos negativos, fibrosis quística, trastornos asociados a las terapias con citoquinas, enfermedad de Crohn, demencia pugilística, enfermedades desmielizantes, fiebre hemorrágica por dengue, dermatitis, dermatitis esclerodermia, condiciones dermatológicas, enfermedad pulmonar asociada a dermatomiositis/polimiositis, diabetes, enfermedad arteriosclerótica diabética, diabetes mellitus, enfermedad con cuerpos de Lewy difusos, cardiomiopatía dilatada, cardiomiopatía congestiva dilatada, lupus eritematoso discoide, trastornos de los ganglios basales, coagulación intravascular diseminada, síndrome de Down en edad intermedia, enfermedad pulmonar intersticial inducida por fármacos, hepatitis inducida por fármacos, trastornos del movimiento inducidos por fármacos que bloquean los receptores de dopamina del SNC, sensibilidad a fármacos, eccema, encefalomielitis, endocarditis, endocrinopatía,

sinovitis enteropática, epiglotitis, infección por virus de Epstein-Barr, eritromelalgia, trastornos extrapiramidales y cerebelosos, linfohistiocitosis hematofagocítica familiar, rechazo de implante de timo fetal, ataxia de Friedreich, trastornos funcionales de las arterias periféricas, infertilidad femenina, fibrosis, enfermedad fibrótica pulmonar, sepsis fúngica, gangrena gaseosa, úlcera gástrica, arteritis de células gigantes, nefritis glomerular, glomerulonefritis, síndrome de Goodpasture, hipotiroidismo autoinmune bocioso (enfermedad de Hashimoto), artritis gotosa, rechazo de injerto de cualquier órgano o tejido, enfermedad de injerto contra huésped, sepsis por Gram negativas, sepsis por Gram positivas, granulomas debidos a organismos intracelulares, infección por estreptococos del grupo B (GBS), enfermedad de Grave, enfermedad pulmonar asociada con hemosiderosis, leucemia de células pilosas, enfermedad de Hallerrorden-Spatz, tiroiditis de Hashimoto, fiebre del heno, rechazo de trasplante cardíaco, hemacromatosis, malignidades hematopoyéticas (leucemia y linfoma), anemia hemolítica, síndrome urémico hemolítico/púrpura trombocitopénica trombolítica, hemorragia, púrpura de Henoch-Schoenlein, Hepatitis A, Hepatitis B, Hepatitis C, infección con VIH /neuropatía por VIH, enfermedad de Hodgkin, hipoparatiroidismo, corea de Huntington, trastornos de movimiento hiperquinético, reacciones de hipersensibilidad, neumonitis por hipersensibilidad, hipertiroidismo, trastornos de movimiento hipoquinético, evaluación del eje hipotalámico-pituitaria-adrenal, enfermedad de Addison idiopática, leucopenia idiopática, fibrosis pulmonar idiopática, trombocitopenia idiopática, enfermedad hepática idiosincrática, atrofia muscular espinal infantil, enfermedades infecciosas, inflamación de la aorta, enfermedad inflamatoria del intestino, diabetes mellitus dependiente de insulina, pneumonitis intersticial, iridociclitis/uveitis/neuritis óptica, lesión por isquemia-reperfusión, ataque isquémico, anemia perniciosa juvenil, artritis reumatoide juvenil, atrofia muscular espinal juvenil, sarcoma de Kaposi, enfermedad de Kawasaki, rechazo en trasplante de riñón, legionella, leishmaniasis, lepra, lesiones del sistema corticoespinal, enfermedad de IgA lineal, lipidema, rechazo en trasplante de hígado, enfermedad de Lyme, linfederma, enfermedad pulmonar infiltrativa linfocítica, malaria, infertilidad masculina idiopática o NOS, histiocitosis maligna, maligna melanoma, meningitis, meningococcemia, vasculitis microscópica de los riñones, dolor de cabeza de tipo migraña, trastorno mitocondrial multi-sistema, enfermedad mixta del tejido conectivo, enfermedad pulmonar asociada con la enfermedad mixta del tejido conectivo, gammapatía monoclonal, mieloma múltiple, degeneraciones de múltiples sistemas (Mencel Dejerine-Thomas Shi-Drager y Machado-Joseph), encefalitis miálgica/enfermedad del Royal Free Hospital, miastenia gravis, vasculitis microscópica de los riñones, *Mycobacterium avium*

intracelular, tuberculosis por *Mycobacterium*, síndrome mielodiplástico, infarto de miocardio, trastornos isquémicos de miocardio, carcinoma nasofaríngeo, enfermedad pulmonar neonatal crónica, nefritis, nefrosis, síndrome nefrótico, enfermedades neurodegenerativas, atrofias musculares neurogénicas I, fiebre neutropénica, esteatohepatitis no alcohólica, oclusión de la aorta abdominal y su ramificaciones, trastornos arteriales oclusivos, rechazo en trasplante de órganos, orquitis/epididimitis, orquitis/procedimientos de reversión de la vasectomía, organomegalia, osteoartrosis, osteoporosis, falla ovárica, rechazo en trasplante de páncreas, enfermedades parasitarias, rechazo en trasplante de paratiroides, enfermedad de Parkinson, enfermedad inflamatoria pélvica, pénfigo vulgar, pénfigo foliáceo, penfigoide, rinitis perenne, enfermedad del pericardio, enfermedad aterloesclerótica periférica, trastornos vasculares periféricos, peritonitis, anemia perniciosa, uveitis facogénica, neumonía por *Pneumocystis carinii*, neumonía, síndrome POEMS (polineuropatía, organomegalia, endocrinopatía, gammapatía monoclonal, y síndrome de cambios en la piel), síndrome posterior a perfusión, síndrome post-bomba, síndrome de cardiotomía post-MI, enfermedad pulmonar intersticial postinfecciosa, falla ovárica prematura, cirrosis biliar primaria, hepatitis esclerosante primaria, mixoedema primario, hipertensión pulmonar primaria, colangitis esclerosante primaria, vasculitis primaria, parálisis supranuclear progresiva, psoriasis, psoriasis de tipo 1, psoriasis de tipo 2, artropatía psoriásica, hipertensión pulmonar secundaria a enfermedad del tejido conectivo, manifestación pulmonar de la poliarteritis nodosa, enfermedad pulmonar intersticial post-inflamatoria, fibrosis por radiación, terapia con radiación, fenómeno y enfermedad de Raynaud, enfermedad de Refsum, taquicardia regular de QRS estrecho, enfermedad de Reiter, piouréter, hipertensión renovascular, lesión por reperfusión, cardiomiopatía restrictiva, enfermedad pulmonar intersticial asociada con artritis reumatoide, espondilitis reumatoide, sarcoidosis, síndrome de Schmidt, esclerodermia, corea senil, demencia senil del tipo con cuerpos de Lewy, síndrome séptico, choque séptico, artropatías seronegativas, choque, anemia de células falciformes, enfermedad pulmonar asociada con enfermedad de Sjögren, síndrome de Sjögren, rechazo de aloinjerto de piel, síndrome de cambios en la piel, rechazo en trasplante de intestino delgado, autoinmunidad de la esperma, esclerosis múltiple (todos los subtipos), ataxia espinal, degeneraciones espinocerebelosas, espondiloartropatía, deficiencia poliglandular de tipo I esporádica, deficiencia poliglandular de tipo II, enfermedad de Still, miositis por estreptococos, apoplejía, lesiones estructurales d cerebelo, panencefalitis esclerosante subaguda, oftalmia simpática, síncope, sífilis del sistema cardiovascular, anafilaxis sistémica, síndrome de respuesta inflamatoria sistémica, artritis reumatoide juvenil de inicio sistémico, lupus eritematoso

sistémico, enfermedad pulmonar asociada con lupus eritematoso sistémico, esclerosis sistémica, enfermedad pulmonar intersticial asociada con esclerosis sistémica, células T o FAB ALL, enfermedad de Takayasu/arteritis, telangiectasia, enfermedades mediada por ayudantes de tipo Th2 y de tipo Th1, tromboangitis obliterante, trombocitopenia, tiroiditis, toxicidad, síndrome de shock tóxico, trasplantes, trauma/hemorragia, hepatitis autoinmune de tipo 2 (hepatitis positiva para anticuerpos anti-LKM), resistencia a la insulina de tipo B con acantosis nigricans, reacciones de hipersensibilidad de tipo III, hipersensibilidad de tipo IV, artropatía colítica ulcerativa, colitis ulcerosa, angina inestable, uremia, urosepsis, urticaria, uveitis, enfermedades cardíacas valvulares, venas varicosas, vasculitis, enfermedad pulmonar vasculítica difusa, enfermedades venosas, trombosis venosa, fibrilación ventricular, vitiligo, enfermedad hepática aguda, infecciones virales y fúngicas, encefalitis vital/meningitis aséptica, síndrome hemafagocítico asociado a condición vital, granulomatosis de Wegener, síndrome de Wernicke-Korsakoff, enfermedad de Wilson, rechazo de xenoinjerto de cualquier órgano o tejido, artropatía asociada *Yersinia* y *Salmonella* y semejantes.

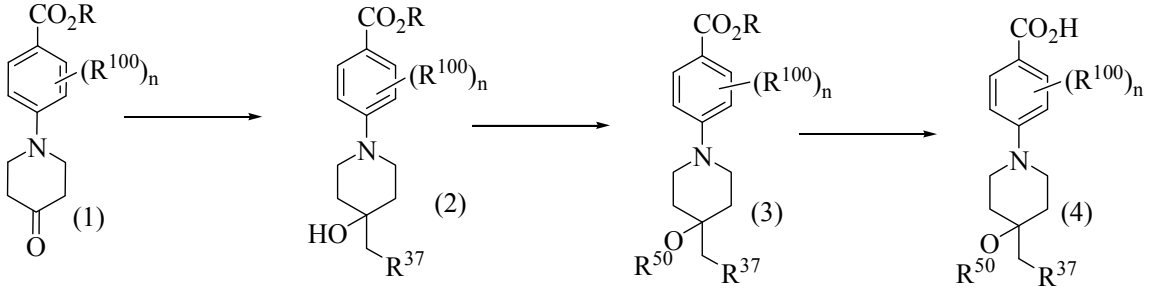
Esquemas y Experimentos

Los siguientes esquemas se ofrecen para proveer lo que se considera la descripción más útil y fácilmente comprensible de los procedimientos y aspectos conceptuales de esta invención. Los compuestos de la presente invención se pueden hacer por procesos de síntesis química, algunos ejemplos de los cuales se muestran aquí. Se desea aclarar que el orden de los pasos en los procesos puede variar, que los reactivos, solventes y las condiciones de reacción se pueden sustituir por aquellas que se mencionan específicamente, y que, de ser necesario, las unidades vulnerables se pueden proteger y desproteger.

Las siguientes abreviaturas tienen los significados que se indican. ADDP significa 1,1'-(azodicarbonil)dipiperidina; AD-mix-β significa una mezcla de $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, y K_2SO_4); 9-BBN significa 9-borabiciclo(3.3.1)nonano; Boc significa tert-butoxicarbonilo; $(DHQD)_2PHAL$ significa hidroquinidina 1,4-ftalazinediilo dietil éter; DBU significa 1,8-diazabiciclo(5.4.0)undec-7-eno; DIBAL significa hidruro de diisobutilaluminio; DIEA significa diisopropiletilamina; DMAP significa N,N-dimetilaminopiridina; DMF significa N,N-dimetilformamida; dmpe significa 1,2-bis(dimetilfosfino)etano; DMSO significa DMSO; dppb significa 1,4-bis(difenilfosfino)-butano; dppe significa 1,2-bis(difenilfosfino)etano; dppf significa 1,1'-bis(difenilfosfino)ferroceno; dppm significa 1,1-bis(difenilfosfino)metano; EDAC·HCl significa 1-(3-dimetilaminopropil)-3-etilcarbodiimida como clorhidrato; Fmoc significa fluorenilmetoxicarbonilo; HATU significa hexafluorofosfato de O-(7-azabenzotriazol-1-il)-

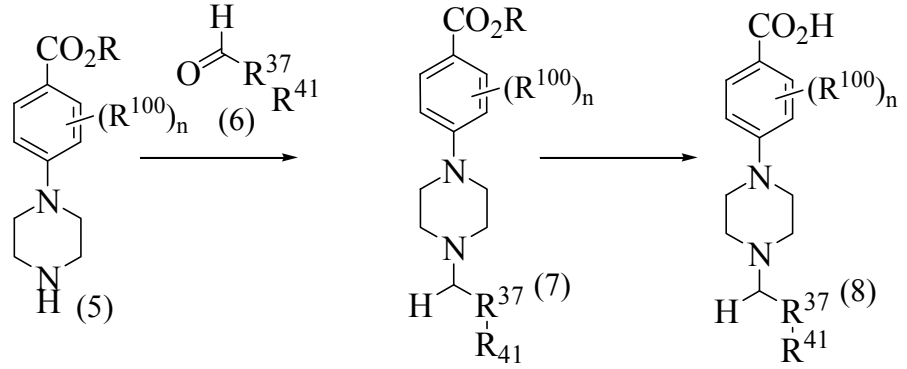
N,N'N'N'-tetrametiluronio; HMPA significa hexametilfosforamida; IPA significa alcohol isopropílico; MP-BH_3 significa cianoborohidruro de metilpoliestireno trietilamonio macroporoso; TEA significa trietilamina; TFA significa ácido trifluoroacético; THF significa tetrahidrofurano; NCS significa N-clorosuccinimida; NMM significa N-metilmorfolina; NMP significa N-metilpirrolidina; PPh_3 significa trifenilfosfina.

ESQUEMA 1



Los compuestos de fórmula (4) se pueden preparar según se muestra en el ESQUEMA 1, y se pueden utilizar según se describe en el ESQUEMA 7 para preparar los compuestos de fórmula (I), que son representativos de los compuestos de la presente invención. Los compuestos de fórmula (1) donde R es alquilo, R^{100} es según se describió para los sustituyentes sobre R^{26}, y n es 1, 2, ó 3; se puede convertir en los compuestos de fórmula (2) usando $R^{37}CH^2MgX^1$, donde X^1 es un halogenuro, en un solvente tal como, pero no taxativamente, un éter o tetrahidrofurano. Los compuestos de fórmula (3) se pueden preparar a partir de compuestos de fórmula (2) usando una base fuerte tal como NaH y $R^{50}X^2$, donde X^2 es un halogenuro y R^{50a} es según se describió aquí. Cuando los compuestos de fórmula (3), se tratan con NaOH o LiOH acuoso, darán los compuestos de fórmula (4).

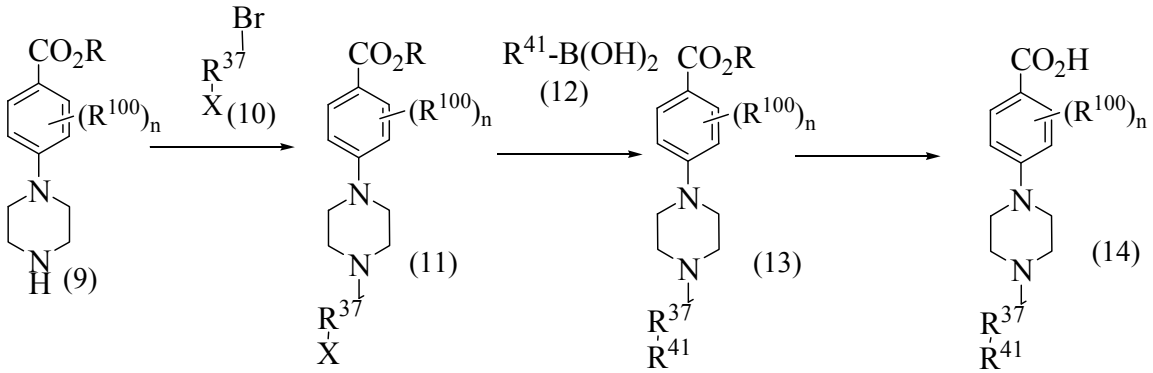
ESQUEMA 2



Tal como se muestra en el ESQUEMA 2, los compuestos de fórmula (5) se pueden hacer reaccionar con compuestos de fórmula (6) y un agente reductor para dar los compuestos de fórmula (7). Los ejemplos de agentes reductores incluyen borohidruro de sodio, cianoborohidruro de sodio, triacetoxiborohidruro de sodio, cianoborohidruro soportado sobre

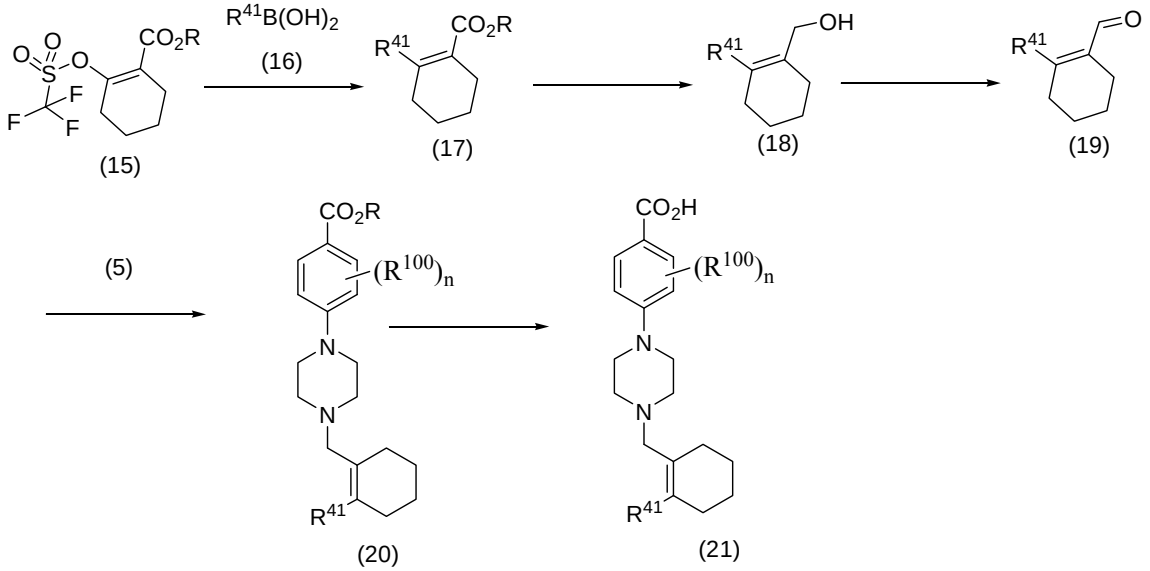
polímero, y semejantes. La reacción típicamente se lleva a cabo en un solvente tal como, pero no taxativamente, metanol, tetrahidrofurano, y diclorometano o mezclas de los mismos. Los compuestos de fórmula (8) se pueden preparar a partir de compuestos de fórmula (7) según se describe en el ESQUEMA 1, y se pueden utilizar según se describe en el ESQUEMA 7 para preparar los compuestos de fórmula (I).

ESQUEMA 3



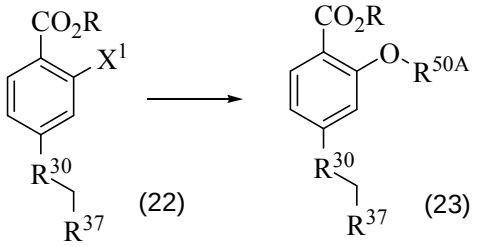
Cuando los compuestos de fórmula (9), se hacen reaccionar con un compuesto de la Fórmula (10) donde X es un halogenuro o triflato, y una base, darán un compuesto de fórmula (11). Las bases útiles en la reacción incluyen trietilamina, diisopropiletilamina y semejantes. Los compuestos de fórmula (13), donde R^{41} es según se describió aquí para los sustituyentes sobre R^{37}, se pueden preparar a partir de compuestos de fórmula (11) y compuestos de fórmula (12) usando condiciones de acoplamiento de Suzuki que son conocidas por aquellos con experiencia en el arte y que se pueden encontrar fácilmente en la literatura. Los compuestos de fórmula (14) se pueden preparar a partir de compuestos de fórmula (13) según se describe en el ESQUEMA 1, y se pueden utilizar según se describe en el ESQUEMA 7 para preparar los compuestos de fórmula (I).

ESQUEMA 4



Tal como se muestra en el ESQUEMA 4, los compuestos de fórmula (17) se pueden preparar a partir de compuestos de fórmula (15) y compuestos de fórmula (16), donde R es alquilo y R^{41} es según se describió aquí, usando condiciones de acoplamiento de Suzuki que son conocidas por aquellos con experiencia en el arte y que se pueden encontrar fácilmente en la literatura. Los compuestos de fórmula (17) se pueden reducir a compuestos de fórmula (18) usando un agente reductor tal como $LiAlH_4$ en un solvente tal como, pero no taxativamente, dietil éter o THF. Los compuestos de fórmula (19) se pueden preparar a partir de compuestos de fórmula (18) usando peryodinano de Dess-Martin o condiciones de oxidación de Swern, que son conocidos por aquellos con experiencia en el arte y se pueden encontrar fácilmente en la literatura. Los compuestos de fórmula (19) se pueden hacer reaccionar con un compuesto de fórmula (5) y un agente reductor para dar los compuestos de fórmula (20). Los ejemplos de agentes reductores incluyen borohidruro de sodio, cianoborohidruro de sodio, triacetoxiborohidruro de sodio, cianoborohidruro soportado sobre polímero, y semejantes. Típicamente, la reacción se lleva a cabo en un solvente tal como, pero no taxativamente, metanol, tetrahidrofurano, 1,2-dicloroetano, y diclorometano o mezclas de los mismos. Los compuestos de fórmula (21) se pueden preparar a partir de compuestos de fórmula (20) según se describe en el ESQUEMA 1, y se pueden utilizar según se describe en el ESQUEMA 7 para preparar compuestos de fórmula (I).

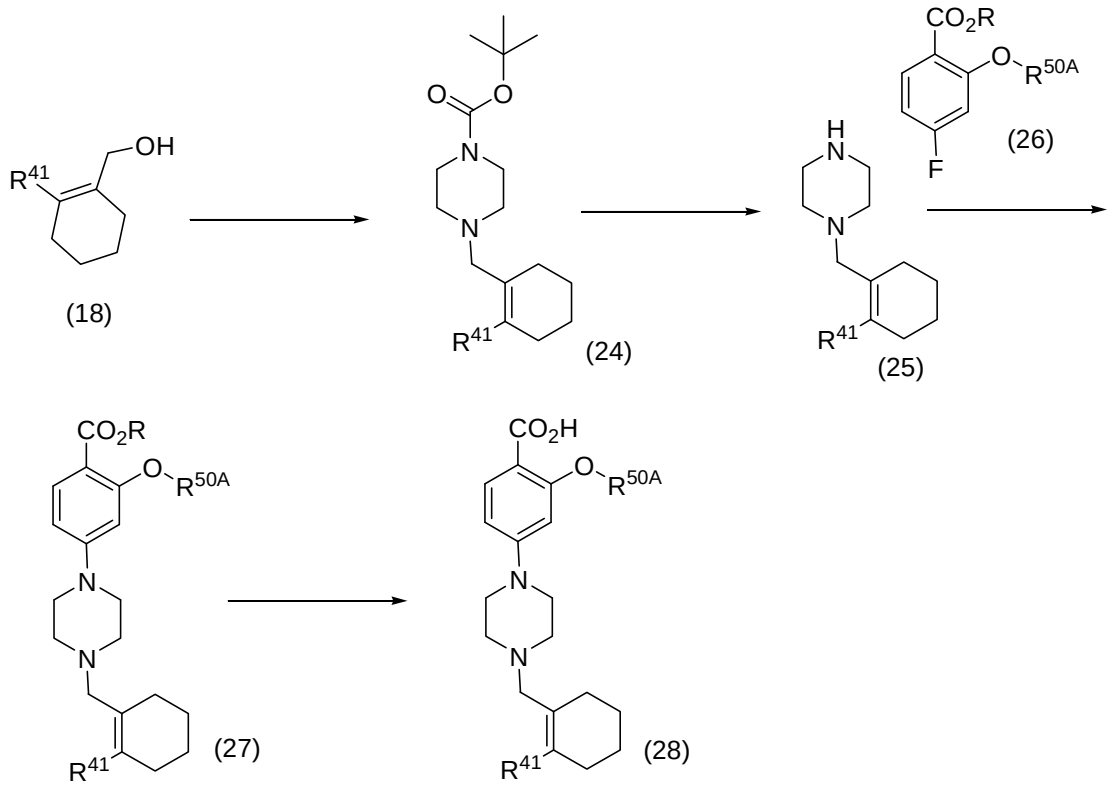
ESQUEMA 5



Tal como se muestra en el ESQUEMA 5, los compuestos de fórmula (22), donde R es alquilo, se pueden convertir en compuestos de fórmula (23) haciendo reaccionar el anterior, donde X^1 es Cl, Br, I, o CF_3SO_3-, y compuestos de fórmula R^{50A}-OH y un catalizador, con una primera base o sin ella. Los ejemplos de catalizadores incluyen complejo de trifluorometanosulfonato de cobre(I) en tolueno, $PdCl_2$, $Pd(OAc)_2$, y $Pd_2(dba)_3$. Los ejemplos de primeras bases incluyen trietilamina, N,N-diisopropiletilamina, Cs_2CO_3, Na_2CO_3, K_3PO_4, y mezclas de las mismas.

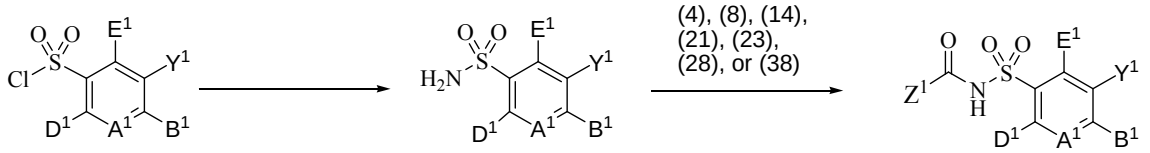
Los compuestos de fórmula (22) también se pueden convertir en compuestos de fórmula (23) haciendo reaccionar los anteriores, cuando X^1 es Cl, F, o NO_2, y compuestos de fórmula R^{50A}-OH con una primera base. Los ejemplos de primeras bases incluyen trietilamina, N,N-diisopropiletilamina, Cs_2CO_3, Na_2CO_3, K_3PO_4, y mezclas de los mismos.

ESQUEMA 6



Los compuestos de fórmula (18) se puede hacer reaccionar con cloruro de mesilo y una base tal como, pero no taxativamente, trietilamina, seguido de N-t-butoxicarbonilpiperazina, para dar los compuestos de fórmula (24). Los compuestos de fórmula (25) se pueden preparar haciendo reaccionar compuestos de fórmula (24) con trietilsilano y ácido trifluoroacético. Los compuestos de fórmula (25) se pueden hacer reaccionar con compuestos de fórmula (26) y HK_2PO_4 para dar los compuestos de fórmula (27) en un solvente tal como, pero no taxativamente, dimetilsulfóxido. Los compuestos de fórmula (28) se pueden preparar a partir de compuestos de fórmula (27) según se describe en el ESQUEMA 1, y se pueden utilizar según se describe en el ESQUEMA 7 para preparar los compuestos de fórmula (I).

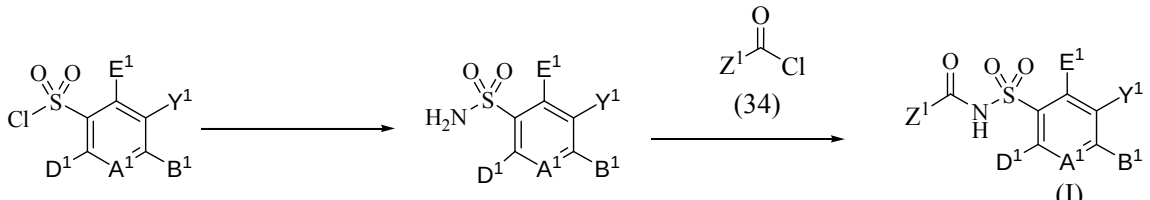
ESQUEMA 7



(32) (33) (I)

Tal como se muestra en el ESQUEMA 7, los compuestos de fórmula (32), que se pueden preparar según se describió aquí, se pueden convertir en compuestos de fórmula (33) haciendo reaccionar los anteriores con amoníaco. Los compuestos de fórmula (33) se pueden convertir en compuestos de fórmula (I) haciendo reaccionar los anteriores y compuestos de fórmula (4), (8), (14), (21), (23), (28), o (38) y un agente de acoplamiento, con una primera base o sin ella. Los ejemplos de agentes de acoplamiento incluyen clorhidrato de 1-etil-3-[3-(dimetilamino)propil]-carbodiimida, hexafluorofosfato de 1,1'-carbonildiimidazol, y benzotriazol-1-il-oxitripirrolidinofosfonio. Los ejemplos de primeras bases incluyen trietilamina, N,N-diisopropiletilamina, 4-(dimetilamino)piridina, y mezclas de las mismas.

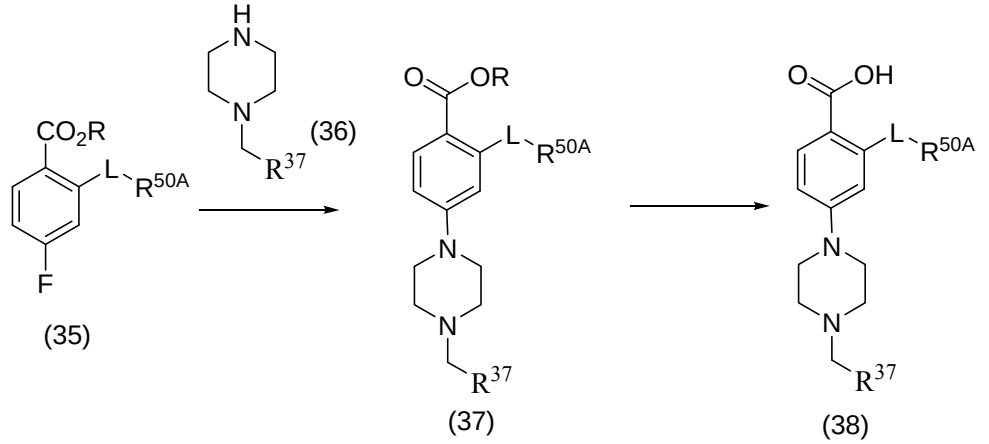
ESQUEMA 8



(32) (33) (I)

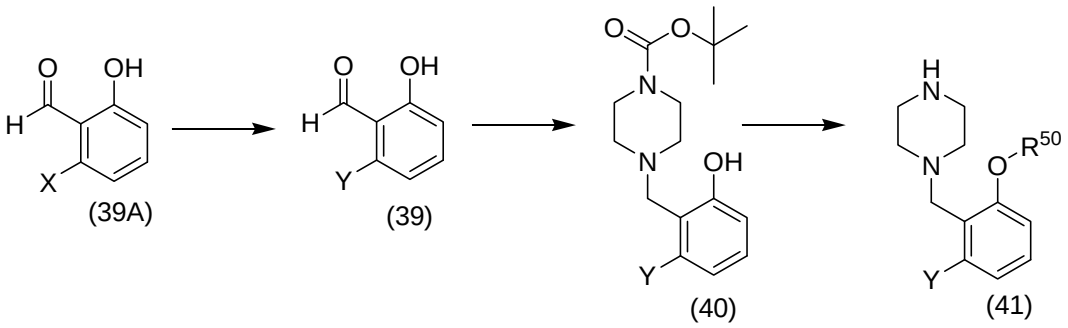
Los compuestos de fórmula (33), preparados según se describe en el ESQUEMA 7, también se pueden convertir en compuestos de fórmula (I) haciendo reaccionar los anteriores y compuestos de fórmula (34), con una primera base. Los ejemplos de primeras bases incluyen pero de manera no taxativa, hidruro de sodio, trietilamina, N,N-diisopropiletilamina, 4-(dimetilamino)piridina, y mezclas de las mismas.

ESQUEMA 9



Tal como se muestra en el ESQUEMA 9, los compuestos de fórmula (35), donde L es una unión, alquilo, O, S, S(O), $S(O)_2$, NH, etc., se pueden hacer reaccionar con compuestos de fórmula (36), para dar los compuestos de fórmula (37). La reacción típicamente se lleva a cabo a altas temperaturas en un solvente tal como, pero no taxativamente, dimetilsulfóxido, y pueden requerir el uso de una base tal como, pero no taxativamente, fosfato de potasio, carbonato de potasio, y semejantes. Los compuestos de fórmula (38) se pueden preparar a partir de compuestos de fórmula (37) según se describe en el ESQUEMA 1, y se pueden utilizar según se describe en el ESQUEMA 7 para preparar los compuestos de fórmula (I).

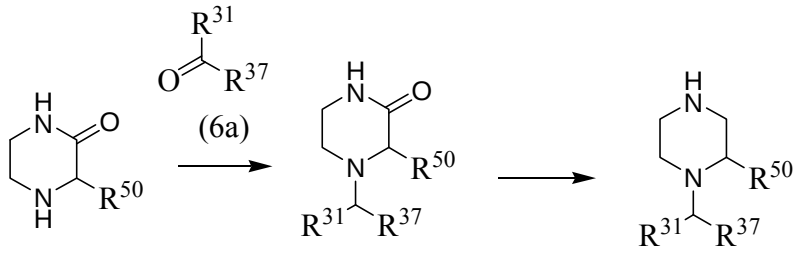
ESQUEMA 10



Los compuestos de fórmula (39), donde Y es según se describió aquí para los sustituyentes sobre R^{37}, se pueden preparar a partir de compuestos de fórmula (39A) donde X es un halogenuro o triflato, e Y-$B(OH)_2$ usando condiciones de acoplamiento de Suzuki que son conocidas por aquellos con experiencia en el arte y que se pueden encontrar fácilmente en la literatura. Los compuestos de fórmula (39) se pueden hacer reaccionar con piperazina-1-carboxilato de tert-butilo y un agente reductor tal como triacetoxiborohidruro de sodio para dar los compuestos de fórmula (40). La reacción típicamente se lleva a cabo en un solvente tal como, pero no taxativamente, cloruro de metileno. Los compuestos de fórmula (41) se pueden preparar a partir de compuestos de fórmula (40) haciendo reaccionar este último con

$R^{50}X$, donde X es un halogenuro, y NaH en un solvente tal como N,N-dimetilformamida, y luego el material que se obtiene como resultado se puede tratar con trietilsilano y ácido trifluoroacético en diclorometano. Los compuestos de fórmula (41) se pueden utilizar según se describe en el ESQUEMA 9 donde CH_2R^{37} es según se muestra en la Fórmula (41).

ESQUEMA 11



(42) (43)

Tal como se muestra en el ESQUEMA 11, se pueden hacer reaccionar piperazin-2-onas sustituidas donde R^{50} es alquilo, con compuestos de fórmula (6a) y un agente reductor tal como triacetoxiborohidruro de sodio en diclorometano para dar los compuestos de fórmula (42). Los compuestos de fórmula (42) se pueden reducir a compuestos de fórmula (43) usando un agente reductor tal como, pero no taxativamente, hidruro de aluminio y litio en un solvente tal como, pero no taxativamente, tetrahidrofurano. Los compuestos de fórmula (43) se pueden utilizar según se describe en el ESQUEMA 9 donde CH_2R^{37} es según se muestra en la Fórmula (43).

Los siguientes ejemplos se ofrecen para proveer lo que se considera la descripción más útil y fácilmente comprensible de los procedimientos y aspectos conceptuales de esta invención. Los compuestos que se ejemplifican se nombraron usando el programa ACD/ChemSketch Versión 5.06 (05 de Junio de 2001, Advanced Chemistry Development Inc.,Toronto, Ontario), ACD/ChemSketch Versión 12.01 (13 de Mayo de 2009), o ChemDraw® Ver 9.0.5 (CambridgeSoft, Cambridge, MA). Los intermediarios se nombraron usando ChemDraw® Ver. 9.0.5 (CambridgeSoft, Cambridge, MA).

EJEMPLO 1

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida

EJEMPLO 1A

4-((4'-clorobifenil-2–il)metil)piperazin-1-carboxilato de tert-butilo

Se combinó 4'-clorobifenil-2-carbaldehido (EJEMPLO 27C) (4,1 g), piperazin-1-carboxilato de tert-butilo (4,23 g), y tetracetoxiborohidruro de sodio (5,61 g) en CH_2Cl_2 (60 mL) y se agitaron durante 24 horas. La reacción se detuvo con metanol y se vertió en éter. La solución se lavó con agua y salmuera, se concentró, y se cromatografió sobre gel de sílice con 2-25% acetato de etilo/hexanos.

EJEMPLO 1B

1-((4'-clorobifenil-2–il)metil)piperazina

EJEMPLO 1A (3,0 g) y trietilsilano (1 mL) se agitaron en CH_2Cl_2 (30 mL) y ácido trifluoroacético (30 mL) por 2 horas, y la reacción se concentró, y luego se capturó en éter y se volvió a concentrar. El producto se usó sin purificación adicional.

EJEMPLO 1C

4-fluoro-2-fenoxibenzoato de metilo

Se agitó 2-bromo-4-fluorobenzoato de metilo (1 g), fenol (0,565 g), carbonato de cesio (1,96 g), complejo triflato de cobre (I) tolueno (0,087 g), y acetato de etilo (0,034 mL) en tolueno (12 mL) a 110°C durante 24 horas. La reacción se enfrió y se cromatografió sobre gel de sílice con acetato de etilo al 5%/hexanos.

EJEMPLO 1D

4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-fenoxibenzoato de metilo

Se agitaron EJEMPLO 1C (630 mg), EJEMPLO 1B , y K_2CO_3 (707 mg) en dimetilsulfóxido a 125°C durante 5 horas. La reacción se enfrió y se cromatografió sobre gel de sílice con acetato de etilo al 10%/hexanos.

EJEMPLO 1E

ácido 4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-fenoxibenzoico

Se agitó EJEMPLO 1D (600 mg) en 25 mL 2:1 dioxano/NaOH 1M a 60°C durante 24 horas. La solución se enfrió y se ajustó a pH 4 con solución de NaH_2PO_4 y HCl concentrado, y se extrajo con acetato de etilo. el extracto se lavó con salmuera y se secó (Na_2SO_4), se filtró y se concentró.

EJEMPLO 1F

3-nitro-4-((tetrahidro-2H-piran-4–il)metilamino)bencensulfonamida

Se agitó 4-fluoro-3-nitrobencensulfonamida (2,18 g), (tetrahidropiran-4–il)metilamina (1,14 g), y trietilamina (1 g) en tetrahidrofurano (30 mL) durante 24 horas. La solución se diluyó con acetato de etilo, se lavó con solución de NaH_2PO_4 y salmuera, y se secó (Na_2SO_4), se filtró y se concentró. El producto se trituró a partir de acetato de etilo.

EJEMPLO 1G

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida

Se agitaron EJEMPLO 1E (90 mg), EJEMPLO 1F (45 mg), clorhidrato de 1-etil-3-[3-(dimetilamino)propil]-carbodiimida (65 mg), y 4-dimetilaminopiridina (22 mg) en CH_2Cl_2 (4 mL) durante 24 horas. La reacción se enfrió y se cromatografió sobre gel de sílice con acetato de etilo al 20-100%/hexanos. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,55 (brs, 1H), 8,63 (t, 1H), 8,47 (d, 1H), 7,75 (d, 1H), 7,46 (m, 6H), 7,35 (m, 2H), 7,24 (m, 3H), 7,15 (d, 1H), 6,99 (dd, 1H), 6,82 (d, 2H), 6,75 (d, 1H), 6,38 (d, 1H), 3,86 (br d, 2H), 3,49 (m, 2H), 3,37 (br s, 2H), 3,15 (br s, 4H), 2,34 (br s, 4H), 1,91 (br s, 4H), 1,64 (br d, 2H), 1,29 (m, 3H).

EJEMPLO 2

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-fenoxi-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 2A

4-((tetrahidro-2H-piran-4–il)metilamino)bencensulfonamida

Se agitó 4-aminobencensulfonamida (6,80 g), tetrahidropiran-4-carboxaldehido (4,96 g), y tetracetoxiborohidruro de sodio (16,74 g) en tetrahidrofurano (300 mL) y ácido acético (15 mL) en durante 24 horas. La reacción se concentró y se capturó en acetato de etilo. La solución resultante se lavó con agua y salmuera, se concentró, y se cromatografió sobre gel de sílice con 50% acetato de etilo/hexanos.

EJEMPLO 2B

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-fenoxi-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 2A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6/D_2O) δ 7,54 (d, 1H), 7,46 (m, 8H), 7,36 (m, 4H), 7,24 (d, 1H), 7,13 (dd, 1H), 6,93 (d, 2H), 6,75 (d, 1H), 6,55 (d, 2H), 6,30 (d, 1H), 3,86 (dd, 2H), 3,36 (s, 2H), 3,28 (t, 2H), 3,10 (br s, 4H), 2,96 (d, 2H), 2,32 (br s, 4H), 1,76 (m, 1H), 1,64 (d, 2H), 1,20 (m, 2H).

EJEMPLO 3

2-(benciloxi)-4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 3A

2-(benciloxi)-4-fluorobenzoato de metilo

Se agitaron 4-fluoro-2-hidroxibenzoato de metilo (2,00 g), bromuro de bencilo (1,54 mL), y carbonato de cesio (4,60 g) en N,N-dimetilformamida (50 mL) durante 24 horas. La reacción se capturó en éter y se lavó con 3x solución de NaOH 1M, y salmuera, luego se concentró para dar el producto puro.

EJEMPLO 3B

2-(benciloxi)-4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 3A en lugar de EJEMPLO 1C en el EJEMPLO 1D.

EJEMPLO 3C

Ácido 2-(benciloxi)-4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 3B en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 3D

2-(benciloxi)-4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 3C en lugar de EJEMPLO 1E en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 10,90 (br s, 1H), 8,66 (m, 1H), 8,59 (s, 1H), 7,82 (d, 1H), 7,33-7,55 (m, 12H), 7,18-7,27 (m, 3H), 6,61

(s, 1H), 6,56 (d, 1H), 5,22 (s, 2H), 3,86 (br d, 2H), 3,40 (m, 2H), 3,31 (m, 8H), 2,34 (br s, 4H), 1,91 (br s, 2H), 1,64 (br d, 2H), 1,29 (m, 3H).

EJEMPLO 4

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(2-feniletoxi)benzamida

EJEMPLO 4A

4-fluoro-2-fenetoxibenzoato de metilo

Se agregó 4-fluoro-2-hidroxibenzoato de metilo (1,00 g) y alcohol fenetílico (0,64 mL) a trifenilfosfina (1,54 g) y diisopropilazodicarboxilato (1,04 mL) en tetrahidrofurano (20 mL) a 0°C, y la reacción se agitó a temperatura ambiente durante 24 horas. La mezcla se cromatografió sobre gel de sílice con acetato de etilo al 5%/hexanos.

EJEMPLO 4B

4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-fenetoxibenzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 4A en lugar de EJEMPLO 1C en el EJEMPLO 1D.

EJEMPLO 4C

ácido 4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-fenetoxibenzoico

El compuesto del título se preparó utilizando EJEMPLO 4B en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 4D

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(2-feniletoxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 4C en lugar de EJEMPLO 1E en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 10,75 (br s, 1H), 8,66 (m, 2H), 7,91 (d, 1H), 7,47 (m, 6H), 7,20-7,40 (m, 8H), 6,53 (d, 1H), 6,47 (s, 1H), 4,35 (t, 2H), 4,03 (m, 1H), 3,85 (br d, 2H), 3,38 (s, 2H), 3,25 (m, 8H), 3,13 (t, 2H), 2,36 (br s, 4H), 2,21 (br s, 2H), 1,62 (br d, 2H), 1,20 (m, 2H), 1,17 (m, 1H).

EJEMPLO 5

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(feniltio)benzamida

EJEMPLO 5A

4-fluoro-2-(feniltio)benzoato de metilo

Se agitó ácido 5-fluoro-2-(metoxicarbonil)fenilborónico (1,00 g), 2-(feniltio)isoindolin-1,3-diona (0,86 g), y (2-hidroxi-3,5-diisopropilbenzoiloxi)cobre (0,29 g) en dioxano (15 mL) a 50°C durante 24 horas. La mezcla de reacción se cromatografió sobre gel de sílice con acetato de etilo al 5%/hexanos.

EJEMPLO 5B

4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-(feniltio)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 5A en lugar de EJEMPLO 1C en el EJEMPLO 1D.

EJEMPLO 5C

ácido 4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-(feniltio)benzoico

El compuesto del título se preparó utilizando EJEMPLO 5B en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 5D

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(feniltio)benzamida

El compuesto del título se preparó utilizando EJEMPLO 5C en lugar de EJEMPLO 1E en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,95 (br s, 1H), 8,59 (m, 2H), 7,93 (d, 1H), 7,63 (d, 1H), 7,15-7,50 (m, 14H), 6,73 (d, 1H), 6,18 (s, 1H), 3,82 (dd, 2H), 3,36 (m, 4H), 3,32 (m, 2H), 2,94 (br s, 4H), 2,30 (br s, 4H), 1,64 (m, 1H), 1,61 (m, 2H), 1,25 (m, 2H).

EJEMPLO 6

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(feniltio)-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 5C en lugar de EJEMPLO 1E y EJEMPLO 2A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR

(500MHz, dimetilsulfóxido-d_6/D_2O) δ 7,65 (d, 2H), 7,55 (d, 1H), 7,33-7,48 (m, 12H), 7,24 (m, 2H), 6,73 (d, 1H), 6,66 (d, 2H), 6,17 (d, 1H), 3,85 (dd, 2H), 3,34 (s, 2H), 3,26 (t, 2H), 2,98 (d, 2H), 2,92 (br s, 4H), 2,25 (br s, 4H), 1,78 (m, 1H), 1,63 (d, 2H), 1,20 (m, 2H).

EJEMPLO 7

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)-2-(feniltio)benzamida

EJEMPLO 7A

4-(3-morfolinopropilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando 3-(N-morfolinil)-1-propilamina en lugar de (tetrahidropiran-4–il)metilamina en el EJEMPLO 1F.

EJEMPLO 7B

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)-2-(feniltio)benzamida

El compuesto del título se preparó utilizando EJEMPLO 5C en lugar de EJEMPLO 1E y EJEMPLO 7A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 10,20 (br s, 1H), 8,69 (m, 1H), 8,57 (d, 1H), 7,95 (dd, 2H), 7,71 (m, 1H), 7,31-7,51 (m, 10H), 7,12-7,26 (m, 3H), 6,68 (dd, 1H), 6,07 (m, 1H), 4,06 (s, 2H), 3,68 (m, 4H), 3,50 (m, 2H), 3,32 (m, 6H), 2,88 (m, 4H), 2,27 (m, 4H), 1,91 (m, 2H).

EJEMPLO 8

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(fenilsulfonil)benzamida

EJEMPLO 8A

4-fluoro-2-(fenilsulfonil)benzoato de metilo

Se agitó EJEMPLO 5A (0,30 g) y $KMnO_4$ (1,80 g) en ácido acético (40 mL) a 60°C durante 24 horas. La mezcla de reacción se filtró a través de un tapón de gel de sílice, se concentró, y se cromatografió sobre gel de sílice con acetato de etilo al 50%/hexanos.

EJEMPLO 8B

4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-(fenilsulfonil)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 8A en lugar de EJEMPLO 1C en el EJEMPLO 1D.

EJEMPLO 8C

Ácido 4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-(fenilsulfonil)benzoico

El compuesto del título se preparó utilizando EJEMPLO 8B en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 8D

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(fenilsulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 8C en lugar de EJEMPLO 1E en el EJEMPLO 1G. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,95 (br s, 1H), 8,54 (s, 1H), 8,41 (dd, 1H), 7,90 (m, 2H), 7,82 (d, 1H), 7,76 (d, 1H), 7,66 (m, 1H), 7,46 (m, 5H), 7,40 (m, 4H), 7,11 (m, 2H), 6,67 (dd, 1H), 6,62 (m, 1H), 4,36 (m, 1H), 3,82 (dd, 2H), 3,39 (m, 6H), 3,19 (m, 6H), 2,37 (br s, 4H), 1,91 (m, 1H), 1,63 (m, 2H), 1,26 (m, 2H).

EJEMPLO 9

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(fenilsulfinil)benzamida

EJEMPLO 9A

4-fluoro-2-(fenilsulfinil)benzoato de metilo

Se agregó OXONE® (Dupont) (5,60 g) por porciones a lo largo de 1 hora a EJEMPLO 5A (1,00 g) en una mezcla de ácido acético (30 mL), agua (30 mL) y CH_2Cl_2 (20 mL), y la reacción se agitó por 1 hora adicional. La mezcla de reacción se capturó en acetato de etilo, se lavó con solución de $Na_2S_2O_3$, agua, y salmuera, se concentró, y se cromatografió sobre gel de sílice con 5-25% acetato de etilo/hexanos.

EJEMPLO 9B

4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-(fenilsulfinil)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 9A en lugar de EJEMPLO 1C en el EJEMPLO 1D.

EJEMPLO 9C

ácido 4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-(fenilsulfinil)benzoico

El compuesto del título se preparó utilizando EJEMPLO 9B en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 9D

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(fenilsulfinil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 9C en lugar de EJEMPLO 1E en el EJEMPLO 1G. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6/D_2O) δ 8,51 (s, 1H), 7,85 (dd, 2H), 7,64 (d, 2H), 7,48 (m, 8H), 7,32 (m, 1H), 7,23 (m, 1H), 7,14 (m, 4H), 6,97 (d, 1H), 3,85 (dd, 2H), 3,35 (d, 2H), 3,34 (m, 6H), 3,27 (t, 2H), 2,74 (br s, 4H),1,93 (m, 1H), 1,64 (d, 2H), 1,28 (m, 2H).

EJEMPLO 10

2-bencil-4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 10A

2-bencil-4-fluorobenzoato de metilo

Se agitó ácido 5-fluoro-2-(metoxicarbonil)fenilborónico (1,00 g), bromuro de bencilo (0,50 mL), K_2CO_3 (1,75 g), y [1,1'-bis(difenilfosfino)ferroceno]dicloropaladio(II) ($PdCl_2$(dppf)) (0,17 g) en tetrahidrofurano (20 mL) a 60°C durante 24 horas. La mezcla de reacción se cromatografió sobre gel de sílice con 2% acetato de etilo/hexanos.

EJEMPLO 10B

2-bencil-4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 10A en lugar de EJEMPLO 1C en el EJEMPLO 1D.

EJEMPLO 10C

ácido 2-bencil-4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 10B en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 10D

2-bencil-4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 10C en lugar de EJEMPLO 1E en el EJEMPLO 1G. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6/D_2O) δ 8,55 (d, 1H), 7,90 (d, 1H), 7,38-7,56 (m, 10H), 7,25 (m, 2H), 6,96 (d, 2H), 6,83 (s, 2H), 6,75 (d, 1H), 4,06 (s, 2H), 3,85 (dd, 2H), 3,48 (s, 2H), 3,37 (d, 2H), 3,25 (t, 2H), 3,20 (br s, 4H), 2,44 (br s, 4H), 1,91 (m, 1H), 1,63 (d, 2H), 1,29 (m, 2H).

EJEMPLO 11

2-bencil-4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 10C en lugar de EJEMPLO 1E y EJEMPLO 2A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,70 (br s, 1H), 7,48 (m, 6H), 6,88 (m, 6H), 6,62 (m, 6H), 6,42 (dd, 2H), 3,83 (dd, 4H), 3,24 (m, 6H), 2,96 (m, 4H), 1,82 (m, 2H), 1,63 (m, 3H), 1,18 (m, 4H).

EJEMPLO 12

2-bencil-4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 10C en lugar de EJEMPLO 1E y EJEMPLO 7A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,90 (br s, 1H), 8,80 (m, 1H), 8,54 (d, 1H), 7,91 (dd, 1H), 7,48 (m, 7H), 7,40 (d, 2H), 7,26 (d, 2H), 6,97 (dd, 2H), 6,86 (m, 2H), 6,76 (d, 1H), 4,04 (m, 5H), 3,72 (m, 4H), 3,56 (m, 2H), 3,40 (m, 8H), 3,21 (m, 4H), 2,34 (m, 2H), 1,98 (m, 2H).

EJEMPLO 13

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(2-feniletil)benzamida

EJEMPLO 13A

4-fluoro-2-fenetilbenzoato de metilo

Se agitó 2-bromo-4-fluorobenzoato de metilo (1,00 g), ácido (E)-estirilborónico (0,89 g), tetrakis(trifenilfosfin)paladio(0) (0,50 g), y K_3PO_4 (2,28 g) en dioxano (17 mL) a 90°C durante 24 horas. La mezcla de reacción se cromatografió sobre gel de sílice con acetato de etilo al 1-5%/hexanos. El producto en metanol (10 ml) se agregó a 20 % en peso de Pd-C al 5% seco fresco y se agitó por 4 días con H_2 en una botella de presión. La mezcla se filtró a través de una membrana de nilon y se concentró.

EJEMPLO 13B

4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-fenetilbenzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 13A en lugar de EJEMPLO 1C en el EJEMPLO 1D.

EJEMPLO 13C

ácido 4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-fenetilbenzoico

El compuesto del título se preparó utilizando EJEMPLO 13B en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 13D

4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-N-(3-nitro-4-((tetrahidro-2H-piran-4–il)metilamino)fenilsulfonil)-2-fenetilbenzamida

El compuesto del título se preparó utilizando EJEMPLO 13C en lugar de EJEMPLO 1E en el EJEMPLO 1G. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6/D_2O) δ 8,62 (d, 1H), 7,95 (d, 1H), 7,91 (m, 1H), 7,35-7,52 (m, 6H), 7,19 (m, 2H), 7,13 (m, 2H), 6,99 (m, 4H), 6,83 (d, 1H), 6,70 (d, 1H), 6,65 (s, 1H), 3,80 (m, 2H), 3,24 (m, 2H), 3,18 (t, 2H), 3,11 (br s, 4H), 2,91 (t, 2H), 2,48 (m, 2H), 2,38 (br s, 4H), 1,81 (m, 1H), 1,54 (d, 2H), 1,23 (m, 2H).

EJEMPLO 14

2-(bencilamino)-4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 14A

2-(bencilamino)-4-fluorobenzoato de metilo

Se agitó 2-amino-4-fluorobenzoato de metilo (0,90 g), benzaldehido (0,54 mL), tetracetoxiborohidruro de sodio (1,58 g) y ácido acético (0,3 mL) en CH_2Cl_2 (20 mL) por 3 horas. La reacción se detuvo con metanol, se concentró, y se cromatografió sobre gel de sílice con acetato de etilo al 5%/hexanos.

EJEMPLO 14B

2-(bencilamino)-4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 14A en lugar de EJEMPLO 1C en el EJEMPLO 1D.

EJEMPLO 14C

ácido 2-(bencilamino)-4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 14B en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 14D

2-(bencilamino)-4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 14C en lugar de EJEMPLO 1E en el EJEMPLO 1G. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6/D_2O) δ 8,58 (d, 1H), 7,92 (d, 1H), 7,87 (m, 1H), 7,59 (d, 2H), 7,48 (m, 2H), 7,43 (m, 4H), 7,20-7,29 (m, 8H), 6,15 (d, 1H), 4,32 (s, 2H), 3,85 (m, 2H), 3,49 (m, 2H), 3,33 (m, 2H), 3,26 (t, 2H), 3,12 (br s, 4H), 2,39 (br s, 4H), 1,90 (m, 1H), 1,62 (d, 2H), 1,27 (m, 2H).

EJEMPLO 15

2-anilino-4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 15A

4-fluoro-2-(fenilamino)benzoato de metilo

Se agitó 2-bromo-4-fluorobenzoato de metilo (1,00 g), anilina (0,47 mL), acetato de paladio(II) (0,048 g), 2,2'-bis(difenilfosfino)-1,1'-binaftilo (0,214 g) y Cs_2CO_3

(2,08 g) en tolueno (12 mL) a 90°C durante 24 horas. La reacción se concentró y se cromatografió sobre gel de sílice con acetato de etilo al 5-50%/hexanos.

EJEMPLO 15B

4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-(fenilamino)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 15A en lugar de EJEMPLO 1C en el EJEMPLO 1D.

EJEMPLO 15C

ácido 4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-(fenilamino)benzoico

El compuesto del título se preparó utilizando EJEMPLO 15B en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 15D

2-anilino-4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 15C en lugar de EJEMPLO 1E en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,55 (br s, 1H), 8,56 (m, 2H), 7,92 (d, 1H), 7,72 (d, 1H), 7,47 (m, 6H), 7,25 (m, 4H), 7,12 (d, 2H), 6,95 (m, 2H), 6,53 (s, 1H), 6,38 (dd, 1H), 3,81 (dd, 2H), 3,37 (br s, 4H), 3,12 (br s, 4H), 2,41 (br s, 4H), 1,91 (m, 1H), 1,61 (br d, 2H), 1,23 (m, 4H).

EJEMPLO 16

2-anilino-4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 15C en lugar de EJEMPLO 1E y EJEMPLO 2A en lugar de EJEMPLO 1F en EJEMPLO 1G. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6/D_2O) δ 7,78 (d, 1H), 7,52 (d, 2H), 7,47 (m, 6H), 7,36 (m, 3H), 7,27 (m, 3H), 7,11 (m, 2H), 6,90 (m, 1H), 6,61 (s, 1H), 6,53 (d, 1H), 6,31 (d, 1H), 4,46 (s, 1H), 3,82 (m, 2H), 3,37 (s, 2H), 3,26 (t, 2H), 3,05 (br s, 4H), 2,93 (d, 2H), 2,37 (br s, 4H), 1,77 (m, 1H), 1,63 (d, 2H), 1,20 (m, 2H).

EJEMPLO 17

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-metoxi-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 17A

4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-metoxibenzoato de metilo

Se agitó ácido metil-4-bromo-2-metoxibenzoico (700 mg), EJEMPLO 1B (983 mg), K_3PO_4 (909 mg), tris(dibencilidenacetona)dipaladio(0) (78 mg), y 2-(di-t-butilfosfino)bifenilo (102 mg) en 1,2-dimetoxietano (10 mL) a 80°C durante 24 horas. La mezcla de reacción se cromatografió sobre gel de sílice con acetato de etilo al 20-50%/hexanos.

EJEMPLO 17B

ácido 4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-metoxibenzoico

El compuesto del título se preparó utilizando EJEMPLO 17A en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 17C

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-metoxi-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 17B en lugar de EJEMPLO 1E en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 10,81 (br s, 1H), 8,64 (m, 2H), 7,96 (d, 1H), 7,20-7,54(m, 10H), 6,52 (d, 1H), 6,46 (s, 1H), 3,90 (s, 3H), 3,40 (m, 4H), 3,27 (br s, 4H), 2,39 (br s, 4H), 1,91 (m, 1H), 1,62 (br d, 2H), 1,27 (m, 4H).

EJEMPLO 18

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)-2-fenoxibenzamida

EJEMPLO 18A

4,4-dimetil-2-(trifluorometilsulfoniloxi)ciclohex-1-encarboxilato de metilo

A una suspensión de NaH lavado con hexano (17 g) en diclorometano (700 mL), se agregó 5,5-dimetil-2-metoxicarbonilciclohexanona (38,5 g) por goteo a 0°C. Luego de agitar por 30 minutos, la mezcla se enfrió a –78°C y se agregó anhídrido trifluorometansulfónico (40 mL). La mezcla de reacción se calentó a temperatura ambiente y

se agitó durante 24 horas. La capa orgánica se lavó con salmuera, se secó, y se concentró para dar el producto.

EJEMPLO 18B

2-(4-clorofenil)-4,4-dimetilciclohex-1-encarboxilato de metilo

Se calentó EJEMPLO 18A (62,15g), ácido 4-clorofenilborónico (32,24 g), CsF (64 g) y tetrakis(trifenilfosfin)paladio(0) (2g) en 2:1 1,2-dimetoxietano/metanol (600 mL) a 70^0C durante 24 horas. La mezcla se concentró. Se agregó éter (4x 200 mL) y la mezcla se filtró. La solución de éter combinada se concentró para dar el producto.

EJEMPLO 18C

(2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metanol

A una mezcla de $LiBH_4$ (13g), EJEMPLO 18B (53,8 g) y éter (400 mL), se agregó metanol (25 mL) lentamente con una jeringa. La mezcla se agitó a temperatura ambiente durante 24 horas. La reacción se detuvo con HCl 1N enfriando con hielo. La mezcla se diluyó con agua y se extrajo con éter (3x 100mL). Los extractos se secaron, y se concentró. El producto crudo se cromatografió sobre gel de sílice con acetato de etilo al 0-30%/hexanos.

EJEMPLO 18D

2-bromo-4-(piperazin-1–il)benzoato de metilo

El compuesto del título se preparó utilizando piperazina en lugar de EJEMPLO 1B y 2-bromo-4-fluorobenzoato de metilo en lugar de EJEMPLO 1C en el EJEMPLO 1D.

EJEMPLO 18E

2-bromo-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1–il)benzoato de metilo

Se agregó MsCl (7,5 mL) con una jeringa a EJEMPLO 18C (29,3 g) y trietilamina (30 mL) en CH_2Cl_2 (500 mL) a 0^0C, y la mezcla se agitó por 1 minuto. Se agregó EJEMPLO 18D (25 g) y la reacción se agitó a temperatura ambiente durante 24 horas. La suspensión se lavó con salmuera, se secó, y se concentró. El producto crudo se cromatografió sobre gel de sílice con acetato de etilo al 10-20%/hexanos.

EJEMPLO 18F

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1–il)-2-fenoxibenzoato de metilo

Se agitó EJEMPLO 18E (500 mg), fenol (195 mg), Cs_2CO_3 (674 mg), ácido 1-naftoico (356 mg), complejo triflato de cobre (I)-tolueno (45 mg), acetato de etilo (0,016 mL), y filtros moleculares de 4A (50 mg) en tolueno (2 mL) a 105°C durante 24 horas. La reacción se enfrió y se capturó en acetato de etilo (100 mL) y agua (40 mL). Las capas se separaron y la capa orgánica se lavó con 2x solución de Na_2CO_3 y salmuera, se secó, y se concentró. El producto crudo se cromatografió sobre gel de sílice con acetato de etilo al 20%/hexanos.

EJEMPLO 18G

ácido 4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1–il)-2-fenoxibenzoico

El compuesto del título se preparó utilizando EJEMPLO 18F en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 18H

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)-2-fenoxibenzamida

El compuesto del título se preparó utilizando EJEMPLO 18G en lugar de EJEMPLO 1E y EJEMPLO 7A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,10 (br s, 1H), 8,76 (m, 1H), 8,46 (d, 1H), 7,76 (dd, 1H), 7,50 (d, 1H), 7,35 (d, 2H), 7,23 (d, 2H), 7,06 (dd, 2H), 6,99 (dd, 1H), 6,81 (d, 2H), 6,74 (d, 1H), 6,34 (s, 1H), 3,62 (m, 4H), 3,46 (m, 2H), 3,13 (m, 4H), 2,76 (m, 2H), 2,48 (m, 2H), 2,22 (m, 6H), 1,97 (m, 2H), 1,82 (m, 2H), 1,40 (t, 2H), 1,06 (m, 7H), 0,94 (s, 3H).

EJEMPLO 19

4-(4-{[2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)-2-fenoxibenzamida

EJEMPLO 19A

5,5-dimetil-2-(trifluorometilsulfoniloxi)ciclohex-1-encarboxilato de metilo

El compuesto del título se preparó utilizando 4,4-dimetil-2-metoxicarbonilciclohexanona en lugar de 5,5-dimetil-2-metoxicarbonilciclohexanona en el EJEMPLO 18A.

EJEMPLO 19B

2-(4-clorofenil)-5,5-dimetilciclohex-1-encarboxilato de metilo

El compuesto del título se preparó utilizando EJEMPLO 19A en lugar de EJEMPLO 18A en el EJEMPLO 18B.

EJEMPLO 19C

(2-(4-clorofenil)-5,5-dimetilciclohex-1-enil)metanol

El compuesto del título se preparó utilizando EJEMPLO 19B en lugar de EJEMPLO 18B en el EJEMPLO 18C.

EJEMPLO 19D

2-bromo-4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-enil)metil)piperazin-1–il)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 19C en lugar de EJEMPLO 18C en el EJEMPLO 18E.

EJEMPLO 19E

4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-enil)metil)piperazin-1–il)-2-fenoxibenzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 19D en lugar de EJEMPLO 18E en el EJEMPLO 18F.

EJEMPLO 19F

ácido 4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-enil)metil)piperazin-1–il)-2-fenoxibenzoico

El compuesto del título se preparó utilizando EJEMPLO 19E en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 19G

4-(4-{[2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)-2-fenoxibenzamida

El compuesto del título se preparó utilizando EJEMPLO 19F en lugar de EJEMPLO 1E y EJEMPLO 7A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,10 (br s, 1H), 8,71(m, 1H), 8,42 (d, 1H), 7,73 (dd, 1H), 7,53 (d, 1H), 7,34 (d, 2H), 7,21 (dd, 2H), 7,10 (d, 2H), 6,96 (dd, 1H), 6,78 (d, 2H), 6,70 (d, 1H), 6,32 (s, 1H), 3,61 (m, 4H), 3,44 (m, 2H), 3,09 (m, 4H), 2,71 (m, 2H), 2,44 (m, 4H), 2,21 (m, 4H), 1,96 (m, 2H), 1,79 (m, 2H), 1,47 (t, 2H), 1,17 (m, 3H), 1,08 (m, 4H), 0,95 (s, 3H).

EJEMPLO 20

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-5–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)benzamida

EJEMPLO 20A

2-(1H-indazol-5–iloxi)-4-fluorobenzoato de etilo

Se agitó 2,4-difluorobenzoato de etilo (1,14 g), K_3PO_4 (1,30 g) y 5-hidroxiindazol (0,90 g) a 110°C en diglima (12 mL) durante 24 horas. La reacción se enfrió y se vertió en éter. La solución se lavó tres veces con solución de NaOH 1M, y salmuera, y se secó. La solución luego se concentró, y el producto crudo se cromatografió sobre gel de sílice con acetato de etilo al 20%/hexanos.

EJEMPLO 20B

4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-carboxilato de tert-butilo

El compuesto del título se preparó utilizando N-t-butoxicarbonilpiperazina en lugar de EJEMPLO 18D en el EJEMPLO 18E.

EJEMPLO 20C

1-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazina

El compuesto del título se preparó utilizando EJEMPLO 20B en lugar de EJEMPLO 1A en el EJEMPLO 1B.

EJEMPLO 20D

2-(1H-indazol-5–iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1–il)benzoato de etilo

Se agitó EJEMPLO 20A (330 mg), EJEMPLO 20C (335 mg), y HK_2PO_4 (191 mg) en dimetilsulfóxido (5 mL) a 140°C durante 24 horas. La reacción se diluyó con acetato de etilo, se lavó tres veces con agua, se lavó con salmuera, se secó, y se concentró. El producto crudo se cromatografió sobre gel de sílice con acetato de etilo al 30%/hexanos.

EJEMPLO 20E

ácido 2-(1H-indazol-5–iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 20D en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 20F

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-5–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 20E en lugar de EJEMPLO 1E y EJEMPLO 7A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 13,03 (br s, 1H), 11,25 (br s, 1H), 8,70 (m, 1H), 8,48 (d, 1H), 7,94 (dd, 1H), 7,68 (dd, 1H), 7,52 (m, 2H), 7,34 (d, 2H), 7,06 (m, 4H), 6,96 (dd, 1H), 6,88 (d, 1H), 6,23 (s, 1H), 3,61 (m, 4H), 3,44 (m, 2H), 3,05 (m, 4H), 2,73 (m, 2H), 2,42 (m, 4H), 2,18 (m, 4H), 1,99 (m, 2H), 1,91 (d, 2H), 1,78 (m, 2H), 1,39 (t, 2H), 1,17 (m, 2H), 0,93 (s, 6H).

EJEMPLO 21

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida

EJEMPLO 21A

4-(1-metilpiperidin-4–ilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando 4-amino-N-metilpiperidina en lugar de (tetrahidropiran-4–il)metilamina en el EJEMPLO 1F.

EJEMPLO 21B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 20E en lugar de EJEMPLO 1E y EJEMPLO 21A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 12,80 (br s, 1H), 10,70 (br s, 1H), 8,34 (s, 1H), 8,02 (d, 1H), 7,87 (d, 1H), 7,70 (dd, 1H), 7,55 (m, 2H), 7,36 (d, 2H), 7,06 (m, 2H), 6,95 (m, 1H), 6,72 (d, 1H), 6,62 (d, 1H), 6,24 (s, 1H), 3,35 (m, 4H), 3,18 (m, 2H), 3,00 (m, 2H), 2,80 (m, 4H), 2,73 (m, 2H), 2,20 (m, 4H), 1,99 (m, 2H), 1,91 (s, 3H), 1,54 (m, 1H), 1,41 (t, 2H), 1,22 (m, 2H), 1,09 (s, 6H).

EJEMPLO 22

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)-2-(1,2,3,4-tetrahidroquinolin-6–iloxi)benzamida

EJEMPLO 22A

4-fluoro-2-(1,2,3,4-tetrahidroquinolin-6–iloxi)benzoato de etilo

El compuesto del título se preparó utilizando 5-hidroxi-1,2,3,4-tetrahidroquinolina en lugar de 5-hidroxiindazol en el EJEMPLO 20A.

EJEMPLO 22B

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1–il)-2-(1,2,3,4-tetrahidroquinolin-6–iloxi)benzoato de etilo

El compuesto del título se preparó utilizando EJEMPLO 22A en lugar de EJEMPLO 20A en el EJEMPLO 20D.

EJEMPLO 22C

ácido 4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1–il)-2-(1,2,3,4-tetrahidroquinolin-6–iloxi)benzoico

El compuesto del título se preparó utilizando EJEMPLO 22B en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 22D

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)-2-(1,2,3,4-tetrahidroquinolin-6–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 22C en lugar de EJEMPLO 1E y EJEMPLO 7A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 10,95 (br s, 1H), 8,83 (m, 1H), 8,60(d, 1H), 7,90 (dd, 1H), 7,46 (d, 1H), 7,35 (d, 2H), 7,21 (dd, 2H), 7,06 (d, 2H), 6,62 (m, 2H), 6,42 (d, 1H), 6,11 (d, 1H), 5,61 (br s, 1H), 4,02 (m, 1H), 3,61 (m, 4H), 3,48 (m, 2H), 3,17 (m, 2H), 3,07 (m, 4H), 2,74 (m, 2H), 2,63 (m, 2H), 2,44 (m, 4H), 2,19 (m, 4H), 1,97 (m, 4H), 1,79 (m, 4H), 1,41 (t, 2H), 1,17 (m, 4H), 0,94 (s, 6H).

EJEMPLO 23

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)-2-(1,2,3,4-tetrahidroquinolin-6–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 22C en lugar de EJEMPLO 1E y EJEMPLO 21A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,10 (br s, 1H), 8,71(m, 1H), 8,42 (d, 1H), 7,73 (dd, 1H), 7,53 (d, 1H), 7,34 (d, 2H), 7,21 (dd, 2H), 7,10 (d, 2H), 6,96 (dd, 1H), 6,78 (d, 2H), 6,70 (d, 1H), 6,32 (s, 1H), 3,61 (m, 4H), 3,44 (m, 2H), 3,09 (m, 4H), 2,71 (m, 2H), 2,44 (m, 4H), 2,21 (m, 4H), 1,96 (m, 2H), 1,79 (m, 2H), 1,47 (t, 2H), 1,17 (m, 3H), 1,08 (m, 4H), 0,95 (s, 3H).

EJEMPLO 24

4-(4-{[4'-cloro-4-(pirrolidin-1–ilmetil)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 24A

5-formil-2-(trifluorometilsulfoniloxi)benzoato de metilo

Se agregó anhídrido tríflico (7,74 mL) a 5-formil-2-hidroxibenzoato de metilo (7,5 g) en 150 mL CH_2Cl_2 a 0°C, y la reacción se agitó y se dejó calentar a temperatura ambiente durante 3 horas. La reacción se diluyó con CH_2Cl_2 (150 mL), se lavó con 3x salmuera, se secó sobre Na_2SO_4, y se concentró. El producto se usó sin purificación adicional.

EJEMPLO 24B

4’-cloro-4-formilbifenil-2-carboxilato de metilo

Se agitó EJEMPLO 24A (14,5 g), ácido 4-clorofenilborónico (6,88 g) CsF (12,2 g), y tetrakis(trifenilfosfin)paladio(0) a 70°C durante 24 horas. La reacción se enfrió, se filtró, y se concentró. El producto crudo se capturó en acetato de etilo (250 mL), se lavó con 3x NaOH 1M, y salmuera, se concentró, y se cromatografió sobre gel de sílice con acetato de etilo al 10%/hexanos.

EJEMPLO 24C

4'-cloro-4-(pirrolidin-1–ilmetil)bifenil-2-carboxilato de metilo

El compuesto del título se preparó utilizando EJEMPLO 24B por 4'-clorobifenil-2-carboxaldehido y pirrolidina en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 24D

(4'-cloro-4-(pirrolidin-1–ilmetil)bifenil-2–il)metanol

Se agregó DIBAL en hexanos (1M, 5,9 mL) a EJEMPLO 24C (650 mg) en CH_2Cl_2 (30 mL) a 0°C, y la reacción se agitó por 20 minutos. La reacción se detuvo mediante la adición lenta de metanol (2 mL), y NaOH 1M (10 mL), y la solución resultante se extrajo dos veces con acetato de etilo. Los extractos se lavaron con salmuera, se secó sobre Na_2SO_4, y se concentró. El producto se usó sin purificación adicional.

EJEMPLO 24E

4'-cloro-4-(pirrolidin-1–ilmetil)bifenil-2-carbaldehido

Se agregó Periodinano de Dess-Martin (1,30 g) a EJEMPLO 24D (770 mg) en CH_2Cl_2 (30 mL) a temperatura ambiente y la reacción se agitó durante 24 horas. La mezcla de reacción se concentró y se cromatografió sobre gel de sílice con trietilamina al 1% en acetato de etilo al 25%/hexanos.

EJEMPLO 24F

2-(1H-indol-4–iloxi)-4-fluorobenzoato de metilo

El compuesto del título se preparó utilizando 4-hidroxiindol en lugar de 5-hidroxiindazol y 2,4-difluorobenzoato de metilo en lugar de 2,4-difluorobenzoato de etilo en el EJEMPLO 20A.

EJEMPLO 24G

4-(3-(1H-indol-4–iloxi)-4-(metoxicarbonil)fenil)piperazin-1-carboxilato de tert-butilo

El compuesto del título se preparó utilizando EJEMPLO 24F en lugar de EJEMPLO 20A y piperazin-1-carboxilato de tert-butilo en lugar de EJEMPLO 20C en el EJEMPLO 20D.

EJEMPLO 24H

2-(1H-indol-4–iloxi)-4-(piperazin-1–il)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 24G en lugar de EJEMPLO 1A en el EJEMPLO 1B.

EJEMPLO 24I

2-(1H-indol-4–iloxi)-4-(4-((4'-cloro-4-(pirrolidin-1–ilmetil)bifenil-2–il)metil)piperazin-1–il)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 24E en lugar de 4'-clorobifenil-2 carboxaldehido y EJEMPLO 24H en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 24J

ácido 2-(1H-indol-4–iloxi)-4-(4-((4'-cloro-4-(pirrolidin-1–ilmetil)bifenil-2–il)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 24I en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 24K

4-(4-{[4'-cloro-4-(pirrolidin-1–ilmetil)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 24J en lugar de EJEMPLO 1E en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,52 (br s, 1H), 11,26 (s, 1H), 10,68 (br s, 1H), 8,61 (dd, 1H), 8,49 (s, 1H), 8,19 (br s, 1H), 7,66 (d, 2H), 7,54 (m, 3H), 7,36 (m, 2H), 7,28 (s, 1H), 7,24 (d, 1H), 7,05 (d, 1H), 6,95 (dd, 1H), 6,75 (d, 1H), 6,35 (m, 2H), 6,26 (s, 1H), 4,38 (m, 3H), 3,85 (dd, 2H), 3,61 (m, 4H), 3,24 (m, 4H), 3,09 (m, 4H), 2,85 (m, 2H), 2,35 (m, 2H), 2,02 (m, 2H), 1,87 (m, 4H), 1,60 (m, 2H), 1,25 (m, 2H).

EJEMPLO 25

4-(4-{[4'-cloro-4-(2-pirrolidin-1–iletil)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 25A

4'-cloro-4-(2-oxoetil)bifenil-2-carboxilato de metilo

A una solución de óxido de (metoximetil)difenilfosfina (1,62 g) en 40 mL tetrahidrofurano a -78°C, se agregó diisopropilamida de litio (2M, 3,3 mL), y luego de agitar por 3 minutos, se agregó EJEMPLO 24B (1,57 g), y la solución se calentó a temperatura ambiente. Se agregó NaH (230 mg), y 40 mL de N,N-dimetilformamida, y la mezcla se calentó a 60°C durante 1 horas. La reacción se enfrió y se vertió en una solución de NaH_2PO_4. La solución resultante se extrajo dos veces con éter, y los extractos combinados se lavaron dos veces con agua y salmuera, y se concentró. La mezcla cruda de éteres enólicos se capturó en HCl 1M (50 mL) y dioxano (50 mL), y se agitó a 60°C durante 3 horas. La reacción se enfrió y se vertió en una solución de $NaHCO_3$. La solución resultante se extrajo dos veces con éter, y los extractos combinados se lavaron con agua, y salmuera, y se concentró. El producto se usó sin purificación adicional.

EJEMPLO 25B

4'-cloro-4-(2-(pirrolidin-1–il)etil)bifenil-2-carboxilato de metilo

El compuesto del título se preparó utilizando EJEMPLO 25A en lugar de 4'-clorobifenil-2-carboxaldehido y pirrolidina en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 25C

(4'-cloro-4-(2-(pirrolidin-1–il)etil)bifenil-2–il)metanol

El compuesto del título se preparó utilizando EJEMPLO 25B en lugar de EJEMPLO 24C en el EJEMPLO 24D.

EJEMPLO 25D

4'-cloro-4-(2-(pirrolidin-1–il)etil)bifenil-2-carbaldehido

El compuesto del título se preparó utilizando EJEMPLO 25C en lugar de EJEMPLO 24D en el EJEMPLO 24E.

EJEMPLO 25E

2-(1H-indol-4–iloxi)-4-(4-((4'-cloro-4-(2-(pirrolidin-1–il)etil)bifenil-2–il)metil)piperazin-1–il)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 25D en lugar de 4'-clorobifenil-2 carboxaldehido y EJEMPLO 24H en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 25F

ácido 2-(1H-indol-4–iloxi)-4-(4-((4'-cloro-4-(2-(pirrolidin-1–il)etil)bifenil-2–il)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 25E en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 25G

4-(4-{[4'-cloro-4-(2-pirrolidin-1–iletil)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 25F en lugar de EJEMPLO 1E en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,15 (s, 1H), 8,47 (t, 1H), 8,42 (s, 1H), 7,68 (dd, 1H), 7,58 (d, 1H), 7,44 (m, 4H), 7,22 (m, 3H), 7,10 (d, 1H), 6,92 (m, 2H), 6,68 (d, 1H), 6,34 (d, 1H), 6,26 (s, 2H), 3,87 (dd, 2H), 3,61 (m, 4H), 3,10-3,24 (m, 11H), 2,97 (m, 4H), 2,31 (m, 4H), 1,89 (m, 4H), 1,61 (m, 2H), 1,26 (m, 2H).

EJEMPLO 26

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1-ciclopentilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida

EJEMPLO 26A

2-(1H-indol-5–iloxi)-4-fluorobenzoato de etilo

El compuesto del título se preparó utilizando 5-hidroxiindol en lugar de 5-hidroxiindazol en el EJEMPLO 20A.

EJEMPLO 26B

2-(1H-indol-5–iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1–il)benzoato de etilo

El compuesto del título se preparó utilizando EJEMPLO 26A en lugar de EJEMPLO 20A en el EJEMPLO 20D.

EJEMPLO 26C

ácido 2-(1H-indol-5–iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 26B en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 26D

4-(1-ciclopentilpiperidin-4–ilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando 1-ciclopentilpiperidin-4-amina en lugar de (tetrahidropiran-4–il)metilamina en el EJEMPLO 1F.

EJEMPLO 26E

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1-ciclopentilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 26C en lugar de EJEMPLO 1E y EJEMPLO 26D en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,13 (br s, 1H), 8,52 (s, 1H), 8,14 (d, 1H), 7,80 (d, 1H), 7,52 (d, 1H), 7,35 (m, 4H), 7,04 (m, 4H), 6,80 (d, 1H), 6,61 (d, 1H), 6,36 (s, 1H), 6,14 (s, 1H), 5,76 (s, 1H), 3,84 (m, 2H), 3,24 (m, 4H), 2,99 (m, 4H), 2,85 (m, 2H), 2,71 (m, 2H), 2,16 (m, 6H), 1,95 (m, 4H), 1,50-1,70 (m, 6H), 1,38 (m, 2H), 1,17 (m, 2H), 0,93 (s, 6H).

EJEMPLO 27

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]-3-isobutilpiperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida

EJEMPLO 27A

2-bromo-4-metilpentanoato de metilo

A HBr concentrado (48%) (20 mL) en agua (214 mL), se agregó KBr (17,6 g, se enfrió a 0 °C, luego nitrito de sodio (5,2 g) todo a la vez, luego DL-leucina (5,2 g) en unas

pocas porciones. La reacción se agitó mecánicamente a 0 °C durante 1,5 horas, luego se extrajo con 2 x 200 mL acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera y se secó sobre Na_2SO_4. Luego de la filtración y la concentración, el aceite resultante se disolvió en CH_2Cl_2/metanol y se trató con 2,0*M* (TMS)CHN_2 en éter (30 mL) a temperatura ambiente durante 10 minutos. La reacción se concentró y luego se purificó por cromatografía flash usando 97,5/2,5 hexano/acetato de etilo.

EJEMPLO 27B

3-isobutilpiperazin-2-ona

Se agregó EJEMPLO 27A (2,2 g) en etanol (15 mL) por goteo a lo largo de un periodo de 2,5 horas a una solución a reflujo en agitación de etan-1,2-diamina (13,2 mL) en etanol (60 mL). El calentamiento se continuó por otras 2,5 horas, luego se agregó NaOEt en etanol (21% en peso, 4,0 mL) y se calentó por otros 90 minutos. La reacción luego se enfrió y se concentró. Luego de la trituración con éter, el compuesto del título se usó sin purificación.

EJEMPLO 27C

4'-clorobifenil-2-carbaldehido

A 2-bromobenzaldehido (2,3 ml) y tetrakis(trifenilfosfin)paladio(0) (0,35 g) en tolueno (50 mL), se agregó ácido 4-clorofenilborónico (4,0 g) y Na_2CO_3 2M (70 ml). La mezcla se calentó bajo reflujo por una hora. La reacción se enfrió, se diluyó con agua y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y las capas acuosas combinadas se extrajeron con acetato de etilo. Las capas orgánicas combinadas se secaron sobre Na_2SO_4. El material crudo se purificó por cromatografía flash usando 97,5/2,5 hexano/acetato de etilo.

EJEMPLO 27D

4-((4'-clorobifenil-2–il)metil)-3-isobutilpiperazin-2-ona

El compuesto del título se preparó utilizando EJEMPLO 27B en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 27E

1-((4'-clorobifenil-2–il)metil)-2-isobutilpiperazina

A una solución de EJEMPLO 27D en tetrahidrofurano (3,6 mL) se agregó complejo borano-sulfuro de metilo (10*M* en tetrahidrofurano) (0,24 mL). La reacción se

calentó bajo reflujo por 16 horas, luego se enfrió en un baño de hielo/agua. Se agregó metanol (5 mL) cuidadosamente, y la mezcla se agitó frío por 75 minutos. Luego se agregó HCl 4N en dioxano (0,65 mL) y la reacción se calentó bajo reflujo por 60 minutos. Luego de enfriar a temperatura ambiente, se agregó NH_4OH 1*N* (2,6 mL) y la reacción se agitó por 15 minutos. Luego la reacción se concentró, se disolvió nuevamente en metanol, se concentró, se disolvió nuevamente en tolueno y se concentró. Los sólidos crudos se colocaron en $CHCl_3$/metanol formando una lechada, los sólidos se retiraron por filtración, y el material filtrado se concentró para dar el compuesto del título.

EJEMPLO 27F

4-(4-((4'-clorobifenil-2–il)metil)-3-isobutilpiperazin-1–il)-2-fenoxibenzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 27E en lugar de EJEMPLO 1B en el EJEMPLO 1D.

EJEMPLO 27G

ácido 4-(4-((4'-clorobifenil-2–il)metil)-3-isobutilpiperazin-1–il)-2-fenoxibenzoico

El compuesto del título se preparó utilizando EJEMPLO 27F en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 27H

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]-3-isobutilpiperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida

Se agitó EJEMPLO 27G (13 mg), EJEMPLO 1F (7 mg), clorhidrato de 1-etil-3-[3-(dimetilamino)propil]-carbodiimida (8 mg), y 4-dimetilaminopiridina (5 mg) en CH_2Cl_2 (1 mL) durante 24 horas. El producto se purificó mediante HPLC preparativa usando una columna C18, 250 x 50 mm, 10□, y eluyendo con un gradiente de 20-100% CH_3CN vs. ácido trifluoroacético al 0,1% en agua, para dar el producto como una sal trifluoroacetato. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11,62 (br s, 1H), 9,10 (br s, 1H), 8,65 (t, 1H), 8,47 (d, 1H), 7,77 (dd, 1H), 7,70 (br s, 1H), 7,50 (m, 5H), 7,39 (m, 3H), 7,25 (m, 2H), 7,18 (d, 1H), 7,01 (dd, 1H), 6,83 (m, 2H), 6,76 (m, 1H), 6,40 (br s, 1H), 4,70 y 4,15 (ambos v br s, total 1H), 3,85 (dd, 2H), 3,60 (v br s, 1H), 3,32, 3,27, 3,24, 3,06 (all m, total 11H), 1,90 (m, 1H), 1,62 (m, 3H), 1,30 (m, 4H), 0,70 (br m, 6H).

EJEMPLO 28

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-{[4-(2,4-dioxo-3-azabiciclo[3,2,0]hept-3–il)fenil]sulfonil}-2-fenoxibenzamida

El compuesto del título se preparó utilizando EJEMPLO 1E en lugar de EJEMPLO 27G y 4-(2,4-dioxo-3-azabiciclo[3,2,0]heptan-3–il)bencensulfonamida en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11,87 (br s, 1H), 9,58 (br s, 1H), 7,93 (d, 2H), 7,71 (br s, 1H), 7,54 (m, 7H), 7,35 (m, 5H), 7,10 (dd, 1H), 6,89 (d, 2H), 6,78 (dd, 1H), 6,42 (s, 1H), 4,37 (br s, 1H), 3,78 (br s, 1H), 3,43 (m, 4H), 3,22, 3,00, 2,85 (all v br s, total 6H), 2,62 (m, 2H), 2,18 (m, 2H).

EJEMPLO 29

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-{[4-(4-metil-6-oxo-1,4,5,6-tetrahidropiridazin-3–il)fenil]sulfonil}-2-fenoxibenzamida

El compuesto del título se preparó utilizando EJEMPLO 1E en lugar de EJEMPLO 27G y 4-(4-metil-6-oxo-1,4,5,6-tetrahidropiridazin-3–il)bezenesulfonamida en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11,87 (br s, 1H), 11,20 (s, 1H), 9,58 (br s, 1H), 7,90 (d, 2H), 7,83 (d, 2H), 7,50 (m, 5H), 7,32 (m, 5H), 7,08 (dd, 1H), 6,85 (d, 2H), 6,76 (dd, 1H), 6,43 (s, 1H), 4,38 (br s, 1H), 3,80 (br s, 1H), 3,60 (m, 2H), 3,40 (m, 2H), 3,21, 3,00, 2,84 (all br s, total 6H), 2,75 (dd, 1H), 2,28 (d, 1H), 1,08 (d, 3H).

EJEMPLO 30

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-{[4-(3,3-dimetil-2-oxoazetidin-1–il)fenil]sulfonil}-2-fenoxibenzamida

El compuesto del título se preparó utilizando EJEMPLO 1E en lugar de EJEMPLO 27G y 4-(3,3-dimetil-2-oxoazetidin-1–il)bencensulfonamida en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11,62 (br s, 1H), 9,58 (br s, 1H), 7,80 (d, 2H), 7,72 (br s, 1H), 7,50 (m, 5H), 7,40 (m, 4H), 7,33 (m, 3H), 7,08 (dd, 1H), 6,85 (d, 2H), 6,76 (dd, 1H), 6,41 (s, 1H), 4,38 (br s, 1H), 3,77 (br s, 1H), 3,58 (s, 2H), 3,45 (m, 2H), 3,21, 3,00, 2,84 (all br s, total 6H), 1,32 (s, 6H).

EJEMPLO 31

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-{[4-(4-nitro-2H-1,2,3-triazol-2–il)fenil]sulfonil}-2-fenoxibenzamida

El compuesto del título se preparó utilizando EJEMPLO 1E en lugar de EJEMPLO 27G y 4-(4-nitro-2*H*-1,2,3-triazol-2–il)bencensulfonamida en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11,98 (br s, 1H), 9,58 (br s, 1H), 9,11 (s, 1H), 8,21 (d, 2H), 8,05 (d, 2H), 7,70 (br s, 1H), 7,50 (m, 5H), 7,39 (m, 2H), 7,30 (m, 1H), 7,24 (m, 2H), 7,00 (dd, 1H), 6,82 (d, 2H), 6,78 (dd, 1H), 6,43 (s, 1H), 4,38 (br s, 1H), 3,77 (br s, 1H), 3,45 (m, 2H), 3,21, 3,00, 2,84 (all br s, total 6H).

EJEMPLO 32

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-fenoxi-N-{[2-(2-piperidin-1–iletoxi)fenil]sulfonil}benzamida

El compuesto del título se preparó utilizando EJEMPLO 1E en lugar de EJEMPLO 27G y 2-(2-(piperidin-1–il)etoxi)bencensulfonamida en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11,65 (br s, 1H), 9,77 (br s, 1H), 8,95 (br s, 1H), 7,80 (dd, 1H), 7,70 (br s, 1H), 7,68 (m, 1H), 7,50 (m, 5H), 7,36 (m, 5H), 7,23 (d, 1H), 7,15 (m, 2H), 6,90 (d, 2H), 6,78 (dd, 1H), 6,42 (s, 1H), 4,40 (m, 3H), 3,80 (br s, 1H), 3,40, 3,20 3,00, 2,90 (todos v br m, total 13H), 1,63 (m, 5H), 1,27 (v br s, 1H).

EJEMPLO 33

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-{[3-({[(1-etilpirrolidin-2–il)metil]amino}carbonil)-4-metoxifenil]sulfonil}-2-fenoxibenzamida

El compuesto del título se preparó utilizando EJEMPLO 1E en lugar de EJEMPLO 27G y *N*-((1-etilpirrolidin-2–il)metil)-2-metoxi-5-sulfamoilbenzamida en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11,75 (br s, 1H), 9,70 (br s, 1H), 9,25 (br s, 1H), 8,62 (t, 1H), 8,25 (d, 1H), 7,90 (dd, 1H), 7,70 (br s, 1H), 7,50 (m, 5H), 7,40 (m, 2H), 7,10 (m, 5H), 7,09 (dd, 1H), 6,85 (d, 2H), 6,76 (dd, 1H), 6,40 (s, 1H), 4,39 (br s, 1H), 3,96 (s, 3H), 3,77 (br s, 1H), 3,60 (m, 4H), 3,55-2,80 (envolvente, 10H), 2,12 (m, 1H), 2,00 (m, 1H), 1,85 (m, 2H), 1,23 (t, 3H).

EJEMPLO 34

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1-naftiloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 34A

2-bromo-4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)benzoato de metilo

El compuesto del título se preparó utilizando 2-bromo-4-fluorobenzoato de metilo en lugar de EJEMPLO 1C en el EJEMPLO 1D.

EJEMPLO 34B

4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-(naftalen-1–iloxi)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 34A en lugar de EJEMPLO 18E y 1-naftol en lugar de fenol en el EJEMPLO 18F.

EJEMPLO 34C

Ácido 4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-(naftalen-1–iloxi)benzoico

El compuesto del título se preparó utilizando EJEMPLO 34B en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 34D

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1-naftiloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 34C en lugar de EJEMPLO 27G en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11,82 (br s, 1H), 9,50 (br s, 1H), 8,58 (t, 1H), 8,29 (d, 1H), 8,18 (d, 1H), 7,85 (d, 1H), 7,70 (br s, 1H), 7,50 (m, 8H), 7,38 (m, 4H), 7,20 (dd, 1H), 6,82 (m, 2H), 6,55 (s, 1H), 6,45 (d, 1H), 4,38 (br s, 1H), 3,85 (dd, 2H), 3,78 (br s, 1H), 3,27 (m, 6H), 3,22, 3,02, 2,85 (all br s, total 6H), 1,84 (m, 1H), 1,60 (m, 2H), 1,29 (m, 2H).

EJEMPLO 35

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(2-naftiloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 35A

1-(difluorometilsulfonil)-2-fluorobenceno

El compuesto del título se preparó utilizando EJEMPLO 34A en lugar de EJEMPLO 18E y 2-naftol en lugar de fenol en el EJEMPLO 18F.

EJEMPLO 35B

Ácido 4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-(naftalen-2–iloxi)benzoico

El compuesto del título se preparó utilizando EJEMPLO 35A en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 35C

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(2-naftiloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 35B en lugar de EJEMPLO 27G en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11,80 (br s, 1H), 9,55 (br s, 1H), 8,50 (t, 1H), 8,39 (d, 1H), 7,83 (m, 2H), 7,69 (br s, 1H), 7,64 (d, 1H), 7,50 (m, 6H), 7,37 (m, 5H), 7,18 (dd, 1H), 7,00 (d, 1H), 6,81 (dd, 1H), 6,77 (d, 1H), 6,56 (d, 1H), 4,38 (br s, 1H), 3,85 (dd, 2H), 3,78 (br s, 1H), 3,27 (m, 6H), 3,22, 3,02, 2,85 (all br s, total 6H), 1,84 (m, 1H), 1,60 (m, 2H), 1,29 (m, 2H).

EJEMPLO 36

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)-2-(2-naftiloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 35B en lugar de EJEMPLO 27G y EJEMPLO 7A en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11,80 (br s, 1H), 9,61 (br s, 2H), 8,57 (t, 1H), 8,40 (d, 1H), 7,83 (m, 2H), 7,66 (m, 2H), 7,50 (m, 6H), 7,40 (m, 5H), 7,18 (dd, 1H), 7,02 (d, 1H), 6,81 (d, 1H), 6,57 (s, 1H), 4,38 (br s, 1H), 4,00 (m, 2H), 3,80 (br s, 1H), 3,40 (m, 8H), 3,30-2,80 (envolvente, 10H), 1,92 (m, 2H).

EJEMPLO 37

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(2-naftiloxi)-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 35B en lugar de EJEMPLO 27G y EJEMPLO 163A en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11,82 (br s, 1H), 9,58 (br s, 1H), 8,03 (d, 1H), 7,90 (m, 2H), 7,70 (d, 1H), 7,69 (br s, 1H), 7,65 (dd, 1H), 7,50 (m, 7H), 7,36 (m, 3H), 7,18 (m, 2H), 7,05 (d, 1H), 6,81 (dd, 1H), 6,75 (d, 1H), 6,56 (d, 1H), 4,38 (br s, 1H), 3,83 (dd, 2H), 3,78 (br s, 1H), 3,23

(m, 4H), 3,22, 3,02, 2,85 (all br s, total 6H), 3,15 (m, 2H), 1,80 (m, 1H), 1,55 (m, 2H), 1,22 (m, 2H).

EJEMPLO 38

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(quinolin-7–iloxi)benzamida

EJEMPLO 38A

4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-(quinolin-7–iloxi)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 34A en lugar de EJEMPLO 18E y quinolin-7-ol en lugar de fenol en el EJEMPLO 18F.

EJEMPLO 38B

ácido 4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-(quinolin-7–iloxi)benzoico

El compuesto del título se preparó utilizando EJEMPLO 38A en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 38C

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(quinolin-7–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 38B en lugar de EJEMPLO 27G en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 8,80 (d, 1H), 8,48 (t, 1H), 8,35 (d, 1H), 8,32 (d, 1H), 7,90 (d, 1H), 7,74 (m, 1H), 7,59 (m, 2H), 7,50 (m, 4H), 7,45 (dd, 1H), 7,38 (d, 2H), 7,30 (m, 2H), 6,95 (d, 1H), 6,86 (dd, 1H), 6,83 (d, 1H), 6,71 (d, 1H), 4,38 (br s, 1H), 3,85 (dd, 2H), 3,78 (br s, 1H), 3,30-2,80 (envolvente, 12H), 1,84 (m, 1H), 1,60 (m, 2H), 1,25 (m, 2H).

EJEMPLO 39

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(quinolin-6–iloxi)benzamida

EJEMPLO 39A

4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-(quinolin-6–iloxi)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 34A en lugar de EJEMPLO 18E y quinolin-6-ol en lugar de fenol en el EJEMPLO 18F.

EJEMPLO 39B

Ácido 4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-(quinolin-6–iloxi)benzoico

El compuesto del título se preparó utilizando EJEMPLO 39A en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 39C

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(quinolin-6–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 39B en lugar de EJEMPLO 27G en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11,90 (br s, 1H), 9,65 (br s, 1H), 8,80 (d, 1H), 8,46 (t, 1H), 8,35 (d, 1H), 7,90 (d, 1H), 7,72 (m, 1H), 7,50 (m, 6H), 7,45 (dd, 1H), 7,37 (m, 4H), 7,02 (d, 1H), 6,83 (dd, 1H), 6,79 (d, 1H), 6,63 (d, 1H), 4,38 (br s, 1H), 3,85 (dd, 2H), 3,78 (br s, 1H), 3,40-2,80 (envolvente 12H), 1,87 (m, 1H), 1,62 (m, 2H), 1,26 (m, 2H).

EJEMPLO 40

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 40A

1-(triisopropilsilil)-1H-indol-5-ol

Se trató 5-benciloxi-indol (1,0 g) con NaH (135 mg) y cloruro de triisopropilsililo (1,0 g) en tetrahidrofurano por 1 hora, se purificó por cromatografía flash (98/2 acetato de etilo/hexanos), luego se desbenciló en etanol (35 mL) usando Catalizador de Pearlman (0,19 g) y un balón de hidrógeno.

EJEMPLO 40B

2-(1H-indol-5–iloxi)-4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 34A en lugar de EJEMPLO 18E y EJEMPLO 40A en lugar de fenol en el EJEMPLO 18F. en este ejemplo, el material crudo de la formación del éter se destiló usando fluoruro de tetrabutilamonio en tetrahidrofurano/agua 95/5 antes de la purificación.

EJEMPLO 40C

ácido 2-(1H-indol-5–iloxi)-4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 40B en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 40D

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 40C en lugar de EJEMPLO 27G en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11,40 (br s, 1H), 11,17 (s, 1H), 9,50 (v br s, 1H), 8,61 (t, 1H), 8,57 (d, 1H), 7,77 (dd, 1H), 7,70 (br s, 1H), 7,50 (m, 5H), 7,36 (m, 5H), 7,10 (s, 1H), 7,08 (d, 1H), 6,83 (dd, 1H), 6,69 (dd, 1H), 6,37 (m, 1H), 6,21 (d, 1H), 4,30 (br s, 1H), 3,84 (dd, 2H), 3,70 (br s, 1H), 3,30 (m, 6H), 3,20, 2,95, 2,80 (all br s, total 6H), 1,86 (m, 1H), 1,60 (m, 2H), 1,25 (m, 2H).

EJEMPLO 41

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(isoquinolin-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 41A

4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-(isoquinolin-5–iloxi)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 34A en lugar de EJEMPLO 18E y isoquinolin-5-ol en lugar de fenol en el EJEMPLO 18F.

EJEMPLO 41B

ácido 4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-(isoquinolin-5–iloxi)benzoico

El compuesto del título se preparó utilizando EJEMPLO 41A en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 41C

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(isoquinolin-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 41B en lugar de EJEMPLO 27G en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11,90 (br s, 1H), 9,55 (v br s, 1H), 9,26 (s, 1H), 8,47 (m, 2H), 8,14 (d, 1H), 7,99 (d, 1H), 7,65 (br s, 1H), 7,60 (d, 1H), 7,45 (m, 6H), 7,29 (m, 4H), 6,80 (m, 2H), 6,60 (m, 2H), 4,38 (br s, 1H), 3,85 (dd, 2H), 3,78 (br s, 1H), 3,24 (m, 6H), 3,22,3,00, 2,85 (all br s, total 6H), 1,87 (m, 1H), 1,62 (m, 2H), 1,26 (m, 2H).

EJEMPLO 42

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(4-{[3-(dimetilamino)propil]amino}-3-nitrofenil)sulfonil]-2-(isoquinolin-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 41B en lugar de EJEMPLO 27G y EJEMPLO 154A en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11,90 (br s, 1H), 9,38 (v br s, 1H), 9,22 (s, 1H), 8,54 (t, 1H), 8,45 (d, 1H), 8,16 (d, 1H), 7,96 (d, 1H), 7,62 (br s, 1H), 7,56 (d, 1H), 7,50 (d, 1H), 7,45 (m, 5H), 7,29 (m, 4H), 6,80 (m, 2H), 6,60 (m, 2H), 4,23 (br s, 1H), 3,78 (br s, 1H), 3,40 (m, 2H), 3,35-2,80 (envolvente, 8H), 3,08 (m, 2H), 2,72, 2,70 (ambos s, total 6H), 1,87 (m, 2H).

EJEMPLO 43

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(4-{[3-(dimetilamino)propil]amino}-3-nitrofenil)sulfonil]-2-(quinolin-6–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 39B en lugar de EJEMPLO 27G y EJEMPLO 154A en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11,96 (br s, 1H), 9,38 (v br s, 1H), 8,77 (dd, 1H), 8,51 (t, 1H), 8,35 (d, 1H), 8,05 (d,1H), 7,90 (d, 1H), 7,70 (br s, 1H), 7,50 (m, 6H), 7,38 (m, 5H), 6,98 (d, 1H), 6,83 (dd, 1H), 6,79 (d, 1H), 6,63 (d, 1H), 4,38 (br s, 1H), 3,78 (br s, 1H), 3,42 (m, 2H), 3,35-2,80 (envolvente, 8H), 3,15 (m, 2H), 2,81, 2,79 (ambos s, total 6H), 1,93 (m, 2H).

EJEMPLO 44

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(4-{[3-(dimetilamino)propil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 40C en lugar de EJEMPLO 27G y EJEMPLO 154A en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11,40 (br s, 1H), 11,18 (s, 1H), 9,30 (v br s, 1H), 8,66 (t, 1H), 8,60 (d, 1H), 7,85 (dd, 1H), 7,52 (d, 1H), 7,50 (m, 5H), 7,40 (m, 4H), 7,30 (br s, 1H), 7,14 (s, 1H), 7,10 (d, 1H), 6,84 (dd, 1H), 6,67 (dd, 1H), 6,39 (m, 1H), 6,20 (s, 1H), 4,35 (br s, 1H), 3,78 (br s, 1H), 3,40 (m, 2H), 3,35-2,80 (envolvente, 8H), 3,10 (m, 2H), 2,78, 2,76 (ambos s, total 6H), 1,95 (m, 2H).

EJEMPLO 45

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 45A

1-(triisopropilsilil)-1H-indol-4-ol

Se trató 4-benciloxi-indol (1,0 g) con NaH (135 mg) y cloruro de triisopropilsililo (1,0 g) en tetrahidrofurano por 1 hora, se purificó por cromatografía flash (98/2 acetato de etilo/hexanos), luego se desbenciló en etanol (35 mL) usando catalizador de Pearlman (0,19 g) y un balón de hidrógeno.

EJEMPLO 45B

2-(1H-indol-4–iloxi)-4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 34A en lugar de EJEMPLO 18E y EJEMPLO 45A en lugar de fenol en el EJEMPLO 18F. En este caso el material crudo de la formación del éter se destiló usando fluoruro de tetra-n-butilamonio en tetrahidrofurano/agua 95/5 antes de la purificación.

EJEMPLO 45C

Ácido 2-(1H-indol-4–iloxi)-4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 45B en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 45D

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 45C en lugar de EJEMPLO 27G en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11,50 (br s, 1H), 11,24 (s, 1H), 9,50 (v br s, 1H), 8,61 (t, 1H), 8,47 (d, 1H), 7,70 (br s, 1H), 7,64 (dd, 1H), 7,50 (m, 5H), 7,30 (m, 4H), 7,15 (d, 2H), 7,04 (d, 2H), 6,92 (dd, 1H), 6,75 (dd, 1H), 6,33 (m, 2H), 6,23 (s, 1H), 4,30 (br s, 1H), 3,84 (dd, 2H), 3,70 (br s, 1H), 3,30 (m, 6H), 3,20, 2,95, 2,80 (all br s, total 6H), 1,86 (m, 1H), 1,60 (m, 2H), 1,25 (m, 2H).

EJEMPLO 46

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(4-{[3-(dimetilamino)propil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 45C en lugar de EJEMPLO 27G y EJEMPLO 154A en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11,50 (v br s, 1H), 11,24 (s, 1H), 9,30 (br s, 1H), 8,66 (t, 1H), 8,53 (d, 1H), 7,85 (dd, 1H), 7,55 (d, 1H), 7,50 (m, 5H), 7,39 (m, 2H), 7,30 (m, 2H), 7,148 (d, 1H), 7,10 (d, 1H), 6,96 (dd, 1H), 6,72 (dd, 1H), 6,41 (d, 1H), 6,32 (s, 1H), 6,23 (s, 1H), 4,35 (br s, 1H), 3,78 (br s, 1H), 3,40 (m, 2H), 3,35-2,80 (envolvente, 8H), 3,10 (m, 2H), 2,78, 2,76 (ambos s, total 6H), 1,95 (m, 2H).

EJEMPLO 47

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(4-{[3-(dimetilamino)propil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-6–iloxi)benzamida

EJEMPLO 47A

1-(triisopropilsilil)-1H-indol-6-ol

Se trató 6-Benciloxi-indol (1,0 g) con NaH (135 mg) y cloruro de triisopropilsililo (1,0 g) en tetrahidrofurano por 1 hora, se purificó por cromatografía flash (98/2 acetato de etilo/hexanos), luego se desbenciló en etanol (35 mL) usando catalizador de Pearlman (0,19 g) y un balón de hidrógeno.

EJEMPLO 47B

2-(1H-indol-6–iloxi)-4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 34A en lugar de EJEMPLO 18E y EJEMPLO 47A en lugar de fenol en el EJEMPLO 18F. En este ejemplo, el material crudo de

la formación del éter se destiló usando fluoruro de tetrabutilamonio en tetrahidrofurano/agua 95/5 antes de la purificación.

EJEMPLO 47C

Ácido 2-(1H-indol-6–iloxi)-4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 47B en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 47D

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(4-{[3-(dimetilamino)propil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-6–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 47C en lugar de EJEMPLO 27G y EJEMPLO 154A en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11,50 (v br s, 1H), 11,00 (s, 1H), 9,38 (br s, 1H), 8,64 (t, 1H), 8,58 (d, 1H), 7,75 (dd, 1H), 7,65 (br s, 1H), 7,55 (d, 1H), 7,50 (m, 5H), 7,39 (m, 2H), 7,30 (m, 2H), 7,00 (d, 1H), 6,90 (s, 1H), 6,70 (m, 2H), 6,42 (m, 1H), 6,30 (s, 1H), 4,35 (br s, 1H), 3,78 (br s, 1H), 3,40 (m, 2H), 3,35-2,80 (envolvente, 8H), 3,10 (m, 2H), 2,78, 2,76 (ambos s, total 6H), 1,95 (m, 2H).

EJEMPLO 48

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(isoquinolin-7–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)benzamida

EJEMPLO 48A

El compuesto del título se preparó utilizando EJEMPLO 34A en lugar de EJEMPLO 18E y isoquinolin-7-ol en lugar de fenol en el EJEMPLO 18F.

EJEMPLO 48B

Ácido4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-(isoquinolin-7–iloxi)benzoico

El compuesto del título se preparó utilizando EJEMPLO 48A en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 48C

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(isoquinolin-7–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 48B en lugar de EJEMPLO 27G y EJEMPLO 7A en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11,98 (v br s, 1H), 9,70 (v br s, 2H), 9,10 (s, 1H), 8,56 (t, 1H), 8,42 (d, 1H), 8,13 (d, 1H), 7,93 (d, 1H), 7,81 (d, 1H), 7,70 (br s, 1H), 7,60 (m, 2H), 7,50 (m, 5H), 7,40 (d, 2H), 7,35 (m, 1H), 7,14 (d, 1H), 6,84 (m, 2H), 6,70 (d, 1H), 4,38 (br s, 1H), 4,00 (m, 2H), 3,80 (br s, 1H), 3,40 (m, 4H), 3,30-2,80 (envolvente, 10H), 3,20 (m, 4H), 1,92 (m, 2H).

EJEMPLO 49

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(4-{[3-(dimetilamino)propil]amino}-3-nitrofenil)sulfonil]-2-(isoquinolin-7–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 48B en lugar de EJEMPLO 27G y EJEMPLO 154A en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ11,98 (v br s, 1H), 9,40 (br s, 2H), 9,10 (s, 1H), 8,56 (t, 1H), 8,40 (d, 1H), 8,13 (d, 1H), 7,93 (d, 1H), 7,81 (d, 1H), 7,70 (br s, 1H), 7,60 (m, 2H), 7,50 (m, 5H), 7,40 (d, 2H), 7,35 (m, 1H), 7,14 (d, 1H), 6,84 (m, 2H), 6,70 (d, 1H), 4,38 (br s, 1H), 3,78 (br s, 1H), 3,42 (m, 2H), 3,35-2,80 (envolvente, 8H), 3,15 (m, 2H), 2,81, 2,79 (ambos s, total 6H), 1,93 (m, 2H).

EJEMPLO 50

4-(4-{[2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)benzamida

EJEMPLO 50A

2-(1H-indol-5–iloxi)-4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-enil)metil)piperazin-1–il)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 19D en lugar de EJEMPLO 34A en el EJEMPLO 40B.

EJEMPLO 50B

Ácido 2-(1H-indol-5–iloxi)-4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-enil)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 50A en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 50C

4-(4-{[2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 50B en lugar de EJEMPLO 27G y EJEMPLO 7A en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11,98 (br s, 1H), 11,20 (s, 1H), 9,70 (v br s, 1H), 9,35 (v br s, 1H), 8,71 (t, 1H), 8,62 (d, 1H), 7,86 (dd, 1H), 7,54 (d, 1H), 7,40 (m, 4H), 7,12 (m, 4H), 6,87 (dd, 1H), 6,70 (dd, 1H), 6,40 (m, 1H), 6,20 (d, 1H), 3,98 (m, 2H), 3,50, 3,40, 3,30 (all m, total 12H), 3,19 (m, 2H), 3,00 (m, 4H), 2,75 (br s, 2H), 2,23 (br m, 2H), 1,97 (br m, 2H), 1,43 (br t, 2H), 0,98 (s, 6H).

EJEMPLO 51

4-(4-{[2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[3-(dimetilamino)propil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 50B en lugar de EJEMPLO 27G y EJEMPLO 154A en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11,42 (br s, 1H), 11,20 (s, 1H), 9,40 (v br s, 1H), 9,30 (v br s, 1H), 8,66 (t, 1H), 8,61 (d, 1H), 7,86 (dd, 1H), 7,54 (d, 1H), 7,40 (m, 4H), 7,18 (d, 1H), 7,12 (m, 3H), 6,87 (dd, 1H), 6,70 (dd, 1H), 6,40 (s, 1H), 6,20 (s, 1H), 3,60 (br s, 2H), 3,50 (m, 4H), 3,35 (br s, 2H), 3,13 (m, 3H), 3,00 (br m, 2H), 2,78, 2,77 (ambos s, total 6H), 2,70 (br s, 1H), 2,12 (br m, 2H), 1,97 (m, 4H), 1,42 (br t, 2H), 0,97 (s, 6H).

EJEMPLO 52

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 26C en lugar de EJEMPLO 27G y EJEMPLO 7A en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11,40 (br s, 1H), 11,20 (s, 1H), 9,60 (v br s, 1H), 9,25 (v br s, 1H), 8,70 (t, 1H), 8,62 (d, 1H), 7,86 (dd, 1H), 7,54 (d, 1H), 7,40 (m, 4H), 7,18 (d, 1H), 7,13 (d, 1H), 7,09 (d, 2H), 6,87 (dd, 1H), 6,70 (dd, 1H), 6,40 (m, 1H), 6,20 (s, 1H), 3,98 (m, 2H),

3,50, 3,40, 3,30 (all m, total 12H), 3,19 (m, 2H), 3,00 (m, 4H), 2,75 (br s, 2H), 2,18 (br m, 2H), 2,00 (br m, 4H), 1,43 (br t, 2H), 0,96 (s, 6H).

EJEMPLO 53

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[3-(dimetilamino)propil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 27G y EJEMPLO 154A en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11,41 (br s, 1H), 11,20 (s, 1H), 9,35 (v br s, 2H), 8,66 (t, 1H), 8,62 (d, 1H), 7,86 (dd, 1H), 7,54 (d, 1H), 7,40 (m, 4H), 7,18 (d, 1H), 7,13 (d, 1H), 7,09 (d, 2H), 6,87 (dd, 1H), 6,70 (dd, 1H), 6,40 (m, 1H), 6,20 (s, 1H), 3,50 (m, 4H), 3,35 (br s, 2H), 3,13 (m, 3H), 3,00 (br m, 2H), 2,78, 2,77 (ambos s, total 6H), 2,70 (br s, 1H), 2,20 (br m, 2H), 2,00 (m, 2H), 1,93 (m, 2H), 1,42 (br t, 2H), 0,97 (s, 6H).

EJEMPLO 54

4-(4-{[2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)benzamida

EJEMPLO 54A

2-(1H-indol-4–iloxi)-4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-enil)metil)piperazin-1–il)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 19D en lugar de EJEMPLO 34A en el EJEMPLO 45B.

EJEMPLO 54B

Ácido 2-(1H-indol-4–iloxi)-4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-enil)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 54A en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 54C

4-(4-{[2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 54B en lugar de EJEMPLO 27G y EJEMPLO 7A en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11,50 (br s, 1H), 11,27 (s, 1H), 9,60 (v br s, 1H), 9,20 (v br s, 1H), 8,65 (t, 1H), 8,55 (d, 1H), 7,80 (dd, 1H), 7,57 (d, 1H), 7,40 (d, 2H), 7,30 (dd, 1H), 7,12 (d, 2H), 7,10 (d, 2H), 7,00 (dd, 1H), 6,73 (dd, 1H), 6,46 (d,1H), 6,30 (s, 1H), 6,23 (m, 1H), 3,98 (m, 2H), 3,60, 3,50, 3,40 (all m, total 12H), 3,19 (m, 2H), 3,00 (m, 4H), 2,75 (br s, 2H), 2,23 (br m, 2H), 1,97 (br m, 4H), 1,43 (br t, 2H), 0,98 (s, 6H).

EJEMPLO 55

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)benzamida

EJEMPLO 55A

2-(1H-indol-4–iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1–il)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 45A en lugar de fenol en el EJEMPLO 18F. En este caso el material crudo de la formación del éter se destiló usando fluoruro de tetrabutilamonio en tetrahidrofurano/agua 95/5 antes de la purificación.

EJEMPLO 55B

Ácido 2-(1H-indol-4–iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 55A en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 55C

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 27G y EJEMPLO 7A en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11,50 (br s, 1H), 11,25 (s, 1H), 9,60 (v br s, 1H), 9,20 (v br s, 1H), 8,65 (t, 1H), 8,55 (d, 1H), 7,80 (dd, 1H), 7,57 (d, 1H), 7,40 (d, 2H), 7,30 (dd, 1H), 7,20 (d, 1H), 7,10 (m, 3H), 7,00 (dd, 1H), 6,73 (dd, 1H), 6,46 (d,1H), 6,30 (s, 1H), 6,23 (m, 1H), 3,98

(m, 2H), 3,60, 3,50, 3,40 (all m, total 12H), 3,19 (m, 2H), 3,00 (m, 4H), 2,75 (br s, 2H), 2,20 (br m, 2H), 2,00 (br m, 4H), 1,43 (br t, 2H), 0,98 (s, 6H).

EJEMPLO 56

4-(4-{[2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[3-(dimetilamino)propil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 54B en lugar de EJEMPLO 27G y EJEMPLO 154A en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11,55 (br s, 1H), 11,27 (s, 1H), 9,40 (v br s, 1H), 9,35 (v br s, 1H), 8,65 (t, 1H), 8,55 (d, 1H), 7,79 (dd, 1H), 7,57 (d, 1H), 7,40 (d, 2H), 7,30 (dd, 1H), 7,20 (d, 1H), 7,10 (m, 3H), 7,00 (dd, 1H), 6,73 (dd, 1H), 6,46 (d,1H), 6,30 (s, 1H), 6,23 (m, 1H), 3,50 (m, 4H), 3,35 (br s, 2H), 3,13 (m, 3H), 3,00 (br m, 2H), 2,78, 2,77 (ambos s, total 6H), 2,70 (br s, 1H), 2,22 (br m, 2H), 1,97 (m, 2H), 1,93 (m, 2H), 1,42 (br t, 2H), 0,97 (s, 6H).

EJEMPLO 57

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[3-(dimetilamino)propil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 27G y EJEMPLO 154A en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11,50 (br s, 1H), 11,25 (s, 1H), 9,60 (v br s, 1H), 9,20 (v br s, 1H), 8,65 (t, 1H), 8,55 (d, 1H), 7,79 (dd, 1H), 7,57 (d, 1H), 7,40 (d, 2H), 7,30 (dd, 1H), 7,20 (d, 1H), 7,10 (m, 3H), 7,00 (dd, 1H), 6,73 (dd, 1H), 6,46 (d,1H), 6,30 (s, 1H), 6,23 (m, 1H), 3,50 (m, 4H), 3,35 (br s, 2H), 3,13 (m, 3H), 3,00 (br m, 2H), 2,78, 2,77 (ambos s, total 6H), 2,70 (br s, 1H), 2,20 (br m, 2H), 2,00 (m, 2H), 1,93 (m, 2H), 1,42 (br t, 2H), 0,97 (s, 6H).

EJEMPLO 58

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 45C en lugar de EJEMPLO 27G y EJEMPLO 7A en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11,50 (br s, 1H), 11,24 (s, 1H), 9,50 (v br s, 1H), 8,67 (t, 1H), 8,52 (d, 1H), 7,78 (dd, 1H), 7,70 (br s, 1H), 7,55 (d, 1H), 7,50 (m, 4H), 7,38 (d, 2H), 7,30 (dd, 2H), 7,18 (d, 1H), 7,08 (d, 1H), 6,96 (dd, 1H), 6,75 (dd, 1H), 6,40 (d, 1H), 6,33 (s, 1H), 6,23 (s,

1H), 4,38 (br s, 1H), 4,00 (m, 2H), 3,80 (br s, 1H), 3,40 (m, 4H), 3,30-2,80 (envolvente, 10H), 3,20 (m, 4H), 1,95 (m, 2H).

EJEMPLO 59

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-5–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 40C en lugar de EJEMPLO 27G y EJEMPLO 7A en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11,40 (br s, 1H), 11,19 (s, 1H), 9,60 (v br s, 1H), 8,69 (t, 1H), 8,60 (d, 1H), 7,83 (dd, 1H), 7,65 (br s, 1H), 7,50 (m, 5H), 7,38 (m, 5H), 7,12 (m, 2H), 6,83 (dd, 1H), 6,69 (dd, 1H), 6,39 (m, 1H), 6,20 (d, 1H), 4,38 (br s, 1H), 4,00 (m, 2H), 3,80 (br s, 1H), 3,40 (m, 4H), 3,30-2,80 (envolvente, 10H), 3,20 (m, 4H), 1,96 (m, 2H).

EJEMPLO 60

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(4-metoxifenil)sulfonil]-2-fenoxibenzamida

El compuesto del título se preparó utilizando EJEMPLO 1E en lugar de EJEMPLO 27G y 4-metoxibencensulfonamida en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,57 (s, 1H), 7,74 (d, 2H), 7,50 (m, 5H), 7,35 (m, 6H), 7,10 (t, 1H), 7,02 (m, 2H), 6,87 (d, 2H), 6,75 (dd, 1H), 6,41 (s, 1H), 4,36 (m, 2H), 3,83 (s, 3H), 3,76 (m, 2H), 3,23 (m, 2H), 3,01 (m, 2H), 2,84 (m, 2H).

EJEMPLO 61

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(4-metilfenil)sulfonil]-2-fenoxibenzamida

El compuesto del título se preparó utilizando EJEMPLO 1E en lugar de EJEMPLO 27G y 4-metilbencensulfonamida en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,64 (s, 1H), 7,68 (d, 2H), 7,50 (m, 5H), 7,38 (m, 2H), 7,32 (m, 6H), 7,11 (t, 1H), 6,87 (d, 2H), 6,75 (dd, 1H), 6,41 (s, 1H), 4,36 (m, 2H), 3,76 (m, 2H), 3,23 (m, 2H), 3,01 (m, 2H), 2,84 (m, 2H), 2,37 (s, 3H).

EJEMPLO 62

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-5–iloxi)-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 40C en lugar de EJEMPLO 27G y EJEMPLO 163A en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,46 (s, 1H), 11,16 (s, 1H), 8,17 (d, 1H), 7,88 (dd, 1H), 7,68 (br s, 1H), 7,50 (m, 5H), 7,36 (m, 6H), 7,13 (s, 1H), 7,03 (d, 1H), 6,84 (dd, 1H), 6,68 (dd, 1H), 6,39 (m, 1H), 6,21 (br s, 1H), 4,32 (s, 2H), 3,84 (dd, 2H), 3,25 (m, 7H), 2,93 (m, 4H), 1,84 (m, 2H), 1,54 (m, 2H), 1,24 (m, 2H).

EJEMPLO 63

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 45C en lugar de EJEMPLO 27G y EJEMPLO 163A en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,58 (s, 1H), 11,27 (s, 1H), 8,12 (d, 1H), 7,71 (m, 2H), 7,52 (m, 5H), 7,32 (m, 5H), 7,18 (d, 1H), 6,96 (m, 2H), 6,74 (dd, 1H), 6,36 (m, 2H), 6,26 (m, 1H), 4,32 (s, 2H), 3,84 (dd, 2H), 3,25 (m, 7H), 2,93 (m, 4H), 1,84 (m, 2H), 1,54 (m, 2H), 1,24 (m, 2H).

EJEMPLO 64

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({4-{[3-(dimetilamino)propil]amino}-3-[(trifluorometil)sulfonil]fenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 40C y EJEMPLO 170A en lugar de EJEMPLO 27G y EJEMPLO 1F respectivamente, en el EJEMPLO 27H. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,46 (br s, 1H), 11,18 (s, 1H), 8,21 (d, 1H), 7,98 (dd, 1H), 7,50 (m, 6H), 7,41 (m, 5H), 7,29 (br s, 1H), 7,17 (s, 1H), 7,08 (d, 1H), 6,84 (dd, 1H), 6,68 (dd, 1H), 6,40 (m, 1H), 6,18 (br s, 1H), 4,32 (br s, 2H), 3,59 (m, 4H), 3,25 (m, 2H), 3,05 (m, 4H), 2,90 (m, 2H), 2,77 (d, 6H), 1,88 (m, 2H).

EJEMPLO 65

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

EJEMPLO 65A

4-(3-morfolinopropilamino)-3-(trifluorometilsulfonil)bencensulfonamida

El compuesto del título se preparó utilizando EJEMPLO 159C y 3-morfolinopropan-1-amina en lugar de 4-fluoro-3-nitrobencensulfonamida y (tetrahidropiran-4–il)metilamina respectivamente, en el EJEMPLO 1F.

EJEMPLO 65B

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 40C y EJEMPLO 65A en lugar de EJEMPLO 27G y EJEMPLO 1F respectivamente, en el EJEMPLO 27H. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,46 (br s, 1H), 11,18 (s, 1H), 8,18 (d, 1H), 7,91 (m, 1H), 7,50 (m, 6H), 7,41 (m, 5H), 7,30 (m, 1H), 7,19 (d, 1H), 7,08 (m, 1H), 6,99 (m, 1H), 6,72 (dd, 1H), 6,48 (br s, 1H), 6,25 (m, 1H), 4,29 (br s, 2H), 4,01 (m, 2H), 3,59 (m, 2H), 3,41 (m, 4H), 3,05 (m, 10H), 2,58 (m, 2H), 1,91 (m, 2H).

EJEMPLO 66

N-[(3-{[cloro(difluoro)metil]sulfonil}-4-{[3-(dimetilamino)propil]amino}fenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)benzamida

EJEMPLO 66A

(difluorometil)(2-fluorofenil)sulfano

Se agitó NaOH en polvo (31,2 g), tris(2-(2-metoxietoxi)etil)amina (5 mL) y 2-fluorobenceno tiol (33,6 mL) en benceno (400 mL) saturado con clorodifluorometano, a 80°C durante 30 minutos y se filtró a través de tierra diatomea (Celite®). El filtrado se lavó con $NaHCO_3$ saturado y la capa acuosa se extrajo con éter dietílico. Los extractos se combinaron y se secó ($MgSO_4$), se filtró y se concentró.

EJEMPLO 66B

1-(difluorometilsulfonil)-2-fluorobenceno

Se trató EJEMPLO 66A (46 g) en 1:1:2 CCl_4/CH_3CN/agua (1,2L) a 25ºC con $NaIO_4$ (164,6 g) y $RuCl_3 \cdot xH_2O$ (534 mg), se agitó por 18 horas, se diluyó con diclorometano y se

filtró a través de tierra diatomea (Celite®). El filtrado se lavó con $NaHCO_3$ saturado y se secó (Na_2SO_4), se filtró y se concentró. El concentrado se filtró a través de gel de sílice.

EJEMPLO 66C

1-(clorodifluorometilsulfonil)-2-fluorobenceno

Se trató EJEMPLO 66B (25 g) y N-clorosuccinimida (17,55 g) en tetrahidrofurano (690 mL) a -78°C con hexametildisilazida de litio (178,5 mL) a lo largo de 1 hora, se agitó por 1 hora y se detuvo con cloruro de amonio. La mezcla se extrajo con acetato de etilo, y el extracto se lavó con salmuera y se secó ($MgSO_4$), se filtró y se concentró. El concentrado se cromatografió sobre gel de sílice con acetato de etilo al 0-5%/hexanos.

EJEMPLO 66D

Cloruro de 3-(clorodifluorometilsulfonil)-4-fluorobenceno-1-sulfonilo

Se agitó EJEMPLO 66C (44 g) en ácido clorosulfónico (36,7 mL) a 120°C por 18 horas, se enfrió a 25ºC, se pipeteó sobre hielo molido y se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera y se secó ($MgSO_4$), se filtró y se concentró.

EJEMPLO 66E

3-(clorodifluorometilsulfonil)-4-fluorobencensulfonamida

Se trató EJEMPLO 66D (22 g) en isopropanol (690 mL) a -78°C con amoníaco acuoso (90 mL) a lo largo de 1 hora, se agitó durante otra hora, se detuvo con HCl 6M (300 mL), se calentó a 25ºC y se concentró. El concentrado se mezcló con agua y se extrajo con acetato de etilo. El extracto se secó ($MgSO_4$), se filtró y se concentró. El concentrado se recristalizó a partir de hexanos/acetato de etilo.

EJEMPLO 66F

3-(clorodifluorometilsulfonil)-4-(3-(dimetilamino)propilamino)bencensulfonamida

El compuesto del título se preparó utilizando EJEMPLO 66E y N,N-dimetilpropan-1,3-diamina en lugar de 4-fluoro-3-nitrobencensulfonamida y (tetrahidropiran-4–il)metilamina respectivamente, en el EJEMPLO 1F.

EJEMPLO 66G

N-[(3-{[cloro(difluoro)metil]sulfonil}-4-{[3-(dimetilamino)propil]amino}fenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 54B y EJEMPLO 66F en lugar de EJEMPLO 27G y EJEMPLO 1F respectivamente, en el EJEMPLO 27H. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,20 (s, 1H), 8,28 (m,1H), 7,99 (m, 1H), 7,55 (m, 2H), 7,38 (m, 2H), 7,21 (m, 3H), 7,09 (d, 2H), 6,98 (m, 1H), 6,71 (m, 1H), 6,41 (m, 2H), 6,21 (m, 1H), 3,57 (m, 2H), 3,28 (m, 4H), 2,84 (m, 6H), 2,67 (m, 5H), 2,19 (m, 2H), 2,02 (m, 2H), 1,77 (br s, 2H), 1,61 (m, 2H), 1,46 (m, 2H), 0,94 (s, 6H).

EJEMPLO 67

N-[(3-{[cloro(difluoro)metil]sulfonil}-4-{[3-(dimetilamino)propil]amino}fenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 26C y EJEMPLO 66F en lugar de EJEMPLO 27G y EJEMPLO 1F respectivamente, en el EJEMPLO 27H. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,20 (s, 1H), 8,28 (m,1H), 8,05 (m, 1H), 7,99 (m, 1H), 7,55 (m, 2H), 7,38 (m, 2H), 7,21 (m, 3H), 7,09 (d, 2H), 6,98 (m, 1H), 6,71 (m, 1H), 6,41 (m, 2H), 6,21 (m, 1H), 3,57 (m, 2H), 3,28 (m, 4H), 3,05 (m, 2H), 2,96 (m, 2H), 2,88 (s, 3H), 2,78 (m, 2H), 2,68 (m, 3H), 2,19 (m, 2H), 2,01 (br s, 2H), 1,72 (m, 2H), 1,45 (m, 2H), 0,93 (s, 6H).

EJEMPLO 68

2-(1H-indol-4–iloxi)-4-(4-{[2-(4-metoxifenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(3-pirrolidin-1–ilpropil)amino]fenil}sulfonil)benzamida

EJEMPLO 68A

(2-bromo-4,4-dimetilciclohex-1-enil)metanol

Se capturó N,N-dimetilformamida (18,41 ml) en cloroformo (64 ml) y la solución resultante se enfrió en un baño de hielo. Se agregó tribromuro de fósforo (20,18 ml) por goteo a lo largo de 15 minutos. La suspensión resultante luego se calentó a 70 °C durante 30 minutos. Se agregó una solución de 3,3-dimetilciclohexanona (10 g) en cloroformo (21 ml) por goteo por 30 minutos. La mezcla se agitó a 70 °C durante otras 2 horas. La mezcla luego se dejó enfriar a temperatura ambiente. La solución se vertió cuidadosamente sobre hielo. Se

agregó bicarbonato de sodio sólido para neutralizar el ácido. La mezcla se extrajo tres veces con éter, y los extractos se lavaron con agua y salmuera y se secó ($MgSO_4$). El solvente se eliminó al vacío, y el material crudo se hizo pasar a través de un tapón de sílice con éter como eluyente. Después de la concentración, el material crudo se disolvió en metanol. Se agregó borohidruro de sodio (1,757 g) cuidadosamente. La mezcla resultante se agitó a temperatura ambiente durante la noche, y se diluyó con acetato de etilo. La mezcla se lavó con agua y salmuera y se secó ($MgSO_4$). El solvente se eliminó al vacío, y el residuo se purificó por cromatografía flash eluyendo con acetato de etilo al 20% en hexanos hasta 100% acetato de etilo.

EJEMPLO 68B

2-(1H-indol-4–iloxi)-4-(piperazin-1–il)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 24F y piperazina en lugar de EJEMPLO 1C y EJEMPLO 1B respectivamente, en el EJEMPLO 1D.

EJEMPLO 68C

2-(1H-indol-4–iloxi)-4-(4-((2-bromo-4,4-dimetilciclohex-1-enil)metil)piperazin-1–il)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 68A y EJEMPLO 68B en lugar de EJEMPLO 18C y EJEMPLO 18D respectivamente, en el EJEMPLO 18E.

EJEMPLO 68D

2-(1H-indol-4–iloxi)-4-(4-((2-(4-metoxifenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1–il)benzoato de metilo

Se combinó EJEMPLO 68C (142mg), ácido 4-metoxifenilborónico (45,6 mg), dicloruro de bis(trifenilfosfin)paladio(II) (8,7 mg), y fluoruro de cesio (114 mg) en dimetoxietano (0,9 mL) y metanol (0,4 mL) y se calentó a 90°C por 2 horas. La mezcla de reacción se diluyó con acetato de etilo y se vertió en agua. La capa orgánica se lavó con agua y con salmuera, se secó ($MgSO_4$), se filtró, y se concentró. El sólido resultante se trituró con metanol, y se filtró.

EJEMPLO 68E

Ácido 2-(1H-indol-4–iloxi)-4-(4-((2-(4-metoxifenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 68D en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 68F

3-nitro-4-(3-(pirrolidin-1–il)propilamino)bencensulfonamida

El compuesto del título se preparó utilizando 3-(pirrolidin-1–il)propan-1-amina en lugar de (tetrahidropiran-4–il)metilamina en el EJEMPLO 1F.

EJEMPLO 68G

2-(1H-indol-4–iloxi)-4-(4-{[2-(4-metoxifenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(3-pirrolidin-1–ilpropil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 68E y EJEMPLO 68F en lugar de EJEMPLO 27G y EJEMPLO 1F respectivamente, en el EJEMPLO 27H. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,56 (brs, 1H), 11,26 (s, 1H), 8,66 (t, 1H), 8,53 (d, 1H), 7,78 (dd, 1H), 7,56 (d, 1H), 7,29 (t, 1H), 7,19 (d, 1H), 7,10 (d, 1H), 6,98 (m, 3H), 6,88 (m, 2H), 6,74 (m, 1H), 6,43 (d, 1H), 6,36 (br s, 1H), 6,23 (m, 1H), 3,73 (s, 3H), 3,62 (m, 2H), 3,52 (m, 4H), 3,22 (m, 4H), 2,99 (m, 4H), 2,18 (m, 2H), 1,99 (m, 6H), 1,84 (m, 2H), 1,45 (m, 2H), 1,23 (m, 2H), 0,94 (s, 6H).

EJEMPLO 69

4-[4-({4,4-dimetil-2-[4-(trifluorometil)fenil]ciclohex-1-en-1–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(3-pirrolidin-1–ilpropil)amino]fenil}sulfonil)benzamida

EJEMPLO 69A

2-(1H-indol-4–iloxi)-4-(4-((4,4-dimetil-2-(4-(trifluorometil)fenil)ciclohex-1-enil)metil)piperazin-1–il)benzoato de metilo

El compuesto del título se preparó utilizando ácido 4-(trifluorometil)fenilborónico en lugar de ácido 4-metoxifenilborónico en el EJEMPLO 68D.

EJEMPLO 69B

ácido 2-(1H-indol-4–iloxi)-4-(4-((4,4-dimetil-2-(4-(trifluorometil)fenil)ciclohex-1-enil)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 69A en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 69C

4-[4-({4,4-dimetil-2-[4-(trifluorometil)fenil]ciclohex-1-en-1–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(3-pirrolidin-1–ilpropil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 69B y EJEMPLO 68F en lugar de EJEMPLO 27G y EJEMPLO 1F respectivamente, en el EJEMPLO 27H. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,55 (br s, 1H), 11,26 (s, 1H), 8,66 (t, 1H), 8,53 (d, 1H), 7,78 (m, 1H), 7,67 (m, 2H), 7,56 (m, 1H), 7,29 (m, 3H), 7,19 (d, 1H), 7,10 (d, 1H), 6,98 (m, 1H), 6,72 (m, 1H), 6,46 (m, 1H), 6,36 (br s, 1H), 6,23 (m, 1H), 3,62 (m, 4H), 3,52 (m, 4H), 3,18 (m, 4H), 3,02 (m, 4H), 2,19 (m, 2H), 2,02 (m, 6H), 1,82 (m, 2H), 1,47 (m, 2H), 0,94 (s, 6H).

EJEMPLO 70

4-[4-({4,4-dimetil-2-[4-(trifluorometoxi)fenil]ciclohex-1-en-1–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(3-pirrolidin-1–ilpropil)amino]fenil}sulfonil)benzamida

EJEMPLO 70A

2-(1H-indol-4–iloxi)-4-(4-((4,4-dimetil-2-(4-(trifluorometoxi)fenil)ciclohex-1-enil)metil)piperazin-1–il)benzoato de metilo

El compuesto del título se preparó utilizando ácido 4-(trifluorometoxi)fenilborónico en lugar de ácido 4-metoxifenilborónico en el EJEMPLO 68D.

EJEMPLO 70B

ácido 2-(1H-indol-4–iloxi)-4-(4-((4,4-dimetil-2-(4-(trifluorometoxi)fenil)ciclohex-1-enil)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 70A en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 70C

4-[4-({4,4-dimetil-2-[4-(trifluorometoxi)fenil]ciclohex-1-en-1–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(3-pirrolidin-1–ilpropil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 70B y EJEMPLO 68F en lugar de EJEMPLO 27G y EJEMPLO 1F respectivamente, en el EJEMPLO 27H. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,56 (br s, 1H), 11,26 (s, 1H), 8,66 (t, 1H), 8,54 (d, 1H),

7,80 (m, 1H), 7,63 (m, 2H), 7,56 (m, 3H), 7,29 (m, 2H), 7,19 (m, 2H), 6,98 (m, 1H), 6,72 (m, 1H), 6,46 (m, 1H), 6,23 (m, 1H), 3,62 (m, 4H), 3,52 (m, 4H), 3,18 (m, 4H), 3,02 (m, 4H), 2,19 (m, 2H), 2,02 (m, 6H), 1,82 (m, 2H), 1,47 (m, 2H), 0,94 (s, 6H).

EJEMPLO 71

4-[4-({4,4-dimetil-2-[3-(trifluorometil)fenil]ciclohex-1-en-1–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(3-pirrolidin-1–ilpropil)amino]fenil}sulfonil)benzamida

EJEMPLO 71A

2-(1H-indol-4–iloxi)-4-(4-((4,4-dimetil-2-(3-(trifluorometil)fenil)ciclohex-1-enil)metil)piperazin-1–il)benzoato de metilo

El compuesto del título se preparó utilizando ácido 3-(trifluorometil)fenilborónico en lugar de ácido 4-metoxifenilborónico en el EJEMPLO 68D.

EJEMPLO 71B

ácido 2-(1H-indol-4–iloxi)-4-(4-((4,4-dimetil-2-(3-(trifluorometil)fenil)ciclohex-1-enil)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 71A en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 71C

4-[4-({4,4-dimetil-2-[3-(trifluorometil)fenil]ciclohex-1-en-1–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(3-pirrolidin-1–ilpropil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 71B y EJEMPLO 68F en lugar de EJEMPLO 27G y EJEMPLO 1F respectivamente, en el EJEMPLO 27H. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,55 (br s, 1H), 11,26 (s, 1H), 8,65 (t, 1H), 8,54 (d, 1H), 7,80 (dd, 1H), 7,63 (m, 2H), 7,56 (m, 3H), 7,38 (m, 2H), 7,29 (t, 1H), 7,19 (d, 1H), 7,11 (d, 1H), 6,98 (t, 1H), 6,72 (m, 1H), 6,46 (m, 1H), 6,31 (m, 1H), 6,23 (m, 1H), 3,58 (m, 7H), 3,18 (m, 4H), 3,02 (m, 4H), 2,19 (m, 3H), 2,02 (m, 6H), 1,82 (m, 2H), 1,47 (m, 2H), 0,96 (s, 6H).

EJEMPLO 72

4-(4-{[2-(3-fluorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(3-pirrolidin-1–ilpropil)amino]fenil}sulfonil)benzamida

EJEMPLO 72A

2-(1H-indol-4–iloxi)-4-(4-((2-(3-fluorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1–il)benzoato de metilo

El compuesto del título se preparó utilizando ácido 3-fluorofenilborónico en lugar de ácido 4-metoxifenilborónico en el EJEMPLO 68D.

EJEMPLO 72B

ácido 2-(1H-indol-4–iloxi)-4-(4-((2-(3-fluorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 72A en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 72C

4-(4-{[2-(3-fluorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(3-pirrolidin-1–ilpropil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 72B y EJEMPLO 68F en lugar de EJEMPLO 27G y EJEMPLO 1F respectivamente, en el EJEMPLO 27H. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,55 (br s, 1H), 11,26 (s, 1H), 8,65 (t, 1H), 8,54 (d, 1H), 7,80 (m, 1H), 7,63 (m, 2H), 7,56 (m, 3H), 7,38 (m, 2H), 7,29 (t, 1H), 7,19 (d, 1H), 7,11 (d, 1H), 6,98 (m, 1H), 6,72 (m, 1H), 6,46 (m, 1H), 6,31 (m, 1H), 6,23 (m, 1H), 3,58 (m, 7H), 3,18 (m, 4H), 3,02 (m, 4H), 2,19 (m, 3H), 2,02 (m, 6H), 1,82 (m, 2H), 1,47 (m, 2H), 0,96 (s, 6H).

EJEMPLO 73

4-(4-{[2-(4-fluorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(3-pirrolidin-1–ilpropil)amino]fenil}sulfonil)benzamida

EJEMPLO 73A

2-(1H-indol-4–iloxi)-4-(4-((2-(4-fluorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1–il)benzoato de metilo

El compuesto del título se preparó utilizando ácido 4-fluorofenilborónico en lugar de ácido 4-metoxifenilborónico en el EJEMPLO 68D.

EJEMPLO 73B

ácido 2-(1H-indol-4–iloxi)-4-(4-((2-(4-fluorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 73A en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 73C

4-(4-{[2-(4-fluorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(3-pirrolidin-1–ilpropil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 73B y EJEMPLO 68F en lugar de EJEMPLO 27G y EJEMPLO 1F respectivamente, en el EJEMPLO 27H. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,56 (br s, 1H), 11,26 (s, 1H), 8,66 (t, 1H), 8,54 (d, 1H), 7,80 (m, 1H), 7,63 (m, 2H), 7,56 (m, 3H), 7,29 (m, 2H), 7,19 (m, 2H), 6,98 (m, 1H), 6,72 (m, 1H), 6,46 (m, 1H), 6,23 (m, 1H), 3,62 (m, 4H), 3,52 (m, 4H), 3,18 (m, 4H), 3,02 (m, 4H), 2,19 (m, 2H), 2,02 (m, 6H), 1,82 (m, 2H), 1,47 (m, 2H), 0,94 (s, 6H).

EJEMPLO 74

N-({3-{[cloro(difluoro)metil]sulfonil}-4-[(1-metilpiperidin-4–il)amino]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida

EJEMPLO 74A

3-(clorodifluorometilsulfonil)-4-(1-metilpiperidin-4–ilamino)bencensulfonamida

El compuesto del título se preparó utilizando EJEMPLO 66E y 1-metilpiperidin-4-amina en lugar de 4-fluoro-3-nitrobencensulfonamida y (tetrahidropiran-4–il)metilamina respectivamente, en el EJEMPLO 1F.

EJEMPLO 74B

N-({3-{[cloro(difluoro)metil]sulfonil}-4-[(1-metilpiperidin-4–il)amino]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 26C y EJEMPLO 74A en lugar de EJEMPLO 1E y EJEMPLO 1F respectivamente, en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,07 (s, 1H), 8,11 (d, 1H), 7,89 (dd, 1H), 7,50 (d, 1H), 7,34 (m, 4H), 7,05 (m, 3H), 6,96 (d, 1H), 6,78 (dd, 1H), 6,60 (m, 2H), 6,36 (s, 1H), 6,13 (d,

1H), 3,67 (m, 1H), 2,97 (m, 6H), 2,71 (s, 2H), 2,59 (m, 2H), 2,46 (s, 3H), 2,16 (m, 6H), 1,98 (m, 4H), 1,55 (m, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 75

4-(4-{[2-(4-clorofenil)ciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida

EJEMPLO 75A

2-(1H-indol-5–iloxi)-4-(4-((2-(4-clorofenil)ciclohex-1-enil)metil)piperazin-1–il)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 149D y EJEMPLO 150A en lugar de 4'-clorobifenil-2-carboxaldehido y piperazin-1-carboxilato de tert-butilo respectivamente, en el EJEMPLO 1A.

EJEMPLO 75B

ácido 2-(1H-indol-5–iloxi)-4-(4-((2-(4-clorofenil)ciclohex-1-enil)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 75A en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 75C

4-(4-{[2-(4-clorofenil)ciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 75B y EJEMPLO 21A en lugar de EJEMPLO 1E y EJEMPLO 1F respectivamente, en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,07 (s, 1H), 8,52 (d, 1H), 8,12 (d, 1H), 7,79 (dd, 1H), 7,52 (d, 1H), 7,34 (m, 4H), 7,05 (m, 4H), 6,79 (dd, 1H), 6,59 (dd, 1H), 6,36 (s, 1H), 6,13 (d, 1H), 3,72 (m, 1H), 2,97 (m, 6H), 2,69 (s, 2H), 2,59 (m, 2H), 2,46 (s, 3H), 2,16 (m, 6H), 2,11 (m, 2H), 1,98 (m, 2H), 1,70 (m, 2H), 1,62 (m, 4H).

EJEMPLO 76

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

EJEMPLO 76A

4-(1-metilpiperidin-4–ilamino)-3-(trifluorometilsulfonil)bencensulfonamida

El compuesto del título se preparó utilizando EJEMPLO 159C y 1-metilpiperidin-4-amina en lugar de 4-fluoro-3-nitrobencensulfonamida y (tetrahidropiran-4–il)metilamina respectivamente, en el EJEMPLO 1F.

EJEMPLO 76B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 26C y EJEMPLO 76A en lugar de EJEMPLO 1E y EJEMPLO 1F respectivamente, en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,08 (s, 1H), 8,11 (d, 1H), 7,89 (dd, 1H), 7,50 (d, 1H), 7,34 (m, 4H), 7,05 (m, 3H), 6,98 (d, 1H), 6,78 (dd, 1H), 6,60 (m, 2H), 6,36 (t, 1H), 6,13 (d, 1H), 3,67 (br s, 1H), 2,97 (m, 6H), 2,71 (s, 3H), 2,63 (m, 1H), 2,47 (s, 3H), 2,17 (m, 6H), 1,98 (m, 4H), 1,60 (m, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 77

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(fenoximetil)benzamida

EJEMPLO 77A

5-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)isobenzofuran-1(3H)-ona

Se agregó 5-bromoisobenzofuran-1(3H)-ona (400 mg), EJEMPLO 1B (646 mg), y fosfato de potasio tribásico (558 mg) a 1,2-dimetoxietano (10 mL). La solución se desgasificó al vacío y hizo pasar nitrógeno tres veces. Se agregó tris(dibencilidenacetona)dipaladio(0) (51,6 mg) y 2-(di-tert-butilfosfino)bifenilo (67,2 mg) y la solución se calentó a 80°C durante 16 horas. La solución se enfrió, se filtró, se concentró, y se purificó por cromatografía de columna flash sobre gel de sílice con acetato de etilo al 30% en hexanos.

EJEMPLO 77B

ácido 4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-(hidroximetil)benzoico

Se agregó EJEMPLO 77A (256 mg) y hidróxido de litio monohidratado (154 mg) a 1,4-dioxano (4 mL) y agua (1 mL). La solución se calentó a 65°C durante 16 horas, se enfrió, se concentró al vacío, y se purificó por cromatografía de columna flash sobre gel de sílice con acetato de etilo. La solución luego se secó con sulfato de sodio anhidro para dar producto crudo de suficiente pureza para su uso posterior.

EJEMPLO 77C

4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-(hidroximetil)benzoato de metilo

Se agregó trimetilsilildiazometano (solución 2M en dietiléter, 0,214 mL) a EJEMPLO 77B (170 mg) disuelto en acetato de etilo (2 mL) y metanol (2 mL). La solución se mezcló por 5 minutos luego de los cuales el solvente se eliminó al vacío para dar producto crudo de suficiente pureza para su uso posterior.

EJEMPLO 77D

4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-(fenoximetil)benzoato de metilo

Se agregó trifenilfosfina (93 mg) a tetrahidrofurano (3 mL) y se enfrió a 0°C. Se agregó dietilazodicarboxilato (solución al 40%, 0,161 mL), y la solución se agitó a 0°C durante 15 minutos. Se agregó fenol (33,3 mg) y EJEMPLO 77C (145 mg), y la solución se dejó tomar la temperatura ambiente y se mezcló durante 16 horas. La solución se concentró al vacío y se purificó por cromatografía de columna flash sobre gel de sílice con acetato de etilo al 30% (hexanos) aumentando a acetato de etilo al 50% (hexanos).

EJEMPLO 77E

ácido 4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-(fenoximetil)benzoico

El compuesto del título se preparó utilizando EJEMPLO 77D en lugar de EJEMPLO 77A en el EJEMPLO 77B.

EJEMPLO 77F

El compuesto del título se preparó utilizando EJEMPLO 77E en lugar de EJEMPLO 1E en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 8,52 (m, 2H), 7,88 (dd, 1H), 7,84 (d, 1H), 7,50 (m, 2H), 7,48 (s, 3H), 7,37 (m, 2H), 7,26 - 7,10 (m, 4H), 7,01 (s, 1H), 6,87 (t, 1H), 6,83 - 6,75 (m, 3 H), 5,22 (ancho s, 2H), 3,84 (dd, 2H), 3,41 - 3,10 (m, 10H), 2,39 (ancho s, 4H), 1,89 (m, 1H), 1,60 (m, 2H), 1,32 - 1,18 (m, 2H).

EJEMPLO 78

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({4-[(3-morfolin-4–ilpropil)amino]fenil}sulfonil)-2-fenoxibenzamida

EJEMPLO 78A

N-(4-sulfamoilfenil)acrilamida

Se agregó 4-aminobencensulfonamida (1,00 g) y piridina (1,41 mL) a 1,4-dioxano (30 mL). Se agregó cloruro de acriloilo (0,49 mL) por goteo y la solución se agitó por 3 horas a temperatura ambiente. Se agregó HCl 1M, y la solución se extrajo con acetato de etilo. Los extractos se secaron usando salmuera y sulfato de sodio anhidro y el solvente se eliminó para dar producto crudo de suficiente pureza para su uso posterior.

EJEMPLO 78B

3-morfolino-N-(4-sulfamoilfenil)propanamida

Se agregó EJEMPLO 78A (359 mg) y morfolina (1,38 mL) a acetonitrilo (10 mL) y N,N-dimetilformamida (1 mL) y se mezcló a temperatura ambiente durante 16 horas. La solución se concentró al vacío, y se purificó por cromatografía de columna flash sobre gel de sílice con metanol al 5% en diclorometano.

EJEMPLO 78C

4-(3-morfolinopropilamino)bencensulfonamida

Se agregó EJEMPLO 78B (268 mg) a tetrahidrofurano (4 mL). Se agregó lentamente borano (1M en tetrahidrofurano, 4,28 mL), y la solución se mezcló a temperatura ambiente durante 16 horas. La reacción se detuvo lentamente con metanol. Se agregó resina de N,N-diisopropiletilamina (3,42 mmol de amina) y la solución se mezcló a temperatura ambiente durante 15 minutos. La solución se filtró, se concentró al vacío, y se purificó por cromatografía de columna flash sobre gel de sílice con metanol al 10% en acetato de etilo.

EJEMPLO 78D

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({4-[(3-morfolin-4–ilpropil)amino]fenil}sulfonil)-2-fenoxibenzamida

El compuesto del título se preparó utilizando EJEMPLO 78C en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 10,98 (ancho s, 1H), 7,51 - 7,44 (m, 9H), 7,40 - 7,31 (m, 3H), 7,26 - 7,21 (m, 1H), 7,13 (tt, 1H), 6,94 (dd, 2H), 6,75

(dd, 1H), 6,66 (t, 1H), 6,54 (d, 2H), 6,32 (d, 1H), 3,57 (t, 4H), 3,35 (m, 2H), 3,16 – 3,04 (m, 6H), 2,35 (m, 10H), 1,60 (m, 2H).

EJEMPLO 79

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(piridin-3–iloxi)benzamida

EJEMPLO 79A

4-bromo-2-fluorobenzoato de metilo

Se agregó ácido 4-bromo-2-fluorobenzoico (5,00 g) a acetato de etilo (35 mL) y metanol (35 mL). Se agregó trimetilsilildiazometano (solución 2M en dietiléter, 12,56 mL) lentamente y la solución se mezcló a temperatura ambiente durante 30 minutos. El solvente se eliminó al vacío, y el material crudo se disolvió en acetato de etilo. La solución se extrajo con hidróxido de sodio 0,5M y se secó con salmuera luego sulfato de sodio anhidro. Luego de la filtración, el solvente se eliminó al vacío para dar producto crudo de suficiente pureza para su uso posterior.

EJEMPLO 79B

4-bromo-2-(piridin-3–iloxi)benzoato de metilo

Se agregó EJEMPLO 79A (500 mg), piridina-3-ol (204 mg), y carbonato de potasio (385 mg) a N,N-dimetilacetamida (18 mL) y la mezcla se calentó a 145°C por 2 horas y luego a 130°C durante 16 horas. La solución se enfrió, se agregó a agua (100 mL), se extrajo con acetato de etilo al 70% en hexanos, y se secó con sulfato de sodio anhidro. Luego de la filtración, la solución se concentró al vacío y se purificó por cromatografía de columna flash sobre gel de sílice con acetato de etilo al 50-70% en hexanos.

EJEMPLO 79C

4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-(piridin-3–iloxi)benzoato de metilo

Se agregó EJEMPLO 79B (367 mg), EJEMPLO 1B (410 mg), y fosfato de potasio tribásico (379 mg) a 1,2-dimetoxietano (6 mL). La solución se desgasificó al vacío y se hizo pasar nitrógeno tres veces. Se agregó tris(dibencilidenacetona)dipaladio(0) (32,7 mg) y 2-(di-tert-butilfosfino)bifenilo (42,6 mg) y la solución se calentó a 80°C durante 16 horas. La solución se enfrió, se filtró, se concentró, y se purificó por cromatografía de columna flash sobre gel de sílice con acetato de etilo al 50-70% en hexanos.

EJEMPLO 79D

ácido 4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-(piridin-3–iloxi)benzoico

El compuesto del título se preparó utilizando EJEMPLO 79C en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 79E

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(piridin-3–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 79D en lugar de EJEMPLO 1E en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,72 (ancho s, 1H), 8,64 (t, 1H), 8,46 (d, 1H), 8,15 (t, 2H), 7,75 (dd, 1H), 7,52 - 7,44 (m, 6H), 7,37 (m, 2H), 7,26 - 7,10 (m, 4H), 6,79 (dd, 1H), 6,50 (d, 1H), 3,87 (dd, 2H), 3,40 (s, 2H), 3,38 – 3,24 (m, 4H), 3,19 (ancho s, 4H), 2,37 (ancho s, 4H), 1,92 (m, 1H), 1,65 (d, 2H), 1,28 (m, 2H).

EJEMPLO 80

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(piridin-3–iloxi)-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 79D en lugar de EJEMPLO 1E y EJEMPLO 2A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,34 (s, 1H), 8,27 (dd, 2H), 7,51 - 7,44 (m, 8H), 7,41 - 7,29 (m, 3H), 7,27 - 7,19 (m, 2H), 6,78 (dd, 1H), 6,72 (t, 1H), 6,56 (d, 2H), 6,44 (d, 1H), 3,86 (dd, 2H), 3,36 (s, 2H), 3,29 – 3,22 (m, 2H), 3,16 (m, 4H), 2,96 (t, 2H), 2,34 (m, 4H), 1,77 (m, 1H), 1,66 (d, 2H), 1,21 (m, 2H).

EJEMPLO 81

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-{[4-({(1R)-3-(dimetilamino)-1-[(feniltio)metil]propil}amino)-3-nitrofenil]sulfonil}-2-fenoxibenzamida

EJEMPLO 81A

(R)-3-(((9H-fluoren-9–il)metoxi)carbonilamino)-4-hidroxibutanoato de tert-butilo

Se agregó Fmoc-D-Asp(OtBu)-OH (9,0g) y *N*,*N*-diisopropiletilamina (4,6 mL) a tetrahidrofurano (100 mL) y se enfrió a –40 ^{o}C. Se agregó cloroformato de isobutilo (3,1 mL), y la solución se calentó gradualmente a 0°C por 30 minutos. La solución se enfrió a –20

^{o}C, y se agregó cuidadosamente borohidruro de sodio (1,64 g, 43,6 mmol) y metanol (10 mL). La solución se calentó gradualmente a temperatura ambiente por dos horas, se diluyó con acetato de etilo (200 mL), se lavó con agua (100 mL) y salmuera (50 mL), se secó con sulfato de magnesio anhidro, se filtró, y se concentró para dar producto crudo de suficiente pureza para su uso posterior.

EJEMPLO 81B

(R)-3-(((9H-fluoren-9–il)metoxi)carbonilamino)-4-(feniltio)butanoato de tert-butilo

Se agregó tri-n-butilfosfina (90 μL) y 1,1'-(azodicarbonil)dipiperidina (91 mg) a tetrahidrofurano (4 mL), se trató con EJEMPLO 81A (90 mg) y tiofenol (21 mg), y se agitó a temperatura ambiente durante 18 horas. La solución se concentró y se purificó por cromatografía de columna flash sobre gel de sílice con acetato de etilo al 50% en hexanos.

EJEMPLO 81C

(R)-3-(2-nitro-4-sulfamoilfenilamino)-4-(feniltio)butanoato de tert-butilo

Se agregó EJEMPLO 81B (600 mg), 4-fluoro-3-nitrobencensulfonamida (298 mg), y *N*,*N*-diisopropiletilamina (3 mL) a N,N-dimetilformamida (3 mL) y se agitó a 60°C durante 12 horas. La mezcla de reacción se diluyó con acetato de etilo (100 mL), se lavó con agua (45 mL) y salmuera (10 mL), se secó con sulfato de magnesio anhidro, se filtró, y se concentró. El residuo se purificó por cromatografía de columna flash sobre gel de sílice con acetato de etilo al 30% en diclorometano.

EJEMPLO 81D

ácido (R)-3-(2-nitro-4-sulfamoilfenilamino)-4-(feniltio)butanoico

Se agitó EJEMPLO 81C (468 mg) y HCl 4 M en 1,4-dioxano (10 mL) a 50°C durante 5 horas. La solución se concentró para dar el producto crudo de suficiente pureza para su uso posterior.

EJEMPLO 81E

(R)-N,N-dimetil-3-(2-nitro-4-sulfamoilfenilamino)-4-(feniltio)butanamida

El compuesto del título se preparó utilizando EJEMPLO 81D en lugar de EJEMPLO 1E y dimetilamina (2M en tetrahidrofurano) en lugar de EJEMPLO 1F en el EJEMPLO 1G.

EJEMPLO 81F

(R)-4-(4-(dimetilamino)-1-(feniltio)butan-2–ilamino)-3-nitrobencensulfonamida

A EJEMPLO 81E (4,06 g) se agregó borano (1 M en tetrahidrofurano, 20,0 mL). La solución se agitó a temperatura ambiente durante 16 horas. La reacción se detuvo lentamente con metanol (5,0 mL) y se agregó HCl acuoso concentrado (2,0 mL). La solución se agitó a 80°C durante tres horas, se enfrió a temperatura ambiente, se basificó cuidadosamente con carbonato de sodio 4 M, se diluyó con acetato de etilo (150 mL), se lavó con agua (50 mL) y salmuera (10 mL), se secó con sulfato de magnesio anhidro, y se filtró. La solución se concentró y se purificó por cromatografía de columna flash sobre gel de sílice con metanol al 20% en diclorometano.

EJEMPLO 81G

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-{[4-({(1R)-3-(dimetilamino)-1-[(feniltio)metil]propil}amino)-3-nitrofenil]sulfonil}-2-fenoxibenzamida

El compuesto del título se preparó utilizando EJEMPLO 81F en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 8,33 (d, 1H), 8,28 (d, 1H), 7,61 (dd, 2H), 7,50 - 7,43 (m, 4H), 7,37 - 7,14 (m, 11H), 6,90 (t, 1H), 6,84 (d, 1H), 6,71 (d, 2H), 6,70 (dd, 1H), 6,32 (d, 1H), 4,06 (m, 1H), 3,36 (s, 2H), 3,33 – 3,30 (m, 2H), 3,08 (t, 4H), 2,86 (m, 2H), 2,53 (s, 6H), 2,35 (t, 4H), 2,04 (m, 2H).

EJEMPLO 82

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(piridin-4–iloxi)benzamida

EJEMPLO 82A

4-bromo-2-(piridin-4–iloxi)benzoato de metilo

Se agregó EJEMPLO 79A (800 mg), piridina-4-ol (359 mg), y carbonato de potasio (617 mg) a N,N-dimetilacetamida (20 mL) y la mezcla se calentó a 125°C durante 16 horas. La solución se concentró al vacío a 48°C y se purificó por cromatografía de columna flash sobre gel de sílice con metanol al 20% en diclorometano.

EJEMPLO 82B

4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-(piridin-4–iloxi)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 82A en lugar de EJEMPLO 79B en el EJEMPLO 79C.

EJEMPLO 82C

ácido 4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-(piridin-4–iloxi)benzoico

El compuesto del título se preparó utilizando EJEMPLO 82B en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 82D

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(piridin-4–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 82C en lugar de EJEMPLO 1E en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 8,40 (t, 1H), 8,37 (d, 1H), 7,76 (dd, 1H), 7,65 (d, 1H), 7,54 - 7,48 (m, 1H), 7,47 (s, 3H), 7,42 - 7,35 (m, 5H), 7,27 - 7,23 (m, 1H), 7,06 (dd, 1H), 6,92 (dd, 1H), 6,88 (d, 1H), 5,91 (d, 2H), 3,85 (dd, 2H), 3,39 (s, 2H), 3,34 – 3,25 (m, 4H), 3,19 (broad, s, 4H), 2,39 (ancho s, 4H), 1,92 (m, 1H), 1,65 (d, 2H), 1,27 (m, 2H).

EJEMPLO 83

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)-2-(piridin-3–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 79D en lugar de EJEMPLO 1E y EJEMPLO 7A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 8,73 (t, 1H), 8,43 (d, 1H), 8,12 (t, 2H), 7,73 (dd, 1H), 7,55 (d, 1H), 7,51 - 7,44 (m, 4H), 7,37 (m, 2H), 7,25 - 7,17 (m, 3H), 7,07 (d, 2H), 6,78 (dd, 1H), 6,47 (d, 1H), 3,65 (t, 4H), 3,47 (q, 2H), 3,38 (s, 2H), 3,28 (m, 2H), 3,17 (br s, 4H), 2,57 (br s, 4H), 2,36 (br s, 4H), 1,84 (m, 2H).

EJEMPLO 84

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)-2-(piridin-4–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 82C en lugar de EJEMPLO 1E y EJEMPLO 7A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 8,55 (t, 1H), 8,37 (d, 1H), 7,77 (dd, 1H), 7,65 (d, 1H), 7,54 - 7,43 (m,

5H), 7,42 – 7,32 (m, 4H), 7,26 - 7,22 (m, 1H), 7,01 (d, 1H), 6,91 (dd, 1H), 6,66 (d, 1H), 5,90 (d, 2H), 3,60 (t, 4H), 3,43 (q, 2H), 3,39 (s, 2H), 3,18 (br s, 4H), 2,38 (m, 10H), 1,80 (t, 2H).

EJEMPLO 85

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(4-{[2-(4-metilpiperazin-1–il)etil]amino}-3-nitrofenil)sulfonil]-2-fenoxibenzamida

EJEMPLO 85A

4-(2-(4-metilpiperazin-1–il)etilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando 2-(4-metilpiperazin-1–il)etanamina en lugar de (tetrahidropiran-4–il)metilamina en el EJEMPLO 1F.

EJEMPLO 85B

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(4-{[2-(4-metilpiperazin-1–il)etil]amino}-3-nitrofenil)sulfonil]-2-fenoxibenzamida

El compuesto del título se preparó utilizando EJEMPLO 85A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 8,61 (t, 1H), 8,40 (d, 1H), 7,72 (dd, 1H), 7,57 (d, 1H), 7,51 - 7,44 (m, 5H), 7,36 (m, 2H), 7,26 - 7,15 (m, 3H), 6,95 (t, 2H), 6,75 (dd, 2H), 6,71 (dd, 1H), 6,34 (d, 1H), 3,45 (q, 2H), 3,36 (s, 2H), 3,34 (m, 2H), 3,10 (t, 4H), 2,79 (ancho s, 4H), 2,68 (t, 2H), 2,60 (ancho s, 2H), 2,49 (s, 3H), 2,35 (t, 4H).

EJEMPLO 86

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(4-{[3-(4-metilpiperazin-1–il)propil]amino}-3-nitrofenil)sulfonil]-2-fenoxibenzamida

EJEMPLO 86A

4-(3-(4-metilpiperazin-1–il)propilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando 3-(4-metilpiperazin-1–il)propan-1-amina en lugar de (tetrahidropiran-4–il)metilamina en el EJEMPLO 1F.

EJEMPLO 86B

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(4-{[3-(4-metilpiperazin-1–il)propil]amino}-3-nitrofenil)sulfonil]-2-fenoxibenzamida

El compuesto del título se preparó utilizando EJEMPLO 86A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 8,57 (t, 1H), 8,38 (d, 1H), 7,71 (dd, 1H), 7,59 (d, 1H), 7,50 - 7,44 (m, 5H), 7,36 (m, 2H), 7,27 - 7,15 (m, 3H), 6,98 (d, 2H), 6,91 (t, 1H), 6,73 (dd, 2H), 6,70 (dd, 2H), 6,33 (d, 1H), 3,43 (q, 2H), 3,36 (s, 2H), 3,34 (m, 2H), 3,09 (t, 4H), 2,82 (ancho s, 4H), 2,56 (ancho s, 2H), 2,49 (s, 3H), 2,35 (t, 4H), 1,79 (t, 2H).

EJEMPLO 87

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({4-[[3-(dimetilamino)propil](metil)amino]-3-nitrofenil}sulfonil)-2-fenoxibenzamida

EJEMPLO 87A

4-((3-(dimetilamino)propil)(metil)amino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando N^1,N^1,N^3-trimetilpropan-1,3-diamina en lugar de 3-(pirrolidin-1–il)propan-1-amina en el EJEMPLO 68F.

EJEMPLO 87B

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({4-[[3-(dimetilamino)propil](metil)amino]-3-nitrofenil}sulfonil)-2-fenoxibenzamida

El compuesto del título se preparó utilizando EJEMPLO 87A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 8,01 (d, 1H), 7,68 (dd, 1H), 7,63 (d, 1H), 7,51 - 7,44 (m, 5H), 7,36 (m, 2H), 7,26 - 7,13 (m, 3H), 6,93 (t, 1H), 6,83 (m, 1H), 6,74 (dd, 2H), 6,69 (dd, 1H), 6,32 (d, 1H), 3,46 (q, 2H), 3,36 (s, 2H), 3,08 (t, 4H), 2,83 (t, 2H), 2,77 (s, 3H), 2,60 (s, 6H), 2,36 (t, 4H), 1,86 (m, 2H).

EJEMPLO 88

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(4-{[(1-metilpiperidin-4–il)metil]amino}-3-nitrofenil)sulfonil]-2-fenoxibenzamida

EJEMPLO 88A

4-((1-metilpiperidin-4–il)metilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando (1-metilpiperidin-4–il)metanamina en lugar de 3-(pirrolidin-1–il)propan-1-amina en el EJEMPLO 68F.

EJEMPLO 88B

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(4-{[(1-metilpiperidin-4–il)metil]amino}-3-nitrofenil)sulfonil]-2-fenoxibenzamida

El compuesto del título se preparó utilizando EJEMPLO 88A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 8,44 (t, 1H), 8,35 (d, 1H), 7,79 (dd, 1H), 7,62 (d, 1H), 7,51 - 7,45 (m, 5H), 7,36 (m, 2H), 7,25 - 7,14 (m, 3H), 6,99 (d, 1H), 6,89 (t, 1H), 6,71 (d, 2H), 6,68 (dd, 1H), 6,31 (d, 1H), 3,36 (s, 2H), 3,34 (m, 4H), 3,07 (t, 4H), 2,73 (m, 2H), 2,62 (s, 3H), 2,36 (t, 4H), 1,90 – 1,82 (m, 3H), 1,47 – 1,31 (m, 2H).

EJEMPLO 89

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)-2-fenoxibenzamida

El compuesto del título se preparó utilizando EJEMPLO 21A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 8,38 (t, 1H), 8,09 (d, 1H), 7,73(m, 1H), 7,59 (d, 1H), 7,52 - 7,44 (m, 5H), 7,36 (m, 2H), 7,26 - 7,22 (m, 1H), 7,17 (t, 1H), 7,05 (d, 1H), 6,90 (t, 1H), 6,83 (m, 1H), 6,72 (d, 2H), 6,70 (dd, 1H), 6,33 (d, 1H), 3,36 (q, 2H), 3,36 (s, 2H), 3,24 – 3,12 (m, 2H), 3,09 (t, 4H), 2,80 (m, 1H), 2,59 (s, 3H), 2,36 (t, 4H), 2,08 (m, 2H), 1,77 (m, 2H).

EJEMPLO 90

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(3-ciano-4-{[3-(dimetilamino)propil]amino}fenil)sulfonil]-2-fenoxibenzamida

EJEMPLO 90A

3-ciano-4-fluorobencensulfonamida

Se enfrió hidróxido de amonio concentrado (solución al 28% en agua, 3,17 mL) a 0°C y se agregó cloruro de 3-ciano-4-fluorobenceno-1-sulfonilo (1,00 g). La solución se mezcló a 0°C durante cuatro minutos. Se agregó HCl 4M (10 mL) lentamente y la solución se extrajo con acetato de etilo. el extracto se secó sobre salmuera y sulfato de sodio anhidro y el solvente se eliminó al vacío.

EJEMPLO 90B

3-ciano-4-(3-(dimetilamino)propilamino)bencensulfonamida

El compuesto del título se preparó utilizando EJEMPLO 90A en lugar de 4-cloro-3-nitrobencensulfonamida y N^1,N^1-dimetilpropan-1,3-diamina en lugar de 3-(pirrolidin-1–il)propan-1-amina en el EJEMPLO 68F.

EJEMPLO 90C

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(3-ciano-4-{[3-(dimetilamino)propil]amino}fenil)sulfonil]-2-fenoxibenzamida

El compuesto del título se preparó utilizando EJEMPLO 90B en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 7,67 (s, 1H), 7,66 (dd, 1H), 7,59 (d, 1H), 7,51 - 7,44 (m, 5H), 7,36 (m, 2H), 7,28 - 7,20 (m, 3H), 6,98 (t, 2H), 6,77 (dd, 2H), 6,70 (d, 2H), 6,33 (d, 1H), 3,36 (s, 2H), 3,27 (q, 2H), 3,09 (t, 4H), 2,82 (t, 2H), 2,54 (s, 6H), 2,35 (t, 4H), 1,82 (m, 2H).

EJEMPLO 91

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(3-pirrolidin-1–ilpropil)amino]fenil}sulfonil)-2-fenoxibenzamida

El compuesto del título se preparó utilizando EJEMPLO 68F en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 8,49 (t, 1H), 8,37 (d, 1H), 7,72 (dd, 1H), 7,62 (d, 1H), 7,50 - 7,43 (m, 5H), 7,35 (m, 2H), 7,26 - 7,14 (m, 3H), 6,97 (d, 1H), 6,90 (t, 1H), 6,72 (d, 2H), 6,69 (dd, 1H), 6,31 (d, 1H), 3,47 (q, 2H), 3,36 (s, 2H), 3,20 (m, 2H), 3,07 (ancho s, 8H), 2,35 (ancho s, 4H), 1,95 – 1,83 (m, 6H).

EJEMPLO 92

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-{[4-{[3-(dimetilamino)propil]amino}-3-(trifluorometil)fenil]sulfonil}-2-fenoxibenzamida

EJEMPLO 92A

4-fluoro-3-(trifluorometil)bencensulfonamida

El compuesto del título se preparó utilizando cloruro de 4-fluoro-3-(trifluorometil)benceno-1-sulfonilo en lugar de cloruro de 3-ciano-4-fluorobenceno-1-sulfonilo en el EJEMPLO 90A.

EJEMPLO 92B

4-(3-(dimetilamino)propilamino)-3-(trifluorometil)bencensulfonamida

El compuesto del título se preparó utilizando EJEMPLO 92A en lugar de 4-fluoro-3-nitrobencensulfonamida y N^1,N^1-dimetilpropan-1,3-diamina en lugar de tetrahidropiran-4–il)metilamina en el EJEMPLO 1F

EJEMPLO 92C

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-{[4-{[3-(dimetilamino)propil]amino}-3-(trifluorometil)fenil]sulfonil}-2-fenoxibenzamida

El compuesto del título se preparó utilizando EJEMPLO 92B en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 7,77 (s, 1H), 7,68 (dd, 1H), 7,57 (d, 1H), 7,51 - 7,45 (m, 5H), 7,36 (m, 2H), 7,29 - 7,21 (m, 3H), 6,99 (t, 1H), 6,82 – 6,68 (m, 5H), 6,32 (d, 1H), 3,36 (s, 2H), 3,28 (q, 2H), 3,09 (t, 4H), 2,73 (m, 2H), 2,48 (s, 6H), 2,35 (t, 4H), 1,79 (m, 2H).

EJEMPLO 93

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-{[4-({3-[isopropil(metil)amino]propil}amino)-3-nitrofenil]sulfonil}-2-fenoxibenzamida

EJEMPLO 93A

metil(3-(2-nitro-4-sulfamoilfenilamino)propil)carbamato de tert-butilo

El compuesto del título se preparó utilizando 3-aminopropil(metil)carbamato de tert-butilo en lugar de 3-(pirrolidin-1–il)propan-1-amina en el EJEMPLO 68F.

EJEMPLO 93B

3-(4-(N-(4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-fenoxibenzoil)sulfamoil)-2-nitrofenilamino)propil(metil)carbamato de tert-butilo

El compuesto del título se preparó utilizando EJEMPLO 93A en lugar de EJEMPLO 1F en el EJEMPLO 1G.

EJEMPLO 93C

4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-N-(4-(3-(metilamino)propilamino)-3-nitrofenilsulfonil)-2-fenoxibenzamida

Se agregó EJEMPLO 93B (112 mg) y trietilsilano (0,082 mL) a diclorometano (2 mL). Se agregó ácido trifluoroacético (0,198 mL), la solución se agitó a temperatura ambiente durante una hora, y el solvente se eliminó al vacío.

EJEMPLO 93D

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-{[4-({3-[isopropil(metil)amino]propil}amino)-3-nitrofenil]sulfonil}-2-fenoxibenzamida

Se agregó EJEMPLO 93C (128 mg), acetona (0,014 mL), y resina de cianonborohidruro de sodio (2,15 mmol/g, 66 mg) a tetrahidrofurano (0,9 mL) y ácido acético (0,3 mL), y la solución se agitó a temperatura ambiente durante 16 horas. Se agregó más acetona (0,014 mL), y resina de cianonborohidruro de sodio (66 mg), y la solución se agitó durante 24 horas. La solución se purificó por cromatografía de columna flash sobre gel de sílice con ácido acético al 1% y metanol al 10% en diclorometano. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,93 (ancho s, 3H), 8,53 (ancho s, 1H), 8,40 (d, 1H), 7,75 (dd, 1H), 7,60 (d, 1H), 7,51 - 7,45 (m, 5H), 7,36 (m, 2H), 7,25 - 7,16 (m, 3H), 7,02 (d, 1H), 6,92 (t, 1H), 6,74 (d, 2H), 6,70 (dd, 1H), 6,32 (d, 1H), 3,47 (m, 4H), 3,36 (s, 2H), 3,09 (t, 4H), 3,01 (ancho s, 2H), 2,58 (s, 3H), 2,35 (t, 4H), 1,94 (m, 1H), 1,18 – 1,14 (m, 6H).

EJEMPLO 94

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({4-[3-(dimetilamino)propoxi]-3-nitrofenil}sulfonil)-2-fenoxibenzamida

EJEMPLO 94A

4-(3-(dimetilamino)propoxi)-3-nitrobencensulfonamida

Se agregó trifenilfosfina (1,398 g) a tetrahidrofurano (20 mL) y se enfrió a 0°C. Se agregó dietilazodicarboxilato (solución al 40%, 2,428 mL), y la solución se agitó a 0°C durante 15 minutos. Se agregó 4-hidroxi-3-nitrobencensulfonamida (1,163 g) y 3-(dimetilamino)propan-1-ol (0,567 mL), y la solución se dejó tomar la temperatura ambiente y se agitó por 16 horas. El solvente se eliminó al vacío y el material se recristalizó usando metanol al 20% (diclorometano). El sólido recristalizado se lavó con diclorometano, se disolvió en metanol / diclorometano, se trató con trietilamina (0,13 mL, 0,924 mmol), y se purificó por cromatografía de columna flash sobre gel de sílice con 10-metanol al 20% en diclorometano.

EJEMPLO 94B

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({4-[3-(dimetilamino)propoxi]-3-nitrofenil}sulfonil)-2-fenoxibenzamida

El compuesto del título se preparó utilizando EJEMPLO 94A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 8,06 (d, 1H), 7,84 (dd, 1H), 7,65 (d, 1H), 7,52 - 7,45 (m, 5H), 7,36 (m, 2H), 7,26 - 7,22 (m, 2H), 7,18 (td, 2H), 6,89 (t, 1H), 6,69 (d, 1H), 6,68 (d, 2H), 6,32 (d, 1H), 4,25 (t, 2H), 3,36 (s, 2H), 3,13 (t, 2H), 3,08 (t, 4H), 2,75 (s, 6H), 2,36 (t, 4H), 2,11 (m, 2H).

EJEMPLO 95

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[2-(4-metilpiperazin-1–il)etil]amino}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 26C en lugar de EJEMPLO 1E y EJEMPLO 85A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,10 (s, 1H), 8,67 (t, 1H), 8,53 (d, 1H), 7,78 (dd, 1H), 7,52 (d, 1H), 7,39 – 7,31 (m, 4H), 7,08 – 7,02 (m, 3H), 6,94 (d, 1H), 6,80 (dd, 1H), 6,61 (dd, 1H), 6,36 (t, 1H), 6,14 (d, 1H), 3,42 (q, 2H), 2,99 (t, 4H), 2,71 (s, 2H), 2,70 – 2,48 (m, 10H), 2,39 (s, 3H), 2,16 (m, 6H), 1,95 (s, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 96

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[3-(4-metilpiperazin-1–il)propil]amino}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 26C en lugar de EJEMPLO 1E y EJEMPLO 86A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,09 (s, 1H), 8,62 (t, 1H), 8,51 (d, 1H), 7,76 (dd, 1H), 7,53 (d, 1H), 7,38 – 7,31 (m, 4H), 7,05 (s, 1H), 7,02 (d, 2H), 6,96 (d, 1H), 6,79 (dd, 1H), 6,60 (dd, 1H), 6,35 (t, 1H), 6,14 (d, 1H), 3,40 (q, 2H), 2,98 (t, 4H), 2,71 (s, 2H), 2,67 (ancho s, 4H), 2,55 – 2,40 (m, 6H), 2,39 (s, 3H), 2,16 (m, 6H), 1,95 (s, 2H), 1,77 (m, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 97

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(3-pirrolidin-1–ilpropil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 26C en lugar de EJEMPLO 1E y EJEMPLO 68F en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,06 (s, 1H), 8,58 (t, 1H), 8,49 (d, 1H), 7,77 (dd, 1H), 7,54 (d, 1H),

7,36 – 7,31 (m, 4H), 7,06 – 7,01 (m, 3H), 6,95 (d, 1H), 6,76 (dd, 1H), 6,57 (dd, 1H), 6,35 (t, 1H), 6,14 (d, 1H), 3,44 (q, 2H), 2,97 (ancho s, 10H), 2,71 (s, 2H), 2,16 (m, 6H), 1,95 (s, 2H), 1,90 – 1,80 (m, 6H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 98

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 26C en lugar de EJEMPLO 1E y EJEMPLO 21A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,08 (s, 1H), 8,51 (d, 1H), 8,13 (d, 1H), 7,78 (dd, 1H), 7,52 (d, 1H), 7,37 – 7,31 (m, 4H), 7,06 - 7,00 (m, 4H), 6,79 (dd, 1H), 6,59 (dd, 1H), 6,35 (t, 1H), 6,14 (d, 1H), 3,73 (m, 1H), 3,05 - 2,95 (m, 6H), 2,71 (s, 2H), 2,60 (m, 2H), 2,48 (s, 3H), 2,16 (m, 6H), 2,01 (m, 2H), 1,95 (s, 2H), 1,70 (m, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 99

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[3-(4-metilpiperazin-1–il)propil]amino}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 1E y EJEMPLO 86A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,16 (s, 1H), 8,59 (t, 1H), 8,45 (d, 1H), 7,72 (dd, 1H), 7,55 (d, 1H), 7,34 (d, 2H), 7,23 (t, 1H), 7,12 (d, 1H), 7,02 (d, 2H), 6,95 (d, 1H), 6,94 (t, 1H), 6,64 (dd, 1H), 6,35 (d, 1H), 6,23 (m, 2H), 3,41 (q, 2H), 2,98 (t, 4H), 2,71 (ancho s, 6H), 2,52 – 2,42 (m, 6H), 2,41 (s, 3H), 2,15 (m, 6H), 1,95 (s, 2H), 1,77 (m, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 100

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[3-(dimetilamino)propoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 26C en lugar de EJEMPLO 1E y EJEMPLO 94A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,03 (s, 1H), 8,23 (d, 1H), 7,91 (dd, 1H), 7,56 (d, 1H), 7,36 – 7,29 (m, 4H), 7,19 (d, 1H), 7,05 (d, 2H), 6,97 (s, 1H), 6,73 (dd, 1H), 6,57 (dd, 1H), 6,33 (t, 1H), 6,15 (d, 1H), 4,23 (t, 2H), 3,04 (m, 2H), 2,96 (t, 4H), 2,72 (s, 2H), 2,67 (s, 6H), 2,22 – 2,02 (m, 8H), 1,95 (s, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 101

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[2-(4-metilpiperazin-1–il)etil]amino}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 1E y EJEMPLO 85A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,18 (s, 1H), 8,64 (t, 1H), 8,47 (d, 1H), 7,73 (dd, 2H), 7,56 (d, 1H), 7,34 (d, 2H), 7,24 (t, 1H), 7,04 (d, 2H), 6,96 (d, 1H), 6,94 (d, 1H), 6,65 (dd, 1H), 6,37 (d, 1H), 6,23 (m, 2H), 3,43 (q, 2H), 2,99 (t, 4H), 2,71 (s, 2H), 2,65 (m, 6H), 2,56 (m, 4H), 2,42 (s, 3H), 2,15 (m, 6H), 1,95 (s, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 102

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(3-pirrolidin-1–ilpropil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 1E y EJEMPLO 68F en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,14 (s, 1H), 8,54 (t, 1H), 8,44 (d, 1H), 7,76 (dd, 1H), 7,59 (d, 1H), 7,34 (d, 2H), 7,22 (t, 1H), 7,10 (d, 1H), 7,05 (d, 2H), 6,98 – 6,89 (m, 2H), 6,62 (dd, 1H), 6,33 (d, 1H), 6,23 (t, 1H), 6,21 (d, 1H), 3,44 (q, 2H), 3,10 - 2,91 (m, 10H), 2,71 (s, 2H), 2,16 (m, 6H), 1,95 (s, 2H), 1,92 – 1,79 (m, 6H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 103

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 1E y EJEMPLO 21A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,14 (s, 1H), 8,44 (d, 1H), 8,11 (d, 1H), 7,75 (dd, 1H), 7,56 (d, 1H), 7,34 (d, 2H), 7,23 (t, 1H), 7,11 (d, 1H), 7,04 (d, 2H), 7,03 (d, 1H), 6,93 (t, 1H), 6,64 (dd, 1H), 6,34 (d, 1H), 6,22 (m, 2H), 3,73 (m, 1H), 3,08 - 2,93 (m, 6H), 2,71 (s, 2H), 2,70 – 2,56 (m, 2H), 2,48 (s, 3H), 2,16 (m, 6H), 2,02 (m, 2H), 1,95 (s, 2H), 1,70 (m, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 104

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(1-metilpiperidin-4–il)metil]amino}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 26C en lugar de EJEMPLO 1E y EJEMPLO 88A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 10,99 (s, 1H), 8,39 (d, 1H), 8,32 (t, 1H), 7,65 (dd, 1H), 7,54 (d, 1H), 7,34 (d, 2H), 7,30 – 7,26 (m, 2H), 7,05 (d, 2H), 6,92 (d, 1H), 6,81 (d, 1H), 6,70 (dd, 1H), 6,53 (dd, 1H), 6,30 (t, 1H), 6,15 (d, 1H), 3,28 – 3,19 (m, 2H), 2,93 (t, 4H), 2,83 (m, 2H), 2,71 (s, 2H), 2,68 – 2,50 (m, 2H), 2,54 (s, 3H), 2,24 – 2,10 (m, 6H), 1,95 (ancho s, 2H), 1,68 (d, 2H), 1,59 (m, 1H), 1,38 (t, 2H), 1,32 – 1,17 (m, 2H), 0,92 (s, 6H).

EJEMPLO 105

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[(1-metilpiperidin-4–il)metil]amino}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 1E y EJEMPLO 88A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,11 (s, 1H), 8,44 (t, 1H), 8,41 (d, 1H), 7,74 (dd, 1H), 7,59 (d, 1H), 7,34 (d, 2H), 7,21 (t, 1H), 7,11 – 7,02 (m, 3H), 6,98 – 6,90 (m, 2H), 6,61 (dd, 1H), 6,31 (d, 1H), 6,23 (t, 1H), 6,20 (d, 1H), 3,20 (m, 2H), 2,95 (t, 4H), 2,71 (s, 2H), 2,62 – 2,49 (m, 4H), 2,55 (s, 3H), 2,16 (m, 6H), 1,95 (s, 2H), 1,86 – 1,78 (m, 3H), 1,42 – 1,31 (m, 4H), 0,92 (s, 6H).

EJEMPLO 106

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[3-(dimetilamino)propoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-4–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 1E y EJEMPLO 94A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,10 (s, 1H), 8,16 (d, 1H), 7,90 (dd, 1H), 7,61 (d, 1H), 7,35 (d, 2H), 7,24 – 7,19 (m, 2H), 7,10 – 7,01 (m, 3H), 6,91 (t, 1H), 6,60 (dd, 1H), 6,28 (d, 1H), 6,23 (t, 1H), 6,20 (d, 1H), 4,23 (t, 2H), 3,03 (t, 2H), 2,95 (t, 4H), 2,72 (s, 2H), 2,67 (s, 6H), 2,17 (m, 6H), 2,07 (m, 2H), 1,95 (s, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 107

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(4-metilpiperazin-1–il)-3-nitrofenil]sulfonil}benzamida

EJEMPLO 107A

4-(4-metilpiperazin-1–il)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando 1-metilpiperazina en lugar de 3-(pirrolidin-1–il)propan-1-amina en el EJEMPLO 68F.

EJEMPLO 107B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(4-metilpiperazin-1–il)-3-nitrofenil]sulfonil}benzamida

El compuesto del título se preparó utilizando EJEMPLO 26C en lugar de EJEMPLO 1E y EJEMPLO 107A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,21 (s, 1H), 8,18 (d, 1H), 7,77 (dd, 1H), 7,57 (d, 1H), 7,34 (d, 2H), 7,26 (t, 1H), 7,22 (d, 1H), 7,16 (d, 1H), 7,07 – 7,02 (m, 2H), 6,96 (t, 1H), 6,87 (dd, 1H), 6,39 (d, 1H), 6,25 (m, 2H), 3,16 (m, 4H), 3,01 (t, 4H), 2,73 (s, 2H), 2,66 (ancho s, 4H), 2,39 (s, 3H), 2,18 (m, 6H), 1,95 (s, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 108

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(3-nitro-4-{[1-(2,2,2-trifluoroetil)piperidin-4–il]amino}fenil)sulfonil]benzamida

EJEMPLO 108A

3-nitro-4-(1-(2,2,2-trifluoroetil)piperidin-4–ilamino)bencensulfonamida

Se agregó 4-cloro-3-nitrobencensulfonamida (1,300 g), clorhidrato de 1-(2,2,2-trifluoroetil)piperidin-4-amina (1,201 g), y trietilamina (2,30 mL) a 1,4-dioxano (50 mL) y agua (5 mL) y se calentó a 90°C durante 16 horas. La solución se concentró al vacío y se purificó por cromatografía de columna flash sobre gel de sílice con acetato de etilo aumentando a metanol al 5% en acetato de etilo.

EJEMPLO 108B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(3-nitro-4-{[1-(2,2,2-trifluoroetil)piperidin-4–il]amino}fenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 1E y EJEMPLO 108A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,24 (s, 1H), 8,50 (d, 1H), 8,25 (d, 1H), 7,71 (dd, 1H), 7,52 (d, 1H), 7,34 (d, 2H), 7,27 (t, 1H), 7,17 (d, 1H), 7,11 (d, 1H), 7,04 (d, 2H), 6,97 (t, 1H), 6,71 (dd, 1H), 6,43 (d, 1H), 6,28 (d, 1H), 6,24 (t, 1H), 3,68 (m, 1H), 3,23(q, 2H), 3,06 (ancho s, 4H), 2,95 - 2,87 (m, 2H), 2,78 – 2,71 (m, 2H), 2,58 (t, 2H), 2,25 – 2,11 (m, 6H), 1,98 – 1,85 (m, 4H), 1,64 (m, 2H), 1,39 (t, 2H), 0,92 (s, 6H).

EJEMPLO 109

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[4-(dimetilamino)-1-metilpiperidin-4–il]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida

EJEMPLO 109A

4-((4-(dimetilamino)-1-metilpiperidin-4–il)metilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando 4-(aminometil)-N,N,1-trimetilpiperidin-4-amina en lugar de clorhidrato de 1-(2,2,2-trifluoroetil)piperidin-4-amina en el EJEMPLO 108A.

EJEMPLO 109B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[4-(dimetilamino)-1-metilpiperidin-4–il]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 26C en lugar de EJEMPLO 1E y EJEMPLO 109A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,06 (s, 1H), 8,56 (ancho s, 1H), 8,50 (d, 1H), 7,81 (dd, 1H), 7,54 (d, 1H), 7,36 – 7,31 (m, 4H), 7,08 – 7,02 (m, 4H), 6,77 (dd, 1H), 6,57 (dd, 1H), 6,34 (t, 1H), 6,13 (d, 1H), 3,50 (d, 2H), 3,04 (m, 2H), 2,96 (t, 4H), 2,87 (m, 2H), 2,71 (s, 2H), 2,58 (s, 3H), 2,28 (s, 6H), 2,16 (m, 6H), 1,98 (m, 2H), 1,95 (s, 2H), 1,65 – 1,54 (m, 2H), 1,38 (t, 2H), 0,94 (s, 6H).

EJEMPLO 110

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(2,3-dihidro-1,4-benzodioxin-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 110A

4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-(2,3-dihidrobenzo[b][1,4]dioxin-5–iloxi)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 34A en lugar de EJEMPLO 18E y 2,3-dihidrobenzo[b][1,4]dioxin-5-ol en lugar de fenol en el EJEMPLO 18F.

EJEMPLO 110B

ácido 4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-(2,3-dihidrobenzo[b][1,4]dioxin-5–iloxi)benzoico

El compuesto del título se preparó utilizando EJEMPLO 110A en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 110C

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(2,3-dihidro-1,4-benzodioxin-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 110B en lugar de EJEMPLO 1E en el EJEMPLO 1G. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ ppm 11,40 (s, 1 H), 8,65 (t, 1 H), 8,55 (d, 1 H), 7,83 (dd, 1 H), 7,46 (m, 6 H), 7,36 (m, 2 H), 7,23 (m, 2 H), 6,77 (d, 1 H), 6,70 (dd, 1 H), 6,42 (m, 2 H), 6,27 (d, 1 H), 4,20 (s, 4 H), 3,85 (dd, 2 H), 3,37 (m, 4 H), 3,25 (m, 2 H), 3,13 (m, 4 H), 2,35 (m, 4 H), 1,90 (m, 1 H), 1,62 (dd, 2 H), 1,27 (m, 2 H).

EJEMPLO 111

5-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-1,1'-bifenil-2-carboxamida

EJEMPLO 111A

5-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)bifenil-2-carboxilato de metilo

Se trató EJEMPLO 34A (100 mg, 0,2 mmol) en tetrahidrofurano (1,5 mL) con ácido fenilborónico (36,6 mg, 0,3 mmol), tris(dibencilidenacetona)dipaladio(0) (9,2 mg, 0,01 mmol), tetrafluoroborato de tri-tert-butilfosfonio (5,8 mg, 0,02 mmol) y fluoruro de cesio (91 mg, 0,6 mmol), se hizo pasar nitrógeno y se agitó durante la noche a temperatura ambiente. La mezcla de reacción se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó ($MgSO_4$), se filtró y se concentró. El concentrado se purificó mediante cromatografía de

columna sobre gel de sílice eluyendo con un gradiente de metanol entre 0 y 3% en CH_2Cl_2 para dar el producto.

EJEMPLO 111B

ácido 5-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)bifenil-2-carboxílico

El compuesto del título se preparó utilizando EJEMPLO 111A en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 111C

5-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-1,1'-bifenil-2-carboxamida

El compuesto del título se preparó utilizando EJEMPLO 111B en lugar de EJEMPLO 27G en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ ppm 12,09 (s, 1H), 8,72 (t, 1H), 8,46 (d, 1H), 7,79 (m, 2H), 7,52 (m, 4H), 7,35 (dd, 5H), 7,16 (m, 1H), 7,04 (m, 4H), 6,91 (dd, 1H), 6,78 (m, 1H), 4,39 (m, 1H), 3,88 (m, 3H), 3,42 (m, 4H), 3,27 (m, 4H), 2,96 (m, 4H), 1,95 (m, 1H), 1,67 (m, 2H), 1,31 (m, 2H).

EJEMPLO 112

5-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(4-{[3-(dimetilamino)propil]amino}-3-nitrofenil)sulfonil]-1,1'-bifenil-2-carboxamida

El compuesto del título se preparó utilizando EJEMPLO 111B en lugar de EJEMPLO 27G y EJEMPLO 154A en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ ppm 12,09 (s, 1H), 8,74 (t, 1H), 8,47 (d, 1H), 7,83 (dd, 1H), 7,70 (m, 1H), 7,40 (m, 8H), 7,27 (m, 1H), 7,20 (m, 1H), 7,07 (m, 4H), 6,91 (dd, 1H), 6,77 (m, 1H), 4,39 (m, 1H), 3,87 (m, 1H), 3,55 (m, 4H), 3,26 (m, 2H), 3,16 (m, 4H), 3,03 (m, 2H), 2,80 (m, 6H), 1,98 (m, 2H).

EJEMPLO 113

4-[4-({4'-cloro-4-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida

EJEMPLO 113A

2-fenoxi-4-(piperazin-1–il)benzoato de metilo

Este ejemplo se realizó utilizando piperazina en lugar de EJEMPLO 1B en el EJEMPLO 1D.

EJEMPLO 113B

4-(4-(2-bromo-5-hidroxibencil)piperazin-1–il)-2-fenoxibenzoato de metilo

Este ejemplo se realizó utilizando 2-bromo-5-hidroxibenzaldehido en lugar de 4'-clorobifenil-2-carboxaldehido y EJEMPLO 113A en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 113C

4-(4-(2-bromo-5-(2-(dimetilamino)etoxi)bencil)piperazin-1–il)-2-fenoxibenzoato de metilo

Una mezcla de EJEMPLO 113B (170 mg), sal clorhidrato de 2-cloro-N,N-dimetiletanamina (80 mg) y carbonato de cesio (278 mg) se suspendió en N,N-dimetilformamida anhidra (3 mL). La mezcla de reacción se calentó a 50°C durante la noche. La mezcla de reacción se enfrió a temperatura ambiente y se diluyó con acetato de etilo. La fase orgánica se lavó con agua y salmuera, y se secó sobre Na_2SO_4 anhidro. El solvente se eliminó al vacío para dar un residuo oleoso el cual se usó en el siguiente paso sin purificación adicional.

EJEMPLO 113D

4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)bifenil-2–il)metil)piperazin-1–il)-2-fenoxibenzoato de metilo

Este ejemplo se realizó utilizando EJEMPLO 113C en lugar de EJEMPLO 68C y ácido 4-clorofenilborónico en lugar de ácido 4-metoxifenilborónico en el EJEMPLO 68D.

EJEMPLO 113E

ácido 4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)bifenil-2–il)metil)piperazin-1–il)-2-fenoxibenzoico

Este ejemplo se realizó utilizando EJEMPLO 113D en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 113F

4-[4-({4'-cloro-4-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida

Este ejemplo se realizó utilizando EJEMPLO 113E en lugar de EJEMPLO 1E en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,69 (br s, 1H), 9,87 (br s, 1H), 8,63 (t, 1H), 8,46 (d, 1H), 7,75 (dd, 1H), 7,50 (m, 3H), 7,34-7,23 (m, 6H), 7,14 (m, 2H), 6,98 (m, 1H), 6,78 (m, 3H), 6,44 (d, 1H), 4,37 (t, 2H), 3,86 (m, 2H), 3,60-3,41 (m, 10H), 3,34 (t, 4H), 3,28(m, 2H), 2,89 (s, 6H), 1,91 (m, 1H), 1,62 (m, 2H), 1,28 (m, 2H).

EJEMPLO 114

4-(4-{[4'-cloro-4-(3-piperidin-1–ilpropoxi)-1,1'-bifenil-2–il]metil}piperazin-1–il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida

EJEMPLO 114A

4-(4-(2-bromo-5-(3-(piperidin-1–il)propoxi)bencil)piperazin-1–il)-2-fenoxibenzoato de metilo

Este ejemplo se realizó utilizando sal clorhidrato de 1-(3-cloropropil)piperidina en lugar de sal clorhidrato de 2-cloro-N,N-dimetiletanamina en el EJEMPLO 113C.

EJEMPLO 114B

4-(4-((4'-cloro-4-(3-(piperidin-1–il)propoxi)bifenil-2–il)metil)piperazin-1–il)-2-fenoxibenzoato de metilo

Este ejemplo se realizó utilizando EJEMPLO 114A en lugar de EJEMPLO 68C y ácido 4-clorofenilborónico en lugar de ácido 4-metoxifenilborónico en el EJEMPLO 68D.

EJEMPLO 114C

ácido 4-(4-((4'-cloro-4-(3-(piperidin-1–il)propoxi)bifenil-2–il)metil)piperazin-1–il)-2-fenoxibenzoico

Este ejemplo se realizó utilizando EJEMPLO 114B en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 114D

4-(4-{[4'-cloro-4-(3-piperidin-1–ilpropoxi)-1,1'-bifenil-2–il]metil}piperazin-1–il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida

Este ejemplo se realizó utilizando EJEMPLO 114C en lugar de EJEMPLO 1E en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,69 (br s, 1H), 9,18 (br s, 1H), 8,63 (t, 1H), 8,46 (d, 1H), 7,75 (dd, 1H), 7,50 (m, 3H), 7,33-7,21 (m, 6H), 7,15 (d, 2H), 6,98

(m, 1H), 6,78 (m, 3H), 6,44 (d, 1H), 4,11 (t, 2H), 3,87 (dd, 2H), 3,60-3,38 (m, 10H), 3,34 (m, 4H), 3,25 (m, 4H), 2,92 (m, 2H), 2,17 (m, 2H), 1,85 (m, 3H), 1,64 (m, 6H), 1,29 (m, 2H).

EJEMPLO 115

4-(4-{[4'-cloro-4-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il]metil}piperazin-1–il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida

EJEMPLO 115A

4-(4-(2-bromo-5-(2-morfolinoetoxi)bencil)piperazin-1–il)-2-fenoxibenzoato de metilo

Este ejemplo se realizó utilizando sal clorhidrato de 4-(2-cloroetil)morfolina en lugar de sal clorhidrato de 2-cloro-N,N-dimetiletanamina en el EJEMPLO 113C.

EJEMPLO 115B

4-(4-((4'-cloro-4-(2-morfolinoetoxi)bifenil-2–il)metil)piperazin-1–il)-2-fenoxibenzoato de metilo

Este ejemplo se realizó utilizando EJEMPLO 115A en lugar de EJEMPLO 68C y ácido 4-clorofenilborónico en lugar de ácido 4-metoxifenilborónico en el EJEMPLO 68D.

EJEMPLO 115C

ácido 4-(4-((4'-cloro-4-(2-morfolinoetoxi)bifenil-2–il)metil)piperazin-1–il)-2-fenoxibenzoico

Este ejemplo se realizó utilizando EJEMPLO 115B en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 115D

4-(4-{[4'-cloro-4-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il]metil}piperazin-1–il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida

Este ejemplo se realizó utilizando EJEMPLO 115C en lugar de EJEMPLO 1E en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,66 (br s, 1H), 8,63 (t, 1H), 8,46 (d, 1H), 7,75 (dd, 1H), 7,50 (m, 3H), 7,31 (m, 4H), 7,23 (m, 2H), 7,15 (m, 2H), 6,98 (m ,1H), 6,78 (m, 3H), 6,44 (d, 1H), 4,41 (m, 2H), 3,87 (m, 6H), 3,60-3,38 (m, 12H), 3,36-3,25 (m, 8H), 1,91 (m, 1H), 1,64 (m, 2H), 1,29 (m, 2H).

EJEMPLO 116

4-[4-({4'-cloro-4-[3-(dimetilamino)propoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida

EJEMPLO 116A

4-(4-(2-bromo-5-(3-(dimetilamino)propoxi)bencil)piperazin-1–il)-2-fenoxibenzoato de metilo

Este ejemplo se realizó utilizando clorhidrato de 3-cloro-N,N-dimetilpropan-1-amina en lugar de sal clorhidrato de 2-cloro-N,N-dimetiletanamina en el EJEMPLO 113C.

EJEMPLO 116B

4-(4-((4'-cloro-4-(3-(dimetilamino)propoxi)bifenil-2–il)metil)piperazin-1–il)-2-fenoxibenzoato de metilo

Este ejemplo se realizó utilizando EJEMPLO 116A en lugar de EJEMPLO 68C y ácido 4-clorofenilborónico en lugar de ácido 4-metoxifenilborónico en el EJEMPLO 68D.

EJEMPLO 116C

ácido 4-(4-((4'-cloro-4-(3-(dimetilamino)propoxi)bifenil-2–il)metil)piperazin-1–il)-2-fenoxibenzoico

Este ejemplo se realizó utilizando EJEMPLO 116B en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 116D

4-[4-({4'-cloro-4-[3-(dimetilamino)propoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida

Este ejemplo se realizó utilizando EJEMPLO 116C en lugar de EJEMPLO 1E en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,64 (br s, 1H), 9,52 (br s, 1H), 8,63 (t, 1H), 8,47 (d, 1H), 7,75 (dd, 1H), 7,50 (m, 3H), 7,34 (m, 2H), 7,23 (m, 4H), 7,14 (d, 1H), 6,98 (m, 2H), 6,78 (m, 3H), 6,42 (s, 1H), 4,09 (t, 2H), 3,86 (m, 2H), 3,50-3,36 (m, 8H), 3,28 (m, 8H), 2,83 (s, 6H), 2,12 (m, 2H), 1,91 (m, 1H), 1,62 (m, 2H), 1,29 (m, 2H).

EJEMPLO 117

4-(4-{[4'-cloro-4-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-fenoxi-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

Este ejemplo se realizó utilizando EJEMPLO 115C en lugar de EJEMPLO 27G y EJEMPLO 163A en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 8,11 (d, 1H), 7,86 (dd, 1H), 7,49 (m, 3H), 7,36-7,26 (m, 7H), 7,10 (m, 3H), 6,84 (d, 2H), 6,77 (dd, 1H), 6,41 (s, 1H), 4,38 (m, 2H), 3,84 (m, 4H), 3,55 (m, 2H), 3,50-3,30 (m, 10H), 3,28 (m, 8H), 3,20 (m, 2H), 1,86 (m, 1H), 1,55 (m, 2H), 1,26 (m, 2H).

EJEMPLO 118

4-(4-{[4'-cloro-4-(3-piperidin-1–ilpropoxi)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-fenoxi-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

Este ejemplo se realizó utilizando EJEMPLO 114C en lugar de EJEMPLO 27G y EJEMPLO 163A en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,65 (br s, 1H), 9,06 (br s, 1H), 8,11 (d, 1H), 7,86 (dd, 1H), 7,49 (m, 3H), 7,36-7,20 (m, 7H), 7,06 (m, 3H), 6,83 (d, 2H), 6,76 (dd, 1H), 6,41 (s, 1H), 4,10 (t, 2H), 3,85 (dd, 2H), 3,40-3,05 (m, 16H), 2,90 (m, 2H), 2,15 (m, 2H), 1,84 (m, 3H), 1,60 (m, 6H), 1,41 (m, 2H), 1,26 (m, 2H).

EJEMPLO 119

4-[4-({4'-cloro-4-[3-(dimetilamino)propoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-fenoxi-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

Este ejemplo se realizó utilizando EJEMPLO 116C en lugar de EJEMPLO 27G y EJEMPLO 163A en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 8,11 (d, 1H), 7,86 (dd, 1H), 7,49 (m, 3H), 7,36-7,26 (m, 7H), 7,06 (m, 3H), 6,84 (d, 2H), 6,76 (dd, 1H), 6,41 (d, 1H), 4,09 (t, 2H), 3,84 (dd, 2H), 3,50-3,24 (m, 14H), 3,10 (m, 2H), 2,83 (s, 6H), 2,12 (m, 2H), 1,86 (m, 1H), 1,55 (m, 2H), 1,26 (m, 2H).

EJEMPLO 120

4-[4-({4'-cloro-4-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-fenoxi-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

Este ejemplo se realizó utilizando EJEMPLO 113E en lugar de EJEMPLO 27G y EJEMPLO 163A en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (400MHz,

dimetilsulfóxido-d_6) δ 11,75 (br s, 1H), 9,90 (br s, 1H), 8,10 (d, 1H), 7,85 (dd, 1H), 7,49 (m, 3H), 7,38-7,25 (m, 7H), 7,11 (d, 2H), 7,03 (m, 1H), 6,82 (d, 2H), 6,77 (dd, 1H), 6,44 (s, 1H), 4,37 (t, 2H), 3,85 (m, 6H), 3,55 (m, 2H), 3,29 (m, 8H), 3,10 (m, 2H), 2,89 (s, 6H), 1,86 (m, 1H), 1,55 (m, 2H), 1,24 (m, 2H).

EJEMPLO 121

4-[4-({4'-cloro-4-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-N-({3-nitro-4-[(3-pirrolidin-1–ilpropil)amino]fenil}sulfonil)-2-fenoxibenzamida

Este ejemplo se realizó utilizando EJEMPLO 113E en lugar de EJEMPLO 27G y EJEMPLO 68F en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,70 (br s, 1H), 9,95 (br s, 1H), 9,73 (br s, 1H), 8,69 (t, 1H), 8,49 (d, 1H), 7,79 (dd, 1H), 7,50 (m, 3H), 7,34 (m, 2H), 7,23 (m, 3H), 7,16 (d, 1H), 7,09 (m, 1H), 7,00 (m, 1H), 6,82 (d, 2H), 6,77 (dd, 1H), 6,42 (s, 1H), 4,37 (m, 2H), 3,70 (m, 6H), 3,54 (m, 8H), 3,21 (m, 4H), 3,19 (m, 2H), 2,88 (s, 6H), 1,97 (m, 4H), 1,85 (m, 2H).

EJEMPLO 122

4-[4-({4'-cloro-3-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida

EJEMPLO 122A

4-(4-(2-bromo-6-hidroxibencil)piperazin-1–il)-2-fenoxibenzoato de metilo

Este ejemplo se realizó utilizando 2-bromo-6-hidroxibenzaldehido en lugar de 4'-clorobifenil-2-carboxaldehido y EJEMPLO113A en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 122B

4-(4-((4'-cloro-3-hidroxibifenil-2–il)metil)piperazin-1–il)-2-fenoxibenzoato de metilo

Este ejemplo se realizó utilizando EJEMPLO 122A en lugar de EJEMPLO 68C y ácido 4-clorofenilborónico en lugar de ácido 4-metoxifenilborónico en el EJEMPLO 68D.

EJEMPLO 122C

4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)bifenil-2–il)metil)piperazin-1–il)-2-fenoxibenzoato de metilo

Se disolvió EJEMPLO 122B (100 mg) y sal clorhidrato de 2-cloro-N,N-dimetiletanamina (30 mg) en una mezcla de solventes de diclorometano (1,5 mL) y solución acuosa al 50% de hidróxido de sodio (0,5 mL), seguido por la adición de yoduro de tetrabutilamonio (15 mg). La mezcla de reacción se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con acetato de etilo, y se lavó con agua y salmuera. La fase orgánica se secó sobre Na_2SO_4 y se concentró. La purificación mediante columna flash se llevó a cabo con metanol al 0-5%/diclorometano para dar el producto.

EJEMPLO 122D

ácido 4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)bifenil-2–il)metil)piperazin-1–il)-2-fenoxibenzoico

Este ejemplo se realizó utilizando EJEMPLO 122C en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 122E

4-[4-({4'-cloro-3-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida

Este ejemplo se realizó utilizando EJEMPLO 122D en lugar de EJEMPLO 1E en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 10,20 (br s, 1H), 9,46 (br s, 1H), 8,65 (t, 1H), 8,47 (d, 1H), 7,78 (d, 1H), 7,75(dd, 1H), 7,52 (m, 4H), 7,38 (m, 3H), 7,23 (m, 3H), 7,12 (m, 1H), 6,98 (m, 2H), 6,78 (d, 2H), 6,76 (dd, 1H), 6,43 (s, 1H), 4,43 (m, 2H), 3,87 (m, 2H), 3,62 (m, 4H), 3,35-3,15 (m, 12H), 2,90 (s, 6H), 1,90 (m, 1H), 1,62 (m, 2H), 1,27 (m, 2H).

EJEMPLO 123

4-[4-({4'-cloro-3-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-N-({3-nitro-4-[(3-pirrolidin-1–ilpropil)amino]fenil}sulfonil)-2-fenoxibenzamida

Este ejemplo se realizó utilizando EJEMPLO 122C en lugar de EJEMPLO 1E y EJEMPLO 68F en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 10,01 (br s, 1H), 9,63 (br s, 1H), 9,32 (br s, 1H), 8,69(t, 1H), 8,49 (d, 1H), 7,80 (dd, 1H), 7,52 (m, 4H), 7,38 (m, 2H), 7,25 (m, 3H), 7,15 (d, 1H), 7,01 (m, 1H), 6,95 (m, 1H), 6,81 (d, 2H), 6,76 (m, 1H), 6,41 (s, 1H), 4,43 (m, 4H), 3,56-3,51 (m, 8H), 3,20 (m, 4H), 3,10 (m, 6H), 2,91 (s, 6H), 1,98 (m, 4H), 1,85 (m, 2H).

EJEMPLO 124

4-[4-({4'-cloro-3-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-fenoxi-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

Este ejemplo se realizó utilizando EJEMPLO 122C en lugar de EJEMPLO 27G y EJEMPLO 163A en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,71 (br s, 1H), 9,89 (br s, 1H), 9,14 (br s, 1H), 8,11(d, 1H), 7,86 (dd, 1H), 7,52 (m, 4H), 7,38 (m, 2H), 7,29 (m, 3H), 7,20 (m, 1H), 7,11 (d, 1H), 7,05 (m, 1H), 6,95 (m, 1H), 6,83 (d, 2H), 6,76 (dd, 1H), 6,40 (s, 1H), 4,41 (m, 2H), 3,85 (m, 2H), 3,59 (m, 4H), 3,44 (m, 2H), 3,28 (m, 8H), 3,06 (m, 2H), 2,91 (s, 6H), 1,84 (m, 1H), 1,55 (m, 2H), 1,26 (m, 2H).

EJEMPLO 125

4-[4-({4'-cloro-4-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 125A

4'-cloro-4-hidroxibifenil-2-carbaldehido

Este ejemplo se realizó utilizando 2-bromo-5-hidroxibenzaldehido en lugar de EJEMPLO 68C y ácido 4-clorofenilborónico en lugar de ácido 4-metoxifenilborónico en el EJEMPLO 68D.

EJEMPLO 125B

4'-cloro-4-(2-(dimetilamino)etoxi)bifenil-2-carbaldehido

Este ejemplo se realizó utilizando EJEMPLO 125A en lugar de EJEMPLO 122B en el EJEMPLO 122C.

EJEMPLO 125C

2-(1H-indol-4–iloxi)-4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)bifenil-2–il)metil)piperazin-1–il)benzoato de metilo

Este ejemplo se realizó utilizando EJEMPLO 125B en lugar de 4’-clorobifenil-2-carboxaldehido y EJEMPLO 68B en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 125D

ácido 2-(1H-indol-4–iloxi)-4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)bifenil-2–il)metil)piperazin-1–il)benzoico

Este ejemplo se realizó utilizando EJEMPLO 125C en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 125E

4-[4-({4'-cloro-4-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

Este ejemplo se realizó utilizando EJEMPLO 125D en lugar de EJEMPLO 1E en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,46 (br s, 1H), 11,25 (s, 1H), 9,80 (br s, 1H), 8,60 (t, 1H), 8,48(d, 1H), 7,65 (dd, 1H), 7,55 (d, 1H), 7,46 (d, 2H), 7,28 (m, 5H), 7,15 (d, 1H), 7,10 (m, 1H), 7,04 (d, 1H), 6,94 (m, 1H), 6,73 (dd, 1H), 6,36 (m, 2H), 6,26 (m, 1H), 4,35 (t, 2H), 3,85 (m, 6H), 3,54 (m, 4H), 3,31 (m, 6H), 3,06 (m, 2H), 2,88 (s, 6H), 1,88 (m, 1H), 1,60 (m, 2H), 1,28 (m, 2H).

EJEMPLO 126

4-[4-({4'-cloro-4-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 126A

2-(1H-indol-5–iloxi)-4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)bifenil-2–il)metil)piperazin-1–il)benzoato de metilo

Este ejemplo se realizó utilizando EJEMPLO 125B en lugar de 4'-clorobifenil-2-carboxaldehido y EJEMPLO 150A en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 126B

ácido 2-(1H-indol-5–iloxi)-4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)bifenil-2–il)metil)piperazin-1–il)benzoico

Este ejemplo se realizó utilizando EJEMPLO 126A en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 126C

4-[4-({4'-cloro-4-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

Este ejemplo se realizó utilizando EJEMPLO 126B en lugar de EJEMPLO 1E en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,35 (br s, 1H), 11,17 (s, 1H), 9,85 (br s, 1H), 8,61 (t, 1H) 8,57(d, 1H), 7,77 (dd, 1H), 7,54 (d, 1H), 7,46 (d, 2H), 7,38 (m, 2H), 7,30 (m, 4H), 7,09 (m, 3H), 6,84 (dd, 1H), 6,69 (dd, 1H), 6,36 (m, 1H), 6,26 (m, 1H), 4,35 (t, 2H), 3,85 (m, 6H), 3,54 (m, 4H), 3,31 (m, 6H), 3,06 (m, 2H), 2,88 (s, 6H), 1,88 (m, 1H), 1,60 (m, 2H), 1,28 (m, 2H).

EJEMPLO 127

4-(4-{[4'-cloro-4-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 127A

4'-cloro-4-(2-morfolinoetoxi)bifenil-2-carbaldehido

Este ejemplo se realizó utilizando EJEMPLO 125A en lugar de EJEMPLO 122B en y sal clorhidrato de 4-(2-cloroetil)morfolina en lugar de sal clorhidrato de 2-cloro-N,N-dimetiletanamina EJEMPLO 122C.

EJEMPLO 127B

2-(1H-indol-5–iloxi)-4-(4-((4'-cloro-4-(2-morfolinoetoxi)bifenil-2–il)metil)piperazin-1–il)benzoato de metilo

Este ejemplo se realizó utilizando EJEMPLO 127A en lugar de 4'-clorobifenil-2-carboxaldehido y EJEMPLO 150A en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 127C

ácido 2-(1H-indol-5–iloxi)-4-(4-((4'-cloro-4-(2-morfolinoetoxi)bifenil-2–il)metil)piperazin-1–il)benzoico

Este ejemplo se realizó utilizando EJEMPLO 127B en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 127D

4-(4-{[4'-cloro-4-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

Este ejemplo se realizó utilizando EJEMPLO 127C en lugar de EJEMPLO 1E en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,35 (br s, 1H), 11,17 (s, 1H), 8,61 (t, 1H), 8,57 (d, 1H), 7,77 (dd, 1H), 7,54 (d, 1H), 7,46 (d, 2H), 7,38 (m, 2H), 7,29 (m, 4H), 7,09 (m, 3H), 6,84 (dd, 1H), 6,69 (dd, 1H), 6,36 (m, 1H), 6,26 (d, 1H), 4,39 (t, 2H), 3,85 (m, 6H), 3,54 (m, 10H), 3,31 (m, 8H), 3,06 (m, 2H), 1,88 (m, 1H), 1,60 (m, 2H), 1,27 (m, 2H).

EJEMPLO 128

4-[4-({4'-cloro-3-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 128A

4'-cloro-3-hidroxibifenil-2-carbaldehido

Este ejemplo se realizó utilizando 2-bromo-6-hidroxibenzaldehido en lugar de EJEMPLO 68C y ácido 4-clorofenilborónico en lugar de ácido 4-metoxifenilborónico en el EJEMPLO 68D.

EJEMPLO 128B

4'-cloro-3-(2-(dimetilamino)etoxi)bifenil-2-carbaldehido

Este ejemplo se realizó utilizando EJEMPLO 128A en lugar de EJEMPLO 122B en el EJEMPLO 122C.

EJEMPLO 128C

2-(1H-indol-4–iloxi)-4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)bifenil-2–il)metil)piperazin-1–il)benzoato de metilo

Este ejemplo se realizó utilizando EJEMPLO 128B en lugar de 4’-clorobifenil-2-carboxaldehido y EJEMPLO 68B en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 128D

ácido 2-(1H-indol-4–iloxi)-4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)bifenil-2–il)metil)piperazin-1–il)benzoico

Este ejemplo se realizó utilizando EJEMPLO 128C en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 128E

4-[4-({4'-cloro-3-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

Este ejemplo se realizó utilizando EJEMPLO 128D en lugar de EJEMPLO 1E en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,15 (s, 1H), 8,47 (t, 1H) 8,45 (d, 1H), 7,68 (dd, 1H), 7,57 (d, 1H), 7,50 (d, 2H), 7,42 (d, 2H), 7,32 (m, 1H), 7,24 (m, 1H), 7,12 (d, 1H), 7,05 (d, 1H), 6,94 (m, 2H), 6,84 (d, 1H), 6,66 (dd, 1H), 6,35 (d, 1H), 6,25 (m, 2H), 4,17 (t, 2H), 3,85 (m, 2H), 3,54 (m, 10H), 3,40 (m, 6H), 3,30 (s, 6H), 3,02 (m, 2H), 2,96 (m, 4H), 2,28 (m, 4H), 1,88 (m, 1H), 1,60 (m, 2H), 1,28 (m, 2H).

EJEMPLO 129

4-[4-({4'-cloro-3-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 129A

2-(1H-indol-5–iloxi)-4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)bifenil-2–il)metil)piperazin-1–il)benzoato de metilo

Este ejemplo se realizó utilizando EJEMPLO 128B en lugar de 4'-clorobifenil-2-carboxaldehido y EJEMPLO 150A en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 129B

ácido 2-(1H-indol-5–iloxi)-4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)bifenil-2–il)metil)piperazin-1–il)benzoico

Este ejemplo se realizó utilizando EJEMPLO 129A en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 129C

4-[4-({4'-cloro-3-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

Este ejemplo se realizó utilizando EJEMPLO 129B en lugar de EJEMPLO 1E en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,38 (br s, 1H), 11,19 (s, 1H), 10,00(br s, 1H), 8,61 (t, 1H) 8,58 (d, 1H), 7,79 (dd, 1H), 7,53 (m, 4H), 7,39 (m, 4H), 7,19 (m, 1H), 7,11 (m, 2H), 6,93 (d, 1H), 6,84 (dd, 1H), 6,69 (dd, 1H), 6,39 (m, 1H), 6,19 (d, 1H), 4,40 (m, 2H), 3,85 (m, 8H), 3,58 (m, 2H), 3,27 (m, 6H), 3,06 (m, 2H), 2,89 (s, 6H), 1,89 (m, 1H), 1,60 (m, 2H), 1,27 (m, 2H).

EJEMPLO 130

4-(4-{[4'-cloro-4-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 130A

2-(1H-indol-4–iloxi)-4-(4-((4'-cloro-4-(2-morfolinoetoxi)bifenil-2–il)metil)piperazin-1–il)benzoato de metilo

Este ejemplo se realizó utilizando EJEMPLO 127A en lugar de 4'-clorobifenil-2-carboxaldehido y EJEMPLO 68B en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 130B

ácido 2-(1H-indol-4–iloxi)-4-(4-((4'-cloro-4-(2-morfolinoetoxi)bifenil-2–il)metil)piperazin-1–il)benzoico

Este ejemplo se realizó utilizando EJEMPLO 130A en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 130C

4-(4-{[4'-cloro-4-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

Este ejemplo se realizó utilizando EJEMPLO 130B en lugar de EJEMPLO 1E en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,47(br s, 1H), 11,23 (s, 1H), 8,59 (t, 1H) 8,47 (d, 1H), 7,63 (dd, 1H), 7,54 (d, 1H), 7,47 (d, 2H), 7,27 (m, 6H), 7,13 (m, 2H), 7,03 (m, 1H), 6,93 (m, 1H), 6,74 (dd, 1H), 6,35 (m, 1H), 6,24 (m, 1H), 4,39 (t, 2H), 3,85 (m, 6H), 3,54 (m, 10H), 3,26 (m, 10H), 1,88 (m, 1H), 1,59 (m, 2H), 1,27 (m, 2H).

EJEMPLO 131

4-(4-{[4'-cloro-3-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 131A

4'-cloro-3-(2-morfolinoetoxi)bifenil-2-carbaldehido

Este ejemplo se realizó utilizando EJEMPLO 128A en lugar de EJEMPLO 122B y sal clorhidrato de 4-(2-cloroetil)morfolina en lugar de sal clorhidrato de 2-cloro-N,N-dimetiletanamina en el EJEMPLO 122C.

EJEMPLO 131B

2-(1H-indol-4–iloxi)-4-(4-((4'-cloro-3-(2-morfolinoetoxi)bifenil-2–il)metil)piperazin-1–il)benzoato de metilo

Este ejemplo se realizó utilizando EJEMPLO 131A en lugar de 4'-clorobifenil-2-carboxaldehido y EJEMPLO 68B en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 131C

ácido 2-(1H-indol-4–iloxi)-4-(4-((4'-cloro-3-(2-morfolinoetoxi)bifenil-2–il)metil)piperazin-1–il)benzoico

Este ejemplo se realizó utilizando EJEMPLO 131B en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 131D

4-(4-{[4'-cloro-3-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

Este ejemplo se realizó utilizando EJEMPLO 131C en lugar de EJEMPLO 1E en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,49 (br s, 1H), 11,25 (s, 1H), 8,59 (t, 1H), 8,50 (d, 1H), 7,68 (dd, 1H), 7,52 (m, 4H), 7,34 (d, 2H), 7,28 (m, 1H), 7,18 (m, 2H), 7,06 (d, 1H), 6,94 (m, 2H), 6,73 (dd, 1H), 6,40 (d, 1H), 6,33 (d, 1H), 6,24 (m, 1H), 4,43(t, 2H), 3,85 (m, 10H), 3,61 (m, 6H), 3,27 (m, 8H), 3,02 (m, 2H), 1,88 (m, 1H), 1,60 (m, 2H), 1,28 (m, 2H).

EJEMPLO 132

4-(4-{[4'-cloro-3-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 132A

2-(1H-indol-5–iloxi)-4-(4-((4'-cloro-3-(2-morfolinoetoxi)bifenil-2–il)metil)piperazin-1–il)benzoato de metilo

Este ejemplo se realizó utilizando EJEMPLO 131A en lugar de 4'-clorobifenil-2-carboxaldehido y EJEMPLO 150A en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 132B

ácido 2-(1H-indol-5–iloxi)-4-(4-((4'-cloro-3-(2-morfolinoetoxi)bifenil-2–il)metil)piperazin-1–il)benzoico

Este ejemplo se realizó utilizando EJEMPLO 132A en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 132C

4-(4-{[4'-cloro-3-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

Este ejemplo se realizó utilizando EJEMPLO 132B en lugar de EJEMPLO 1E en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,34 (br s, 1H), 11,17 (s, 1H), 8,60 (t, 1H), 8,58 (d, 1H), 7,79 (dd, 1H), 7,50 (m, 4H), 7,39 (m, 4H), 7,19 (d, 1H), 7,14 (d, 1H), 7,09 (d, 1H), 6,93 (d, 1H), 6,84 (dd, 1H), 6,69 (dd, 1H), 6,39 (m, 1H), 6,19 (d, 1H), 4,40 (m, 2H), 3,85 (m, 6H), 3,48 (m, 8H), 3,27 (m, 10H), 3,06 (m, 2H), 1,89 (m, 1H), 1,60 (m, 2H), 1,27(m, 2H).

EJEMPLO 133

4-[4-({4'-cloro-4-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)-2-fenoxibenzamida

Este ejemplo se realizó utilizando EJEMPLO 113D en lugar de EJEMPLO 27G y EJEMPLO 21A en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 8,34 (d, 1H), 8,05 (d, 1H), 7,69 (dd, 1H), 7,59 (d, 1H), 7,42 (m, 4H), 7,14 (m, 3H), 7,09 (d, 1H), 6,98 (d, 1H), 6,92 (dd, 1H), 6,87 (m, 1H), 6,84 (m, 3H), 6,30 (d,

1H), 4,16 (t, 2H), 3,07 (m, 6H), 2,95 (m, 4H), 2,56 (m, 2H), 2,45 (s, 3H), 2,35 (m, 4H), 2,03 (m, 2H), 1,68 (m, 2H).

EJEMPLO 134

4-[4-({4'-cloro-3-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(3-pirrolidin-1–ilpropil)amino]fenil}sulfonil)benzamida

Este ejemplo se realizó utilizando EJEMPLO 129B en lugar de EJEMPLO 27G y EJEMPLO 68F en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,34 (br s, 1H), 11,17 (s, 1H), 9,65 (br s, 1H), 8,63 (t, 1H), 8,60 (d, 1H), 7,86 (dd, 1H), 7,53 (d, 2H), 7,41 (m, 6H), 7,15 (m, 3H), 6,92 (m, 1H), 6,84 (dd, 1H), 6,66 (dd, 1H), 6,38 (m, 1H), 6,16 (d, 1H), 4,37 (m, 2H), 3,50 (m, 12H), 3,17 (m, 4H), 2,97 (m, 4H), 2,88 (s, 6H), 1,95 (m, 4H), 1,85 (m, 2H).

EJEMPLO 135

4-[4-({4'-cloro-4-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(3-pirrolidin-1–ilpropil)amino]fenil}sulfonil)benzamida

Este ejemplo se realizó utilizando EJEMPLO 126B en lugar de EJEMPLO 27G y EJEMPLO 68F en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,29 (br s, 1H), 11,16 (s, 1H), 9,56 (br s, 1H), 8,63 (t, 1H), 8,60 (d, 1H), 7,85 (dd, 1H), 7,53 (d, 1H), 7,41 (m, 4H), 7,32 (m, 3H), 7,24 (m, 1H), 7,12 (m, 3H), 6,84 (dd, 1H), 6,66 (dd, 1H), 6,38 (m, 1H), 6,18 (d, 1H), 4,33 (t, 2H), 3,50 (m, 12H), 3,17 (m, 4H), 2,97 (m, 4H), 2,86 (s, 6H), 1,95 (m, 4H), 1,85 (m, 2H).

EJEMPLO 136

4-(4-{[4'-cloro-4-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(3-pirrolidin-1–ilpropil)amino]fenil}sulfonil)benzamida

Este ejemplo se realizó utilizando EJEMPLO 127C en lugar de EJEMPLO 27G y EJEMPLO 68F en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,29 (br s, 1H), 11,16 (s, 1H), 9,54 (br s, 1H), 8,63 (t, 1H), 8,60 (d, 1H), 7,85 (dd, 1H), 7,53 (d, 1H), 7,45 (d, 2H), 7,38 (m, 2H), 7,31(d, 2H), 7,23 (m, 2H), 7,12 (m, 3H), 6,84 (dd, 1H), 6,66 (dd, 1H), 6,38 (m, 1H), 6,18 (d, 1H), 4,36 (t, 2H), 3,82 (m, 4H), 3,50 (m, 8H), 3,17 (m, 10H), 2,98 (m, 4H), 1,95 (m, 6H), 1,85 (m, 2H).

EJEMPLO 137

4-[4-({4'-cloro-4-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-N-[(3-nitro-4-{[1-(2,2,2-trifluoroetil)piperidin-4–il]amino}fenil)sulfonil]-2-fenoxibenzamida

Este ejemplo se realizó utilizando EJEMPLO 113E en lugar de EJEMPLO 27G y EJEMPLO 108A en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,71 (br s, 1H), 9,81 (br s, 1H), 8,46(d, 1H), 8,29 (d, 1H), 7,75 (dd, 1H), 7,50 (m, 3H), 7,30 (m, 4H), 7,21(m, 3H), 7,10 (m, 1H), 6,97 (m, 1H), 6,77 (m, 3H), 6,43 (s, 1H), 4,36 (t, 2H), 3,72 (m, 2H), 3,58 (m, 4H), 3,23 (m, 6H), 2,95 (m, 4H), 2,89 (s, 6H), 2,60 (m, 2H), 1,92 (m, 2H), 1,68 (m, 2H).

EJEMPLO 138

4-(4-{[4'-cloro-4-(2-pirrolidin-1–iletoxi)-1,1'-bifenil-2–il]metil}piperazin-1–il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida

EJEMPLO 138A

4-(4-((4'-cloro-4-hidroxibifenil-2–il)metil)piperazin-1–il)-2-fenoxibenzoato de metilo

Este ejemplo se realizó utilizando EJEMPLO 113B en lugar de EJEMPLO 68C y ácido 4-clorofenilborónico en lugar de ácido 4-metoxifenilborónico en el EJEMPLO 68D.

EJEMPLO 138B

4-(4-((4'-cloro-4-(2-(pirrolidin-1–il)etoxi)bifenil-2–il)metil)piperazin-1–il)-2-fenoxibenzoato de metilo

Este ejemplo se realizó utilizando EJEMPLO 138A en lugar de EJEMPLO 113B y sal clorhidrato de 1-(2-cloroetil)pirrolidina en lugar de sal clorhidrato de 2-cloro-N,N-dimetiletanamina en el EJEMPLO 113C.

EJEMPLO 138C

ácido 4-(4-((4'-cloro-4-(2-(pirrolidin-1–il)etoxi)bifenil-2–il)metil)piperazin-1–il)-2-fenoxibenzoico

Este ejemplo se realizó utilizando EJEMPLO 138B en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 138D

4-(4-{[4'-cloro-4-(2-pirrolidin-1–iletoxi)-1,1'-bifenil-2–il]metil}piperazin-1–il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida

Este ejemplo se realizó utilizando EJEMPLO 138C en lugar de EJEMPLO 1E en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,64 (br s, 1H), 9,98 (br s, 1H), 8,62(d, 1H), 8,47 (d, 1H), 7,75(dd, 1H), 7,50 (m, 3H), 7,26 (m, 6H), 7,14 (m, 2H), 6,99 (m, 1H), 6,81 (d, 2H), 6,77 (dd, 1H), 6,43 (d, 1H), 4,36 (t, 2H), 3,86 (dd, 2H), 3,62 (m, 8H), 3,28 (m, 8H), 3,10 (m, 4H), 2,04 (m, 2H), 1,90(m, 3H), 1,65 (m, 2H), 1,29 (m, 2H).

EJEMPLO 139

4-[4-({4'-cloro-4-[2-(diisopropilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida

EJEMPLO 139A

4-(4-((4'-cloro-4-(2-(diisopropilamino)etoxi)bifenil-2–il)metil)piperazin-1–il)-2-fenoxibenzoato de metilo

Este ejemplo se realizó utilizando EJEMPLO 138A en lugar de EJEMPLO 113B y sal clorhidrato de cloruro de 2-diisopropilaminoetilo en lugar de sal clorhidrato de 2-cloro-N,N-dimetiletanamina en el EJEMPLO 113C.

EJEMPLO 139B

ácido 4-(4-((4'-cloro-4-(2-(diisopropilamino)etoxi)bifenil-2–il)metil)piperazin-1–il)-2-fenoxibenzoico

Este ejemplo se realizó utilizando EJEMPLO 139A en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 139C

4-[4-({4'-cloro-4-[2-(diisopropilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida

Este ejemplo se realizó utilizando EJEMPLO 139B en lugar de EJEMPLO 1E en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,65 (br s, 1H), 8,75 (br s, 1H), 8,62 (d, 1H), 8,47 (d, 1H), 7,75 (dd, 1H), 7,50 (m, 3H), 7,31 (m, 4H), 7,23 (m, 2H), 7,13 (m, 2H), 6,99 (m, 1H), 6,79 (m, 3H), 6,44 (m, 1H), 4,31 (t, 2H), 3,86 (dd, 2H), 3,62 (m, 10H), 3,28 (m, 6H), 1,91(m, 1H), 1,62 (m, 2H), 1,32(m, 14H).

EJEMPLO 140

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(2,3-dihidro-1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

Una suspensión de EJEMPLO 40D (22,57 mg) y cianoborohidruro de sodio (25 mg) en ácido acético (5 ml) se agitó a temperatura ambiente por 2 horas. El producto se particionó entre diclorometano y agua. La capa orgánica se separó, se secó sobre Na_2SO_4, y se concentró. El producto crudo se purificó mediante RP HPLC (C8, 30 - 100 acetonitrilo/agua/ácido trifluoroacético al 0,1%). ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11,56 (s, 1H), 9,60 (s, 1H), 8,66 (t, 1H), 8,57 (d, 1H), 7,85 (dd, 1H), 7,71 (s, 1H), 7,46 - 7,60 (m, 5H), 7,29 - 7,42 (m, 3H), 7,25 (d, 1H), 6,95 (s, 1H), 6,82 (s, 1H), 6,73 (d, 1H), 6,36 (s, 1H), 4,32 (bs, 2H), 3,85 (dd, 4H), 3,59 (t, 4H), 3,35 (t, 2H), 3,27 (t, 2H), 3,02 (t, 4H), 1,80 - 1,99 (m, 1H), 1,62 (d, 2H), 1,15 - 1,36 (m, 2H).

EJEMPLO 141

4-(4-{[2-(4-clorofenil)ciclohept-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(3-pirrolidin-1–ilpropil)amino]fenil}sulfonil)benzamida

EJEMPLO 141A

(Z)-2-(trifluorometilsulfoniloxi)ciclohept-1-encarboxilato de metilo

El compuesto del título se preparó utilizando 2-oxociclohepta necarboxilato de metilo en lugar de 5,5-dimetil-2-metoxicarbonilciclohexanona en el EJEMPLO 18A.

EJEMPLO 141B

(Z)-2-(4-clorofenil)ciclohept-1-encarboxilato de metilo

El compuesto del título se preparó utilizando EJEMPLO 141A en lugar de EJEMPLO 18A en el EJEMPLO 18B.

EJEMPLO 141C

(Z)-(2-(4-clorofenil)ciclohept-1-enil)metanol

El compuesto del título se preparó utilizando EJEMPLO 141B en lugar de EJEMPLO 18B en el EJEMPLO 18C.

EJEMPLO 141D

(Z)-2-(4-clorofenil)ciclohept-1-encarbaldehido

El compuesto del título se preparó utilizando EJEMPLO 141C en lugar de EJEMPLO 143C en el EJEMPLO 143D.

EJEMPLO 141E

(Z)-2-(1H-indol-4–iloxi)-4-(4-((2-(4-clorofenil)ciclohept-1-enil)metil)piperazin-1–il)benzoato de etilo

El compuesto del título se preparó utilizando EJEMPLO 141D en lugar de 4'-clorobifenil-2-carboxaldehido y EJEMPLO 68B en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 141F

ácido (Z)-2-(1H-indol-4–iloxi)-4-(4-((2-(4-clorofenil)ciclohept-1-enil)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 141E en lugar de EJEMPLO 143E en el EJEMPLO 143F.

EJEMPLO 141G

4-(4-{[2-(4-clorofenil)ciclohept-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(3-pirrolidin-1–ilpropil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 141F en lugar de EJEMPLO 1E y EJEMPLO 68F en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11,45 (m, 1H), 10,03 (m, 1H), 8,58 (m, 2H), 8,30 (m, 1H), 7,26 (m, 11H), 6,25 (m, 2H), 3,14 (m, 12H), 2,73 (m, 5H), 1,94 (m, 12H), 1,54 (m, 5H).

EJEMPLO 142

4-(4-{[2-(4-clorofenil)ciclooct-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(3-pirrolidin-1–ilpropil)amino]fenil}sulfonil)benzamida

EJEMPLO 142A

(Z)-2-(trifluorometilsulfoniloxi)ciclooct-1-encarboxilato de etilo

El compuesto del título se preparó utilizando 2-oxociclooctanocarboxilato de etilo en lugar de 5,5-dimetil-2-metoxicarbonilciclohexanona en el EJEMPLO 18A.

EJEMPLO 142B

(Z)-2-(4-clorofenil)ciclooct-1-encarboxilato de etilo

El compuesto del título se preparó utilizando EJEMPLO 142A en lugar de EJEMPLO 18A en el EJEMPLO 18B.

EJEMPLO 142C

(Z)-(2-(4-clorofenil)ciclooct-1-enil)metanol

El compuesto del título se preparó utilizando EJEMPLO 142B en lugar de EJEMPLO 18B en el EJEMPLO 18C.

EJEMPLO 142D

(Z)-2-(4-clorofenil)ciclooct-1-encarbaldehido

El compuesto del título se preparó utilizando EJEMPLO 142C en lugar de EJEMPLO 143C en el EJEMPLO 143D.

EJEMPLO 142E

(Z)-2-(1H-indol-4–iloxi)-4-(4-((2-(4-clorofenil)ciclooct-1-enil)metil)piperazin-1–il)benzoato de etilo

El compuesto del título se preparó utilizando EJEMPLO 142D en lugar de 4'-clorobifenil-2-carboxaldehido y EJEMPLO 68B en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 142F

ácido (Z)-2-(1H-indol-4–iloxi)-4-(4-((2-(4-clorofenil)ciclooct-1-enil)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 142E en lugar de EJEMPLO 143E en el EJEMPLO 143F.

EJEMPLO 142G

4-(4-{[2-(4-clorofenil)ciclooct-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(3-pirrolidin-1–ilpropil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 142F en lugar de EJEMPLO 1E y EJEMPLO 68F en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300 MHz, dimetilsulfóxido-d6) δ 11,51 (m, 1H), 10,01 (m, 1H), 8,58 (m, 2H), 7,26 (m, 12H), 6,35 (m, 2H), 3,14 (m, 13H), 2,73 (m, 5H), 1,88 (m, 7H), 1,45 (m, 10H).

EJEMPLO 143

4-(4-{[2-(4-clorofenil)ciclopent-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(3-pirrolidin-1–ilpropil)amino]fenil}sulfonil)benzamida

EJEMPLO 143A

2-(trifluorometilsulfoniloxi)ciclopent-1-encarboxilato de etilo

El compuesto del título se preparó utilizando 2-oxociclopentancarboxilato de etilo en lugar de 5,5-dimetil-2-metoxicarbonilciclohexanona en el EJEMPLO 18A.

EJEMPLO 143B

2-(4-clorofenil)ciclopent-1-encarboxilato de etilo

El compuesto del título se preparó utilizando EJEMPLO 143A en lugar de EJEMPLO 18A en el EJEMPLO 18B.

EJEMPLO 143C

(2-(4-clorofenil)ciclopent-1-enil)metanol

El compuesto del título se preparó utilizando EJEMPLO 143B en lugar de EJEMPLO 18B en el EJEMPLO 18C.

EJEMPLO 143D

2-(4-clorofenil)ciclopent-1-encarbaldehido

A una solución de cloruro de oxalilo (1,1g) en diclorometano (30 ml) a -78°C se agregó dimetilsulfóxido (6,12 ml). La mezcla se agitó a -78°C durante 30 minutos, y luego se agregó una solución de EJEMPLO 143C (1,2 g) en diclorometano (10 ml). La mezcla se agitó a -78°C por 2 horas antes de agregar trietilamina (10 ml). La mezcla se agitó durante la noche y la temperatura se dejó elevar a temperatura ambiente. La mezcla se diluyó con éter (300 ml) y se lavó con agua, salmuera y se secó sobre Na_2SO_4. Se evaporó el solvente y se purificó en columna (acetato de etilo al 5% en hexano) para dar el producto.

EJEMPLO 143E

2-(1H-indol-4–iloxi)-4-(4-((2-(4-clorofenil)ciclopent-1-enil)metil)piperazin-1–il)benzoato de etilo

El compuesto del título se preparó utilizando EJEMPLO 143D en lugar de 4'-clorobifenil-2-carboxaldehido y EJEMPLO 68B en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 143F

ácido 2-(1H-indol-4–iloxi)-4-(4-((2-(4-clorofenil)ciclopent-1-enil)metil)piperazin-1–il)benzoico

A una solución de EJEMPLO 143E (254 mg) en tetrahidrofurano (4 ml), metanol (2 ml) y agua (2 ml) se agregó LiOH-H_2O (126 mg). La mezcla se agitó durante la noche. La mezcla luego se neutralizó con HCl al 5% y se diluyó con acetato de etilo (200 ml). Luego de lavar con salmuera, se secó sobre Na_2SO_4. La evaporación del solvente dio el producto.

EJEMPLO 143G

4-(4-{[2-(4-clorofenil)ciclopent-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(3-pirrolidin-1–ilpropil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 143F en lugar de EJEMPLO 1E y EJEMPLO 68F en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300 MHz, dimetilsulfóxido-d6) δ ppm 11,41 (m, 1H), 10,19 (m, 1H), 8,58 (m, 2H), 7,26 (m, 14H), 6,33 (m, 2H), 3,80 (m, 4H), 3,13 (m, 12H), 2,69 (m, 5H), 1,95 (m, 7H).

EJEMPLO 144

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclopent-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida

EJEMPLO 144A

4,4-dimetil-2-oxociclopentancarboxilato de metilo

Este compuesto se preparó de acuerdo con WO 2006/035061(página 53).

EJEMPLO 144B

4,4-dimetil-2-(trifluorometilsulfoniloxi)ciclopent-1-encarboxilato de metilo

El compuesto del título se preparó utilizando 2-oxociclopentancarboxilato de etilo en lugar de 5,5-dimetil-2-metoxicarbonilciclohexanona en el EJEMPLO 18A.

EJEMPLO 144C

2-(4-clorofenil)-4,4-dimetilciclopent-1-encarboxilato de etilo

El compuesto del título se preparó utilizando EJEMPLO 144B en lugar de EJEMPLO 18A en el EJEMPLO 18B.

EJEMPLO 144D

(2-(4-clorofenil)-4,4-dimetilciclopent-1-enil)metanol

El compuesto del título se preparó utilizando EJEMPLO 144C en lugar de EJEMPLO 18B en el EJEMPLO 18C.

EJEMPLO 144E

2-(4-clorofenil)-4,4-dimetilciclopent-1-encarbaldehido

El compuesto del título se preparó utilizando EJEMPLO 144D en lugar de EJEMPLO 143C en el EJEMPLO 143D.

EJEMPLO 144F

2-(1H-indol-4–iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclopent-1-enil)metil)piperazin-1–il)benzoato de etilo

El compuesto del título se preparó utilizando EJEMPLO 144E en lugar de 4'-clorobifenil-2-carboxaldehido y EJEMPLO 68B en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 144G

ácido 2-(1H-indol-4–iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclopent-1-enil)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 144F en lugar de EJEMPLO 143E en el EJEMPLO 143F.

EJEMPLO 144H

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclopent-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 144G en lugar de EJEMPLO 1E y EJEMPLO 21A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300 MHz, dimetilsulfóxido-d6) δ 11,59 (m, 1H), 11,25 (s, 1H), 9,53 (m, 1H), 8,50 (d, 1H),

8,16 (d, 1H), 8,16 (d, 1H), 7,80 (m, 1H), 7,56 (d, 1H), 7,26 (m, 7H), 6,95 (m, 1H), 6,77 (dd, 1H), 6,41 (m, 2H), 6,23 (s, 1H), 2,87 (m, 10H), 2,28 (m, 12H), 1,11 (m, 6H).

EJEMPLO 145

4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida

EJEMPLO 145A

6,6-dimetil-4-oxotetrahidro-2H-piran-3-carboxilato de metilo

A una suspensión de NaH lavado con hexano (0,72 g, 60%) en tetrahidrofurano (30 ml) se agregó una solución de 2,2-dimetildihidro-2H-piran-4(3H)-ona (2,0 g) en tetrahidrofurano (20 ml). La suspensión se agitó por 30 minutos. El carbonato de dimetilo (6,31 ml) se agregó por goteo con una jeringa. La mezcla se calentó a reflujo por 4 horas. La mezcla se acidificó con HCl al 5% y se extrajo con diclorometano (3x 100ml) y se lavó con agua , salmuera y se secó sobre Na_2SO_4. Luego de la evaporación, el producto crudo se cargó en una columna y se eluyó con acetato de etilo al 10% en hexano para dar el producto.

EJEMPLO 145B

6,6-dimetil-4-(trifluorometilsulfoniloxi)-5,6-dihidro-2H-piran-3-carboxilato de metilo

El compuesto del título se preparó utilizando EJEMPLO 145A en lugar de 5,5-dimetil-2-metoxicarbonilciclohexanona en el EJEMPLO 18A.

EJEMPLO 145C

4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-carboxilato de metilo

El compuesto del título se preparó utilizando EJEMPLO 145B en lugar de EJEMPLO 18A en el EJEMPLO 18B.

EJEMPLO 145D

(4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3–il)metanol

El compuesto del título se preparó utilizando EJEMPLO 145C en lugar de EJEMPLO 18B en el EJEMPLO 18C.

EJEMPLO 145E

4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-carbaldehido

El compuesto del título se preparó utilizando EJEMPLO 145D en lugar de EJEMPLO 143C en el EJEMPLO 143D.

EJEMPLO 145F

2-(1H-indol-4–iloxi)-4-(4-((4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3–il)metil)piperazin-1–il)benzoato de etilo

El compuesto del título se preparó utilizando EJEMPLO 145E en lugar de 4'-clorobifenil-2-carboxaldehido y EJEMPLO 68B en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 145G

ácido 2-(1H-indol-4–iloxi)-4-(4-((4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3–il)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 145F en lugar de EJEMPLO 143E en el EJEMPLO 143F.

EJEMPLO 145H

4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 145G en lugar de EJEMPLO 1E y EJEMPLO 21A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300 MHz, dimetilsulfóxido-d6) δ 11,56 (m, 1H), 11,26 (s, 1H), 9,52 (m, 1H), 8,51 (m, 1H), 8,16 (d, 1H), 7,80 (dd, 1H), 7,55 (d, 1H), 7,41 (d, 2H), 7,28 (t, 1H), 7,17 (m, 4H), 6,96 (m, 2H), 6,74 (d, 1H), 6,39 (m, 2H), 6,23 (s, 1H), 4,18 (s, 2H), 3,85 (m, 3H), 2,93 (m, 10H), 2,10 (m, 7H), 1,22 (s, 6H).

EJEMPLO 146

4-(4-{[2-(4-clorofenil)ciclooct-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 142F en lugar de EJEMPLO 1E y EJEMPLO 21A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300 MHz, dimetilsulfóxido-d6) δ 11,59 (s, 1H), 11,25 (s, 1H), 9,36 (m, 2H), 8,50 (d, 1H), 8,16 (d, 1H), 7,79 (dd, 1H), 7,55 (d, 1H), 7,40 (d, 2H), 7,28 (m, 1H), 7,14 (m, 5H), 6,96 (t, 1H), 6,74 (dd, 1H), 6,38 (m, 2H), 6,23 (s, 1H), 2,91 (m, 14H), 2,27 (m, 6H), 1,49 (m, 11H).

EJEMPLO 147

4-(4-{[2-(4-clorofenil)ciclohept-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 141F en lugar de EJEMPLO 1E y EJEMPLO 21A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300 MHz, dimetilsulfóxido-d6) δ 11,60 (s, 1H), 11,26 (s, 1H), 9,32 (m, 2H), 8,51 (m, 1H), 8,16 (d, 1H), 7,79 (m, 1H), 7,55 (d, 1H), 7,39 (d, 2H), 7,29 (t, 1H), 7,14 (m, 4H), 6,97 (t, 1H), 6,75 (dd, 1H), 6,40 (m, 2H), 6,22 (s, 1H), 2,94 (m, 17H), 2,27 (m, 4H), 1,80 (m, 4H), 1,55 (m, 5H).

EJEMPLO 148

4-(4-{[2-(4-clorofenil)ciclopent-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 143F en lugar de EJEMPLO 1E y EJEMPLO 21A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300 MHz, dimetilsulfóxido-d6) δ 11,60 (s, 1H), 11,26 (s, 1H), 9,47 (m, 2H), 8,51 (m, 1H), 8,16 (d, 1H), 7,77 (m, 1H), 7,56 (d, 1H), 7,43 (d, 2H), 7,20 (m, 6H), 6,96 (t, 1H), 6,77 (dd, 1H), 6,41 (m, 2H), 6,24 (s, 1H), 2,93 (m, 17H), 2,01 (m, 8H).

EJEMPLO 149

4-(4-{[2-(4-clorofenil)ciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida

EJEMPLO 149A

2-(trifluorometilsulfoniloxi)ciclohex-1-encarboxilato de etilo

El compuesto del título se preparó utilizando 2-oxociclohexanocarboxilato de etilo en lugar de 5,5-dimetil-2-metoxicarbonilciclohexanona en el EJEMPLO 18A.

EJEMPLO 149B

2-(4-clorofenil)ciclohex-1-encarboxilato de etilo

El compuesto del título se preparó utilizando EJEMPLO 149A en lugar de EJEMPLO 18A en el EJEMPLO 18B.

EJEMPLO 149C

(2-(4-clorofenil)ciclohex-1-enil)metanol

El compuesto del título se preparó utilizando EJEMPLO 149B en lugar de EJEMPLO 18B en el EJEMPLO 18C.

EJEMPLO 149D

2-(4-clorofenil)ciclohex-1-encarbaldehido

El compuesto del título se preparó utilizando EJEMPLO 149C en lugar de EJEMPLO 143C en el EJEMPLO 143D.

EJEMPLO 149E

2-(1H-indol-4–iloxi)-4-(4-((2-(4-clorofenil)ciclohex-1-enil)metil)piperazin-1–il)benzoato de etilo

El compuesto del título se preparó utilizando EJEMPLO 149D en lugar de 4'-clorobifenil-2-carboxaldehido y EJEMPLO 68B en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 149F

ácido 2-(1H-indol-4–iloxi)-4-(4-((2-(4-clorofenil)ciclohex-1-enil)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 149E en lugar de EJEMPLO 143E en el EJEMPLO 143F.

EJEMPLO 149G

4-(4-{[2-(4-clorofenil)ciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 149F en lugar de EJEMPLO 1E y EJEMPLO 21A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300 MHz, dimetilsulfóxido-d6) δ 11,14 (s, 1H), 8,44 (d, 1H), 8,10 (d, 1H), 7,74 (dd, 1H), 7,56 (d, 1H), 7,34 (d, 2H), 7,23 (m, 1H), 7,01 (m, 5H), 6,63 (dd, 1H), 6,34 (d, 1H), 6,22 (m, 2H), 3,74 (m, 1H), 3,03 (m, 7H), 2,67 (m, 5H), 2,07 (m, 11H), 1,67 (m, 7H).

EJEMPLO 150

4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida

EJEMPLO 150A

2-(1H-indol-5–iloxi)-4-(piperazin-1–il)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 26A en lugar de EJEMPLO 1C y piperazina en lugar de EJEMPLO 1B en el EJEMPLO 1D.

EJEMPLO 150B

2-(1H-indol-5–iloxi)-4-(4-((4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3–il)metil)piperazin-1–il)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 145E en lugar de 4'-clorobifenil-2-carboxaldehido y EJEMPLO 150A en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 150C

ácido 2-(1H-indol-5–iloxi)-4-(4-((4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3–il)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 150B en lugar de EJEMPLO 143E en el EJEMPLO 143F.

EJEMPLO 150D

4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 150C en lugar de EJEMPLO 1E y EJEMPLO 21A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300 MHz, dimetilsulfóxido-d6) δ 11,00 (s, 1H), 8,42 (d, 1H), 8,07 (d, 1H), 7,67 (dd, 1H), 7,52 (d, 1H), 7,37 (d, 2H), 7,29 (m, 1H), 7,14 (d, 2H), 6,93 (d, 1H), 6,86 (d, 1H), 6,72 (dd, 1H), 6,55 (dd, 1H), 6,31 (s, 1H), 6,15 (d, 1H), 5,85 (m, 3H), 4,11 (s, 2H), 3,00 (m, 8H), 2,82 (s, 2H), 2,73 (m, 3 H), 2,23 (m, 8H), 1,57 (m, 2H), 1,18 (s, 6H).

EJEMPLO 151

4-(4-{[2-(4-clorofenil)ciclohept-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida

EJEMPLO 151A

(Z)-2-(1H-indol-5–iloxi)-4-(4-((2-(4-clorofenil)ciclohept-1-enil)metil)piperazin-1–il)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 141D en lugar de 4'-clorobifenil-2-carboxaldehido y EJEMPLO 150A en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 151B

ácido (Z)-2-(1H-indol-5–iloxi)-4-(4-((2-(4-clorofenil)ciclohept-1-enil)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 151A en lugar de EJEMPLO 143E en el EJEMPLO 143F.

EJEMPLO 151C

4-(4-{[2-(4-clorofenil)ciclohept-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 151B en lugar de EJEMPLO 1E y EJEMPLO 21A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300 MHz, dimetilsulfóxido-d6) δ 11,06 (s, 1H), 8,48 (d, 1H), 8,11 (d, 1H), 7,74 (dd, 1H), 7,52 (d, 1H), 7,33 (m, 4H), 7,01 (m, 4H), 6,76 (dd, 1H), 6,58 (dd, 1H), 6,34 (s, 1H), 6,14 (d, 1H), 5,75 (s, 1H), 3,69 (m, 1H), 2,96 (m, 6H), 2,71 (m, 2H), 2,36 (m, 8H), 2,21 (s, 5H), 1,98 (m, 2H), 1,63 (m, 8H).

EJEMPLO 152

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)-2-fenoxibenzamida

Este compuesto se realizó utilizando EJEMPLO 18G en lugar de EJEMPLO 1E y EJEMPLO 21A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (400 MHz, dimetilsulfóxido-d_6) δ 8,43 (m, 1H) 8,18 (d, 1H) 7,82 (dd, 1H) 7,52 (d, 1H) 7,40 (m, 2H) 7,22 (m, 3H) 7,11 (m, 2H) 7,01 (t, 1H) 6,79 (m, 3H) 6,45 (d, 1H) 3,06 (m, 14H) 2,20 (m, 4H) 2,04 (s, 3H) 1,85 (m, 2H) 1,47 (m, 2H) 0,96 (s, 6H).

EJEMPLO 153

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(4-{[2-(dimetilamino)etil]amino}-3-nitrofenil)sulfonil]-2-fenoxibenzamida

EJEMPLO 153A

4-(2-(dimetilamino)etilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando N,N-dimetiletilendiamina en lugar de (tetrahidropiran-4–il)metilamina en el EJEMPLO 1F.

EJEMPLO 153B

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(4-{[2-(dimetilamino)etil]amino}-3-nitrofenil)sulfonil]-2-fenoxibenzamida

El compuesto del título se preparó utilizando EJEMPLO 153A en lugar de EJEMPLO 1F y EJEMPLO 1E en lugar de EJEMPLO 27G en el EJEMPLO 27H. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,75 (br s, 1H), 9,78 (br s, 1H), 9,44 (br s, 1H), 8,66 (t, 1H), 8,49 (d, 1H), 7,83 (d, 1H), 7,70 (m, 2H), 7,51 (m, 4H), 7,38 (d, 2H), 7,33 (m, 1H), 7,24 (d, 2H), 7,18 (d, 1H), 7,02 (dd, 1H), 6,81 (d, 2H), 6,76 (d, 1H), 6,44 (s, 1H), 4,30 (m, 1H), 3,83 (m, 4H), 3,31 (m, 6H), 3,15 (m, 2H), 3,04 (m, 2H), 2,85 (s, 6H).

EJEMPLO 154

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(4-{[3-(dimetilamino)propil]amino}-3-nitrofenil)sulfonil]-2-fenoxibenzamida

EJEMPLO 154A

4-(3-(dimetilamino)propilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando N,N-dimetil-1,3-propandiamina en lugar de (tetrahidropiran-4–il)metilamina en el EJEMPLO 1F.

EJEMPLO 154B

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(4-{[3-(dimetilamino)propil]amino}-3-nitrofenil)sulfonil]-2-fenoxibenzamida

El compuesto del título se preparó utilizando EJEMPLO 154A en lugar de EJEMPLO 1F y EJEMPLO 1E en lugar de EJEMPLO 27G en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,68 (br s, 1H), 9,38 (br s, 1H), 8,66 (t, 1H), 8,49 (d, 1H), 7,80 (d, 1H), 7,68 (m, 2H), 7,51 (m, 4H), 7,38 (d, 1H), 7,33 (m, 2H), 7,24 (d, 2H), 7,16 (d,

1H), 7,02 (dd, 1H), 6,81 (d, 2H), 6,76 (d, 1H), 6,43 (s, 1H), 4,25 (m, 1H), 3,50 (m, 4H), 3,30 (m, 4H), 3,12 (m, 6H), 2,78 (s, 6H), 1,95 (m, 2H).

EJEMPLO 155

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)-2-fenoxibenzamida

El compuesto del título se preparó utilizando EJEMPLO 7A en lugar de EJEMPLO 1F y EJEMPLO 1E en lugar de EJEMPLO 27G en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,70 (br s, 1H), 9,72 (br s, 1H), 8,68 (t, 1H), 8,49 (d, 1H), 7,81 (d, 1H), 7,70 (m, 2H), 7,51 (m, 4H), 7,37 (d, 2H), 7,33 (m, 1H), 7,24 (d, 2H), 7,15 (d, 1H), 7,03 (dd, 1H), 6,81 (d, 2H), 6,76 (d, 1H), 6,44 (s, 1H), 4,24 (m, 1H), 3,97 (m, 2H), 3,63 (m, 4H), 3,28 (m, 4H), 3,18 (m, 4H), 3,06 (m, 4H), 2,88 (m, 4H), 1,99 (m, 2H).

EJEMPLO 156

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(4-{[4-(dimetilamino)butil]amino}-3-nitrofenil)sulfonil]-2-fenoxibenzamida

EJEMPLO 156A

4-(4-(dimetilamino)butilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando N,N-dimetil-1,4-butandiamina en lugar de (tetrahidropiran-4–il)metilamina en el EJEMPLO 1F.

EJEMPLO 156B

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(4-{[4-(dimetilamino)butil]amino}-3-nitrofenil)sulfonil]-2-fenoxibenzamida

El compuesto del título se preparó utilizando EJEMPLO 156A en lugar de EJEMPLO 1F y EJEMPLO 1E en lugar de EJEMPLO 27G en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,70 (br s, 1H), 9,34 (br s, 1H), 8,63 (t, 1H), 8,48 (d, 1H), 7,79 (d, 1H), 7,70 (m, 2H), 7,51 (m, 4H), 7,39 (d, 2H), 7,33 (m, 1H), 7,24 (d, 2H), 7,12 (d, 1H), 7,01 (dd, 1H), 6,80 (d, 2H), 6,75 (d, 1H), 6,44 (s, 1H), 4,28 (m, 1H), 3,83 (m, 4H), 3,45 (m, 10H), 3,10 (m, 4H), 2,85 (s, 6H), 1,66 (m, 4H).

EJEMPLO 157

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(3-nitro-4-{[1-(fenilsulfonil)piperidin-4–il]amino}fenil)sulfonil]-2-fenoxibenzamida

EJEMPLO 157A

4-(2-nitro-4-sulfamoilfenilamino)piperidin-1-carboxilato de tert-butilo

El compuesto del título se preparó utilizando 1-Boc-4-aminopiperidina en lugar de (tetrahidropiran-4–il)metilamina en el EJEMPLO 1F.

EJEMPLO 157B

3-nitro-4-(piperidin-4–ilamino)bencensulfonamida

El compuesto del título se preparó utilizando EJEMPLO 157A en lugar de EJEMPLO 1A en el EJEMPLO 1B.

EJEMPLO 157C

3-nitro-4-(1-(fenilsulfonil)piperidin-4–ilamino)bencensulfonamida

Una mezcla de EJEMPLO 157B (84 mg), cloruro de bencensulfonilo (46 mg), y trietilamina (101 mg) en CH_2Cl_2 (2 mL) se agitó por 1 hora. El producto se cromatografió sobre gel de sílice con acetato de etilo al 25%/hexanos.

EJEMPLO 157D

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(3-nitro-4-{[1-(fenilsulfonil)piperidin-4–il]amino}fenil)sulfonil]-2-fenoxibenzamida

El compuesto del título se preparó utilizando EJEMPLO 157C en lugar de EJEMPLO 1F y EJEMPLO 1E en lugar de EJEMPLO 27G en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,68 (br s, 1H), 9,65 (br s, 1H), 8,42 (s, 1H), 8,19 (d, 1H), 7,78 (m, 2H), 7,70 (m, 4H), 7,51 (m, 5H), 7,37 (m, 3H), 7,19 (m, 3H), 6,94 (dd, 1H), 6,75 (m, 3H), 6,44 (s, 1H), 4,28 (m, 1H), 3,73 (m, 4H), 3,50 (m, 4H), 3,17 (m, 2H), 3,03 (m, 2H), 2,86 (m, 2H), 1,99 (m, 2H), 1,74 (m, 2H).

EJEMPLO 158

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(3-nitro-4-{[1-(quinolin-8–ilsulfonil)piperidin-4–il]amino}fenil)sulfonil]-2-fenoxibenzamida

EJEMPLO 158A

3-nitro-4-(1-(quinolin-8–ilsulfonil)piperidin-4–ilamino)bencensulfonamida

El compuesto del título se preparó utilizando cloruro de quinolin-8-sulfonilo en lugar de cloruro de bencensulfonilo en el EJEMPLO 157C.

EJEMPLO 158B

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(3-nitro-4-{[1-(quinolin-8–ilsulfonil)piperidin-4–il]amino}fenil)sulfonil]-2-fenoxibenzamida

El compuesto del título se preparó utilizando EJEMPLO 158A en lugar de EJEMPLO 1F y EJEMPLO 1E en lugar de EJEMPLO 27G en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,66 (br s, 1H), 9,10 (dd, 1H), 8,55 (s, 1H), 8,41 (m, 2H), 8,32 (d, 1H), 8,20 (d, 1H), 7,78 (dd, 2H), 7,72 (d, 2H), 7,48 (m, 4H), 7,39 (dd, 2H), 7,33 (m, 1H), 7,17 (m, 3H), 6,95 (dd, 1H), 6,76 (m, 3H), 6,42 (s, 1H), 4,35 (m, 1H), 3,90 (d, 2H), 3,77 (m, 2H), 3,34 (m, 6H), 2,99 (m, 4H), 1,97 (m, 2H), 1,65 (m, 2H).

EJEMPLO 159

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-fenoxi-N-({4-{[1-(fenilsulfonil)piperidin-4–il]amino}-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

EJEMPLO 159A

(2-fluorofenil)(trifluorometil)sulfano

Se trató clorhidrato ácido de metilo (1,17 g) en N,N-dimetilformamida (80 mL) a 25ºC saturado con yoduro de trifluorometilo, con 2-fluorobencenotiol (9,7 mL) y trietilamina (20 mL), se agitó durante 24 horas, se diluyó con agua (240 mL) y se extrajo con dietiléter. El extracto se lavó con NaOH 1M, cloruro de amonio saturado y salmuera y se concentró.

EJEMPLO 159B

1-fluoro-2-(trifluorometilsulfonil)benceno

Se trató EJEMPLO 159A (17,346 g) en 1:1:2 tetracloruro de carbono:acetonitrilo:agua (800 mL) a 25ºC con periodato de sodio (56,8 g) y cloruro de rutenio(III) hidratado (183 mg), se agitó por 18 horas, se diluyó con diclorometano (100 mL) y se filtró a través de tierra diatomea (Celite®). El filtrado se lavó con bicarbonato de sodio saturado y se extrajo con diclorometano. el extracto se lavó con salmuera y se secó ($MgSO_4$), se filtró y se concentró. El concentrado se filtró a través de gel de sílice.

EJEMPLO 159C

4-fluoro-3-(trifluorometilsulfonil)bencensulfonamida

Se agitó EJEMPLO 159B (37,3 g) en ácido clorosulfónico (32,8 mL) a 120°C por 18 horas, se enfrió a 25ºC y se volcó con una pipeta sobre hielo triturado. La mezcla se extrajo con acetato de etilo, y el extracto se lavó con agua y salmuera y se secó ($MgSO_4$), se filtró y se concentró. El producto crudo se capturó en isopropanol (706 mL) a -78°C, se trató con hidróxido de amonio (98 mL) a lo largo de 1 hora, se agitó por 1 hora, se detuvo con HCl 6M (353 mL), se calentó a 25ºC y se concentró. El concentrado se mezcló con agua y se extrajo con acetato de etilo. El extracto se secó sobre $MgSO_4$, se filtró y se concentró. El concentrado se recristalizó a partir de acetato de etilo/hexano.

EJEMPLO 159D

4-(4-sulfamoil-2-(trifluorometilsulfonil)fenilamino)piperidin-1-carboxilato de tert-butilo

El compuesto del título se preparó utilizando 1-Boc-4-aminopiperidina en lugar de (tetrahidropiran-4–il)metilamina y EJEMPLO 159C durante 4-fluoro-3-nitrobencensulfonamida en el EJEMPLO 1F.

EJEMPLO 159E

4-(piperidin-4–ilamino)-3-(trifluorometilsulfonil)bencensulfonamida

El compuesto del título se preparó utilizando EJEMPLO 159D en lugar de EJEMPLO 1A en el EJEMPLO 1B.

EJEMPLO 159F

4-(1-(fenilsulfonil)piperidin-4–ilamino)-3-(trifluorometilsulfonil)bencensulfonamida

El compuesto del título se preparó utilizando EJEMPLO 159E en lugar de EJEMPLO 157B en el EJEMPLO 157C.

EJEMPLO 159G

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-fenoxi-N-({4-{[1-(fenilsulfonil)piperidin-4–il]amino}-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 159F en lugar de EJEMPLO 1F y EJEMPLO 1E en lugar de EJEMPLO 27G en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,72 (br s, 1H), 9,70 (br s, 1H), 8,07 (s, 1H), 7,67-7,82 (m,

7H), 7,52 (d, 2H), 7,47 (d, 2H), 7,36 (m, 3H), 7,24 (dd, 2H), 7,14 (d, 1H), 7,01 (m, 1H), 6,78 (d, 2H), 6,72 (m, 2H), 6,44 (d, 1H), 4,27 (m, 1H), 3,73 (m, 4H), 3,46 (m, 4H), 3,17 (m, 2H), 3,03 (m, 2H), 2,87 (m, 2H), 1,97 (m, 2H), 1,64 (m, 2H).

EJEMPLO 160

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-fenoxi-N-({4-{[1-(quinolin-8–ilsulfonil)piperidin-4–il]amino}-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

EJEMPLO 160A

4-(1-(quinolin-8–ilsulfonil)piperidin-4–ilamino)-3-(trifluorometilsulfonil)bencensulfonamida

El compuesto del título se preparó utilizando EJEMPLO 159E en lugar de EJEMPLO 157B y cloruro de quinolin-8-sulfonilo en lugar de cloruro de bencensulfonilo en el EJEMPLO 157C.

EJEMPLO 160B

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-fenoxi-N-({4-{[1-(quinolin-8–ilsulfonil)piperidin-4–il]amino}-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 160A en lugar de EJEMPLO 1F y EJEMPLO 1E en lugar de EJEMPLO 27G en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,74 (br s, 1H), 9,50 (br s, 1H), 9,08 (dd, 1H), 8,55 (s, 1H), 8,39 (d, 1H), 8,33 (d, 1H), 8,06 (s, 1H), 7,82 (dd, 2H), 7,70 (m, 1H), 7,50 (m, 3H), 7,40 (dd, 2H), 7,33 (m, 1H), 7,21 (m, 2H), 7,08 (m, 2H), 6,99 (dd, 1H), 6,95 (s, 1H), 6,78 (d, 1H), 6,73 (m, 2H), 6,42 (s, 1H), 4,35 (m, 1H), 3,75 (m, 4H), 3,34 (m, 6H), 3,05 (m, 4H), 1,93 (m, 2H), 1,55 (m, 2H..

EJEMPLO 161

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(4-{[(1S)-3-(dimetilamino)-1-tien-2–ilpropil]amino}-3-nitrofenil)sulfonil]-2-fenoxibenzamida

EJEMPLO 161A

ácido (S)-3-(benciloxicarbonilamino)-3-(tiofen-2–il)propanoico

Se agitó ácido (S)-3-amino-3-(tiofen-2–il)propanoico (0,894 g) y cloruro de benciloxicarbonilo (0,980 g) en NaOH 2M (8 mL) y dioxano (26 mL) a 0°C durante 24 horas. La mezcla de reacción se acidificó con HCl acuoso concentrado, se extrajo dos veces con

acetato de etilo, y los extractos se secaron sobre $MgSO_4$, se filtró, se concentró, y se cromatografió sobre gel de sílice con acetato de etilo al 50%/hexanos.

EJEMPLO 161B

(S)-3-(dimetilamino)-3-oxo-1-(tiofen-2–il)propilcarbamato de bencilo

El compuesto del título se preparó utilizando EJEMPLO 161A en lugar de EJEMPLO 1E y dimetilamina en lugar de EJEMPLO 1F en el EJEMPLO 1G.

EJEMPLO 161C

(S)-N^1,N^1-dimetil-3-(tiofen-2–il)propan-1,3-diamina

Una solución de EJEMPLO 161B (400 mg) y borano en tetrahidrofurano (1M, 2,5 mL) en tetrahidrofurano (6 mL) se agitó durante 24 horas. La reacción se detuvo con metanol, se colocó en una solución amortiguadora de pH 7, y se extrajo tres veces con acetato de etilo. Los extractos combinados se lavaron con salmuera y se concentró. El producto crudo se capturó en HBr en ácido acético (1,1 mL) y se agitó por 2 horas. La reacción se vertió en CH_2Cl_2 (50 mL) y se lavó con solución de NaOH 1M. La capa orgánica se secó sobre Na_2SO_4, y se concentró.

EJEMPLO 161D

(S)-4-(3-(dimetilamino)-1-(tiofen-2–il)propilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando EJEMPLO 161C durante (tetrahidropiran-4–il)metilamina en el EJEMPLO 1F.

EJEMPLO 161E

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(4-{[(1S)-3-(dimetilamino)-1-tien-2–ilpropil]amino}-3-nitrofenil)sulfonil]-2-fenoxibenzamida

El compuesto del título se preparó utilizando EJEMPLO 161D en lugar de EJEMPLO 1F y EJEMPLO 1E en lugar de EJEMPLO 27G en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6/D_2O) δ 11,72 (br s, 1H), 9,51 (br s, 1H), 8,60 (d, 1H), 8,48 (s, 1H), 7,75 (d, 1H), 7,70 (m, 1H), 7,51 (m, 4H), 7,38 (d, 2H), 7,32 (m, 1H), 7,25 (d, 1H), 7,16 (m, 3H), 7,06 (d, 1H), 6,92 (m, 1H), 6,75 (d, 3H), 6,44 (d, 1H), 5,31 (m, 1H), 4,30 (m, 1H), 3,54 (m, 8H), 3,20 (m, 2H), 3,07 (m, 2H), 2,80 (s, 6H), 2,35 (m, 2H).

EJEMPLO 162

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(tien-2–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida

EJEMPLO 162A

3-nitro-4-(tiofen-2–ilmetilamino)bencensulfonamida

El compuesto del título se preparó utilizando 2-tiofenemetilamina en lugar de (tetrahidropiran-4–il)metilamina en el EJEMPLO 1F.

EJEMPLO 162B

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(tien-2–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida

El compuesto del título se preparó utilizando EJEMPLO 162B en lugar de EJEMPLO 1F y EJEMPLO 1E en lugar de EJEMPLO 27G en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6/D_2O) δ 11,67 (br s, 1H), 9,55 (br s, 1H), 9,11 (t, 1H), 8,47 (s, 1H), 7,70 (m, 2H), 7,51 (m, 4H), 7,38 (d, 2H), 7,33 (m, 1H), 7,15 (m, 4H), 7,02 (d, 1H), 6,94 (m, 1H), 6,74 (d, 3H), 6,44 (d, 1H), 4,87 (m, 2H), 4,37 (m, 1H), 3,34 (m, 8H), 3,03 (m, 2H).

EJEMPLO 163

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-fenoxi-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

EJEMPLO 163A

4-((tetrahidro-2H-piran-4–il)metilamino)-3-(trifluorometilsulfonil)bencensulfonamida

El compuesto del título se preparó utilizando EJEMPLO 159C durante 4-fluoro-3-nitrobencensulfonamida en el EJEMPLO 1F.

EJEMPLO 163B

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-fenoxi-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 163A en lugar de EJEMPLO 1F y EJEMPLO 1E en lugar de EJEMPLO 27G en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,71 (br s, 1H), 8,10 (d, 1H), 7,86 (d, 1H), 7,10 (m, 1H), 7,50 (m, 4H), 7,37 (m, 2H), 7,27 (m, 3H), 7,08 (m, 1H), 7,03 (dd, 1H), 6,95 (d, 1H), 6,82 (d,

1H), 6,76 (d, 1H), 6,43 (s, 1H), 4,35 (m, 1H), 3,84 (dd, 2H), 3,35 (m, 8H), 3,22 (m, 2H), 3,03 (m, 2H), 2,86 (m, 2H), 1,86 (m, 1H), 1,55 (m, 2H), 1,26 (m, 2H).

EJEMPLO 164

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(3-nitro-4-{[2-(1H-1,2,3-triazol-1–il)etil]amino}fenil)sulfonil]-2-fenoxibenzamida

EJEMPLO 164A

4-(2-hidroxietilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando 2-aminoetanol en lugar de (tetrahidropiran-4–il)metilamina en el EJEMPLO 1F.

EJEMPLO 164B

4-(2-(tert-butildimetilsililoxi)etilamino)-3-nitrobencensulfonamida

Se agitó EJEMPLO 164A (131 mg), cloruro de t-butildimetilsililo (75 mg) e imidazol (68 mg) en CH_2Cl_2 (17 mL) durante 24 horas. La mezcla de reacción se cromatografió sobre gel de sílice con acetato de etilo al 10%/hexanos.

EJEMPLO 164C

N-(4-(2-(tert-butildimetilsililoxi)etilamino)-3-nitrofenilsulfonil)-4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-fenoxibenzamida

El compuesto del título se preparó utilizando EJEMPLO 164B en lugar de EJEMPLO 1F en el EJEMPLO 1G.

EJEMPLO 164D

4-metilbencensulfonato de 2-(4-(N-(4-(4-((4'-clorobifenil-2–il)metil)piperazin-1–il)-2-fenoxibenzoil)sulfamoil)-2-nitrofenilamino)etilo

Se agitó EJEMPLO 164C (150 mg) y HCl acuoso concentrado (0,020 mL) en tetrahidrofurano (1 mL) y metanol (1 mL) por 1 horas. La mezcla se filtró a través de una columna corta de gel de sílice. El producto se capturó en CH_2Cl_2 (1 mL) y al mismo se agregó trietilamina (0,074 mL) y anhídrido p-toluensulfónico (58 mg) y la reacción se agitó durante 24 horas. La mezcla de reacción se cromatografió sobre gel de sílice con acetato de etilo al 10%/hexanos.

EJEMPLO 164E

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(3-nitro-4-{[2-(1H-1,2,3-triazol-1–il)etil]amino}fenil)sulfonil]-2-fenoxibenzamida

Se agitó EJEMPLO 164D (30 mg), 1,2,3-triazol (7 mg) y carbonato de cesio (55 mg) en N,N-dimetilformamida (0,2 mL) durante 24 horas. La reacción se detuvo con cloruro de amonio, y se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtró, y se concentró. El producto se purificó mediante HPLC preparativa usando una columna C18, 250 x 50 mm, 10□, y eluyendo con un gradiente de 20-100% CH_3CN vs. ácido trifluoroacético al 0,1% en agua, para dar el producto como una sal trifluoroacetato. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,75 (br s, 1H), 9,62 (br s, 1H), 8,66 (dd, 1H), 8,44 (d, 1H), 8,18 (s, 1H), 7,72 (m, 3H), 7,51 (m, 5H), 7,36 (m, 3H), 7,19 (dd, 2H), 7,06 (m, 1H), 6,93 (dd, 1H), 6,75 (d, 2H), 6,45 (s, 1H), 4,70 (t, 2H), 3,93 (dt, 2H), 3,61 (m, 4H), 3,22 (m, 2H), 3,01 (m, 2H), 2,84 (m, 2H).

EJEMPLO 165

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(3-nitro-4-{[2-(2H-1,2,3-triazol-2–il)etil]amino}fenil)sulfonil]-2-fenoxibenzamida

El compuesto del título se preparó en la misma reacción que la de EJEMPLO 164E. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,75 (br s, 1H), 9,70 (br s, 1H), 8,67 (dd, 1H), 8,42 (s, 1H), 7,80 (s, 1H), 7,75 (m, 1H), 7,68 (d, 2H), 7,51 (m, 5H), 7,37 (m, 3H), 7,18 (dd, 2H), 6,97 (m, 1H), 6,92 (dd, 1H), 6,75 (d, 2H), 6,46 (s, 1H), 4,76 (t, 2H), 3,93 (dt, 2H), 3,67 (m, 4H), 3,22 (m, 2H), 3,03 (m, 2H), 2,84 (m, 2H).

EJEMPLO 166

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(4-{[3-(dimetilamino)propil]amino}-3-nitrofenil)sulfonil]-2-(2-naftiloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 35B en lugar de EJEMPLO 27G y EJEMPLO 154A en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,83 (br s, 1H), 9,46 (br s, 1H), 8,53 (t, 1H), 8,40 (s, 1H), 7,81 (d, 2H), 7,71 (m, 1H), 7,63 (m, 2H), 7,51 (m, 5H), 7,37 (m, 4H), 7,17 (d, 1H), 7,03 (s, 1H), 6,82 (d, 2H), 6,57 (d, 1H), 4,27 (m, 1H), 3,62 (m, 6H), 3,39 (m, 2H), 3,09 (m, 2H), 2,80-3,25 (m, 6H), 2,79 (s, 6H), 1,91 (m, 2H).

EJEMPLO 167

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(3-nitro-4-{[2-(2-oxopiridin-1(2H)–il)etil]amino}fenil)sulfonil]-2-fenoxibenzamida

El compuesto del título se preparó utilizando piridin-2-ol en lugar de 1,2,3-triazol en el EJEMPLO 164E. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,70 (br s, 1H), 9,65 (br s, 1H), 8,75 (t, 1H), 8,44 (d, 1H), 7,72 (d, 2H), 7,64 (d, 1H), 7,51 (m, 5H), 7,37 (m, 3H), 7,20 (m, 3H), 6,95 (t, 1H), 6,77 (d, 3H), 6,46 (s, 1H), 6,41 (d, 1H), 6,21 (t, 1H), 4,31 (m, 1H), 4,17 (t, 2H), 3,74 (dt, 2H), 3,60 (m, 6H), 3,20 (m, 2H), 3,03 (m, 2H), 2,87 (m, 2H).

EJEMPLO 168

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-[(3-nitro-4-{[2-(piridin-2–iloxi)etil]amino}fenil)sulfonil]-2-fenoxibenzamida

El compuesto del título se preparó utilizando piridin-2-ol en lugar de 1,2,3-triazol en el EJEMPLO 164E. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,71 (br s, 1H), 9,65 (br s, 1H), 8,84 (t, 1H), 8,44 (d, 1H), 8,19 (d, 1H), 7,74 (m, 3H), 7,51 (m, 5H), 7,37 (m, 3H), 7,20 (m, 3H), 7,00 (dd, 1H), 6,92 (t, 1H), 6,83 (d, 1H), 6,76 (m, 2H), 6,45 (d, 1H), 4,56 (t, 2H), 4,31 (m, 1H), 3,81 (dt, 2H), 3,71 (m, 6H), 3,23 (m, 2H), 3,04 (m, 2H), 2,89 (m, 2H).

EJEMPLO 169

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(2-piridin-4–iletil)amino]fenil}sulfonil)-2-fenoxibenzamida

EJEMPLO 169A

3-nitro-4-(2-(piridin-4–il)etilamino)bencensulfonamida

El compuesto del título se preparó utilizando 2-(piridin-4–il)etanamina en lugar de (tetrahidropiran-4–il)metilamina en el EJEMPLO 1E.

EJEMPLO 169B

4-{4-[(4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-N-({3-nitro-4-[(2-piridin-4–iletil)amino]fenil}sulfonil)-2-fenoxibenzamida

El compuesto del título se preparó utilizando EJEMPLO 169A en lugar de EJEMPLO 1F y EJEMPLO 1E en lugar de EJEMPLO 27G en el EJEMPLO 27H. ^{1}H NMR

(400MHz, dimetilsulfóxido-d_6) δ 11,71 (br s, 1H), 9,70 (br s, 1H), 8,69 (d, 1H), 8,61 (t, 1H), 8,46 (s, 1H), 7,79 (dd, 1H), 7,72 (d, 3H), 7,51 (m, 5H), 7,37 (d, 2H), 7,32 (d, 1H), 7,21 (m, 3H), 6,95 (t, 1H), 6,78 (d, 2H), 6,75 (d, 1H), 6,44 (d, 1H), 4,23 (m, 1H), 3,76 (dt, 2H), 3,63 (m, 4H), 3,13 (t, 2H), 2,76-3,24 (m, 6H).

EJEMPLO 170

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-{[3-(dimetilamino)propil]amino}-3-[(trifluorometil)sulfonil]fenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida

EJEMPLO 170A

4-(3-(dimetilamino)propilamino)-3-(trifluorometilsulfonil)bencensulfonamida

El compuesto del título se preparó utilizando N,N-dimetil-1,3-propandiamina en lugar de (tetrahidropiran-4–il)metilamina y EJEMPLO 159C durante 4-fluoro-3-nitrobencensulfonamida en el EJEMPLO 1F.

EJEMPLO 170B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-{[3-(dimetilamino)propil]amino}-3-[(trifluorometil)sulfonil]fenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 170A en lugar de EJEMPLO 1F y EJEMPLO 26C en lugar de EJEMPLO 27G en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,42 (br s, 1H), 11,17 (s, 1H), 9,37 (br s, 1H), 8,22 (d, 1H), 7,98 (d, 1H), 7,52 (d, 1H), 7,35-7,45 (m, 4H), 7,19 (d, 1H), 7,08 (m, 3H), 6,85 (dd, 1H), 6,67 (dd, 1H), 6,40 (d, 1H), 6,19 (d, 1H), 3,55 (m, 8H), 3,04 (m, 4H), 2,77 (s, 6H), 2,72 (m, 2H), 2,17 (m, 2H), 2,00 (m, 2H), 1,88 (m, 2H), 1,44 (m, 2H), 0,93 (s, 6H).

EJEMPLO 171

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-{[3-(dimetilamino)propil]amino}-3-(trifluorometil)fenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 26C en lugar de EJEMPLO 27G y EJEMPLO 92B en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,19 (br s, 1H), 9,33 (br s, 1H), 7,94 (d, 1H), 7,85 (d, 1H),

7,54 (d, 1H), 7,35-7,45 (m, 4H), 7,20 (d, 1H), 7,07 (d, 2H), 6,88 (dd, 2H), 6,67 (dd, 1H), 6,58 (m, 1H), 6,41 (s, 1H), 6,18 (s, 1H), 3,57 (m, 6H), 3,33 (m, 2H), 3,09 (m, 2H), 3,04 (m, 2H), 2,77 (s, 6H), 2,74 (m, 2H), 2,17 (m, 2H), 2,00 (m, 2H), 1,87 (m, 2H), 1,44 (m, 2H), 0,93 (s, 6H).

EJEMPLO 172

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(3-ciano-4-{[3-(dimetilamino)propil]amino}fenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 26C en lugar de EJEMPLO 27G y EJEMPLO 90B en lugar de EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,19 (br s, 1H), 9,38 (br s, 1H), 7,98 (s, 1H), 7,81 (d, 1H), 7,55 (d, 1H), 7,35-7,45 (m, 4H), 7,20 (s, 1H), 7,16 (t, 1H), 7,07 (d, 2H), 6,86 (dd, 2H), 6,68 (dd, 1H), 6,41 (s, 1H), 6,18 (s, 1H), 3,57 (m, 6H), 3,31 (m, 2H), 3,09 (m, 2H), 3,04 (m, 2H), 2,77 (s, 6H), 2,74 (m, 2H), 2,17 (m, 2H), 2,00 (m, 2H), 1,87 (m, 2H), 1,44 (m, 2H), 0,93 (s, 6H).

EJEMPLO 173

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida

EJEMPLO 173A

1-(tetrahidro-2H-piran-4–il)piperidin-4–ilcarbamato de tert-butilo

Una mezcla de piperidin-4–ilcarbamato de tert-butilo (45 g) y dihidro-2H-piran-4(3H)-ona (24,74 g) en diclorometano (1000 mL) se trató con tetracetoxiborohidruro de sodio (61,9 g), se agitó a temperatura ambiente durante 16 horas, se lavó con hidróxido de sodio 1M y se secó con sulfato de sodio anhidro, se filtró y se concentró. El concentrado se cromatografió en una columna flash sobre gel de sílice con metanol al 10-20%/diclorometano.

EJEMPLO 173B

1-(tetrahidro-2H-piran-4–il)piperidin-4-amina

Una solución de EJEMPLO 173A (52,57 g) en diclorometano (900 mL) se trató con HCl 4M (462 mL), se mezcló enérgicamente a temperatura ambiente durante 16 horas y se concentró.

EJEMPLO 173C

3-nitro-4-(1-(tetrahidro-2H-piran-4–il)piperidin-4–ilamino)bencensulfonamida

Una mezcla de EJEMPLO 173B (22,12 g), agua (43 mL), y trietilamina (43,6 mL) en 1,4-dioxano (300 mL) se agitó a temperatura ambiente hasta que EJEMPLO 173B se disolvió completamente. La solución luego se trató con 4-cloro-3-nitrobencensulfonamida, se calentó a 90°C durante 16 horas, se enfrió y se concentró. Se agregó metanol al 10% en diclorometano, y la solución se agitó enérgicamente a temperatura ambiente hasta que se formó una suspensión fina y la mezcla se filtró.

EJEMPLO 173D

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida

Una mezcla de EJEMPLO 26C (3,95 g), EJEMPLO 173C (2,66 g), clorhidrato de 1-etil-3-[3-(dimetilamino)propil]-carbodiimida (2,66 g), y 4-dimetilaminopiridina (0,846 g) en diclorometano (70 mL) y acetonitrilo (20 mL) se agitó a 35ºC durante 24 horas, se enfrió y se cromatografió sobre gel de sílice con metanol al 0-10% en acetato de etilo, luego metanol al 10% en 1:1 acetato de etilo/diclorometano. Las fracciones combinadas se concentraron, se disolvieron en de metanol al 5%/acetato de etilo (1,5L), y la solución se lavó con solución saturada de NaH_2PO_4 y salmuera y se secó sobre Na_2SO_4, se filtró, se concentró a 300 mL, se enfrió, y se filtró. La solución restante se concentró parcialmente y se filtró nuevamente para aislar más producto. ^{1}H NMR (300MHz, dimetisulfóxido-d_6) δ 11,17 (brs, 1H), 10,70 (br s, 1H), 8,60 (d, 1H), 8,20 (br d, 1H), 7,88 (dd, 1H), 7,50 (d, 1H), 7,39 (m, 2H), 7,33 (d, 2H), 7,16 (m, 2H), 7,03 (d, 2H), 6,85 (dd, 1H), 6,65 (dd, 1H), 6,39 (s, 1H), 6,14 (s, 1H), 3,97 (m, 4H), 3,44 (m, 4H), 3,04 (m, 6H), 2,75 (m, 2H), 2,14 (m, 8H), 1,95 (m, 6H), 1,66 (m, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 174

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida

EJEMPLO 174A

4-(4-metilpiperazin-1–ilamino)-3-nitrobencensulfonamida

Una mezcla de 4-cloro-3-nitrobencensulfonamida (1 g), diclorhidrato de 4-metilpiperazin-1-amina (1 g) y N^1,N^1,N^2,N^2-tetrametiletan-1,2-diamina (3 mL) en dioxano (10 mL) se mantuvo a reflujo por 12 horas, se enfrió a temperatura ambiente y se filtró. El filtrado se agregó a una columna de gel de sílice (Analogix, SF65-200g) y se purificó eluyendo con metanol al 1-5%/diclorometano).

EJEMPLO 174B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida

Una mezcla de EJEMPLO 26C (0,108 g), EJEMPLO 174A (64 mg), clorhidrato de 1-etil-3-[3-(dimetilamino)propil]-carbodiimida (0,08 g) y 4-dimetilaminopiridina (0,08 g) en diclorometano (3 mL) se agitó a temperatura ambiente durante la noche y se concentró. El concentrado se agregó a una columna de HPLC preparativa y se eluyó con acetonitrilo al 20-100%/agua con ácido trifluoroacético al 0,1%. la solución de la sal de ácido trifluoroacético se neutralizó con $NaHCO_3$ y se extrajo con diclorometano. Esta solución se lavó con $NaHCO_3$ saturado, se secó sobre Na_2SO_4, y se filtró y se concentró. ^{1}H NMR (500 MHz, dimetisulfóxido-d_6) δ 11,14 (s, 1H), 9,17 (s, 1H), 8,52 (s, 1H), 7,83 (m, 1H), 7,53 (m, 2H), 7,36 (m, 4H), 7,12 (s, 1H), 7,03 (d, 2H), 6,83 (m, 1H), 6,62 (m, 1H), 6,38 (s, 1H), 6,13 (m, 1H), 5,76 (s, 2H), 2,85 (m, 12H), 2,35 (m, 4H), 2,14 (m, 6H), 1,94 (m, 2H), 1,38 (m, 2H), 0,92 (s, 6H).

EJEMPLO 175

4-{4-[1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 175A

1-(4'-clorobifenil-2–il)etanona

Una mezcla de 1-(2-bromofenil)etanona (3,1 g, 15,57 mmol)ácido 4-clorofenilborónico (2,92 g), $(Ph_3P)_2PdCl_2$ (dicloruro de bis(trifenilfosfin)paladio(II)) (1,202 g) y Na_2CO_3 (3,30 g) en dimetoxietan-etanol-agua (7:2:3, 50 mL) se calentó a 100ºC durante 3 horas y se concentró. El concentrado se suspendió en diclorometano (30 mL) y el material

insoluble se eliminó por filtración. El filtrado se cargó en una columna de gel de sílice, eluyendo con diclorometano al 0% - 50% en hexano para dar el compuesto del título.

EJEMPLO 175B

4-(1-(4'-clorobifenil-2–il)etil)piperazin-1-carboxilato de tert-butilo

Se disolvió EJEMPLO 175A (1,9 g) en diclorometano (3 mL) y se agregó cloruro de titanio(IV) (9,06 mL, 9,06 mmol). La solución se enfrió a 0ºC y se agregó piperazin-1-carboxilato de tert-butilo (3,07 g). La mezcla resultante se agitó a temperatura ambiente por 3 horas y se agregó $NaCNBH_3$ (0,828 g) en metanol (5 mL). La mezcla resultante se agitó a temperatura ambiente durante la noche y se neutralizó con NaOH acuoso, y luego se concentró. Al concentrado se agregó acetato de etilo y el material insoluble se retiró por filtración. La capa orgánica se lavó con agua y se concentró. El concentrado se disolvió en una mezcla de metanol-ácido trifluoroacético-dimetisulfóxido, se cargó en una columna C18 de fase inversa, y se eluyó con acetonitrilo al 0 - 80% en ácido trifluoroacético al 0,1% en agua por 70 minutos.

EJEMPLO 175C

1-(1-(4'-clorobifenil-2–il)etil)piperazina

A una solución de EJEMPLO 175B (650mg) en diclorometano (6 mL) se agregó ácido trifluoroacético (6 mL) a 0ºC. La mezcla de reacción se agitó a 0ºC durante 50 minutos y se concentró. El concentrado se disolvió en diclorometano, se lavó con $NaHCO_3$ acuoso y la capa orgánica se secó sobre Na_2SO_4, y se concentró.

EJEMPLO 175D

2-(1H-indol-4–iloxi)-4-(4-(1-(4'-clorobifenil-2–il)etil)piperazin-1–il)benzoato de etilo

Se trató EJEMPLO 175C (193mg) y 2-(1H-indol-4–iloxi)-4-fluorobenzoato de etilo (211 mg) en dimetisulfóxido (15 mL) se trató con fosfato ácido de potasio (168 mg) a 135ºC durante la noche y se enfrió. La mezcla de reacción se diluyó con diclorometano y se lavó con agua. La capa orgánica se concentró. El concentrado se disolvió en diclorometano, se cargó en una columna de gel de sílice, eluyendo con amoníaco 10 M en metanol al 0%-10% en diclorometano.

EJEMPLO 175E

ácido 2-(1H-indol-4–iloxi)-4-(4-(1-(4'-clorobifenil-2–il)etil)piperazin-1–il)benzoico

Se trató EJEMPLO 175D (200mg) en tetrahidrofurano (10 mL) y metanol (10 mL) con NaOH al 10% (3 mL) a 50ºC durante la noche y se neutralizó con HCl. La mezcla se concentró y el concentrado se capturó en agua y se extrajo con diclorometano. La capa orgánica se secó sobre Na_2SO_4 y se concentró.

EJEMPLO 175F

4-(4-(1-(4'-cloro-1,1'-bifenil-2–il)etil)piperazin-1–il)-2-(1*H*-indol-4–iloxi)-*N*-((3-nitro-4-((tetrahidro-2*H*-piran-4–ilmetil)amino)fenil)sulfonil)benzamida

A una mezcla de EJEMPLO 175E (66 mg), 3-nitro-4-((tetrahidro-2H-piran-4–il)metilamino)bencensulfonamida (75 mg) y 4-dimetilaminopiridina (58,4 mg) en diclorometano (5 mL) se agregó clorhidrato de 1-etil-3-[3-(dimetilamino)propil]-carbodiimida (45,8 mg). La mezcla se agitó a temperatura ambiente durante la noche y se concentró. El concentrado se purificó por RP HPLC (acetonitrilo al 10-70% en ácido trifluoroacético al 0,1% agua / 70 minutos). Las fracciones deseadas se concentraron para eliminar acetonitrilo y el concentrado se diluyó con diclorometano y se neutralizó con $NaHCO_3$ acuoso. La capa de diclorometano se secó sobre Na_2SO_4 y se concentró para dar el compuesto del título. ^{1}H NMR (500 MHz, dimetisulfóxido-d_6) δ ppm 11,31 (1 H, s), 11,25 (1 H, s), 8,62 (1 H, t), 8,50 (1 H, d), 7,68 (1 H, dd), 7,53 (2 H, d), 7,46 (2 H, d), 7,37 (1 H, t), 7,24 - 7,31 (4 H, m), 7,17 (1 H, d), 7,12 (1 H, dd), 7,07 (1 H, d), 6,96 (1 H, t), 6,69 (1 H, dd), 6,42 (1 H, d), 6,26 (2 H, s), 3,85 (2 H, dd), 3,21 - 3,33 (5 H, m), 3,01 (4 H, s), 2,29 - 2,39 (2 H, m), 2,15 - 2,22 (2 H, m), 1,83 - 1,94 (1 H, m), 1,57 - 1,68 (2 H, m), 1,22 - 1,31 (2 H, m), 1,17 (3 H, d).

EJEMPLO 176

N-[(4-{[(4-aminotetrahidro-2H-piran-4–il)metil]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)benzamida

EJEMPLO 176A

4-((4-aminotetrahidro-2*H*-piran-4–il)metilamino)-3-nitrobencensulfonamida

Una mezcla de 4-cloro-3-nitrobencensulfonamida, sal de ácido bos-clorhídrico de 4-(aminometil)tetrahidro-2H-piran-4-amina y trietilamina en dioxano (10 mL) se calentó a 110 ºC durante la noche. Luego de enfriar, la mezcla de reacción se diluyó con agua (10 mL), y el sólido se filtró para dar el compuesto del título.

EJEMPLO 176B

N-((4-(((4-aminotetrahidro-2*H*-piran-4–il)metil)amino)-3-nitrofenil)sulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1*H*-indol-4–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 1F y EJEMPLO 176A (4-aminotetrahidro-2H-piran-4–il)metilamino)-3-nitrobencensulfonamida) en lugar de EJEMPLO 1G en el EJEMPLO 1H. ^{1}H NMR (500MHz, dimetisulfóxido-d_6) δ 11,15 (s, 1H), 8,51 (s, 1H), 8,45 (d, J = 2,14 Hz, 1H), 7,70 (dd, J = 9,0, 1,98 Hz, 1H), 7,59 (d, J = 8,85 Hz, 1H), 7,34 (d, J = 8,24 Hz, 2H), 7,22 (t, J = 2,59 Hz, 1H), 7,11-7,12 (m, 2H), 7,04 (d, J = 8,54 Hz, 2H), 6,93 (t, J = 7,78 Hz, 1H), 6,62 (dd, J = 9,0, 1,98 Hz, 1H), 6,34 (d, J = 7,63 Hz, 1H), 6,20-6,23 (m, 2H), 3,55-3,70 (m, 6H), 2,96 (m, 3H), 2,71 (s, 2H), 2,16 (m, 6H), 1,95 (m, 2H), 1,70-1,74 (m, 2H), 1,55-1,59 (m, 2H), 1,37-1,39 (m, 2H), 0,92 (s, 6H).

EJEMPLO 177

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

Una mezcla de EJEMPLO 26C (2,85 g, 10 mmol), EJEMPLO 1F (1,577 g, 5 mmol), clorhidrato de 1-etil-3-[3-(dimetilamino)propil]-carbodiimida (1,917 g, 10 mmol), 4-(dimetilamino)piridina (1,222 g, 10 mmol), y trietilamina (2,8 mL, 20 mmol) se trató con CH_2Cl_2 (20 mL) y N,N-dimetilformamida (2 mL). La mezcla de reacción se agitó durante la noche. El solvente se eliminó, y el residuo se particionó entre agua y acetato de etilo. Las capas orgánicas se lavaron con HCl al 1% dos veces, luego con $NaHCO_3$ saturado, salmuera, se secó, se filtró, y se concentró. El residuo se purificó por HPLC de fase inversa en una columna C18 usando un gradiente de acetonitrilo al 40-60%/TFA al 0,1% en agua para dar el compuesto del título como la sal trifluoroacetato. La sal TFA se disolvió en diclorometano (6 ml) y se lavó con $NaHCO_3$ acuoso al 50%. La capa orgánica se secó sobre Na_2SO_4 anhidro y se concentró para dar el compuesto del título. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,18 (s, 2H), 8,59-8,64 (m, 2H), 7,80 (dd, 1H), 7,52 (d, 1H), 7,39-7,42 (m, 2H), 7,33 (d, 2H), 7,16 (d, 1H), 7,10 (d,1H), 7,03 (d, 2H), 6,8 (dd, 1H), 6,65 (dd, 1H), 6,40)s, 1H), 6,14 (d, 1H), 3,85 (dd, 2H), 3,24-3,32 (m, 4H), 3,03 (s, 3H), 2,73 (s, 2H), 2,12-2,17 (m, 5H), 1,68-1,94 (m, 3H), 1,61 (d, 2H), 1,37 (t, 2H), 1,24-1,27 (m, 2H), 0,92 (s, 6H).

EJEMPLO 178

Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-morfolin-4–ilciclohexil)amino]-3-nitrofenil}sulfonil)benzamida

EJEMPLO 178A

Trans-4-(4-morfolinociclohexilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando 4-amino-N-morfolinilpiperidina en lugar de 1-(tetrahidropiran-4–il)metilamina en el EJEMPLO 1F.

EJEMPLO 178B

Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-morfolin-4–ilciclohexil)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó como en el EJEMPLO 177 reemplazando EJEMPLO 1F por EJEMPLO 178A. ^{1}H NMR (500 MHz, piridina-d_5) δ 12,29 (s, 1H), 9,29 (d, *J*=2,1 Hz, 1H), 8,37 (d, *J*=7,6 Hz, 1H), 8,32 (dd, *J*=9,3, 2,3 Hz, 1H), 8,18 (d, *J*=8,8 Hz, 1H), 7,52 - 7,57 (m, 2H), 7,39 - 7,47 (m, 3H), 7,10 (dd, *J*=8,7, 2,3 Hz, 1H), 7,05 - 7,08 (m, 2H), 6,90 (d, *J*=9,5 Hz, 1H), 6,74 (dd, *J*=9,0, 2,3 Hz, 1H), 6,59 - 6,63 (m, 1H), 6,55 (d, *J*=2,4 Hz, 1H), 3,72 - 3,78 (m, 4H), 3,33 - 3,43 (m, 1H), 2,99 - 3,09 (m, 4H), 2,76 (s, 2H), 2,46 - 2,54 (m, 4H), 2,16 - 2,29 (m, 3H), 2,09 - 2,14 (m, 4H), 2,05 (d, *J*=11,9 Hz, 2H), 1,97 (d, *J*=1,8 Hz, 2H), 1,87 (d, *J*=11,6 Hz, 2H), 1,19 - 1,42 (m, 6H), 0,93 (s, 6H).

EJEMPLO 179

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(2-metoxietil)amino]-3-nitrofenil}sulfonil)benzamida

EJEMPLO 179A

4-(2-metoxietilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando 2-metoxietilamina en lugar de 1-(tetrahidropiran-4–il)metilamina en el EJEMPLO IF.

EJEMPLO 179B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(2-metoxietil)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó en lugar de en el EJEMPLO 177 reemplazando EJEMPLO 1F con EJEMPLO 179A. ^{1}H NMR (400 MHz, DMSO- d_6) δ 11,20 (br. s, 1H) 11,15 (s, 1H) 8,59 (m, 2H) 7,81 (dd, 1H) 7,50 (d, 1H) 7,36 (m, 4H) 7,08 (m, 4H) 6,85 (dd, 1H) 6,65 (dd, 1H) 6,38 (m, 1H) 6,14 (m, 1H) 3,58 (m, 4H) 3,30 (s, 3H) 3,03 (m, 4H) 2,73 (s, 2H) 2,15 (m, 6H) 1,96 (s, 2H) 1,38 (t, 2H) 0,92 (s, 6H).

EJEMPLO 180

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[(3S)-tetrahidro-2H-piran-3–ilmetil]amino}fenil)sulfonil]benzamida

EJEMPLO 180A

(R)-3-nitro-4-((tetrahidro-2H-piran-3–il)metilamino)bencensulfonamida y (S)-3-nitro-4-((tetrahidro-2H-piran-3–il)metilamino)bencensulfonamida

El compuesto del título se preparó utilizando (tetrahidro-2H-piran-3–il)metanamina en lugar de 1-(tetrahidropiran-4–il)metilamina en el EJEMPLO IF.

EJEMPLO 180B

(S)-3-nitro-4-((tetrahidro-2H-piran-3–il)metilamino)bencensulfonamida

La mezcla racémica de EJEMPLO 180A se resolvió mediante SFC quiral en una columna AD (21mm i.d.x 250 mm en longitud) usando un gradiente de dietilamina al 0,1% al 10-30% en metanol en CO_2 por 15 min (temperatura de horno: 40°C; velocidad de flujo: 40mL/min) para dar el compuesto del título.

EJEMPLO 180C

(R)-3-nitro-4-((tetrahidro-2H-piran-3–il)metilamino)bencensulfonamida

La mezcla racémica de EJEMPLO 180A se resolvió mediante SFC quiral en una columna AD (21mm i.d.x 250 mm en longitud) usando un gradiente de dietilamina al 0,1% al 10-30% metanol en CO_2 por 15 min (temperatura de horno: 40°C; velocidad de flujo: 40mL/min) para dar el compuesto del título.

EJEMPLO 180D

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[(3S)-tetrahidro-2H-piran-3–ilmetil]amino}fenil)sulfonil]benzamida

El compuesto del título se preparó como en el EJEMPLO 177 reemplazando EJEMPLO 1F con EJEMPLO 180B. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11,17 (s, 2 H), 8,53 - 8,65 (m, 2 H), 7,80 (d, 1 H), 7,51 (d, 1 H), 7,38 - 7,44 (m, 2 H), 7,33 (d, 2 H), 7,15 (s, 1 H), 7,02 - 7,09 (m, 3 H), 6,82 - 6,92 (m, 1 H), 6,65 (d, 1 H), 6,39 (s, 1 H), 6,14 (s, 1 H), 3,68 - 3,82 (m, 2 H), 3,22 - 3,32 (m, 2 H), 3,13 - 3,22 (m, 1 H), 3,03 (s, 4 H), 2,72 (s, 2 H), 2,09 - 2,23 (m, 6 H), 1,78 - 1,98 (m, 4 H), 1,56 - 1,66 (m, 1 H), 1,43 - 1,51 (m, 1 H), 1,37 (t, 2 H), 1,22 - 1,33 (m, 1 H), 0,92 (s, 6 H).

EJEMPLO 181

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[(3R)-tetrahidro-2H-piran-3–ilmetil]amino}fenil)sulfonil]benzamida

El compuesto del título se preparó como en el EJEMPLO 177 reemplazando EJEMPLO 1F con EJEMPLO 180C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11,17 (s, 2 H), 8,53 - 8,65 (m, 2 H), 7,80 (d, 1 H), 7,51 (d, 1 H), 7,38 - 7,44 (m, 2 H), 7,33 (d, 2 H), 7,15 (s, 1 H), 7,02 - 7,09 (m, 3 H), 6,82 - 6,92 (m, 1 H), 6,65 (d, 1 H), 6,39 (s, 1 H), 6,14 (s, 1 H), 3,68 - 3,82 (m, 2 H), 3,22 - 3,32 (m, 2 H), 3,13 - 3,22 (m, 1 H), 3,03 (s, 4 H), 2,72 (s, 2 H), 2,09 - 2,23 (m, 6 H), 1,78 - 1,98 (m, 4 H), 1,56 - 1,66 (m, 1 H), 1,43 - 1,51 (m, 1 H), 1,37 (t, 2 H), 1,22 - 1,33 (m, 1 H), 0,92 (s, 6 H).

EJEMPLO 182

4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó como en el EJEMPLO 177 reemplazando EJEMPLO 26C con EJEMPLO 150C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11,20 (br s, 1H), 11,17(s, 1H), 8,63 (t, 1 H), 8,59 (d, 1 H), 7,79 (dd, 1 H), 7,51 (d, 1 H), 7,36 (m, 3 H), 7,13 (m, 2 H), 6,86 (dd, 1 H), 6,66 (dd, 1 H), 6,39 (s, 1 H), 6,15 (d, 1 H), 4,10 (s, 2 H), 3,85 (m, 3 H), 3,50 (m, 2 H), 3,42 (m, 2 H), 3,24 (m, 4 H), 3,02 (m, 4 H), 2,82 (m, 2 H), 2,16 (m, 2 H), 1,61 (m, 3 H), 1,25 (m, 4 H), 1,17 (s, 6 H).

EJEMPLO 183

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-hidroxi-1-metilpiperidin-4–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida

EJEMPLO 183A

4-((4-hidroxi-1-metilpiperidin-4–il)metilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando 4-(aminometil)-1-metilpiperidin-4-ol en lugar de (tetrahidropiran-4–il)metilamina en el EJEMPLO 1F.

EJEMPLO 183B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-hidroxi-1-metilpiperidin-4–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 183A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,04 (s, 1H), 8,46-8,48 (m, 2H), 7,92 (s, 1H), 7,74 (d, 1H), 7,54 (d, 1H), 7,32-7,34 (m, 5H), 6,97-7,05 (m, 5H), 6,74-6,76 (m, 1H), 6,55-6,57 (m, 1H), 6,33 (s, 1H), 6,13 (d, 1H), 5,10 (s, 1H), 3,14-3,17 (m, 2H), 2,95 (br, 5H), 2,71 (br, 2H), 2,14-2,17 (m, 6H), 1,95 (br s, 2H), 1,70 (br, 4H), 1,36-1,39 (m, 2H), 1,24-1,26 (m, 2H), 0,92 (s, 6H).

EJEMPLO 184

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-3-fluoro-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida

EJEMPLO 184A

2-(1H-indol-5–iloxi)-3,4-difluorobenzoato de etilo

El compuesto del título se preparó utilizando 2,3,4-trifluorobenzoato de etilo en lugar de 2,4-difluorobenzoato de etilo y 5-hidroxiindol en lugar de 5-hidroxiindazol en el EJEMPLO 20A.

EJEMPLO 184B

2-(1H-indol-5–iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1–il)-3-fluorobenzoato de etilo

El compuesto del título se preparó utilizando EJEMPLO 184A en lugar de EJEMPLO 20A en el EJEMPLO 20D.

EJEMPLO 184C

ácido 2-(1H-indol-5–iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1–il)-3-fluorobenzoico

El compuesto del título se preparó utilizando EJEMPLO 184B en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 184D

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-3-fluoro-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 184C en lugar de EJEMPLO 1E y EJEMPLO 21A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 10,98 (br s, 1H), 8,35 (d, 1H), 7,98 (dd, 1H), 7,59 (dd, 1H), 7,35 (m, 3H), 7,28 (t, 1H), 7,21 (d, 1H), 7,06 (d, 2H), 6,78 (m, 2H), 6,67 (m, 2H), 6,22 (s, 1H), 3,74 (dd, 2H), 3,39 (m, 4H), 3,06 (m, 3H), 2,97 (m, 4H), 2,79 (m, 2H), 2,73 (s, 3H), 2,29 (m, 2H), 2,18 (m, 2H), 2,05 (m, 2H), 1,81 (m, 2H), 1,41 (t, 2H), 0,94 (s, 6H).

EJEMPLO 185

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-3-fluoro-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 184C en lugar de EJEMPLO 1E y EJEMPLO 173C en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 10,98 (br s, 1H), 8,33 (d, 1H), 8,02 (dd, 1H), 7,50 (dd, 1H), 7,35 (m, 3H), 7,26 (t, 1H), 7,19 (d, 1H), 7,06 (d, 2H), 6,77 (dd, 2H), 6,67 (m, 2H), 6,22 (s, 1H), 3,90 (dd, 2H), 3,57 (m, 5H), 3,30 (dd, 2H), 3,06 (m, 3H), 2,94 (m, 4H), 2,78 (m, 2H), 2,27 (m, 4H), 2,18 (m, 2H), 1,98 (m, 4H), 1,80 (m, 2H), 1,55 (m, 2H), 1,41 (t, 2H), 0,94 (s, 6H).

EJEMPLO 186

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-hidroxi-1-metilpiperidin-4–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 183A en lugar de EJEMPLO 1F y EJEMPLO 55B en lugar de EJEMPLO 26C en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,12 (s, 1H), 8,49 (s, 1H), 8,42 (s, 1H), 7,73-7,75 (m, 1H), 7,58 (d, 1H), 7,34 (d, 2H), 7,22 (s, 1H), 7,09 (d, 1H), 7,01-7,05 (m, 3H), 6,92 (t, 1H), 6,61-

6,62 (m, 1H), 6,31 (d, 1H), 6,23 (s, 1H), 6,20 (s, 1H), 5,16 (s, 1H), 4,05 (s, 3H), 2,95 (br s, 6H), 2,71 (br s, 2H), 2,62 (br, 3H), 2,16 (br s, 6H), 1,95 (br s, 2H), 1,72 (br, 4H), 1,37-1,39 (m, 2H), 0,92 (s, 6H).

EJEMPLO 187

N-[(4-{[(3S,4R)-1-bencil-3-hidroxipiperidin-4–il]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida

EJEMPLO 187A

2-(1H-indol-5–iloxi)-N-(4-cloro-3-nitrofenilsulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1–il)benzamida

El compuesto del título se preparó utilizando 4-cloro-3-nitrobencensulfonamida en lugar de EJEMPLO 1F y EJEMPLO 26C en lugar de EJEMPLO 1E en el EJEMPLO 1G.

EJEMPLO 187B

N-[(4-{[(3S,4R)-1-bencil-3-hidroxipiperidin-4–il]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida

Una mezcla de EJEMPLO 187A (0,158 g), (3S,4R)-4-amino-1-bencilpiperidin-3-ol, ácido clorhídrico (0,049 g), y trietilamina (0,1 mL) en dioxano (2 mL) se calentó a 100 ºC durante la noche. El solvente se eliminó, y el residuo se disolvió nuevamente en 1:1 metanol:dimetilsulfóxido (3 mL). Luego se purificó mediante HPLC preparativa de fase inversa. El residuo se purificó por HPLC de fase inversa en una columna C18 usando un gradiente de acetonitrilo al 20-80%/TFA al 0,1% en agua. Las fracciones deseadas se recogieron, y el solvente orgánico se eliminó parcialmente bajo presión reducida. La mezcla resultante se trató con una mezcla acuosa saturada de $NaHCO_3$. Luego se extrajo con acetato de etilo tres veces. Las capas orgánicas combinadas se lavaron con salmuera, se secó ($MgSO_4$), se filtró, y se concentró para dar el producto deseado. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,14 (s, 1H), 8,69 (d, 1H), 8,14 (d, 1H), 7,77 (dd, 1H), 7,51 (d, 1H), 7,29-7,41 (m, 9H), 7,10-7,13 (m, 1H), 7,13 (d, 2H), 6,84 (dd, 1H), 6,63 (dd, 1H), 6,38 (s, 1H), 6,13 (d, 1H), 5,21-5,22 (br s, 1H), 3,82 (m, 2H), 3,62 (br s, 2H), 3,01 (br s, 4H), 2,71-2,82 (m , 4H), 2,12-2,15 (m, 7H), 1,94 (br s, 2H), 1,81 (br s, 2H), 1,36-1,39 (m, 2H), 0,92 (s, 6H).

EJEMPLO 188

N-[(4-{[(4-aminotetrahidro-2H-piran-4–il)metil]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando 4-(aminometil)tetrahidro-2H-piran-4-amina en lugar de (3S,4R)-4-amino-1-bencilpiperidin-3-ol, ácido clorhídrico en el EJEMPLO 187B. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,08 (s, 1H), 8,60 (br s, 1H), 8,51 (d, 1H), 7,80 (dd, 1H), 7,54 (d, 1H), 7,32-7,36 (m, 4H), 7,12 (d, 1H), 7,03-7,05 (m, 3H), 6,77 (dd, 1H), 6,58 (dd, 1H), 6,35 (s, 1H), 6,13 (d, 1H), 3,61-3,70 (m, 4H), 3,53 (br s, 2H), 2,97 (br, 4H), 2,71 (br, 2H), 2,16 (br s, 6H), 1,94 (br s, 2H), 1,67-1,72 (m, 2H), 1,52-1,57 (m, 2H), 1,36-1,39 (m, 2H), 0,92 (s, 6H).

EJEMPLO 189

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[1-(2-metoxietil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]benzamida

EJEMPLO 189A

4-[1-(2-metoxi-etil)-piperidin-4–ilamino]-3-nitro-bencensulfonamida

Se agregó 1-(2-metoxi-etil)-piperidin-4–ilamina (2,01 g) y trietilamina (3,24 mL, 2,35 g) a 1,4-dioxano (60 mL). Se agregó 4-cloro-3-nitrobencensulfonamida (2,50 g), y la mezcla se calentó a 90°C durante 16 horas. La mezcla se enfrió y el material se purificó por cromatografía de columna flash sobre gel de sílice usando metanol al 10% en diclorometano.

EJEMPLO 189B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[1-(2-metoxietil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 26C en lugar de EJEMPLO 1E y EJEMPLO 189A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,12 (br s, 1H), 8,52 (d, 1H), 8,18 (d, 1H), 7,76 (dd, 1H), 7,51 (d, 1H), 7,39-7,31 (m, 4H), 7,08-7,05 (m, 4H), 6,80 (dd, 1H), 6,61, (dd, 1H), 6,36 (t, 1H), 6,14 (d, 1H), 3,70 (m, 1H), 3,50 (t, 2H), 3,27 (s, 3H), 2,99 (m, 6H), 2,71 (br s, 4H), 2,16 (m, 6H), 2,02-1,90 (m, 6H), 1,65 (m, 2H), 1,37 (t, 2H), 0,92 (s, 6H).

EJEMPLO 190

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 174A en lugar de EJEMPLO 1F y EJEMPLO 55B en lugar de EJEMPLO 26C en el EJEMPLO 177. ^{1}H NMR (400 MHz, dimetilsulfóxido-d_6) δ 11,21 (br s, 1H), 9,14 (s, 1H), 8,45 (d, 1H), 7,71 (dd, 1H), 7,52 (m, 2H), 7,34 (m, 2H), 7,26 (m, 1H), 7,15 (d, 1H), 7,04 (m, 2H), 6,95 (t, 1H), 6,67 (m, 1H), 6,38 (d, 1H), 6,25 (m, 2H), 3,01 (m, 4H), 2,87 (m, 5H), 2,72 (m, 2H), 2,33 (m, 4H), 2,15 (m, 6H), 1,95 (s, 2H), 1,39 (m, 2H), 0,92 (s, 6H).

EJEMPLO 191

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(2-hidroxietil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida

EJEMPLO 191A

4-(4-(N-(2-(1*H*-indol-4–iloxi)-4-(-4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1–il)benzoil)sulfamoil)-2-nitrofenilamino)piperidin-1-carboxilato de tert-butilo

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 1E y EJEMPLO 157A en lugar de EJEMPLO 1F en el EJEMPLO 1G, excepto que se usó metanol al 5-7% en CH_2Cl_2 para la cromatografía.

EJEMPLO 191B

2-(1*H*-indol-4–iloxi)-N-(4-(1-(2-(*tert*-butildimetilsililoxi)etil)piperidin-4–ilamino)-3-nitrofenilsulfonil)-4-(-4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1–il)benzamida

Se disolvió EJEMPLO 191A (400 mg) en CH_2Cl_2 (2,5 mL) y HCl 4N en dioxano (2,5 mL), luego se agitó a temperatura ambiente durante 30 minutos. La reacción se concentró y luego se particionó entre CH_2Cl_2 y $NaHCO_3$ acuoso saturado. La capa orgánica se lavó con salmuera y se secó sobre Na_2SO_4. Luego de la filtración y la concentración la amina cruda resultante se colocó en CH_2Cl_2 formando una lechada (2,5 mL) y se agregó (*tert*-butildimetilsililoxi)acetaldehido (73 mg). Luego de agitar por 15 minutos, se agregó

tetracetoxiborohidruro de sodio (400 mg) y la reacción se agitó a temperatura ambiente durante la noche. La reacción se diluyó con CH_2Cl_2 y se lavó con $NaHCO_3$ acuoso saturado. La capa orgánica se lavó con salmuera y se secó sobre Na_2SO_4. El producto se purificó usando cromatografía de columna usando metanol al 1,0-2,5 % en CH_2Cl_2

EJEMPLO 191C

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(2-hidroxietil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida

Se disolvió EJEMPLO 191B (46 mg) en tetrahidrofurano (0,8 mL), luego se agregó fluoruro de tetrabutilamonio 1,0*M* en 95/5 tetrahidrofurano/H_2O (0,075 mL) y la reacción se agitó a temperatura ambiente durante la noche. La reacción se concentró y se purificó con cromatografía de columna usando metanol al 2-6 % en CH_2Cl_2. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,15 (br s, 1H), 8,44 (d, 1H), 8,13 (br d, 1H), 7,74 (dd, 1H), 7,55 (d, 1H), 7,33 (d, 2H), 7,23 (s, 1H), 7,11 (d, 1H), 7,03 (m, 3H), 6,93 (dd, 1H), 6,64 (d, 1H), 6,33 (d, 1H), 6,23 (s, 1H), 6,22 (s, 1H), 3,75 (br s, 1H), 3,61 (br s, 2H), 3,40 (br s, 2H), 3,10 (br s, 2H), 2,98 br s, 4H), 2,78 (br s, 2H), 2,71 (s, 2H), 2,16 (br m, 6H), 2,00 (br d, 2H), 1,95 (s, 2H), 1,72 (br s, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 194

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[1-(2-metoxietil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 1E y EJEMPLO 189A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,19 (br s, 1H), 8,46 (d, 1H), 8,17 (d, 1H), 7,72 (dd, 1H), 7,55 (d, 1H), 7,35 (d, 2H), 7,25 (t, 1H), 7,12 (d, 1H), 7,07-7,02 (m, 3H), 6,94 (t, 1H), 6,66, (dd, 1H), 6,36 (d, 1H), 6,24 (m, 2H), 3,73 (m, 1H), 3,52 (t, 2H), 3,27 (s, 3H), 3,00 (m, 6H), 2,79 (m, 2H), 2,72 (br s, 2H), 2,16 (m, 6H), 2,04-1,93 (m, 6H), 1,68 (m, 2H), 1,37 (t, 2H), 0,92 (s, 6H).

EJEMPLO 195

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(3-hidroxipropil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida

EJEMPLO 195A

4-(1-(3-(tert-butildimetilsililoxi)propil)piperidin-4–ilamino)-3-nitrobencensulfonamida

Una mezcla de EJEMPLO 157B (300 mg), (3-bromopropoxi)(tert-butil)dimetilsilano (304 mg) y carbonato de cesio (967 mg) se suspendió en N,N-dimetilformamida anhidro (5 mL). La mezcla de reacción se calentó a 70°C durante la noche. La mezcla de reacción se enfrió a temperatura ambiente y se diluyó con acetato de etilo. La fase orgánica se lavó con agua, salmuera, se secó sobre sulfato de sodio anhidro, y se concentró. El material crudo se purificó usando purificación de columna flash con metanol al 3-10%/diclorometano para dar el compuesto del título.

EJEMPLO 195B

2-(1H-indol-4–iloxi)-N-(4-(1-(3-(tert-butildimetilsililoxi)propil)piperidin-4–ilamino)-3-nitrofenilsulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1–il)benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 1E y EJEMPLO 195A en lugar de EJEMPLO 1F en el EJEMPLO 1G.

EJEMPLO 195C

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(3-hidroxipropil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida

Una mezcla de EJEMPLO 195B (180 mg) en tetrahidrofurano anhidro (1mL) y fluoruro de tetrabutilamonio (0,5 mL 1M en tetrahidrofurano) se agitó a temperatura ambiente por 2 horas. El solvente se eliminó al vacío. El residuo se purificó por HPLC de fase inversa en una columna C18 usando un gradiente de acetonitrilo al 40-70%/ácido trifluoroacético al 0,1% en agua para dar el compuesto del título como la sal trifluoroacetato. La sal de ácido trifluoroacético se disolvió en diclorometano (6 ml) y se lavó con $NaHCO_3$ acuoso al 50%. La capa orgánica se secó sobre Na_2SO_4 anhidro, se filtró, y se concentró para dar el compuesto del título. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,16 (s, 1H), 8,43 (d, 1H), 8,10 (m, 1H), 7,74 (dd, 1H), 7,57 (d, 1H), 7,34 (d, 2H), 7,23 (m, 1H), 7,10 (m, 1H), 7,02 (m, 3H), 6,93 (m, 1H), 6,65 (dd, 1H), 6,34 (d, 1H), 6,22 (m, 2H), 3,74 (m, 2H), 3,47 (m, 4H), 3,14 (m, 2H), 2,97 (m, 4H), 2,74 (m, 4H), 2,60 (m, 1H), 2,17 (m, 4H), 1,97 (m, 4H), 1,69 (m, 4H), 1,40 (m, 2H), 0,93 (s, 6H).

EJEMPLO 196

4-[4-({4'-cloro-3-[3-(dimetilamino)propil]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 196A

4'-cloro-3-hidroxibifenil-2-carbaldehido

El compuesto del título se preparó como se describe en el EJEMPLO 175A reemplazando 1-(2-bromofenil)etanona con 2-bromo-6-hidroxibenzaldehido.

EJEMPLO 196B

4-((4'-cloro-3-hidroxibifenil-2–il)metil)piperazin-1-carboxilato de tert-butilo

El compuesto del título se preparó como se describe en el EJEMPLO 1A reemplazando 4'-clorobifenil-2-carboxaldehido con EJEMPLO 196A.

EJEMPLO 196C

4-((4'-cloro-3-(trifluorometilsulfoniloxi)bifenil-2–il)metil)piperazin-1-carboxilato de tert-butilo

A una mezcla de EJEMPLO 196B (390 mg) en piridina (5 ml) a 0ºC se agregó por goteo anhídrido trifluorometansulfónico (0,326 ml). La mezcla de reacción se agitó en un baño de hielo por 1 hora y se diluyó con acetato de etilo. La mezcla resultante se lavó con salmuera extensivamente y la capa orgánica se secó sobre Na_2SO_4, se filtró, y se concentró para dar el compuesto del título.

EJEMPLO 196D

4-((4'-cloro-3-(3-(dimetilamino)prop-1-inil)bifenil-2–il)metil)piperazin-1-carboxilato de tert-butilo

A una mezcla de EJEMPLO 196C (380 mg), N,N-dimetilprop-2-in-1-amina (0,227 ml), tetrakis(trifenilfosfin)paladio(0) (123 mg) y trietilamina (0,492) en N,N-dimetilformamida (1,5 ml) se agregó yoduro de cobre (I) (27,1 mg) y ^{t}BuNI (394 mg). La mezcla de reacción se calentó a 100ºC durante 4 horas, se enfrió y se diluyó con acetato de etilo. La capa orgánica se secó sobre Na_2SO_4 y se concentró. El residuo se purificó por cromatografía flash, eluyendo con una mezcla de metanol, diclorometano y trietilamina para dar el compuesto del título.

EJEMPLO 196E

4-((4'-cloro-3-(3-(dimetilamino)propil)bifenil-2–il)metil)piperazin-1-carboxilato de tert-butilo

Se trató EJEMPLO 196D (200 mg) en metanol (8 ml) con óxido de platino(IV) (29,1 mg) bajo una atmósfera de H_2 durante la noche. El material insoluble se retiró por filtración y el material filtrado se concentró para dar el compuesto del título.

EJEMPLO 196F

3-(4'-cloro-2-(piperazin-1–ilmetil)bifenil-3–il)-N,N-dimetilpropan-1-amina

El compuesto del título se preparó como se describe en el EJEMPLO 175C reemplazando EJEMPLO 175B con EJEMPLO 196E.

EJEMPLO 196G

2-(1H-indol-4–iloxi)-4-(4-((4'-cloro-3-(3-(dimetilamino)propil)bifenil-2–il)metil)piperazin-1–il)benzoato de etilo

El compuesto del título se preparó como se describe en el EJEMPLO 175D reemplazando EJEMPLO 175C con EJEMPLO 196F.

EJEMPLO 196H

ácido 2-(1H-indol-4–iloxi)-4-(4-((4'-cloro-3-(3-(dimetilamino)propil)bifenil-2–il)metil)piperazin-1–il)benzoico

El compuesto del título se preparó como se describe en el EJEMPLO 175E reemplazando EJEMPLO 175D con EJEMPLO 196G.

EJEMPLO 196I

4-[4-({4'-cloro-3-[3-(dimetilamino)propil]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 175F reemplazando EJEMPLO 175E con EJEMPLO 196H. ^{1}H NMR (500 MHz, dimetilsulfóxido-d_6) δ 11,11 (s, 1H), 8,38 - 8,44 (m, 2H), 7,68 (dd, 1H), 7,56 (d, 1H), 7,44 (d, 2H), 7,19 - 7,29 (m, 5H), 7,07 (d, 1H), 6,99 (dd, 1H), 6,87 - 6,93 (m, 2H), 6,59 (dd, 1H), 6,26 (d, 1H), 6,23 (s, 1H), 6,19 (d, 1H), 3,84 (dd, 2H), 3,22 - 3,29 (m, 4H), 2,87 (s, 6H), 2,69 - 2,75 (m, 2H), 2,59 (s, 5H), 2,14 (s, 4H), 1,83 - 1,92 (m, 3H), 1,56 - 1,65 (m, 2H), 1,19 - 1,31 (m, 4H), 0,81 - 0,90 (m, 1H)

EJEMPLO 197

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(3-hidroxipropil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida

EJEMPLO 197A

2-(1H-indol-5–iloxi)-N-(4-(1-(3-(tert-butildimetilsililoxi)propil)piperidin-4–ilamino)-3-nitrofenilsulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1–il)benzamida

El compuesto del título se preparó utilizando EJEMPLO 26C en lugar de EJEMPLO 1E y EJEMPLO 195A en lugar de EJEMPLO 1F en el EJEMPLO 1G.

EJEMPLO 197B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(3-hidroxipropil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 197A en lugar de EJEMPLO 195B en el EJEMPLO 195C. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,07 (bs, 1H), 8,50 (d, 1H), 8,14 (d, , 1H), 7,75 (dd, 1H), 7,52 (d, 1H), 7,34 (m, 4H), 7,02 (m, 4H), 6,78 (dd, 1H), 6,59 (dd, 1H), 6,34 (m, 1H), 6,14 (d, 1H), 3,46 (m, 4H), 3,16 (m, 2H), 2,98 (m, 4H), 2,68 (m, 4H), 2,60 (m, 1H), 2,16 (m, 6H), 1,97 (m, 4H), 1,68 (m, 4H), 1,38 (t, 2H), 0,93 (s, 6H).

EJEMPLO 198

4-{4-[(4'-cloro-4-morfolin-4–il-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 198A

4-((4'-cloro-4-hidroxibifenil-2–il)metil)piperazin-1-carboxilato de tert-butilo

El compuesto del título se preparó utilizando EJEMPLO 125A en lugar de 4'-clorobifenil-2-carboxaldehido en el EJEMPLO 1A.

EJEMPLO 198B

4-((4'-cloro-4-(trifluorometilsulfoniloxi)bifenil-2–il)metil)piperazin-1-carboxilato de tert-butilo

Una mezcla de EJEMPLO 198A (3,0 g), anhídrido trifluorometansulfónico (3,14 g) en piridina anhidra (50 mL) se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con acetato de etilo. La fase orgánica se lavó con agua, salmuera, se secó sobre sulfato de sodio anhidro y se concentró. El residuo se usó en el siguiente paso sin purificación adicional.

EJEMPLO 198C

4-((4'-cloro-4-morfolinobifenil-2–il)metil)piperazin-1-carboxilato de tert-butilo

Una suspensión de EJEMPLO 198B (500 mg), morfolina (80 mg), acetato de paladio (II) (22 mg), bifenil-2–ildi-tert-butilfosfina (50 mg) y carbonato de cesio (427 mg) en tetrahidrofurano anhidro (6 mL) se calentó a 50°C durante la noche. La mezcla de reacción se enfrió a temperatura ambiente y se diluyó con acetato de etilo. La fase orgánica se lavó con agua, salmuera, se secó sobre sulfato de sodio anhidro, se filtró y se concentró. El material crudo se purificó por purificación de columna flash con acetato de etilo al 30-50%/hexano para dar el compuesto del título.

EJEMPLO 198D

4-(4'-cloro-2-(piperazin-1–ilmetil)bifenil-4–il)morfolina

El compuesto del título se preparó utilizando EJEMPLO 198C en lugar de EJEMPLO 1A en el EJEMPLO 1B.

EJEMPLO 198E

2-(1H-indol-4–iloxi)-4-(4-((4'-cloro-4-morfolinobifenil-2–il)metil)piperazin-1–il)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 24F en lugar de EJEMPLO 20A y EJEMPLO 198D en lugar de EJEMPLO 20C en el EJEMPLO 20D.

EJEMPLO 198F

ácido 2-(1H-indol-4–iloxi)-4-(4-((4'-cloro-4-morfolinobifenil-2–il)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 198E en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 198G

4-{4-[(4'-cloro-4-morfolin-4–il-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 198F en lugar de EJEMPLO 26C en el EJEMPLO 177. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,26 (bs, 1H), 8,63 (t, 1H), 8,49 (d, 1H), 7,66 (dd, 1H), 7,54 (d, 1H), 7,40 (m, 4H), 7,29 (m, 1H), 7,02 (m, 6H), 6,73 (dd, 1H), 6,39 (d, 1H), 6,30 (m, 2H), 3,85 (dd, 2H), 3,74 (m, 4H), 3,24 (m, 6H), 3,10 (m, 8H), 2,29 (m, 4H), 1,89 (m, 1H), 1,63 (m, 2H), 1,28 (m, 2H).

EJEMPLO 199

4-[4-({4'-cloro-3-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida

EJEMPLO 199A

4-((4'-cloro-3-hidroxibifenil-2–il)metil)piperazin-1-carboxilato de tert-butilo

El compuesto del título se preparó como se describe en el EJEMPLO 1A reemplazando EJEMPLO 27C con EJEMPLO 196A.

EJEMPLO 199B

4-((4'-cloro-3-(2-(dimetilamino)etoxi)bifenil-2–il)metil)piperazin-1-carboxilato de tert-butilo

A una mezcla de EJEMPLO 199A (1,5 g) en N,N-dimetilformamida (20 ml) se agregó hidruro de sodio al 60% (0,596 g). La mezcla se agitó a temperatura ambiente durante 30 minutos y se agregó sal clorhidrato de cloruro de dimetilaminoetilo (1,073 g). Luego de agitar la mezcla resultante durante la noche, se agregó hidruro de sodio al 60% adicional (0,596 g) y sal clorhidrato de cloruro de dimetilaminoetilo (1,073 g). La mezcla de reacción se agitó adicionalmente durante la noche, se diluyó con acetato de etilo y se lavó con agua, $NaHCO_3$ saturado y salmuera. La capa orgánica se secó sobre Na_2SO_4, se filtró, y se concentró para dar el compuesto del título.

EJEMPLO 199C

2-(4'-cloro-2-(piperazin-1–ilmetil)bifenil-3–iloxi)-N,N-dimetiletanamina

A una mezcla de EJEMPLO 199B (2 g) en diclorometano (10 ml) se agregó ácido trifluoroacético (10 ml) a 0ºC. La mezcla de reacción se agitó a temperatura ambiente durante 30 minutos y se concentró. El residuo se cargó en una columna C18, y se eluyó con

ácido trifluoroacético al 0,1% al 0- 50%/agua en acetonitrilo. El compuesto del título se obtuvo como una sal de ácido trifluoroacético.

EJEMPLO 199D

2-(1H-indol-4–iloxi)-4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)bifenil-2–il)metil)piperazin-1–il)benzoato de etilo

El compuesto del título se preparó como se describe en el EJEMPLO 175D reemplazando EJEMPLO 175C con EJEMPLO 199C.

EJEMPLO 199E

ácido 2-(1H-indol-4–iloxi)-4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)bifenil-2–il)metil)piperazin-1–il)benzoico

El compuesto del título se preparó como se describe en el EJEMPLO 175E reemplazando EJEMPLO 175D con EJEMPLO 199D.

EJEMPLO 199F

4-[4-({4'-cloro-3-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 175F reemplazando EJEMPLO 175E y EJEMPLO 1F con EJEMPLO 199E y EJEMPLO 173C, respectivamente. ^{1}H NMR (500 MHz, dimetilsulfóxido-d_6) δ 11,13 (s, 1H), 8,41 (d, 1H), 8,12 (d, 1H), 7,70 (dd, 1H), 7,58 (d, 1H), 7,52 (d, 2H), 7,43 (d, 2H), 7,31 (t, 1H), 7,22 (t, 1H), 7,06 (dd, 2H), 6,89 - 6,97 (m, 2H), 6,84 (d, 1H), 6,64 (dd, 1H), 6,30 (d, 1H), 6,24 (dd, 2H), 4,14 (t, 2H), 3,90 (dd, 2H), 3,53 - 3,73 (m, 2H), 3,22 - 3,32 (m, 4H), 2,93 (s, 6H), 2,34 - 2,46 (m, 7H), 2,29 (s, 5H), 1,97 (d, 2H), 1,73 (d, 2H), 1,41 - 1,62 (m, 4H).

EJEMPLO 201

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(dietilamino)ciclohexil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida

EJEMPLO 201A

4-(4-(dietilamino)ciclohexilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando N^1,N^1-dietilciclohexano-1,4-diamina en lugar de 1-(2-metoxi-etil)-piperidin-4–ilamina en el EJEMPLO 189A.

EJEMPLO 201B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(dietilamino)ciclohexil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 26C en lugar de EJEMPLO 1E y EJEMPLO 201A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (500 MHz, piridina-d_5) δ ppm 12,28 (s, 1H), 9,29 (d, 1H), 8,29 - 8,38 (m, 2H), 8,19 (d, 1H), 7,52 - 7,57 (m, 2H), 7,40 - 7,47 (m, 3H), 7,10 (dd, 1H), 7,06 (d, 2H), 6,92 (d, 1H), 6,74 (dd, 1H), 6,61 (s, 1H), 6,55 (d, 1H), 3,31 - 3,42 (m, 1H), 3,00 - 3,08 (m, 4H), 2,76 (s, 2H), 2,54 - 2,61 (m, 1H), 2,51 (q, 4H), 2,21 - 2,28 (m, 2H), 2,08 - 2,15 (m, 4H), 2,04 (d, 2H), 1,97 (s, 2H), 1,81 (d, 2H), 1,38 (t, 2H), 1,29 - 1,36 (m, 2H), 1,17 - 1,28 (m, 2H), 1,05 (t, 6H), 0,93 (s, 6H).

EJEMPLO 202

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(dimetilamino)ciclohexil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida

EJEMPLO 202A

4-(4-(dimetilamino)ciclohexilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando N^1,N^1-dimetilciclohexano-1,4-diamina en lugar de 1-(2-metoxi-etil)-piperidin-4–ilamina en el EJEMPLO 189A.

EJEMPLO 202B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(dimetilamino)ciclohexil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 1E y EJEMPLO 202A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (500 MHz, piridina-d_5) δ ppm 12,45 (s, 1H), 9,21 (d, 1H), 8,33 (d, 1H), 8,27 (dd, 1H), 8,18 (d, 1H), 7,48 (t, 1H), 7,45 (d, 2H), 7,40 (d, 1H), 7,11 (t, 1H), 7,08 (d, 2H), 6,87 (d, 1H), 6,72 - 6,81 (m, 3H), 6,67 (d, 1H), 3,31 - 3,41 (m, 1H), 3,00 - 3,06 (m, 4H), 2,77 (s, 2H), 2,31 (s, 6H), 2,25 (t, 2H), 2,20 - 2,25 (m, 1H), 2,10 - 2,16 (m, 4H), 2,00 - 2,07 (d, 2H), 1,97 (s, 2H), 1,88 (d, 2H), 1,39 (t, 3H), 1,34 (d, 2H), 1,15 - 1,28 (m, 4H), 0,94 (s, 6H).

EJEMPLO 203

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(dietilamino)ciclohexil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 1E y EJEMPLO 201A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (500 MHz, piridina-d_5) δ 12,44 (s, 1H), 9,21 (d, 1H), 8,34 (d, 1H), 8,28 (dd, 1H), 8,18 (d, 1H), 7,47 - 7,50 (m, 1H), 7,45 (d, 2H), 7,40 (d, 1H), 7,11 (t, 1H), 7,08 (d, 2H), 6,90 (d, 1H), 6,73 - 6,81 (m, 3H), 6,67 (d, 1H), 3,32 - 3,40 (m, 1H), 2,99 - 3,06 (m, 4H), 2,76 (s, 2H), 2,52 - 2,60 (m, 1H), 2,49 (q, 4H), 2,25 (t, 2H), 2,09 - 2,16 (m, 4H), 2,04 (d, 2H), 1,97 (s, 2H), 1,79 (d, 2H), 1,29 - 1,42 (m, 4H), 1,16 - 1,28 (m, 2H), 1,04 (t, 6H), 0,92 - 0,95 (m, 6H).

EJEMPLO 204

Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(4-morfolin-4–ilciclohexil)amino]-3-nitrofenil}sulfonil)benzamida

EJEMPLO 204A

trans-4-(4-morfolinociclohexilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando trans-4-morfolinociclohexanamina en lugar de 1-(2-metoxi-etil)-piperidin-4–ilamina en el EJEMPLO 189A.

EJEMPLO 204B

trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(4-morfolin-4–ilciclohexil)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 1E y EJEMPLO 204A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (500 MHz, piridina-d_5) δ 12,45 (s, 1H), 9,21 (d, 1H), 8,36 (d, 1H), 8,26 (dd, 1H), 8,16 (d, 1H), 7,47 - 7,51 (m, 1H), 7,45 (d, 1H), 7,40 (d, 1H), 7,12 (t, 1H), 6,87 (d, 1H), 6,73 - 6,81 (m, 3H), 6,68 (d, 1H), 3,71 - 3,78 (m, 2H), 3,33 - 3,42 (m, 1H), 3,00 - 3,06 (m, 4H), 2,76 (s, 2H), 2,44 - 2,52 (m, 4H), 2,25 (t, 2H), 2,16 - 2,23 (m, 2H), 2,09 - 2,16 (m, 4H), 2,06 (d, 2H), 1,97 (s, 2H), 1,86 (s, 2H), 1,39 (t, 2H), 1,17 - 1,35 (m, 6H), 0,94 (s, 6H).

EJEMPLO 205

4-[4-({4'-cloro-3-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 177 reemplazando EJEMPLO 26C y EJEMPLO 1F con EJEMPLO 199E y EJEMPLO 21A, respectivamente. ^{1}H NMR (500 MHz, diclorometano-d_2) δ 8,70 (d, 1H), 8,56 (s, 1H), 8,40 (d, 1H), 7,95 (dd, 1H), 7,91 (d, 1H), 7,46 (d, 2H), 7,24 - 7,35 (m, 5H), 7,15 (t, 1H), 6,90 (dd, 2H), 6,83 (d, 1H), 6,75 (d, 1H), 6,60 (dd, 1H), 6,41 (d, 1H), 6,19 (d, 1H), 4,05 (t, 2H), 3,58 (s, 1H), 3,32 (s, 2H), 2,95 - 3,02 (m, 4H), 2,66 - 2,80 (m, 4H), 2,30 - 2,35 (m, 4H), 2,24 - 2,29 (m, 9H), 2,15 - 2,23 (m, 2H), 2,05 (d, 2H), 1,63 - 1,73 (m, 2H)

EJEMPLO 206

4-{4-[1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 177 reemplazando EJEMPLO 26C y EJEMPLO 1F con EJEMPLO 175E y EJEMPLO 21A, respectivamente. ^{1}H NMR (400 MHz, diclorometano-d_2) δ 8,70 (d, 1H), 8,51 (s, 1H), 8,40 (d, 1H), 7,94 (dd, 1H), 7,90 (d, 1H), 7,54 (d, 1H), 7,33 (t, 4H), 7,21 - 7,27 (m, 2H), 7,10 - 7,19 (m, 4H), 6,91 (d, 1H), 6,73 (d, 1H), 6,55 - 6,60 (m, 1H), 6,41 (s, 1H), 6,16 (d, 1H), 3,52 - 3,63 (m, 1H), 3,36 (q, 1H), 2,96 - 3,07 (m, 4H), 2,72 - 2,79 (m, 2H), 2,33 - 2,41 (m, 2H), 2,27 (s, 3H), 2,14 - 2,27 (m, 4H), 2,00 - 2,09 (m, 2H), 1,63 - 1,74 (m, 2H), 1,19 (d, 3H).

EJEMPLO 207

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[4-(dimetilamino)tetrahidro-2H-piran-4–il]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando 4-(aminometil)-N,N-dimetiltetrahidro-2H-piran-4-amina en lugar de (3S,4R)-4-amino-1-bencilpiperidin-3-ol, ácido clorhídrico en el EJEMPLO 187B. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,17 (s, 1H), 8,84 (br s, 1H), 8,59 (d, 1H), 7,84 (dd, 1H), 7,51 (d, 1H), 7,39-7,43 (m, 2H), 7,33 (d, 2H), 7,17-7,21 (m, 2H), 7,03 (d, 2H), 6,89 (dd, Hz, 1H), 6,64 (d, 1H), 6,40 (s, 1H), 6,13 (d, 1H), 3,72-3,75 (m, 2H), 3,34-3,57 (m, 4H), 3,02 (br, 4H), 2,71 (br, 2H), 2,27 (s, 6H), 2,16 (br s, 6H), 1,94 (br s, 2H), 1,78-1,85 (m, 2H), 1,36-1,39 (m, 2H), 0,92 (s, 6H).

EJEMPLO 208

N-({4-[(2-aminociclohexil)amino]-3-nitrofenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida

EJEMPLO 208A

El compuesto del título se preparó utilizando 2-aminociclohexilcarbamato de tert-butilo en lugar de (3S,4R)-4-amino-1-bencilpiperidin-3-ol, ácido clorhídrico en el EJEMPLO 187B.

EJEMPLO 208B

N-({4-[(2-aminociclohexil)amino]-3-nitrofenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida

Se calentó EJEMPLO 208A (0,1 g) en dimetilsulfóxido (4 mL) en condiciones de microondas (200°C, 1 hora). El residuo se purificó por HPLC de fase inversa en una columna C18 usando un gradiente de acetonitrilo al 30-70%/TFA al 0,1% en agua. Las fracciones deseadas se recogieron, y el solvente orgánico se eliminó parcialmente bajo presión reducida. La mezcla resultante se trató con una mezcla acuosa saturada de $NaHCO_3$. Luego se extrajo con acetato de etilo tres veces. Las capas orgánicas combinadas se lavaron con salmuera, se secó ($MgSO_4$), se filtró, y se concentró para dar el compuesto del título. ^1H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,02 (s, 1H), 8,45 (s, 1H), 8,05 (d, 1H), 7,79-7,81 (m, 1H), 7,56 (d, 1H), 7,30-7,34 (m, 4H), 6,98-7,06 (m, 4H), 6,73 (d, 1H), 6,54 (dd, 1H), 6,33 (s, 1H), 6,11 (d, 1H), 3,64-3,70 (m, 1H), 2,93 (br, 4H), 2,71 (br, 2H), 2,14-2,16 (br s, 6H), 1,95 (br s, 2H), 1,67-1,73 (m, 2H), 1,36-1,39 (m, 2H), 0,92 (s, 6H).

EJEMPLO 209

4-[4-({4'-cloro-4-[3-(dimetilamino)prop-1-inil]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 209A

4-((4'-cloro-4-(3-(dimetilamino)prop-1-ynil)bifenil-2–il)metil)piperazin-1-carboxilato de tert-butilo

Una suspensión de EJEMPLO 198B (800 mg), N,N-dimetilprop-2-in-1-amina (373 mg), yoduro de cobre (I) (57 mg), tetrakis(trifenilfosfin)paladio(0) (259 mg), trietilamina (757 mg) y yoduro de tert-butilamonio (829 mg) en N,N-dimetilformamida anhidra (5 mL) se calentó a 100°C durante 5 horas. La mezcla de reacción se enfrió a

temperatura ambiente y se diluyó con acetato de etilo. La fase orgánica se lavó con agua, salmuera, se secó sobre sulfato de sodio anhidro, se filtró, y se concentró. El material crudo se purificó por purificación de columna flash con metanol al 0-3%/diclorometano para dar el compuesto del título.

EJEMPLO 209B

3-(4'-cloro-2-(piperazin-1–ilmetil)bifenil-4–il)-N,N-dimetilprop-2-in-1-amina

El compuesto del título se preparó utilizando EJEMPLO 209A en lugar de EJEMPLO 1A en el EJEMPLO 1B.

EJEMPLO 209C

2-(1H-indol-4–iloxi)-4-(4-((4'-cloro-4-(3-(dimetilamino)prop-1-inil)bifenil-2–il)metil)piperazin-1–il)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 24F en lugar de EJEMPLO 20A y EJEMPLO 209B en lugar de EJEMPLO 20C en el EJEMPLO 20D.

EJEMPLO 209D

ácido 2-(1H-indol-4–iloxi)-4-(4-((4'-cloro-4-(3-(dimetilamino)prop-1-inil)bifenil-2–il)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 209C en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 209E

4-[4-({4'-cloro-4-[3-(dimetilamino)prop-1-inil]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 209D en lugar de EJEMPLO 26C en el EJEMPLO 177. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,23 (bs, 1H), 8,57 (t, 1H), 8,47 (d, 1H), 7,67 (dd, 1H), 7,54 (m, 2H), 7,43 (m, 5H), 7,24 (m, 2H), 7,14 (m, 1H), 7,03 (m, 1H), 6,94 (m, 1H), 6,71 (d, 1H), 6,38 (d, 1H), 6,27 (d, 2H), 3,85 (m, 2H), 3,60 (m, 2H), 3,23 (m, 6H), 3,04 (m, 4H), 2,35 (s, 6H), 2,28 (m, 4H), 1,88 (m, 1H), 1,58 (m, 2H), 1,24 (m, 2H).

EJEMPLO 210

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(3-nitro-4-{[1-(4,4,4-trifluorobutil)piperidin-4–il]amino}fenil)sulfonil]benzamida

EJEMPLO 210A

3-nitro-4-(1-(4,4,4-trifluorobutil)piperidin-4–ilamino)bencensulfonamida

Se combinó EJEMPLO 157B (600 mg) con 1,1,1-trifluoro-4-yodobutano (595 mg) y carbonato de potasio (829 mg) en acetonitrilo (15 mL). La reacción se calentó a 70°C durante la noche. La reacción se concentró, y luego se capturó en éter y se volvió a concentrar. El producto se usó en el siguiente paso sin purificación adicional.

EJEMPLO 210B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(3-nitro-4-{[1-(4,4,4-trifluorobutil)piperidin-4–il]amino}fenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 210A en lugar de EJEMPLO 1F y EJEMPLO 55B en lugar de EJEMPLO 1E en el EJEMPLO 1G. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,20 (s, 1H), 8,47 (d, 1H), 8,20 (d, 1H), 7,72 (dd, 1H), 7,54 (d,1H), 7,34 (d, 2H), 7,25 (t, 1H), 7,14 (d, 1H), 7,05 (m, 3H), 6,95 (t, 1H), 6,68 (dd, 1H), 6,38 (d, 1H), 6,25 (s, 2H), 3,71 (m, 1H), 3,01 (m, 4H), 2,92 (m, 2H), 2,72 (s, 2H), 2,40 (m, 2H), 2,30 (m, 2H), 2,16 (m, 6H), 1,95 (m, 4H), 1,68 (m, 4H), 1,38 (t, 2H), 1,24 (br s, 1H), 0,92 (s, 6H).

EJEMPLO 211

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[2-(4-hidroxi-1-metilpiperidin-4–il)etil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando 4-(2-aminoetil)-1-metilpiperidin-4-ol en lugar de (3S,4R)-4-amino-1-bencilpiperidin-3-ol, ácido clorhídrico en el EJEMPLO 187B. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,05 (s, 1H), 8,61 (s, 1H), 8,47 (d, 1H), 7,77 (dd, 1H), 7,54 (d, 1H), 7,32-7,34 (m, 4H), 7,04 (d, 2H), 7,01 (s, 1H), 6,90 (d, 2H), 6,76 (dd, 1H), 6,57 (dd, 1H), 6,33 (s, 1H), 6,13 (d, 1H), 4,92 (s, 1H), 3,43-3,46 (m, 2H), 2,95-3,01 (br, 8H), 2,71 (br, 2H), 2,65 (s, 3H), 2,12-2,16 (br s, 6H), 1,95 (br s, 2H), 1,77-1,80 (m, 2H), 1,67-1,71 (m, 4H), 1,36-1,39 (m, 2H), 0,92 (s, 6H).

EJEMPLO 212

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[1-(1,3-tiazol-2–il)piperidin-4–il]amino}fenil)sulfonil]benzamida

El compuesto del título se preparó utilizando 4-(2-aminoetil)-1-metilpiperidin-4-ol en lugar de (3S,4R)-4-amino-1-bencilpiperidin-3-ol, ácido clorhídrico en el EJEMPLO 187B. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,16 (s, 1H), 8,58 (s, 1H), 8,28 (d, 1H), 7,82 (dd, 1H), 7,51 (d, 1H), 7,39-7,42 (m, 2H), 7,33 (d, 2H), 7,20 (d, 1H), 7,17 (d, 1H), 7,14 (d, 1H), 7,03 (d, 2H), 6,86 (d, 1H), 6,85 (d, 1H), 6,65 (dd, 1H), 6,39 (s, 1H), 6,15 (d, 1H), 3,87-3,90 (m, 2H), 3,20-3,24 (m, 2H), 3,04 (br, 4H), 2,73 (br, 2H), 2,11-2,17 (m, 5H), 1,95 (br s, 2H), 1,71-1,75 (m, 2H), 1,36-1,39 (m, 2H), 0,92 (s, 6H).

EJEMPLO 213

4-(4-{[4'-cloro-4-(2-hidroxietoxi)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 213A

4-(2-(tert-butildimetilsililoxi)etoxi)-4'-clorobifenil-2-carbaldehido

Una mezcla de EJEMPLO 125A (0,5 g), (2-bromoetoxi)(tert-butil)dimetilsilano (0,771 g) y carbonato de cesio (1,4 g) se suspendió en N,N-dimetilformamida anhidro (5 mL). La mezcla de reacción se calentó a 70°C durante la noche. La mezcla de reacción se enfrió a temperatura ambiente y se diluyó con acetato de etilo. La fase orgánica se lavó con agua, salmuera, se secó sobre sulfato de sodio anhidro, se filtró, y se concentró. El material crudo se purificó por purificación de columna flash con acetato de etilo al 0-5%/hexano para dar el compuesto del título.

EJEMPLO 213B

2-(1H-indol-4–iloxi)-4-(4-((4-(2-(tert-butildimetilsililoxi)etoxi)-4'-clorobifenil-2–il)metil)piperazin-1–il)benzoato de metilo

Este ejemplo se realizó utilizando EJEMPLO 213A en lugar de 4’-clorobifenil-2-carboxaldehido y EJEMPLO 68B en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 213C

ácido 2-(1H-indol-4–iloxi)-4-(4-((4-(2-(tert-butildimetilsililoxi)etoxi)-4'-clorobifenil-2–il)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 213B en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 213D

2-(1H-indol-4–iloxi)-4-(4-((4-(2-(tert-butildimetilsililoxi)etoxi)-4'-clorobifenil-2–il)metil)piperazin-1–il)-N-(3-nitro-4-((tetrahidro-2H-piran-4–il)metilamino)fenilsulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 213C en lugar de EJEMPLO 1E en el EJEMPLO 1G.

EJEMPLO 213E

4-(4-{[4'-cloro-4-(2-hidroxietoxi)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 213D en lugar de EJEMPLO 195B en el EJEMPLO 195C. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,24 (m, 1H), 8,62 (t, 1H), 8,50 (d, 1H), 7,67 (dd, 1H), 7,54 (m, 1H), 7,43 (d, 2H), 7,37 (d, 2H), 7,28 (m, 1H), 7,15 (m, 2H), 7,05 (m, 2H), 6,96 (m, 1H), 6,90 (dd, 1H), 6,73 (dd, 1H), 6,40 (d, 1H), 6,31 (m, 1H), 6,27 (m, 1H), 4,82 (t, 1H), 3,99 (t, 2H), 3,86 (m, 2H), 3,71 (m, 2H), 3,26 (m, 6H), 2,66 (m, 2H), 2,31 (m, 5H), 1,89 (m, 1H), 1,63 (m, 2H), 1,27 (m, 2H).

EJEMPLO 214

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(ciclopropilmetil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida

EJEMPLO 214A

1-(ciclopropilmetil)piperidin-4–ilcarbamato de tert-butilo

El compuesto del título se preparó utilizando ciclopropancarbaldehido en lugar de 4'-clorobifenil-2-carboxaldehido y piperidin-4–ilcarbamato de tert-butilo en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 214B

bis(2,2,2-trifluoroacetato) de 1-(ciclopropilmetil)piperidin-4-amina

El compuesto del título se preparó utilizando EJEMPLO 214A en lugar de EJEMPLO 1A en el EJEMPLO 1B.

EJEMPLO 214C

4-(1-(ciclopropilmetil)piperidin-4–ilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando EJEMPLO 214B en lugar de 1-(2-Metoxi-etil)-piperidin-4–ilamina en el EJEMPLO 189A.

EJEMPLO 214D

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(ciclopropilmetil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 26C en lugar de EJEMPLO 1E y EJEMPLO 214C en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (500 MHz, piridina-d_5) δ 12,28 (s, 1H), 9,30 (d, 1H), 8,49 (d, 1H), 8,34 (dd, 1H), 8,18 (d, 1H), 7,52 - 7,56 (m, 2H), 7,41 - 7,46 (m, 3H), 7,09 (dd, 1H), 7,06 (d, 2H), 6,91 (d, 1H), 6,73 (dd, 1H), 6,61 (d, 1H), 6,54 (d, 1H), 3,45 - 3,56 (m, 1H), 3,00 - 3,08 (m, 4H), 2,87 (d, 2H), 2,76 (s, 2H), 2,25 (t, 2H), 2,19 (d, 4H), 2,09 - 2,14 (m, 4H), 1,97 (s, 4H), 1,63 - 1,73 (m, 2H), 1,38 (t, 2H), 0,84 - 0,91 (m, 1H), 0,43 - 0,50 (m, 2H), 0,11 (q, H).

EJEMPLO 215

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

EJEMPLO 215A

4-(4-metilpiperazin-1–ilamino)-3-(trifluorometilsulfonil)bencensulfonamida

El compuesto del título se preparó utilizando 4-metilpiperazin-1-amina en lugar de (tetrahidropiran-4–il)metanamina y EJEMPLO 159C durante 4-fluoro-3-nitrobencensulfonamida en el EJEMPLO 1F.

EJEMPLO 215B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 215A en lugar de EJEMPLO 1F y EJEMPLO 55B en lugar de EJEMPLO 26C en el EJEMPLO 177. ^{1}H NMR

(500 MHz, dimetilsulfóxido-d_6) δ 11,21 (br s, 1H), 8,09 (m, 1H), 7,98 (m, 1H), 7,83 (dd, 1H), 7,53 (d, 1H), 7,45 (d, 1H), 7,34 (d, 2H), 7,26 (t, 1H), 7,16 (d, 1H), 7,04 (d, 2H), 6,97 (t, 1H), 6,66 (dd, 1H), 6,39 (d, 1H), 6,24 (m, 2H), 2,87 (m, 13H), 2,38 (s, 3H), 2,17 (m, 6H), 1,95 (s, 2H), 1,39 (t, 2H), 0,93 (s, 6H)

EJEMPLO 216

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[1-(4,4,4-trifluorobutil)piperidin-4–il]amino}fenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 26C en lugar de EJEMPLO 1E y EJEMPLO 210A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,13 (s, 1H), 10,89 (br s, 1H), 8,55 (d, 1H), 8,22 (d, 1H), 7,79 (dd, 1H), 7,50 (d,1H), 7,34 (m, 4H), 7,07 (m, 4H), 6,83 (dd, 1H), 6,63 (dd, 1H), 6,37 (m, 1H), 6,15 (d, 1H), 3,71 (m, 1H), 3,01 (m, 4H), 2,92 (m, 2H), 2,72 (s, 2H), 2,40 (m, 2H), 2,30 (m, 2H), 2,16 (m, 6H), 1,95 (m, 4H), 1,68 (m, 4H), 1,38 (t, 2H), 1,24 (br s, 1H), 0,92 (s, 6H).

EJEMPLO 217

4-{4-[1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 177 reemplazando EJEMPLO 26C y EJEMPLO 1F con EJEMPLO 175E y EJEMPLO 174A, respectivamente. ^{1}H NMR (400 MHz, dimetilsulfóxido-d_6) δ 11,21 (s, 1H), 9,15 (s, 1H), 8,45 (d, 1H), 7,70 (dd, 1H), 7,43 - 7,56 (m, 5H), 7,34 - 7,41 (m, 1H), 7,24 - 7,31 (m, 4H), 7,10 - 7,16 (m, 2H), 6,94 (t, 1H), 6,66 (dd, 1H), 6,37 (d, 1H), 6,24 (dd, 2H), 2,80 - 3,02 (m, 10H), 2,28 - 2,39 (m, 5H), 2,14 - 2,24 (m, 2H), 1,16 (d, 3H).

EJEMPLO 218

4-[4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}-3-(hidroximetil)piperazin-1–il]-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida

EJEMPLO 218A

2-(4-clorofenil)-4,4-dimetilciclohex-1-encarbaldehido

El compuesto del título se preparó utilizando EJEMPLO 18C en lugar de EJEMPLO 143C en el EJEMPLO 143D.

EJEMPLO 218B

4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)-3-(hidroximetil)piperazin-1-carboxilato de tert-butilo

El compuesto del título se preparó utilizando EJEMPLO 218A en lugar de EJEMPLO 27C y 3-(hidroximetil)piperazin-1-carboxilato de tert-butilo en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 218C

(1-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-2–il)metanol

El compuesto del título se preparó utilizando EJEMPLO 218B en lugar de EJEMPLO 1A en el EJEMPLO 1B.

EJEMPLO 218D

2-(1H-indol-5–iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)-3-(hidroximetil)piperazin-1–il)benzoato de etilo

El compuesto del título se preparó utilizando EJEMPLO 218C en lugar de EJEMPLO 20C y EJEMPLO 26A en lugar de EJEMPLO 20A en el EJEMPLO 20D.

EJEMPLO 218E

ácido 2-(1H-indol-5–iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)-3-(hidroximetil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 218D en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 218F

4-[4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}-3-(hidroximetil)piperazin-1–il]-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 218E en lugar de EJEMPLO 26C y EJEMPLO 21A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,07 (s, 1H), 8,50 (d, 1H), 8,14 (d, 1H), 7,45 (d, J = 9,46 Hz, 1H), 7,52 (d, 1H), 7,32-7,35 (m, 4H), 6,99-7,05 (m, 4H), 6,78 (dd, 1H), 6,58-6,59 (m, 1H), 6,34 (s, 1H), 6,14 (d, 1H), 4,42-4,44 (m, 1H), 3,72 (br s, 1H), 3,10-3,25 (m, 6H), 3,00 (br, 2H), 2,58-2,69 (m, 6H), 1,82-2,01 (m, 6H), 1,70 (br, 2H), 1,36-1,39 (m, 2H), 0,92 (s, 6H).

EJEMPLO 219

4-[4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}-3-(hidroximetil)piperazin-1–il]-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 218E en lugar de EJEMPLO 26C y EJEMPLO 173C en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,11 (s, 1H), 8,52 (d, 1H), 8,20 (d, 1H), 7,77 (dd, 1H), 7,52 (d, 1H), 7,32-7,38 (m, 4H), 7,03-7,07 (m, 4H), 6,81 (dd,, 1H), 6,58-6,60 (m, 1H), 6,36 (s, 1H), 6,14 (d, 1H), 4,44 (s, 1H), 3,92 (dd, 2H), 3,71 (br s, 1H), 3,41-3,43 (m, 2H), 3,02-3,06 (m, 4H), 2,55-2,72 (m, 6H), 2,18-2,24 (m, 2H), 1,91-2,00 (m, 8H), 1,76-1,80 (m, 2H), 1,63-1,65 (m, 2H), 1,49-1,51 (m, 2H), 1,35-1,38 (m, 2H), 0,92 (s, 6H).

EJEMPLO 220

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 215A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (500 MHz, dimetilsulfóxido-d_6) δ 11,14 (s, 1H), 8,15 (d, 1H), 8,04 (s, 1H), 7,95 (dd, 1H), 7,50 (t, 2H), 7,35 (m, 4H), 7,12 (d, 1H), 7,04 (d, 2H), 6,83 (dd, 1H), 6,61 (dd, 1H), 6,39 (m, 1H), 6,12 (d, 1H), 2,92 (m, 10H), 2,71 (s, 2H), 2,35 (s, 3H), 2,17 (m, 6H), 1,95 (s, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 221

4-(4-{[4'-cloro-4-(2-hidroxietoxi)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida

EJEMPLO 221A

2-(1H-indol-4–iloxi)-4-(4-((4-(2-(tert-butildimetilsililoxi)etoxi)-4'-clorobifenil-2–il)metil)piperazin-1–il)-N-(4-(1-metilpiperidin-4–ilamino)-3-nitrofenilsulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 213C en lugar de EJEMPLO 1E y EJEMPLO 21A en lugar de EJEMPLO 1F en el EJEMPLO 1G.

EJEMPLO 221B

4-(4-{[4'-cloro-4-(2-hidroxietoxi)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 221A en lugar de EJEMPLO 195B en el EJEMPLO 195. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,12 (s, 1H), 8,42 (d, 1H), 8,10 (d, 1H), 7,74 (dd, 1H), 7,58 (d, 1H), 7,40 (m, 4H), 7,21 (m, 1H), 7,06 (m, 4H), 6,90 (m, 2H), 6,65 (m, 1H), 6,31 (d, 1H), 6,23 (m, 2H), 4,84 (t, 1H), 4,00 (t, 2H), 3,71 (m, 3H), 3,24 (m, 4H), 3,02 (m, 6H), 2,66 (m, 2H), 2,32 (m, 5H), 2,00 (m, 2H), 1,69 (m, 2H).

EJEMPLO 222

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[3-(3-oxopiperazin-1–il)propil]amino}fenil)sulfonil]benzamida

EJEMPLO 222A

3-nitro-4-[3-(3-oxo-piperazin-1–il)-propilamino]-bencensulfonamida

Se agregó 4-(3-amino-propil)-piperazin-2-ona (3,45 g) y trietilamina (5,18 mL, 3,76 g) a 1,4-dioxano (100 mL) y N,N-dimetilacetamida (20 mL) y se mezcló hasta disolver. Se agregó 4-cloro-3-nitrobencensulfonamida (4,00 g), y la mezcla se calentó a 90°C durante 16 horas. La mezcla se enfrió y el solvente se eliminó al vacío. El material se purificó por recristalización a partir de metanol al 20% en diclorometano con subsiguiente lavado del sólido recristalizado con metanol al 10% en diclorometano seguido por el lavado con diclorometano al 100%.

EJEMPLO 222B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[3-(3-oxopiperazin-1–il)propil]amino}fenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 26C en lugar de EJEMPLO 1E y EJEMPLO 222A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,16 (br s, 1H), 8,85 (t, 1H), 8,58 (d, 1H), 7,79 (dd, 1H), 7,74 (br s, 1H), 7,51 (d, 1H), 7,43-7,37 (m, 2H), 7,34 (d, 2H), 7,16 (d, 1H), 7,07-7,01 (m, 3H), 6,86 (dd, 1H), 6,65, (d, 1H), 6,39 (t, 1H), 6,15 (d, 1H), 3,43 (q, 2H), 3,17 (t, 2H), 3,03 (m, 4H), 2,95 (s, 2H), 2,72 (s, 2H), 2,56 (t, 2H), 2,47 (t, 2H), 2,16 (m, 6H), 1,95 (br s, 2H), 1,79 (m, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 223

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(3-nitro-4-{[3-(3-oxopiperazin-1–il)propil]amino}fenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 1E y EJEMPLO 222A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,24 (br s, 1H), 8,83 (t, 1H), 8,50 (d, 1H), 7,75 (br s, 1H), 7,68 (dd, 1H), 7,53 (d, 1H), 7,34 (d, 2H), 7,28 (t, 1H), 7,18 (d, 1H), 7,04 (d, 2H), 7,02-6,94 (m, 2H), 6,71 (dd, 1H), 6,42 (d, 1H), 6,29-6,23 (m, 2H), 3,43 (q, 2H), 3,17 (m, 2H), 3,05 (m, 4H), 2,96 (s, 2H), 2,72 (s, 2H), 2,57 (t, 2H), 2,48 (t, 2H), 2,17 (m, 6H), 1,95 (br s, 2H), 1,79 (m, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 224

4-(4-{[2-(4-clorofenil)-5-hidroxiciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida

EJEMPLO 224A

2-cloro-5-hidroxiciclohex-1-encarbaldehido

Se agregó oxicloruro de fósforo (4,08 mL) a N,N-dimetilformamida fría (-10°C) (20 mL). La temperatura se mantuvo bajo 0°C. La agitación se continuó por otros 30 minutos antes de agregar 4-(tert-butildimetilsililoxi)ciclohexanona (10 g). La mezcla luego se agitó a temperatura ambiente por 2 horas antes se diluir con acetato de etilo (300 mL) y se lavó con agua (3x), salmuera y se secó sobre Na_2SO_4. Luego de la filtración y la concentración, el producto crudo se usó directamente en la reacción siguiente sin purificación adicional.

EJEMPLO 224B

2-(4-clorofenil)-5-hidroxiciclohex-1-encarbaldehido

A una mezcla de ácido 4-clorofenilborónico (6,88 g), EJEMPLO 224A (4,65 g), acetato de paladio(II) (131 mg), K_2CO_3 (18,24 g) y bromuro de tetrabutilamonio (14,18 g) se agregó agua (200 mL). La mezcla se agitó a 50°C durante 4 horas, se enfrió, y se diluyó con acetato de etilo (400 mL) y se lavó con agua (3x) y salmuera y se secó sobre Na_2SO_4. Luego de la filtración y la concentración, el residuo se cargó en una columna y se eluyó con acetato de etilo al 5-20% en hexano para dar el compuesto del título.

EJEMPLO 224C

2-(1H-indol-5–iloxi)-4-(4-((2-(4-clorofenil)-5-hidroxiciclohex-1-enil)metil)piperazin-1–il)benzoato de metilo

A una mezcla de EJEMPLO 224B (0,8 g) y EJEMPLO 150A (1,2 g) en diclorometano (20 mL) se agregó tetracetoxiborohidruro de sodio (1,2 g). La mezcla se agitó durante la noche. La mezcla se diluyó con acetato de etilo (200 mL) y se lavó con NaOH al 2%, agua y salmuera. Luego de secar sobre Na_2SO_4, el solvente se evaporó al vacío y el residuo se cargó en una columna y se eluyó con metanol al 5-10% en diclorometano para dar el compuesto del título.

EJEMPLO 224D

ácido 2-(1H-indol-5–iloxi)-4-(4-((2-(4-clorofenil)-5-hidroxiciclohex-1-enil)metil)piperazin-1–il)benzoico

A una mezcla de EJEMPLO 224C (1,78 g) en tetrahidrofurano (30 mL), metanol (10 mL) y agua (10 mL) se agregó $LiOH \cdot H_2O$ (0,262 g). La mezcla se agitó durante la noche. La mezcla luego se neutralizó con HCl acuoso al 5% y se extrajo con acetato de etilo (3x) y las capas orgánicas combinadas se lavaron con salmuera y se secó sobre Na_2SO_4. La evaporación del solvente dio el compuesto del título.

EJEMPLO 224E

4-(4-{[2-(4-clorofenil)-5-hidroxiciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 224D en lugar de EJEMPLO 1E y EJEMPLO 21A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,08 (s, 1H), 8,50 (d, 1H), 8,13 (d, 1H), 7,77 (dd, 1H), 7,52 (d, 1H), 7,34 (m, 4H), 7,04 (m, 4H), 6,78 (dd, 1H), 6,59 (dd, 1H), 6,35 (s, 1H), 6,13 (d, 1H), 4,59 (d, 1H), 3,74 (m, 2H), 3,39 (m, 1H), 3,03 (m, 7H), 2,68 (m, 3H), 2,41 (m, 4H), 2,17 (m, 7H), 2,00 (m, 3H), 1,71 (m, 3H).

EJEMPLO 225

4-(4-{[2-(4-clorofenil)-5-hidroxiciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 224D en lugar de EJEMPLO 1E y EJEMPLO 173C en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR

(300MHz, dimetilsulfóxido-d_6) δ 11,07 (s, 1H), 8,47 (d, 1H), 8,14 (d, 1H), 7,92 (s, 1H), 7,72 (dd, 1H), 7,52 (d, 1H), 7,46 (d, 1H), 7,33 (m, 4H), 7,07 (d, 2H), 6,98 (d, 1H), 6,77 (m, 1H), 6,58 (dd, 1H), 6,34 (s, 1H), 6,14 (d, 1H), 4,59 (m, 1H), 3,90 (dd, 2H), 3,70 (m, 1H), 3,01 (m, 8H), 2,71 (m, 6H), 2,56 (m, 8H), 2,19 (m, 4H), 1,94 (m, 3H), 1,56 (m, 3H).

EJEMPLO 226

4-(4-{[2-(4-clorofenil)-5-hidroxiciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 224D en lugar de EJEMPLO 1E y EJEMPLO 174A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,13 (s, 1H), 9,13 (s, 1H), 8,52 (d, 1H), 7,83 (dd, 1H), 7,53 (t, 2H), 7,36 (m, 4H), 7,09 (m, 3H), 6,83 (dd, 1H), 6,61 (dd, 1H), 6,38 (s, 1H), 6,12 (d, 1H), 4,59 (d, 1H), 3,75 (m, 1H), 2,81 (m, 12H), 2,27 (m, 12H), 1,79 (m, 4H).

EJEMPLO 227

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(2,3-dihidro-1H-inden-2–il)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida

EJEMPLO 227A

4-(1-indan-2–il-piperidin-4–ilamino)-3-nitro-bencensulfonamida

Se agregó 2-Aminoindano (12,84 g) y trietilamina (15,04 mL, 10,92 g) a 1,4-dioxano (150 mL) y la mezcla se agitó hasta que los sólidos se disolvieron. Se agregó 4-cloro-3-nitrobencensulfonamida (12,77 g), y la mezcla se calentó a 90°C durante 16 horas. La mezcla se enfrió y el precipitado se filtró al vacío, se lavó con metanol al 20% en diclorometano, y se lavó con 100% diclorometano.

EJEMPLO 227B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(2,3-dihidro-1H-inden-2–il)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 1E y EJEMPLO 227A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR

(300MHz, dimetilsulfóxido-d_6) δ 11,20 (br s, 1H), 8,48 (d, 1H), 8,21 (d, 1H), 7,73 (dd, 1H), 7,54 (d, 1H), 7,34 (d, 2H), 7,26-7,21 (m, 3H), 7,16-7,12 (m, 2H), 7,09-7,02 (m, 3H), 6,95 (t, 2H), 6,68 (dd, 1H), 6,39 (d, 1H), 6,24 (m, 2H), 3,74 (m, 1H), 3,18-2,80 (m, 13H), 2,72 (br s, 2H), 2,16 (m, 6H), 2,03 (m, 2H), 1,95 (br s, 2H), 1,68 (m, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 228

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(2,3-dihidro-1H-inden-2–il)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 26C en lugar de EJEMPLO 1E y EJEMPLO 227A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,12 (br s, 1H), 8,55 (d, 1H), 8,23 (d, 1H), 7,79 (dd, 1H), 7,51 (d, 1H), 7,41-7,31 (m, 4H), 7,22 (m, 2H), 7,16-7,09 (m, 3H), 7,07-7,01 (m, 3H), 6,83 (dd, 1H), 6,63 (dd, 1H), 6,37 (t, 1H), 6,15 (d, 1H), 3,73 (m, 1H), 3,16-2,82 (m, 13H), 2,71 (br s, 2H), 2,16 (m, 6H), 2,02 (m, 2H), 1,95 (br s, 2H), 1,67 (m, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 229

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(1-morfolin-4–ilciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó utilizando (1-morfolinociclohexil)metanamina en lugar de (3S,4R)-4-amino-1-bencilpiperidin-3-ol, ácido clorhídrico en el EJEMPLO 187B. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,19 (s, 1H), 9,08 (s, 1H), 8,60 (d, 1H), 7,81 (dd, 1H), 7,51 (d, 1H), 7,43 (d, 1H), 7,39 (t, 1H), 7,33 (d, 2H), 7,16-7,18 (m, 2H), 7,03 (d, 2H), 6,88 (dd, 1H), 6,65 (dd, 1H), 6,40 (s, 1H), 6,13 (d, 1H), 3,60 (s, 4H), 3,42-3,43 (m, 2H), 3,01 (br s, 4H), 2,72 (br s, 2H), 2,57 (br s, 4H), 2,12-2,16 (m, 7H), 1,94 (br s, 2H), 1,46-1,60 (m, 12H), 1,36-1,39 (m, 2H), 0,92 (s, 6H).

EJEMPLO 230

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[1-(1,3-tiazol-2–ilmetil)piperidin-4–il]amino}fenil)sulfonil]benzamida

EJEMPLO 230A

1-(tiazol-2–ilmetil)piperidin-4–ilcarbamato de tert-butilo

El compuesto del título se preparó utilizando tiazol-2-carbaldehido en lugar de EJEMPLO 27C y piperidin-4–ilcarbamato de tert-butilo en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 230B

1-(tiazol-2–ilmetil)piperidin-4-amina

El compuesto del título se preparó utilizando EJEMPLO 230A en lugar de EJEMPLO 1A en el EJEMPLO 1B.

EJEMPLO 230C

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[1-(1,3-tiazol-2–ilmetil)piperidin-4–il]amino}fenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 230B en lugar de (3S,4R)-4-amino-1-bencilpiperidin-3-ol, ácido clorhídrico en el EJEMPLO 187B. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,14 (s, 1H), 8,23 (d, 1H), 7,76-7,79 (m, 2H), 7,65 (s, 1H), 7,53 (d, 1H), 7,38-7,40 (m, 2H), 7,34 (d, 2H), 7,17 (d, 1H), 7,11 (s, 1H), 7,04 (d, 2H), 6,82 (dd, 1H), 6,62 (d, 1H), 6,38 (s, 1H), 6,14 (d, 1H), 4,19 (s, 2H), 3,01 (s, 4H), 2,91-2,96 (m, 2H), 2,72 (s, 2H), 2,12-2,17 (m, 6H), 1,95-1,99 (m, 4H), 1,47-1,51 (m, 2H), 1,36-1,39 (m, 2H), 0,92 (s, 6H).

EJEMPLO 231

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[1-(1,3-tiazol-4–ilmetil)piperidin-4–il]amino}fenil)sulfonil]benzamida

EJEMPLO 231A

1-(tiazol-4–ilmetil)piperidin-4–ilcarbamato de tert-butilo

El compuesto del título se preparó utilizando tiazol-4-carbaldehido en lugar de EJEMPLO 27C y piperidin-4–ilcarbamato de tert-butilo en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 231B

1-(tiazol-4–ilmetil)piperidin-4-amine

El compuesto del título se preparó utilizando EJEMPLO 231A en lugar de EJEMPLO 1A en el EJEMPLO 1B.

EJEMPLO 231C

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[1-(1,3-tiazol-4–ilmetil)piperidin-4–il]amino}fenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 231B en lugar de (3S,4R)-4-amino-1-bencilpiperidin-3-ol, ácido clorhídrico en el EJEMPLO 187B. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,11 (s, 1H), 9,06 (s, 1H), 8,21 (d, 1H), 7,98 (s, 1H), 7,77 (dd, 1H), 7,54 (d, 1H), 7,33-7,38 (m, 4H), 7,13 (d, 2H), 7,03-7,07 (m, 3H), 6,79 (dd, 1H), 6,60 (dd, 1H), 6,37 (s, 1H), 6,14 (d, 1H), 4,23 (s, 2H), 2,99 (s, 4H), 2,89-2,94 (m, 2H), 2,71 (s, 2H), 2,12-2,17 (m, 6H), 1,95-1,99 (m, 4H), 1,47-1,51 (m, 2H), 1,36-1,39 (m, 2H), 0,92 (s, 6H).

EJEMPLO 232

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[4-(hidroximetil)tetrahidro-2H-piran-4–il]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando (4-(aminometil)tetrahidro-2H-piran-4–il)metanol en lugar de (3S,4R)-4-amino-1-bencilpiperidin-3-ol, ácido clorhídrico en el EJEMPLO 187B. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,17 (s, 1H), 9,10 (t, 1H), 8,59 (d, 1H), 7,81 (dd, 1H), 7,51 (d, 1H), 7,42 (d, 1H), 7,39 (t, 1H), 7,16-7,18 (m, 2H), 7,03 (d, 2H), 6,87 (dd, 1H), 6,65 (d, 1H), 6,39 (s, 1H), 6,14 (d, 1H), 5,22 (t, 1H), 3,51-3,62 (m, 6H), 3,19 (d, 2H), 3,03 (s, 4H), 2,72 (s, 2H), 2,12-2,17 (m, 6H), 1,94 (s, 2H), 1,45-1,49 (m, 4H), 1,36-1,39 (m, 2H), 0,92 (s, 6H).

EJEMPLO 233

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(2-hidroxietil)piperazin-1–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida

EJEMPLO 233A

4-(4-(2-hidroxietil)piperazin-1–ilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando 2-(4-aminopiperazin-1–il)etanol en lugar de (tetrahidro-2H-piran-4–il)metanamina en el EJEMPLO 1F.

EJEMPLO 233B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(2-hidroxietil)piperazin-1–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 233A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (500 MHz, dimetilsulfóxido-d $_6$) δ 11,15 (s, 1H), 9,17 (m, 1H), 8,53 (d, 1H), 7,83 (dd, 1H), 7,56 (d, 1H), 7,51 (d, 1H), 7,36 (m, 4H), 7,13 (m, 1H), 7,03 (m, 2H), 6,84 (dd, 1H), 6,62 (dd, 1H), 6,38 (m, 1H), 6,12 (m, 1H), 4,57 (m, 1H), 3,54 (m, 2H), 2,95 (m, 10H), 2,71 (s, 2H), 2,57 (m, 2H), 2,15 (m, 6H), 1,94 (s, 2H), 1,38 (t, 2H), 0,93 (s, 6H)

EJEMPLO 234

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(3S)-1-metilpirrolidin-3–il]amino}-3-nitrofenil)sulfonil]benzamida

EJEMPLO 234A

(S)-1-metilpirrolidin-3–ilcarbamato de tert-butilo

A una mezcla de (S)-1-metilpirrolidin-3–ilcarbamato de tert-butilo (438 mg) en metanol (10 mL) se agregó una mezcla al 37% de formaldehido en agua (0,53 mL) y borohidruro de sodio (267 mg). La mezcla de reacción se agitó durante la noche a temperatura ambiente y luego se concentró. El residuo se disolvió en cloroformo (15 mL), se lavó con salmuera y solución de $NaHCO_3$, se secó sobre $MgSO_4$, se filtró y se concentró. El compuesto del título se usó en el siguiente paso sin purificación adicional.

EJEMPLO 234B

(S)-1-metilpirrolidin-3-amina

El compuesto del título se preparó utilizando EJEMPLO 234A en lugar de EJEMPLO 1A en el EJEMPLO 1B.

EJEMPLO 234C

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(3S)-1-metilpirrolidin-3–il]amino}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 234B en lugar de 1-(2-metoxi-etil)-piperidin-4–ilamina y EJEMPLO 310B en lugar de 4-cloro-3-nitrobencensulfonamida en el EJEMPLO 189A. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 10,98 (s, 1H), 8,38 (d, 1H), 8,16 (d, 1H), 7,64 (dd, 1H), 7,53 (d, 1H), 7,34 (d, 2H), 7,28 (m,

2H), 7,05 (d, 2H), 6,89 (d, 1H), 6,72 (d, 1H), 6,68 (dd, 1H), 6,53 (dd, 1H), 6,29 (t, 1H), 6,15 (d, 1H), 4,14 (br s, 1H), 2,93 (m, 4H), 2,71 (m, 4H), 2,33 (m, 2H), 2,27 (s, 3H), 2,16 (m, 6H), 1,95 (s, 2H), 1,61 (m, 1H), 1,38 (t, 2H), 1,24 (br s, 1H), 0,92 (s, 6H).

EJEMPLO 235

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(3-fluoropropil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida

EJEMPLO 235A

4-(1-(3-fluoropropil)piperidin-4–ilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando 1-fluoro-3-iodopropano en lugar de 1,1,1-trifluoro-4-yodobutano en el EJEMPLO 210A.

EJEMPLO 235B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(3-fluoropropil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 235A en lugar de EJEMPLO 1F y EJEMPLO 26C en lugar de EJEMPLO 1E en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,12 (s, 1H), 10,89 (br s, 1H), 8,48 (d, 1H), 8,152 (d, 1H), 7,79 (dd, 1H), 7,50 (d,1H), 7,34 (m, 4H), 7,03 (m, 4H), 6,83 (dd, 1H), 6,63 (dd, 1H), 6,37 (m, 1H), 6,15 (d, 1H), 3,71 (br s, 1H), 3,01 (m, 4H), 2,92 (m, 2H), 2,72 (m, 2H), 2,56 (m, 1H), 2,30 (m, 2H), 2,16 (m, 6H), 1,95 (m, 5H), 1,83 (m, 1H), 1,68 (m, 2H), 1,38 (m, 2H), 1,24 (br s, 1H), 0,92 (s, 6H).

EJEMPLO 236

4-[4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}-3-(hidroximetil)piperazin-1–il]-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 218E en lugar de EJEMPLO 26C en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,17 (s, 2H), 8,62 (s, 1H), 8,58 (s, 1H), 7,78 (d, 1H), 7,52 (d, 1H), 7,39-7,42 (m, 2H), 7,33 (d, 1H), 7,14 (s, 1H), 7,09 (d, 1H), 7,04 (d, 1H), 6,86 (d, 1H), 6,62 (d, 1H), 6,39 (s, 1H), 6,14 (s, 1H), 4,46 (m, 1H), 3,85 (dd, 2H), 3,17-3,25 (m, 8H), 2,76 (br s, 2H), 2,58 (br s. 2H), 1,89-2,01 (m, 6H), 1,80 (br, 2H), 1,29-1,38 (m, 2H), 0,91 (s, 6H).

EJEMPLO 237

N-[(4-{[(4-aminotetrahidro-2H-piran-4–il)metil]amino}-3-nitrofenil)sulfonil]-4-[4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}-3-(hidroximetil)piperazin-1–il]-2-(1H-indol-5–iloxi)benzamida

EJEMPLO 237A

4-((4-aminotetrahidro-2H-piran-4–il)metilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando 4-(aminometil)tetrahidro-2H-piran-4-amina en lugar de (tetrahidropiran-4–il)metilamina en el EJEMPLO 1F.

EJEMPLO 237B

N-[(4-{[(4-aminotetrahidro-2H-piran-4–il)metil]amino}-3-nitrofenil)sulfonil]-4-[4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}-3-(hidroximetil)piperazin-1–il]-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 218E en lugar de EJEMPLO 26C y EJEMPLO 237A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,46 (s, 1H), 11,19 (s, 1H), 8,16 (d, 1H), 8,51-8,55 (m, 1H), 8,11 (s, 2H), 7,88 (d, 1H), 7,53 (d, 1H), 7,32-7,43 (m, 5H), 7,15 (s, 1H), 7,09 (d, 1H), 6,85 (dd, 1H), 6,68 (s, 1H), 6,40 (s, 1H), 6,21 (s, 1H), 3,81-3,82 (m, 2H), 3,70-3,72 (m, 4H), 3,10 (br s, 2H), 2,02-2,09 (m, 2H), 1,60-1,85 (m, 2H), 1,66-1,73 (m, 2H), 1,35-1,38 (m, 2H), 0,93 (s, 6H).

EJEMPLO 238

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1-hidroxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando 1-(aminometil)ciclohexanol en lugar de (3S,4R)-4-amino-1-bencilpiperidin-3-ol, ácido clorhídrico en el EJEMPLO 187B. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,17 (s, 2H), 8,69 (t, 1H), 8,60 (d, 1H), 7,80 (dd, , 1H), 7,51 (d, 1H), 7,39-7,43 (m, 2H), 7,33 (d, 2H), 7,17 (d, 2H), 7,14 (d, 1H), 7,03 (d, 2H), 6,87 (dd, 1H), 6,65 (d, 1H), 6,40 (s, 1H), 6,14 (d, 1H), 4,73 (s, 1H), 3,03 (s, 4H), 2,74 (s, 2H), 2,12-2,18 (m, 6H), 1,94 (s, 2H), 1,54-1,58 (m, 4H), 1,36-1,43 (m, 7H), 0,92 (s, 6H).

EJEMPLO 239

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(2-metoxietil)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 179A en lugar de EJEMPLO 1F y EJEMPLO 55B en lugar de EJEMPLO 26C en el EJEMPLO 177. ^{1}H NMR (500 MHz, dimetilsulfóxido-d_6) δ11,25 (s, 2H), 8,57 (m, 1H), 8,50 (d, 1H), 7,70 (dd, 1H), 7,52 (d, 1H), 7,34 (d, 2H), 7,28 (t, 1H), 7,17 (d, 1H), 7,05 (m, 3H), 6,97 (t, 1H), 6,71 (dd, 1H), 6,42 (d, 1H), 6,26 (m, 2H), 3,58 (m, 4H), 3,31 (s, 3H), 3,05 (m, 4H), 2,73 (s, 2H), 2,17 (m, 6H), 1,96 (s, 2H), 1,38 (t, 2H), 0,93 (s, 6H)

EJEMPLO 240

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(hidroximetil)tetrahidro-2H-piran-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida

EJEMPLO 240A

4-(4-(hidroximetil)tetrahidro-2H-piran-4–ilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando (4-aminotetrahidro-2H-piran-4–il)metanol en lugar de (tetrahidropiran-4–il)metilamina y 4-fluoro-3-nitrobencensulfonamida en lugar de 4-cloro-3-nitrobencensulfonamida en el EJEMPLO 1F.

EJEMPLO 240B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(hidroximetil)tetrahidro-2H-piran-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 240A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,14 (s, 2H), 8,63 (d, 1H), 8,50 (s, 1H), 7,92 (s, 1H), 7,79 (dd, 1H), 7,52 (d, 1H), 7,39-7,43 (m, 2H), 7,33-7,34 (m, 3H), 7,18 (s, 1H), 7,03 (d, 2H), 6,87 (dd, 1H), 6,65 (dd, 1H), 6,40 (s, 1H), 6,13 (d, 1H), 5,04 (t, 1H), 3,67-3,72 (m, 4H), 3,56 (t, 2H), 3,02 (s, 4H), 2,72 (br, 2H), 2,12-2,16 (m, 6H), 1,94-2,01 (m, 3H), 1,81-1,85 (m, 2H), 1,36-1,39 (m, 2H), 1,24 (m, 6H), 0,92 (s, 6H).

EJEMPLO 241

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(hidroximetil)tetrahidro-2H-piran-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 240A en lugar de EJEMPLO 1F y EJEMPLO 55B en lugar de EJEMPLO 26 C en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,26 (s, 2H), 8,55 (d, J = 2,14 Hz, 1H), 8,48 (s, 1H), 7,66 (dd, 1H), 7,54 (d, 1H), 7,34 (d, 2H), 7,27-7,29 (m, 2H), 7,19 (d, 2H), 7,03 (d, 2H), 6,99 (t, 1H), 6,70 (dd, 1H), 6,44 (d, 1H), 6,27 (s, 1H), 5,04 (t, 1H), 3,67-3,72 (m, 4H), 3,56 (t, 2H), 3,04 (s, 4H), 2,74 (s, 2H), 2,12-2,17 (m, 6H), 1,95-2,01 (m, 5H), 1,80-1,85 (m, 2H), 1,38 (t, 2H), 1,24 (m, 4H), 0,92 (s, 6H).

EJEMPLO 242

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2-hidroxi-1-tetrahidro-2H-piran-4–iletil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando 2-amino-2-(tetrahidro-2H-piran-4–il)etanol en lugar de (3S,4R)-4-amino-1-bencilpiperidin-3-ol, ácido clorhídrico en el EJEMPLO 187B. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,18 (s, 1H), 8,60 (d, 1H), 8,57 (d, 1H), 7,79 (dd, 1H), 7,52 (d, 1H), 7,43 (d, 1H), 7,40 (t, 1H), 7,33 (d, 2H), 7,23 (d, 1H), 7,19 (d, 1H), 7,03 (d, 2H), 6,88 (dd, 1H), 6,65 (dd, 1H), 6,41 (s, 1H), 6,13 (d, 1H), 5,03 (t, 1H), 3,83-3,87 (m, 2H), 3,56-3,73 (m, 4H), 3,26 (t, 2H), 3,03 (s, 4H), 2,72 (s, 2H), 2,12-2,17 (br s, 4H), 1,58-1,62 (m, 2H), 1,36-1,39 (m, 2H), 0,92 (s, 6H).

EJEMPLO 243

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-({1-[2-(1H-pirazol-1–il)etil]piperidin-4–il}amino)fenil]sulfonil}benzamida

EJEMPLO 243A

4-(1-(2-(1H-pirazol-1–il)etil)piperidin-4–ilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando 1-(2-bromoetil)-1H-pirazol en lugar de 1,1,1-trifluoro-4-yodobutano en el EJEMPLO 210A. Luego de concentrar la mezcla de reacción, el compuesto del título se recogió por filtración de la lechada de éter.

EJEMPLO 243B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-({1-[2-(1H-pirazol-1–il)etil]piperidin-4–il}amino)fenil]sulfonil}benzamida

El compuesto del título se preparó utilizando EJEMPLO 243A en lugar de EJEMPLO 1F y EJEMPLO 26C en lugar de EJEMPLO 1E en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,25 (br s, 1H), 11,14 (s, 1H), 8,55 (d, 1H), 8,22 (d, 1H), 7,74 (m, 2H), 7,50 (d, 1H), 7,40 (m, 3H), 7,33 (d, 2H), 7,10 (m, 1H), 7,03 (d, 2H), 6,83 (dd, 1H), 6,63 (dd, 1H), 6,38 (t, 1H), 6,22 (t, 1H), 6,15 (d, 1H), 4,24 (t, 2H), 3,65 (br s, 1H), 3,02 (m, 4H), 2,78 (m, 6H), 2,27 (m, 2H), 2,16 (m, 6H), 1,94 (m, 3H), 1,60 (m, 2H), 1,38 (t, 2H), 1,23 (br s, 1H), 0,92 (s, 6H).

EJEMPLO 244

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 26 C en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,26 (s, 2H), 8,61 (t, 1H), 8,50 (d, 1H), 7,69 (dd, 1H), 7,28 (t, 1H), 7,18 (d, 2H), 7,07 (d, 1H), 7,04 (d, 2H), 6,97 (t, 1H), 6,71 (dd, 1H), 6,43 (d, 1H), 6,28 (d, 1H), 6,26 (d, 1H), 5,04 (t, 1H), 3,85 (dd, 2H), 3,25-3,31 (m, 6H), 3,05 (s, 4H), 2,74 (s, 2H), 2,14-2,18 (m, 6H), 1,87-1,90 (m, 2H), 1,61-1,63 (m, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 245

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(metilamino)-3-nitrofenil]sulfonil}benzamida

EJEMPLO 245A

4-(metilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando metanamina en lugar de (tetrahidro-2H-piran-4–il)metanamina en el EJEMPLO 1F.

EJEMPLO 245B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(metilamino)-3-nitrofenil]sulfonil}benzamida

El compuesto del título se preparó utilizando EJEMPLO 245A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (500 MHz, dimetilsulfóxido-d_6) δ 11,12 (m, 2H), 8,54 (m, 2H), 7,76 (m, 1H), 7,51 (d, 1H), 7,35 (m, 4H), 7,06 (m, 3H), 6,85 (m, 2H), 6,63 (d, 1H), 6,37 (m, 1H), 6,15 (d, 1H), 3,01 (m, 4H), 2,96 (d, 3H), 2,71 (s, 2H), 2,15 (m, 6H), 1,94 (s, 2H), 1,38 (t, 2H), 0,92 (s, 6H)

EJEMPLO 246

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[4-(metilamino)-3-nitrofenil]sulfonil}benzamida

El compuesto del título se preparó utilizando EJEMPLO 245A en lugar de EJEMPLO 1F y EJEMPLO 55B en lugar de EJEMPLO 26C en el EJEMPLO 177. ^{1}H NMR (500 MHz, dimetilsulfóxido-d_6) δ 11,32 (br s, 1H), 11,20 (br s, 1H), 8,54 (br s, 1H), 8,46 (s, 1H), 7,70 (dd, 1H), 7,53 (d, 1H), 7,34 (d, 2H), 7,26 (m, 1H), 7,14 (d, 1H), 7,04 (d, 2H), 6,94 (t, 1H), 6,87 (m, 1H), 6,67 (m, 1H), 6,37 (m, 1H), 6,25 (m, 2H), 3,02 (m, 4H), 2,97 (d, 3H), 2,72 (s, 2H), 2,16 (m, 6H), 1,94 (s, 2H), 1,38 (t, 2H), 0,93 (s, 6H).

EJEMPLO 247

4-{4-[1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 175E en lugar de EJEMPLO 1E y EJEMPLO 7A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (500 MHz, PIRIDINE-d_5) δ ppm 12,45 (s, 1H), 9,24 (d, 1H), 8,96 (t, 1H), 8,26 (dd, 1H), 8,16 (d, 1H), 7,65 (d, 1H), 7,46 (m, 5H), 7,35 (t, 1H), 7,30 (d, 2H), 7,24 (d, 1H), 7,15 (t, 1H), 6,86 (d, 1H), 6,79 (d, 1H), 6,74 (m, 2H), 6,61 (d, 1H), 3,78 (t, 4H), 3,41 (q, 1H), 3,31 (m, 2H), 2,94 (m, 4H), 2,34 (m, 6H), 2,24 (m, 2H), 2,10 (m, 2H), 1,72 (m, 2H), 1,15 (d, 3H).

EJEMPLO 248

4-(4-{[2-(4-clorofenil)-5-hidroxiciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 224D en lugar de EJEMPLO 1E en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,17 (s, 1H), 8,60 (m, 1H), 7,80 (dd, 1H), 7,52 (d, 1H), 7,38 (m, 4H), 7,11 (m, 4H), 6,87 (dd, 1H), 6,65

(dd, 1H), 6,40 (s, 1H), 6,13 (d, 1H), 4,59 (d, 1H), 3,85 (m, 2H), 3,28 (m, 6H), 3,03 (m, 2H), 2,72 (m, 2H), 2,18 (m, 3H), 1,87 (m, 3H), 1,53 (m, 5H), 1,26 (m, 7H).

EJEMPLO 249

4-(4-{[2-(4-clorofenil)-5-morfolin-4–ilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 249A

8-cloro-1,4-dioxaspiro[4,5]dec-7-en-7-carbaldehido

El compuesto del título se preparó utilizando 1,4-dioxaspiro[4,5]decan-8-ona en lugar de 4-(tert-butildimetilsililoxi)ciclohexanona en el EJEMPLO 224A.

EJEMPLO 249B

8-(4-clorofenil)-1,4-dioxaspiro[4,5]dec-7-ene-7-carbaldehido

El compuesto del título se preparó utilizando EJEMPLO 249A en lugar de EJEMPLO 224A en el EJEMPLO 224B.

EJEMPLO 249C

2-(1H-indol-5–iloxi)-4-(4-((8-(4-clorofenil)-1,4-dioxaspiro[4,5]dec-7-en-7–il)metil)piperazin-1–il)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 249B en lugar de EJEMPLO 224B en el EJEMPLO 224C.

EJEMPLO 249D

ácido 2-(1H-indol-5–iloxi)-4-(4-((8-(4-clorofenil)-1,4-dioxaspiro[4,5]dec-7-en-7–il)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 249C en lugar de EJEMPLO 224C en el EJEMPLO 224D.

EJEMPLO 249E

2-(1H-indol-5–iloxi)-4-(4-((8-(4-clorofenil)-1,4-dioxaspiro[4,5]dec-7-en-7–il)metil)piperazin-1–il)-N-(3-nitro-4-((tetrahidro-2H-piran-4–il)metilamino)fenilsulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 249D en lugar de EJEMPLO 1E en el EJEMPLO 1G.

EJEMPLO 249F

2-(1H-indol-5–iloxi)-4-(4-((2-(4-clorofenil)-5-oxociclohex-1-enil)metil)piperazin-1–il)-N-(3-nitro-4-((tetrahidro-2H-piran-4–il)metilamino)fenilsulfonil)benzamida

Una mezcla de EJEMPLO 249E (20 mg) y p-toluensulfonato de piridinio (16,8 mg) en acetona/H_2O (1:1, 3 mL) se calentó en un microondas a 135°C durante 8 minutos. La mezcla se diluyó con diclorometano (100 mL), se lavó con agua y salmuera, y se secó sobre Na_2SO_4. La filtración y la evaporación del solvente dieron el producto.

EJEMPLO 249G

4-(4-{[2-(4-clorofenil)-5-morfolin-4–ilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

A una mezcla de EJEMPLO 249F (120 mg) en diclorometano (2 mL) y metanol (0,5 mL) se agregó morfolina (37mg) y complejo 2-picolino borano (15,04 mg). La mezcla se agitó durante la noche. La mezcla luego se diluyó con diclorometano (200 mL) y se lavó con $NaHCO_3$ acuoso, agua, y salmuera, y se secó sobre Na_2SO_4. El residuo, luego de la evaporación del solvente, se disolvió en diclorometano y se cromatografió con NH_3 7N al 0-10% en metanol al 5% en diclorometano para dar el compuesto del título. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,15 (s, 1H), 8,58 (m, 2H), 7,79 (dd, 1H), 7,53 (m, 1H), 7,35 (m, 4H), 7,17 (m, 1H), 7,07 (m, 2H), 6,85 (dd, 1H), 6,64 (dd, 1H), 6,39 (s, 1H), 6,13 (d, 1H), 3,84 (m, 2H), 3,58 (m, 5H), 3,01 (m, 5H), 2,63 (m, 6H), 2,10 (m, 14H), 1,61 (m, 3H), 1,26 (m, 3H).

EJEMPLO 250

N-[(4-{[(1-aminociclohexil)metil]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando 1-(aminometil)ciclohexanamina, ácido clorhídrico en lugar de (3S,4R)-4-amino-1-bencilpiperidin-3-ol, ácido clorhídrico en el EJEMPLO 187B. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,04 (s, 1H), 8,47 (d, 1H), 8,39 (s, 1H), 7,79 (dd, 1H), 7,55 (d, 1H), 7,31-7,34 (m, 4H), 6,99-7,08 (m, 4H), 6,73 (dd, 1H), 6,65 (dd, 1H), 6,33 (s, 1H), 6,12 (d, 1H), 3,55 (d, 2H), 2,94 (s, 4H), 2,71 (s, 2H), 2,14-2,17 (m, 6H), 1,95 (s, 2H), 1,50-1,64 (m, 8H), 1,36-1,39 (m, 2H), 0,92 (s, 6H).

EJEMPLO 251

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[2-(2-oxopirrolidin-1–il)etil]amino}fenil)sulfonil]benzamida

El compuesto del título se preparó utilizando 1-(2-aminoetil)pirrolidin-2-ona en lugar de (3S,4R)-4-amino-1-bencilpiperidin-3-ol, ácido clorhídrico en el EJEMPLO 187B. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,17 (s, 1H), 8,58-8,60 (m, 2H), 7,84 (dd, 1H), 7,51 (d, 1H), 7,39-7,32 (m, 2H), 7,33 (d, 2H), 7,18 (d, 1H), 7,12 (d, 1H), 7,03 (d, 2H), 6,87 (dd, 1H), 6,65 (dd, 1H), 6,40 (s, 1H), 6,17 (d, 1H), 3,53-3,56 (m, 2H), 3,45 (t, 2H), 3,39 (t, 2H), 3,04 (s, 4H), 2,74 (s, 2H), 2,11-2,18 (m, 8H), 1,94 (s, 2H), 1,83-1,90 (m, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 252

4-{4-[1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 252A

2-(1H-indol-5–iloxi)-4-(4-(1-(4'-clorobifenil-2–il)etil)piperazin-1–il)benzoato de metilo

El compuesto del título se preparó como se describe en el EJEMPLO 175D reemplazando 2-(1H-indol-4–iloxi)-4-fluorobenzoato de etilo con EJEMPLO 26A.

EJEMPLO 252B

ácido 2-(1H-indol-5–iloxi)-4-(4-(1-(4'-clorobifenil-2–il)etil)piperazin-1–il)benzoico

El compuesto del título se preparó como se describe en el EJEMPLO 175E reemplazando EJEMPLO 175D con v 252A.

EJEMPLO 252C

4-{4-[1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 175F reemplazando EJEMPLO 175E con EJEMPLO 252B. ^{1}H NMR (500 MHz, dimetilsulfóxido-d_6) δ 11,20 (s, 1H), 11,16 (s, 1H), 8,62 (t, 1H), 8,58 (d, 1H), 7,79 (dd, 1H), 7,48 - 7,54 (m, 2H), 7,45 (d, 2H), 7,35 - 7,41 (m, 3H), 7,25 - 7,29 (m, 3H), 7,15 (d, 1H), 7,08 - 7,13 (m, 2H), 6,86 (dd, 1H), 6,63 (dd, 1H), 6,38 (s, 1H), 6,13 (d, 1H), 3,85 (dd, 2H), 3,22 - 3,32 (m, 4H),

3,00 (s, 4H), 2,33 (s, 2H), 2,18 (s, 2H), 1,84 - 1,95 (m, 1H), 1,56 - 1,66 (m, 2H), 1,21 - 1,31 (m, 3H), 1,16 (d, 3H).

EJEMPLO 253

4-(4-{1-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]etil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 253A

1-(2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)etanol

A una mezcla de EJEMPLO 218A (3,52 g) en tetrahidrofurano (30 ml) se agregó lentamente cloruro de metilmagnesio (3 M en tetrahidrofurano, 7,08 ml) a -78ºC. Luego de completarse la adición, la mezcla de reacción se agitó a 0ºC durante 30 minutos y se agregó hielo-agua. La mezcla resultante se extrajo con diclorometano y la capa orgánica se secó sobre Na_2SO_4 y se concentró. El residuo se purificó por cromatografía flash, eluyendo con diclorometano al 0-100% en hexano para dar el compuesto del título.

EJEMPLO 253B

1-(2-(4-clorofenil)-4, 4-dimetilciclohex-1-enil)etanona

A una mezcla de EJEMPLO 253A (1,18 g) en diclorometano (20 ml) se agregó lentamente Periodinano de Dess-Martin (2,457 g). La mezcla de reacción se agitó a temperatura ambiente durante 3 horas y se diluyó con éter. La mezcla resultante se lavó con NaOH acuoso y agua. La capa orgánica se secó sobre Na_2SO_4 y se concentró. El residuo se purificó por cromatografía flash, eluyendo con diclorometano al 0-100% en hexano para dar el compuesto del título.

EJEMPLO 253C

4-(1-(2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)etil)piperazin-1-carboxilato de tert-butilo

Se trató EJEMPLO 253B (2,06 g) y piperazin-1-carboxilato de tert-butilo (2,92 g) con isopropóxido de titanio(IV) (4,59 ml) a temperatura ambiente durante 24 horas. Se agregó cianoborohidruro de sodio (0,493 g) en metanol (10 ml). La mezcla de reacción se agitó durante la noche y se agregó NaOH acuoso. La mezcla resultante se diluyó con acetato de etilo (300 ml). El precipitado se retiró por filtración y se lavó con acetato de etilo. La capa orgánica se separó y se lavó con salmuera, se secó sobre Na_2SO_4, se filtró, y se concentró. El

residuo se disolvió en diclorometano y se cargó en una columna de gel de sílice, se eluyó con acetato de etilo al 0-25% en diclorometano para dar el compuesto del título.

EJEMPLO 253D

1-(1-(2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)etil)piperazina

El compuesto del título se preparó como se describe en el EJEMPLO 175C reemplazando EJEMPLO 175B con EJEMPLO 253C.

EJEMPLO 253E

2-(1H-indol-5–iloxi)-4-(4-(1-(2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)etil)piperazin-1–il)benzoato de etilo

El compuesto del título se preparó como se describe en el EJEMPLO 175D reemplazando 2-(1H-indol-4–iloxi)-4-fluorobenzoato de etilo y EJEMPLO 175C con EJEMPLO 26A y EJEMPLO 253D, respectivamente.

EJEMPLO 253F

ácido 2-(1H-indol-5–iloxi)-4-(4-(1-(2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)etil)piperazin-1–il)benzoico

El compuesto del título se preparó como se describe en el EJEMPLO 175E reemplazando EJEMPLO 175D con EJEMPLO 253E.

EJEMPLO 253G

4-(4-{1-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]etil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 177 reemplazando EJEMPLO 26C con EJEMPLO 253F. ^{1}H NMR (500 MHz, dimetilsulfóxido-d$_6$) δ 11,18 (s, 2H), 8,62 (t, 1H), 8,59 (d, 1H), 7,81 (dd, 1H), 7,52 (d, 1H), 7,38 - 7,44 (m, 2H), 7,34 (d, 2H), 7,17 (d, 1H), 7,11 (d, 1H), 7,01 (d, 2H), 6,87 (dd, 1H), 6,65 (dd, 1H), 6,40 (t, 1H), 6,13 (d, 1H), 3,85 (dd, 2H), 3,22 - 3,31 (m, 4H), 3,02 (s, 4H), 2,57 - 2,73 (m, 1H), 2,23 (s, 4H), 1,78 - 2,15 (m, 5H), 1,57 - 1,65 (m, 2H), 1,32 - 1,42 (m, 2H), 1,19 - 1,31 (m, 2H), 1,01 (d, 3H), 0,91 (d, 6H).

EJEMPLO 254

4-(4-{1-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]etil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 175F reemplazando EJEMPLO 175E y EJEMPLO 1F con EJEMPLO 253F y EJEMPLO 174A. ^{1}H NMR (500 MHz, dimetilsulfóxido-d $_6$) δ 11,15 (s, 1H), 9,19 (s, 1H), 8,54 (d, 1H), 7,85 (dd, 1H), 7,57 (d, 1H), 7,52 (d, 1H), 7,37 - 7,41 (m, 2H), 7,34 (d, 2H), 7,14 (d, 1H), 7,01 (d, 2H), 6,84 (dd, 1H), 6,62 (dd, 1H), 6,39 (s, 1H), 6,12 (d, 1H), 2,81 - 3,04 (m, 10H), 2,58 - 2,67 (m, 1H), 2,29 - 2,45 (m, 5H), 2,15 - 2,28 (m, 4H), 1,92 - 2,13 (m, 3H), 1,82 (d, 1H), 1,29 - 1,41 (m, 2H), 1,00 (d, 3H), 0,91 (d, 6H).

EJEMPLO 255

4-{4-[(1R)-1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se obtuvo mediante la separación de la mezcla racémica de EJEMPLO 175F en una HPLC quiral. ^{1}H NMR (500 MHz, dimetisulfóxido-d_6) δ 11,31 (1H, s), 11,25 (1H, s), 8,62 (1H, t), 8,50 (1H, d), 7,68 (1H, dd), 7,53 (2H, d), 7,46 (2H, d), 7,37 (1H, t), 7,24 - 7,31 (4H, m), 7,17 (1H, d), 7,12 (1H, dd), 7,07 (1H, d), 6,96 (1H, t), 6,69 (1H, dd), 6,42 (1H, d), 6,26 (2H, s), 3,85 (2H, dd), 3,21 - 3,33 (5H, m), 3,01 (4H, s), 2,29 - 2,39 (2H, m), 2,15 - 2,22 (2H, m), 1,83 - 1,94 (1H, m), 1,57 - 1,68 (2H, m), 1,22 - 1,31 (2H, m), 1,17 (3H, d).

EJEMPLO 256

4-{4-[(1S)-1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se obtuvo mediante la separación de la mezcla racémica de EJEMPLO 175F en una HPLC quiral. ^{1}H NMR (500 MHz, dimetisulfóxido-d_6) δ11,31 (1H, s), 11,25 (1H, s), 8,62 (1H, t), 8,50 (1H, d), 7,68 (1H, dd), 7,53 (2H, d), 7,46 (2H, d), 7,37 (1H, t), 7,24 - 7,31 (4H, m), 7,17 (1H, d), 7,12 (1H, dd), 7,07 (1H, d), 6,96 (1H, t), 6,69 (1H, dd), 6,42 (1H, d), 6,26 (2H, s), 3,85 (2H, dd), 3,21 - 3,33 (5H, m), 3,01 (4H, s), 2,29 - 2,39 (2H, m), 2,15 - 2,22 (2H, m), 1,83 - 1,94 (1H, m), 1,57 - 1,68 (2H, m), 1,22 - 1,31 (2H, m), 1,17 (3H, d).

EJEMPLO 257

4-(4-{1-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]etil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 175F reemplazando EJEMPLO 175E y EJEMPLO 1F con EJEMPLO 253F y EJEMPLO 7A. ^{1}H NMR (500 MHz, dimetilsulfóxido-d_6) δ 8,79 (t, 1H), 8,57 (d, 1H), 7,80 (dd, 1H), 7,51 (d, 1H), 7,37 - 7,44 (m, 2H), 7,34 (d, 2H), 7,15 (d, 1H), 7,06 (d, 1H), 7,01 (d, 2H), 6,85 (dd, 1H), 6,63 (dd, 1H), 6,39 (s, 1H), 6,13 (d, 1H), 3,60 (t, 4H), 3,43 (q, 2H), 3,01 (s, 4H), 2,63 (d, 1H), 2,33 - 2,47 (m, 6H), 2,22 (d, 4H), 1,94 - 2,15 (m, 3H), 1,75 - 1,86 (m, 3H), 1,32 - 1,40 (m, 2H), 1,00 (d, 3H), 0,91 (s, 3H), 0,90 (s, 3H).

EJEMPLO 258

4-(4-{1-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]etil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 175F reemplazando EJEMPLO 175E y EJEMPLO 1F con EJEMPLO 253F y EJEMPLO 173C. ^{1}H NMR (500 MHz, dimetilsulfóxido-d_6) δ 11,12 (s, 1H), 8,53 (d, 1H), 8,19 (d, 1H), 7,79 (dd, 1H), 7,52 (d, 1H), 7,32 - 7,40 (m, 4H), 6,99 - 7,12 (m, 4H), 6,81 (dd, 1H), 6,60 (dd, 1H), 6,37 (s, 1H), 6,13 (d, 1H), 3,92 (dd, 2H), 3,72 (s, 1H), 3,26 - 3,31 (m, 2H), 2,98 (s, 6H), 2,77 (s, 1H), 2,54 - 2,66 (m, 3H), 2,15 - 2,30 (m, 4H), 1,94 - 2,14 (m, 5H), 1,73 - 1,87 (m, 3H), 1,57 - 1,68 (m, 2H), 1,44 - 1,54 (m, 2H), 1,31 - 1,40 (m, 2H), 1,00 (d, 3H), 0,91 (d, 2H).

EJEMPLO 259

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(ciclohexilmetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida

EJEMPLO 259A

4-(ciclohexilmetilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando ciclohexilmetilamina en lugar de (tetrahidropiran-4–il)metilamina en el EJEMPLO 1F.

EJEMPLO 259B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(ciclohexilmetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 259A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,10 (s, 1H), 8,53 (m, 1H), 8,52 (d, 1H), 7,72 (dd, 1H), 7,44 (d, 1H), 7,32, (d, 1H), 7,31 (dd, 1H), 7,26 (d, 2H), 7,08 (d, 1H), 6,99 (d, 1H), 6,96 (d, 2H), 6,80 (dd, 1H), 6,58 (dd, 1H), 6,32 (s, 1H), 6,07 (d, 1H), 3,18 (t, 2H), 2,96 (br m, 4H), 2,65 (d, 2H), 2,06 (br m, 6H), 1,87 (s, 2H), 1,63 (m, 4H), 1,56 (m, 2H), 1,30 (t, 2H), 1,11 (m, 2H), 0,91 (m, 3H), 0,85 (s, 6H).

EJEMPLO 260

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(morfolin-4–ilamino)-3-nitrofenil]sulfonil}benzamida

EJEMPLO 260A

4-(morfolinoamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando morfolin-4-amina en lugar de 1-(2-metoxi-etil)-piperidin-4–ilamina en el EJEMPLO 189A.

EJEMPLO 260B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(morfolin-4–ilamino)-3-nitrofenil]sulfonil}benzamida

El compuesto del título se preparó utilizando EJEMPLO 26C en lugar de EJEMPLO 1E y EJEMPLO 260A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (500 MHz, piridina-d5) δ 9,28 (s, 1H), 9,25 (d, 1H), 8,39 (dd, 1H), 8,18 (d, 1H), 7,66 (d, 1H), 7,52 - 7,56 (m, 2H), 7,40 - 7,46 (m, 3H), 7,09 (dd, 1H), 7,06 (d, 2H), 6,73 (dd, 1H), 6,60 (s, 1H), 6,54 (d, 1H), 3,87 (s, 2H), 3,74 (d, 2H), 3,00 - 3,08 (m, 4H), 2,89 (d, 4H), 2,76 (s, 2H), 2,24 (t, 2H), 2,08 - 2,15 (m, 4H), 1,97 (s, 2H), 1,38 (t, 2H), 0,93 (s, 6H).

EJEMPLO 261

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-3–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 175F reemplazando EJEMPLO 175E y EJEMPLO 1F con EJEMPLO 26C y EJEMPLO 180A, respectivamente. ^{1}H NMR (500 MHz, dimetilsulfóxido-d_6) δ 11,17 (s, 2H), 8,45 - 8,70 (m, 2H), 7,80 (dd, 1H), 7,51 (d, 1H), 7,38 - 7,42 (m, 2H), 7,33 (d, 2H), 7,16 (d, 1H), 7,07 (d, 1H),

7,03 (d, 2H), 6,86 (dd, 1H), 6,65 (dd, 1H), 6,39 (s, 1H), 6,14 (d, 1H), 3,79 (dd, 1H), 3,68 - 3,75 (m, 1H), 3,23 - 3,38 (m, 3H), 3,18 (dd, 1H), 3,03 (s, 4H), 2,72 (s, 2H), 2,07 - 2,21 (m, 6H), 1,79 - 1,96 (m, 4H), 1,57 - 1,64 (m, 1H), 1,41 - 1,51 (m, 1H), 1,37 (t, 2H), 1,22 - 1,33 (m, 1H), 0,92 (s, 6H).

EJEMPLO 262

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[4-(morfolin-4–ilamino)-3-nitrofenil]sulfonil}benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 1E y EJEMPLO 260A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (500 MHz, piridina-d5) δ 12,45 (s, 1H), 9,26 (s, 1H), 9,17 (d, 1H), 8,27 (dd, 1H), 8,17 (d, 1H), 7,61 (d, 1H), 7,48 (t, 1H), 7,45 (d, 2H), 7,39 (d, 1H), 7,05 - 7,13 (m, 3H), 6,71 - 6,81 (m, 3H), 6,67 (d, *J*=2,1 Hz, 1H), 3,87 (s, 2H), 3,61 - 3,78 (m, 2H), 2,99 - 3,08 (m, 4H), 2,89 (d, 4H), 2,76 (s, 2H), 2,25 (t, 2H), 2,08 - 2,16 (m, 4H), 1,97 (s, 2H), 1,39 (t, 2H), 0,94 (s, 6H).

EJEMPLO 263

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(tetrahidro-2H-piran-4–ilamino)fenil]sulfonil}benzamida

El compuesto del título se preparó utilizando tetrahidro-2H-piran-4-amina, ácido clorhídrico en lugar de (3S,4R)-4-amino-1-bencilpiperidin-3-ol, ácido clorhídrico en el EJEMPLO 187B. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,15 (s, 2H), 8,57 (d, 1H), 8,24 (d, 1H), 7,78 (dd, 1H), 7,49 (d, 1H), 7,37-7,40 (m, 3H), 7,32 (d, 2H), 7,12-7,16 (m, 2H), 7,22 (d, 2H), 6,84 (dd, 1H), 6,64 (dd, 1H), 6,37 (s, 1H), 6,13 (d, 1H), 3,85-3,87 (m, 2H), 3,45 (t, 2H), 3,02 (s, 4H), 2,71 (s, 2H), 2,11-2,16 (m, 7H), 1,87-1,93 (m 4H), 1,58-1,62 (m, 2H), 1,36 (t, 2H), 0,90 (s, 6H).

EJEMPLO 264

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(3-metiloxetan-3–il)metil]amino}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó utilizando (3-metiloxetan-3–il)metanamina en lugar de (3S,4R)-4-amino-1-bencilpiperidin-3-ol, ácido clorhídrico en el EJEMPLO 187B. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,14 (s, 2H), 8,67 (t, 1H), 8,58 (d, 1H), 7,81 (dd, 1H), 7,49 (d, 1H), 7,36-7,39 (m, 2H), 7,32 (d, 2H), 7,12-7,14 (m, 2H), 7,02 (d, 2H), 6,84 (dd,

1H), 6,63 (dd, 1H), 6,37 (s, 1H), 6,13 (d, 1H), 4,44 (d, 2H), 4,30 (d, 2H), 3,55 (d, 2H), 3,01 (s, 4H), 2,70 (s, 2H), 2,11-2,15 (m, 7H), 1,93 (s 3H), 1,36 (t, 2H), 0,90 (s, 6H).

EJEMPLO 265

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-metoxiciclohexil)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando 4-metoxiciclohexanamina en lugar de (3S,4R)-4-amino-1-bencilpiperidin-3-ol, ácido clorhídrico en el EJEMPLO 187B. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,16 (s, 2H), 8,83 (d, 1H), 8,30 (d, 1H), 7,79 (dd, 1H), 7,50 (d, 1H), 7,37-7,41 (m, 2H), 7,33 (d, 2H), 7,10-7,14 (m, 2H), 7,03 (d, 2H), 6,85 (dd, 1H), 6,65 (dd, 1H), 6,39 (s, 1H), 6,14 (d, 1H), 3,24-3,25 (m, 5H), 3,03 (s, 4H), 2,72 (s, 2H), 2,14-2,17 (m, 8H), 1,92 (m 3H), 1,63-1,65 (m,2 H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 266

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[3-(1,1-dioxidotiomorfolin-4–il)propil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 187A en lugar de 4-cloro-3-nitrobenceno sulfonamida y 4-(3-aminopropil)tiomorfolin-1,1-dióxido en lugar de 1-(2-metoxi-etil)-piperidin-4–ilamina en el EJEMPLO 189A. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,16 (s, 1H), 8,86 (t, 1H), 8,58 (d, 1H), 7,82 (dd, 1H), 7,50 (t, 1H), 7,40 (m, 2H), 7,33 (d, 2H), 7,15 (m, 1H), 7,04 (m, 3H), 6,85 (dd, 1H), 6,64 (m, 1H), 6,38 (m, 1H), 6,13 (m, 1H), 3,43 (m, 2H), 3,12 (m, 4H), 3,01 (m, 4H), 2,89 (m, 4H), 2,72 (m, 2H), 2,57 (t, 2H), 2,16 (m, 6H), 1,94 (m, 2H), 1,78 (t, 2H), 1,37 (t, 2H), 0,93 (s, 6H).

EJEMPLO 267

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[2-(2-oxopiperidin-1–il)etil]amino}fenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 187A en lugar de 4-cloro-3-nitrobenceno sulfonamida y 1-(2-aminoetil)piperidin-2-ona en lugar de 1-(2-metoxi-etil)-piperidin-4–ilamina en el EJEMPLO 189A. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,12 (s, 1H), 8,61 (m, 1H), 8,52 (m, 1H), 7,78 (d, 1H), 7,51 (d, 1H), 7,37 (m, 2H), 7,33 (d, 2H), 7,10 (m, 2H), 7,04 (d, 2H), 6,81 (m, 1H), 6,61 (d, 1H), 6,37 (s, 1H), 6,13 (d, 1H), 3,52

(m, 4H), 3,28 (t, 2H), 3,00 (m, 4H), 2,71 (m, 2H), 2,17 (m, 8H), 1,94 (m, 2H), 1,63 (m, 4H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 268

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[2-(2-oxoimidazolidin-1–il)etil]amino}fenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 187A en lugar de 4-cloro-3-nitrobenceno sulfonamida y 1-(2-aminoetil)-2-imidazolidona en lugar de 1-(2-metoxi-etil)-piperidin-4–ilamina en el EJEMPLO 189A. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,17 (s, 1H), 8,60 (t, 1H), 8,56 (d, 1H), 7,81 (dd, 1H), 7,50 (m, 1H), 7,39 (m, 2H), 7,33 (d, 2H), 7,15 (m, 1H), 7,08 (d, 1H), 7,02 (d, 2H), 6,85 (dd, 1H), 6,65 (m, 1H), 6,39 (m, 2H), 6,15 (m, 1H), 3,51 (m, 2H), 3,39 (t, 2H), 3,30 (m, 2H), 3,21 (t, 2H), 3,03 (m, 4H), 2,72 (m, 2H), 2,14 (m, 6H), 1,93 (m, 2H), 1,37 (t, 2H), 0,92 (s, 6H).

EJEMPLO 269

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(2-piridin-4–iletil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando 4-(2-aminoetil)piridina en lugar de 1-(2-metoxietil)-piperidin-4–ilamina y EJEMPLO 187A en lugar de 4-cloro-3-nitrobencensulfonamida en el EJEMPLO 189A, excepto que el material se purificó mediante HPLC preparativa en una columna Fenomenex Luna C8(2) 5 um 100Å AXIA (30mm × 75mm). Se usó un gradiente de acetonitrilo y ácido trifluoroacético al 0,1% en agua, a una velocidad de flujo de 50 mL/minuto (0-0,5 minutos acetonitrilo al 10%, 0,5-6,0 minutos gradiente lineal de acetonitrilo al 10-100%, 6,0-7,0 minutos acetonitrilo al 100%, 7,0-8,0 minutos gradiente lineal de acetonitrilo al 100-10%) para aislar el compuesto del título como la sal bis de ácido trifluoroacético. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,45 (br s, 1H), 11,18 (br s, 1H), 8,77 (d, 2H), 8,61 (t, 1H), 8,60 (d, 1H), 7,86 (dd, 1H), 7,84 (d, 2H), 7,54 (d, 1H), 7,43-7,37 (m, 4H), 7,22 (d, 1H), 7,15 (d, 1H), 7,08 (d, 2H), 6,85 (dd, 1H), 6,70 (dd, 1H), 6,38 (t, 1H), 6,22 (d, 1H), 3,77 (q, 2H), 3,68-3,54 (m, 4H), 3,27 (m, 2H), 3,16 (t, 2H), 3,00 (m, 2H), 2,74 (m, 2H), 2,18 (m, 2H), 2,01 (d, 2H), 1,45 (t, 2H), 0,94 (s, 6H).

EJEMPLO 270

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-morfolin-4–il-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 187A en lugar de 4-cloro-3-nitrobencensulfonamida y morfolina en lugar de 1-(2-metoxi-etil)-piperidin-4–ilamina en el EJEMPLO 189A, excepto que el material crudo se purificó mediante HPLC preparativa usando una columna C18, 250 x 50 mm, 10□, y eluyendo con un gradiente de 20-100% CH_3CN vs. ácido trifluoroacético al 0,1% en agua, para dar el compuesto del título como una sal trifluoroacetato. La sal se disolvió en diclorometano (6 mL) y se lavó con $NaHCO_3$ acuoso al 50%. La capa orgánica se secó sobre Na_2SO_4 anhidro, se filtró, y se concentró para dar el compuesto del título. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,17 (s, 1H), 8,31 (d, 1H), 7,87 (dd, 1H), 7,53 (d, 1H), 7,41 (m, 2H), 7,33 (d, 2H), 7,24 (d, 1H), 7,16 (s, 1H), 7,02 (d, 2H), 6,85 (dd, 1H), 6,64 (dd, 1H), 6,40 (s, 1H), 6,14 (s, 1H), 3,69 (t, 4H), 3,13 (t, 4H), 3,03 (br s, 4H), 2,75 (s, 2H), 2,19 (br s, 4H), 2,14 (br t, 2H), 1,95 (s, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 271

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(4-metoxipiperidin-1–il)-3-nitrofenil]sulfonil}benzamida

El compuesto del título se preparó utilizando EJEMPLO 187A en lugar de 4-cloro-3-nitrobencensulfonamida y 4-metoxi-piperidina en lugar de 1-(2-metoxi-etil)-piperidin-4–ilamina en el EJEMPLO 189A, excepto que el material crudo se purificó mediante HPLC preparativa usando una columna C18, 250 x 50 mm, 10□, y eluyendo con un gradiente de CH_3CN al 20-100% vs. ácido trifluoroacético al 0,1% en agua, para dar el producto como una sal trifluoroacetato. La sal se disolvió en diclorometano (6 mL) y se lavó con $NaHCO_3$ acuoso al 50%. La capa orgánica se secó sobre Na_2SO_4 anhidro , se filtró, y se concentró para dar el compuesto del título. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,17 (s, 1H), 8,28 (d, 1H), 7,81 (dd, 1H), 7,53 (d, 1H), 7,41 (m, 2H), 7,33 (d, 2H), 7,22 (d, 1H), 7,16 (s, 1H), 7,04 (d, 2H), 6,86 (dd, 1H), 6,64 (dd, 1H), 6,40 (s, 1H), 6,14 (s, 1H), 3,42 (m, 1H), 3,27 (s, 3H), 3,25 (m, 2H), 3,00 (m, 6H), 2,73 (s, 2H), 2,18 (br s, 4H), 2,13 (br t, 2H), 1,94 (s, 2H), 1,91 (m, 2H), 1,56 (m, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 272

4-(4-{[2-(4-clorofenil)-5-pirrolidin-1–ilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando pirrolidina en lugar de morfolina en el EJEMPLO 249G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,04 (s, 1H), 8,44 (d, 1H), 8,42 (m, 1H), 7,70 (dd, 1H), 7,55 (d, 1H), 7,37 (d, 2H), 7,32 (m, 2H), 7,09 (d, 2H), 7,00 (d, 1H), 6,89 (d, 1H), 6,76 (d, 1H), 6,54 (d, 1H), 6,32 (d, 1H), 6,13 (d, 1H), 3,83 (m, 3H), 3,06 (m, 15H), 2,23 (m, 6H), 1,84 (m, 6H), 1,62 (m, 4H), 1,24 (m, 3H).

EJEMPLO 273

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[2-(3-oxopiperazin-1–il)etil]amino}fenil)sulfonil]benzamida

EJEMPLO 273A

3-nitro-4-[2-(3-oxo-piperazin-1–il)-etilamino]-bencensulfonamida

Se agregó 4-(2-amino-etil)-piperazin-2-ona (5,51 g) y trietilamina (9,07 mL, 6,59 g) a 1,4-dioxano (100 mL), N,N-dimetilacetamida (20 mL), y agua (10 mL) y se mezcló hasta disolver. Se agregó 4-cloro-3-nitrobencensulfonamida (7,00 g), y la mezcla se calentó a 90°C durante 16 horas. La mezcla se enfrió y el solvente se eliminó al vacío. El material crudo se purificó por recristalización a partir de metanol al 20% en diclorometano con subsiguiente lavado del sólido recristalizado con metanol al 10% en diclorometano seguido por el lavado con diclorometano al 100%.

EJEMPLO 273B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[2-(3-oxopiperazin-1–il)etil]amino}fenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 26C en lugar de EJEMPLO 1E y EJEMPLO 273A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,15 (br s, 1H), 8,73 (t, 1H), 8,58 (d, 1H), 7,82 (dd, 1H), 7,76 (br s, 1H), 7,51 (d, 1H), 7,42-7,38 (m, 2H), 7,34 (d, 2H), 7,16 (d, 1H), 7,06-7,01 (m, 3H), 6,85 (dd, 1H), 6,65 (dd, 1H), 6,38 (t, 1H), 6,15 (d, 1H), 3,48 (q, 2H), 3,17 (m, 2H), 3,04 (m, 6H), 2,72 (br s, 2H), 2,70-2,62 (m, 2H), 2,16 (m, 8H), 1,95 (br s, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 274

4-[4-({4'-cloro-4-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 125D en lugar de EJEMPLO 26C y EJEMPLO 174A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,62 (s, 1H), 11,33 (s, 1H), 9,55 (d, 1H), 8,49 (d, 1H), 7,74 (dd, 1H), 7,55 (m, 5H), 7,35 (m, 2H), 7,30 (m, 1H), 7,19 (dd, 2H), 6,96 (m, 2H), 6,73 (dd, 1H), 6,40 (m, 1H), 6,33 (m, 1H), 6,24 (s, 1H), 4,37 (m, 2H), 3,53 (m, 8H), 3,30 (m, 8H), 3,23 (m, 4H), 2,90 (s, 6H), 2,84 (s, 3H).

EJEMPLO 275

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1,1-dioxidotetrahidrotien-3–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 187A en lugar de 4-cloro-3-nitrobenceno sulfonamida y clorhidrato de (1,1-dioxidotetrahidrotien-3–il)metilamina en lugar de 1-(2-metoxi-etil)-piperidin-4–ilamina en el EJEMPLO 189A,1H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,17 (s, 1H), 8,72 (t, 1H), 8,59 (d, 1H), 7,82 (dd, 1H), 7,51 (d, 1H), 7,40 (m, 2H), 7,33 (d, 2H), 7,16 (m, 2H), 7,03 (d, 2H), 6,86 (dd, 1H), 6,65 (dd, 1H), 6,40 (m, 1H), 6,14 (d, 1H), 3,55 (t, 2H), 3,28 (m, 1H), 3,23 (m, 1H), 3,05 (m, 5H), 2,91 (m, 1H), 2,74 (m, 3H), 2,27 (m, 1H), 2,15 (m, 6H), 1,95 (m, 2H), 1,86 (m, 1H), 1,38 (t, 2H), 0,91 (s, 6H).

EJEMPLO 276

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1,1-dioxidotetrahidrotien-3–il)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 187A en lugar de 4-cloro-3-nitrobenceno sulfonamida y 1,1-dioxidotetrahidrotien-3ilamina en lugar de 1-(2-metoxi-etil)-piperidin-4–ilamina en el EJEMPLO 189A. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,20 (bs, 1H), 11,15 (s, 1H), 8,59 (d, 1H), 8,50 (d, 1H), 7,86 (dd, 1H), 7,50 (d, 1H), 7,39 (m, 2H), 7,33 (d, 2H), 7,19 (d, 1H), 7,14 (m, 1H), 7,03 (d, 2H), 6,85 (dd, 1H), 6,65 (dd, 1H), 6,39 (m, 1H), 6,15 (d, 1H), 4,63 (m, 1H), 3,64 (m, 1H), 3,37 (m, 2H), 3,20 (m, 1H), 3,03 (m, 4H), 2,73 (m, 2H), 2,57 (m, 1H), 2,28 (m, 1H), 2,15 (m, 6H), 1,95 (m, 2H), 1,38 (t, 2H), 0,91 (s, 6H).

EJEMPLO 277

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-[(tetrahidro-2H-piran-4–ilmetil)amino]-3-(trifluorometil)fenil]sulfonil}benzamida

EJEMPLO 277A

4-((tetrahidro-2H-piran-4–il)metilamino)-3-(trifluorometil)bencensulfonamida

Una mezcla de 4-fluoro-3-(trifluorometil)bencensulfonamida (1,056 g), (tetrahidro-2H-piran-4–il)metanamina (0,5 g) y N,N-diisopropiletilamina (1,68 g) en solución de dimetilsulfóxido anhidro (15 mL) se calentó a 90°C durante la noche. La mezcla de reacción se enfrió a temperatura ambiente y se diluyó con acetato de etilo. La fase orgánica se lavó con agua, salmuera, se secó sobre sulfato de sodio anhidro, se filtró y se concentró para dar el compuesto del título.

EJEMPLO 277B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-[(tetrahidro-2H-piran-4–ilmetil)amino]-3-(trifluorometil)fenil]sulfonil}benzamida

El compuesto del título se preparó utilizando EJEMPLO 277A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11. 22 (s, 1H), 11,20 (s, 1H), 7,91 (d, 1H), 7,76 (dd, 1H), 7,55 (d, 1H), 7,41 (m, 4H), 7,20 (m, 1H), 7,08 (d, 2H), 6,88 (m, 2H), 6,70 (dd, 1H), 6,58 (m, 1H), 6,42 (m, 1H), 6,19 (m, 1H), 3,83 (m, 2H), 3,56 (m, 4H), 3,25 (m, 4H), 3,15 (m, 2H), 2,99 (m, 2H), 2,74 (m, 2H), 2,18 (m, 2H), 2,02 (m, 2H), 1,84 (m, 1H), 1,57 (m, 2H), 1,44 (m, 2H), 1,19 (m, 2H), 0,93 (s, 6H).

EJEMPLO 278

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[2-(1,3-dioxolan-2–il)etil]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida

Una mezcla de EJEMPLO 187A (0,079 g), diciclohexil(2',6'-dimetoxibifenil-2–il)fosfina (0,016 g), y acetato de paladio (0,0045 g) en tetrahidrofurano (1 mL) se agitó a temperatura ambiente durante 5 minutos. A esta mezcla se agregó bromuro de (2-(1,3-dioxolan-2–il)etil)cinc(II) (0,6 mL). La mezcla de reacción se agitó durante la noche. El solvente se eliminó, y el residuo se purificó por HPLC preparativa de fase inversa. Las fracciones deseadas se combinaron, y el solvente orgánico se eliminó parcialmente. La mezcla resultante se trató con $NaHCO_3$ acuoso saturado, se extrajo con acetato de etilo, se

secó sobre $MgSO_4$, se filtró, y se concentró para dar el compuesto del título. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,14 (s, 1H), 8,37 (s, 1H), 8,00 (s, 1H), 7,55 (br s., 1H), 7,52 (d, 1H), 7,33-7,39 (m, 4H), 7,08 (br s, 1H), 7,04 (d, 2H), 6,83 (dd, 1H), 6,62 (d, 1H), 6,38 (s, 1H), 6,15 (d, 1H), 4,85 (t, 1H), 3,87-3,89 (m, 2H), 3,76-3,79 (m, 2H), 3,04 (s, 4H), 2,91-2,94 (m, 2H), 2,11-2,15 (m, 4H), 1,88-1,91 (s, 4H), 1,39 (t, 2H), 0,92 (s, 6H).

EJEMPLO 279

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(tetrahidro-2H-piran-4–ilmetoxi)fenil]sulfonil}benzamida

EJEMPLO 279A

3-nitro-4-((tetrahidro-2H-piran-4–il)metoxi)bencensulfonamida

Se trató (tetrahidro-2H-piran-4–il)metanol (2,0 g) en tetrahidrofurano (20 mL) con NaH al 60% (1,377 g). La mezcla se agitó por 20 minutos a temperatura ambiente. A esta mezcla se agregó 4-fluoro-3-nitrobencensulfonamida (2,84 g) por porciones. La reacción se agitó por otras 2 horas. La mezcla se vertió en agua, se neutralizó con HCl al 10 %, y se extrajo con acetato de etilo tres veces. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre $MgSO_4$, se filtró, y se concentró. El residuo se purificó con cromatografía flash de columna sobre gel de sílice eluyendo con acetato de etilo al 20%-60% en hexanos.

EJEMPLO 279B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(tetrahidro-2H-piran-4–ilmetoxi)fenil]sulfonil}benzamida

El compuesto del título se preparó utilizando EJEMPLO 279A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,16 (s, 1H), 8,38 (d, 1H), 8,05 (dd, 1H), 7,51 (d, 1H), 7,38-7,41 (m, 3H), 7,34 (d, 1H), 7,15 (d, 1H), 7,04 (d, 2H), 6,85 (dd, 1H), 6,65 (dd, 1H), 6,39 (s, 1H), 6,15 (d, 1H), 4,08 (d, 2H), 3,88 (dd, 2H), 3,04 (s, 4H), 2,77 (s, 2H), 2,12-2,22 (m, 4H), 1,95 (br s, 2H), 1,64 (dd, 2H), 1,36-1,39 (m, 2H), 0,92 (s, 6H).

EJEMPLO 280

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(3-nitro-4-{[2-(3-oxopiperazin-1–il)etil]amino}fenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 1E y EJEMPLO 273A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,24 (br s, 1H), 8,72 (t, 1H), 8,51 (d, 1H), 7,76 (br s, 1H), 7,72 (dd, 1H), 7,53 (d, 1H), 7,34 (d, 2H), 7,28 (t, 1H), 7,18 (d, 1H), 7,04 (d, 2H), 6,97 (t, 2H), 6,70 (dd, 1H), 6,43 (d, 1H), 6,28-6,23 (m, 2H), 3,48 (q, 2H), 3,17 (m, 2H), 3,04 (m, 6H), 2,70 (br s, 2H), 2,68-2,63 (m, 2H), 2,16 (m, 8H), 1,95 (br s, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 281

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metil-5-oxopirrolidin-3–il)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 187A en lugar de 4-cloro-3-nitrobencensulfonamida y clorhidrato de 4-amino-1-metilpirrolidin-2-ona en lugar de 1-(2-metoxi-etil)-piperidin-4–ilamina en el EJEMPLO 189A, excepto que el producto crudo se purificó mediante HPLC preparativa usando una columna C18, 250 x 50 mm, 10□, y eluyendo con un gradiente de CH_3CN al 20-100% vs. ácido trifluoroacético al 0,1% en agua, para dar el producto como una sal trifluoroacetato. La sal se disolvió en diclorometano (6 mL) y se lavó con $NaHCO_3$ acuoso al 50%. La capa orgánica se secó sobre Na_2SO_4 anhidro, se filtró, y se concentró para dar el compuesto del título. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,14 (s, 1H), 8,56 (d, 1H), 8,34 (br d, 1H), 7,82 (dd, 1H), 7,53 (d, 1H), 7,39 (m, 2H), 7,33 (d, 2H), 7,11 (s, 1H), 7,04 (m, 3H), 6,83 (dd, 1H), 6,64 (dd, 1H), 6,38 (s, 1H), 6,15 (s, 1H), 4,45 (m, 1H), 3,80 (dd, 1H), 3,35 (m, 1H), 3,02 (br s, 4H), 2,81 (dd, 1H), 2,75 (s, 3H), 2,71 (s, 2H), 2,40 (dd, 1H), 2,15 (m, 6H), 1,94 (s, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 282

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metil-6-oxopiperidin-3–il)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 187A en lugar de 4-cloro-3-nitrobencensulfonamida y clorhidrato de 5-amino-1-metilpiperidin-2-ona en lugar de 1-(2-metoxi-etil)-piperidin-4–ilamina en el EJEMPLO 189A, excepto que el material crudo se purificó mediante HPLC preparativa usando una columna C18, 250 x 50 mm, 10□, y eluyendo con un gradiente de CH_3CN al 20-100% vs. ácido trifluoroacético al 0,1% en agua, para dar el producto como una sal trifluoroacetato. La sal se disolvió en diclorometano (6 mL) y se lavó con $NaHCO_3$ acuoso al 50%. La capa orgánica se secó sobre Na_2SO_4 anhidro y

se concentró para dar el compuesto del título. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,16 (s, 1H), 8,58 (d, 1H), 8,31 (br d, 1H), 7,85 (dd, 1H), 7,53 (d, 1H), 7,39 (m, 2H), 7,33 (d, 2H), 7,25 (d, 1H), 7,14 (s, 1H), 7,03 (d, 2H), 6,85 (dd, 1H), 6,64 (dd, 1H), 6,39 (s, 1H), 6,14 (s, 1H), 4,22 (m, 1H), 3,57 (dd, 1H), 3,02 (br s, 4H), 2,84 (m, 1H), 2,83 (s, 3H), 2,72 (s, 2H), 2,36 (m, 2H), 2,16 (m, 6H), 2,05 (m, 2H), 1,94 (s, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 283

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[3-nitro-4-(piperidin-1–ilamino)fenil]sulfonil}benzamida

EJEMPLO 283A

3-nitro-4-(piperidin-1–ilamino)bencensulfonamida

El compuesto del título se preparó utilizando piperidin-1-amina en lugar de (tetrahidro-2H-piran-4–il)metanamina en el EJEMPLO 1F.

EJEMPLO 283B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[3-nitro-4-(piperidin-1–ilamino)fenil]sulfonil}benzamida

El compuesto del título se preparó utilizando EJEMPLO 283A en lugar de EJEMPLO 1F y EJEMPLO 55B en lugar de EJEMPLO 26C en el EJEMPLO 177. ^{1}H NMR (500 MHz, dimetilsulfóxido-d_6) δ 11,27 (brs, 1H), 11,33 (s, 1H), 9,14 (s, 1H), 8,48 (d, 1H), 7,66 (dd, 1H), 7,52 (t, 2H), 7,34 (d, 2H), 7,29 (t, 1H), 7,19 (d, 1H), 7,04 (d, 2H), 6,97 (t, 1H), 6,71 (dd, 1H), 6,41 (d, 1H), 6,28 (m, 2H), 3,05 (m, 4H), 2,78 (m, 6H), 2,17 (m, 6H), 1,95 (s, 2H), 1,67 (m, 6H), 1,38 (t, 2H), 0,93 (s, 6H).

EJEMPLO 284

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(piperidin-1–ilamino)fenil]sulfonil}benzamida

El compuesto del título se preparó utilizando EJEMPLO 283A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (500 MHz, dimetilsulfóxido-d_6) δ 11,28 (s, 1H), 11,11 (s, 1H), 9,02 (s, 1H), 8,50 (s, 1H), 7,79 (dd, 1H), 7,52 (m, 2H), 7,35 (m, 4H), 7,07 (m, 3H), 6,82 (m, 1H), 6,60 (m, 1H), 6,36 (m, 1H), 6,14 (m, 1H), 2,99 (m, 4H), 2,75 (m, 6H), 2,16 (m, 6H), 1,99 (m, 2H), 1,94 (m, 2H), 1,64 (m, 4H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 285

4-(4-{[4-(4-clorofenil)-1-metil-1H-pirazol-5–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 285A

4-(4-clorofenil)-1-metil-1H-pirazol-5-carbaldehido

Se agitó 4-bromo-1-metil-1H-pirazol-5-carbaldehido (0,500 g), ácido 4-clorofenilborónico (0,455 g), bromuro de tetrabutilamonio (0,853 g), carbonato de potasio (0,914 g) y acetato de paladio (0,030 g) juntos en 5 mL de agua y se calentó a 45°C. Luego de agitar por 2,5 horas, la reacción se diluyó con acetato de etilo (75 mL) y se lavó con agua (25 mL), salmuera (50 mL), se secó sobre sulfato de magnesio, se filtró y se concentró para dar el material crudo. El sólido se cromatografió sobre gel de sílice (SF40-80) eluyendo con un gradiente de acetato de etilo entre 5% y 25%/hexanos durante 30 minutos.

EJEMPLO 285B

2-(1H-indol-5–iloxi)-4-(4-((4-(4-clorofenil)-1-metil-1H-pirazol-5–il)metil)piperazin-1–il)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 285A en lugar de 4'-clorobifenil-2 carboxaldehido y 2-(1H-indol-5–iloxi)-4-(piperazin-1–il)benzoato de metilo en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 285C

ácido 2-(1H-indol-5–iloxi)-4-(4-((4-(4-clorofenil)-1-metil-1H-pirazol-5–il)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 285B en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 285D

2-(1H-indol-5–iloxi)-4-(4-((4-(4-clorofenil)-1-metil-1H-pirazol-5–il)metil)piperazin-1–il)-N-(3-nitro-4-((tetrahidro-2H-piran-4–il)metilamino)fenilsulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 285C en lugar de EJEMPLO 1E en el EJEMPLO 1G. ^{1}H NMR (300 MHz, CDCL3) δ 10,30 (s, 1H), 8,85 (d, 1H), 8,50 (s, 1H), 8,30 (s, 1H), 8,12 (dd, 1H), 7,95 (d, 1H), 7,49 (s, 1H), 7,43 (d, 1H), 7,36 – 7,22 (m, 6H), 6,97 (dd, 1H), 6,87 (d, 1H), 6,53 (d, 2H), 6,08 (s, 1H), 4,08 – 3,98 (m, 2H),

3,92 (s, 3H), 3,55 (s, 2H), 3,42 (s, 2H), 3,33 – 3,19 (m, 2H), 3,08 (s, 4H), 2,38 (s, 4H), 1,98 (d, 1H), 1,72 (s, 2H), 1,52 – 1,33 (m, 2H).

EJEMPLO 286

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(3-metiloxetan-3–il)metoxi]-3-nitrofenil}sulfonil)benzamida

EJEMPLO 286A

4-((3-metiloxetan-3–il)metoxi)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando (3-metiloxetan-3–il)metanol en lugar de (tetrahidro-2H-piran-4–il)metanol en el EJEMPLO 279A.

EJEMPLO 286B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(3-metiloxetan-3–il)metoxi]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 286A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,08 (s, 1H), 8,26 (d, 1H), 8,18 (d, 1H), 7,92 (m, 1H), 7,53 (m, 1H), 7,34 (m, 3H), 7,25 (m, 1H), 7,04 (m, 3H), 6,91 (m, 1H), 6,76 (m, 1H), 6,59 (m, 1H), 6,35 (m, 1H), 6,15 (d, 1H), 4,47 (d, 1H), 4,29 (d, 1H), 3,40 (m, 2H), 3,13 (m, 2H), 2,98 (m, 4H), 2,72 (m, 2H), 2,16 (m, 6H), 1,94 (m, 2H), 1,36 (m, 5H), 0,93 (s, 6H).

EJEMPLO 287

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[(1-oxidotetrahidro-2H-tiopiran-4–il)metil]amino}fenil)sulfonil]benzamida

EJEMPLO 287A

3-nitro-4-((tetrahidro-2H-tiopiran-4–il)metilamino)bencensulfonamida

El compuesto del título se preparó utilizando (tetrahidro-2H-tiopiran-4–il)metanamina, clorhidrato en lugar de (tetrahidropiran-4–il)metilamina en el EJEMPLO 1F.

EJEMPLO 287B

3-nitro-4-((1-oxidotetrahidro-2H-tiopiran-4–il)metilamino)bencensulfonamida

Se suspendió EJEMPLO 287A (150 mg) en metanol (5 mL). La mezcla de reacción se enfrió a 0°C, seguido por la adición de Oxone® (220 mg) en agua (3 mL). La mezcla de reacción se agitó a temperatura ambiente por 2 horas. El precipitado se filtró y se lavó con solución de $Na_2S_2O_3$ y agua. El sólido se secó en un horno de vacío durante la noche, y se usó en el siguiente paso sin purificación adicional.

EJEMPLO 287C

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[(1-oxidotetrahidro-2H-tiopiran-4–il)metil]amino}fenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 287B en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,17 (s, 1H), 8,69 (t, 1H), 8,58 (d, 1H), 7,81 (dd, 1H), 7,51 (d, 1H), 7,40 (m, 2H), 7,33 (d, 2H), 7,15 (m, 2H), 7,03 (d, 2H), 6,86 (dd, 1H), 6,65 (dd, 1H), 6,40 (m, 1H), 6,13 (m, 1H), 3,38 (m, 4H), 3,05 (m, 6H), 2,73 (m, 2H), 2,11 (m, 8H), 1,95 (m, 3H), 1,67 (m, 2H), 1,38 (t, 2H), 0,90 (s, 6H).

EJEMPLO 288

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1,3-tiazol-5–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando tiazol-5–ilmetanamina, ácido clorhídrico en lugar de (3S,4R)-4-amino-1-bencilpiperidin-3-ol, ácido clorhídrico en el EJEMPLO 187B. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,18 (s, 2H), 9,13 (t, 1H), 8,99 (s, 1H), 8,60 (d, 1H), 7,95 (s, 1H), 7,82 (dd, 1H), 7,50 (d, 1H), 7,39-7,42 (, 2H), 7,33 (d, 2H), 7,17 (d, 1H), 7,14 (d, 1H), 7,03 (d, 2H), 6,85 (dd, 1H), 6,64 (dd, 1H), 6,40 (s, 1H), 6,13 (d, 1H), 4,91 (d, 2H), 3,03 (s, 4H), 2,73 (s, 2H), 2,12-2,18 (m, 6H), 1,94 (s, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 289

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[3-nitro-4-(tetrahidro-2H-piran-4–ilmetoxi)fenil]sulfonil}benzamida

El compuesto del título se preparó utilizando EJEMPLO 279A en lugar de EJEMPLO 1F y EJEMPLO 55B en lugar de EJEMPLO 26C en el EJEMPLO 177. ^{1}H NMR

(500MHz, dimetilsulfóxido-d_6) δ 11,25 (s, 1H), 8,21 (d, J = 2,14 Hz, 1H), 7,95 (dd, 1H), 7,54 (d, 1H), 7,33-7,38 (m, 3H), 7,28 (t, 1H), 7,17 (d, 1H), 7,04 (d, 2H), 6,97 (t, 1H), 6,70 (dd, 1H), 6,41 (d, 1H), 6,27-6,29 (m, 2H), 4,08 (d, 2H), 3,88 (dd, 2H), 3,07 (s, 4H), 2,80 (s, 2H), 2,24 (br s, 2H), 2,12-2,16 (m, 2H), 1,96 (s, 2H), 1,65 (dd, 2H), 1,37-1,40 (m, 2H), 0,92 (s, 6H).

EJEMPLO 290

4-(4-{[2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 290A

2-(4-clorofenil)-5,5-dimetilciclohex-1-encarbaldehido

El compuesto del título se preparó como se describe en el EJEMPLO 253B reemplazando EJEMPLO 253A con EJEMPLO 19C.

EJEMPLO 290B

4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-enil)metil)piperazin-1-carboxilato de tert-butilo

El compuesto del título se preparó como se describe en el EJEMPLO 1A reemplazando EJEMPLO 27C con EJEMPLO 290A.

EJEMPLO 290C

1-((2-(4-clorofenil)-5,5-dimetilciclohex-1-enil)metil)piperazina

El compuesto del título se preparó como se describe en el EJEMPLO 1B reemplazando EJEMPLO 1A con EJEMPLO 290B.

EJEMPLO 290D

2-(1H-indol-5–iloxi)-4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-enil)metil)piperazin-1–il)benzoato de etilo

El compuesto del título se preparó como se describe en el EJEMPLO 20D reemplazando EJEMPLO 20A y EJEMPLO 20C con EJEMPLO 26A y EJEMPLO 290C, respectivamente.

EJEMPLO 290E

ácido 2-(1H-indol-5–iloxi)-4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-enil)metil)piperazin-1–il)benzoico

El compuesto del título se preparó como se describe en el EJEMPLO 1E reemplazando EJEMPLO 1D con EJEMPLO 290D.

EJEMPLO 290F

2-(1H-indol-5–iloxi)-4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-enil)metil)piperazin-1–il)-N-(3-nitro-4-((tetrahidro-2H-piran-4–il)metilamino)fenilsulfonil)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 175F reemplazando EJEMPLO 175E con EJEMPLO 290E. ^{1}H NMR (500 MHz, dimetilsulfóxido-d_6) δ 11,17 (s, 2H), 8,62 (t, 1H), 8,58 (d, 1H), 7,80 (dd, 1H), 7,51 (d, 1H), 7,38 - 7,43 (m, 2H), 7,33 (d, 2H), 7,16 (d, 1H), 7,10 (d, 1H), 7,07 (d, 3H), 6,86 (dd, 1H), 6,65 (dd, 1H), 6,39 (s, 1H), 6,14 (d, 1H), 3,85 (dd, 2H), 3,23 - 3,31 (m, 4H), 3,02 (s, 4H), 2,68 (s, 2H), 2,17 (d, 6H), 1,85 - 1,95 (m, 3H), 1,61 (d, 2H), 1,39 (t, 2H), 1,20 - 1,30 (m, 2H), 0,92 (s, 6H).

EJEMPLO 291

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(2-tetrahidro-2H-piran-4–iletil)amino]fenil}sulfonil)benzamida

EJEMPLO 291A

3-nitro-4-(2-(tetrahidro-2H-piran-4–il)etilamino)bencensulfonamida

El compuesto del título se preparó como se describe en el EJEMPLO 1F reemplazando (tetrahidropiran-4–il)metilamina con 2-(tetrahidro-2H-piran-4–il)etanamina.

EJEMPLO 291B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(2-tetrahidro-2H-piran-4–iletil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 175F reemplazando EJEMPLO 175E y EJEMPLO 1F con EJEMPLO 26C y EJEMPLO 291A, respectivamente. ^{1}H NMR (500 MHz, dimetilsulfóxido-d_6) δ 11,16 (s, 2H), 8,57 (d, 1H), 8,53 (t, 1H), 7,80 (dd, 1H), 7,51 (d, 1H), 7,37 - 7,42 (m, 2H), 7,33 (d, 2H), 7,14 (d, 1H), 7,01 - 7,05 (m, 3H), 6,85 (dd, 1H), 6,64 (dd, 1H), 6,39 (s, 1H), 6,14 (d, 1H), 3,83 (dd, 2H), 3,41 (q, 2H), 3,23 - 3,30 (m, 2H), 3,02 (s, 4H), 2,71 (s, 2H), 2,08 - 2,21 (m, 6H), 1,94 (s, 2H), 1,52 - 1,67 (m, 5H), 1,37 (t, 2H), 1,14 - 1,25 (m, 2H), 0,92 (s, 6H).

EJEMPLO 292

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(3-nitro-4-{[2-(trifluorometoxi)etil]amino}fenil)sulfonil]benzamida

EJEMPLO 292A

3-nitro-4-(2-(trifluorometoxi)etilamino)bencensulfonamida

El compuesto del título se preparó utilizando piperidin-1-amina en lugar de (tetrahidro-2H-piran-4–il)metanamina en el EJEMPLO 1F.

EJEMPLO 292B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(3-nitro-4-{[2-(trifluorometoxi)etil]amino}fenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 292A en lugar de EJEMPLO 1F y EJEMPLO 55B en lugar de EJEMPLO 26C en el EJEMPLO 177. ^{1}H NMR (500 MHz, dimetilsulfóxido-d $_{6}$) δ 11.07 (s, 1H), 8.36 (m, 2H), 7.72 (dd, 1H), 7.58 (d, 1H), 7.34 (d, 2H), 7.19 (m, 1H), 7.05 (m, 3H), 6.91 (m, 2H), 6.59 (d, 1H), 6.21 (m, 3H), 4.28 (t, 2H), 3.72 (q, 2H), 2.94 (m, 4H), 2.71 (s, 2H), 2.15 (m, 6H), 1.95 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

EJEMPLO 293

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[2-(2-metoxietoxi)etil]amino}-3-nitrofenil)sulfonil]benzamida

EJEMPLO 293A

4-(2-(2-metoxietoxi)etilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando 2-(2-metoxietoxi)etanamina en lugar de (tetrahidro-2H-piran-4–il)metanamina en el EJEMPLO 1F.

EJEMPLO 293B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[2-(2-metoxietoxi)etil]amino}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 293A en lugar de EJEMPLO 1F y EJEMPLO 55B en lugar de EJEMPLO 26C en el EJEMPLO 177. ^{1}H NMR

(500 MHz, dimetilsulfóxido-d $_6$) δ11.28 (s, 1H), 11.23 (s, 1H), 8.59 (m, 1H), 8.50 (d, 1H), 7.70 (dd, 1H), 7.52 (d, 1H), 7.34 (d, 2H), 7.28 (t, 1H), 7.17 (d, 1H), 7.05 (m, 3H), 6.96 (t, 1H), 6.71 (dd, 1H), 6.42 (d, 1H), 6.26 (m, 2H), 3.67 (t, 2H), 3.56 (m, 4H), 3.45 (m, 2H), 3.22 (s, 3H), 3.04 (m, 4H), 2.74 (s, 2H), 2.16 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.93 (s, 6H).

EJEMPLO 294

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[3-(metilsulfonil)propil]amino}-3-nitrofenil)sulfonil]benzamida

EJEMPLO 294A

4-(3-(metiltio)propilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando 3-(metiltio)propan-1-amina en lugar de (tetrahidropiran-4–il)metilamina en el EJEMPLO 1F.

EJEMPLO 294B

4-(3-(metilsulfonil)propilamino)-3-nitrobencensulfonamida

Se suspendió el EJEMPLO 294A (150 mg) en diclorometano anhidro (5mL) y se agregó ácido meta-cloroperoxibenzoico (848 mg) a 0°C. La mezcla de reacción se agitó a temperatura ambiente durante la noche. La suspensión turbia se filtró. Se lavó el sólido con solución $Na_2S_2O_3$ acuosa, solución $NaHCO_3$ acuosa saturada y agua. El sólido se secó y used en el próximo paso sin purificación adicional.

EJEMPLO 294C

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[3-(metilsulfonil)propil]amino}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 26C y EJEMPLO 294B en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11.25 (m, 1H), 8.65 (t, 1H), 8.51 (d, 1H), 7.69 (dd, 1H), 7.52 (d, 1H), 7.34 (d, 2H), 7.28 (m, 1H), 7.18 (m, 1H), 7.05 (m, 3H), 6.97 (m, 1H), 6.70 (dd, 1H), 6.42 (d, 1H), 6.26 (m, 2H), 3.55 (m, 2H), 3.23 (t, 2H), 3.05 (t, 4H), 2.98 (s , 3H), 2.76 (m, 2H), 2.18 (m, 6H), 2.02 (m, 2H), 1.96 (m, 2H), 1.38 (t, 2H), 0.93 (s, 6H).

EJEMPLO 295

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[3-(1,1-dioxidotiomorfolin-4–il)propil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 337A en lugar de 4-cloro-3-nitrobenceno sulfonamida y 4-(3-aminopropil)tiomorfoline-1,1-dioxide en lugar de 1-(2-metoxi-etil)-piperidin-4–ilamina en el EJEMPLO 189A. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11.23 (s, 1H), 8.79 (s, 1H), 8.48 (d, 1H), 7.72 (dd, 1H), 7.54 (d, 1H), 7.34 (d, 2H), 7.26 (t, 1H), 7.15 (d, 1H), 6.99 (m, 4H), 6.67 (dd, 1H), 6.40 (d, 1H), 6.24 (m, 2H), 3.42 (q, 2H), 3.11 (m, 4H), 3.01 (m, 4H), 2.90 (m, 4H), 2.72 (m, 2H), 2.56 (t, 2H), 2.16 (m, 6H), 1.95 (m, 2H), 1.78 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EJEMPLO 296

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(2-tetrahidro-2H-piran-4–iletil)fenil]sulfonil}benzamida

EJEMPLO 296A

Bromuro de (2-(tetrahidro-2H-piran-4–il)etil)zinc(II)

Un matraz de fondo redondo de 25 mL se secó a 120 ºC durante 6 horas. Se enfrió por una corriente de N_2 seco. Este matraz se cargó con zinc (0.508 g). El matraz se calentó a 70 ºC bajo alto vacío por 30 minutos. Después de rellenar con N_2, se añadieron yodo (0.033 g) y N,N-dimetilacetamida (5.2 mL) , y la mezcla resultante se agitó hasta que el color rojo del yodo se desvaneció. Luego se agregó, 4-(2-bromoetil)tetrahidro-2H-piran (1.0 g) a la mezcla anterior a través de una jeringa. A la mezcla de reacción se le dejó agitarse por 12 horas a 70 ºC. Después de enfriar, la mezcla de reacción se usó directamente para el paso siguiente.

EJEMPLO 296B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(2-tetrahidro-2H-piran-4–iletil)fenil]sulfonil}benzamida

El compuesto del título se preparó utilizando EJEMPLO 296A para bromuro de (2-(1,3-dioxolan-2–il)etil)zinc(II) en el EJEMPLO 278. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11.15 (s, 2H), 8.38 (d, 1H), 8.01 (d, 1H), 7.57 (d, 1H), 7.51 (d, 1H), 7.38-7.40 (m, 2H), 7.34 (d, 2H), 7.12 (d, 1H), 7.04 (d, 2H), 6.82 (dd, 1H), 6.64 (dd, 1H), 6.38 (s, 1H), 6.16 (d, 1H), 3.83 (dd, 2H), 3.24-3.29 (m, 4H), 3.06 (s, 4H), 2.83-2.86 (m, 3H), 2.27

(br s, 2H), 2.12-2.14 (m, 4H), 1.96 (s, 2H), 1.95 (s, 2H), 1.46-1.62 (m, 6H), 1.37-1.40 (m, 2H), 0.92 (s, 6H).

EJEMPLO 297

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-(1,4-dioxan-2–ilmetoxi)-3-nitrofenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida

EJEMPLO 297A

4-((1,4-dioxan-2–il)metoxi)-3-nitrobencensulfonamida

(1,4-Dioxan-2–il)metanol (380 mg) en tetrahidrofurano (30 ml) se trató con hidruro de sodio (60%) (245 mg) a temperatura ambiente durante 30 minutos. La mezcla de reacción se enfrió en un baño helado y se agregó 4-fluoro-3-nitrobencensulfonamida (675 mg). La mezcla resultante se agitó a temperatura ambiente por 2 horas y se agregó otra porción de hidruro de sodio (60%, 245 mg). La mezcla de reacción se agitó durante la noche y se detuvo con ice agua (3 ml). La mezcla turbia se filtró y el filtrado se concentró. El residuo se trituró con metanol para dar el compuesto del título.

EJEMPLO 297B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-(1,4-dioxan-2–ilmetoxi)-3-nitrofenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 175F por reemplazo de EJEMPLO 175E y EJEMPLO 1F con EJEMPLO 26C y EJEMPLO 297A, respectivamente. ^{1}H NMR (500 MHz, dimetilsulfóxido-d $_6$) δ 11.16 (s, 2H), 8.39 (d, 1H), 8.06 (dd, 1H), 7.51 (d, 1H), 7.38 - 7.43 (m, 3H), 7.34 (d, 2H), 7.15 (d, 1H), 7.04 (d, 2H), 6.85 (dd, 1H), 6.64 (dd, 1H), 6.39 (s, 1H), 6.15 (d, 1H), 4.20 - 4.28 (m, 2H), 3.85 - 3.91 (m, 1H), 3.82 (dd, 1H), 3.74 - 3.78 (m, 1H), 3.59 - 3.69 (m, 2H), 3.40 - 3.51 (m, 2H), 3.05 (s, 4H), 2.78 (s, 2H), 2.23 (s, 4H), 2.14 (s, 2H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EJEMPLO 298

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[2-(2-metoxietoxi)etil]amino}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 293A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (500 MHz, dimetilsulfóxido-d $_6$) δ 11.17 (s, 1H), 11.15 (s, 1H), 8.59 (m, 2H), 7.80 (dd, 1H), 7.50 (d, 1H), 7.36 (m, 4H), 7.15 (d, 1H), 7.09

(d, 1H), 7.03 (d, 2H), 6.85 (dd, 1H), 6.65 (dd, 1H), 6.39 (m, 1H), 6.14 (d, 1H), 3.67 (t, 2H), 3.56 (m, 4H), 3.44 (m, 2H), 3.22 (s, 3H), 3.03 (m, 4H), 2.72 (s, 2H), 2.16 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EJEMPLO 299

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1,1-dioxidotetrahidrotien-3–il)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-4–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 337A en lugar de 4-cloro-3-nitrobenceno sulfonamida y 1,1-dioxidotetrahidrotiene-3ilamina en lugar de 1-(2-metoxi-etil)-piperidin-4–ilamina en el EJEMPLO 189A. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11.35 (s, 1H), 11.23 (s, 1H), 8.49 (m, 2H), 7.78 (dd, 1H), 7.52 (d, 1H), 7.34 (d, 2H), 7.27 (m, 1H), 7.16 (m, 2H), 7.04 (d, 1H), 6.97 (m, 1H), 6.70 (dd, 1H), 6.42 (d, 1H), 6.26 (m, 2H), 4.63 (m, 1H), 3.64 (dd, 1H), 3.37 (m, 2H), 3.20 (m, 1H), 3.05 (m, 4H), 2.74 (m, 2H), 2.58 (m, 1H), 2.28 (m, 1H), 2.16 (m, 6H), 1.95 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EJEMPLO 300

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[2-(trifluorometoxi)etil]amino}fenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 292A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (500 MHz, dimetilsulfóxido-d_6) δ 11.17 (m, 2H), 8.64 (t, 1H), 8.59 (d, 1H), 7.84 (dd, 1H), 7.51 (d, 1H), 7.40 (m, 2H), 7.33 (d, 2H), 7.16 (m, 2H), 7.04 (d, 2H), 6.85 (dd, 1H), 6.64 (dd, 1H), 6.39 (m, 1H), 6.14 (d, 1H), 4.31 (t, 2H), 3.78 (q, 2H), 3.04 (m, 4H), 2.74 (s, 2H), 2.17 (m, 6H), 1.94 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6 H).

EJEMPLO 301

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1,1-dioxidotetrahidro-2H-tiopiran-4–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida

EJEMPLO 301A

3-nitro-4-((1-dioxidotetrahidro-2H-tiopiran-4–il)metilamino)bencensulfonamida

El compuesto del título se preparó utilizando EJEMPLO 287A en lugar de EJEMPLO 294A en el EJEMPLO 294B.

EJEMPLO 301B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1,1-dioxidotetrahidro-2H-tiopiran-4–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 26C y EJEMPLO 301A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11.26 (s, 1H), 8.68 (t, 1H), 8.51 (d, 1H), 7.73 (dd, 1H), 7.53 (d, 1H), 7.34 (d, 2H), 7.29 (m, 1H), 7.19 (d, 1H), 7.12 (d, 1H), 7.04 (d, 2H), 6.99 (m, 1H), 6.70 (dd, 1H), 6.46 (d, 1H), 6.26 (m, 2H), 3.38 (t, 2H), 3.09 (m, 8H), 2.75 (m, 2H), 2.16 (m, 6H), 2.07 (m, 2H), 1.95 (m, 3H), 1.70 (m, 2H), 1.38 (t, 2H), 0.91 (s, 6H).

EJEMPLO 302

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2,2-difluoroetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida

EJEMPLO 302A

4-(2,2-difluoroetilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando 2,2-difluoroetanamina en lugar de (tetrahidro-2H-piran-4–il)metanamina en el EJEMPLO 1F.

EJEMPLO 302B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2,2-difluoroetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 302A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (500 MHz, dimetilsulfóxido-d_6) δ 11.22 (s, 1H), 11.05 (s, 1H), 8.46 (m, 2H), 7.76 (m, 1H), 7.53 (d, 1H), 7.33 (m, 4H), 7.05 (m, 4H), 6.76 (m, 1H), 6.57 (d, 1H), 6.34 (m, 1H), 6.14 (m, 1H), 3.89 (m, 2H), 2.97 (m, 4H), 2.71 (s, 2H), 2.16 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EJEMPLO 303

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 26C y EJEMPLO 163A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11.28 (m, 1H), 8.13 (d, 1H), 7.78 (dd, 1H), 7.52 (d, 1H), 7.34 (d, 2H), 7.29 (m, 2H), 7.20 (d, 1H), 7.01 (m, 4H), 6.70 (dd, 1H), 6.45 (d, 1H), 6.27 (m, 2H), 3.85 (dd, 2H), 3.26 (t, 4H), 3.05 (m, 4H), 2.75 (m, 2H), 2.16 (m, 6H), 1.95 (m, 2H), 1.84 (m, 1H), 1.55 (m, 2H), 1.38 (t, 2H), 1.23 (m, 2H), 0.92 (s, 6H).

EJEMPLO 304

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 163A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11.46 (s, 1H), 11.20 (s, 1H), 9.23 (s, 1H), 8.19 (d, 1H), 7.90 (dd, 1H), 7.53 (d, 1H), 7.41 (m, 4H), 7.33 (m, 1H), 7.17 (d, 1H), 6.86 (dd, 1H), 6.70 (dd, 1H), 6.41 (m, 1H), 6.21 (d, 1H), 3.84 (dd, 2H), 3.57 (m, 4H), 3.26 (m, 6H), 3.00 (m, 2H), 2.74 (s, 2H), 2.18 (s, 2H), 2.01 (s, 2H), 1.83 (m, 1H), 1.54 (m, 2H), 1.45 (t, 2H), 1.23 (m, 2H), 0.94 (s, 6H).

EJEMPLO 305

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4,4-difluorociclohexil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando 4,4-difluorociclohexanamina, ácido clorhídrico en lugar de (3S,4R)-4-amino-1-bencilpiperidin-3-ol, ácido clorhídrico en el EJEMPLO 187B. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11.16 (s, 2H), 8.59 (d, 1H), 8.25 (d, 1H), 7.84 (dd, 1H), 7.50 (d, 2H), 7.39-7.41 (m, 2H), 7.33 (d, 2H), 7.15-7.18 (m, 2H), 7.03 (d, 2H), 6.85 (dd, 1H), 6.65 (dd, 1H), 6.39 (s, 1H), 6.14 (d, 1H), 3.86 (d, 1H), 3.04 (s, 4H), 2.74 (s, 2H), 1.95-2.18 (m, 14H), 1.69-1.73 (m, 2H), 1.38 (d, 2H), 0.92 (s, 6H).

EJEMPLO 306

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-4–iloxi)benzamida

EJEMPLO 306A

1,6-dioxaspiro[2.5]octano-2-carbonitrilo

Una mezcla de dihidro-2H-piran-4(3H)-ona (10.0g) y 2-cloroacetonitrilo (7.55 g) en tert-butanol (10 mL) se trató con 1.0 N tert-butóxido de potasio (100 mL) por goteo durante 20 minutos. La mezcla de reacción se agitó a temperatura ambiente durante 16 horas. It se diluyó con agua (10 mL) y 10% HCl (20 mL). La mezcla de reacción se concentró a un tercio de su volumen original, y se extrajo con dietiléter cuatro veces. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre $MgSO_4$, se filtró, y se concentró. El residuo se purificó con cromatografía de columna flash sobre gel de sílice eluyendo con 20-40% acetato de etilo en hexanos para dar el compuesto del título.

EJEMPLO 306B

2-(4-fluorotetrahidro-2H-piran-4–il)-2-hidroxiacetonitrilo

EJEMPLO 306A (11.5 g) se disolvió en diclorometano (40 mL) en una botella de polipropileno. La botella se enfrió a 0°C. A esta mezcla se agregó 70% fluoruro de hidrógeno-piridina (10.31 mL) lentamente. La mezcla se dejó tomar la temperatura ambiente durante 3 horas, y se agitó durante 24 horas. La mezcla de reacción se diluyó con acetato de etilo (200 mL) y vertida en $NaHCO_3$ acuoso saturado. Sólido adicional $NaHCO_3$ se usó para neutralizar la mezcla cuidadosamente hasta que cesó el burbujeo. La capa orgánica se aisló, y la capa acuosa se extrajo con acetato de etilo adicional tres veces (150 mL cada una).Las capas orgánicas combinadas se lavaron con 1% HCl, salmuera, se secó ($MgSO_4$), se filtró y se concentró para dar el compuesto deseado que se usó directamente en la reacción siguiente.

EJEMPLO 306C

(4-fluorotetrahidro-2H-piran-4–il)metanol

EJEMPLO 306B (11.78 g) en 2-propanol (150 mL) y agua (37.5 mL) se enfrió a 0 ºC. A esta mezcla se agregó borohidruro de sodio (4.2 g). La mezcla se agitó y permitió calentarse a temperatura ambiente durante 3 horas. La reacción se detuvo con acetona, y se agitó durante otra 1 hora. El líquido claro se separó del sólido por decantación. Acetato de etilo adicional se usó para lavar el sólido, y se decantó. La solución orgánica combinada se

concentró. El residuo se purificó con cromatografía de columna flash sobre gel de sílice eluyendo con 20-40% acetato de etilo en hexanos para dar el compuesto del título.

EJEMPLO 306D

4-((4-fluorotetrahidro-2H-piran-4–il)metoxi)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando EJEMPLO 306C durante (tetrahidro-2H-piran-4–il)metanol en el EJEMPLO 279A.

EJEMPLO 306E

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-4–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 306D en lugar de EJEMPLO 1F y EJEMPLO 55B en lugar de EJEMPLO 26C en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11.24 (s, 1H), 8.28 (d, 1H), 7.98 (dd, 1H), 7.54 (d, 1H), 7.42 (d, 1H), 7.34 (d, 2H), 7.28 (t, 1H), 7.17 (d, 1H), 7.04 (d, 2H), 6.97 (t, 1H), 6.70 (dd, 1H), 6.41 (d, 1H), 6.26-6.28 (m, 2H), 4.38 (d, 2H), 3.76-3.80 (m, 2H), 3.57-3.62 (m, 2H), 3.06 (s, 4H), 2.80 (s, 2H), 2.24 (br s, 2H), 2.15-2.25 (m, 2H), 1.96 (s, 2H), 1.82-1.89 (m, 4H), 1.39 (t, 2H), 0.93 (s, 6H).

EJEMPLO 307

4-(4-{[4-(4-clorofenil)-1-isopropil-6-oxo-1,6-dihidropiridin-3–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 307A

4-(4-clorofenil)-2-fluoro-5-metilpiridina

Una mezcla de 2-fluoro-4-iodo-5-metilpiridina (1.9 g), ácido 4-clorofenilborónico (1.504 g), tetrakis(trifenilfosfina)paladio(0) (0.463 g), y carbonato de sodio (2.55 g) en etanol (20 mL), agua (10 mL) y tolueno (10 mL) se calentó bajo reflujo por 6 horas. La mezcla de reacción se particionó entre acetato de etilo y agua. La capa orgánica se separó, y las capas acuosas se extrajeron con acetato de etilo adicional tres veces. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre $MgSO_4$, se filtró, y se concentró. El residuo se purificó con cromatografía de columna flash sobre gel de sílice usando 5% acetato de etilo en hexanos para dar el compuesto del título.

EJEMPLO 307B

5-(bromometil)-4-(4-clorofenil)-2-fluoropiridina

Una mezcla de EJEMPLO 307A (1.2 g), *N*-bromosuccinimida (1.06 g) y AIBN (azobisisobutironitrilo) (0.178 g) en CCl_4 (30 mL) se calentó bajo reflujo por 6 horas. Después de enfriar, el sólido se filtró. El filtrado se concentró y se cargó en una columna de gel de sílice eluyendo con 3% acetato de etilo en hexanos para dar el compuesto del título.

EJEMPLO 307C

carboxilato de 4-((4-(4-clorofenil)-6-fluoropiridin-3–il)metil)piperazin-1-tert-butilo

Una mezcla de EJEMPLO 307B (1.24 g), carboxilato de piperazin-1-tert-butilo (0.768 g), y carbonato de potasio (0.570) en N,N-dimetilformamida (20 mL) se agitó a temperatura ambiente por 2 horas. La mezcla de reacción se particionó entre acetato de etilo y agua. La capa orgánica se separó, y la capa acuosa se extrajo con acetato de etilo adicional tres veces. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre $MgSO_4$, se filtró, y se concentró. El residuo se purificó con cromatografía de columna flash sobre gel de sílice usando 10% acetato de etilo en hexanos para dar el compuesto del título.

EJEMPLO 307D

carboxilato de 4-((4-(4-clorofenil)-6-oxo-1,6-dihidropiridin-3–il)metil)piperazin-1-tert-butilo

Una mezcla de EJEMPLO 307C (1.6 g) y 5% HCl (20 mL) en tetrahidrofurano (20 mL) se calentó a 80 ºC durante la noche. El solvente se eliminó hasta sequedad. Este sólido se re-disolvió y se agregó a tetrahidrofurano (50 mL). A esta mezcla se añadieron BOC_2O (di-t-butil-dicarbonato) (1.118 g), trietilamina (0.72 mL), y 4-dimetilamionpiridina (1.4 g). El solvente se eliminó, y el residuo se particionó entre agua y acetato de etilo. La mezcla de reacción se agitó durante la noche. La capa orgánicas se secaron ($MgSO_4$), se filtró, y se concentró. El residuo se purificó por Prep HPLC eluyendo con 20-100% acetonitrilo/agua con 0.1% ácido trifluoroacético para dar el compuesto del título.

EJEMPLO 307E

carboxilato de 4-((4-(4-clorofenil)-1-isopropil-6-oxo-1,6-dihidropiridin-3–il)metil)piperazin-1- tert-butilo

EJEMPLO 307D (0.404 g) en N,N-dimetilformamida (5 mL) se trató con 60% hidruro de sodio (0.24 g) a temperatura ambiente. A esta mezcla se agregó 2-iodopropano (0.204 g). La mezcla se agitó durante la noche. La mezcla de reacción se particionó entre

acetato de etilo y agua. La capa orgánica se separó, y las capas acuosas se extrajeron con acetato de etilo adicional tres veces. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre $MgSO_4$, se filtró, y se concentró. El residuo se purificó con cromatografía de columna flash sobre gel de sílice usando 10% acetato de etilo en hexanos para dar EJEMPLO 307E y EJEMPLO 307F.

EJEMPLO 307F

carboxilato de 4-((4-(4-clorofenil)-6-isopropoxipiridin-3–il)metil)piperazin-1-tert-butilo

Este compuesto se aisló como un subproducto durante la preparación de EJEMPLO 307E.

EJEMPLO 307G

4-(4-clorofenil)-1-isopropil-5-(piperazin-1–ilmetil)piridin-2(1H)-ona

El compuesto del título se preparó utilizando EJEMPLO 307E en lugar de EJEMPLO 1A en el EJEMPLO 1B.

EJEMPLO 307H

benzoato de 2-(1H-indol-5–iloxi)-4-(4-((4-(4-clorofenil)-1-isopropil-6-oxo-1,6-dihidropiridin-3–il)metil)piperazin-1–il)etilo

El compuesto del título se preparó utilizando EJEMPLO 307G en lugar de EJEMPLO 20C y EJEMPLO 26A en lugar de EJEMPLO 20A en el EJEMPLO 20D.

EJEMPLO 307I

ácido 2-(1H-indol-5–iloxi)-4-(4-((4-(4-clorofenil)-1-isopropil-6-oxo-1,6-dihidropiridin-3–il)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 307H en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 307J

4-(4-{[4-(4-clorofenil)-1-isopropil-6-oxo-1,6-dihidropiridin-3–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 307I en lugar de EJEMPLO 26C en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11.07 (s, 1H), 8.62 (t, 1H), 8.59 (d, 1H), 7.79 (dd, 1H), 7.59 (s, 1H), 7.52-7.53 (m, J 3H), 7.38-7.45 (m,

4H), 7.15 (d, 1H), 7.10 (d, 1H), 6.87 (dd, 1H), 6.68 (dd, 1H), 6.39 (s, 1H), 6.22 (s, 1H), 6.17 (d, 1H), 5.01-5.06 (m, 1H), 3.85 (dd, 2H), 3.24-3.31 (m, 6H), 3.09 (s, 2H), 3.00 (s, 4H), 2.26 (m, 4H), 2.09 (m, 2H), 1.60-1.63 (m, 2H), 1.30 (d, 6H).

EJEMPLO 308

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(tetrahidro-2H-piran-4–ilmetil)amino]carbonil}fenil)sulfonil]benzamida

EJEMPLO 308A

4-sulfamoil-N-((tetrahidro-2H-piran-4–il)metil)benzamida

Ácido 4-Sulfamoilbenzoico (201 mg), (tetrahidro-2H-piran-4–il)metanamina (144 mg), 1-hidroxibenzotriazol hidrato (230 mg), y clorhidrato de 1-etil-3-[3-(dimetilamino)propil]-carbodiimida (288 mg) se combinaron en acetonitrilo. La mezcla se agitó a temperatura ambiente durante la noche. El sólidos se filtraron y la mezcla de reacción se concentró. El material crudo se purificó por cromatografía flash eluyendo con un gradiente de 2% metanol/diclorometano a 10% metanol/diclorometano.

EJEMPLO 308B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(tetrahidro-2H-piran-4–ilmetil)amino]carbonil}fenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 308A en lugar de EJEMPLO 1F y EJEMPLO 26C en lugar de EJEMPLO 1E en el EJEMPLO 1G. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11.19 (s, 1H), 8.57 (t, 1H), 7.94 (m, 4H), 7.48 (d, 1H), 7.43 (d, 1H), 7.40 (t, 1H), 7.33 (d, 2H), 7.21 (d, 1H), 7.03 (d, 2H), 6.88 (dd, 1H), 6.63 (dd, 1H), 6.42 (t, 1H), 6.13 (d, 1H), 3.84 (dd, 2H), 3.26 (m, 2H), 3.16 (t, 2H), 3.03 (br s, 4H), 2.74 (br s, 2H), 2.15 (m, 6H), 1.95 (s, 2H), 1.79 (m, 1H), 1.59 (d, 2H), 1.38 (t, 2H), 1.19 (m, 2H), 0.92 (s, 6H).

EJEMPLO 309

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(2-metoxietil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

EJEMPLO 309A

4-(2-metoxietilamino)-3-(trifluorometilsulfonil)bencensulfonamida

El compuesto del título se preparó utilizando EJEMPLO 159C durante 4-fluoro-3-nitrobencensulfonamida y 2-metoxietilamina en lugar de (tetrahidropiran-4–il)metilamina en el EJEMPLO 1F.

EJEMPLO 309B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(2-metoxietil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 26C y EJEMPLO 309A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11.26 (s, 1H), 8.13 (d, 1H), 7.79 (dd, 1H), 7.51 (d, 1H), 7.34 (d, 2H), 7.29 (t, 1H), 7.24 (m, 1H), 7.19 (d, 1H), 7.04 (d, 2H), 6.99 (m, 3H), 6.70 (dd, 1H), 6.44 (d, , 1H), 6.27 (m, 2H), 3.52 (m, 4H), 3.28 (s, 3H), 3.05 (m, 4H), 2.75 (s, 2H), 2.17 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EJEMPLO 310

Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-hidroxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida

EJEMPLO 310A

4-(aminometil)ciclohexanol

El compuesto del título se preparó como se describe en el EJEMPLO 311A por reemplazo de (4-metoxifenil)metanamina con (4-hidroxifenil)metanamina.

EJEMPLO 310B

2-(1H-indol-5–iloxi)-N-(4-cloro-3-nitrofenilsulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1–il)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 1G por reemplazo de EJEMPLO 1E y EJEMPLO 1F con EJEMPLO 26C y 4-cloro-3-nitrobencensulfonamida.

EJEMPLO 310C

Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-hidroxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida

Una mezcla de EJEMPLO 310B (100 mg), trietilamina (0.2 ml) y EJEMPLO 310A (35 mg) en dioxano (5 ml) se calentó a 100°C durante 20 horas y se concentró. El

residuo se purificó by RP-HPLC (10-70% acetonitrilo en 0.1% ácido trifluoroacético agua / 70 minutos) para dar el compuesto del título como una sal de ácido trifluoroacético. ^{1}H NMR (500 MHz, dimetilsulfóxido-d $_6$) δ 11.40 (s, 1H), 11.18 (s, 1H), 9.20 (s, 1H), 8.60 (t, 1H), 8.58 (d, 1H), 7.77 (dd, 1H), 7.54 (d, 1H), 7.42 (s, 1H), 7.37 - 7.41 (m, 3H), 7.14 (d, 1H), 7.04 - 7.09 (m, 3H), 6.86 (dd, 1H), 6.69 (dd, 1H), 6.39 (s, 1H), 6.21 (s, 1H), 3.50 - 3.68 (m, 3H), 3.20 - 3.27 (m, 3H), 2.93 - 3.07 (m, 2H), 2.66 - 2.82 (m, 2H), 2.13 - 2.22 (m, 2H), 2.01 (s, 2H), 1.83 (d, 2H), 1.67 - 1.77 (m, 3H), 1.50 - 1.60 (m, 1H), 1.44 (s, 2H), 0.96 - 1.17 (m, 4H), 0.94 (s, 6H).

EJEMPLO 311

Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(4-metoxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida

EJEMPLO 311A

(4-metoxiciclohexil)metanamina

(4-Metoxifenil)metanamina (1 g) en etanol (10 ml) se trató con 5% Rh-Al_2O_3 seco (0.5 g) bajo H_2 (500 psi) a 60 °C durante 6 horas y luego a 125°C durante 26 horas. El material insoluble se filtró y el filtrado se concentró para dar el compuesto del título.

EJEMPLO 311B

4-(((Trans-4-metoxiciclohexil)metilamino)-3-nitrobencensulfonamida

4-fluoro-3-nitrobencensulfonamida (15 g) y EJEMPLO 311A (11.71 g) en tetrahidrofurano (200 ml) se trató con trietilamina (28.5 ml) durante la noche. La reacción se concentró y el residuo se cargó en una columna C18, y eludía con 40-55% acetonitrilo en agua para dar el compuesto del título.

EJEMPLO 311C

4-(((Cis-4-metoxiciclohexil)metilamino)-3-nitrobencensulfonamida

Este compuesto se fabricó desde el mismo procedimiento que también produjo EJEMPLO 311B.

EJEMPLO 311D

Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(4-metoxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 175F por reemplazo de EJEMPLO 175E y EJEMPLO 1F con EJEMPLO 26C y EJEMPLO 311B,

respectivamente. ^{1}H NMR (500 MHz, dimetilsulfóxido-d $_6$) δ 11.17 (s, 2H), 8.55 - 8.62 (m, 2H), 7.78 (dd, 1H), 7.51 (d, 1H), 7.37 - 7.43 (m, 2H), 7.33 (d, 2H), 7.15 (d, 1H), 7.01 - 7.08 (m, 3H), 6.86 (dd, 1H), 6.65 (dd, 1H), 6.39 (s, 1H), 6.14 (d, 1H), 3.25 (t, 2H), 3.22 (s, 3H), 3.00 - 3.10 (m, 5H), 2.72 (s, 2H), 2.15 (d, 6H), 2.00 (d, 2H), 1.94 (s, 2H), 1.78 (d, 2H), 1.53 - 1.65 (m, 1H), 1.38 (t, 2H), 0.96 - 1.12 (m, 4H), 0.92 (s, 6H).

EJEMPLO 312

Cis-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-hidroxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida

El compuesto del título (sal de ácido trifluoroacético) se obtuvo durante la purificación de EJEMPLO 310C. ^{1}H NMR (500 MHz, dimetilsulfóxido-d $_6$) δ 11.39 (s, 1H), 11.18 (s, 1H), 9.17 (s, 1H), 8.61 (t, 1H), 8.58 (d, 1H), 7.78 (dd, 1H), 7.54 (d, 1H), 7.34 - 7.43 (m, 5H), 7.14 (d, 1H), 7.07 (t, 3H), 6.85 (dd, 1H), 6.69 (d, 1H), 6.39 (s, 1H), 6.21 (s, 1H), 3.77 (s, 1H), 3.58 (s, 2H), 3.24 - 3.29 (m, 2H), 2.91 - 3.07 (m, 2H), 2.60 - 2.81 (m, 2H), 2.17 (s, 2H), 2.00 (s, 2H), 1.57 - 1.72 (m, 4H), 1.43 (t, 7H), 0.94 (s, 6H).

EJEMPLO 313

Cis-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(4-metoxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 175F por reemplazo de EJEMPLO 175E y EJEMPLO 1F con EJEMPLO 26C y EJEMPLO 311C, respectivamente. ^{1}H NMR (500 MHz, dimetilsulfóxido-d $_6$) δ 11.17 (s, 2H), 8.60 (t, 1H), 8.58 (d, 1H), 7.78 (dd, 1H), 7.51 (d, 1H), 7.37 - 7.44 (m, 2H), 7.33 (d, 2H), 7.16 (d, 1H), 7.07 (d, 1H), 7.03 (d, 2H), 6.86 (dd, 1H), 6.65 (dd, 1H), 6.39 (s, 1H), 6.14 (d, 1H), 3.36 - 3.39 (m, 1H), 3.26 (t, 2H), 3.20 (s, 3H), 3.03 (s, 4H), 2.72 (s, 2H), 2.15 (d, 6H), 1.94 (s, 2H), 1.81 (dd, 2H), 1.63 - 1.73 (m, 1H), 1.48 (dd, 2H), 1.23 - 1.41 (m, 6H), 0.92 (s, 6H).

EJEMPLO 314

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[3-nitro-4-(2-tetrahidro-2H-piran-4–iletoxi)fenil]sulfonil}benzamida

EJEMPLO 314A

3-nitro-4-(2-(tetrahidro-2H-piran-4–il)etoxi)bencensulfonamida

El compuesto del título se preparó utilizando 2-(tetrahidro-2H-piran-4–il)etanol en lugar de (tetrahidro-2H-piran-4–il)metanol en el EJEMPLO 279A.

EJEMPLO 314B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[3-nitro-4-(2-tetrahidro-2H-piran-4–iletoxi)fenil]sulfonil}benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 26C y EJEMPLO 314A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11.25 (s, 1H), 8.25 (d, 1H), 7.95 (dd, 1H), 7.54 (d, 1H), 7.39 (d, 1H), 7.34 (d, 2H), 7.29 (m, 1H), 7.17 (m, 1H), 7.04 (d, 2H), 6.97 (m, 1H), 6.70 (dd, 1H), 6.41 (d, 1H), 6.28 (m, 2H), 4.26 (t, 2H), 3.83 (m, 2H), 3.27 (m, 2H), 3.07 (m, 4H), 2.80 (m, 2H), 2.15 (m, 6H), 1.96 (s, 2H), 1.70 (m, 3H), 1.60 (m, 2H), 1.39 (t, 2H), 1.22 (m, 2H), 0.93 (s, 6H).

EJEMPLO 315

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(2-metoxietil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 309A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11.17 (s, 1H), 8.18 (d, 1H), 7.92 (dd, 1H), 7.49 (d, 1H), 7.40 (m, 2H), 7.33 (d, 2H), 7.26 (m, 1H), 7.17 (d, 1H), 7.04 (m, 3H), 6.86 (dd, 1H), 6.65 (dd, 1H), 6.40 (m, 1H), 6.14 (d, 1H), 3.51 (m, 4H), 3.28 (s, 3H), 3.03 (s, 4H), 2.74 (m, 2H), 2.16 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EJEMPLO 316

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[3-(metilsulfonil)propoxi]-3-nitrofenil}sulfonil)benzamida

EJEMPLO 316A

4-(3-(metiltio)propoxi)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando 3-(metiltio)propan-1-ol en lugar de (tetrahidro-2H-piran-4–il)metanol en el EJEMPLO 279A.

EJEMPLO 316B

4-(3-(metilsulfonil)propoxi)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando EJEMPLO 316A en lugar de EJEMPLO 294A en el EJEMPLO 294B.

EJEMPLO 316C

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[3-(metilsulfonil)propoxi]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 26C y EJEMPLO 316B en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11.24 (s, 1H), 8.28 (d, 1H), 7.96 (dd, 1H), 7.54 (d, 1H), 7.35 (m, 3H), 7.29 (t, 1H), 7.17 (d, 1H), 7.04 (d, 2H), 6.96 (m, 1H), 6.71 (dd, 1H), 6.39 (d, 1H), 6.29 (m, 2H), 4.34 (t, 2H), 3.27 (m, 4H), 3.07 (m, 4H), 3.03 (s, 3H), 2.81 (s, 2H), 2.21 (m, 6H), 1.96 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

EJEMPLO 317

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(3-metoxipropil)amino]-3-nitrofenil}sulfonil)benzamida

EJEMPLO 317A

4-(3-metoxipropilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando 3-metoxipropan-1-amina en lugar de (tetrahidropiran-4–il)metilamina en el EJEMPLO 1F.

EJEMPLO 317B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(3-metoxipropil)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 26C en lugar de EJEMPLO 1E y EJEMPLO 317A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (500 MHz, piridina-d5) δ 12.24 (s, 1H), 9.30 (d, 1H), 8.88 (t, 1H), 8.28 (dd, 1H), 8.19 (d, 1H), 7.51 - 7.56 (m, 2H), 7.41 - 7.46 (m, 3H), 7.04 - 7.12 (m, 3H), 6.78 (d, 1H), 6.73 (dd, 1H), 6.60 (s, 1H), 6.55 (d, 1H), 3.40 (t, 2H), 3.29 - 3.36 (m, 2H), 3.27 (s, 3H), 3.01 - 3.08 (m, 4H), 2.76 (s, 2H), 2.25 (t, 2H), 2.06 - 2.15 (m, 4H), 1.97 (s, 2H), 1.78 - 1.86 (m, 2H), 1.38 (t, 2H), 0.93 (s, 6H).

EJEMPLO 318

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(3-metoxipropil)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 1E y EJEMPLO 317A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (500 MHz, piridina-d_5) δ 12.39 (s, 1H), 9.21 (d, 1H), 8.86 (t, 1H), 8.15 - 8.24 (m, 2H), 7.42 -

7.50 (m, 3H), 7.38 (d, 1H), 7.04 - 7.13 (m, 3H), 6.73 - 6.81 (m, 4H), 6.67 (d, 1H), 3.39 (t, 2H), 3.32 (q, 2H), 3.27 (s, 3H), 2.96 - 3.07 (m, 4H), 2.76 (s, 2H), 2.25 (t, 2H), 2.07 - 2.16 (m, 4H), 1.97 (s, 2H), 1.77 - 1.87 (m, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

EJEMPLO 319

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2-cianoetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida

EJEMPLO 319A

4-(2-cianoetilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando 3-aminopropanenitrilo en lugar de (tetrahidropiran-4–il)metilamina en el EJEMPLO 1F.

EJEMPLO 319B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2-cianoetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 26C en lugar de EJEMPLO 1E y EJEMPLO 319A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (500 MHz, piridina-d_5) δ 9.26 (d, 1H), 9.06 (t, 1H), 8.34 (dd, 1H), 8.18 (d, 1H), 7.51 - 7.57 (m, 2H), 7.39 - 7.47 (m, 3H), 7.04 - 7.11 (m, 3H), 7.00 (d, 1H), 6.74 (dd, 1H), 6.60 (s, 1H), 6.54 (d, 1H), 3.83 (q, *J*=6.7 Hz, 2H), 3.01 - 3.08 (m, 4H), 2.98 (t, 2H), 2.76 (s, 2H), 2.25 (t, 2H), 2.07 - 2.15 (m, 4H), 1.97 (s, 2H), 1.38 (t, 2H), 0.93 (s, 6H).

EJEMPLO 320

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2-cianoetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-4–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 1E y EJEMPLO 319A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (500 MHz, piridina-d_5) δ 12.41 (s, 1H), 9.16 (d, 1H), 9.05 (t, 1H), 8.31 (dd, 1H), 8.17 (d, 1H), 7.39 (d, 1H), 7.05 - 7.13 (m, 3H), 6.99 (d, 1H), 6.78 (dd, 1H), 6.72 - 6.76 (m, 2H), 6.66 (d, 1H), 3.83 (q, 2H), 3.01 - 3.07 (m, 4H), 2.98 (t, 2H), 2.76 (s, 2H), 2.25 (t, 2H), 2.08 - 2.16 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

EJEMPLO 321

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[(3R)-4-hidroxi-1-adamantil]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 310C por reemplazo de EJEMPLO 310A con 5-aminometil-admantan-2-ol. ^{1}H NMR (500 MHz,

dimetilsulfóxido-d_6) δ 11.17 (s, 2H), 8.57 (d, 1H), 8.51 (t, 1H), 7.76 (dd, 1H), 7.50 (d, 1H), 7.38 - 7.42 (m, 2H), 7.33 (d, 2H), 7.11 - 7.16 (m, 2H), 7.03 (d, 2H), 6.86 (dd, 1H), 6.65 (dd, 1H), 6.39 (s, 1H), 6.14 (d, 1H), 4.61 (d, 1H), 3.63 (d, 1H), 3.13 (d, 2H), 3.03 (s, 4H), 2.73 (s, 2H), 2.11 - 2.21 (m, 6H), 2.04 (d, 2H), 1.95 (s, 2H), 1.78 - 1.86 (m, 3H), 1.49 - 1.60 (m, 6H), 1.38 (t, 2H), 1.29 (d, 2H), 0.92 (s, 6H).

EJEMPLO 322

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[Cis-4-hidroxi-1-adamantil]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 310C por reemplazo de EJEMPLO 310A con 5-aminometil-admantan-2-ol. ^{1}H NMR (500 MHz, dimetilsulfóxido-d_6) δ 11.16 (s, 2H), 8.57 (d, 1H), 8.52 (t, 1H), 7.71 - 7.80 (m, 1H), 7.51 (d, 1H), 7.37 - 7.42 (m, 2H), 7.33 (d, 2H), 7.09 - 7.17 (m, 2H), 7.03 (d, 2H), 6.85 (dd, 1H), 6.65 (dd, 1H), 6.39 (s, 1H), 6.14 (d, 1H), 4.61 (d, 1H), 3.61 (d, 1H), 3.08 (d, 2H), 3.03 (s, 4H), 2.72 (s, 2H), 2.09 - 2.21 (m, 6H), 1.82 - 1.96 (m, 7H), 1.55 - 1.69 (m, 4H), 1.49 (s, 2H), 1.38 (t, 2H), 1.19 - 1.27 (m, 3H), 0.92 (s, 6H).

EJEMPLO 323

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(3,3,3-trifluoropropil)amino]fenil}sulfonil)benzamida

EJEMPLO 323A

3-nitro-4-(3,3,3-trifluoropropilamino)bencensulfonamida

El compuesto del título se preparó utilizando 3,3,3-trifluoropropan-1-amina en lugar de (tetrahidro-2H-piran-4–il)metanamina en el EJEMPLO 1F.

EJEMPLO 323B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(3,3,3-trifluoropropil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 323A en lugar de EJEMPLO 1F y EJEMPLO 55B en lugar de EJEMPLO 26C en el EJEMPLO 177. ^{1}H NMR (500 MHz, dimetilsulfóxido-d_6) δ 11.34 (s, 1H), 11.19 (s, 1H), 8.53 (m, 1H), 8.47 (s, 1H), 7.74 (dd, 1H), 7.54 (d, 1H), 7.34 (d, 2H), 7.25 (m, 1H), 7.13 (d, 1H), 6.99 (m, 4H), 6.67 (d, 1H), 6.36 (d, 1H), 6.24 (m, 2H), 3.65 (q, 2H), 3.01 (m, 4H), 2.68 (m, 4H), 2.16 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.93 (s, 6H).

EJEMPLO 324

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(3,3,3-trifluoropropil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 323A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (500 MHz, dimetilsulfóxido-d $_6$) δ 11.06 (s, 1H), 8.44 (m, 2H), 7.75 (dd, 1H), 7.54 (d, 1H), 7.33 (m, 4H), 7.02 (m, 3H), 6.90 (d, 1H), 6.76 (dd, 1H), 6.58 (dd, 1H), 6.33 (m, 1H), 6.15 (d, 1H), 3.63 (q, 2H), 2.97 (m, 4H), 2.68 (m, 4H), 2.16 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EJEMPLO 325

N-({5-bromo-6-[(tetrahidro-2H-piran-4–ilmetil)amino]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)benzamida

EJEMPLO 325A

5-bromo-6-((tetrahidro-2H-piran-4–il)metilamino)piridina-3-sulfonamida

La mezcla de EJEMPLO 329A (93 mg), (tetrahidro-2H-piran-4–il)metanamina (40 mg) y trietilamina (0.144 mL) en dioxano anhidro (4 mL) se calentó a 110°C durante la noche. El solvente orgánico se eliminó al vacío. El residuo se suspendió en diclorometano. El sólido se filtró y se secó para dar el compuesto del título.

EJEMPLO 325B

N-({5-bromo-6-[(tetrahidro-2H-piran-4–ilmetil)amino]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 26C y EJEMPLO 325A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11.28 (s, 1H), 11.10 (s, 1H), 8.38 (d, 1H), 7.93 (d, 1H), 7.57 (d, 1H), 7.32 (m, 4H), 7.22 (d, 1H), 7.02 (m, 3H), 6.71 (dd, 1H), 6.51 (d, 1H), 6.27 (m, 2H), 3.82 (dd, 2H), 3.31 (m, 2H), 3.23 (m, 2H), 3.05 (m, 4H), 2.74 (s, 2H), 2.16 (m, 6H), 1.95 (s, 2H), 1.88 (m, 1H), 1.55 (m, 2H), 1.37 (m, 2H), 1.18 (m, 2H), 0.92 (s, 6H).

EJEMPLO 326

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1,1-dioxidotetrahidrotien-3–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 337A en lugar de 4-cloro-3-nitrobenceno sulfonamida y clorhidrato de (1,1-dioxidotetrahidrotien-3–il)metilamina en lugar de 1-(2-metoxi-etil)-piperidin-4–ilamina en el EJEMPLO 189A. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11.25 (s, 1H), 8.71 (m, 1H), 8.51 (d, 1H), 7.72 (dd, 1H), 7.53 (d, 1H), 7.34 (d, 2H), 7.29 (m, 1H), 7.18 (d, 1H), 7.12 (d, 1H), 7.04 (d, 2H), 6.98 (m, 1H), 6.70 (dd, 1H), 6.44 (d, 1H), 6.26 (dd, 2H), 3.55 (t, 2H), 3.27 (m, 2H), 3.04 (m, 5H), 2.91 (m, 1H), 2.74 (s, 3H), 2.28 (m, 1H), 2.16 (m, 6H), 1.95 (s, 2H), 1.85 (m, 1H), 1.38 (t, 2H), 0.92 (s, 6H).

EJEMPLO 327

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 306D en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11.16 (s, 2H), 8.41 (d, 1H), 8.10 (dd, 1H), 7.51 (d, 1H), 7.39-7.46 (m, 3H), 7.34 (d, 2H), 7.16 (s, 1H), 7.04 (d2H), 6.85 (dd, 1H), 6.64 (dd, 1H), 6.40 (d, 1H), 6.15 (d, 1H), 4.38 (d, 2H), 3.76-3.80 (m, 2H), 3.56-3.61 (m, 2H), 3.05 (s, 4H), 2.78 (s, 2H), 2.12-2.23 (m, 6H), 1.95 (s, 2H), 1.80-1.89 (m, 4H), 1.38 (t, 2H), 0.92 (s, 6H).

EJEMPLO 328

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-(metilamino)-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

EJEMPLO 328A

4-(metilamino)-3-(trifluorometilsulfonil)bencensulfonamida

El compuesto del título se preparó utilizando EJEMPLO 159C durante 4-fluoro-3-nitrobencensulfonamida y metilamina en lugar de (tetrahidropiran-4–il)metilamina en el EJEMPLO 1F.

EJEMPLO 328B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-(metilamino)-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 328A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11.17 (s, 1H), 8.17 (d, 1H), 7.91 (dd, 1H), 7.49 (d, 1H), 7.40 (m, 3H), 7.33 (d, 2H), 7.16 (m, 1H), 7.04

(d, 2H), 6.87 (m, 2H), 6.65 (dd, 1H), 6.40 (m, 1H), 6.14 (d, 1H), 3.03 (m, 4H), 2.91 (d, 3H), 2.73 (s, 2H), 2.15 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EJEMPLO 329

N-{[5-bromo-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida

EJEMPLO 329A

5-bromo-6-cloropiridina-3-sulfonamida

Cloruro de 5-Bromo-6-cloropiridina-3-sulfonilo (8.2 g) en metanol (20 mL) se enfrió a 0 ºC. A esta mezcla se agregó 7N NH_3 en metanol (80 mL). La mezcla de reacción se agitó durante la noche. El solvente se eliminó a baja temperatura, y el residuo se particionó entre acetato de etilo y agua. La capa acuosa se extrajo con acetato de etilo tres veces. Las capas orgánicas combinadas se lavaron con salmuera, se secó ($MgSO_4$), se filtró, y se concentró. El sólido se purificó por cromatografía de columna flash sobre gel de sílice usando 10-50% acetato de etilo en hexanos para dar el compuesto del título.

EJEMPLO 329B

5-bromo-6-((tetrahidro-2H-piran-4–il)metoxi)piridina-3-sulfonamida

(Tetrahidro-2H-piran-4–il)metanol (0.65 g) en tetrahidrofurano (20 mL) se trató con 60% hidruro de sodio (0.895 g). La mezcla de reacción se agitó por 10 minutos. A esta mezcla se agregó EJEMPLO 329A (1.519 g). La mezcla de reacción se agitó durante la noche. Se vertió en agua, neutralizó con 10 % HCl acuoso, y se extrajo con acetato de etilo tres veces. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre $MgSO_4$, se filtró, y se concentró. El residuo se purificó con cromatografía de columna flash sobre gel de sílice eluyendo con 20%-60% acetato de etilo en hexanos para dar el compuesto del título.

EJEMPLO 329C

N-{[5-bromo-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 329B en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11.15 (s, 1H), 8.60 s, 1H), 8.38 (d, 1H), 7.54 (d, 1H), 7.38-7.42 (m, 2H), 7.34 (d, 2H), 7.17 (s, 1H), 7.04 (d,

2H), 6.85 (dd, 1H), 6.64 (dd, 1H), 6.39 (s, 1H), 6.14 (d, 1H), 4.25 (d, 2H), 3.87 (dd, 2H), 3.05 (s, 4H), 2.80 (s, 2H), 2.25 (s, 4H), 2.12-2.14 (m, 4H), 1.95 (s, 2H), 1.63-1.66 (m, 2H), 1.37-1.40 (m, 2H), 0.92 (s, 6H).

EJEMPLO 330

4-(4-{[4-(4-clorofenil)-6-isopropoxipiridin-3–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 330A

1-((4-(4-clorofenil)-6-isopropoxipiridin-3–il)metil)piperazina

El compuesto del título se preparó utilizando EJEMPLO 307F en lugar de EJEMPLO 1A en el EJEMPLO 1B.

EJEMPLO 330B

benzoato de 2-(1H-indol-5–iloxi)-4-(4-((4-(4-clorofenil)-6-isopropoxipiridin-3–il)metil)piperazin-1–il)etilo

El compuesto del título se preparó utilizando EJEMPLO 330A en lugar de EJEMPLO 20C y EJEMPLO 26A en lugar de EJEMPLO 20A en el EJEMPLO 20D.

EJEMPLO 330C

Ácido 2-(1H-indol-5–iloxi)-4-(4-((4-(4-clorofenil)-6-isopropoxipiridin-3–il)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 330B en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 330D

4-(4-{[4-(4-clorofenil)-6-isopropoxipiridin-3–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 330C en lugar de EJEMPLO 26C en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11.21, (s, 1H), 11.17 (s, 1H), 8.63 (t, 1H), 8.59 (d, 1H), 8.08 (s, 1H), 7.79 (dd1H), 7.54-7.56 (m, 3H), 7.47 (d, 2H), 7.38-7.42 (m, 2H), 7.15 (d, 1H), 7.10 (d, 1H), 6.87 (dd, 1H), 6.68 (dd, 1H), 6.59 (s, 1H), 6.39 (s, 1H), 6.17 (d, 1H), 5.23-5.28 (m, 1H), 3.85 (dd, 2H), 3.24-3.31 (m, 4H), 3.02 (s, 4H), 2.29 (s, 4H), 1.86-1.91 (m, 1H), 1.61-1.63 (m, 2H), 1.28 (d, 6H).

EJEMPLO 331

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[6-(tetrahidro-2H-piran-4–ilmetoxi)-5-(1,3-tiazol-2–il)piridin-3–il]sulfonil}benzamida

EJEMPLO 331A

6-((tetrahidro-2H-piran-4–il)metoxi)-5-(tiazol-2–il)piridina-3-sulfonamida

Una mezcla de EJEMPLO 329B (0.070 g), 2-(tributilstannil)tiazol (0.090 g), y tetrakis(trifenilfosfina)paladio(0) (0.069 g) en dioxano (2 mL) se calentó a 90 ºC durante 4 horas. Después de enfriar, la mezcla se cargó en una columna de gel de sílice y eluyendo con 1:3 acetato de etilo:hexanos para dar el compuesto del título.

EJEMPLO 331B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[6-(tetrahidro-2H-piran-4–ilmetoxi)-5-(1,3-tiazol-2–il)piridin-3–il]sulfonil}benzamida

El compuesto del título se preparó utilizando EJEMPLO 331A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11.14 (s, 1H), 9.09 (s, 1H), 8.73 (s, 1H), 8.06 (d, 1H), 7.98 (d, 1H), 7.50 (d, 1H), 7.37-7.38 (m, 2H), 7.33 (d, 2H), 7.17 (d, 1H), 7.03 (d, 2H), 6.84 (dd, 1H), 6.62 (dd, 1H), 6.37 (s, 1H), 6.11 (d, 1H), 4.46 (d, 2H), 3.91 (dd, 2H), 3.36-3.39 (m, 4H), 3.02 (s, 4H), 2.76 (s, 2H), 2.12-2.20 (s, 8H), 1.94 (s, 2H), 1.45-1.47 (m, 2H), 1.37 (t, 2H), 0.91 (s, 6H).

EJEMPLO 332

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(2-metoxietil)amino]carbonil}fenil)sulfonil]benzamida

EJEMPLO 332A

N-(2-metoxietil)-4-sulfamoilbenzamida

El compuesto del título se preparó utilizando 2-metoxietanamina en lugar de (tetrahidro-2H-piran-4–il)metanamina en el EJEMPLO 308A.

EJEMPLO 332B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(2-metoxietil)amino]carbonil}fenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 332A en lugar de EJEMPLO 1F y EJEMPLO 26C en lugar de EJEMPLO 1E en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11.28 (br s, 1H), 11.17 (s, 1H), 8.71 (m, 1H), 7.94 (m, 4H), 7.48 (d, 1H), 7.41 (m, 2H), 7.33 (d, 2H), 7.21 (d, 1H), 7.03 (d, 2H), 6.88 (dd, 1H), 6.63 (dd, 1H), 6.42 (t, 1H), 6.13 (d, 1H), 3.45 (m, 4H), 3.27 (s, 3H), 3.03 (m, 4H), 2.73 (br s, 2H), 2.16 (m, 6H), 1.95 (br s, 2H), 1.38 (m, 2H), 0.92 (s, 6H).

EJEMPLO 333

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-ciano-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indol-5–iloxi)benzamida

EJEMPLO 333A

5-ciano-6-((tetrahidro-2H-piran-4–il)metoxi)piridina-3-sulfonamida

Una mezcla de EJEMPLO 329B (0.702 g), dicianozinc (0.129 g), y tetrakis(trifenilfosfina)paladio(0) (0.231 g) en N,N-dimetilformamida (2 mL) se desgasificó a través de ciclo de vacío/nitrógeno tres veces. La mezcla de reacción se calentó a 120 ºC durante 3 horas. Después de enfriar, fue vertida en agua y se extrajo con acetato de etilo tres veces. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre $MgSO_4$, se filtró, y se concentró. El residuo se purificó con cromatografía de columna flash sobre gel de sílice eluyendo con 20%-60% acetato de etilo en hexanos para dar el compuesto del título.

EJEMPLO 333B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-ciano-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 333A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11.17 (s, 1H), 8.84 (d, 1H), 8.64 (d, 1H), 7.57 (d, 1H), 7.38-7.41 (m, 4H), 7.12 (d, 1H), 7.08 (d, 2H), 6.87 (dd, 1H), 6.71 (dd, 1H), 6.38 (s, 1H), 6.23 (d, 1H), 4.31 (d, 2H), 3.88 (dd, 2H), 3.54 (br s, 2H), 3.02 (br s, 4H), 2.76 (br s, 2H), 2.18(s, 4H), 2.01 (s, 2H), 1.63-1.66 (m, 2H), 1.49 (t, 2H), 0.94 (s, 6H).

EJEMPLO 334

N-({4-[(1-acetilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando 1-acetilpiperidin-4-amina en lugar de 1-(2-metoxi-etil)-piperidin-4–ilamina y EJEMPLO 310B en lugar de 4-cloro-3-nitrobencensulfonamida en el EJEMPLO 189A. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11.16 (br s, 1H), 8.58 (d, 1H), 8.25 (d, 1H), 7.81 (dd, 1H), 7.51 (d, 1H), 7.43-7.37 (m, 2H), 7.34 (d, 2H), 7.19 (d, 1H), 7.15 (d, 1H), 7.04 (d, 2H), 6.85 (dd, 1H), 6.65 (dd, 1H), 6.39 (t, 1H), 6.15 (d, 1H), 4.32-4.23 (m, 1H), 3.96-3.77 (m, 2H), 3.21 (m, 2H), 3.03 (m, 4H), 2.80 (m, 2H), 2.73 (br s, 2H), 2.16 (m, 6H), 2.02 (s, 3H), 1.95 (br s, 2H), 1.65-1.44 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EJEMPLO 335

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[1-(metilsulfonil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó utilizando 1-(metilsulfonil)piperidin-4-amina en lugar de 1-(2-metoxi-etil)-piperidin-4–ilamina y EJEMPLO 187A en lugar de 4-cloro-3-nitrobencensulfonamida en el EJEMPLO 189A. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11.15 (br s, 1H), 8.59 (d, 1H), 8.25 (d, 1H), 7.82 (dd, 1H), 7.51 (d, 1H), 7.43-7.38 (m, 2H), 7.34 (d, 2H), 7.14 (m, 2H), 7.04 (d, 2H), 6.85 (dd, 1H), 6.65 (dd, 1H), 6.39 (t, 1H), 6.15 (d, 1H), 3.80 (m, 1H), 3.57 (m, 2H), 3.04 (m, 4H), 2.95 (m, 2H), 2.92 (br s, 3H), 2.73 (m, 2H), 2.15 (m, 6H), 2.06-1.98 (m, 2H), 1.95 (br s, 2H), 1.70 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EJEMPLO 336

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1,4-dioxan-2–ilmetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida

EJEMPLO 336A

4-((1,4-dioxan-2–il)metilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó como se describe en el EJEMPLO 1F por reemplazo de (tetrahidro-2H-piran-4–il)metanamina con (1,4-dioxan-2–il)metanamina.

EJEMPLO 336B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1,4-dioxan-2–ilmetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 175F por reemplazo de EJEMPLO 175E y EJEMPLO 1F con EJEMPLO 26C y EJEMPLO 336A, respectivamente. ^{1}H NMR (500 MHz, dimetilsulfóxido-d $_6$) δ 11.16 (s, 2H), 8.54 - 8.63 (m, 2H), 7.82 (dd, 1H), 7.50 (d, 1H), 7.38 - 7.42 (m, 2H), 7.33 (d, 2H), 7.16 (d, 1H), 7.10 (d, 1H), 7.03 (d, 2H), 6.86 (dd, 1H), 6.65 (dd, 1H), 6.39 (s, 1H), 6.14 (d, 1H), 3.76 - 3.82 (m, 3H), 3.57 - 3.68 (m, 2H), 3.45 - 3.52 (m, 2H), 3.36 - 3.42 (m, 1H), 3.03 (s, 4H), 2.73 (d, 2H), 2.10 - 2.22 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EJEMPLO 337

N-({4-[(1-acetilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)benzamida

EJEMPLO 337A

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 1E y 4-cloro-3-nitrobencensulfonamida en lugar de EJEMPLO 1F en el EJEMPLO 1G.

EJEMPLO 337B

N-({4-[(1-acetilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)benzamida

El compuesto del título se preparó utilizando 1-acetilpiperidin-4-amina en lugar de 1-(2-metoxi-etil)-piperidin-4–ilamina y EJEMPLO 337A en lugar de 4-cloro-3-nitrobencensulfonamida en el EJEMPLO 189A. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11.24 (br s, 1H), 8.50 (d, 1H), 8.24 (d, 1H), 7.73 (dd, 1H), 7.52 (d, 1H), 7.34 (d, 2H), 7.27 (t, 1H), 7.19-7.13 (m, 2H), 7.04 (t, 2H), 6.97 (t, 1H), 6.70 (dd, 1H), 6.42 (d, 1H), 6.27 (dd, 1H), 6.24 (t, 1H), 4.29 (m, 1H), 3.97-3.78 (m, 2H), 3.22 (m, 2H), 3.05 (m, 4H), 2.81 (m, 2H), 2.72 (br s, 2H), 2.15 (m, 6H), 2.03 (s, 3H), 1.95 (br s, 2H), 1.66-1.44 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EJEMPLO 338

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[1-(metilsulfonil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó utilizando 1-(metilsulfonil)piperidin-4-amina en lugar de 1-(2-metoxi-etil)-piperidin-4–ilamina y EJEMPLO 337A en lugar de 4-cloro-3-

nitrobencensulfonamida en el EJEMPLO 189A. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11.24 (br s, 1H), 8.50 (d, 1H), 8.25 (d, 1H), 7.74 (dd, 1H), 7.52 (d, 1H), 7.34 (d, 2H), 7.27 (t, 1H), 7.17 (d, 1H), 7.12 (d, 1H), 7.04 (d, 2H), 6.97 (t, 1H), 6.70 (dd, 1H), 6.42 (d, 1H), 6.27 (d, 1H), 6.24 (t, 1H), 3.81 (m, 1H), 3.58 (m, 2H), 3.05 (m, 4H), 2.96 (m, 2H), 2.92 (s, 3H), 2.74 (m, 2H), 2.16 (m, 6H), 2.06-1.98 (m, 2H), 1.95 (br s, 2H), 1.70 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EJEMPLO 339

4-(4-{[4'-cloro-5-(trifluorometil)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 339A

benzoato de 2-(1H-indol-5–iloxi)-4-(4-(2-bromo-4-(trifluorometil)bencil)piperazin-1–il)metilo

El compuesto del título se preparó utilizando 4-trifluorometil-2-bromobenzaldehido en lugar de EJEMPLO 27C y EJEMPLO 150A en lugar de carboxilato de piperazin-1-tert-butilo en el EJEMPLO 1A.

EJEMPLO 339B

benzoato de 2-(1H-indol-5–iloxi)-4-(4-((4'-cloro-5-(trifluorometil)bifenil-2–il)metil)piperazin-1–il)metilo

El compuesto del título se preparó utilizando EJEMPLO 339A en lugar de 2-fluoro-4-iodo-5-metilpiridina en el EJEMPLO 307A.

EJEMPLO 339C

Ácido 2-(1H-indol-5–iloxi)-4-(4-((4'-cloro-5-(trifluorometil)bifenil-2–il)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 339B en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 339D

4-(4-{[4'-cloro-5-(trifluorometil)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 339C en lugar de EJEMPLO 26C en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11.24, (s, 1H), 11.17 (s, 1H), 8.63 (t, 1H), 7.79 (dd, 1H), 7.72 (m, 2H), 7.38-7.53 (m, 8H), 7.15 (d, 1H), 7.10 (d, 1H), 6.87 (dd, 1H), 6.67 (dd, 1H), 6.39 (s, 1H), 6.16 (d, 1H), 3.85 (dd, 2H), 3.41 (s, 2H), 3.24-3.31 (m, 6H), 3.04 (s, 4H), 2.29 (s, 4H), 1.60-1.63 (m, 2H), 1.24-1.28 (m, 2H).

EJEMPLO 340

4-(4-{[4'-cloro-5-(trifluorometil)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(tetrahidro-2H-piran-4–ilmetoxi)fenil]sulfonil}benzamida

El compuesto del título se preparó utilizando EJEMPLO 339C en lugar de EJEMPLO 26C y EJEMPLO 279A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11.40, (s, 1H), 11.17 (s, 1H), 8.41 (d, 1H), 8.07 (dd, 1H), 7.70-7.74 (m, 2H), 7.38-7.53 (m, 8H), 7.16 (d, 1H), 6.87 (dd, 1H), 6.67 (dd, 1H), 6.40 (s, 1H), 6.17 (d, 1H), 4.09 (d, 2H), 3.88 (dd, 2H), 3.42 (s, 2H), 3.05 (s, 4H), 2.30 (s, 4H), 2.00-2.05 (m, 1H), 1.63-1.66 (m, 2H), 1.31-1.37 (m, 2H).

EJEMPLO 341

4-{4-[(5-tert-butil-4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 341A

Benzoato de 2-(1H-indol-5–iloxi)-4-(4-(2-bromo-4-tert-butilbencil)piperazin-1–il)metilo

El compuesto del título se preparó utilizando 4-tert-butil-2-bromobenzaldehido en lugar de EJEMPLO 27C y EJEMPLO 150A en lugar de carboxilato de piperazin-1-tert-butilo en el EJEMPLO 1A.

EJEMPLO 341B

benzoato de 2-(1H-indol-5–iloxi)-4-(4-((5-tert-butil-4'-clorobifenil-2–il)metil)piperazin-1–il) metilo

El compuesto del título se preparó utilizando EJEMPLO 341A en lugar de 2-fluoro-4-iodo-5-metilpiridina en el EJEMPLO 307A.

EJEMPLO 341C

Ácido 2-(1H-indol-5–iloxi)-4-(4-((5-tert-butil-4'-clorobifenil-2–il)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 341B en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 341D

4-{4-[(5-tert-butil-4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 341C en lugar de EJEMPLO 26C en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11.22, (s, 1H), 11.16 (s, 1H), 8.62 (t, 1H), 8.58 (d, 1H), 7.79 (dd, 1H), 7.53 (d, 1H), 7.34-7.44 (m, 8H), 7.18 (s, 1H), 7.14 (d, 1H), 7.09 (d, 1H), 6.86 (dd, 1H), 6.67 (dd, 1H), 6.39 (s, 1H), 6.17 (d, 1H), 3.85 (dd, 2H), 3.24-3.30 (m, 6H), 3.04 (s, 4H), 2.29 (s, 4H), 1.86-1.91 (m, 1H), 1.60-1.63 (m, 2H), 1.28 (s, 9H).

EJEMPLO 342

4-{4-[(5-tert-butil-4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(tetrahidro-2H-piran-4–ilmetoxi)fenil]sulfonil}benzamida

El compuesto del título se preparó utilizando EJEMPLO 341C en lugar de EJEMPLO 26C y EJEMPLO 279A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11.25, (br s, 1H), 11.16 (s, 1H), 8.40 (d, 1H), 8.06 (dd, 1H), 7.52 (d, 1H), 7.35-7.46 (m, 8H), 7.19 (s, 1H), 7.15 (d, 1H), 6.85 (dd, 1H), 6.66 (dd, 1H), 6.39 (s, 1H), 6.17 (d, 1H), 4.08 (d, 2H), 3.88 (dd, 2H), 3.05 (s, 4H), 2.32 (s, 4H), 1.64 (dd, 2H), 1.32-1.37 (m, 2H), 1.28 (s, 9H).

EJEMPLO 343

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(2,2,2-trifluoroetil)amino]fenil}sulfonil)benzamida

EJEMPLO 343A

3-nitro-4-(2,2,2-trifluoroetilamino)bencensulfonamida

El compuesto del título se preparó utilizando 2,2,2-trifluoroetanamina en lugar de (tetrahidro-2H-piran-4–il)metanamina en el EJEMPLO 1F.

EJEMPLO 343B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(2,2,2-trifluoroetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 343A en lugar de EJEMPLO 1F y EJEMPLO 55B en lugar de EJEMPLO 26C en el EJEMPLO 177. ^{1}H NMR (500 MHz, dimetilsulfóxido-d $_6$) δ 10.98 (s, 1H), 8.41 (m, 2H), 7.75 (dd, 1H), 7.54 (d, 1H), 7.34 (d, 2H), 7.28 (m, 2H), 7.06 (m, 3H), 6.93 (m, 1H), 6.70 (dd, 1H), 6.53 (dd, 1H), 6.30 (m, 1H), 6.14 (d, 1H), 4.32 (m, 2H), 2.93 (m, 4H), 2.71 (s, 2H), 2.16 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EJEMPLO 344

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(2,2,2-trifluoroetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 343A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (500 MHz, dimetilsulfóxido-d $_6$) δ 11.05 (s, 1H), 8.40 (m, 2H), 7.77 (dd, 1H), 7.60 (d, 1H), 7.34 (d, 2H), 7.18 (m, 1H), 7.12 (d, 1H), 7.04 (m, 3H), 6.88 (t, 1H), 6.58 (dd, 1H), 6.22 (m, 3H), 4.33 (m, 2H), 2.93 (m, 4H), 2.71 (s, 2H), 2.16 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.93 (s, 6H).

EJEMPLO 345

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-{[(tetrahidro-2H-piran-4–ilmetil)amino]carbonil}fenil)sulfonil]benzamida

EJEMPLO 345A

3-sulfamoil-N-((tetrahidro-2H-piran-4–il)metil)benzamida

El compuesto del título se preparó utilizando ácido 3-sulfamoilbenzoico en lugar de ácido 4-sulfamoilbenzoico en el EJEMPLO 308A.

EJEMPLO 345B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-{[(tetrahidro-2H-piran-4–ilmetil)amino]carbonil}fenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 345A en lugar de EJEMPLO 1F y EJEMPLO 26C en lugar de EJEMPLO 1E en el EJEMPLO 1G. ^{1}H NMR

(300MHz, dimetilsulfóxido-d_6) δ 11.28 (br s, 1H), 11.18 (s, 1H), 8.75 (t, 1H), 8.41 (m, 1H), 8.10 (d, 1H), 8.01 (d, 1H), 7.60 (t, 1H), 7.48 (d, 1H), 7.41 (m, 2H), 7.33 (d, 2H), 7.23 (d, 1H), 7.03 (d, 2H), 6.88 (dd, 1H), 6.83 (dd, 1H), 6.42 (t, 1H), 6.11 (d, 1H), 3.83 (dd, 2H), 3.19 (m, 4H), 3.02 (m, 4H), 2.73 (m, 2H), 2.16 (m, 6H), 1.94 (br s, 2H), 1.80 (m, 1H), 1.58 (dd, 2H), 1.37 (t, 2H), 1.24 (m, 2H), 0.92 (s, 6H).

EJEMPLO 346

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2R)-1,4-dioxan-2–ilmetoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida

EJEMPLO 346A

(R)-4-((1,4-dioxan-2–il)metoxi)-3-nitrobencensulfonamida

La mezcla racémica de EJEMPLO 297A se resolvió sobre una columna AD quiral SFC para dar el compuesto del título.

EJEMPLO 346B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2R)-1,4-dioxan-2–ilmetoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 175F por reemplazo de EJEMPLO 175E y EJEMPLO 1F con EJEMPLO 26C y EJEMPLO 346A, respectivamente. ^{1}H NMR (500 MHz, dimetilsulfóxido-d_6) δ 11.16 (s, 2H), 8.39 (d, 1H), 8.06 (dd, 1H), 7.51 (d, 1H), 7.38 - 7.43 (m, 3H), 7.34 (d, 2H), 7.15 (d, 1H), 7.04 (d, 2H), 6.85 (dd, 1H), 6.64 (dd, 1H), 6.39 (s, 1H), 6.15 (d, 1H), 4.20 - 4.28 (m, 2H), 3.85 - 3.91 (m, 1H), 3.82 (dd, 1H), 3.74 - 3.78 (m, 1H), 3.59 - 3.69 (m, 2H), 3.40 - 3.51 (m, 2H), 3.05 (s, 4H), 2.78 (s, 2H), 2.23 (s, 4H), 2.14 (s, 2H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EJEMPLO 347

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2S)-1,4-dioxan-2–ilmetoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida

EJEMPLO 347A

(S)-4-((1,4-dioxan-2–il)metoxi)-3-nitrobencensulfonamida

La mezcla racémica de EJEMPLO 297A se resolvió sobre una columna AD quiral SFC para dar el compuesto del título.

EJEMPLO 347B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2S)-1,4-dioxan-2–ilmetoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 175F por reemplazo de EJEMPLO 175E y EJEMPLO 1F con EJEMPLO 26C y EJEMPLO 347A, respectivamente. ^{1}H NMR (500 MHz, dimetilsulfóxido-d $_6$) δ 11.16 (s, 2H), 8.39 (d, 1H), 8.06 (dd, 1H), 7.51 (d, 1H), 7.38 - 7.43 (m, 3H), 7.34 (d, 2H), 7.15 (d, 1H), 7.04 (d, 2H), 6.85 (dd, 1H), 6.64 (dd, 1H), 6.39 (s, 1H), 6.15 (d, 1H), 4.20 - 4.28 (m, 2H), 3.85 - 3.91 (m, 1H), 3.82 (dd, 1H), 3.74 - 3.78 (m, 1H), 3.59 - 3.69 (m, 2H), 3.40 - 3.51 (m, 2H), 3.05 (s, 4H), 2.78 (s, 2H), 2.23 (s, 4H), 2.14 (s, 2H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EJEMPLO 348

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

EJEMPLO 348A

4-(3-morfolinopropilamino)-3-(trifluorometilsulfonil)bencensulfonamida

El compuesto del título se preparó utilizando EJEMPLO 159C durante 4-fluoro-3-nitrobencensulfonamida y 3-morfolinopropan-1-amina en lugar de (tetrahidropiran-4–il)metilamina en el EJEMPLO 1F.

EJEMPLO 348B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

5–iloxi)-N-({4-(metilamino)-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 348A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (400MHz, dimetilsulfóxido-d$_6$) δ 11.17 (s, 1H), 8.17 (d, 1H), 7.91 (dd, 1H), 7.49 (d, 1H), 7.40 (m, 3H), 7.33 (d, 2H), 7.15 (d, 1H), 7.03 (m, 3H), 6.85 (dd, 1H), 6.64 (dd, 1H), 6.40 (s, 1H), 6.13 (d, 1H), 3.59 (m, 4H), 3.38 (m, 4H), 3.02 (m, 4H), 2.72 (s, 2H), 2.40 (m, 6H), 2.15 (m, 6H), 1.95 (s, 2H), 1.73 (m, 2H), 0.92 (s, 6H).

EJEMPLO 349

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 26C y EJEMPLO 348A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11.25 (s, 1H), 11.08 (m, 1H), 8.12 (d, 1H), 7.81 (dd, 1H), 7.52 (d, 1H), 7.36 (m, 3H), 7.28 (m, 1H), 7.19 (d, 1H), 7.04 (d, 2H), 6.98 (m, 2H), 6.69 (dd, 1H), 6.44 (d, 1H), 6.25 (m, 2H), 3.60 (m, 4H), 3.38 (m, 2H), 3.03 (m, 4H), 2.73 (s, 2H), 2.43 (m, 6H), 2.16 (m, 6H), 1.95 (s, 2H), 1.73 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EJEMPLO 350

N-({5-bromo-6-[(tetrahidro-2H-piran-4–ilmetil)amino]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 325A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11.19 (s, 1H), 11.02(s, 1H), 8.47 (d, 1H), 8.07 (d, 1H), 7.55 (d, 1H), 7.39 (m, 5H), 7.25 (d, 1H), 7.03 (d, 2H), 6.89 (dd, 1H), 6.65 (dd, 1H), 6.42 (s, 1H), 6.11 (d, 1H), 3.82 (dd, 2H), 3.31 (m, 2H), 3.24 (m, 2H), 3.03 (m, 4H), 2.72 (s, 2H), 2.15 (m, 6H), 1.94 (s, 2H), 1.89 (m, 1H), 1.54 (m, 2H), 1.38 (t, 2H), 1.17 (m, 2H), 0.92 (s, 6H).

EJEMPLO 351

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(2-morfolin-4–iletil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

EJEMPLO 351A

4-(2-morfolinoetilamino)-3-(trifluorometilsulfonil)bencensulfonamida

El compuesto del título se preparó utilizando EJEMPLO 159C durante 4-fluoro-3-nitrobencensulfonamida y 2-morfolinoetanamina en lugar de (tetrahidropiran-4–il)metilamina en el EJEMPLO 1F.

EJEMPLO 351B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(2-morfolin-4–iletil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 351A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11.22 (s, 1H), 11.17 (s, 1H), 8.17 (d, 1H), 7.92 (dd, 1H), 7.61 (s, 1H), 7.48 (d, 1H), 7.40 (m, 2H), 7.33 (d, 2H), 7.15 (d, 1H), 7.03 (d, 2H), 6.93 (d, 1H), 6.85 (dd, 1H), 6.64 (dd, 1H), 6.40 (s, 1H), 6.13 (m, 1H), 3.57 (m, 4H), 3.35 (m, 2H), 3.02 (m, 4H), 2.72 (s, 2H), 2.58 (t, 2H), 2.42 (m, 4H), 2.15 (m, 6H), 1.95 (s, 2H), 1.37 (m, 2H), 0.92 (s, 6H).

EJEMPLO 352

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-ciano-6-[(tetrahidro-2H-piran-4–ilmetil)amino]piridin-3–il}sulfonil)-2-(1H-indol-5–iloxi)benzamida

EJEMPLO 352A

5-ciano-6-((tetrahidro-2H-piran-4–il)metilamino)piridina-3-sulfonamida

El compuesto del título se preparó utilizando EJEMPLO 325A en lugar de EJEMPLO 329B en el EJEMPLO 333A.

EJEMPLO 352B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-ciano-6-[(tetrahidro-2H-piran-4–ilmetil)amino]piridin-3–il}sulfonil)-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 352A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11.18 (s, 1H), 8.65 (d, 1H), 8.27 (d, 1H), 8.15 (s, 1H), 7.56 (d, 1H), 7.41 (m, 2H), 7.34 (d, 2H), 7.22 (d, 1H), 7.04 (d, 2H), 6.88 (dd, 1H), 6.65 (dd, 1H), 6.41 (m, 1H), 6.12 (d, 1H), 3.82 (dd, 2H), 3.33 (m, 2H), 3.24 (t, 2H), 3.04 (m, 4H), 2.75 (s, 2H), 2.16 (m, 6H), 1.95 (s, 2H), 1.89 (m, 1H), 1.55 (m, 2H), 1.38 (t, 2H), 1.19 (m, 2H), 0.91 (s, 6H).

EJEMPLO 353

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)oxi]-3-nitrofenil}sulfonil)benzamida

EJEMPLO 353A

4-(1-metilpiperidin-4–iloxi)-3-nitrobencensulfonamida

To una mezcla de 1-metilpiperidin-4-ol (0.542 g) en tetrahidrofurano (10 mL) a 0°C se agregó NaH (60% en mineral oil) (0.753 g). Después de agitar por 15 minutos, 4-fluoro-3-nitrobencensulfonamida (1.036 g) se agregó como una solución en tetrahidrofurano (10 mL). La reacción se eliminó del baño helado y permitió calentarse a temperatura ambiente. Después de 1 hora, la reacción fue vertida en agua y el pH se ajusto a ~7 con 1N HCl acuoso. La reacción se extrajo con diclorometano (3 x 100 mL), se lavó con salmuera, se secó sobre sulfato de magnesio, se filtró, y se concentró. El producto se suspendió en diclorometano (mL), sonicated y luego filtrado para dar el compuesto del título.

EJEMPLO 353B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)oxi]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 26C en lugar de EJEMPLO 1E y EJEMPLO 353A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300 MHz, dimetilsulfóxido) δ 11.03 (s, 1H), 8.21 (d, 1H), 7.87 (dd, 1H), 7.55 (d, 1H), 7.33 (dd, 4H), 7.25 (d, 1H), 7.04 (d, 2H), 6.98 (d, 1H), 6.73 (dd, 1H), 6.56 (d, 1H), 6.33 (s, 1H), 6.14 (d, 1H), 4.79 (s, 1H), 2.96 (s, 6H), 2.72 (s, 2H), 2.57 (s, 3H), 2.18 (s, 6H), 1.94 (m, 6H), 1.39 (m, 2H), 0.92 (s, 6H).

EJEMPLO 354

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)metoxi]-3-nitrofenil}sulfonil)benzamida

EJEMPLO 354A

4-((1-metilpiperidin-4–il)metoxi)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando (1-metilpiperidin-4–il)metanol en lugar de 1-metilpiperidin-4-ol en el EJEMPLO 353A.

EJEMPLO 354B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)metoxi]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 26C en lugar de EJEMPLO 1E y EJEMPLO 354A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300 MHz, dimetilsulfóxido) δ 11.01 (s, 1H), 8.19 (d, 1H), 7.87 (dd, 1H), 7.55 (d, 1H), 7.39 -

7.26 (m, 4H), 7.16 (d, 1H), 7.08 - 7.01 (m, 2H), 6.96 (d, 1H), 6.72 (dd, 1H), 6.54 (d, 1H), 6.32 (s, 1H), 6.14 (d, 1H), 4.05 (d, 2H), 2.95 (s, 4H), 2.89 - 2.59 (m, 7H), 2.17 (s, 6H), 2.00 - 1.78 (m, 5H), 1.53 (s, 2H), 1.37 (m, 2H), 0.92 (s, 6H).

EJEMPLO 355

4-(4-{[4-(4-clorofenil)-1-(3-hidroxipropil)-1,2,5,6-tetrahidropiridin-3–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 355A

carboxilato de 4-cloro-3-formil-5,6-dihidropiridina-1(2H)-tert-butilo

A N,N-dimetilformamida (3.87 mL) a 0°C, oxicloruro de fósforo (3.73 mL) se agregó por goteo, manteniendo la temperatura debajo de 5°C. La mezcla resultante se diluyó con diclorometano (15 mL) y agitada a temperatura ambiente durante 1.5 horas. La reacción luego se enfrió en un baño helado. Carboxilato de 4-oxopiperidin-1-tert-Butilo (4.98 g) se agregó como una solución en diclorometano (20 mL) y la reacción se agitó a temperatura ambiente por 1 hora. La mezcla de reacción se vertió sobre hielo y acetato de sodio sólido, se agitó por 15 minutos, y se extrajo con diclorometano. Los extractos se lavaron exhaustivamente con agua y con salmuera, se secó sobre $MgSO_4$, se filtró, y concentró para obtener el compuesto del título.

EJEMPLO 355B

Carboxilato de 4-(4-clorofenil)-3-formil-5,6-dihidropiridina-1(2H)-tert-butilo

EJEMPLO 355A (6.14 g), ácido 4-clorofenilborónico (4.10 g) y paladio(II) acetato (0.112 g) se combinaron en agua para dar a suspensión. Carbonato de potasio (8.98 g) y bromuro tetrabutilamonio (4.03 g) se añadieron . La mezcla resultante se agitó a 45 °C durante la noche, se enfrió, y la mezcla de reacción se diluyó con acetato de etilo (200 mL) de forma de disolver cualquier material insoluble, luego se lavó exhaustivamente con agua, se secó sobre $MgSO_4$, se filtró, y se concentró. El material crudo se purificó por cromatografía flash eluyendo con un gradiente de 10% acetato de etilo/hexanos a 40% acetato de etilo /hexanos.

EJEMPLO 355C

Carboxilato de 3-((4-(3-(1H-indol-4–iloxi)-4-(metoxicarbonil)fenil)piperazin-1–il)metil)-4-(4-clorofenil)-5,6-dihidropiridina-1(2H)-tert-butilo

El compuesto del título se preparó utilizando EJEMPLO 355B en lugar de 4'-clorobifenil-2-carboxaldehido y EJEMPLO 68B en lugar de carboxilato de piperazin-1-tert-butilo en el EJEMPLO 1A.

EJEMPLO 355D

Benzoato de 2-(1H-indol-4–iloxi)-4-(4-((4-(4-clorofenil)-1,2,5,6-tetrahidropiridin-3–il)metil)piperazin-1–il)metilo

El compuesto del título se preparó utilizando EJEMPLO 355C en lugar de EJEMPLO 1A en el EJEMPLO 1B.

EJEMPLO 355E

Benzoato de 2-(1H-indol-4–iloxi)-4-(4-((4-(4-clorofenil)-1-(3-hidroxipropil)-1,2,5,6-tetrahidropiridin-3–il)metil)piperazin-1–il)metilo

EJEMPLO 355D (539 mg), 3-bromopropan-1-ol (83 mg) y trietilamina (0.42 mL) se combinaron en acetonitrilo. La mezcla se calentó a 60°C durante la noche, se concentró y luego triturada con éter y se filtró para dar el compuesto del título.

EJEMPLO 355F

Ácido 2-(1H-indol-4–iloxi)-4-(4-((4-(4-clorofenil)-1-(3-hidroxipropil)-1,2,5,6-tetrahidropiridin-3–il)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 355E en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 355G

4-(4-{[4-(4-clorofenil)-1-(3-hidroxipropil)-1,2,5,6-tetrahidropiridin-3–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 355F en lugar de EJEMPLO 1E en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11.17 (s, 1H), 8.49 (br s, 1H), 8.44 (s, 1H), 7.69 (dd, 1H), 7.56 (d, 1H), 7.40 (d, 1H), 7.24 (m, 1H), 7.13 (m, 3H), 6.98 (m, 1H), 6.94 (t, 1H), 6.86 (dd, 1H), 6.36 (m, 1H), 6.24 (m, 2H), 3.84 (dd,

2H), 3.47 (t, 2H), 3.26 (m, 4H), 2.99 (br s, 4H), 2.80 (m, 3H), 2.44 (m, 2H), 2.21 (m, 4H), 1.86 (m, 1H), 1.73 (m, 2H), 1.62 (m, 2H), 1.26 (m, 5H), 1.17 (m, 2H).

EJEMPLO 356

Carboxilato de 4-({[4-({[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzoil]amino}sulfonil)-2-nitrofenil]amino}metil)piperidin-1-bencilo

EJEMPLO 356A

Carboxilato de 4-((2-nitro-4-sulfamoilfenilamino)metil)piperidin-1-bencilo

El compuesto del título se preparó como se describe en el EJEMPLO 1F por reemplazo de (tetrahidro-2H-piran-4–il)metanamina con carboxilato de 4-(aminometil)piperidin-1-bencilo

EJEMPLO 356B

carboxilato de 4-({[4-({[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzoil]amino}sulfonil)-2-nitrofenil]amino}metil)piperidin-1-bencilo

El compuesto del título se preparó como se describe en el EJEMPLO 175F por reemplazo de EJEMPLO 175E y EJEMPLO 1F con EJEMPLO 26C y EJEMPLO 356A, respectivamente. ^{1}H NMR (500 MHz, dimetilsulfóxido-d $_6$) δ 11.17 (s, 2H), 8.63 (t, 1H), 8.58 (d, 1H), 7.79 (dd, 1H), 7.51 (d, 1H), 7.30 - 7.42 (m, 8H), 7.16 (d, 1H), 7.10 (d, 1H), 7.03 (d, 2H), 6.86 (dd, 1H), 6.65 (dd, 1H), 6.39 (s, 1H), 6.14 (d, 1H), 5.07 (s, 2H), 4.02 (d, 2H), 3.29 - 3.34 (m, 2H), 3.03 (s, 4H), 2.70 - 2.88 (m, 4H), 2.08 - 2.23 (m, 6H), 1.94 (s, 2H), 1.81 - 1.89 (m, 1H), 1.71 (d, 2H), 1.37 (t, 2H), 1.07 - 1.16 (m, 2H), 0.92 (s, 6H).

EJEMPLO 357

N-{[3-(aminocarbonil)-4-(tetrahidro-2H-piran-4–ilmetoxi)fenil]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida

EJEMPLO 357A

3-ciano-4-((tetrahidro-2H-piran-4–il)metoxi)bencensulfonamida

To (tetrahidro-2H-piran-4–il)metanol (0.206 g) en tetrahidrofurano (5 mL) se agregó hidruro de sodio (0.284 g) y la reacción agitada a temperatura ambiente durante 20 minutos. La reacción se enfrió a 0°C y 3-ciano-4-fluorobencensulfonamida (0.355 g) en tetrahidrofurano (2 mL) se agregó por goteo y la reacción se dejó calentar a temperatura ambiente. Después 3 horas, la reacción fue vertida en agua, hecha acídica (pH=1) con 1N HCl y se extrajo con diclorometano (2 x 75 mL). Los orgánicos se combinaron, se lavó con salmuera (50 mL), se secó sobre sulfato de magnesio, se filtró y se concentró para dar el compuesto del título.

EJEMPLO 357B

5-sulfamoil-2-((tetrahidro-2H-piran-4–il)metoxi)benzamida

Una mezcla de EJEMPLO 357A (0.455 g) en etanol (3 mL) y tetrahidrofurano (1 mL) se agregó a peróxido de hidrógeno (30%, 2 mL) seguido por NaOH (1.024 ml) y calentada a 35°C durante 3 horas. La mezcla fue vertida en diclorometano (50 mL) y 1N HCl acuoso (25 mL), luego de lo cual se formó un precipitado. El compuesto del título se extrajo en diclorometano (3 x 50 mL). La capa orgánica contenía un sólido que se recolectó por filtración y se secó para dar el compuesto del título.

EJEMPLO 357C

N-{[3-(aminocarbonil)-4-(tetrahidro-2H-piran-4–ilmetoxi)fenil]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 26C en lugar de EJEMPLO 1E y EJEMPLO 357B en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300 MHz, CDCL3) δ 10.35 (s, 1H), 8.80 (d, 1H), 8.35 (dd, 2H), 7.91 (d, 1H), 7.44 (d, 2H), 7.39 (d, 1H), 7.34 - 7.29 (m, 1H), 7.22 (d, 2H), 7.07 (d, 1H), 6.99 (dd, 1H), 6.93 - 6.87 (m, 2H), 6.58 (s, 1H), 6.48 (dd, 1H), 6.06 (d, 1H), 5.80 (s, 1H), 4.05 (dd, 4H), 3.46 (dd, 2H), 3.03 (s, 4H), 2.73 (s, 2H), 2.19 (m, 7H), 1.96 (s, 2H), 1.74 (m, 2H), 1.43 (m, 4H), 0.93 (s, 6H).

EJEMPLO 358

4-(4-{[4'-cloro-5-(trifluorometil)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 339C en lugar de EJEMPLO 26C y EJEMPLO 173C en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR

(500MHz, dimetilsulfóxido-d_6) δ 11.11 (s, 1H), 8.54 (d, 1H), 8.19 (d, 1H), 7.78 (dd, 1H), 7.71-7.74 (m, 2H), 7.44-7.54 (m, 7H), 7.36-7.38 (m, 2H), 7.04-7.07 (m, 2H), 6.87 (dd, 1H), 6.63 (dd, J = 8.7, 1.68 Hz, 1H), 6.36 (s, 1H), 6.16 (d, 1H), 3.93 (dd, 2H), 3.75 (br s, 2H), 3.41 (s, 2H), 3.01-3.07 (m, 6H), 2.66-2.68 (m, 2H), 2.30 (s, 4H), 1.77-1.80 (m, 2H), 1.47-1.53 (m, 2H).

EJEMPLO 359

4-{4-[(5-tert-butil-4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 341C en lugar de EJEMPLO 26C y EJEMPLO 173C en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11.11, (s, 1H), 8.53 (t, 1H), 8.19 (d, 1H), 7.76 (dd, 1H), 7.53 (d, 1H), 7.36-7.44 (m, 8H), 7.19 (s, 1H), 7.04-7.07 (m, 2H), 6.81 (dd, 1H), 6.63 (dd, 1H), 6.36 (s, 1H), 6.17 (d, 1H), 3.93 (dd, 2H), 3.74-3.75 (m, 2H), 3.01-3.07 (m, 6H), 2.64-2.67 (m, 2H), 2.29 (s, 4H), 1.99-2.03 (m, 4H), 1.77-1.80 (m, 2H), 1.65-1.67 (m, 2H), 1.28 (s, 9H).

EJEMPLO 360

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(1-metil-1H-imidazol-5–il)metil]amino}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó utilizando (1-metil-1H-imidazol-5–il)metanamina en lugar de (3S,4R)-4-amino-1-bencilpiperidin-3-ol, ácido clorhídrico en el EJEMPLO 187B. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11.17 (s, 1H), 8.81 (t, 1H), 8.59 (d, 1H), 7.83 (dd, 1H), 7.64 (s, 1H), 7.50 (d, 1H), 7.39-7.42 (m, 2H), 7.33 (d, 2H), 7.16-7.17 (m, 2H), 7.03 (d, 2H), 6.98 (s, 1H), 6.85 (dd, 1H), 6.63 (dd, 1H), 6.40 (s, 1H), 6.13 (d, 1H), 4.66 (d, 2H), 3.64 (s, 3H), 3.02 (s, 4H), 2.72 (s, 2H), 2.12-2.16 (m, 6H), 1.94 (s, 2H), 1.37 (t, 2H), 0.92 (s, 6H).

EJEMPLO 361

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(morfolin-4–ilsulfonil)fenil]sulfonil}benzamida

EJEMPLO 361A

4-(morfolinosulfonil)bencensulfonamida

El compuesto del título se preparó utilizando cloruro de 4-(morfolinosulfonil)benceno-1-sulfonilo en lugar de EJEMPLO 66D en el EJEMPLO 66E.

EJEMPLO 361B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(morfolin-4–ilsulfonil)fenil]sulfonil}benzamida

El compuesto del título se preparó utilizando EJEMPLO 361A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (500 MHz, dimetilsulfóxido-d $_6$) δ 10.99 (s, 1H), 7.76 (d, 2H), 7.57 (d, 1H), 7.46 (d, 2H), 7.35 (d, 2H), 7.28 (m, 2H), 7.05 (d, 2H), 6.89 (d, 1H), 6.70 (dd, 1H), 6.57 (dd, 1H), 6.31 (m, 1H), 6.21 (m, 1H), 3.60 (m, 4H), 2.97 (m, 4H), 2.79 (m, 4H), 2.72 (s, 2H), 2.18 (m, 6H), 1.96 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

EJEMPLO 362

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1,1-dioxidotiomorfolin-4–il)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida

EJEMPLO 362A

4-[(1,1-dioxidotiomorfolin-4–il)amino]-3-nitrofenil}sulfonamida

El compuesto del título se preparó utilizando 4-aminotiomorfolin-1,1-dioxido en lugar de (tetrahidropiran-4–il)metilamina en el EJEMPLO 1F.

EJEMPLO 362B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1,1-dioxidotiomorfolin-4–il)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 362A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (400MHz, dimetilsulfóxido-d$_6$) δ 11.19 (s, 1H), 11.17 (s, 1H), 9.64 (s, 1H), 8.55 (d, 1H), 7.86 (m, 1H), 7.78 (m, 1H), 7.51 (d, 1H), 7.40 (m, 2H), 7.33 (d, 2H), 7.16 (s, 1H), 7.03 (d, 2H), 6.86 (dd, 1H), 6.64 (dd, 1H), 6.39 (s, 1H), 6.13 (d, 1H), 3.50 (m, 4H), 3.17 (m, 4H), 3.02 (m, 4H), 2.72 (s, 2H), 2.15 (m, 6H), 1.94 (s, 2H), 1.37 (t, 2H), 0.91 (s, 6H).

EJEMPLO 363

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-morfolin-4–ilciclohexil)amino]-3-nitrofenil}sulfonil)benzamida

EJEMPLO 363A

tert-butilo cis-4-morfolinociclohexilcarbamato

A una mezcla de morfolina (4.08 ml) y tert-butilo 4-oxociclohexilcarbamato (10 g) agitado durante 24 horas a temperatura ambiente en titanio(IV) isopropoxido (27.5 ml), metanol (10 ml) se agregó seguido por el agregado cuidadoso de borohidruro de sodio (3.55 g). La mezcla de reacción se congeló con agua, se extrajo con éter (2 x 100 mL), se secó sobre sulfato de magnesio, se filtró y se concentró. El producto crudo se purificó por FC (gel de sílice 200g, 30% - 100% acetona / hexanos) proveyendo dos productos, el compuesto del título y trans 4-morfolinociclohexilcarbamato.

EJEMPLO 363B

cis-4-morfolinociclohexanamina bis(2,2,2-trifluoroacetato)

El compuesto del título se preparó utilizando EJEMPLO 363A en lugar de EJEMPLO 1A en el EJEMPLO 1B.

EJEMPLO 363C

4-(cis-4-morfolinociclohexilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando EJEMPLO 363B en lugar de (tetrahidropiran-4–il)metilamina en el EJEMPLO 1F.

EJEMPLO 363D

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[cis-(4-morfolin-4–ilciclohexil)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 26C en lugar de EJEMPLO 1E y EJEMPLO 363C en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (500 MHz, piridina-d_5) δ 12.28 (s, 1H), 9.31 (d, 1H), 8.65 (d, 1H), 8.34 (dd, 1H), 8.17 (d, 1H), 7.53 - 7.57 (m, 2H), 7.40 - 7.47 (m, 3H), 7.03 - 7.12 (m, 3H), 6.89 (d, 1H), 6.72 (dd, 1H), 6.62 (s, 1H), 6.54 (d, 1H), 3.69 - 3.75 (m, 4H), 3.67 (s, 1H), 3.00 - 3.07 (m, 4H), 2.75 (s, 2H), 2.41 - 2.47 (m, 4H), 2.24 (t, 2H), 2.07 - 2.16 (m, 5H), 1.97 (s, 2H), 1.76 - 1.85 (m, 2H), 1.54 - 1.65 (m, 6H), 1.38 (t, 2H), 0.93 (s, 6H).

EJEMPLO 364

N-{[5-bromo-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 26C y EJEMPLO 329B en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11.17 (s, 1H), 8.65 (d, 1H), 8.33 (s, 1H), 7.58 (d, 1H), 7.35 (d, 2H), 7.24 (t, 1H), 7.07 (m, 3H), 6.89 (m, 1H), 6.67 (dd, 1H), 6.27 (m, 3H), 4.29 (d, 2H), 3.88 (dd, 2H), 3.35 (m, 4H), 3.09 (m, 4H), 2.88 (m, 2H), 2.34 (m, 2H), 2.17 (s, 2H), 2.06 (m, 1H), 1.98 (m, 2H), 1.65 (m, 2H), 1.36 (m, 4H), 0.93 (s, 6H).

EJEMPLO 365

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[6-[(tetrahidro-2H-piran-4–ilmetil)amino]-5-(1,3-tiazol-2–il)piridin-3–il]sulfonil}benzamida

El compuesto del título se preparó utilizando EJEMPLO 325B en lugar de EJEMPLO 329B en el EJEMPLO 331A. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11.22 (s, 1H), 9.76 (t, 1H), 9.12 (m, 1H), 8.50 (d, 1H), 8.26 (d, 1H), 8.02 (d, 1H), 7.87 (d, 1H), 7.58 (d, 1H), 7.38 (d, 2H), 7.23 (t, 1H), 7.15 (d, 1H), 7.08 (d, 2H), 6.96 (m, 1H), 6.74 (dd, 1H), 6.47 (d, 1H), 6.33 (s, 1H), 6.22 (s, 1H), 3.86 (dd, 2H), 3.52 (t, 6H), 3.29 (m, 4H), 2.99 (m, 2H), 2.74 (m, 2H), 2.18 (s, 2H), 2.01 (s, 2H), 1.88 (m, 1H), 1.62 (m, 2H), 1.45 (t, 2H), 1.28 (m, 2H), 0.94 (s, 6H).

EJEMPLO 366

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-ciano-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(1H-indol-4–iloxi)benzamida

EJEMPLO 366A

3-ciano-4-((tetrahidro-2H-piran-4–il)metilamino)bencensulfonamida

3-Ciano-4-fluorobencensulfonamida (500 mg), (tetrahidropiran-4–il)metilamina (288 mg), y N,N-diisopropiletilamina (1.3 mL) se calentaron a 80°C en tetrahidrofurano (15 mL) durante la noche. La mezcla se diluyó con acetato de etilo, se lavó con solución $NaHCO_3$ y salmuera, y se secó (Na_2SO_4), se filtró y se concentró. El producto se trituró a partir de acetato de etilo.

EJEMPLO 366B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-ciano-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(1H-indol-4–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 26C y EJEMPLO 366A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11.30 (s, 1H), 11.08 (m, 1H), 7.81 (d, 1H), 7.63 (dd, 1H), 7.55 (d, 1H), 7.32 (m, 3H), 7.22 (d, 1H), 7.17 (m, 1H), 7.02 (m, 3H), 6.79 (d, 1H), 6.71 (dd, 1H), 6.47 (d, 1H), 6.28 (m, 2H), 3.84 (dd, 2H), 3.25 (t, 2H), 3.13 (t, 2H), 3.05 (m, 4H), 2.73 (s, 2H), 2.15 (m, 6H), 1.95 (s, 2H), 1.82 (m, 1H), 1.59 (m, 2H), 1.38 (t, 2H), 1.20 (m, 2H), 0.92 (s, 6H).

EJEMPLO 367

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-ciano-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 366A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11.20 (s, 1H), 10.99 (s, 1H), 7.94 (d, 1H), 7.74 (dd, 1H), 7.53 (d, 1H), 7.44 (d, 1H), 7.41 (m, 1H), 7.33 (d, 2H), 7.21 (m, 2H), 7.04 (d, 2H), 6.89 (dd, 1H), 6.82 (d, 1H), 6.66 (dd, 1H), 6.42 (s, 1H), 3.83 (dd, 2H), 3.25 (t, 2H), 3.13 (t, 2H), 3.03 (m, 4H), 2.72 (s, 2H), 2.14 (m, 6H), 1.94 (s, 2H), 1.83 (m, 1H), 1.57 (m, 2H), 1.37 (m, 2H), 1.21 (m, 2H), 0.92 (s, 6H).

EJEMPLO 368

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(3,3-dimetilbutil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando 3,3-dimetilbutilamina en lugar de 1-(2-metoxi-etil)-piperidin-4–ilamina y EJEMPLO 187A en lugar de 4-cloro-3-nitrobencensulfonamida en el EJEMPLO 189A.

EJEMPLO 369

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1S)-1-(hidroximetil)-3-metilbutil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando L-leucinol en lugar de 1-(2-metoxi-etil)-piperidin-4–ilamina y EJEMPLO 187A en lugar de 4-cloro-3-nitrobencensulfonamida en el EJEMPLO 189A.

EJEMPLO 370

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[(2R)-tetrahidrofuran-2–ilmetil]amino}fenil)sulfonil]benzamida

El compuesto del título se preparó utilizando (R)-(-)-tetrahidrofurfurilamina en lugar de 1-(2-metoxi-etil)-piperidin-4–ilamina y EJEMPLO 187A en lugar de 4-cloro-3-nitrobencensulfonamida en el EJEMPLO 189A.

EJEMPLO 371

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1R)-1-(hidroximetil)-2-metilpropil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando D-valinol en lugar de 1-(2-metoxi-etil)-piperidin-4–ilamina y EJEMPLO 187A en lugar de 4-cloro-3-nitrobencensulfonamida en el EJEMPLO 189A.

EJEMPLO 372

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-metoxifenil)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando 4-anisidine en lugar de 1-(2-metoxi-etil)-piperidin-4–ilamina y EJEMPLO 187A en lugar de 4-cloro-3-nitrobencensulfonamida en el EJEMPLO 189A.

EJEMPLO 373

N-[(4-{[2-(1,3-benzodioxol-5–il)etil]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando 2-benzo[1,3]dioxol-5–il-etilamina en lugar de 1-(2-metoxi-etil)-piperidin-4–ilamina y EJEMPLO 187A en lugar de 4-cloro-3-nitrobencensulfonamida en el EJEMPLO 189A.

EJEMPLO 374

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[3-(2-oxopirrolidin-1–il)propil]amino}fenil)sulfonil]benzamida

El compuesto del título se preparó utilizando 1-(3-amino-propil)-pirrolidin-2-one for 1-(2-metoxi-etil)-piperidin-4–ilamina y EJEMPLO 187A en lugar de 4-cloro-3-nitrobencensulfonamida en el EJEMPLO 189A.

EJEMPLO 375

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-hidroxifenil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando 4-aminofenol en lugar de 1-(2-metoxi-etil)-piperidin-4–ilamina y EJEMPLO 187A en lugar de 4-cloro-3-nitrobencensulfonamida en el EJEMPLO 189A.

EJEMPLO 376

N-{[4-({2-[4-(aminosulfonil)fenil]etil}amino)-3-nitrofenil]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando 4-(2-aminoetil)bencensulfonamida en lugar de 1-(2-metoxi-etil)-piperidin-4–ilamina y EJEMPLO 187A en lugar de 4-cloro-3-nitrobencensulfonamida en el EJEMPLO 189A.

EJEMPLO 377

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[3-(1H-imidazol-1–il)propil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando 1-(3-aminopropil)imidazol for 1-(2-metoxi-etil)-piperidin-4–ilamina y EJEMPLO 187A en lugar de 4-cloro-3-nitrobencensulfonamida en el EJEMPLO 189A.

EJEMPLO 378

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[(1S)-1-feniletil]amino}fenil)sulfonil]benzamida

El compuesto del título se preparó utilizando (S)-(-)-1-feniletilamina en lugar de 1-(2-metoxi-etil)-piperidin-4–ilamina y EJEMPLO 187A en lugar de 4-cloro-3-nitrobencensulfonamida en el EJEMPLO 189A.

EJEMPLO 379

N-({2-cloro-5-fluoro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida

EJEMPLO 379A

2-cloro-5-fluoro-4-((tetrahidro-2H-piran-4–il)metilamino)bencensulfonamida

2-Cloro-4,5-difluorobencensulfonamida (0.683 g), (tetrahidro-2H-piran-4–il)metanamina (0.346 g), N,N-diisopropiletilamina (0.681 ml) y dioxano (10 ml) se calentaron a 65 °C durante 2.5 días. Se añadieron (tetrahidro-2H-piran-4–il)metanamina (0.346 g) y N,N-diisopropiletilamina (0.681 ml) adicionales y el calentamiento se continuó a 70 ºC durante 1.5 días. La mezcla de reacción se concentró y se cromatografió en columna sobre gel de sílice con 0-3% metanol en diclorometano como eluyente. El sólido obtenido se trituró con diclorometano para dar el compuesto del título.

EJEMPLO 379B

N-({2-cloro-5-fluoro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 26C en lugar de EJEMPLO 1E y EJEMPLO 379A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ ppm 11.23 (s, 1H), 11.02 (s, 1H), 7.61 (m, 2H), 7.44 (m, 2H), 7.33 (d, 2H), 7.30 (m, 1H), 7.03 (d, 2H), 6.95 (m, 1H), 6.88 (m, 2H), 6.67 (dd, 1H), 6.44 (m, 1H), 6.09 (d, 1H), 3.82 (dd, 2H), 3.22 (m, 2H), 3.03 (m, 6H), 2.72 (m, 2H), 2.14 (m, 6H), 1.94 (m, 2H), 1.81 (m, 1H), 1.61 (m, 2H), 1.37 (t, 2H), 1.18 (m, 2H), 0.91 (s, 6H).

EJEMPLO 380

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[2-(2-metoxietoxi)etil]tio}-3-nitrofenil)sulfonil]benzamida

EJEMPLO 380A

4-(2-(2-metoxietoxi)etiltio)-3-nitrobencensulfonamida

En un matraz de fondo redondo de 100 mL se agregó hidruro de sodio (0.6 g) en tetrahidrofurano (10 ml) para dar una suspensión. 2-(2-Metoxietoxi)etanetiol (1 g) se agregó lentamente. Después la mezcla se agitó por 30 minutos, 4-fluoro-3-nitrobencensulfonamida (1.616 g) en 10 ml tetrahidrofurano se agregó lentamente. Después la mezcla agitada durante la noche, agua se agregó lentamente, y acetato de etilo (20 ml x 3) se usó para extraer el producto. Las capas orgánicas combinadas se secaron sobre Na_2SO_4. Después la mezcla se filtró y concentró, el producto crudo se agregó a una columna de gel de sílice y se purificó eluyendo con 0-10% metanol en diclorometano.

EJEMPLO 380B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[2-(2-metoxietoxi)etil]tio}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 380A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (500 MHz, dimetilsulfóxido-d $_6$) δ 10.99 (s, 1H), 8.42 (s, 1H), 7.75 (d, 1H), 7.56 (d, 1H), 7.34 (m, 5H), 7.05 (d, 2H), 6.90 (d, 1H), 6.69 (dd, 1H), 6.55 (dd, 1H), 6.30 (m, 1H), 6.17 (d, 1H), 3.67 (t, 2H), 3.54 (m, 2H), 3.43 (m, 2H), 3.21 (m, 5H), 2.95 (m, 4H), 2.71 (s, 2H), 2.17 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EJEMPLO 381

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[2-(2-metoxietoxi)etil]tio}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 380A en lugar de EJEMPLO 1F y EJEMPLO 55B en lugar de EJEMPLO 26C en el EJEMPLO 177. ^{1}H NMR (500 MHz, dimetilsulfóxido-d $_6$) δ 11.06 (s, 1H), 8.37 (d, 1H), 7.80 (dd, 1H), 7.61 (d, 1H), 7.45 (d, 1H), 7.34 (d, 2H), 7.18 (t, 1H), 7.04 (m, 3H), 6.87 (t, 1H), 6.60 (dd, 1H), 6.22 (m, 3H), 3.68 (t, 2H), 3.55 (m, 2H), 3.43 (m, 2H), 3.22 (m, 5H), 2.94 (m, 4H), 2.72 (s, 2H), 2.16 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EJEMPLO 382

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(metilsulfonil)fenil]sulfonil}benzamida

El compuesto del título se preparó utilizando 4-(metilamino)-3-nitrobencensulfonamida en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (500 MHz, dimetilsulfóxido-d $_6$) δ 11.17 (s, 1H), 8.05 (m, 4H), 7.51 (d, 1H), 7.38 (m, 4H), 7.14 (m, 1H), 7.04 (d, 2H), 6.85 (d, 1H), 6.64 (dd, 1H), 6.40 (m, 1H), 6.17 (d, 1H), 3.27 (s, 3H), 3.05 (m, 4H), 2.79 (m, 2H), 2.21 (m, 6H), 1.96 (s, 2H), 1.39 (t, 2H), 0.92 (s, 6H).

EJEMPLO 383

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[4-(metilsulfonil)fenil]sulfonil}benzamida

El compuesto del título se preparó utilizando 4-(metilamino)-3-nitrobencensulfonamida en lugar de EJEMPLO 1F y EJEMPLO 55B en lugar de EJEMPLO 26C en el EJEMPLO 177. ^{1}H NMR (500 MHz, dimetilsulfóxido-d $_6$) δ 11.26 (s, 1H), 7.96 (m, 4H), 7.54 (d, 1H), 7.35 (d, 2H), 7.30 (m, 1H), 7.18 (d, 1H), 7.05 (d, 2H), 6.97 (t, 1H), 6.70 (dd, 1H), 6.37 (d, 1H), 6.30 (m, 2H), 3.25 (s, 3H), 3.08 (m, 4H), 2.84 (m, 2H), 2.26 (m, 6H), 1.97 (s, 2H), 1.40 (t, 2H), 0.93 (s, 6H).

EJEMPLO 384

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2,2-dimetiltetrahidro-2H-piran-4–il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida

EJEMPLO 384A

El compuesto del título se preparó como se describe en el EJEMPLO 297A por reemplazo de (1,4-dioxan-2–il)metanol con (2,2-dimetiltetrahidro-2H-piran-4–il)metanol.

EJEMPLO 384B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2,2-dimetiltetrahidro-2H-piran-4–il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 175F por reemplazo de EJEMPLO 175E y EJEMPLO 1F con EJEMPLO 26C y EJEMPLO 384A, respectivamente. ^{1}H NMR (400 MHz, dimetilsulfóxido-d_6) δ 11.17 (s, 2H), 8.38 (d, 1H), 8.05 (dd, 1H), 7.51 (d, 1H), 7.31 - 7.43 (m, 5H), 7.15 (d, 1H), 7.04 (d, 2H), 6.85 (dd, 1H),

6.65 (dd, 1H), 6.40 (s, 1H), 6.15 (d, 1H), 3.98 - 4.07 (m, 2H), 3.54 - 3.67 (m, 2H), 3.05 (s, 4H), 2.78 (s, 2H), 2.09 - 2.31 (m, 7H), 1.95 (s, 2H), 1.56 - 1.68 (m, 2H), 1.38 (t, 2H), 1.08 - 1.27 (m, 8H), 0.92 (s, 6H).

EJEMPLO 385

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-ciano-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-2-(1H-indol-5–iloxi)benzamida

EJEMPLO 385A

5-bromo-6-((4-fluorotetrahidro-2H-piran-4–il)metoxi)piridina-3-sulfonamida

El compuesto del título se preparó utilizando EJEMPLO 306C durante (tetrahidro-2H-piran-4–il)metanol en el EJEMPLO 329B.

EJEMPLO 385B

5-ciano-6-((4-fluorotetrahidro-2H-piran-4–il)metoxi)piridina-3-sulfonamida

El compuesto del título se preparó utilizando EJEMPLO 385A en lugar de EJEMPLO 329B en el EJEMPLO 333A.

EJEMPLO 385C

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-ciano-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 385B en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11.10 (s, 1H), 8.79 (s, 1H), 8.59 (s, 1H), 7.54 (d, 1H), 7.34-7.38 (m, 4H), 7.04-7.06 (m, 3H), 6.79 (dd, 1H), 6.62 (dd, 1H), 6.35 (s, 1H), 6.17 (d, 1H), 4.28 (d, 2H), 3.76-3.79 (m, 2H), 3.56-3.62 (m, 2H), 3.07 (br s, 4H), 2.12-2.17(m, 4H), 1.96 (s, 2H), 1.80-1.84 (m, 2H), 1.40 (t, 2H), 0.94 (s, 6H).

EJEMPLO 386

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-ciano-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indol-4–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 26C y EJEMPLO 335A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR

(500MHz, dimetilsulfóxido-d_6) δ 11.20 (s, 1H), 8.67 (d, 1H), 8.35 (d, 1H), 7.57 (d, 1H), 7.36 (d, 2H), 7.26 (t, 1H), 7.11 (d, 1H), 7.05 (d, 2H), 6.90 (t, 1H), 6.70 (dd, 1H), 6.31 (d, 1H), 6.30 (d, 1H), 6.27 (s, 1H), 4.30 (d, 2H), 3.88 (dd, 2H), 3.35 (m, 2H), 3.12 (br s, 4H), 2.96 (br s, 2H), 2.40 (br s, 4H), 2.16 (br m, 2H), 2.06 (m, 1H), 1.98 (s, 2H), 1.65 (d, 2H), 1.41 (t, 2H), 1.36 (m, 2H), 0.93 (s, 6H).

EJEMPLO 387

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-cloro-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indol-4–iloxi)benzamida

EJEMPLO 387A

5,6-dicloropiridina-3-sulfonamida

El compuesto del título se preparó utilizando cloruro de 5,6-dicloropiridina-3-sulfonilo en lugar de cloruro de 5-bromo-6-cloropiridina-3-sulfonilo en el EJEMPLO 329A.

EJEMPLO 387B

5-cloro-6-((tetrahidro-2H-piran-4–il)metoxi)piridina-3-sulfonamida

El compuesto del título se preparó utilizando EJEMPLO 387A en lugar de EJEMPLO 329A en el EJEMPLO 329B.

EJEMPLO 387C

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-cloro-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indol-4–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 26C y EJEMPLO 387B en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11.24 (s, 1H), 8.45 (d, 1H), 8.05 (d, 1H), 7.56 (d, 1H), 7.36 (d, 2H), 7.28 (t, 1H), 7.15 (d, 1H), 7.05 (d, 2H), 6.95 (t, 1H), 6.71 (dd, 1H), 6.39 (d, 1H), 6.30 (d, 1H), 6.27 (s, 1H), 4.26 (d, 2H), 3.88 (dd, 2H), 3.35 (m, 2H), 3.09 (br s, 4H), 2.85 (br s, 2H), 2.30 (br s, 4H), 2.15 (br m, 2H), 2.07 (m, 1H), 1.96 (s, 2H), 1.65 (d, 2H), 1.41 (t, 2H), 1.35 (m, 2H), 0.93 (s, 6H).

EJEMPLO 388

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-ciano-6-(2-morfolin-4–iletoxi)piridin-3–il]sulfonil}-2-(1H-indol-5–iloxi)benzamida

EJEMPLO 388A

5-bromo-6-(2-morfolinoetoxi)piridina-3-sulfonamida

El compuesto del título se preparó utilizando 2-morfolinoetanol en lugar de (tetrahidro-2H-piran-4–il)metanol en el EJEMPLO 329B.

EJEMPLO 388B

5-ciano-6-(2-morfolinoetoxi)piridina-3-sulfonamida

El compuesto del título se preparó utilizando EJEMPLO 388A en lugar de EJEMPLO 329B en el EJEMPLO 335A.

EJEMPLO 388C

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-ciano-6-(2-morfolin-4–iletoxi)piridin-3–il]sulfonil}-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 388B en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11.09 (s, 1H), 8.77 (s, 1H), 8.55 (s, 1H), 7.55 (d, 1H), 7.34-7.36 (m, 4H), 7.04-7.06 (m, 3H), 6.78 (dd, 1H), 6.63 (d, 1H), 6.35 (s, 1H), 6.16 (s, 1H), 4.61 (t, 2H), 3.58 (m, 4H), 3.05 (br s, 4H), 2.89 (br s, 4H), 2.65 (br s, 4H), 2.32-2 (br s, 2H), 2.15 (br s, 2H), 1.96 (s, 2H), 1.39 (t, 2H), 0.92 (s, 6H).

EJEMPLO 389

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)oxi]fenil}sulfonil)benzamida

EJEMPLO 389A

1-(tetrahidro-2H-piran-4–il)piperidin-4-ol

Piperidin-4-ol (7.8 g) y dihidro-2H-piran-4(3H)-ona (5.0 g) se disolvieron en titanio(IV) isopropoxido (30 mL) y la reacción se agitó a temperatura ambiente durante la noche. Metanol (40 mL) se agregó y la reacción se enfrió a 0°. $NaBH_4$ (3.8 g) se agregó en varias porciones durante una hora. Luego de dos horas se agregó 1*N* NaOH acuoso, seguido por la adición de acetato de etilo. Después de la filtración a través de celite, las capas fueron separadas, la capa acuosa se extrajo con acetato de etilo, y las capas orgánicas combinadas se secaron sobre Na_2SO_4. El material crudo se purificó por cromatografía de columna usando CH_2Cl_2 con 5-10% 7*N* NH_3 en metanol.

EJEMPLO 389B

3-nitro-4-(1-(tetrahidro-2H-piran-4–il)piperidin-4–iloxi)bencensulfonamida

EJEMPLO 389A (370 mg) se disolvió en tetrahidrofurano (10 mL), y se agregó 95% NaH (200 mg). Después de agitar por 10 minutos, 4-fluoro-3-nitrobencensulfonamida (420 mg) se agregó y la reacción se agitó a temperatura ambiente durante la noche. La reacción se purificó por cromatografía de columna usando CH_2Cl_2 con 6-10% 7*N* NH_3 en metanol, seguido por lechada en dietiléter y filtrar el producto sólido.

EJEMPLO 389C

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)oxi]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 26C en lugar de EJEMPLO 1E y EJEMPLO 389B en lugar de EJEMPLO 1F en el EJEMPLO 1G, excepto aquí se usó 5-7% metanol en CH_2Cl_2 para la cromatografía. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11.07 (br s, 1H), 8.27 (s, 1H), 7.92 (d, 1H), 7.55 (d, 1H), 7.33 (m, 5H), 7.04 (m, 3H), 6.77 (dd, 1H), 6.58 (d, 1H), 6.35 (s, 1H), 6.14 (s, 1H), 4.85 (s, 1H), 3.93 (dd, 2H), 3.27 (m, 4H), 2.98 (br m, 7H), 2.72 (s, 2H), 2.16 (m, 6H), 2.04 (m, 2H), 1.95 (s, 2H), 1.84 (m, 4H), 1.55 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EJEMPLO 390

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-morfolin-4–ilbut-2-ynil)oxi]-3-nitrofenil}sulfonil)benzamida

EJEMPLO 390A

4-morfolinobut-2-in-1-ol

A una mezcla de morfolina (4.36 g) en tolueno (15 mL) se agregó 4-clorobut-2-in-1-ol (2.09 g) en tolueno (5 mL). La mezcla se agitó a 85 ºC durante tres horas. Después de enfriar, el sólido se filtró. El filtrado se sometió a destilado por vacío para dar el compuesto del título.

EJEMPLO 390B

4-(4-morfolinobut-2-iniloxi)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando EJEMPLO 390A en lugar de (tetrahidro-2H-piran-4–il)metanol en el EJEMPLO 279A.

EJEMPLO 390C

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-morfolin-4–ilbut-2-ynil)oxi]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 390B en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11.17 (s, 1H), 8.40 (d, 1H), 8.11 (dd, 1H), 7.49-7.53 (m, 2H), 7.39-7.42 (m, 4H), 7.34 (d, 2H), 7.17 (d, 1H), 7.04 (d, J = 8.54 Hz, 2H), 6.85 (dd, 1H), 6.64 (dd, 1H), 6.40 (s, 1H), 6.14 (d, 1H), 5.15 (s, 2H), 3.52-3.54 (m, 4H), 3.04 (br s, 4H), 2.78 (br s, 2H), 2.37-2.39 (m, 4H), 2.12-2.20 (br s, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EJEMPLO 391

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-etinil-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indol-4–iloxi)benzamida

EJEMPLO 391A

6-((tetrahidro-2H-piran-4–il)metoxi)-5-((triisopropilsilil)etinil)piridina-3-sulfonamida

EJEMPLO 329B (0.176 g), cloruro de bis(trifenilfosfina)paladio(II) (0.176 g), ioduro de cobre(I) (0.010 g), dimetilacetamida (2.5 ml) y trietilamina (0.105 ml) se combinaron, lavaron con nitrógeno y se agitaron por 2 minutos. (Triisopropil)acetileno (0.135 ml) se agregó y la mezcla de reacción se lavó con nitrógeno nuevamente, se calentó a 60 ºC durante la noche, se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó ($MgSO_4$), se filtró, se concentró y se cromatografió sobre gel de sílice con 10-30% acetato de etilo en hexanos como eluyente para dar el compuesto del título.

EJEMPLO 391B

5-etinil-6-((tetrahidro-2H-piran-4–il)metoxi)piridina-3-sulfonamida

EJEMPLO 391A (0.205 g) en tetrahidrofurano (3 ml) a temperatura ambiente se trató con fluoruro de tetrabutilamonio (1 M en tetrahidrofurano) (0.906 ml) y se agitó a temperatura ambiente por 4 horas. Se agregó fluoruro de tetrabutilamonio (1 M en tetrahidrofurano) (1.8 mL) adicional y la mezcla se calentó a 40 ºC durante 45 minutos. Se agregó fluoruro de tetrabutilamonio sólido(0.253 g) y se continuó calentando por 30 minutos.

La mezcla de reacción se concentró y luego se cromatografió sobre gel de sílice usando 0-2% metanol en diclorometano como eluyente para dar el compuesto del título.

EJEMPLO 391C

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-etinil-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indol-4–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 26C y EJEMPLO 391B en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ ppm 11.23 (s, 1H), 8.50 (d, 1H), 8.09 (d, 1H), 7.56 (d, 1H), 7.34 (m, 2H), 7.28 (m, 1H), 7.18 (d, 1H), 7.04 (m, 2H), 6.98 (t, 1H), 6.70 (dd, 1H), 6.44 (d, 1H), 6.27 (m, 2H), 4.55 (s, 1H), 4.25 (d, 2H), 3.87 (dd, 2H), 3.34 (m, 2H), 3.06 (m, 4H), 2.81 (m, 1H), 2.20 (m, 6H), 2.04 (m, 1H), 1.96 (m, 2H), 1.65 (dd, 2H), 1.35 (m, 5H), 0.92 (m, 6H).

EJEMPLO 392

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-ciano-6-(2-morfolin-4–iletoxi)piridin-3–il]sulfonil}-2-(1H-indol-4–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 26C y EJEMPLO 388B en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11.15 (s, 1H), 10.99 (s, 1H), 8.64 (d, 1H), 8.33 (d, 1H), 7.58 (d, 1H), 7.35 (d, 2H), 7.24 (m, 1H), 7.07 (m, 3H), 6.89 (m, 1H), 6.66 (dd, 1H), 6.26 (m, 3H), 4.59 (t, 2H), 3.58 (m, 4H), 3.05 (m, 4H), 2.87 (m, 4H), 2.62 (m, 4H), 2.24 (m, 6H), 1.98 (m, 2H), 1.40 (t, 2H), 0.93 (s, 6H).

EJEMPLO 393

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-ciano-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-2-(1H-indol-4–iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 55B en lugar de EJEMPLO 26C y EJEMPLO 385B en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11.17 (s, 1H), 8.66 (s, 1H), 8.36 (s, 1H), 7.58 (d, 1H), 7.36 (d, 2H), 7.25 (s, 1H), 7.07 (m, 3H), 6.89 (m, 1H), 6.68 (m, 1H), 6.27 (m, 3H), 4.60 (s, 1H),

4.54 (s, 1H), 3.78 (m, 2H), 3.60 (m, 2H), 3.33 (m, 2H), 3.09 (m, 4H), 2.92 (m, 2H), 2.36 (m, 2H), 2.16 (m, 2H), 1.97 (s, 2H), 1.87 (m, 4H), 1.40 (t, 2H), 0.93 (s, 6H).

EJEMPLO 394

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(3-hidroxi-4-metoxifenil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida

El compuesto del título se preparó utilizando 5-amino-2-metoxifenol en lugar de 1-(2-metoxi-etil)-piperidin-4–ilamina y EJEMPLO 187A en lugar de 4-cloro-3-nitrobencensulfonamida en el EJEMPLO 189A.

EJEMPLO 395

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(2,3-dihidro-1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida

EJEMPLO 103 (676 mg) y $NaCNBH_3$ (49 mg) se combinaron en ácido acético (10 mL) y se agitaron a temperatura ambiente durante la noche. La reacción se diluyó con agua y se extrajo con 95/5 CH_2Cl_2/metanol. La capa orgánica se concentró y el material crudo se purificó por HPLC preparativa usando una columna C18, 250 x 50 mm, 10□, y eluyendo con un gradiente de 20-100% CH_3CN vs. 0.1% ácido trifluoroacético en agua, dando el compuesto del título como una sal de bistrifluoroacetato. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11.57 (br s, 1H), 9.70, 9.50 (ambos v br s, total 2H), 8.57 (d, 1H), 8.20 (br d, 1H), 7.85 (dd, 1H), 7.50 (d, 1H), 7.40 (d, 2H), 7.26 (d, 1H), 7.10 (d, 2H), 6.82 (dd, 1H), 6.75 (dd, 1H), 6.40 (d, 1H), 6.27 (d, 1H), 5.94 (d, 1H), 4.00, 3.70 (ambos v br m, total 8H),3.55 (v br m, 3H), 3.42 (t, 2H), 3.37 (v br m, 1H), 3.10 (br m, 2H), 2.80 (m, 6H), 2.20 (br m, 4H), 2.03 (s, 2H), 1.82 (br m, 2H), 1.46 (t, 2H), 0.96 (s, 6H).

EJEMPLO 396

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)-2-(piridin-3–ilamino)benzamida

EJEMPLO 396A

benzoato de 4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1–il)-2-(piridin-3–ilamino)metilo

Una solución de EJEMPLO 18E (500 mg), carbonato de cesio (429 mg), paladio (II) acetato (21 mg), rac-2,2'-bis(difenilfosfino)-1,1'-binaftilo (58.5 mg) y tolueno (6.4 mL) se

desgasificó con N_2. La mezcla se agitó a 115°C durante 5 minutos. Después de enfriar a temperatura ambiente, piridin-3-amina (106 mg) se agregó y la mezcla de reacción se desgasificó nuevamente con N_2 y se agitó a 115°C durante 45 minutos. La mezcla se enfrió a temperatura ambiente, se diluyó con acetato de etilo y se lavó con H_2O, salmuera, se secó ($MgSO_4$), se filtró y se concentró. El producto crudo se purificó por cromatografía flash sobre gel de sílice, eluyendo con CH_2Cl_2 / 1% metanol para dar el compuesto del título.

EJEMPLO 396B

Ácido 4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1–il)-2-(piridin-3–ilamino)benzoico, 2 Ácido clorhídrico

El compuesto del título se preparó utilizando EJEMPLO 396A en lugar de EJEMPLO 224C en el EJEMPLO 224D.

EJEMPLO 396C

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1–il)-N-(4-(1-metilpiperidin-4–ilamino)-3-nitrofenilsulfonil)-2-(piridin-3–ilamino)benzamida

El compuesto del título se preparó utilizando EJEMPLO 396B en lugar de EJEMPLO 26C y EJEMPLO 21A en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 11.32 - 11.40 (br s, 1H), 9.21 - 9.39 (br s, 1H), 8.51 (d, 1H), 8.33 (d, 1H), 8.09 (dd, 1H), 7.98 - 8.07 (m, 1H), 7.94 (dd, 1H), 7.81 (d, 1H), 7.52 - 7.58 (m, 1H), 7.36 (d, 2H), 7.24 - 7.30 (m, 1H), 7.15 (d, 1H), 7.08 (d, 2H), 6.53 (d, 1H), 6.33 (dd, 1H), 3.81 - 3.96 (br s, 2H), 3.02 - 3.12 (br s, 6H), 2.67 - 2.80 (m, 5H), 2.07 - 2.32 (m, 8H), 1.98 (s, 3H), 1.70 - 1.85 (br s, 1H), 1.41 (t, 3H), 0.95 (s, 6H).

EJEMPLO 397

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)-2-(piridin-3–ilamino)benzamida

El compuesto del título se preparó utilizando EJEMPLO 396B en lugar de EJEMPLO 26C y EJEMPLO 173C en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 9.10 - 9.33 (br s, 1H), 8.53 (d, 1H), 8.36 (d, 1H), 8.12 (dd, 1H), 8.00 - 8.07 (m, 1H), 7.96 (dd, 1H), 7.80 (d, 1H), 7.53 - 7.59 (m, 1H), 7.38 (d, 2H), 7.25 - 7.31 (m, 1H), 7.20 (d, 1H), 7.09 (d, 2H), 6.53 (s, 1H), 6.36 (m, 1H), 4.28 - 4.75

(br s, 1H), 3.90 - 4.09 (m, 8H), 3.51 - 3.61 (m, 2H), 3.35 (m, 8H), 3.01 - 3.18 (br s, 4H), 2.15 - 2.26 (m, 1H), 1.88 - 2.09 (m, 5H), 1.56 - 1.86 (m, 4H), 1.44 (t, 2H), 0.96 (s, 6 H).

EJEMPLO 398

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)-2-(piridin-3–iloxi)benzamida

EJEMPLO 398A

Metiléster de ácido 4-Fluoro-2-(piridin-3–iloxi)-benzoico

El compuesto del título se preparó utilizando 2,4-difluorobenzoato de metilo en lugar 2,4-difluorobenzoato de etilo y 3-hidroxipiridina en lugar de 5-hidroxiindazol en el EJEMPLO 20A.

EJEMPLO 398B

Metiléster de ácido 4-{4-[2-(4-Cloro-fenil)-4,4-dimetil-ciclohex-1-enilmetil]-piperazin-1–il}-2-(piridin-3–iloxi)-benzoico

El compuesto del título se preparó utilizando EJEMPLO 398A en lugar de EJEMPLO 20A en el EJEMPLO 20D.

EJEMPLO 398C

Ácido 4-{4-[2-(4-Cloro-fenil)-4,4-dimetil-ciclohex-1-enilmetil]-piperazin-1–il}-2-(piridin-3–iloxi)-benzoico

El compuesto del título se preparó utilizando EJEMPLO 398B en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 398D

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(piridin-3–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 398C en lugar de EJEMPLO 1E y EJEMPLO 173C en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 8.36 (d, 1H), 8.11 (t, 1H), 8.08 (t, 2H), 7.70 (dd, 1H), 7.60 (d, 1H), 7.37 (d, 2H), 7.15 (dd, 1H), 7.10-7.03 (m, 3H), 7.00 (dd, 1H), 6.73 (dd, 1H), 6.43 (d,

1H), 3.99-3.93 (m, 3H), 3.86 (m, 1H), 3.13 (m, 6H), 2.78 (br s, 2H), 2.30-2.05 (m, 10H), 1.98 (br s, 2H), 1.92-1.67 (m, 6H), 1.57 (m, 2H), 1.41 (t, 2H), 0.94 (s, 6H).

EJEMPLO 399

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(1,2,3,4-tetrahidroisoquinolin-5–iloxi)benzamida

EJEMPLO 399A

carboxilato de 5-hidroxi-3,4-dihidroisoquinolin-2(1H)- tert-butilo

Una mezcla de 1,2,3,4-tetrahidroisoquinolin-5-ol ácido clorhídrico (1.0 g), di-tert-butilo dicarbonato (1.27 g) y 1.0 N NaOH (14.5 mL) en dioxano (20 mL) se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción se particionó entre agua y acetato de etilo. La capa acuosa se neutralizó con 5% HCl. Las capas orgánicas combinadas se lavaron con salmuera, se secó ($MgSO_4$), se filtró, y se concentró. El residuo se purificó por cromatografía flash sobre gel de sílice para dar el compuesto del título.

EJEMPLO 399B

Carboxilato de 5-(2-(etoxicarbonil)-5-fluorofenoxi)-3,4-dihidroisoquinolin-2(1H)- tert-butilo

El compuesto del título se preparó utilizando EJEMPLO 399A en lugar de 5-hidroxiindazol en el EJEMPLO 20A.

EJEMPLO 399C

Carboxilato de 5-(5-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1–il)-2-(etoxicarbonil)fenoxi)-3,4-dihidroisoquinolin-2(1H)- tert-butilo

El compuesto del título se preparó utilizando EJEMPLO 399B en lugar de EJEMPLO 20A en el EJEMPLO 20D.

EJEMPLO 399D

Ácido 2-(2-(tert-butoxicarbonil)-1,2,3,4-tetrahidroisoquinolin-5–iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1–il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 399C en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 399E

Anhidrido 2-(2-(tert-butoxicarbonil)-1,2,3,4-tetrahidroisoquinolin-5–iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1–il)benzoic 3-nitro-4-((tetrahidro-2H-piran-4–il)metilamino)bencensulfónico

El compuesto del título se preparó utilizando EJEMPLO 399D en lugar de EJEMPLO 26C en el EJEMPLO 177.

EJEMPLO 399F

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(1,2,3,4-tetrahidroisoquinolin-5–iloxi)benzamida

Una mezcla de EJEMPLO 399E (0.058 g) y ácido trifluoroacético (1 mL) en diclorometano (10 mL) se agitó por 2 horas. El solvente se eliminó, y el residuo se tomó en acetato de etilo. Entonces se lo lavó con $NaHCO_3$ saturado, salmuera, se secó sobre $MgSO_4$, se filtró, y concentró para dar el compuesto del título. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 8.36 (t, 1H), 8.27 (d, 1H), 7.65 (d, 1H), 7.36 (d, 2H), 7.07 (d, 2H) 6.93-6.97 (m, 2H), 6.73 (d 1H), 6.69 (dd, 1H), 6.33(d, 1H), 6.26 (d, 1H), 4.19 (s, 2H), 3.85 (dd, 2H), 3.05-3.09 (m, 6H), 2.77 (s, 2H), 2.17-2.24 (m, 6H), 1.98-1.99 (m, 2H), 1.60-1.63 (m, 2H0, 1.41 (t, 2H), 0.94 (s, 6H).

EJEMPLO 400

4-(4-{[2-(4-Clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 400A

Éster *tert*-butílico de ácido 4-hidroxi-indazol-1-carboxílico y éster *tert*-butílico de ácido 4-hidroxi-indazol-2-carboxílico

Se agregó 4-hidroxiindazol (3,94 g) a tetrahidrofurano (250 mL) y se enfrió a 0°C usando un baño de hielo. Se agregó hidruro de sodio (dispersión 60% en aceite mineral, 1,23 g), y la mezcla se agitó a 0°C durante cinco minutos. La mezcla se dejó tomar la temperatura ambiente y se agitó durante 20 minutos adicionales. La mezcla se enfrió nuevamente a 0°C usando un baño de hielo, y se agregó *tert*-butildimetilclorosilano (4,65 g). La mezcla se dejó llegar a temperatura ambiente y se agitó durante 16 horas. Se redujo el volumen de solvente al vacío, el residuo se filtró por vacío sobre un relleno de gel de sílice y se lavó con acetato de

etilo, y el solvente se eliminó al vacío. Al residuo se agregó acetonitrilo (200 mL), dicarbonato de di-*tert*-butilo (7,06 g), y 4-(dimetilamino)piridina (0,359 g). La mezcla se agitó a temperatura ambiente durante tres horas, y el solvente se eliminó al vacío. Al residuo se agregó tetrahidrofurano (200 mL) y fluoruro de tetrabutilamonio (1M en tetrahidrofurano, 82 mL). La mezcla se agitó a temperatura ambiente durante cuatro días, el solvente se eliminó al vacío, y el residuo se recogió en acetato de etilo. La mezcla se extrajo con cloruro de amonio acuoso saturado, se extrajo con salmuera, y se secó sobre sulfato de sodio anhidro. La mezcla se filtró en vació sobre gel de sílice, y el solvente se eliminó al vacío para dar una mezcla de los dos productos, que se usó en el próximo paso sin purificación adicional.

EJEMPLO 400B

Éster metílico de ácido 4-fluoro-2-(1H-indazol-4-iloxi)-benzoico

Se agregó EJEMPLO 400A (5,56 g) a diglima (200 mL), y se agregó *tert*-butóxido de potasio (1M en tetrahidrofurano, 30,8 mL). La mezcla se mezcló a temperatura ambiente durante 15 minutos, se agregó 2,4-difluorobenzoato de metilo, y la mezcla se calentó a 115°C durante 16 horas. La mezcla se enfrió, el solvente se eliminó al vacío, el residuo se capturó en diclorometano (100 mL), y se agregó ácido trifluoroacético (22,6 mL). La mezcla se agitó a temperatura ambiente durante 16 horas, el solvente se eliminó al vacío, el residuo se capturó en acetato de etilo y se lavó con una mezcla de bicarbonato de sodio acuoso saturado, y la capa orgánica se secó con sulfato de sodio anhidro. El material se purificó por cromatografía de columna rápida sobre gel de sílice usando acetato de etilo 30% (en hexanos) aumentando a acetato de etilo 40% (en hexanos).

EJEMPLO 400C

Éster metílico de ácido 2-(1H-Indazol-4-iloxi)-4-piperazin-1-il-benzoico

Se agregó EJEMPLO 400B (2,00 g) y piperazina (2.71 g) a dimetilsulfóxido (60 mL) y se calentó a 100°C durante una hora. La mezcla se enfrió, se agregó a diclorometano, se lavó dos veces con agua, se lavó con una mezcla de bicarbonato de sodio acuoso saturado, y se secó sobre sulfato de sodio anhidro. Luego de la filtración, el solvente se eliminó al vacío.

EJEMPLO 400D

Éster metílico de ácido 4-{4-[2-(4-cloro-fenil)-4,4-dimetil-ciclohex-1-enilmetil]-piperazin-1-il}-2-(1H-indazol-4-iloxi)-benzoico

El compuesto del título se preparó utilizando EJEMPLO 218A en lugar de 4'-clorobifenil-2-carboxaldehído y EJEMPLO 400C en lugar de piperazin-1-carboxilato de *tert*-butilo en el EJEMPLO 1A.

EJEMPLO 400E

Ácido 4-{4-[2-(4-Cloro-fenil)-4,4-dimetil-ciclohex-1-enilmetil]-piperazin-1-il}-2-(1H-indazol-4-iloxi)-benzoico

El compuesto del título se preparó utilizando EJEMPLO 400D en lugar de EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 400F

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 400E en lugar de EJEMPLO 1E en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 13,09 (s, 1H), 8,56 (t, 1H), 8,38 (d, 1H), 7,80 (s, 1H), 7,56 (dd, 1H), 7,53 (d, 1H), 7,36 (d, 2H), 7,16-7,05 (m, 4H), 6,99 (d, 1H), 6,80 (dd, 1H), 6,52 (d, 1H), 6,19 (dd, 1H), 3,87 (dd, 2H), 3,25-3,12 (m, 6H), 2,78 (m, 2H), 2,30-2,16 (m, 6H), 1,97 (s ancho, 2H), 1,90 (m, 1H), 1,63 (m, 2H), 1,53 (m, 1H), 1,40 (t, 2H), 1,29 (m, 3H), 0,94 (s, 6H).

EJEMPLO 401

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4-ilpiperidin-4-il)amino]fenil}sulfonil)benzamida

EJEMPLO 401A

N-[(4-cloro-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 400E en lugar de EJEMPLO 1E y 4-cloro-3-nitrobencensulfonamida en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 13,04 (s, 1H), 8,17 (s ancho, 1H), 7,75 (s, 1H), 7,73 (d, 1H), 7,66-7,61 (m, 2H), 7,38 (d, 2H), 7,11-7,01 (m, 4H), 6,79 (dd, 1H), 6,54 (d, 1H), 6,10 (dd, 1H), 3,38-3,05 (m, 8H), 2,73 (s ancho, 2 H), 2,19 (m, 2H), 2,00 (s ancho, 2H), 1,44 (t, 2H), 0,95 (s, 6H).

EJEMPLO 401B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4-ilpiperidin-4-il)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 173B en lugar de 1-(2-metoxi-etil)-piperidin-4-ilamina y EJEMPLO 401A en lugar de 4-cloro-3-nitrobencensulfonamida en el EJEMPLO 189A. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 13,05 (s ancho, 1H), 8,35 (d, 1H), 8,13 (d, 1H), 7,78 (s, 1H), 7,61-7,52 (m, 2H), 7,35 (d, 2H), 7,11-7,03 (m, 4H), 6,98 (d, 1H), 6,77 (dd, 1H), 6,48 (d, 1H), 6,18 (m, 1H), 3,69-3,52 (m, 4H), 3,12 (m, 6H), 2,76 (s ancho, 2H), 2,67 (m, 4H), 2,28-2,16 (m, 6H), 2,09-2,01 (m, 2H), 1,97 (s ancho, 2H), 1,95 (m, 2H), 1,50-1,38 (m, 6H), 0,93 (s, 6H).

EJEMPLO 402

Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-({4-[(4-morfolin-4-ilciclohexil)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando trans-4-morfolin-4-il-ciclohexilamina en lugar de 1-(2-metoxi-etil)-piperidin-4-ilamina y EJEMPLO 401A en lugar de 4-cloro-3-nitrobencensulfonamida en el EJEMPLO 189A. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 13,02 (s ancho, 1H), 8,35 (d, 1H), 8,12 (m, 1H), 7,75 (s, 1H), 7,65-7,55 (m, 2H), 7,35 (d, 2H), 7,10-7,03 (m, 4H), 6,97 (m, 1H), 6,76 (dd, 1H), 6,44 (m, 1H), 6,17 (t, 1H), 3,95 (m, 2H), 3,77 (m, 1H), 3,62 (m, 1H), 3,10 (m, 6H), 2,75 (s ancho, 2H), 2,28-2,14 (m, 8H), 2,06 (m, 2H), 1,97 (s ancho, 2H), 1,85 (m, 2H), 1,71 (m, 2H), 1,55 (m, 4H), 1,40 (t, 2H), 0,93 (s, 6H).

EJEMPLO 403

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 403A

4-fluoro-2-(3-fluoro-2-nitofenoxi)benzoato de metilo

A una solución de 4-fluoro-2-hidroxibenzoato de metilo (3,0 g) en tetrahidrofurano (65 mL) se agregó t-butóxido de potasio (1,979 g) en porciones. La solución resultante se agitó a temperatura ambiente durante 30 minutos y se agregó por goteo una solución de 1,3-

difluoro-2-nitrobenceno (2,338 g) en tetrahidrofurano (15 mL). Luego de 1 hora, la reacción se calentó a reflujo durante 18 horas. La reacción se detuvo con agua (10 mL), se diluyó con salmuera (75 mL) y se extrajo con cloruro de metileno (2x 75 mL). El producto crudo se aisló por concentración y se purificó gel de sílice, se eluyó con un gradiente en pasos de acetato de etilo 10, 20, 50 % en hexano para dar el compuesto del título.

EJEMPLO 403B

2(3-(bis(4-metoxifenil)metilamino)-2-mitrofenoxi)-4-fluorobenzoato de metilo

A una solución de EJEMPLO 403A (3,82 g) y bis(4-metoxifenil)metanamina (4,51 g) en N-metil-2-pirrolidinona (65 mL) se agregó N-etil-N-isopropilpropan-2-amina (4,30 mL) y la mezcla se calentó a 100 º C durante 24 horas. El producto crudo, se aisló por concentración, se purificó sobre gel de sílice, y se eluyó con un gradiente en pasos de acetato de etilo 10, 25, y 65 % en hexano para dar el compuesto del título.

EJEMPLO 403C

2-(2-amino-3-(bis(4-metoxifenil)metilamino)fenoxi)-4-fluorobenzoato de metilo

A una solución de EJEMPLO 403B (2,76 g) en tetrahidrofurano (125 mL) en una botella de presión de acero inoxidable se agregó catalizador níquel (2,76 g). La mezcla se agitó durante 1 hora bajo hidrógeno a 30 psi y temperatura ambiente. La mezcla se filtró a través de una membrana de nilon para eliminar el catalizador, y se concentró para dar el producto.

EJEMPLO 403D

2-(1-(bis(4-metoxifenil)metil)-1*H*-benzo[*d*]imidazol-4-iloxi)-4-fluorobenzoato de metilo

A una solución de EJEMPLO 403C (1.25 g) en ortoformiato de trietilo (30 mL) se agregó ácido clorhídrico concentrado (0,75 mL). La mezcla se agitó durante 18 horas, se finalizó por medio de la adición lenta de solución 50% de carbonato de sodio acuoso (100 mL) y se extrajo con acetato de etilo (2 x 100 mL). El producto crudo se aisló por concentración y se purificó sobre gel de sílice, y se eluyó con un gradiente en pasos de acetato de etilo 25, 50, y 70% en hexano para dar el compuesto del título.

EJEMPLO 403E

2-(1-(bis(4-metoxifenil)metil)-1*H*-benzo[*d*]imidazol-4-iloxi)-4-(piperazin-1-il)benzoato de metilo

Una solución de EJEMPLO 403D (500 mg), y piperazina (420 mg) en dimetilsulfóxido (9 mL) se calentó a 100 ºC durante 3 horas. El producto crudo se aisló por concentración y, luego de un procesamiento con agua, se purificó sobre gel de sílice, y se eluyó con un gradiente en pasos de metanol 5 y 10% en cloruro de metileno para dar el compuesto del título.

EJEMPLO 403F

2-(1-(bis(4-metoxifenil)metil)-1*H*-benzo[*d*]imidazol-4-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoato de metilo

A una solución de EJEMPLO 403E (430 mg) y EJEMPLO 218A (259 mg) en diclorometano (13 mL) se agregó tetracetoxiborohidruro de sodio (323 mg) en porciones. Luego de una agitación de 42 horas, la reacción se detuvo lentamente con solución de bicarbonato de sodio acuoso saturado (80 mL) y se extrajo con cloruro de metileno (2 X 70 mL). El producto crudo se aisló por concentración y se purificó sobre gel de sílice, y se eluyó con un gradiente en pasos de metanol 0, 2, 10% en cloruro de metileno para dar el compuesto del título.

EJEMPLO 403G

Ácido 2-(1-(bis(4-metoxifenil)metil)-1*H*-benzo[*d*]imidazol-4-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoico

A una solución de EJEMPLO 403F (545 mg) en una mezcla de metanol (7,50 mL) y tetrahidrofurano (7,50 mL) se agregó una solución de hidróxido de sodio (269 mg) en agua (3,0 mL). La mezcla de reacción se calentó a 50º C durante 18 horas y luego se concentró. El residuo se mezcló con agua (100 mL) y el pH se ajustó a aproximadamente 7 con ácido clorhídrico acuoso 1M. La mezcla se extrajo con metanol 10 % en cloruro de metileno (10 X 50 mL), y las capas orgánicas combinadas se concentraron para dar el compuesto del título.

EJEMPLO 403H

2-(1-(bis(4-metoxifenil)metil)-1*H*-benzo[*d*]imidazol-4-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-*N*-(3-nitro-4-((tetrahidro-2*H*-piran-4-il)metilamino)fenilsulfonil)benzamida

A una solución de EJEMPLO 403G (200 mg), EJEMPLO 1F (99 mg), trietilamina (0,122 mL), N,N-dimetilpiridin-4-amina (77 mg) en una mezcla de diclorometano (8 mL) y N, N-dimetilformamida (1 mL) se agregó ácido N^1-((etilimino)metilen)-N^3,N^3-dimetilpropan-

1,3-diaminoclorhídrico (96 mg). La mezcla de reacción se agitó 18 horas y luego se concentró. El producto crudo se purificó sobre gel de sílice y se eluyó con un gradiente en pasos de acetato de etilo 80 y 100 % en hexano para dar el compuesto del título.

EJEMPLO 403I

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)benzamida

Una solución de EJEMPLO 403H (174 mg) y diclorometano (25 mL) se enfrió en un baño de hielo y se agregó 2,2,2-ácido trifluoroacético (25 mL) lentamente por goteo. La mezcla de reacción se agitó 30 minutos bajo nitrógeno y se quitó el baño de hielo. La reacción se agitó 18 horas y luego se concentró. El producto crudo se purificó por cromatografía en fase reversa con solución amortiguadora de acetato de amonio en acetonitrilo para dar el compuesto del título. ^{1}H NMR (400 MHz, piridina-d_5) δ 9,30 (d, 1H), 8,69 (t, 1H), 8,59 (s, 1H), 8,42 (dd, 1H), 7,99 (d, 1H), 7,53 (d, 1H), 7,43 (d, 2H), 7,26 (m, 1H), 7,18 (m, 1H), 7,06 (d, 2H), 6,94 (d, 1H), 6,72 - 6,66 (m, 2H), 5,53 (m, 2H), 3,98 (m, 2H), 3,32 (m, 2H), 3,18 (t, 2H), 2,03 (m, 4H), 2,76 (s, 2H), 2,25 (m, 2H), 2,13 (m, 4H), 1,97 (s, 2H), 1,83 (m, 1H), 1,60 (m, 2H), 1,40 - 1,29 (m, 4H), 0,94 (s, 6H).

EJEMPLO 404

N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 404A

5-cloro-6-((4-fluorotetrahidro-2H-piran-4-il)metoxi)piridina-3-sulfonamida

El compuesto del título se preparó utilizando EJEMPLO 387A en lugar de EJEMPLO 329A y EJEMPLO 306C en lugar de (tetrahidro-2H-piran-4-il)metanol en el EJEMPLO 329B.

EJEMPLO 404B

N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 404A en lugar de EJEMPLO 1F y EJEMPLO 400E en lugar de EJEMPLO 26C en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 13,09 (s, 1H), 8,27 (d, 1H), 7,88 (d, 1H), 7,80 (s, 1H), 7,60 (d, 1H), 7,37 (d, 2H), 7,03-7,10 (m, 4H), 6,79 (dd, 1H), 6,53 (d, 1H), 6,13 (d, 1H), 4,50 (d, 2H), 3,76-3,81 (m, 2H), 3,57-3,63 (m, 2H), 3,04 (s ancho, 4H), 2,84 (s ancho, 2H), 2,18 (m, 2H), 1,82-1,92 (m, 4H), 1,42 (t, 2H), 0,94 (s, 6H).

EJEMPLO 405

N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 404A en lugar de EJEMPLO 1F y EJEMPLO 55B en lugar de EJEMPLO 26C en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 11,21 (s, 1H), 8,43 (d, 1H), 8,06 (d, 1H), 7,55 (d, 1H), 7,34 (d, 2H), 7,27 (t, 1H), 7,13 (d, 1H), 7,04 (d, 2H), 6,93 (t, 1H), 6,69 (dd, 1H), 6,36 (d, 1H), 6,28 (d, 1H), 6,26 (d, 1H), 4,51 (d, 2H), 3,73-3,79 (m, 2H), 3,55-3,61 (m, 2H), 3,08 (s ancho, 4H), 2,86 (s ancho, 2H), 2,31 (s ancho, 2H), 2,18 (m, 2H), 1,95 (s, 2H), 1,79-1,90 (m, 4H), 1,36 (t, 2H), 0,92 (s, 6H).

EJEMPLO 406

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({5-ciano-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 385B en lugar de EJEMPLO 1F y EJEMPLO 400E en lugar de EJEMPLO 26C en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 13,03 (s, 1H), 8,48 (d, 1H), 8,17 (s, 1H), 7,74 (s, 1H), 7,63 (d, 1H), 7,37 (d, 2H), 7,00-7,08 (m, 4H), 6,77 (dd, 1H), 6,51 (s, 1H), 6,07 (d, 1H), 4,55 (d, 2H), 3,77-3,81 (m, 2H), 3,58-3,63 (m, 2H), 3,20 (s ancho, 4H), 2,19 (s ancho, 2H), 1,99 (s, 2H), 1,85-1,92 (m, 4H), 1,42 (t, 2H), 0,94 (s, 6H).

EJEMPLO 407

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3R)-1-(2,2-difluoroetil)pirrolidin-3-il]amino}-3-nitrofenil)sulfonil]benzamida

EJEMPLO 407A

(*R*)-*tert*-butil 1-(2, 2-difluoroetil)pirrolidin-3-ilcarbamato

A una solución de (R)-*tert*-butil pirrolidin-3-ilcarbamato (500 mg), 1,1-difluoro-2-iodoetano (618 mg) en N,N-dimetilformamida (6 mL) se agregó N-etil-N-isopropilpropan-2-amina (1,403 mL) y la reacción se agitó durante 72 horas a 70 ºC. La mezcla de reacción se concentró y el producto crudo se purificó sobre un gel de sílice y se eluyó con un gradiente en pasos de metanol 0, 2, y 5 % en cloruro de metileno para dar el compuesto del título.

EJEMPLO 407B

(*R*)-1-(2, 2-difluoroetil)pirrolidin-3-amina

A una solución de EJEMPLO 407A (525 mg) en una mezcla de diclorometano (3 mL) y metanol (2,0 mL) se agregó cloruro de hidrógeno, 4M en dioxano (5,24 mL). La reacción se agitó durante 3 horas, y se concentró para dar el compuesto del título.

EJEMPLO 407C

(*R*)-4-(1-(2, 2-difluoroetil)pirrolidin-3-ilamino)-3-nitrobencensulfonamida

A una solución de EJEMPLO 407B (468 mg) en tetrahidrofurano (20 mL), N-etil-N-isopropilpropan-2-amina (2,193 mL) y N,N-dimetilformamida (2 mL) se agregó 4-fluoro-3-nitrobencensulfonamida (473 mg) y la mezcla de reacción se agitó 72 horas. El producto crudo se aisló por concentración y se purificó sobre gel de sílice, y se eluyó con un gradiente en pasos de metanol 0,5, 2,5, y 5 % en cloruro de metileno para obtener el compuesto del título.

EJEMPLO 407D

(*R*)-2-(1-(bis(4-metoxifenil)metil)-1*H*-benzo[*d*]imidazol-4-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-nitrofenilsulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 407C en lugar de EJEMPLO 1F en el EJEMPLO 403H.

EJEMPLO 407E

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3R)-1-(2,2-difluoroetil)pirrolidin-3-il]amino}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 407D en lugar de EJEMPLO 403H en el EJEMPLO 403I. ^{1}H NMR (400 MHz, piridina-d_5) δ 9,26 (d, 1H), 8,60 - 8,55 (m, 2H), 8,39 (m, 1H), 7,99 (d, 1H), 7,53 (d, 1H), 7,43 (d, 2H), 7,25 (m, 1H), 7,17 (m, 1H), 7,06 (d, 2H), 6,86 (d, 1H), 6,72 - 6,69 (m, 2H), 6,00 - 6,33 (m, 1H), 5,27 (m, 2H), 4,09 (m, 1H), 3,03 (m, 4H), 2,96 - 2,86 (m, 4H), 2,81 - 2,74 (m, 3H), 2,48 (m, 1H), 2,26 (m, 3H), 2,13 (m, 4H), 1,97 (s, 2H), 1,67 (m, 1H), 1,38 (t, 2H), 0,94 (s, 6H).

EJEMPLO 408

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]-3-nitrofenil}sulfonil)benzamida

EJEMPLO 408A

2-(1-(bis(4-metoxifenil)metil)-1*H*-benzo[*d*]imidazol-4-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-*N*-(4-((4-fluorotetrahidro-2*H*-piran-4-il)metoxi)-3-nitorofenilsulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 306D en lugar de EJEMPLO 1F en el EJEMPLO 403H.

EJEMPLO 408B

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 408A en lugar de EJEMPLO 403H en el EJEMPLO 403I. ^{1}H NMR (400 MHz, piridina-d_5) δ 9,01 (d, 1H), 8,57 (m, 2H), 7,99 (d, 1H), 7,53 (d, 1H), 7,44 (d, 2H), 7,25 (m, 1H), 7,21 (m, 1H), 7,12 (d, 1H), 7,07 (d, 2H), 6,73 - 6,70 (m, 2H), 5,35 (m, 2H), 4,36 (s, 1H), 4,31 (s, 1H), 3,88 (m, 2H), 3,78 (m, 2H), 3,05 (m, 4H), 2,77 (s, 2H), 2,26 (m, 2H), 2,15 (m, 4H), 2,07 - 192 (m, 6H), 1,39 (t, 2H), 0,94 (s, 6H).

EJEMPLO 409

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4-fluorotetrahidro-2H-piran-4-il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 409A

Metanosulfonato de (4-fluorotetrahidro-2H-piran-4-il)metilo

Una mezcla de EJEMPLO 306C (1,4 g), cloruro de metanosulfonilo (1,054 mL), trietilamina (2,99 mL), y 4-(dimetilamino)piridina (0,051 g) en CH_2Cl_2 (20 mL) se agitó a 0 ºC durante 2 horas, se concentró y se separó por cromatografía sobre gel de sílice con acetato de etilo 30% en hexanos como eluyente para dar el producto.

EJEMPLO 409B

2-((4-fluorotetrahidro-2H-piran-4-il)metil)isoindolin-1,3-diona

Una mezcla de EJEMPLO 409A (1,8 g) y ftalimida de potasio (2,356 g) en N,N-dimetilformamida (30 mL) se calentó a 150 ºC durante la noche, se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó ($MgSO_4$), se filtró, se concentró y se separó por cromatografía sobre gel de sílice con acetato de etilo 30% en hexanos como eluyente para dar el producto.

EJEMPLO 409C

(4-fluorotetrahidro-2H-piran-4-il)metanamina

Una mezcla de EJEMPLO 409B (1,4 g) e hidrazina (1,548 mL) en etanol (40 mL) se calentó a 70 ºC durante la noche, se enfrió a temperatura ambiente, se formó una lechada con CH_2Cl_2 (200 mL) y se eliminó el sólido por filtración. El filtrado se concentró y se separó por cromatografía sobre gel de sílice con 100:5:1 acetato de etilo/metanol/NH_4OH como eluyente para dar el producto.

EJEMPLO 409D

4-((4-fluorotetrahidro-2H-piran-4-il)metilamino)-3-nitrobencensulfonamida

Una mezcla de 4-fluoro-3-nitrobencensulfonamida (0,44 g), EJEMPLO 409C (0,266 g), y trietilamina (1,11 mL) en tetrahidrofurano (10 mL) se calentó a 70 °C durante la noche, se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó ($MgSO_4$), se filtró, se concentró y se separó por cromatografía sobre gel de sílice con acetato de etilo 50% en hexanos como eluyente para dar el producto.

EJEMPLO 409E

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4-fluorotetrahidro-2H-piran-4-il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 409D en lugar de EJEMPLO 1F y EJEMPLO 400E en lugar de EJEMPLO 26C en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 13,09 (s, 1H), 8,59 (t, 1H), 8,37 (d, 1H), 7,80 (s, 1H), 7,59 (dd, 1H), 7,37 (d, 2H), 7,04-7,13 (m, 5H), 6,79 (dd, 1H), 6,51 (d, 1H), 6,18 (d, 1H), 3,70-3,79 (m, 4H), 3,50-3,56 (m, 2H), 3,15 (s ancho, 4H), 2,78 (s ancho, 2H), 2,32 (s ancho, 4H), 2,17 (s ancho, 2H), 1,97 (s, 2H), 1,75-1,83 (m, 4H), 1,40 (t, 2H), 0,93 (s, 6H).

EJEMPLO 410

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]-5-(trifluorometil)piridin-3-il]sulfonil}-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 410A

5-nitro-3-(trifluorometil)piridin-2-ol

Se agregó 3-(trifluorometil)piridin-2-ol (2,3 g) a ácido sulfúrico concentrado (15 mL) a 0 ºC. La mezcla se agitó a 0 ºC durante 5 minutos. A esta solución se le agregó ácido nítrico (fumante) (6 mL) por goteo durante 5 minutos. La mezcla de reacción se agitó a temperatura ambiente durante 2 horas, y se calentó a 50 ºC durante 3 horas. Luego de enfriar, la mezcla de reacción se vertió sobre hielo (200 g), y la mezcla se extrajo con acetato de etilo tres veces. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$, se filtraron, y se concentraron bajo presión reducida para dar el compuesto del título.

EJEMPLO 410B

2-cloro-5-nitro-3-(trifluorometil)piridina

Se calentó una mezcla de EJEMPLO 410A (1,69 g), pentacloruro de fósforo (2,03 g), y tricloruro de fosforilo (0,97 mL) a 90 ºC durante 3 horas. Luego de enfriar, la mezcla de reacción se vertió sobre hielo, y se extrajo con acetato de etilo tres veces. El extracto se lavó con salmuera, se secó sobre $MgSO_4$, se filtró, y se concentro bajo presión reducida. El residuo se purificó por cromatografía de columna rápida sobre gel de sílice eluyendo con 1:9 acetato de etilo/hexanos para dar el compuesto del título.

EJEMPLO 410C

Se agitó una mezcla de hierro (1,5 g) y cloruro de amonio (2,38 g) en agua (40 mL) a temperatura ambiente durante 5 minutos. A esta suspensión se le agregó EJEMPLO 410B en metanol (40 mL). La mezcla de reacción se agitó a temperatura ambiente durante 1 hora. Se agregó hierro adicional (1,8 g) a la mezcla de reacción, y se agitó durante otras 3 horas. El sólido de la mezcla de reacción se quitó por filtración, y el filtrado se particionó entre agua y acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$, se filtraron, y se concentraron bajo presión reducida. El residuo se purificó por cromatografía de columna rápida sobre gel de sílice eluyendo con 1:4 acetato de etilo/hexanos para dar el compuesto del título.

EJEMPLO 410D

Cloruro de 6-cloro-5-(trifluorometil)piridina-3-sulfonilo

Bajo enfriamiento con hielo, se agregó cloruro de tionilo (4 mL) por goteo durante 20 minutos a agua (27 mL). La mezcla se agitó durante la noche durante 12 horas para dar una solución conteniendo SO_2. En forma separada, se agregó EJEMPLO 410C (1,14 g) en dioxano (5 mL) a HCl concentrado (20 mL) a 0 ºC. La solución se agitó durante 5 minutos. A esta mezcla se agregó nitrito de sodio (0,44 g) en agua (6 mL) por goteo a 0 ºC. La solución se agitó a 0 ºC durante tres horas. Durante este tiempo, cualquier sólido formado se aplastó con un vástago de vidrio para asegurarse que el EJEMPLO 410C reaccionó por completo. Se agregó cloruro de cobre(I) (0,115 g) a la solución conteniendo SO_2. Luego, a esta solución se le agregó el EJEMPLO 410C diazotizado a 0 ºC. La solución se agitó durante 30 minutos. La mezcla de reacción se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$, se filtraron, y se concentraron bajo presión reducida. El residuo se purificó por cromatografía de columna rápida sobre gel de sílice eluyendo con 1:20 acetato de etilo/hexanos para dar el compuesto del título.

EJEMPLO 410E

6-cloro-5-(trifluorometil)piridina-3-sulfonamida

El compuesto del título se preparó utilizando EJEMPLO 410D en lugar de cloruro de 5-bromo-6-cloropiridina-3-sulfonilo en el EJEMPLO 329A.

EJEMPLO 410F

El compuesto del título se preparó utilizando EJEMPLO 410E en lugar de EJEMPLO 329A y EJEMPLO 306C en lugar de (tetrahidro-2H-piran-4-il)metanol en el EJEMPLO 329B.

EJEMPLO 410G

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]-5-(trifluorometil)piridin-3-il]sulfonil}-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 410F en lugar de EJEMPLO 1F y EJEMPLO 400E en lugar de EJEMPLO 26C en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 13,05 (s, 1H), 8,59 (s, 1H), 8,17 (d, 1H), 7,76 (s, 1H), 7,62 (d, 1H), 7,37 (d, 2H), 7,00-7,08 (m, 4H), 6,78 (dd, 1H), 6,51 (s, 1H), 6,11 (d, 1H), 4,56 (d, 2H), 3,77-3,80 (m, 2H), 3,57-3,62 (m, 2H), 3,18 (s ancho, 2H), 2,32 (s ancho, 4H), 2,18 (s ancho, 2H), 1,99 (s, 2H), 1,81-1,90 (m, 4H), 1,42 (t, 2H), 0,94 (s, 6H).

EJEMPLO 411

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4-ciclopropilmorfolin-2-il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 400E en lugar de EJEMPLO 1E y EJEMPLO 432A en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 13,09 (s, 1H), 8,57 (m, 1H), 8,37 (d, 1H), 7,81 (s, 1H), 7,56 (dd, 1H), 7,52 (d, 1H), 7,38-7,31 (m, 3H), 7,11-7,07 (m, 3H), 6,97 (d, 1H), 6,80 (dd, 1H), 6,52 (d, 1H), 6,17 (d, 1H), 3,84 (d, 1H), 3,24-3,10 (m, 6H), 2,93 (d, 2H), 2,76 (m, 2H), 2,73 (s, 2H), 2,34-2,10 (m, 8H), 1,97 (bs, 2H), 1,67 (m, 1H), 1,40 (t, 2H), 0,93 (s, 6H), 0,47-0,26 (m, 4H).

EJEMPLO 412

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4,4-difluorociclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 412A

(4,4-difluorociclohexil)metilcarbamato de *tert*-butilo

Se agitó (4-oxociclohexil)metilcarbamato de *tert*-butilo (5 g) y trifluoruro de dietilaminosulfuro (7,45 g) en diclorometano (100 mL) durante 24 horas. La mezcla se detuvo con solución amortiguadora de pH 7 (100 mL), y se vertió en éter (400 mL). La

solución resultante se separó, y se lavó la capa orgánica dos veces con agua, y una vez con salmuera, y luego se concentró para dar el producto crudo y fluoroolefina en una relación 3:2. El producto crudo se capturó en tetrahidrofurano (70 mL) y agua (30 mL), y se añadieron N-metilmorfolin-N-óxido (1,75 g), y OsO_4 (2,5 % en peso de solución en t-butanol), y la mezcla se agitó durante 24 horas. Luego se agregó $Na_2S_2O_3$ (10 g), y la mezcla se agitó durante 30 minutos. La mezcla luego se diluyó con éter (300 mL), y la solución resultante se separó, y se lavó dos veces con agua, y una vez con salmuera, y se concentró. El producto crudo se separó por cromatografía sobre gel de sílice usando acetato de etilo entre 5 y 10% en hexanos para dar el compuesto del título.

EJEMPLO 412B

(4,4-difluorociclohexil)metanamina

Una solución de EJEMPLO 412A (3 g) en diclorometano (35 mL), ácido trifluoroacético (15 mL), y trietilsilano (1 mL) se agitó durante 2 horas. La solución se concentró, luego se concentró desde tolueno, y se dejó en alto vacío durante 24 horas. El semisólido se capturó en éter/hexano y se filtró para dar el producto como su sal de ácido trifluoroacético.

EJEMPLO 412C

4-((4,4-difluorociclohexil)metilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando EJEMPLO 412B en lugar de 1-(2-metoxi-etil)-piperidin-4-ilamina en el EJEMPLO 189A.

EJEMPLO 412D

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4,4-difluorociclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 400E en lugar de EJEMPLO 1E y EJEMPLO 412C en lugar de EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 13,16 (s, 1H), 11,70 (s ancho, 1H), 8,65 (m, 1H), 8,44 (d, 1H), 7,87 (d, 1H), 7,61 (dd, 2H), 7,41 (d, 2H), 7,02-7,20 (m, 4H), 6,88 (dd, 1H), 6,58 (d, 1H), 6,26 (dd, 1H), 3,22 (m, 4H), 2,86 (m, 2H), 2,20-2,35 (m, 7H), 2,14 (s, 2H), 2,10 (m, 2H), 2,03 (m, 2H), 1,91 (m, 2H), 1,87 (m, 2H), 1,46 (m, 2H), 1,27-1,39 (m, 3H), 1,00 (s, 6H).

EJEMPLO 413

N-[(5-cloro-6-{[(4-fluorotetrahidro-2H-piran-4-il)metil]amino}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 413A

El compuesto del título se preparó utilizando EJEMPLO 387A en lugar de 4-fluoro-3-nitrobencensulfonamida y EJEMPLO 409C durante (tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

EJEMPLO 413B

N-[(5-cloro-6-{[(4-fluorotetrahidro-2H-piran-4-il)metil]amino}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 413A en lugar de EJEMPLO 1F y EJEMPLO 400E en lugar de EJEMPLO 26C en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 13,14 (s, 1H), 8,19 (d, 1H), 7,87 (s, 1H), 7,60 (d, 1H), 7,56 (d, 1H), 7,36 (d, 2H), 7,31 (s ancho, 1H), 7,08-7,17 (m, 2H), 7,06 (d, 2H), 6,80 (dd, 1H), 6,53 (d, 1H), 6,20 (d, 1H), 3,70-3,78 (m, 4H), 3,43-3,54 (m, 2H), 3,18 (s ancho, 4H), 2,81 (s, 2H), 2,26 (s ancho, 4H), 2,17 (s ancho, 2H), 1,97 (s, 2H), 1,64-1,80 (m, 4H), 1,40 (t, 2H), 0,94 (s, 6H).

EJEMPLO 414

Trans-N-({5-cloro-6-[(4-metoxiciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 414A

Cis-(4-metoxiciclohexil)metanol y trans-(4-metoxiciclohexil)metanol

Se trató 4-metoxiciclohexanocarboxilato de etilo (1 g) en tetrahidrofurano (10 mL) con $LiAlH_4$ 1,0 N en THF (2 mL) a 0ºC. La mezcla se agitó durante 2 horas. La reacción se detuvo con agua (0,6 mL) seguido por NaOH acuoso 2,0 N (0,2 mL). La mezcla se agitó durante otros 20 minutos, y el sólido se eliminó por filtración. El filtrado se recibió en acetato de etilo, se lavó con salmuera, se secó sobre $MgSO_4$, se filtró, y se concentró para dar el compuesto del título como una mezcla de cis y trans isómeros.

EJEMPLO 414B

5-cloro-6-((trans-4-metoxiciclohexil)metoxi)piridina-3-sulfonamida

El compuesto del título se preparó utilizando EJEMPLO 387A en lugar de EJEMPLO 329A y EJEMPLO 414A en lugar de (tetrahidro-2H-piran-4-il)metanol en el EJEMPLO 329B. El isómero trans se aisló por cromatografía de columna rápida sobre gel de sílice.

EJEMPLO 414C

Trans-N-({5-cloro-6-[(4-metoxiciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 414B en lugar de EJEMPLO 1F y EJEMPLO 400E en lugar de EJEMPLO 26C en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 13,10 (s, 1H), 8,27 (d, 1H), 7,85 (d, 1H), 7,80 (s, 1H), 7,59 (d, 1H), 7,36 (d, 2H), 7,03-7,10 (m, 4H), 6,79 (dd, 1H), 6,53 (d, 1H), 6,14 (d, 1H), 4,19 (d, 2H), 3,24 (s, 3H), 3,20 (m, 4H), 3,07-3,10 (m, 2H), 2,93 (s ancho, 2H), 2,39 (s, 4H), 2,18 (s, 2H), 1,98-2,02 (m, 4H), 1,70-1,86 (m, 3H), 1,42 (t, 2H), 1,08-1,17 (m, 4H), 0,94 (s, 6H).

EJEMPLO 415

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({[4-(2,2-difluoroetil)morfolin-2-il]metil}amino)-3-nitrofenil]sulfonil}benzamida

EJEMPLO 415A

2-((2-Nitro-4-sulfamoilfenilamino)metil)morfolin-4-carboxilato de *tert*-butilo

El compuesto del título se preparó utilizando 2-(aminometil)morfolin-4-carboxilato de *tert*-butilo en lugar de (tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

EJEMPLO 415B

4-(morfolin-2-ilmetilamino)-3-nitrobencensulfonamida

Se agitó una solución de EJEMPLO 415A (0,8 g) en cloruro de metileno (10 mL) y ácido trifluoroacético (10 mL) a temperatura ambiente durante 2 horas. Los solventes se evaporaron y el residuo se trituró con dietiléter. El sólido resultante se disolvió en solución de carbonato de sodio acuoso 5% (20 mL). La solución se evaporó hasta sequedad y el sólido

resultante se trituró con una solución de 10% metanol en diclorometano muchas veces. La evaporación de la solución orgánica dio el compuesto del título.

EJEMPLO 415C

4-((4-(2, 2-difluoroetil)morfolin-2-il)metilamino)-3-nitrobencensulfonamida

A una solución de EJEMPLO 415B (633 mg) en *N*,*N*-dimetilformamida anhidra (10 mL) se agregó carbonato de sodio (254 mg) e yoduro de 2,2-difluoroetilo (422 mg). Luego de agitar a 110°C durante 48 horas, la mezcla se concentró. El residuo se mezcló con agua (20 mL) y se extrajo con acetato de etilo. El producto crudo se purificó en una columna gel de sílice eluyendo con metanol 10% en cloruro de metileno para dar el compuesto del título.

EJEMPLO 415D

2-(1*H*-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-*N*-{[4-({[4-(2,2-difluoroetil)morfolin-2-il]metil}amino)-3-nitrofenil]sulfonil}benzamida

El compuesto del título se preparó utilizando EJEMPLO 415C en lugar de EJEMPLO 428D en el EJEMPLO 428E. ^{1}H NMR (500MHz, piridina-d_5) δ 9,26 (d, 1H), 8,87 (t, 1H), 8,57 (s, 1H), 8,37 (dd, 1H), 7,99 (d, 1H), 7,53 (d, 1H), 7,43 (d, 2H), 7,25 (m, 2H), 7,17 (d, 1H), 7,06 (d, 2H), 6,96 (d, 1H), 6,72-6,69 (m, 2H), 6,31, 6,20, 6,09 (tt, 1H), 3,90 (m, 1H), 3,86 (d, 1H), 3,68 (dt, 1H), 3,54-3,41 (m, 2H), 3,03 (m, 4H), 2,97 (d, 1H), 2,83-2,75 (m, 4H), 2,69 (d, 1H), 2,35 (dt, 1H), 2,27-2,23 (m, 3H), 2,14 (m, 4H), 1,97 (s, 2H), 1,38 (t, 2H), 0,94 (s, 6H).

EJEMPLO 416

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({5-fluoro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 416A

5-bromo-3-fluoro-2-((4-fluorotetrahidro-2H-piran-4-il)metoxi)piridina

El compuesto del título se preparó utilizando EJEMPLO 306C en lugar de (tetrahidro-2H-piran-4-il)metanol y 5-bromo-2,3-difluoropiridina en lugar de 4-fluoro-3-nitrobencensulfonamida en el EJEMPLO 279A.

EJEMPLO 416B

5-fluoro-6-((4-fluorotetrahidro-2H-piran-4-il)metoxi)piridin-3-ilcarbamato de *tert*-butilo

Se combinaron EJEMPLO 416A (0,658 g), carbamato de *tert*-butilo (0,300 g), acetato de paladio(II) (0,024 g), 4,5-bis(difenilfosfino)-9,9-dimetilxanteno (0,093 g) y carbonato de cesio (1,044 g) en un vial de 20-mL con dioxano (10,7 ml). El vial se limpió con nitrógeno, se tapó y se agitó a 100 °C durante la noche. La mezcla de reacción se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó ($MgSO_4$), se filtró, se concentró y se separó por cromatografía sobre gel de sílice con acetato de etilo 20% en hexanos como eluyente.

EJEMPLO 416C

Cloruro de 5-fluoro-6-((4-fluorotetrahidro-2H-piran-4-il)metoxi)piridina-3-sulfonilo

Bajo enfriamiento con hielo, se agregó cloruro de tionilo (1,563 mL) por goteo durante 20 minutos a agua (9 mL). La mezcla se agitó durante 12 horas para dar una solución conteniendo SO_2. En forma separada, se agregó EJEMPLO 416B (0,295 g) a una mezcla de dioxano (3,2 mL) y concentrado HCl (8 ml) a 0 ºC. La solución se agitó durante 15 minutos, se trató con una solución de nitrito de sodio (0,065 g) en agua (2 mL) por goteo a 0 ºC y se agitó a 0 ºC durante tres horas. Se enfrió la solución conteniendo SO_2 a 0 ºC, se trató secuencialmente con cloruro de cobre(I) (0,042 g) y la mezcla diazotizada, y se agitó durante 30 minutos. La mezcla de reacción luego se extrajo con acetato de etilo y la capa orgánica se secó ($MgSO_4$), se filtró y se concentró. El concentrado se separó por cromatografía sobre gel de sílice con acetato de etilo entre 5 y 10% en hexanos como eluyente.

EJEMPLO 416D

5-fluoro-6-((4-fluorotetrahidro-2H-piran-4-il)metoxi)piridina-3-sulfonamida

El EJEMPLO 416C (0,08 g,) en isopropanol (2 mL) a 0 °C se trató con hidróxido de amonio (1,70 mL) y se agitó durante la noche. La mezcla de reacción se concentró hasta sequedad, se formó una lechada en agua, se filtró, se lavó con agua y se secó al vacío para dar el compuesto del título.

EJEMPLO 416E

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({5-fluoro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 400E en lugar de EJEMPLO 26C y EJEMPLO 416D en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (400 MHz, PIRIDINE-d_5) δ 14,67 (s, 1H), 8,84 (d, 1H), 8,38 (d, 1H), 8,06 (d, 1H), 8,00 (dd, 1H), 7,46 (m, 2H), 7,35 (d, 1H), 7,12 (m, 3H), 6,87 (m, 2H), 6,47 (d, 1H), 4,56 (d, 2H), 3,80 (m, 4H), 3,18 (m, 4H), 2,83 (s, 2H), 2,31 (t, 2H), 2,24 (m, 4H), 1,99 (s, 2H), 1,86 (m, 4H), 1,41 (t, 2H), 0,96 (s, 6H).

EJEMPLO 417

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4-ilpiperidin-4-il)amino]fenil}sulfonil)benzamida

EJEMPLO 417A

2-(1-(bis(4-metoxifenil)metil)-1*H*-benzo[*d*]imidazol-4-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-*N*-(3-nitro-4-(1-(tetrahidro-2*H*-piran-4-il)piperidin-4-ilamino)fenilsulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 173C en lugar de EJEMPLO 1F en el EJEMPLO 403H.

EJEMPLO 417B

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4-ilpiperidin-4-il)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 417A en lugar de EJEMPLO 403H en el EJEMPLO 403I. ^{1}H NMR (500 MHz, piridina-d_5) δ 9,27 (m, 1H), 8,59 (s, 1H), 8,47 (d, 1H), 8,43 (d, 1H), 8,01 (d, 1H), 7,53 (d, 1H), 7,43 (d, 2H), 7,24 (m, 1H), 7,18 (m, 1H), 7,07 (d, 2H), 6,96 (d, 1H), 6,70 (m, 2H), 5,34 (m, 2H), 4,03 (m, 2H), 3,53 (m, 1H), 3,31 (m, 2H), 3,03 (m, 4H), 2,82 (m, 2H), 2,76 (s, 2H), 2,42 (m, 1H), 2,32 (m, 2H), 2,26 - 2,19 (m, 2H), 2,14 (m, 4H), 1,98 (m, 4H), 1,67 - 1,52 (m, 6H), 1,38 (m, 2H), 0,94 (s, 6H).

EJEMPLO 418

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(1-metilpiperidin-4-il)amino]-3-nitrofenil}sulfonil)benzamida

EJEMPLO 418A

2-(1-(bis(4-metoxifenil)metil)-1*H*-benzo[*d*]imidazol-4-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-*N*-(4-(1-metilpiperidin-4-ilamino)-3-nitrofenilsulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 21A en lugar de EJEMPLO 1F en el EJEMPLO 403H.

EJEMPLO 418B

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(1-metilpiperidin-4-il)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 418A en lugar de EJEMPLO 403H en el EJEMPLO 403I. ^{1}H NMR (500 MHz, piridina-d_5) δ 9,25 (m, 1H), 8,58 (s, 1H), 8,42 (m, 2H), 8,02 (d, 1H), 7,52 (d, 1H), 7,43 (d, 2H), 7,23 (m, 1H), 7,14 (d, 1H), 7,07 (d, 2H), 6,92 (d, 1H), 6,70 (m, 2H), 5,52 (m, 2H), 3,50 (m, 1H), 3,03 (m, 4H), 2,77 (s, 2H), 2,68 (m, 2H), 2,25 (m, 2H), 2,20 (s, 3H), 2,14 (m, 6H), 1,97 - 1,90 (m, 4H), 1,67 (m, 2H), 1,38 (t, 2H), 0,94 (s, 6H).

EJEMPLO 419

N-[(5-cloro-6-{[1-(cianometil)-4-fluoropiperidin-4-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 419A

4-fluoro-4-(hidroximetil)piperidin-1-carboxilato de *tert*-butilo

Se trató 4-fluoropiperidin-1,4-dicarboxilato de 1-*Tert*-butil-4-etilo (1,0 g) en tetrahidrofurano (10 mL) a 0 °C con una solución de $LiAlH_4$ 1 N en tetrahidrofurano (2,54 mL), se agitó durante 2 horas a temperatura ambiente, se trató secuencialmente por goteo con agua (0,2 mL) y una solución acuosa de NaOH 2 N (0,6 mL), y se agitó durante 1 hora. El sólido se eliminó por filtración a través de un relleno de tierras de diatomeas lavando con acetato de etilo. El filtrado se lavó con agua y salmuera, se secó ($MgSO_4$), se filtró y se concentró para dar el compuesto del título.

EJEMPLO 419B

4-((3-cloro-5-sulfamoilpiridin-2-iloxi)metil)-4-fluoropiperidin-1-carboxilato de *tert*-butilo

El compuesto del título se preparó utilizando EJEMPLO 419A en lugar de (tetrahidro-2H-piran-4-il)metanol y EJEMPLO 387A en lugar de 4-fluoro-3-nitrobencensulfonamida en el EJEMPLO 279A.

EJEMPLO 419C

5-cloro-6-((4-fluoropiperidin-4-il)metoxi)piridina-3-sulfonamida, sal de 2•ácido trifluoroacético

El compuesto del título se preparó utilizando EJEMPLO 419B en lugar de EJEMPLO 1A en el EJEMPLO 1B.

EJEMPLO 419D

5-cloro-6-((1-(cianometil)-4-fluoropiperidin-4-il)metoxi)piridina-3-sulfonamida

Se trató EJEMPLO 419C (0,166 g) en acetonitrilo (3,00 mL) con 2-cloroacetonitrilo (0,027 g) y carbonato de sodio (0,064 g), se calentó a 60 °C durante la noche, se enfrió a temperatura ambiente y se separó por cromatografía sobre gel de sílice con metanol entre 0 y 3% en CH_2Cl_2 como eluyente. El sólido obtenido se formó una lechada en agua, se filtró, se lavó con agua y dietiléter, y se secó en un horno de vacío a 80 °C para dar el compuesto del título.

EJEMPLO 419E

N-[(5-cloro-6-{[1-(cianometil)-4-fluoropiperidin-4-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 400E en lugar de EJEMPLO 26C y EJEMPLO 419D en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (400 MHz, PIRIDINE-d_5) δ 14,70 (s, 1H), 8,91 (d, 1H), 8,39 (d, 2H), 8,10 (d, 1H), 7,46 (m, 2H), 7,35 (d, 1H), 7,11 (m, 3H), 6,87 (m, 2H), 6,50 (d, 1H), 4,49 (d, 2H), 3,72 (s, 2H), 3,17 (m, 4H), 2,82 (s, 2H), 2,72 (m, 4H), 2,31 (m, 2H), 2,23 (m, 4H), 2,06 (m, 2H), 1,99 (s, 2H), 1,89 (m, 2H), 1,41 (t, 2H), 0,96 (s, 6H).

EJEMPLO 420

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[5-cloro-6-(tetrahidrofuran-3-ilmetoxi)piridin-3-il]sulfonil}-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 420A

5-cloro-6-((tetrahidrofuran-3-il)metoxi)piridina-3-sulfonamida

El compuesto del título se preparó utilizando EJEMPLO 387A en lugar de EJEMPLO 329A y (tetrahidrofuran-3-il)metanol en lugar de (tetrahidro-2H-piran-4-il)metanol en el EJEMPLO 329B.

EJEMPLO 420B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[5-cloro-6-(tetrahidrofuran-3-ilmetoxi)piridin-3-il]sulfonil}-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 420B en lugar de EJEMPLO 1F y EJEMPLO 400E en lugar de EJEMPLO 26C en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 13,07 (s, 1H), 8,25 (d, 1H), 7,85 (d, 1H), 7,79 (s, 1H), 7,60 (d, 1H), 7,36 (d, 2H), 7,03-7,09 (m, 4H), 6,78 (dd, 1H), 6,51 (d, 1H), 6,13 (dd, 1H), 4,25-4,37 (m, 2H), 3,77-3,81 (m, 2H), 3,64-3,70 (m, 2H), 3,54-3,57 (m, 2H), 3,17 (s ancho, 4H), 2,89 (s ancho, 2H), 2,68-2,71 (m, 1H), 2,33 (m, 3H), 2,16-2,18 (m, 2H), 1,98-2,01 (m, 3H), 1,66-1,71 (m, 1H), 1,41 (t, 2H), 0,94 (s, 6H).

EJEMPLO 421

Trans-N-({5-cloro-6-[(4-hidroxiciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 421A

6-((trans-4-(*tert*-butildimetilsililoxi)ciclohexil)metoxi)-5-cloropiridina-3-sulfonamida

El compuesto del título se preparó utilizando EJEMPLO 387A en lugar de EJEMPLO 329A y trans-4-(*tert*-butildimetilsililoxi)ciclohexilmetanol, sintetizado de acuerdo al procedimiento informado en WO 2008/124878 (Page 100), en lugar de (tetrahidro-2H-piran-4-il)metanol en el EJEMPLO 329B.

EJEMPLO 421B

Trans-N-({5-cloro-6-[(4-hidroxiciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 421A en lugar de EJEMPLO 1F y EJEMPLO 400E en lugar de EJEMPLO 26C en el EJEMPLO 177, luego de la eliminación del grupo *tert*-butildimetilsililo con ácido trifluoroacético. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 13,12 (s, 1H), 8,29 (d, 1H), 7,88 (d, 1H), 7,84 (s, 1H), 7,40 (d, 2H), 7,07-7,13 (m, 4H), 6,83 (dd, 1H), 6,56 (s, 1H), 6,17 (d, 1H), 4,58 (d, 1H), 4,21 (d, 2H), 3,22 (s ancho, 4H), 2,36-2,40 (m, 3H), 2,20-2,24 (m, 2H), 2,02-2,03 (m, 2H), 1,75-1,89 (m, 5H), 1,45 (t, 2H), 1,11-1,21 (m, 4H), 0,98 (s, 6H).

EJEMPLO 422

N-[(5-cloro-6-{[(3R)-1-(2,2-difluoroetil)pirrolidin-3-il]oxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 422A

3-(3-cloro-5-sulfamoilpiridin-2-iloxi)pirrolidine-1-carboxilato de (R)-*tert*-butilo

El compuesto del título se preparó utilizando 3-hidroxipirrolidin-1-carboxilato de (R)-*tert*-butilo en lugar de (tetrahidro-2H-piran-4-il)metanol en el EJEMPLO 387B.

EJEMPLO 422B

Sal clorhidrato de (R)-5-cloro-6-(pirrolidin-3-iloxi)piridina-3-sulfonamida

Se disolvió el EJEMPLO 422A (480 mg) en tetrahidrofurano anhidro (10 mL) seguido por la adición de cloruro de hidrógeno en solución de dioxano (4M, 2,5 mL). La mezcla de reacción se agitó a temperatura ambiente durante la noche. El solvente se eliminó al vacío para dar el compuesto del título.

EJEMPLO 422C

(R)-5-cloro-6-(1-(2,2-difluoroetil)pirrolidin-3-iloxi)piridina-3-sulfonamida

Se calentó una mezcla de reacción de EJEMPLO 422B (353 mg), 1,1-difluoro-2-iodoetano (268 mg) y Na_2CO_3 (283 mg) en N,N-dimetilformamida (10 mL) a 80ºC durante la noche. La mezcla de reacción se enfrió a temperatura ambiente y se diluyó con acetato de etilo. La fase orgánica se lavó con agua y salmuera, se secó sobre sulfato de sodio anhidro, y se concentró. El material crudo se purificó con entre 2,5 y 3% metanol/diclorometano para obtener el compuesto del título.

EJEMPLO 422D

N-[(5-cloro-6-{[(3R)-1-(2,2-difluoroetil)pirrolidin-3-il]oxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 400E en lugar de EJEMPLO 26C y EJEMPLO 422C en lugar de EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 12,98 (s, 1H), 8,17 (d, 1H), 7,80 (d, 1H), 7,73 (s, 1H), 7,66 (d, 1H), 7,35 (d, 2H), 7,05 (m, 4H), 6,73 (m, 1H), 6,41 (d, 1H), 6,10 (m, 2H), 5,37 (m, 1H), 2,92 (m, 11H), 2,56 (m, 2H), 2,24 (m, 7H), 1,99 (m, 2H), 1,82 (m, 1H), 1,39 (m, 2H), 0,93 (s, 6H).

EJEMPLO 423

2-(1H-benzimidazol-4-iloxi)-N-[(5-cloro-6-{[(2S)-4-(N,N-dimetilglicil)morfolin-2-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida

EJEMPLO 423A

2-((3-cloro-5-sulfamoilpiridin-2-iloxi)metil)morfolin-4-carboxilato de (*S*)-*tert*-Butilo

El compuesto del título se preparó utilizando 2-(hidroximetil)morfolin-4-carboxilato de (*S*)-*tert*-butilo en lugar de 4-hidroximetil-tetrahidropirano en el EJEMPLO 387B.

EJEMPLO 423B

(*S*)-5-cloro-6-(morfolin-2-ilmetoxi)piridina-3-sulfonamida

El compuesto del título se preparó utilizando EJEMPLO 423A en lugar de EJEMPLO 415A en el EJEMPLO 415B.

EJEMPLO 423C

(*S*)-5-cloro-6-((4-(2-(dimetilamino)acetil)morfolin-2-il)metoxi)piridina-3-sulfonamida

A una solución de EJEMPLO 423B (0,32 g) en N,N-dimetilformamida anhidra (10 mL) se agregó carbonato de sodio (0,165 g) yclorhidrato 2-(dimetilamino)acetilo (0.40 g). Luego de agitar a temperatura ambiente durante la noche, la mezcla se concentró hasta sequedad. El residuo se mezcló con Na_2CO_3 acuoso 5% (20 mL) y se extrajo con acetato de etilo. El producto crudo se purificó en una columna de gel de sílice eluyendo con metanol 10% en diclorometano saturado con amoníaco para dar el compuesto del título.

EJEMPLO 423D

2-(1*H*-benzimidazol-4-iloxi)-*N*-[(5-cloro-6-{[(2*S*)-4-(*N*,*N*-dimetilglicil)morfolin-2-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida

El compuesto del título se preparó utilizando EJEMPLO 423C en lugar de EJEMPLO 428D en el EJEMPLO 428E. ^{1}H NMR (500MHz, piridina-d_5) δ 9,08 (d, 1H), 8,60 (t, 1H), 8,57 (s, 1H), 8,01 (d, 1H), 7,53 (d, 1H), 7,43 (d, 2H), 7,25 (m, 2H), 7,15 (m, 1H), 7,07 (d, 2H), 6,73-6,69 (m, 2H), 4,86-4,36 (m, 4H), 4,05-3,90 (m, 1H), 3,88 (d, 1H), 3,62-3,18 (m, 4H), 3,04 (m, 4H), 2,87 (t, 1H), 2,77 (s, 2H), 2,33 (m, 6H), 2,26 (m, 2H), 2,15 (m, 4H), 1,97 (s, 2H), 1,39 (t, 2H), 0,94 (s, 6H).

EJEMPLO 424

2-(1H-benzimidazol-4-iloxi)-N-[(5-cloro-6-{[(2R)-4-(N,N-dimetilglicil)morfolin-2-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida

EJEMPLO 424A

2-((3-cloro-5-sulfamoilpiridin-2-iloxi)metil)morfolin-4-carboxilato de (*R*)-*tert*-butilo

El compuesto del título se preparó utilizando 2-(hidroximetil)morfolin-4-carboxilato de (*R*)-*tert*-butilo en lugar de 4-hidroximetil-tetrahidropirano en el EJEMPLO 387B.

EJEMPLO 424B

(R)-5-cloro-6-(morfolin-2-ilmetoxi)piridina-3-sulfonamida

El compuesto del título se preparó utilizando EJEMPLO 424A en lugar de EJEMPLO 415A en el EJEMPLO 415B.

EJEMPLO 424C

(*R*)-5-cloro-6-((4-(2-(dimetilamino)acetil)morfolin-2-il)metoxi)piridina-3-sulfonamida

El compuesto del título se preparó utilizando EJEMPLO 424B en lugar de EJEMPLO 423B en el EJEMPLO 423C.

EJEMPLO 424D

2-(1*H*-benzimidazol-4-iloxi)-*N*-[(5-cloro-6-{[(2*R*)-4-(*N*,*N*-dimetilglicil)morfolin-2-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida

El compuesto del título se preparó utilizando EJEMPLO 424C en lugar de EJEMPLO 428D en el EJEMPLO 428E. ^{1}H NMR (500MHz, piridina-d_5) δ 9,08 (d, 1H), 8,60 (t, 1H), 8,57 (s, 1H), 8,01 (d, 1H), 7,53 (d, 1H), 7,43 (d, 2H), 7,25 (m, 2H), 7,15 (m, 1H), 7,07 (d, 2H), 6,73-6,69 (m, 2H), 4,86-4,36 (m, 4H), 4,05-3,90 (m, 1H), 3,88 (d, 1H), 3,62-3,18 (m, 4H), 3,04 (m, 4H), 2,87 (t, 1H), 2,77 (s, 2H), 2,33 (m, 6H), 2,26 (m, 2H), 2,15 (m, 4H), 1,97 (s, 2H), 1,39 (t, 2H), 0,94 (s, 6H).

EJEMPLO 425

N-[(5-cloro-6-{[(2S)-4-(N,N-dimetilglicil)morfolin-2-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 400E en lugar de EJEMPLO 1E y EJEMPLO 423C en lugar de EJEMPLO 1F en el EJEMPLO 1G, y se purificó por HPLC en fase reversa usando un sistema Waters Preparative LC4000 con columna Fenomenex Luna C18 y una fase móvil de agua-acetonitrilo amortiguada con acetato de amonio. ^{1}H NMR (500MHz, piridina-d_5) δ 8,87 (dd, 1H), 8,40 (t, 2H), 8,13 (dd, 1H), 7,46 (d, 2H), 7,35 (d, 1H), 7,15-7,10 (m, 3H), 6,87 (d, 1H), 6,85 (s, 1H), 6,50 (dd, 1H), 4,84-4,46 (m, 4H), 4,02-3,90 (m, 1H), 3,88 (m, 1H), 3,60-3,33 (m, 2H), 3,25-3,15 (m, 6H), 2,89-2,84 (m, 1H), 2,83 (s, 2H), 2,32-2,23 (m, 12H), 1,99 (s, 2H), 1,41 (t, 2H), 0,96 (s, 6H).

EJEMPLO 426

N-[(5-cloro-6-{[(2R)-4-(N,N-dimetilglicil)morfolin-2-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 400E en lugar de EJEMPLO 1E y EJEMPLO 424C en lugar de EJEMPLO 1F en el EJEMPLO 1G, y se purificó por HPLC en fase reversa usando un sistema Waters Preparative LC4000 con columna Phenomenex Luna C18 y una fase móvil de agua-acetonitrilo amortiguada con acetato de amonio. ^{1}H NMR (500MHz, piridina-d_5) δ 8,87 (dd, 1H), 8,40 (t, 2H), 8,13 (dd, 1H), 7,46 (d, 2H), 7,35 (d, 1H), 7,15-7,10 (m, 3H), 6,87 (d, 1H), 6,85 (s, 1H), 6,50 (dd, 1H), 4,84-4,46 (m,

4H), 4,02-3,90 (m, 1H), 3,88 (m, 1H), 3,60-3,33 (m, 2H), 3,25-3,15 (m, 6H), 2,89-2,84 (m, 1H), 2,83 (s, 2H), 2,32-2,23 (m, 12H), 1,99 (s, 2H), 1,41 (t, 2H), 0,96 (s, 6H).

EJEMPLO 427

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[5-cloro-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil}-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 387B en lugar de EJEMPLO 1F y EJEMPLO 400E en lugar de EJEMPLO 26C en el EJEMPLO 177. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 13,09 (s, 1H), 8,27 (d, 1H), 7,85 (d, 1H), 7,80 (s, 1H), 7,59 (d, 1H), 7,36 (d, 2H), 7,03-7,10 (m, 4H), 6,79 (dd, 1H), 6,52 (d, 1H), 6,13 (d, 1H), 4,27 (d, 2H), 3,88 (dd, 2H), 3,19 (s ancho, 4H), 2,91 (s ancho, 2H), 2,36-2,40 (s ancho, 3H), 2,18 (m, 2H), 2,05 (m, 1H), 1,98 (s, 2H), 1,64-1,68 (m, 2H), 1,34-1,43 (m, 4H), 1,11-1,21 (m, 4H), 0,94 (s, 6H).

EJEMPLO 428

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3R)-1-(cianometil)pirrolidin-3-il]amino}-3-nitrofenil)sulfonil]benzamida

EJEMPLO 428A

8-{4-[2-(4-clorofenil)-4,4-dimetilciclohex-1-enilmetil]piperazin-1-il}-6-oxa-2,11a-diazadibenzo[c,d,g]azulen-11-ona

Se enfrió una solución de EJEMPLO 403G (4,5 g) en diclorometano anhidro (100 mL) en un baño de hielo y se agregó N,N-dimetilformamida catalítico. Esto se siguió por la adición por goteo de una solución de dicloruro de oxalilo (1,231 mL) en cloruro de metileno anhidro (5 mL). Se quitó el baño de hielo y la reacción se agitó durante 1 hora mientras se calentó a temperatura ambiente. La reacción se detuvo por la adición de hielo (150 mL) y solución saturada de bicarbonato de sodio (100 mL). La mezcla se diluyó adicionalmente con solución saturada de bicarbonato de sodio (200 mL) y cloruro de metileno (200 mL). La capa orgánica se purificó sobre gel de sílice, y se eluyó con un gradiente en pasos de acetato de etilo 0, 10, 25, y 100 % en cloruro de metileno para dar el compuesto del título.

EJEMPLO 428B

3-(2-nitro-4-sulfamoilfenilamino)pirrolidine-1-carboxilato de (*R*)-*tert*-butilo

A una solución de 3-aminopirrolidin-1-carboxilato de (R)-*tert*-butilo (1,0 g), tetrahidrofurano (50 ml), N-etil-N-isopropilpropan-2-amina (5,61 mL) y N,N-dimetilformamida (10 mL) se agregó 4-fluoro-3-nitrobencensulfonamida (1,212 g) y la mezcla se agitó durante 18 horas. El producto crudo se aisló por concentración y el material se purificó sobre gel de sílice, y se eluyó con un gradiente en pasos de acetato de etilo 30, 50, y 75 % en hexano para dar el compuesto del título.

EJEMPLO 428C

(*R*)-3-nitro-4-(pirrolidin-3-ilamino)bencensulfonamida

Se enfrió una suspensión de EJEMPLO 428B (2,018 g) en diclorometano anhidro (25 mL) en un baño de hielo y se agregó 2,2,2-ácido trifluoroacético (20 mL). Luego de agitar durante 15 minutos, se quitó el baño de hielo y la reacción se dejó llegar a temperatura ambiente durante 2 horas. La mezcla de reacción se concentró y el residuo se disolvió en agua y llevó a básico con solución acuosa de carbonato de sodio. La mezcla se extrajo repetidamente con metanol 10 % en cloruro de metileno y los orgánicos se concentraron para dar el compuesto del título.

EJEMPLO 428D

(*R*)-4-(1-(cianometil)pirrolidin-3-ilamino)-3-nitrobencensulfonamida

Se agregó carbonato de sodio (132 mg) a una solución de EJEMPLO 428C (440 mg) en N, N-dimetilformamida anhidra (10 mL). A la suspensión resultante se agregó 2-bromoacetonitrilo (0,077 mL) y la mezcla se calentó a 60º C durante 18 horas. El material crudo se aisló por concentración y se purificó sobre gel de sílice, y se eluyó con un gradiente en pasos de metanol 0,5, 2,5, y 5% en cloruro de metileno para dar el compuesto del título.

EJEMPLO 428E

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3R)-1-(cianometil)pirrolidin-3-il]amino}-3-nitrofenil)sulfonil]benzamida

Se agregó 2,3,4,6,7,8,9,10-octahidropirimido[1,2-a]azepina (0,063 mL) a una solución de EJEMPLO 428D (82,6 mg) en tetrahidrofurano (7 mL). Esta mezcla se agitó a temperatura ambiente durante 45 minutos y se agregó una solución de EJEMPLO 428A (117 mg) en tetrahidrofurano (3 mL). Luego de agitar 18 horas, el producto crudo se aisló por concentración y se purificó por cromatografía en fase reversa con solución amortiguadora de

acetato de amonio en acetonitrilo para dar el compuesto del título. ^{1}H NMR (400 MHz, piridina-d_5) δ 9,27 (d, 1H), 8,59 (s, 1H), 8,55 (d, 1H), 8,40 (dd, 1H), 7,99 (d, 1H), 7,54 (m, 1H), 7,43 (d, 2H), 7,25 (m, 1H), 7,16 (m, 1H), 7,07 (d, 2H), 6,86 (d, 1H), 6,69 (m, 2H), 5,73 (m, 2H), 4,15 (m, 1H), 3,90 (s, 2H), 3,03 (m, 4H), 2,96 - 287, (m, 2H), 2,81 - 2,76 (m, 3H), 2,58 (m, 1H), 2,32 - 2,23 (m, 3H), 2,14 (m, 4H), 1,97 (s, 2H), 1,73 (m, 1H), 1,38 (t, 2H), 0,94 (s, 6H).

EJEMPLO 429

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({(3R)-1-[2-(2-metoxietoxi)etil]pirrolidin-3-il}amino)-3-nitrofenil]sulfonil}benzamida

EJEMPLO 429A

(*R*)-4-(1-(2-(2-metoxietoxi)etil)pirrolidin-3-ilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando 1-bromo-2-(2-metoxietoxi)etano en lugar de 2-bromoacetonitrilo en el EJEMPLO 428D.

EJEMPLO 429B

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({(3R)-1-[2-(2-metoxietoxi)etil]pirrolidin-3-il}amino)-3-nitrofenil]sulfonil}benzamida

El compuesto del título se preparó utilizando EJEMPLO 429A en lugar de EJEMPLO 428D en el EJEMPLO 428E. ^{1}H NMR (400 MHz, piridina-d_5) δ 9,26 (d, 1H), 8,58 (m, 2H), 8,38 (dd, 1H), 8,01 (d, 1H), 7,53 (d, 1H), 7,43 (d, 2H), 7,25 (d, 1H), 7,16 (d, 1H), 7,07 (d, 2H), 6,85 (d, 1H), 6,71 - 6,69 (m, 2H), 5,33 (m, 2H), 4,05 (m, 1H), 3,63 (m, 4H), 3,54 (m, 2H), 3,29 (s, 3H), 3,03 (m, 4H), 2,86 (m, 1H), 2,77 (m, 4H), 2,70 (t, 2H), 2,38 (m, 1H), 2,27 - 2,18 (m, 3H), 2,14 (m, 4H), 1,97 (s, 2H), 1,64 (m, 1H), 1,38 (t, 2H), 0,94 (s, 6H).

EJEMPLO 430

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3R)-1-(N,N-dimetilglicil)pirrolidin-3-il]amino}-3-nitrofenil)sulfonil]benzamida

EJEMPLO 430A

R)-4-(1-(2-(dimetilamino)acetil)pirrolidin-3-ilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando cloruro de 2-(dimetilamino)acetilo en lugar de 2-bromoacetonitrilo en el EJEMPLO 428D.

EJEMPLO 430B

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3R)-1-(N,N-dimetilglicil)pirrolidin-3-il]amino}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 430A en lugar de EJEMPLO 428D en el EJEMPLO 428E. ^{1}H NMR (400 MHz, piridina-d_5) δ 9,25 (m, 1H), 8,59 (d, 1H), 8,47 - 8,35 (m, 2H), 8,01 (d, 1H), 7,54 (d, 1H), 7,44 (d, 2H), 7,25 - 7,20 (m, 2H), 7,16 - 6,92 (m, 4H), 6,71 (m, 2H), 5,55 (m, 1H), 4,34 - 4,18 (m, 1H), 4,03 (m, 1H), 3,84 - 3,63 (m, 3H), 3,44 - 3,34 (m, 2H), 3,03 (m, 4H), 2,77 (s, 2H), 2,43 (m, 6H), 2,25 (m, 3H), 2,14 (m, 4H), 2,03 - 1,83 (m, 3H), 1,38 (t, 2H), 0,94 (s, 6H).

EJEMPLO 431

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({[4-(cianometil)morfolin-2-il]metil}amino)-3-nitrofenil]sulfonil}benzamida

EJEMPLO 431A

4-((4-(cianometil)morfolin-2-il)metilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando 2-bromo-acetonitrilo en lugar de yoduro de 2, 2-difluoroetilo en el EJEMPLO 415C a temperatura ambiente.

EJEMPLO 431B

2-(1*H*-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-*N*-{[4-({[4-(cianometil)morfolin-2-il]metil}amino)-3-nitrofenil]sulfonil}benzamida

El compuesto del título se preparó utilizando EJEMPLO 431A en lugar de EJEMPLO 428D en el EJEMPLO 428E. ^{1}H NMR (500MHz, piridina-d_5) δ 9,25 (d, 1H), 8,87 (t, 1H), 8,58 (s, 1H), 8,38 (dd, 1H), 8,00 (d, 1H), 7,53 (d, 1H), 7,43 (d, 2H), 7,25 (m, 2H), 7,16 (d, 1H), 7,07 (d, 2H), 6,97 (d, 1H), 6,73-6,68 (m, 2H), 3,96-3,85 (m, 2H), 3,78 (s, 2H), 3,66 (dt,

1H), 3,53-3,42 (m, 2H), 3,03 (m, 4H), 2,90 (d, 1H), 2,76 (s, 2H), 2,61 (d, 1H), 2,51 (dt, 1H), 2,40 (t, 1H), 2,25 (m, 2H), 2,14 (m, 4H), 1,97 (s, 2H), 1,38 (t, 2H), 0,94 (s, 6H).

EJEMPLO 432

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4-ciclopropilmorfolin-2-il)metil]amino}-3-nitrofenil)sulfonil]benzamida

EJEMPLO 432A

4-((4-ciclopropilmorfolin-2-il)metilamino)-3-nitrobencensulfonamida

Una solución de EJEMPLO 415B (0,633 g) y (1-etoxiciclopropoxi)trimetilsilano (1,601 ml) en metanol anhidro (15 mL) y ácido acético (1,7 ml) se calentó a reflujo durante 30 minutos y se dejó enfriar a temperatura ambiente. Luego se agregó cianoborohidruro de sodio (0,377 g) y la mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se concentró hasta sequedad. El residuo se mezcló con solución acuosa de Na_2CO_3 5% (25 mL) y se extrajo con acetato de etilo. El producto crudo se purificó en una columna de gel de sílice eluyendo con 5% y 10% metanol en diclorometano para dar el compuesto del título.

EJEMPLO 432B

2-(1*H*-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-*N*-[(4-{[(4-ciclopropilmorfolin-2-il)metil]amino}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 432A en lugar de EJEMPLO 428D en el EJEMPLO 428E. ^{1}H NMR (500MHz, piridina-d_5) δ 9,25 (d, 1H), 8,89 (t, 1H), 8,57 (s, 1H), 8,38 (dd, 1H), 8,00 (d, 1H), 7,53 (d, 1H), 7,43 (d, 2H), 7,25 (m, 2H), 7,16 (d, 1H), 7,07 (d, 2H), 6,98 (d, 1H), 6,73-6,68 (m, 2H), 3,90-3,83 (m, 2H), 3,60 (dt, 1H), 3,55-3,41 (m, 2H), 3,03 (m, 4H), 2,96 (d, 1H), 2,76 (s, 2H), 2,69 (d, 1H), 2,35 (dt, 1H), 2,26-2,20 (m, 3H), 2,14 (m, 4H), 1,97 (s, 2H), 1,59 (m, 1H), 1,38 (t, 2H), 0,94 (s, 6H), 0,47-0,37 (m, 4H).

EJEMPLO 433

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{[(4-oxetan-3-ilmorfolin-2-il)metil]amino}fenil)sulfonil]benzamida

EJEMPLO 433A

3-nitro-4-((4-(oxetan-3-il)morfolin-2-il)metilamino)bencensulfonamida

El compuesto del título se preparó utilizando oxetan-3-ona en lugar de (1-etoxiciclopropoxi)-trimetilsilano en el EJEMPLO 432A.

EJEMPLO 433B

2-(1*H*-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-*N*-[(3-nitro-4-{[(4-oxetan-3-ilmorfolin-2-il)metil]amino}fenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 433A en lugar de EJEMPLO 428D en el EJEMPLO 428E. ^{1}H NMR (500MHz, piridina-d_5) δ 9,25 (d, 1H), 8,87 (t, 1H), 8,57 (s, 1H), 8,38 (dd, 1H), 8,02 (d, 1H), 7,53 (d, 1H), 7,44 (d, 2H), 7,24 (m, 2H), 7,13 (d, 1H), 7,07 (d, 2H), 6,98 (d, 1H), 6,73-6,68 (m, 2H), 4,69-4,62 (m, 4H), 3,98-3,88 (m, 2H), 3,69 (dt, 1H), 3,55-3,35 (m, 3H), 3,03 (m, 4H), 2,77 (s, 2H), 2,74 (d, 1H), 2,44 (d, 1H), 2,25 (m, 2H), 2,14 (m, 4H), 1,97 (s, 2H), 1,94 (m, 1H), 1,87 (t, 1H), 1,38 (t, 2H), 0,94 (s, 6H).

EJEMPLO 434

N-{[5-cloro-6-({(3R)-1-[2-fluoro-1-(fluorometil)etil]pirrolidin-3-il}oxi)piridin-3-il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 434A

Se resuspendieron (R)-5-cloro-6-(1-(1,3-difluoropropan-2-il)pirrolidin-3-iloxi)piridin-3-sulfonamida

EJEMPLO 422B (278 mg) y 1,3-difluoropropan-2-ona (94 mg) en dicloroetano (10 ml). Se agregó N,N-dimetilformamida (1,5 mL) en forma de gotas hasta que se formó una suspensión blanca lechosa. La mezcla de reacción se agitó a temperatura ambiente durante 15 minutos, seguido por agregado de tetracetoxiborohidruro de sodio (424 mg). La mezcla de reacción se agitó a temperatura ambiente durante la noche. El solvente se eliminó al vacío, y

el material crudo se purificó con entre 2,5 y 5% de metanol/diclorometano para conseguir el compuesto del título.

EJEMPLO 434B

N-{[5-cloro-6-({(3R)-1-[2-fluoro-1-(fluorometil)etil]pirrolidin-3-il}oxi)piridin-3-il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 400E en lugar del EJEMPLO 26C y el EJEMPLO 434A en lugar del EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 12,96 (s, 1H), 8,16 (d, 1H), 7,79 (m, 1H), 7,69 (m, 2H), 7,35 (d, 2H), 7,05 (m, 4H), 6,72 (m, 1H), 6,39 (d, 1H), 6,09 (dd, 3,05Hz, 1H), 5,37 (m, 1H), 4,66 (t, 2H), 4,54 (t, 2H), 2,91 (m, 12H), 2,23 (m, 7H), 1,97 (s, 2H), 1,82 (m, 1H), 1,40 (t, 2H), 0,93 (s, 6H).

EJEMPLO 435

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({(3R)-1-[2-fluoro-1-(fluorometil)etil]pirrolidin-3-il}amino)-3-nitrofenil]sulfonil}-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 435A

(R)-1-(1,3-difluoropropan-2-il)pirrolidin-3-amina

Sobre una solución de (R)-tert-butilpirrolidin-3-ilcarbamato (0,500 g) y 1,3-difluoropropan-2-ona (0,278 g) en diclorometano (5 mL) se agregó tetracetoxiborohidruro de sodio (0,853 g). Luego de agitar durante una hora, la reacción se detuvo con solución acuosa saturada de $NaHCO_3$ (5 mL). La mezcla se extrajo con diclorometano (25 mL), y se secó la fase orgánica sobre sulfato de magnesio anhidro, se filtró, y se concentró. El residuo resultante se trató con HCl (4,0 M en 1,4-dioxano, 4 mL) y metanol (1 mL) y se agitó durante una hora. La mezcla se concentró para dar el compuesto del título.

EJEMPLO 435B

(R)-4-(1-(1,3-difluoropropan-2-il)pirrolidin-3-ilamino)-3-nitrobencensulfonamida

Sobre 4-fluoro-3-nitrobencensulfonamida (0,272 g) y el EJEMPLO 435A (0,195 g) en tetrahidrofurano (3,0 mL) se agregó N-etil-N-isopropilpropan-2-amina (0,512 mL) y la reacción se agitó a temperatura ambiente. Luego de agitar durante seis horas, la reacción se

concentró, se cargó en un gel de sílice (Reveleris 40 g) y el producto se eluyó usando un gradiente entre 25 y 100% de acetato de etilo/hexanos en 30 minutos para dar el compuesto del título.

EJEMPLO 435C

Éster metílico de ácido 4-{4-[2-(4-Cloro-fenil)-4,4-dimetil-ciclohex-1-enilmetil]-piperazin-1-il}-2-[1-(2-trimetilsilanil-etoximetil)-1H-indazol-4-iloxi]-benzoico

Se disolvió EJEMPLO 400D (1000 mg) en N,N-dimetilformamida (12 mL) y se agregó hidruro de sodio (60% en aceite mineral, 45 mg). La solución se agitó a temperatura ambiente durante 15 minutos, se agregó cloruro de 2-(trimetilsilil)etoximetilo (299 mg), y la solución se agitó a temperatura ambiente durante 45 minutos. La solución se agregó a agua y se extrajo con acetato de etilo. El extracto se lavó con salmuera, se secó sobre sulfato de sodio anhidro, se filtró, se concentró y se purificó por cromatografía rápida en columna sobre gel de sílice usando entre 30 y 50% de acetato de etilo en hexanos.

EJEMPLO 435D

Ácido 4-{4-[2-(4-cloro-fenil)-4,4-dimetil-ciclohex-1-enilmetil]-piperazin-1-il}-2-[1-(2-trimetilsilanil-etoximetil)-1H-indazol-4-iloxi]-benzoico

El compuesto del título se preparó utilizando el EJEMPLO 435C en lugar del EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 435E

N-{4-{4-[2-(4-Cloro-fenil)-4,4-dimetil-ciclohex-1-enilmetil]-piperazin-1-il}-2-[1-(2-trimetilsilanil-etoximetil)-1H-indazol-4-iloxi]-benzoil}-4-[(R)-1-(2-fluoro-1-fluorometil-etil)-pirrolidin-3-ilamino]-3-nitro-bencensulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 435D en lugar del EJEMPLO 1E y el EJEMPLO 435B en lugar del EJEMPLO 1F en el EJEMPLO 1G.

EJEMPLO 435F

4-(4-{[2-(4-Clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({(3R)-1-[2-fluoro-1-(fluorometil)etil]pirrolidin-3-il}amino)-3-nitrofenil]sulfonil}-2-(1H-indazol-4-iloxi)benzamida

Se disolvió EJEMPLO 435E (103 mg) en ácido trifluoroacético (1,8 mL) y agua (0,2 mL) y se agitó a temperatura ambiente durante 90 minutos. Se eliminaron los solventes al

vacío, el residuo se disolvió en 1,4-dioxano (2 mL) y se trató con hidróxido de sodio 1M (1 mL), y la solución se agitó a temperatura ambiente durante 30 minutos. La solución se agregó a una solución acuosa saturada de bicarbonato de sodio y se extrajo con diclorometano. El extracto se lavó con salmuera, se secó sobre sulfato de sodio anhidro, se filtró, y el solvente removed al vacío. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 13,09 (s ancho, 1H), 8,37 (m, 2H), 7,84 (d, 1H), 7,58-7,45 (m, 2H), 7,36 (d, 2H), 7,17-7,03 (m, 4H), 6,95 (dd, 1H), 6,84-6,76 (m, 1H), 6,53 (dd, 1H), 6,17 (t, 1H), 4,72 (d, 2H), 4,56 (d, 2H), 4,23 (m, 1H), 3,17 (m, 4H), 3,12-3,03 (m, 2H), 3,02-2,91 (m, 2H), 2,86-2,73 (m, 4H), 2,40-2,14 (m, 6H), 1,97 (s ancho, 2H), 1,70 (m, 1H), 1,40 (t, 2H), 0,94 (s, 6H).

EJEMPLO 436

4-(4-{[2-(4-Clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(1-ciclopropilpiperidin-4-il)amino]-3-nitrofenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 436A

4-(1-Ciclopropil-piperidin-4-ilamino)-3-nitro-bencensulfonamida

El compuesto del título se preparó utilizando 1-ciclopropil-piperidin-4-ilamina en lugar de 1-(2-metoxi-etil)-piperidin-4-ilamina en el EJEMPLO 189A.

EJEMPLO 436B

N-{4-{4-[2-(4-clorofenil)-4,4-dimetil-ciclohex-1-enilmetil]-piperazin-1-il}-2-[1-(2-trimetilsilanil-etoximetil)-1H-indazol-4-iloxi]-benzoil}-4-(1-ciclopropil-piperidin-4-ilamino)-3-nitro-bencensulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 435D en lugar del EJEMPLO 1E y el EJEMPLO 436A en lugar del EJEMPLO 1F en el EJEMPLO 1G.

EJEMPLO 436C

4-(4-{[2-(4-Clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(1-ciclopropilpiperidin-4-il)amino]-3-nitrofenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 436B en lugar del EJEMPLO 435E en el EJEMPLO 435F. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 13,05 (s ancho, 1H), 8,35 (d, 1H), 8,17 (d, 1H), 7,77 (s ancho, 1H), 7,57 (td, 2H), 7,35 (d, 2H), 7,09-7,03 (m, 4H), 6,98 (d, 1H), 6,77 (dd, 1H), 6,48 (s ancho, 1H), 6,17 (m, 1H), 3,66 (m, 1H), 3,12 (s ancho, 4H), 2,92 (m, 2H), 2,76 (s ancho, 2H), 2,21 (m, 8H), 1,97 (s ancho, 2H), 1,94

(m, 2H), 1,73 (m, 1H), 1,55 (m, 2H), 1,40 (t, 2H), 0,93 (s, 6H), 0,46 (d, 2H), 0,35 (s ancho, 2H).

EJEMPLO 437

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({[(2R)-4-(N,N-dimetilglicil)morfolin-2-il]metil}amino)-3-nitrofenil]sulfonil}benzamida

EJEMPLO 437A

2-((2-Nitro-4-sulfamoilfenilamino)metil)morfolin-4-carboxilato de (*R*)-*tert*-butilo

El compuesto del título se preparó utilizando 2-(aminometil)morfolin-4-carboxilato de (*R*)-*tert*-butilo en lugar de (tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

EJEMPLO 437B

(*S*)-4-(morfolin-2-ilmetilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 437A en lugar del EJEMPLO 415A en el EJEMPLO 415B.

EJEMPLO 437C

(*R*)-4-((4-(2-(dimetilamino)acetil)morfolin-2-il)metilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 437B en lugar del EJEMPLO 423B en el EJEMPLO 423C.

EJEMPLO 437D

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({[(2R)-4-(N,N-dimetilglicil)morfolin-2-il]metil}amino)-3-nitrofenil]sulfonil}benzamida

El compuesto del título se preparó utilizando el EJEMPLO 437C en lugar del EJEMPLO 428D en el EJEMPLO 428E. ^{1}H NMR (500MHz, piridin-d_5) δ 9,25 (s, 1H), 8,86 (t, 1H), 8,57 (s, 1H), 8,38 (t, 1H), 8,02 (d, 1H), 7,53 (d, 1H), 7,44 (d, 2H), 7,24 (m, 2H), 7,13 (d, 1H), 7,07 (d, 2H), 6,97 (dd, 1H), 6,73-6,68 (m, 2H), 4,75, 4,50 (dd, 1H), 4,33,4,02 (dd, 1H), 3,93 (m, 1H), 3,85-3,70 (m, 1H), 3,65-3,40 (m, 3H), 3,33 (dd, 1H), 3,25-3,10 (m, 2H), 3,03 (m, 4H), 2,90 (m, 1H), 2,77 (s, 2H), 2,27-2,25 (m, 8H), 2,14 (m, 4H), 1,97 (s, 2H), 1,38 (t, 2H), 0,94 (s, 6H).

EJEMPLO 438

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({[(2S)-4-(N,N-dimetilglicil)morfolin-2-il]metil}amino)-3-nitrofenil]sulfonil}benzamida

EJEMPLO 438A

2-((2-nitro-4-sulfamoilfenilamino)metil)morfolin-4-carboxilato de (*S*)-*tert*-butilo

El compuesto del título se preparó utilizando 2-(aminometil)morfolin-4-carboxilato de (*S*)-*tert*-butilo en lugar de (tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

EJEMPLO 438B

(*R*)-4-(morfolin-2-ilmetilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 438A en lugar del EJEMPLO 415A en el EJEMPLO 415B.

EJEMPLO 438C

(*S*)-4-((4-(2-(dimetilamino)acetil)morfolin-2-il)metilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 438B en lugar del EJEMPLO 423B en el EJEMPLO 423C.

EJEMPLO 438D

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({[(2S)-4-(N,N-dimetilglicil)morfolin-2-il]metil}amino)-3-nitrofenil]sulfonil}benzamida

El compuesto del título se preparó utilizando el EJEMPLO 438C en lugar del EJEMPLO 428D en el EJEMPLO 428E. ^{1}H NMR (500MHz, piridin-d_5) δ 9,25 (s, 1H), 8,86 (t, 1H), 8,57 (s, 1H), 8,38 (t, 1H), 8,02 (d, 1H), 7,53 (d, 1H), 7,44 (d, 2H), 7,24 (m, 2H), 7,13 (d, 1H), 7,07 (d, 2H), 6,97 (dd, 1H), 6,73-6,68 (m, 2H), 4,75, 4,50 (dd, 1H), 4,33,4,02 (dd, 1H), 3,93 (m, 1H), 3,85-3,70 (m, 1H), 3,65-3,40 (m, 3H), 3,33 (dd, 1H), 3,25-3,10 (m, 2H), 3,03 (m, 4H), 2,90 (m, 1H), 2,77 (s, 2H), 2,27-2,25 (m, 8H), 2,14 (m, 4H), 1,97 (s, 2H), 1,38 (t, 2H), 0,94 (s, 6H).

EJEMPLO 439

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(tetrahidrofuran-3-ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 439A

3-nitro-4-((tetrahidrofuran-3-il)metilamino)bencensulfonamida

El compuesto del título se preparó utilizando (tetrahidrofuran-3-il)metilamina en lugar de (tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

EJEMPLO 439B

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(tetrahidrofuran-3-ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 439A en lugar del EJEMPLO 428D en el EJEMPLO 428E. ^{1}H NMR (500MHz, piridin-d_5) δ 9,26 (d, 1H), 8,70 (t, 1H), 8,57 (s, 1H), 8,40 (dd, 1H), 8,01 (d, 1H), 7,51 (d, 1H), 7,44 (d, 2H), 7,24 (m, 2H), 7,14 (d, 1H), 7,07 (d, 2H), 6,89 (d, 1H), 6,73-6,68 (m, 2H), 3,93-3,89 (m, 1H), 3,83 (dd, 1H), 3,83-3,68 (m, 2H), 3,33-3,23 (m, 2H), 3,03 (m, 4H), 2,77 (s, 2H), 2,55-2,50 (m, 1H), 2,25 (m, 2H), 2,14 (m, 4H), 2,00-1,93 (m, 3H), 1,65-1,58 (m, 1H), 1,38 (t, 2H), 0,94 (s, 6H).

EJEMPLO 440

Trans-2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4-metoxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó utilizando el EJEMPLO 311B en lugar del EJEMPLO 428D en el EJEMPLO 428E. ^{1}H NMR (500 MHz, piridin-d_5) δ 9,29 (d, 1H), 8,67 (t, 1H), 8,59 (s, 1H), 8,41 (dd, 1H), 7,99 (d, 1H), 7,52 (d, 1H), 7,43 (d, 2H), 7,24 (m, 1H), 7,17 (m, 1H), 7,07 (d, 2H), 6,90 (d, 1H), 6,72 - 6,68 (m, 2H), 5,97 (m, 2H), 3,29 (s, 3H), 3,14 (t, 2H), 3,02 (m, 5H), 2,76 (s, 2H), 2,25 (m, 2H), 2,13 (m, 4H), 2,07 (m, 2H), 1,97 (s, 2H), 1,82 (m, 2H), 1,57 (m, 1H), 1,38 (t, 2H), 1,22 (m, 2H), 1,01 (m, 2H), 0,94(s, 6H).

EJEMPLO 441

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4-fluorotetrahidro-2H-piran-4-il)metil]amino}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó utilizando el EJEMPLO 409D en lugar del EJEMPLO 428D en el EJEMPLO 428E. ^{1}H NMR (500 MHz, piridin-d_5) δ 9,27 (d, 1H), 8,84 (t, 1H), 8,57 (s, 1H), 8,41 (dd, 1H), 7,99 (d, 1H), 7,52 (d, 1H), 7,43 (d, 2H), 7,23 (m, 1H), 7,15 (m, 1H), 7,14 - 7,02 (m, 3H), 6,70 (m, 2H), 6,49 (m, 2H), 3,86 (m, 2H), 3,76 - 3,69 (m, 3H), 3,65 (d, 1H), 3,03 (m, 4H), 2,76 (s, 2H), 2,25 (m, 2H), 2,14 (m, 4H), 1,97 (s, 2H), 1,92 - 1,76 (m, 4H), 1,38 (t, 2H), 0,94 (s, 6H).

EJEMPLO 442

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({5-fluoro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 416D en lugar del EJEMPLO 428D en el EJEMPLO 428E. ^{1}H NMR (500 MHz, piridin-d_5) δ 9,02 (d, 1H), 8,59 (s, 1H), 8,35 (m, 1H), 8,01 (d, 1H), 7,51 (d, 1H), 7,44 (d, 2H), 7,22 (m, 2H), 7,12 (d, 1H), 7,07 (d, 2H), 6,84 (m, 1H), 6,73 (m, 2H), 4,59 (s, 1H), 4,54 (s, 1H), 3,89 - 3,74 (m, 4H), 3,05 (m, 4H), 2,78 (s, 2H), 2,26 (m, 2H), 2,16 (m, 4H), 2,02 - 1,81 (m, 6H), 1,39 (t, 2H), 0,94 (s, 6H).

EJEMPLO 443

2-(1H-benzimidazol-4-iloxi)-N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 404A en lugar del EJEMPLO 428D en el EJEMPLO 428E. ^{1}H NMR (500 MHz, piridin-d_5) δ 9,12 (d, 1H), 8,68 (d, 1H), 8,59 (s, 1H), 7,99 (d, 1H), 7,52 (d, 1H), 7,44 (d, 2H), 7,24 (d, 1H), 7,15 (d, 1H), 7,07 (d, 2H), 6,73 - 6,69 (m, 3H), 6,56 (m, 1H), 4,56 (s, 1H), 4,51 (s, 1H), 3,91 - 3,76 (m, 4H), 3,04 (m, 4H), 2,77 (s, 2H), 2,26 (m, 2H), 2,15 (m, 4H), 1,99 - 1,85 (m, 6H), 1,39 (t, 2H), 0,94 (s, 6H).

EJEMPLO 444

N-{[5-cloro-6-({(3R)-1-[2-fluoro-1-(fluorometil)etil]pirrolidin-3-il}metoxi)piridin-3-il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 444A

(R)-5-cloro-6-((1-(1,3-difluoropropan-2-il)pirrolidin-3-il)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 445B en lugar del EJEMPLO 422B en el EJEMPLO 434A.

EJEMPLO 444B

N-{[5-cloro-6-({(3R)-1-[2-fluoro-1-(fluorometil)etil]pirrolidin-3-il}metoxi)piridin-3-il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 400E en lugar del EJEMPLO 26C y el EJEMPLO 444A en lugar del EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 12,98 (s, 1H), 8,19 (d, 1H), 7,81 (d, 1H), 7,73 (s, 1H), 7,66 (d, 1H), 7,35 (d, 2H), 7,05 (m, 4H), 6,73 (dd, 1H), 6,42 (d, 1H), 6,10 (m, 1H), 4,64 (s, 2H), 4,54 (d, 2H), 4,24 (m, 2H), 3,07 (s, 4H), 2,89 (s, 2H), 2,74 (m, 4H), 2,56 (m, 2H), 2,20 (m, 6H), 1,98 (m, 4H), 1,54 (m, 1H), 1,40 (t, 2H), 0,91 (s, 6H).

EJEMPLO 445

N-[(5-cloro-6-{[(3R)-1-(2,2-difluoroetil)pirrolidin-3-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 445A

3-((3-cloro-5-sulfamoilpiridin-2-iloxi)metil)pirrolidin-1-carboxilato de (R)-tert-butilo

El compuesto del título se preparó utilizando 3-(hidroximetil)pirrolidin-1-carboxilato de (R)-tert-butilo en lugar de (tetrahidro-2H-piran-4-il)metanol en el EJEMPLO 387B.

EJEMPLO 445B

(R)-5-cloro-6-(pirrolidin-3-ilmetoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 445A en lugar del EJEMPLO 422A en el EJEMPLO 422B.

EJEMPLO 445C

(R)-5-cloro-6-((1-(2,2-difluoroetil)pirrolidin-3-il)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 445B en lugar del EJEMPLO 422B en el EJEMPLO 422C.

EJEMPLO 445D

N-[(5-cloro-6-{[(3R)-1-(2,2-difluoroetil)pirrolidin-3-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 400E en lugar del EJEMPLO 26C y el EJEMPLO 445C en lugar del EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 12,98 (s, 1H), 8,19 (d, 1H), 7,81 (d, 1H), 7,73 (s, 1H), 7,66 (d, 1H), 7,35 (d, 2H), 7,05 (m, 4H), 6,72 (dd, 1H), 6,41 (d, 1H), 6,10 (m, 2H), 4,23 (m, 2H), 3,07 (s, 4H), 2,82 (m, 5H), 2,62 (m, 3H), 2,24 (s, 4H), 2,17 (s, 2H), 1,94 (m, 3H), 1,53 (m, 1H), 1,40 (t, 2H), 0,93 (s, 6H).

EJEMPLO 446

Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-[(4-{[(4-metoxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida

EJEMPLO 446A

2-[1-(2-trimetilsilanil-etoximetil)-1H-indazol-4-iloxi]-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-N-(4-((trans-4-metoxiciclohexil)metilamino)-3-nitrofenilsulfonil)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 435D en lugar del EJEMPLO 1E y el EJEMPLO 311B en lugar del EJEMPLO 1F en el EJEMPLO 1G.

EJEMPLO 446B

Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-[(4-{[(4-metoxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó utilizando el EJEMPLO 446A en lugar del EJEMPLO 435E en el EJEMPLO 435F. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 13,08 (s ancho, 1H), 8,53 (t, 1H), 8,37 (d, 1H), 7,84 (d, 1H), 7,53 (m, 2H), 7,35 (d, 2H), 7,09 (d, 2H),

7,05 (d, 2H), 6,94 (d, 1H), 6,79 (m, 1H), 6,51 (dd, 1H), 6,18 (m, 1H), 3,23 (s, 3H), 3,17-3,00 (m, 5H), 2,78 (s ancho, 2H), 2,30-2,13 (m, 8H), 2,02 (m, 2H), 1,97, (s ancho, 2H), 1,80 (m, 2H), 1,60 (m, 1H), 1,40 (t, 2H), 1,07 (m, 4H), 0,93 (s, 6H).

EJEMPLO 447

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-(1,4-dioxan-2-ilmetoxi)-3-nitrofenil]sulfonil}-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 447A

N-{4-{4-[2-(4-Cloro-fenil)-4,4-dimetil-ciclohex-1-enilmetil]-piperazin-1-il}-2-[1-(2-trimetilsilanil-etoximetil)-1H-indazol-4-iloxi]-benzoil}-4-([1,4]dioxan-2-ilmetoxi)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 435D en lugar del EJEMPLO 1E y el EJEMPLO 297A en lugar del EJEMPLO 1F en el EJEMPLO 1G.

EJEMPLO 447B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-(1,4-dioxan-2-ilmetoxi)-3-nitrofenil]sulfonil}-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 447A en lugar del EJEMPLO 435E en el EJEMPLO 435F. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 13,04 (s ancho, 1H), 8,07 (s ancho, 1H), 7,78 (t, 2H), 7,59 (d, 1H), 7,36 (d, 2H), 7,25 (d, 1H), 7,08 (d, 2H), 7,06 (d, 2H), 6,77 (d, 1H), 6,48 (s ancho, 1H), 6,15 (m, 1H), 4,20 (t, 2H), 3,92-3,76 (m, 3H), 3,65 (m, 2H), 3,48 (td, 2H), 3,14 (s ancho, 4H), 2,80 (m, 2H), 2,38-2,13 (m, 6H), 1,97 (s ancho, 2H), 1,40 (t, 2H), 0,94 (s, 6H).

EJEMPLO 448

N-({5-cloro-6-[(1-ciclopropilpiperidin-4-il)amino]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 448A

Amida de ácido 5-cloro-6-(1-ciclopropil-piperidin-4-ilamino)-piridin-3-sulfónico

El compuesto del título se preparó utilizando 1-ciclopropil-piperidin-4-ilamina en lugar de 1-(2-metoxi-etil)-piperidin-4-ilamina y el EJEMPLO 387A en lugar de 4-cloro-3-nitrobencensulfonamida en el EJEMPLO 189A.

EJEMPLO 448B

Ácido 4-{4-[2-(4-cloro-fenil)-4,4-dimetil-ciclohex-1-enilmetil]-piperazin-1-il}-2-[1-(2-trimetilsilanil-etoximetil)-1H-indazol-4-iloxi]-benzoilamida 5-Cloro-6-(1-ciclopropil-piperidin-4-ilamino)-piridin-3-sulfónico

El compuesto del título se preparó utilizando el EJEMPLO 435D en lugar del EJEMPLO 1E y el EJEMPLO 448A en lugar del EJEMPLO 1F en el EJEMPLO 1G.

EJEMPLO 448C

N-({5-cloro-6-[(1-ciclopropilpiperidin-4-il)amino]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 448B en lugar del EJEMPLO 435E en el EJEMPLO 435F. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 13,03 (s ancho, 1H), 8,18 (d, 1H), 7,79 (s ancho, 1H), 7,65-7,58 (m, 2H), 7,36 (d, 2H), 7,33 (m, 1H), 7,10 (d, 2H), 7,06 (d, 2H), 6,74 (dd, 1H), 6,43 (s ancho, 1H), 6,19 (m, 1H), 3,95 (m, 1H), 3,08 (m, 4H), 2,96 (m, 2H), 2,75 (s ancho, 2H), 2,37-2,10 (m, 9H), 1,97 (s ancho, 2H), 1,78 (m, 2H), 1,56 (m, 2H), 1,40 (t, 2H), 0,93 (s, 6H), 0,42 (d, 2H), 0,33 (s ancho, 2H).

EJEMPLO 449

2-(1H-benzimidazol-4-iloxi)-N-({5-cloro-6-[(1-ciclopropilpiperidin-4-il)amino]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida

EJEMPLO 449A

5-cloro-6-(1-ciclopropilpiperidin-4-ilamino)piridin-3-sulfonamida

Una mezcla del EJEMPLO 387A (0,4 g), 1-ciclopropilpiperidin-4-amina (0,3 g) y N,N-diisopropiletilamina (0,37 mL) en dioxano (3 mL) se calentó a 100° C durante 18 horas.

Se aisló el producto crudo mediante concentración y se purificó sobre gel de sílice, el cual se eluyó con acetato de etilo para dar el compuesto del título.

EJEMPLO 449B

2-(1H-benzimidazol-4-iloxi)-N-({5-cloro-6-[(1-ciclopropilpiperidin-4-il)amino]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 449A en lugar del EJEMPLO 428D en el EJEMPLO 428E. ^{1}H NMR (500 MHz, piridin-d_5) δ 9,22 (m, 1H), 8,55 (s, 1H), 8,47 (s, 1H), 8,00 (d, 1H), 7,54 (d, 1H), 7,44 (d, 2H), 7,25 (m, 1H), 7,19 (m, 1H), 7,07 (d, 2H), 7,01 (m, 1H), 6,68 (m, 2H), 5,35 (m, 2H), 4,22 (m, 1H), 3,04 - 2,95 (m, 6H), 2,77 (s, 2H), 2,29 - 2,24 (m, 4H), 2,14 (m, 4H), 2,03 (m, 2H), 1,97 (s, 2H), 1,70 (m, 2H), 1,52 (m, 1H), 1,38 (t, 2H), 0,94 (s, 6H), 0,35 (m, 4H).

EJEMPLO 450

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(1,4-dioxan-2-ilmetil)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 336A en lugar del EJEMPLO 428D en el EJEMPLO 428E. ^{1}H NMR (500 MHz, piridin-$d_5$5) δ 9,24 (m, 1H), 8,81 (m, 1H), 8,56 (s, 1H), 8,37 (dd, 1H), 8,03 (d, 1H), 7,52 (d, 1H), 7,44 (d, 2H), 7,21 (m, 1H), 7,11 (m, 1H), 7,07 (d, 2H), 6,92 (d, 1H), 6,71 (m, 2H), 5,33 (m, 2H), 3,94 (m, 2H), 3,78 (m, 1H), 3,73 - 3,66 (m, 2H), 3,58 (m, 1H), 3,51 - 3,36 (m, 3H), 3,03 (m, 4H), 2,77 (s, 2H), 2,26 (m, 2H), 2,15 (m, 4H), 1,97 (s, 2H), 1,39 (t, 2H), 0,94 (s, 6H).

EJEMPLO 451

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(1-ciclopropilpiperidin-4-il)amino]-3-nitrofenil}sulfonil)benzamida

EJEMPLO 451A

4-(1-ciclopropilpiperidin-4-ilamino)-3-nitrobencensulfonamida

Sobre una solución de 4-fluoro-3-nitrobencensulfonamida (1,26 g) y 1-ciclopropilpiperidin-4-amina (0,802 g) en tetrahidrofurano (20 mL) se agregó N,N-diisopropiletilamina (2,22 g) y 4-dimetilaminopiridina (35 mg). La mezcla se calentó a

reflujo durante 18 horas y al enfriarse se diluyó con acetato de etilo (200 mL) y $NaHCO_3$ acuoso. El producto crudo se aisló mediante concentración de la fase orgánica y se purificó sobre gel de sílice, el cual se eluyó con amoníaco metanólico al 5% en cloruro de metileno para dar el compuesto del título.

EJEMPLO 451B

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(1-ciclopropilpiperidin-4-il)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 451 A en lugar del EJEMPLO 428D en el EJEMPLO 428E. ^{1}H NMR (500 MHz, piridin-d_5) δ 9,26 (m, 1H), 8,59 (s, 1H), 8,46 (d, 1H), 8,42 (dd, 1H), 8,01 (d, 1H), 7,53 (d, 1H), 7,43 (d, 2H), 7,25 (d, 1H), 7,17 (d, 1H), 7,07 (d, 2H), 6,96 (d, 1H), 6,72 - 6,67 (m, 2H), 5,48 (m, 2H), 3,54 (m, 1H), 3,03 (m, 4H), 2,90 (m, 2H), 2,76 (s, 2H), 2,37 (m, 2H), 2,25 (m, 2H), 2,14 (m, 4H), 1,98 - 1,91 (m, 4H), 1,56 (m, 3H), 1,38 (t, 2H), 0,94 (s, 6H), 0,42 (m, 4H).

EJEMPLO 452

Trans-2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-morfolin-4-ilciclohexil)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 204A en lugar del EJEMPLO 428D en el EJEMPLO 428E. ^{1}H NMR (500 MHz, piridin-d_5) δ 9,27 (m, 1 H), 8,59 (s, 1 H), 8,42 (dd, 1 H), 8,36 (d, 1 H), 8,01 (d, 1 H), 7,53 (d, 1 H), 7,43 (d, 2 H), 7,25 (m, 1 H), 7,17 (m, 1 H), 7,07 (d, 2 H), 6,95 (d, 1 H), 6,71 (d, 2 H), 6,33 (m, 2 H), 3,76 (m, 4 H), 3,40 (m, 1 H), 3,03 (m, 4 H), 2,76 (s, 2 H), 2,52 (m, 4 H), 2,25 (m, 3 H), 2,14 (m, 4 H), 2,07 (m, 2 H), 1,97 (m, 2 H), 1,89 (m, 2 H), 1,42 - 1,21 (m, 6 H), 0,94 (s, 6 H).

EJEMPLO 453

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-metilpiperazin-1-il)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 174A en lugar del EJEMPLO 428D en el EJEMPLO 428E. ^{1}H NMR (500 MHz, piridin-d_5) δ 9,25 (m, 2H), 8,59 (s, 1H), 8,44 (m, 1H), 8,00 (d, 1H), 7,68 (d, 1H), 7,53 (d, 1H), 7,43 (d, 2H), 7,25 (m, 1H),

7,17 (m, 1H), 7,06 (d, 2H), 6,72 - 6,67 (m, 2H), 6,36 (m, 1H), 2,02 (m, 4H), 2,93 (m, 4H), 2,76 (s, 2H), 2,74 - 2,61 (m, 2H), 2,35 - 2,22 (m, 5H), 2,19 (s, 3H), 2,16 - 2,10 (m, 4H), 1,97 (m, 2H), 1,38 (t, 2H), 0,94 (s, 6H).

EJEMPLO 454

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(1-metilpiperidin-4-il)metil]amino}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó utilizando el EJEMPLO 88A en lugar del EJEMPLO 428D en el EJEMPLO 428E. ^{1}H NMR (500 MHz, piridin-d_5) δ 9,28 (m, 1H), 8,66 (m, 1H), 8,58 (s, 1H), 8,40 (dd, 1H), 8,02 (d, 1H), 7,53 (d, 1H), 7,44 (d, 2H), 7,24 (m, 1H), 7,15 (m, 1H), 7,07 (d, 2H), 6,89 (d, 1H), 6,73 - 6,69 (m, 2H), 5,86 (m, 2H), 3,17 (t, 2H), 3,01 - 3,04 (m, 4H), 2,86 (m, 2H), 2,77 (s, 2H), 2,25 (m, 5H), 2,14 (m, 4H), 1,96 - 1,97 (s, 2H), 1,92 (m, 2H), 1,70 (m, 2H), 1,60 (m, 1H), 1,48 - 1,37 (m, 4H), 0,94 (s, 6H).

EJEMPLO 455

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[({(2R)-4-[2-(2-metoxietoxi)etil]morfolin-2-il}metil)amino]-3-nitrofenil}sulfonil)benzamida

EJEMPLO 455A

(*R*)-4-((4-(2-(2-metoxietoxi)etil)morfolin-2-il)metilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 437B en lugar del EJEMPLO 415B y bromuro de 2-(2-metoxietoxi)etilo en lugar de ioduro de 2,2-difluoroetilo en el EJEMPLO 415C.

EJEMPLO 455B

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[({(2R)-4-[2-(2-metoxietoxi)etil]morfolin-2-il}metil)amino]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 455A en lugar del EJEMPLO 428D en el EJEMPLO 428E. ^{1}H NMR (500MHz, piridin-d_5) δ 9,24 (d, 1H), 8,85 (t, 1H), 8,56 (s, 1H), 8,36 (dd, 1H), 8,03 (d, 1H), 7,51 (d, 1H), 7,44 (d, 2H), 7,24 (m, 2H), 7,12 (d, 1H), 7,07 (d, 2H), 6,91 (d, 1H), 6,73-6,68 (m, 2H), 3,93-3,86 (m, 2H), 3,72-3,61 (m,

5H), 3,53 (m, 2H), 3,48-3,40 (m, 2H), 3,28 (s, 3H), 3,03 (m, 4H), 2,95 (d, 1H), 2,77 (s, 2H), 2,70 (d, 1H), 2,69 (t, 2H), 2,27-2,10 (m, 8H), 1,97 (s, 2H), 1,38 (t, 2H), 0,94 (s, 6H).

EJEMPLO 456

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4,4-difluorociclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó utilizando el EJEMPLO 412C en lugar del EJEMPLO 428D en el EJEMPLO 428E. ^{1}H NMR (500MHz, piridin-d_5) δ 9,29 (d, 1H), 8,73 (t, 1H), 8,58 (s, 1H), 8,42 (dd, 1H), 7,99 (d, 1H), 7,52 (d, 1H), 7,43 (d, 2H), 7,24 (m, 2H), 7,17 (d, 1H), 7,07 (d, 2H), 6,94 (d, 1H), 6,72 (d, 1H), 6,69 (dd, 1H), 3,22 (t, 2H), 3,03 (m, 4H), 2,76 (s, 2H), 2,25 (m, 2H), 2,13 (m, 6H), 1,97 (s, 2H), 1,85-1,70 (m, 5H), 1,38 (t, 2H), 1,36-1,33 (m, 2H), 0,94 (s, 6H).

EJEMPLO 457

N-[(4-{[(4-acetilmorfolin-2-il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida

EJEMPLO 457A

4-((4-acetilmorfolin-2-il)metilamino)-3-nitrobencensulfonamida

Una solución del EJEMPLO 415B (145 mg) y *N*-etil-*N*-isopropilpropan-2-amina (120 µl) en diclorometano anhidro (5 mL) y N,N-dimetilformamida (2 mL) se enfrió con un baño de hielo y anhídrido acético (56 µl) se agregó por goteo. La mezcla se agitó a temperatura ambiente durante 3 horas y se concentró a sequedad. El residuo se trituró con agua. El sólido resultante se secó al vacío para dar el compuesto del título.

EJEMPLO 457B

N-[(4-{[(4-acetilmorfolin-2-il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 457A en lugar del EJEMPLO 428D en el EJEMPLO 428E. ^{1}H NMR (500MHz, piridin-d_5) δ 9,24 (d, 1H), 8,83 (t, 1H), 8,56 (s, 1H), 8,38 (dd, 1H), 8,03 (d, 1H), 7,51 (d, 1H), 7,43 (d, 2H), 7,24 (m, 2H), 7,09 (d, 1H), 7,07 (d, 2H), 6,91 (dd, 1H), 6,72 (m, 2H), 3,89 (m, 1H), 3,80-3,70 (m, 1H),

3,60-3,40 (m, 4H), 3,06 (m, 1H), 3,03 (m, 4H), 2,77 (s, 2H), 2,70 (m, 1H), 2,26 (m, 2H), 2,18-2,13 (m, 5H), 2,09 (s, 3H), 1,97 (s, 2H), 1,38 (t, 2H), 0,94 (s, 6H).

EJEMPLO 458

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({[4-(metilsulfonil)morfolin-2-il]metil}amino)-3-nitrofenil]sulfonil}benzamida

EJEMPLO 458A

4-((4-(metilsulfonil)morfolin-2-il)metilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando cloruro de metanosulfonilo en lugar de anhídrido acético en el EJEMPLO 457A.

EJEMPLO 458B

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({[4-(metilsulfonil)morfolin-2-il]metil}amino)-3-nitrofenil]sulfonil}benzamida

El compuesto del título se preparó utilizando el EJEMPLO 458A en lugar del EJEMPLO 428D en el EJEMPLO 428E. ^{1}H NMR (500MHz, piridin-d_5) δ 9,23 (d, 1H), 8,85 (t, 1H), 8,57 (s, 1H), 8,37 (dd, 1H), 8,01 (d, 1H), 7,52 (d, 1H), 7,43 (d, 2H), 7,24 (m, 2H), 7,15 (d, 1H), 7,07 (d, 2H), 6,97 (d, 1H), 6,72 (m, 2H), 4,00-3,90 (m, 3H), 3,68-3,59 (m, 3H), 3,58-3,48 (m, 1H), 3,06-3,02 (m, 7H), 2,98-2,89 (m, 2H), 2,77 (s, 2H), 2,25 (m, 2H), 2,14 (m, 4H), 1,97 (s, 2H), 1,38 (t, 2H), 0,94 (s, 6H).

EJEMPLO 459

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[6-({4-fluoro-1-[2-fluoro-1-(fluorometil)etil]piperidin-4-il}metoxi)-5-(trifluorometil)piridin-3-il]sulfonil}-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 459A

4-fluoro-4-((5-sulfamoil-3-(trifluorometil)piridin-2-iloxi)metil)piperidin-1-carboxilato de tert-butilo

El compuesto del título se preparó utilizando el EJEMPLO 410E en lugar del EJEMPLO 329A y el EJEMPLO 419A en lugar de (tetrahidro-2H-piran-4-il)metanol en el EJEMPLO 329B.

EJEMPLO 459B

6-((4-fluoropiperidin-4-il)metoxi)-5-(trifluorometil)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 459A en lugar del EJEMPLO 422A en el EJEMPLO 422B.

EJEMPLO 459C

6-((1-(1,3-difluoropropan-2-il)-4-fluoropiperidin-4-il)metoxi)-5-(trifluorometil)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 459B en lugar del EJEMPLO 422B en el EJEMPLO 434A.

EJEMPLO 459D

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[6-({4-fluoro-1-[2-fluoro-1-(fluorometil)etil]piperidin-4-il}metoxi)-5-(trifluorometil)piridin-3-il]sulfonil}-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 400E en lugar del EJEMPLO 26C y el EJEMPLO 459C en lugar del EJEMPLO 1F en el EJEMPLO 177. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 12,94 (d, 1H), 8,40 (d, 1H), 8,11 (d, 1H), 7,68 (m, 2H), 7,35 (d, 2H), 7,06 (d, 2H), 6,99 (d, 2H), 6,71 (dd, 1H), 6,39 (d, 1H), 6,06 (t, 1H), 4,67 (d, 2H), 4,55 (d, 2H), 4,47 (d, 2H), 3,07 (m, 5H), 2,74 (m, 6H), 2,19 (m, 6H), 1,90 (m, 6H), 1,40 (t, 2H), 0,93 (s, 6H).

EJEMPLO 460

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida

El compuesto del título se preparó como se describió en el EJEMPLO 177 utilizando el EJEMPLO 26C en lugar del EJEMPLO 18G. ^{1}H NMR (400 MHz, dimetilsulfóxido-d_6) δ 12,87 (s, 1H), 11,60 (s, 1H), 8,58 (s, 1H), 8,47 (d, 1H), 8,11 (s, 1H), 7,81 - 7,91 (m, 1H), 7,76 (dd, 1H), 7,59 - 7,66 (m, 1H), 7,48 (d, 1H), 7,34 (d, 2H), 7,00 - 7,11 (m, 5H), 6,73 (dd, 1H), 6,67 (dd, 1H), 6,08 (d, 1H), 3,85 (dd, 2H), 3,20 - 3,30 (m, 4H), 3,04 (s, 4H), 2,77 (s, 2H),

2,17 (d, 6H), 1,96 (s, 2H), 1,81 - 1,92 (m, 1H), 1,55 - 1,66 (m, 2H), 1,39 (t, 2H), 1,17 - 1,32 (m, 2H), 0,93 (s, 6H).

EJEMPLO 461

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[5-cloro-6-(2-tetrahidrofuran-2-iletoxi)piridin-3-il]sulfonil}-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 461A

5-cloro-6-(2-(tetrahidrofuran-2-il)etoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 387A en lugar del EJEMPLO 329A y 2-(tetrahidrofuran-2-il)etanol en lugar de (tetrahidro-2H-piran-4-il)metanol en el EJEMPLO 329B.

EJEMPLO 461B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[5-cloro-6-(2-tetrahidrofuran-2-iletoxi)piridin-3-il]sulfonil}-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 461A en lugar del EJEMPLO 1F y el EJEMPLO 400E en lugar del EJEMPLO 26C en el EJEMPLO 177C. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 13,08 (s, 1H), 8,27 (d, J = 2,17 Hz, 1H), 7,83 (d, J = 1,83 Hz, 1H), 7,80 (s, 1H), 7,58 (d, J = 8,85 Hz, 1H), 7,36 (d, J = 8,54 Hz, 2H), 7,03-7,10 (m, 4H), 6,79 (dd, J = 9, 2,29 Hz, 1H), 6,54 (d, J = 1,53 Hz, 1H), 6,13 (d, J = 7,02 Hz, 1H), 4,41-4,47 (m, 2H), 3,91-3,94 (m, 1H), 3,71-3,80 (m, 1H), 3,56-3,63 (m, 2H), 3,25 (s ancho, 2H), 2,33 (s ancho, 2H), 2,16-2,18 (m, 2H), 1,92-2,01 (m, 5H), 1,80-1,86 (m, 2H), 1,47-1,53 (m, 1H), 1,42 (t, J = 6,26 Hz, 2H), 0,94 (s, 6H).

EJEMPLO 462

Trans-2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4-cianociclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida

EJEMPLO 462A

2-(trans-4-(aminometil)ciclohexil)acetonitrilo

Sobre una solución de (trans-4-(cianometil)ciclohexil)metilcarbamato de tert-butilo (500 mg) en diclorometano (5 mL) se agregó lentamente ácido trifluoroacético (3 mL) a 0°C.

La mezcla se entibió a temperatura ambiente, se agitó por 1 hora. El compuesto del título se obtuvo mediante concentración.

EJEMPLO 462B

4-((trans-4-cianociclohexil)metilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 462A en lugar de (tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

EJEMPLO 462C

Trans-2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4-cianociclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó utilizando el EJEMPLO 462B en lugar del EJEMPLO 428D en el EJEMPLO 428E. ^{1}H NMR (500 MHz, piridin-d_5) δ 9,29 (d, 1H), 8,67 (t, 1H), 8,59 (s, 1H), 8,41 (dd, 1H), 7,98 (d, 1H), 7,53 (d, 1H), 7,43 (d, 2H), 7,25 (m, 1H), 7,19 (m, 1H), 7,07 (d, 2H), 6,91 (d, 1H), 6,73 - 6,68 (m, 2H), 5,24 (m, 2H), 3,13 (t, 2H), 3,03 (m, 4H), 2,76 (s, 2H), 2,43 (m, 1H), 2,25 (m, 2H), 2,13 (m, 4H), 1,99 - 1,94 (m, 4H), 1,77 (m, H), 1,59 (m, 1H), 1,46 (m, 2H), 1,38 (t, 2H), 0,99 - 0,90 (m, 8H).

EJEMPLO 463

2-(1H-benzimidazol-4-iloxi)-N-({5-cloro-6-[(4,4-difluorociclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida

EJEMPLO 463A

(4,4-difluorociclohexil)metanol

Sobre una lechada de hidruro de aluminio y litio (0,24 g) en éter dietílico (15 mL) se agregó en forma de gotas 4,4-difluorociclohexanocarboxilato de etilo (1,0 g) en éter dietílico (2 mL). La reacción se calentó a reflujo bajo nitrógeno durante 4 horas. La reacción se enfrió a 0° C, seguido por agregado cuidadoso de agua (0,24 mL), NaOH 4 N acuoso (0,24 mL), y agua (0,72 mL). La reacción se diluyó con éter dietílico (40 mL) y se agitó con sulfato de sodio durante 30 minutos. La mezcla se filtró a través de tierras de diatomeas y el filtrado se concentró para dar el compuesto del título.

EJEMPLO 463B

5-cloro-6-((4,4-difluorociclohexil)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 463A en lugar de (tetrahidro-2H-piran-4-il)metanol y el EJEMPLO 387A en lugar del EJEMPLO 329A en el EJEMPLO 329B.

EJEMPLO 463C

2-(1H-benzimidazol-4-iloxi)-N-({5-cloro-6-[(4,4-difluorociclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 463B en lugar del EJEMPLO 428D en el EJEMPLO 428E. ^{1}H NMR (500 MHz, piridin-d_5) δ 9,15 (d, 1H), 8,69 (m, 1H), 8,59 (s, 1H), 7,99 (d, 1H), 7,53 (d, 1H), 7,44 (d, 2H), 7,24 (m, 1H), 7,16 (m, 1H), 7,07 (d, 2H), 6,70 (m, 2H), 5,45(m, 2H), 4,22 (d, 2H), 3,04 (m, 4H), 2,77 (s, 2H), 2,26 (m, 2H), 2,16 - 2,08 (m, 6H), 1,97 (s, 2H), 1,86 - 1,68 (m, 5H), 1,47 - 1,36 (m, 4H), 0,94 (m, 6H).

EJEMPLO 464

N-({3-cloro-4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 464A

3-cloro-4-((4-fluorotetrahidro-2H-piran-4-il)metoxi)bencensulfonamida

El compuesto del título se preparó utilizando 3,4-diclorobencensulfonamida en lugar del EJEMPLO 329A y el EJEMPLO 306C en lugar de (tetrahidro-2H-piran-4-il)metanol en el EJEMPLO 329B.

EJEMPLO 464B

N-(3-cloro-4-((4-fluorotetrahidro-2H-piran-4-il)metoxi)fenilsulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-2-(1-((2-(trimetilsilil)etoxi)metil)-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 435D en lugar del EJEMPLO 1E y el EJEMPLO 464A en lugar del EJEMPLO 1F en el EJEMPLO 1G.

EJEMPLO 464C

N-({3-cloro-4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 464B en lugar del EJEMPLO 435E en el EJEMPLO 435F. ^{1}H NMR (300 MHz, dimetilsulfóxido-d_6) δ 13,15 (s, 1H), 11,74 - 11,31 (m, 1H), 7,85 (s, 1H), 7,67 (d, 1H), 7,62 - 7,49 (m, 2H), 7,35 (d, 2H), 7,22 - 7,09 (m, 3H), 7,05 (d, 2H), 6,80 (d, 1H), 6,53 (s, 1H), 6,23 (d, 1H), 4,26 (d, 2H), 3,79 (d, 2H), 3,62 (dd, 2H), 3,17 (s, 4H), 2,77 (d, 2H), 2,22 (d, 6H), 1,88 (dd, 6H), 1,40 (t, 2H), 0,94 (s, 6H).

EJEMPLO 465

N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 465A

2-(1H-indazol-4-iloxi)-4-(4-((4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il)metil)piperazin-1-il)benzoato de metilo

El compuesto del título se preparó utilizando el EJEMPLO 400C en lugar de piperazin-1-carboxilato de tert-butilo y el EJEMPLO 145E en lugar del EJEMPLO 27C en el EJEMPLO 1A.

EJEMPLO 465B

4-(4-((4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il)metil)piperazin-1-il)-2-(1-((2-(trimetilsilil)etoxi)metil)-1H-indazol-4-iloxi)benzoato de metilo

El compuesto del título se preparó utilizando el EJEMPLO 465A en lugar del EJEMPLO 400D en el EJEMPLO 435C.

EJEMPLO 465C

Ácido 4-(4-((4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il)metil)piperazin-1-il)-2-(1-((2-(trimetilsilil)etoxi)metil)-1H-indazol-4-iloxi)benzoico

El compuesto del título se preparó utilizando el EJEMPLO 465B en lugar del EJEMPLO 175D en el EJEMPLO 175E.

EJEMPLO 465D

N-(5-cloro-6-((4-fluorotetrahidro-2H-piran-4-il)metoxi)piridin-3-ilsulfonil)-4-(4-((4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il)metil)piperazin-1-il)-2-(1-((2-(trimetilsilil)etoxi)metil)-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 465C en lugar del EJEMPLO 27G y el EJEMPLO 404A en lugar del EJEMPLO 1F en el EJEMPLO 27H.

EJEMPLO 465E

N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 465D en lugar del EJEMPLO 435E en EJEMPLO 435F, excepto que aquí el compuesto final se purificó mediante HPLC preparativa usando una columna C18, de 250 x 50 mm, 10 □, y eluyendo con un gradiente de entre 20 y 100% de CH_3CN vs. 0,1% de ácido trifluoroacético en agua, seguido por cromatografía en columna eluyendo con diclorometano/metanol 98/2. ^{1}H NMR (400 MHz, dimetilsulfóxido-d_6) δ 13,13 (s, 1H), 8,28 (d, 1H), 7,90 (d, 1H), 7,83 (s, 1H), 7,58 (d, 1H), 7,39 (d, 2H), 7,17 (d, 2H), 7,08 (m, 2H), 6,82 (dd, 1H), 6,57 (d, 1H), 6,14 (d, 1H), 4,52 (d, 2H), 4,15 (s, 2H), 3,80 (m, 2H), 3,60 (m, 2H), 3,20 (v m ancho, 4H), 2,98 (v s ancho, 2H), 2,35 (v m ancho, 4H), 2,18 (s, 2H), 1,87 (m, 4H), 1,20 (s, 6H).

Ejemplo 466

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-*N*-{[5-ciano-6-(2-tetrahidro-2*H*-piran-4-iletoxi)piridin-3-il]sulfonil}-2-(1*H*-indazol-4-iloxi)benzamida

EJEMPLO 466A

5-bromo-6-(2-(tetrahidro-2H-piran-4-il)etoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando 2-(tetrahidro-2H-piran-4-il)etanol en lugar de (tetrahidro-2H-piran-4-il)metanol en el EJEMPLO 329B.

EJEMPLO 466B

5-ciano-6-(2-(tetrahidro-2H-piran-4-il)etoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 466A en lugar del EJEMPLO 329A en el EJEMPLO 333A.

EJEMPLO 466C

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-*N*-{[5-ciano-6-(2-tetrahidro-2*H*-piran-4-iletoxi)piridin-3-il]sulfonil}-2-(1*H*-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 466B en lugar del EJEMPLO 1F y el EJEMPLO 400E en lugar del EJEMPLO 26C en el EJEMPLO 177C. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 13,04 (s, 1H), 8,48 (d, 1H), 8,13 (s, 1H), 7,75 (s, 1H), 7,62 (d, 1H), 7,37 (d, 2H), 7,01-7,08 (m, 4H), 6,76 (dd, 1H), 6,51 (d, 1H), 6,08 (d, 1H), 4,47 (t, 2H), 3,81-3,85 (m, 2H), 3,71-3,80 (m, 1H), 2,18 (m, 2H), 1,99 (m, 2H), 1,62-1,72 (m, 5H), 1,42 (t, 2H), 1,23 (m, 2H), 0,94 (s, 6H).

EJEMPLO 467

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indol-5-iloxi)-N-[(4-{[(1R,5S)-8-metil-8-azabiciclo[3,2,1]oct-3-il]amino}-3-nitrofenil)sulfonil]benzamida

EJEMPLO 467A

4-((1R,3R,5S)-8-metil-8-azabiciclo[3,2,1]octan-3-ilamino)-3-nitrobencensulfonamida

El compuesto del título se preparó utilizando (1R,3R,5S)-8-metil-8-azabiciclo[3,2,1]octan-3-amina en lugar de 1-(2-metoxi-etil)-piperidin-4-ilamina en el EJEMPLO 189A.

EJEMPLO 467B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indol-5-iloxi)-N-[(4-{[(1R,5S)-8-metil-8-azabiciclo[3,2,1]oct-3-il]amino}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó utilizando el EJEMPLO 26C en lugar del EJEMPLO 1E y el EJEMPLO 467A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (500MHz, dimetilsulfóxido -d_6) δ 11,47 (s ancho, 1H), 11,17 (s, 1H), 9,43 (s ancho, 1H), 8,69 (d, 1H), 8,62 (d, 1H), 7,90 (dd, 1H), 7,52 (d, 1H), 7,40 (m, 3H), 7,15 (d, 1H), 7,06 (m, 3H), 6,85 (dd, 1H), 6,68 (m, 1H), 6,39 (t, 1H), 6,19 (s ancho, 1H), 4,01 (m, 1H), 3,91 (m,

2H), 3,58 (m, 3H), 3,01 (m, 3H), 2,73 (m, 5H), 2,32 (m, 6H), 2,16 (m, 6H), 2,0 (m, 2H), 1,45 (m, 2H), 0,94 (s, 6H).

EJEMPLO 468

N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-fenoxi-4-(4-{(3-fenilpropanoil)[(1S,2S,3S,5R)-2,6,6-trimetilbiciclo[3,1,1]hept-3-il]amino}piperidin-1-il)benzamida

EJEMPLO 468A

2-fenoxi-4-(1,4-dioxa-8-azaspiro[4,5]decan-8-il)benzoato de metilo

Se agitó 1,4-dioxa-8-azaspiro[4,5]decano (1,18 g), 4-fluoro-2-fenoxibenzoato de metilo (1,85 g), y K_2CO_3 (1,14 g) a 125°C en dimetilsulfóxido (25 mL) durante 24 horas. La mezcla se enfrió, se agregó sobre 300 mL de agua, se extrajo tres veces con éter, y se combinaron los extractos etéreos, se lavaron tres veces con agua, y salmuera, y se concentraron. El residuo se separó por cromatografía sobre gel de sílice usando entre 10 y 30% de acetato de etilo en hexanos como eluyente para dar el compuesto del título.

EJEMPLO 468B

4-(4-oxopiperidin-1-il)-2-fenoxibenzoato de metilo

Se calentó EJEMPLO 468A (23,7 g) a 80°C en una mezcla de ácido acético (30 mL), tetrahidrofurano (40 mL) y agua (30 mL) durante 24 horas. La mezcla se enfrió y se concentró. El producto crudo se separó por cromatografía sobre gel de sílice usando 25% de acetato de etilo en hexanos como eluyente para dar el compuesto del título.

EJEMPLO 468C

2-fenoxi-4-(4-((1S,2S,3S,5R)-2,6,6-trimetilbiciclo[3,1,1]heptan-3-ilamino)piperidin-1-il)benzoato de metilo

Se calentaron a reflujo EJEMPLO 468B (0,99 g) y (1S,2S,3S,5R)-2,6,6-trimetilbiciclo[3,1,1]heptan-3-amina (0,51 mL) en 200 mL de metanol bajo una trampa de Dean-Stark durante 24 horas. El solvente se concentró por hervor a un volumen de 75 mL, y la mezcla se enfrió a temperatura ambiente. Se agregó $NaBH_4$ (0,115 g) y la mezcla se agitó por 30 minutos. La reacción se detuvo con 10 mL de agua, se concentró en forma parcial, y se separó por cromatografía sobre gel de sílice usando 1% de trietilamina en acetato de etilo como eluyente para dar el compuesto del título.

EJEMPLO 468D

2-fenoxi-4-(4-(3-fenil-N-((1S,2S,3S,5R)-2,6,6-trimetilbiciclo[3,1,1]heptan-3-il)propanamido)piperidin-1-il)benzoato de metilo

Se agitaron EJEMPLO 468C (320 mg), cloruro de 3-fenilpropanoilo (0,113 mL), y trietilamina (0,116 mL) en diclorometano (15 mL) durante 24 horas. La mezcla de reacción se concentró parcialmente y el residuo se separó por cromatografía sobre gel de sílice usando 20% de acetato de etilo en hexanos como eluyente para dar el compuesto del título.

EJEMPLO 468E

Ácido 2-fenoxi-4-(4-(3-fenil-N-((1S,2S,3S,5R)-2,6,6-trimetilbiciclo[3,1,1]heptan-3-il)propanamido)piperidin-1-il)benzoico

El compuesto del título se preparó utilizando el EJEMPLO 468D en lugar del EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 468F

N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-fenoxi-4-(4-{(3-fenilpropanoil)[(1S,2S,3S,5R)-2,6,6-trimetilbiciclo[3,1,1]hept-3-il]amino}piperidin-1-il)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 468E en lugar del EJEMPLO 1E en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 8,32 (m, 2H), 7,64 (m, 2H), 7,11-7,29 (m, 6H), 6,95 (dd, 1H), 6,89 (dd, 1H), 6,70 (m, 3H), 6,32 (m, 1H), 3,85 (m, 3H), 3,70 (m, 3H), 2,91 (m, 6H), 2,65-2,80 (m, 6H), 1,91 (s, 6H), 1,61 (m, 4H), 1,16-1,36 (m, 4H), 1,11 (m, 6H), 0,95 (m, 4H), 0,87 (d, 2H).

EJEMPLO 469

N-({4-[(3-morfolin-4-ilpropil)amino]-3-nitrofenil}sulfonil)-2-fenoxi-4-(4-{(3-fenilpropanoil)[(1S,2S,3S,5R)-2,6,6-trimetilbiciclo[3,1,1]hept-3-il]amino}piperidin-1-il)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 468E en lugar del EJEMPLO 1E y el EJEMPLO 7A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 8,72 (m, 1H), 8,44 (d, 1H), 7,73 (dd, 1H), 7,54 (m, 1H), 7,12-7,28 (m, 6H), 7,05 (dd, 1H), 6,95 (dd, 1H), 6,82 (d, 1H), 6,74 (m, 2H), 6,34 (m, 1H),

3,77 (m, 2H), 3,63 (m, 4H), 3,10 (m, 4H), 3,05 (m, 4H), 2,78 (m, 6H), 1,75-2,10 (m, 8H), 1,55 (m, 2H), 1,40 (m, 2H), 1,19 (m, 6H), 1,01 (m, 2H), 0,95 (m, 2H), 0,88 (d, 2H).

EJEMPLO 470

N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-fenoxi-4-(4-{(3-fenilpropil)[(1S,2S,3S,5R)-2,6,6-trimetilbiciclo[3,1,1]hept-3-il]amino}piperidin-1-il)benzamida

EJEMPLO 470A

2-fenoxi-4-(4-((3-fenilpropil)((1S,2S,3S,5R)-2,6,6-trimetilbiciclo[3,1,1]heptan-3-il)amino)piperidin-1-il)benzoato de metilo

Se agitaron EJEMPLO 468C (320 mg), 3-fenilpropanal (111 mg), y $NaBH(OAc)_3$ (205 mg) en diclorometano (15 mL) durante 24 horas. La mezcla de reacción se separó por cromatografía sobre gel de sílice usando 20% de acetato de etilo en hexanos como eluyente para dar el compuesto del título.

EJEMPLO 470B

Ácido 2-fenoxi-4-(4-((3-fenilpropil)((1S,2S,3S,5R)-2,6,6-trimetilbiciclo[3,1,1]heptan-3-il)amino)piperidin-1-il)benzoico

El compuesto del título se preparó utilizando el EJEMPLO 470A en lugar del EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 470C

N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-fenoxi-4-(4-{(3-fenilpropil)[(1S,2S,3S,5R)-2,6,6-trimetilbiciclo[3,1,1]hept-3-il]amino}piperidin-1-il)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 470B en lugar del EJEMPLO 1E en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 8,57 (m, 1H), 8,47 (d, 1H), 7,50 (m, 1H), 7,32 (m, 1H), 7,12-7,31 (m, 7H), 6,99 (dd, 1H), 6,81 (m, 3H), 6,37 (d, 1H), 4,44 (t, 1H), 3,84 (m, 4H), 3,37 (m, 2H), 3,25 (m, 2H), 3,06 (m, 2H), 2,70 (m, 4H), 2,57 (m, 4H), 1,82 (m, 2H), 1,77 (m, 4H), 1,52-1,71 (m, 8H), 1,25 (m, 3H), 1,15 (s, 3H), 0,95 (d, 2H), 0,93 (s, 3H), 0,74 (d, 2H).

EJEMPLO 471

N-({4-[(3-morfolin-4-ilpropil)amino]-3-nitrofenil}sulfonil)-2-fenoxi-4-(4-{(3-fenilpropil)[(1S,2S,3S,5R)-2,6,6-trimetilbiciclo[3,1,1]hept-3-il]amino}piperidin-1-il)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 470B en lugar del EJEMPLO 1E y el EJEMPLO 7A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 8,68 (m, 1H), 8,40 (d, 1H), 7,70 (dd, 1H), 7,55 (d, 1H), 7,11-7,29 (m, 7H), 7,01 (dd, 1H), 6,95 (dd, 1H), 6,76 (d, 2H), 6,34 (m, 1H), 3,75 (m, 2H), 3,61 (m, 4H), 3,43 (m, 4H), 3,05 (m, 6H), 2,75 (m, 2H), 2,60 (m, 2H), 2,41 (m, 4H), 2,15 (m, 1H), 1,82 (m, 4H), 1,69 (m, 2H), 1,51 (m, 1H), 1,18 (m, 8H), 0,96 (m, 1H), 0,94 (s, 3H).

EJEMPLO 472

4-[4-(2-{[(1R,5S)-8-metil-8-azabiciclo[3,2,1]oct-3-il]amino}bencil)piperazin-1-il]-N-({4-[(3-morfolin-4-ilpropil)amino]-3-nitrofenil}sulfonil)-2-fenoxibenzamida

EJEMPLO 472A

Se disolvieron 4-fluoro-2-fenoxibenzoato de etilo (600 mg) y piperazina (596 mg) en dimetilsulfóxido anhidro y se calentaron a 130ºC durante la noche. La mezcla de reacción se enfrió a temperatura ambiente y se diluyó con acetato de etilo. Se lavó la fase orgánica con agua y salmuera, se secó sobre sulfato de sodio anhidro, se filtró, y se concentró para conseguir el compuesto del título.

EJEMPLO 472B

Se resuspendieron EJEMPLO 472A (400 mg), 1-(bromometil)-2-nitrobenceno (277 mg) y carbonato de sodio (408 mg) en N,N-dimetilformamida anhidra (20 mL). La mezcla de reacción se agitó a temperatura ambiente durante 4 horas. La mezcla de reacción se diluyó con acetato de etilo. Se lavó la fase orgánica con agua y salmuera, se secó sobre sulfato de sodio anhidro, se filtró, y se concentró. Se hizo una purificación en columna rápida con entre 10 y 40% de acetato de etilo/hexano para conseguir el compuesto del título.

EJEMPLO 472C

Se agregó una solución del EJEMPLO 472B (0,6 g) en metanol (20 ml) a Ra-Ni, se lavó con solvente (0,480 g) en una botella de presión de 250 mL y se agitó durante 3 horas a 30 psi a temperatura ambiente. La mezcla se filtró a través de una membrana de nylon y se concentró para conseguir el producto.

EJEMPLO 472D

El compuesto del título se preparó utilizando (1R,5S)-8-metil-8-azabiciclo[3,2,1]octan-3-ona en lugar de 4'-clorobifenil-2-carboxaldehído y el EJEMPLO 472C en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 472E

El compuesto del título se preparó utilizando el EJEMPLO 472D en lugar del EJEMPLO 175D en el EJEMPLO 175E.

EJEMPLO 472F

4-[4-(2-{[(1R,5S)-8-metil-8-azabiciclo[3,2,1]oct-3-il]amino}bencil)piperazin-1-il]-N-({4-[(3-morfolin-4-ilpropil)amino]-3-nitrofenil}sulfonil)-2-fenoxibenzamida

El compuesto del título se preparó utilizando el EJEMPLO 472E en lugar del EJEMPLO 27G y el EJEMPLO 7A en lugar del EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,66 (s ancho, 1H), 9,90 (s ancho, 1H), 9,56 (s, 1H), 8,69 (t, 1H), 8,50 (d, 1H), 7,81 (dd, 1H), 7,54 (d, 1H), 7,22 (m, 5H), 7,01 (m, 1H), 6,83 (m, 3H), 6,47 (s, 1H), 3,84 (m, 4H), 3,65 (d, 6H), 3,54 (m, 4H), 3,43 (m, 2H), 3,19 (m, 8H), 2,68 (d, 3H), 2,34 (m, 2H), 2,25 (m, 4H), 1,99 (m, 4H).

EJEMPLO 473

4-[4-(2-{[(1R,5S)-8-metil-8-azabiciclo[3,2,1]oct-3-il]amino}bencil)piperazin-1-il]-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida

El compuesto del título se preparó utilizando el EJEMPLO 472E en lugar del EJEMPLO 27G en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,61 (s ancho, 1H), 9,38 (s ancho, 1H), 8,64 (s, 1H), 8,47 (d, 1H), 7,75 (dd, 1H), 7,55 (d, 1H), 7,23 (t, 3H), 7,15 (d, 2H), 6,98 (t, 1H), 6,82 (d, 3H), 6,47 (s, 2H), 3,85 (m, 6H), 3,31 (m, 12H), 2,68 (d, 3H), 2,06 (m, 9H), 1,62 (m, 2H), 1,29 (m, 2H).

EJEMPLO 474

4-{4-[2-(3-azabiciclo[3,2,2]non-3-il)bencil]piperazin-1-il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida

EJEMPLO 474A

Se resuspendieron 2-fluorobenzaldehído (264 mg), (1S,5S)-3-azabiciclo[3,2,2]nonano (500 mg) y carbonato de sodio (846 mg) en dimetilsulfóxido anhidro (3mL). La mezcla de reacción se calentó a 135ºC durante la noche. La mezcla de reacción se enfrió a temperatura ambiente y se diluyó con acetato de etilo. Se lavó la fase orgánica con agua y salmuera, se secó sobre sulfato de sodio anhidro, se filtró, y se concentró. Una purificación por columna rápida con entre 0 y 10% de acetato de etilo/hexano proveyó el compuesto del título.

EJEMPLO 474B

El compuesto del título se preparó utilizando el EJEMPLO 474A en lugar de 4'-clorobifenil-2-carboxaldehído y el EJEMPLO 113A en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 474C

El compuesto del título se preparó utilizando el EJEMPLO 474B en lugar del EJEMPLO 175D en el EJEMPLO 175E.

EJEMPLO 474D

4-{4-[2-(3-azabiciclo[3,2,2]non-3-il)bencil]piperazin-1-il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida

El compuesto del título se preparó utilizando el EJEMPLO 474C en lugar del EJEMPLO 27G en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,74 (s ancho, 1H), 8,64 (t, 1H), 8,47 (d, 1H), 7,76 (dd, 1H), 7,54 (m, 2H), 7,43 (d, 2H), 7,23 (m, 3H), 7,15 (d, 1H), 6,98 (t, 1H), 6,83 (m, 3H), 6,53 (d, 1H), 4,45(s ancho, 2H), 3,87 (m, 4H), 3,30 (m, 6H), 3,06 (m, 8H), 1,89 (m, 7H), 1,64 (m, 6H), 1,29 (m, 2H).

EJEMPLO 475

4-{4-[2-(3-azabiciclo[3,2,2]non-3-il)bencil]piperazin-1-il}-2-fenoxi-N-({4-[(tetrahidro-2H-piran-4-ilmetil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 474C en lugar del EJEMPLO 27G y el EJEMPLO 163A en lugar del EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,78 (s ancho, 1H), 8,11 (d, 1H), 7,86 (dd, 1H), 7,54 (d, 2H), 7,44 (d, 2H), 7,28 (m, 4H), 7,11 (d, 1H), 7,04 (m, 1H), 6,85 (m, 3H), 6,53 (d, 1H), 4,46 (m, 2H), 3,86 (m, 4H), 3,28 (m, 6H), 3,10 (m, 4H), 2,98 (d, 4H), 1,97 (s, 2H), 1,84 (m, 5H), 1,64 (m, 6H), 1,26 (m, 2H).

EJEMPLO 476

4-{4-[2-(3-azabiciclo[3,2,2]non-3-il)bencil]piperazin-1-il}-2-fenoxi-N-({4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 474C en lugar del EJEMPLO 27G y el EJEMPLO 2A en lugar del EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,19 (s ancho, 1H), 9,83 (s ancho, 1H), 7,52 (m, 6H), 7,33 (m, 3H), 7,12 (t, 1H), 6,93 (d, 2H), 6,83 (m, 1H), 6,56 (d, 2H), 6,47 (d, 1H), 4,47 (s, 2H), 3,85 (m, 4H), 3,26 (m, 2H), 3,11 (m, 4H), 2,96 (m, 6H), 1,97 (s, 2H), 1,81 (m, 6H), 1,64 (m, 7H), 1,22 (m, 2H).

EJEMPLO 477

4-{4-[2-(3-azabiciclo[3,2,2]non-3-il)bencil]piperazin-1-il}-N-({4-[(3-morfolin-4-ilpropil)amino]-3-nitrofenil}sulfonil)-2-fenoxibenzamida

El compuesto del título se preparó utilizando el EJEMPLO 474C en lugar del EJEMPLO 27G y el EJEMPLO 7A en lugar del EJEMPLO 1F en el EJEMPLO 27H. ^{1}H NMR (400MHz, dimetilsulfóxido-d_6) δ 11,77 (s ancho, 1H), 10,04 (s ancho, 1H), 8,69 (t, 1H), 8,50 (d, 1H), 7,81 (dd, 1H), 7,55 (d, 2H), 7,43 (d, 2H), 7,24 (m, 3H), 7,15 (d, 1H), 7,01 (t, 1H), 6,84 (m, 3H), 6,52 (d, 1H), 4,44 (s, 2H), 3,97 (s, 2H), 3,54 (m, 6H), 3,39 (m, 4H), 3,19 (m, 8H), 2,97 (d, 4H), 1,99 (m, 4H), 1,83 (m, 4H), 1,64 (m, 4H).

EJEMPLO 478

4-(4-{2-[(4R,7S)-2,3,3a,4,7,7a-hexahidro-1H-4,7-metanoinden-5-il]bencil}piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida

EJEMPLO 478A

Éster tert-butílico de ácido 4-(4-Metoxicarbonil-3-fenoxi-fenil)-piperazin-1-carboxílico

El compuesto del título se preparó utilizando éster tert-butílico de ácido piperazin-1-carboxílico en lugar del EJEMPLO 1B en el EJEMPLO 1D.

EJEMPLO 478B

Éster tert-butílico de ácido 4-(4-Carboxi-3-fenoxi-fenil)-piperazin-1-carboxílico

El compuesto del título se preparó utilizando el EJEMPLO 478A en lugar del EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 478C

Éster tert-butílico de ácido 4-(4-{3-Nitro-4-[(tetrahidro-piran-4-ilmetil)-amino]-bencensulfonilaminocarbonil}-3-fenoxi-fenil)-piperazin-1-carboxílico

El compuesto del título se preparó utilizando el EJEMPLO 478B en lugar del EJEMPLO 1E en el EJEMPLO 1G.

EJEMPLO 478D

3-Nitro-N-(2-fenoxi-4-piperazin-1-il-benzoil)-4-[(tetrahidro-piran-4-ilmetil)-amino]-bencensulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 478C en lugar del EJEMPLO 1A en el EJEMPLO 1B para aislar el compuesto del título como mono sal de ácido trifluoroacético.

EJEMPLO 478E

Éster de ácido (4R,7S)-(2,3,3a,4,7,7a-hexahidro-1H-4,7-metano-inden-5-il) trifluorometanosulfónico

Se disolvió (4R,7R)-octahidro-4,7-metano-inden-5-ona (2,00 g) en tetrahidrofurano (25 mL) y se enfrió a -78°C usando una baño de alcohol isopropílico/ hielo seco. Se agregó lentamente bis(trimetilsilil)-amida de sodio (1M en tetrahidrofurano, 14,65 mL). La solución se dejó entibiar a temperatura ambiente, se agitó durante una hora, se enfrió a -78°C usando un baño de alcohol isopropílico/ hielo seco, y se agregó N-feniltrifluorometanosulfonimida (5,23 g). La solución se dejó llegar a temperatura ambiente y se agitó durante 16 horas. Se agregó hexano y la solución se agitó a temperatura ambiente durante una hora, se filtró, y se eliminó el solvente al vacío.

EJEMPLO 478F

(4R,7S)-2-(2,3,3a,4,7,7a-Hexahidro-1H-4,7-metano-inden-5-il)-benzaldehído

Se agregaron EJEMPLO 478E (941 mg), ácido 2-formilfenilborónico (600 mg), y fosfato de potasio tribásico (1416 mg) a tetrahidrofurano (20 mL). Se desgaseó la solución y trató rápidamente con nitrógeno tres veces. Se agregó tetraquis(trifenilfosfina)paladio(0) (244 mg) y la solución se calentó a 60°C durante 16 horas. La solución se enfrió, se agregó sobre agua, y se extrajo con 50% de acetato de etilo (hexanos). El extracto se lavó con salmuera, se

secó sobre sulfato de sodio anhidro, se concentró y se purificó por cromatografía rápida en columna sobre gel de sílice usando 10% de acetato de etilo (hexanos).

EJEMPLO 478G

4-(4-{2-[(4R,7S)-2,3,3a,4,7,7a-hexahidro-1H-4,7-metanoinden-5-il]bencil}piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida

Se agregaron EJEMPLO 478D (200 mg), EJEMPLO 478F (74 mg), y resina de cianoborohidruro de sodio (2,15 mmol/g, 144 mg) a tetrahidrofurano (3 mL) y ácido acético (0,7 mL) y se agitó a temperatura ambiente durante 16 horas. La solución se concentró al vacío y se purificó por cromatografía rápida en columna sobre gel de sílice usando metanol al 5% (diclorometano) para dar el compuesto del título como sal de mono ácido acético. ^{1}H NMR (300MHz, dimetilsulfóxido-d_6) δ 11,94 (s ancho, 1H), 8,64 (t, 1H), 8,48 (d, 1H), 7,76 (dd, 1H), 7,51 (d, 1H), 7,40 (m, 1H), 7,27-7,18 (m, 5H), 7,16 (d, 1H), 6,99 (tt, 1H), 6,83 (dt, 2H), 6,78 (dd, 1H), 6,41 (d, 1H), 6,23 (d, 1H), 3,87 (dd, 2H), 3,50 (m, 2H), 3,34 (t, 2H), 3,21 (s ancho, 4H), 2,73 (s ancho, 1H), 2,63 (s ancho, 1H), 2,46 (m, 4H), 2,11 (m, 2H), 1,95-1,75 (m, 4H), 1,91 (s, 3H), 1,66-1,52 (m, 6H), 1,28 (m, 2H), 1,02 (m, 2H), 0,85 (m, 1H).

EJEMPLO 479

4-[4-(2-{5-[(1R,5S)-8-azabiciclo[3,2,1]oct-8-ilmetil]tien-2-il}bencil)piperazin-1-il]-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida

EJEMPLO 479A

4-(4-(metoxicarbonil)-3-fenoxifenil)piperazin-1-carboxilato de tert-butilo

El compuesto del título se preparó utilizando piperazin-1-carboxilato de tert-butilo en lugar del EJEMPLO 1B en el EJEMPLO 1D.

EJEMPLO 479B

Ácido 4-(4-(tert-butoxicarbonil)piperazin-1-il)-2-fenoxibenzoico

El compuesto del título se preparó utilizando el EJEMPLO 479A en lugar del EJEMPLO 1D en el EJEMPLO 1E.

EJEMPLO 479C

4-(4-(3-nitro-4-((tetrahidro-2H-piran-4-il)metilamino)fenilsulfonilcarbamoil)-3-fenoxifenil)piperazin-1-carboxilato de tert-butilo

El compuesto del título se preparó utilizando el EJEMPLO 479B en lugar del EJEMPLO 1E en el EJEMPLO 1G.

EJEMPLO 479D

N-(3-nitro-4-((tetrahidro-2H-piran-4-il)metilamino)fenilsulfonil)-2-fenoxi-4-(piperazin-1-il)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 479C en lugar del EJEMPLO 1A en el EJEMPLO 1B.

EJEMPLO 479E

Ácido 2-((4-(4-(3-nitro-4-((tetrahidro-2H-piran-4-il)metilamino)fenilsulfonilcarbamoil)-3-fenoxifenil)piperazin-1-il)metil)fenilborónico

Se agregaron EJEMPLO 479D (213 mg), ácido 2-formilfenilborónico (54 mg), y resina de cianoborohidruro de sodio (2,38 mmol/g, 252 mg) a tetrahidrofurano (3,5 mL) y ácido acético (1,1 mL), y la solución se agitó a temperatura ambiente durante 16 horas. La solución se purificó por cromatografía rápida en columna sobre gel de sílice con 1% de ácido acético y 10% de metanol en diclorometano.

EJEMPLO 479F

Clorhidrato de 8-((5-bromotiofen-2-il)metil)-8-azabiciclo[3,2,1]octano

El compuesto del título se preparó utilizando 5-bromotiofene-2-carbaldehído en lugar de 4'-clorobifenil-2-carboxaldehído y clorhidrato de 8-azabiciclo[3,2,1]octano en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 479G

4-(4-(2-(5-(8-azabiciclo[3,2,1]octan-8-ilmetil)tiofen-2-il)bencil)piperazin-1-il)-N-(3-nitro-4-((tetrahidro-2H-piran-4-il)metilamino)fenilsulfonil)-2-fenoxibenzamida

Se combinaron EJEMPLO 479E (80 mg), EJEMPLO 479F (42,5 mg), dicloruro de bis(trifenilfosfina)paladio(II) (7,7 mg), e hidróxido de litio (10,5 mg) en una mezcla de dimetoxietano (1,6 mL), metanol (0,5 mL) y agua (0,7 mL) en un vial de microondas. La mezcla de reacción se calentó en un reactor de microondas CEM Discover a 150°C durante 15 minutos. El material crudo se purificó por cromatografía rápida eluyendo con un gradiente de 1% de metanol/diclorometano a 5% de metanol/diclorometano. ^{1}H NMR (500MHz, dimetilsulfóxido-d_6) δ 8,33 (m, 2H), 7,64 (m, 2H), 7,44 (m, 1H), 7,39 (m, 1H), 7,32 (m, 2H),

7,12 (m, 3H), 6,90 (m, 2H), 6,85 (t, 1H), 6,68 (m, 3H), 6,30 (d, 1H), 3,83 (dd, 2H), 3,65 (s, 2H), 3,51 (s, 2H), 3,17 (m, 4H), 3,08 (m, 4H), 2,45 (m, 6H), 1,92 (m, 2H), 1,62 (m, 4H), 1,54 (m, 3H), 1,28 (m, 6H).

EJEMPLO 480

4-[4-(2-{5-[(1R,5S)-8-azabiciclo[3,2,1]oct-8-ilmetil]tien-2-il}benciliden)piperidin-1-il]-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida

EJEMPLO 480A

2-fenoxi-4-(1,4-dioxa-8-azaspiro[4,5]decan-8-il)benzoato de metilo

Se combinaron 4-fluoro-2-fenoxibenzoato de metilo (2 g) y 1,4-dioxa-8-azaspiro[4,5]decano (1,279 g) en dimetilsulfóxido (12 mL) en un balón de 250 ml. Se agregó carbonato de sodio (1,291 g). Se selló el recipiente de reacción y se calentó a 130 °C durante la noche. La mezcla de reacción se diluyó con acetato de etilo, se lavó exhaustivamente con agua y con salmuera, y se secó sobre $MgSO_4$, se filtró y se concentró para obtener el producto deseado.

EJEMPLO 480B

4-(4-oxopiperidin-1-il)-2-fenoxibenzoato de metilo

Se capturó EJEMPLO 480A en ácido acético (30%, 20 mL) y tetrahidrofurano (10 mL). La mezcla de reacción se calentó a 75°C durante la noche. Se redujo el volumen al vacío y el residuo se neutralizó con solución de hidróxido de sodio, y se extrajo con acetato de etilo. Los extractos se lavaron con agua y con salmuera, se secaron sobre $MgSO_4$, se filtraron y se concentraron al vacío para obtener el producto deseado.

EJEMPLO 480C

4-(4-(2-bromobenciliden)piperidin-1-il)-2-fenoxibenzoato de metilo

Se calentó dimetilsulfóxido (22,88 mL) con hidruro de sodio (0,332 g) a 70 °C durante 1 hora, luego se enfrió a temperatura ambiente y se agregó bromuro de (2-bromobencil)trifenilfosfonio (3,40 g) en varias partes, y luego se agitó a temperatura ambiente durante 1 hora. Luego se agregó una solución de 4-(4-oxopiperidin-1-il)-2-fenoxibenzoato de metilo (1,8 g) en dimetilsulfóxido (5,20 mL) y la reacción se calentó a 70 °C durante el fin de semana. La reacción se acidificó con solución de HCl acuosa 1 M y se extrajo con éter. Los extractos combinados se lavaron exhaustivamente con agua y salmuera,

se secaron sobre $MgSO_4$, se filtraron y se concentraron al vacío. El residuo se purificó por cromatografía rápida eluyendo con entre 0 y 20% de acetato de etilo en hexanos.

EJEMPLO 480D

2-fenoxi-4-(4-(2-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benciliden)piperidin-1-il)benzoato de metilo

Se combinaron EJEMPLO 480C (259 mg), bis(pinacolato)de diboro (206 mg), [1,1'-bis(difenilfosfino)ferroceno]dicloropaladio(II) diclorometano (22 mg), y acetato de potasio (159 mg) en dimetilsulfóxido (2,7 mL). La reacción se calentó a 90°C durante 36 horas. La mezcla de reacción se diluyó con acetato de etilo, se lavó exhaustivamente con agua y con salmuera, y se secó sobre $MgSO_4$, se filtró y se concentró al vacío. Se lavó el sólido crudo con hexanos y con hexanos/éter (2:1) para obtener el producto deseado.

EJEMPLO 480E

Ácido 4-(4-(2-(5-(8-azabiciclo[3,2,1]octan-8-ilmetil)tiofen-2-il)benciliden)piperidin-1-il)-2-fenoxibenzoico

El compuesto del título se preparó utilizando el EJEMPLO 480D en lugar del EJEMPLO 479E en el EJEMPLO 479G.

EJEMPLO 480F

4-(4-(2-(5-(8-azabiciclo[3,2,1]octan-8-ilmetil)tiofen-2-il)benciliden)piperidin-1-il)-N-(3-nitro-4-((tetrahidro-2H-piran-4-il)metilamino)fenilsulfonil)-2-fenoxibenzamida

El compuesto del título se preparó utilizando el EJEMPLO 480E en lugar del EJEMPLO 1E en el EJEMPLO 1G. ^{1}H NMR (500MHz, dimetilsulfóxido -d_6) δ 11,54 (s, 1H), 9,36 (s ancho, 1H), 8,48 (d, 1H), 7,76 (dd, 1H), 7,53 (m, 2H), 7,34 (m, 3H), 7,25 (m, 4H), 7,16 (d, 1H), 7,00 (t, 1H), 6,84 (d, 2H), 6,81 (dd, 1H), 6,44 (d, 1H), 6,37 (s ancho, 1H), 4,36 (d, 2H), 3,85 (m, 3H), 3,44 (m, 2H), 3,28 (m, 6H), 2,36 (m, 3H), 2,23 (m, 4H), 1,90 (m, 3H), 1,81 (m, 2H), 1,62 (m, 5H), 1,47 (m, 1H), 1,29 (m, 2H).

EJEMPLO 481

4-[4-(3-{5-[(1R,5S)-8-azabiciclo[3,2,1]oct-8-ilmetil]tien-2-il}bencil)piperazin-1-il]-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida

EJEMPLO 481A

Ácido 3-((4-(4-(3-nitro-4-((tetrahidro-2H-piran-4-il)metilamino)fenilsulfonilcarbamoil)-3-fenoxifenil)piperazin-1-il)metil)fenilborónico

El compuesto del título se preparó utilizando ácido 3-formilfenilborónico en lugar de ácido 2-formilfenilborónico en el EJEMPLO 479E.

EJEMPLO 481B

4-(4-(3-(5-(8-azabiciclo[3,2,1]octan-8-ilmetil)tiofen-2-il)bencil)piperazin-1-il)-N-(3-nitro-4-((tetrahidro-2H-piran-4-il)metilamino)fenilsulfonil)-2-fenoxibenzamida

El compuesto del título se preparó utilizando el EJEMPLO 481A en lugar del EJEMPLO 479E en el EJEMPLO 479G. ^{1}H NMR (500MHz, dimetilsulfóxido -d_6) δ 11,76 (s ancho, 1H), 9,55 (s ancho, 1H), 8,55 (t, 1H), 8,46 (d, 1H), 7,75 (m, 2H), 7,54 (m, 2H), 7,40 (m, 1H), 7,20 (m, 4H), 6,97 (m, 1H), 6,86 (m, 1H), 6,82 (m, 3H), 6,55 (m, 1H), 4,41 (d, 2H), 3,88 (m, 6H), 3,43 (m, 3H), 3,30 (m, 6H), 3,06 (m, 6H), 1,90 (m, 4H), 1,65 (m, 5H), 1,30 (m, 3H).

EJEMPLO 482

N-({5-cloro-6-[(4,4-difluorociclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 482A

(4,4-difluorociclohexil)metanol

Se formó una lechada con hidruro de litio y aluminio (0,24 g) en éter dietílico (15 mL), se agregó 4,4-difluorociclohexanocarboxilato de etilo (1,0 g) en éter dietílico (2 mL) por goteo, y la reacción se agitó bajo reflujo bajo nitrógeno por 4 horas. La reacción se enfrió a 0° C, seguido por la adición cuidadosa de agua (0,24 mL), NaOH acuoso 4N (0,24 mL), y agua (0,72 mL). Se agregó Na_2SO_4 y éter dietílico (40 mL) y la mezcla se agitó a temperatura ambiente por 30 minutos. El filtrado a través de tierra diatomea y la concentración del material filtrado dieron el compuesto del título el cual se usó sin purificación.

EJEMPLO 482B

5-cloro-6-((4,4-difluorociclohexil)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando EJEMPLO 482A en lugar de (tetrahidro-2H-piran-4-il)metanol y 5,6-dicloropiridin-3-sulfonamida en lugar de EJEMPLO 329A en EJEMPLO 329B.

EJEMPLO 482C

N-(5-cloro-6-((4,4-difluorociclohexil)metoxi)piridin-3-ilsulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-2-(1-((2-(trimetilsilil)etoxi)metil)-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 482B en lugar de EJEMPLO 1F y EJEMPLO 435D en lugar de EJEMPLO 27G en EJEMPLO 27H.

EJEMPLO 482D

N-({5-cloro-6-[(4,4-difluorociclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 482C en lugar de EJEMPLO 435E en EJEMPLO 435F. ^{1}H NMR (500MHz, sulfóxido de dimetilo-d_6) δ 13,12 (br s, 1H), 8,28 (d, 1H), 7,87 (d, 1H), 7,80 (s, 1H), 7,59 (d, 1H), 7,37 (d, 2H), 7,08 (m, 4H), 6,80 (dd, 1H), 6,55 (d, 1H), 6,14 (d, 1H), 4,25 (d, 2H), 3,24 (br s, 4H), 3,00 (v br s, 2H), 2,45 (v br s, 4H), 2,20 (br m, 2H), 2,05 (m, 2H), 1,98 (s, 2H), 1,97 (m, 1H), 1,90 (m, 4H), 1,42 (t, 2H), 1,38 (m, 2H), 0,94 (s, 6H).

EJEMPLO 483

N-({6-[(trans-4-carbamoilciclohexil)metoxi]-5-cloropiridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 483A

Trans-N-(bis(4-metoxifenil)metil)-4-(hidroximetil)ciclohexanocarboxamida

A una solución de bis(4-metoxifenil)metanamina (846 mg), ácido trans-4-(hidroximetil)ciclohexanocarboxílico (500 mg), y trietilamina (1,322 mL) en N,N-dimetilformamida (30 mL) se agregó reactivo hexafluorofosfato de benzotriazol-1-iloxitris(dimetilamino)fosfonio (1,677g). La mezcla resultante se agitó por 3 horas, se diluyó con acetato de etilo, se lavó con agua, NaOH acuoso y salmuera. La capa orgánica se secó sobre Na_2SO_4, se filtró, y se concentró. El residuo se disolvió en diclorometano y se cargó en un cartucho de sílice, se eluyó con 0 - 100% acetato de etilo en hexano para dar el compuesto del título.

EJEMPLO 483B

(1r,4r)-N-(bis(4-metoxifenil)metil)-4-((3-cloro-5-sulfamoilpiridin-2-iloxi)metil)ciclohexanocarboxamida

Se trató EJEMPLO 483A (1,2 g) y EJEMPLO 387A (0,711 g) en tetrahidrofurano (30 mL) con NaH (60%, 0,51 g) durante la noche. La reacción se detuvo con NH_4Cl acuoso y el valor del pH de la mezcla se ajustó a 4-5 con HCl acuoso diluido. La mezcla resultante se extrajo con diclorometano. La capa de diclorometano se lavó con salmuera y se concentró. El residuo se purificó mediante cromatografía sobre gel de sílice, y se eluyó con acetato de etilo al 20% - 30% en hexano para dar el compuesto del título.

EJEMPLO 483C

N-(6-((trans-4-(bis(4-metoxifenil)metilcarbamoil)ciclohexil)metoxi)-5-cloropiridin-3-ilsulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-2-(1-((2-(trimetilsilil)etoxi)metil)-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó como se describe en EJEMPLO 177 reemplazando EJEMPLO 26C y EJEMPLO 1F con EJEMPLO 435D y EJEMPLO 483B, respectivamente.

EJEMPLO 483D

N-({6-[(trans-4-carbamoilciclohexil)metoxi]-5-cloropiridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

Se trató EJEMPLO 483C (500 mg) en diclorometano (10 mL) con agua (1 mL) y ácido trifluoroacético (5 mL) por 2 horas. La mezcla de la reacción se concentró y el residuo se purificó mediante HPLC Gilson de fase inversa, se eluyó con 40% - 70% acetonitrilo en ácido trifluoroacético al 0,1% agua a lo largo de 40 minutos. Las fracciones deseadas se concentraron para eliminar el acetonitrilo, se neutralizó con $NaHCO_3$ y se extrajo con diclorometano. La capa de diclorometano se secó sobre Na_2SO_4, se filtró, y se concentró para dar el compuesto del título. ^1H NMR (500 MHz, sulfóxido de dimetilo-d_6) δ 13,11 (s, 1H), 8,28 (d, 1H), 7,86 (d, 1H), 7,81 (s, 1H), 7,59 (d, 1H), 7,36 (d, 2H), 7,19 (s, 1H), 7,03 - 7,12 (m, 4H), 6,80 (dd, 1H), 6,66 (s, 1H), 6,54 (d, 1H), 6,14 (d, 1H), 4,20 (d, 2H), 3,14 - 3,26 (m, 4H), 2,96 (s, 2H), 2,30 - 2,47 (m, 3H), 2,18 (s, 2H), 2,02 - 2,09 (m, 1H), 1,98 (s, 2H), 1,71 - 1,89 (m, 5H), 1,31 - 1,46 (m, 4H), 1,03 - 1,16 (m, 2H), 0,94 (s, 6H).

EJEMPLO 484

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(trans-4-cianociclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 484A

trans-4-(aminometil)ciclohexanocarbonitrilo

A una solución de (trans-4-cianociclohexil)metilcarbamato de tert-butilo (500 mg) en diclorometano (10 mL) se agregó lentamente ácido trifluoroacético (2 mL) a 0°C. La mezcla de la reacción se calentó a temperatura ambiente, se agitó por 1 hora y se concentró para dar el compuesto del título.

EJEMPLO 484B

4-((trans-4-cianociclohexil)metilamino)-3-nitrobencenosulfonamida

Una mezcla de 4-fluoro-3-nitrobencenosulfonamida (347 mg) y EJEMPLO 484A (300 mg) en tetrahidrofurano (20 mL) se trató con trietilamina (1,4 mL) durante la noche y se concentró. El residuo se trituró con acetato de etilo para dar el compuesto del título.

EJEMPLO 484C

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(trans-4-cianociclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida

Una mezcla de 4-dimetilaminopiridina (115,0 mg), clorhidrato de 1-etil-3-[3-(dimetilamino)propil]-carbodiimida (51,4 mg), EJEMPLO 435D (165 mg) y EJEMPLO 484B (96 mg) en diclorometano (6 mL) se agitó durante la noche. A esta mezcla se agregó ácido trifluoroacético (5 mL) y la mezcla resultante se agitó por 2 horas y se concentró. El residuo se purificó mediante HPLC Gilson de fase inversa, se eluyó con 40% - 70% acetonitrilo en ácido trifluoroacético al 0,1% agua a lo largo de 40 minutos. Las fracciones deseadas se concentraron para eliminar acetonitrilo, se neutralizó con $NaHCO_3$ y se extrajo con diclorometano. La capa de diclorometano se secó sobre Na_2SO_4, se filtró, y se concentró para dar el compuesto del título. ^{1}H NMR (400 MHz, sulfóxido de dimetilo-d_6) δ 13,10 (s, 1H), 11,54 (s, 1H), 8,56 (t, 1H), 8,37 (d, 1H), 7,81 (s, 1H), 7,49 - 7,59 (m, 2H), 7,35 (d, 2H), 7,02 - 7,14 (m, 4H), 6,95 (d, 1H), 6,80 (dd, 1H), 6,52 (d, 1H), 6,19 (d, 1H), 3,25 (t, 2H), 3,16 (s, 4H), 2,80 (s, 2H), 2,60 - 2,70 (m, 1H), 2,21 (d, 6H), 1,94 - 2,08 (m, 4H), 1,74 - 1,84 (m, 2H), 1,58 - 1,71 (m, 1H), 1,36 - 1,54 (m, 4H), 0,98 - 1,12 (m, 2H), 0,93 (s, 6H).

EJEMPLO 485

N-({5-cloro-6-[2-(1H-imidazol-1-il)etoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 485A

El compuesto del título se preparó utilizando 2-(1H-imidazol-1-il)etanol en lugar de (tetrahidro-2H-piran-4-il)metanol y EJEMPLO 387A en lugar de EJEMPLO 329A en EJEMPLO 329B.

EJEMPLO 485B

N-(6-(2-(1H-imidazol-1-il)etoxi)-5-cloropiridin-3-ilsulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-2-(1-((2-(trimetilsilil)etoxi)metil)-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 485A en lugar de EJEMPLO 1F y EJEMPLO 435D en lugar de EJEMPLO 1E en EJEMPLO 1G.

EJEMPLO 485C

N-({5-cloro-6-[2-(1H-imidazol-1-il)etoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 485B en lugar de EJEMPLO 435E en EJEMPLO 435F. ^{1}H NMR (500MHz, sulfóxido de dimetilo-d_6) δ 13,03 (s, 1H), 8,28 (m, 2H), 7,85 (d, 1H), 7,77 (s, 1H), 7,61 (d, 1H), 7,44 (s, 1H), 7,36 (d, 2H), 7,06 (d, 2H), 7,01-7,03 (m, 2H), 6,76 (dd, 1H), 6,49 (d, 1H), 6,10 (dd, 1H), 4,65 (t, 2H), 4,50 (t, 2H), 3,11 (s, 4H), 2,88 (bs, 2H), 2,32-2,36 (m, 4H), 2,17-2,19 (m, 2H), 1,97-1,99 (m, 2H), 1,41 (t, 2H), 1,14-1,23 (m, 4H), 0,94 (s, 6H).

EJEMPLO 486

N-({5-cloro-6-[(1-metil-1H-imidazol-5-il)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 486A

5-cloro-6-((1-metil-1H-imidazol-5-il)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando (1-metil-1H-imidazol-5-il)metanol en lugar de (tetrahidro-2H-piran-4-il)metanol y EJEMPLO 387A en lugar de EJEMPLO 329A en EJEMPLO 329B.

EJEMPLO 486B

N-(5-cloro-6-((1-metil-1H-imidazol-5-il)metoxi)piridin-3-ilsulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-2-(1-((2-(trimetilsilil)etoxi)metil)-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 486A en lugar de EJEMPLO 1F y EJEMPLO 435D en lugar de EJEMPLO 1E en EJEMPLO 1G.

EJEMPLO486C

N-({5-cloro-6-[(1-metil-1H-imidazol-5-il)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 486B en lugar de EJEMPLO 435E en EJEMPLO 435F. ^{1}H NMR (500MHz, sulfóxido de dimetilo-d_6) δ 13,05 (s, 1H), 8,29 (s, 1H), 7,86 (d, 1H), 7,78 (s, 1H), 7,62 (d, 1H), 7,36 (d, 2H), 7,04-7,07 (m, 4H), 6,77 (dd, 1H), 6,49 (d, 1H), 6,12 (dd, 1H), 5,46 (s, 2H), 3,70 (s, 3H), 3,15 (s, 54H), 2,87 (bs, 2H), 2,32-2,36 (m, 4H), 2,17-2,19 (m, 2H), 1,98 (s, 2H), 1,41 (t, 2H), 0,94 (s, 6H).

EJEMPLO 487

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[5-fluoro-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil}-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 487A

5-bromo-3-fluoro-2-((tetrahidro-2H-piran-4-il)metoxi)piridina

El compuesto del título se preparó utilizando 5-bromo-2,3-difluoropiridina en lugar de 4-fluoro-3-nitrobencenosulfonamida en EJEMPLO 279A.

EJEMPLO 487B

5-fluoro-6-((tetrahidro-2H-piran-4-il)metoxi)piridin-3-ilcarbamato de tert-butilo

El compuesto del título se preparó utilizando EJEMPLO 487A en lugar de EJEMPLO 416A en EJEMPLO 416B.

EJEMPLO 487C

cloruro de 5-fluoro-6-((tetrahidro-2H-piran-4-il)metoxi)piridin-3-sulfonilo

El compuesto del título se preparó utilizando EJEMPLO 487B en lugar de EJEMPLO 416B en EJEMPLO 416C.

EJEMPLO 487D

5-fluoro-6-((tetrahidro-2H-piran-4-il)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando EJEMPLO 487C en lugar de EJEMPLO 416C en EJEMPLO 416D.

EJEMPLO 487E

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-N-(5-fluoro-6-((tetrahidro-2H-piran-4-il)metoxi)piridin-3-ilsulfonil)-2-(1-((2-(trimetilsilil)etoxi)metil)-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 435D en lugar de EJEMPLO 1E y EJEMPLO 487D en lugar de EJEMPLO 1F en EJEMPLO 1G.

EJEMPLO 487F

Se trató EJEMPLO 487E (0,195 g) con ácido trifluoroacético (2,311 mL) y se agitó a temperatura ambiente por 3 horas. La mezcla de la reacción se concentró, se disolvió en dioxano (3,0 mL), se trató con NaOH 1N (2,0 mL), y se agitó por 3 días. Se agregó NaOH 4N (1,0 mL) y la agitación se continuó por 4 horas. Se agregó solución saturada de $NaHCO_3$ y la mezcla se extrajo con CH_2Cl_2. Las capas orgánicas se combinaron, se lavó con solución saturada de NH_4Cl, se secó ($MgSO_4$), se filtró, se concentró y se cromatografió sobre gel de sílice con metanol entre 0 y 4% en CH_2Cl_2 como eluyente. El producto se disolvió en CH_3CN, se concentró y se secó en un horno de vacío a 80 ºC. ^{1}H NMR (400 MHz, piridin-d_5) δ 14,70 (s, 1H), 8,86 (d, 1H), 8,39 (d, 1H), 8,06 (d, 1H), 8,00 (dd, 1H), 7,47 (m, 2H), 7,35 (d, 1H), 7,12 (m, 3H), 6,88 (m, 2H), 6,48 (d, 1H), 4,21 (d, 2H), 3,96 (dd, 2H), 3,30 (m, 2H), 3,18 (m, 4H), 2,83 (s, 2H), 2,31 (t, 2H), 2,24 (m, 4H), 1,95 (m, 3H), 1,57 (dd, 2H), 1,38 (m, 4H), 0,96 (s, 6H).

EJEMPLO 488

N-{[5-cloro-6-(1,4-dioxan-2-ilmetoxi)piridin-3-il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 488A

6-((1,4-dioxan-2-il)metoxi)-5-cloropiridin-3-sulfonamida

El compuesto del título se preparó utilizando (1,4-dioxan-2-il)metanol en lugar de (tetrahidro-2H-piran-4-il)metanol y EJEMPLO 387A en lugar de EJEMPLO 329A en EJEMPLO 329B.

EJEMPLO 488B

N-(6-((1,4-dioxan-2-il)metoxi)-5-cloropiridin-3-ilsulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-2-(1-((2-(trimetilsilil)etoxi)metil)-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 488A en lugar de EJEMPLO 1F y EJEMPLO 435D en lugar de EJEMPLO 1E en EJEMPLO 1G.

EJEMPLO488C

N-{[5-cloro-6-(1,4-dioxan-2-ilmetoxi)piridin-3-il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 488B en lugar de EJEMPLO 435E en EJEMPLO 435F. ^{1}H NMR (500MHz, sulfóxido de dimetilo-d_6) δ 13,06 (s, 1H), 8,23 (s, 1H), 7,85 (d, 1H), 7,79 (s, 1H), 7,60 (d, 1H), 7,36 (d, 2H), 7,02-7,09 (m, 4H), 6,76-6,79 (m, 1H), 6,51 (s, 1H), 6,11 (d, 1H), 4,35-4,37 (m, 2H), 3,75-3,92 (m, 4H), 3,59-3,68 (m, 2H), 3,41-3,54 (m, 4H), 3,17 (s, 54H), 2,89 (s, 2H), 2,34 (bs, 4H), 2,17-2,19 (m, 2H), 1,98 (s, 2H), 1,41 (t, 2H), 0,94 (s, 6H).

EJEMPLO 490

N-({5-cloro-6-[(4,4-difluoro-1-hidroxiciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 490A

1,1-difluoro4-metilenciclohexano

Se agregó butillitio (12,32 mL, solución 2,5 M en hexanos) a una solución de cloruro de metiltrifenilfosfonio (9,63 g) en tetrahidrofurano (50 mL) a 0°C, y la reacción se agitó por 5 minutos. Luego se agregó 4,4-difluorociclohexanona (3,76 g) en dioxano (150 mL), y la reacción se agitó por 30 minutos. Se agregó agua (3 mL), y luego se agregó hexano (150 mL) lentamente, la reacción se filtró, y la solución se llevó al siguiente paso.

EJEMPLO 490B

4,4-difluoro-1-(hidroximetil)ciclohexanol

A la solución del Ejemplo 490A se agregó agua (75 mL), luego N-óxido de N-metilmorfolina (6,4 mL, solución al 50% en agua) y OsO_4 (14,2 g, 2,5 % en peso solución en tert-butanol), y la reacción se agitó por 96 horas a 50°C. La solución se enfrió a temperatura ambiente, se trató con solución acuosa saturada de $Na_2S_2O_3$ (100 mL) por 30 minutos, y luego se acidificó con HCl acuoso concentrado. La solución luego se extrajo tres veces con acetato de etilo, y las capas orgánicas se combinaron, se lavó con 1M HCl acuoso, y salmuera, y se concentró. La mezcla cruda se cromatografió sobre gel de sílice usando acetato de etilo al 10-100% en hexanos, y luego metanol al 5% en acetato de etilo para dar el producto.

EJEMPLO 490C

5-cloro-6-((4,4-difluoro-1-hidroxiciclohexil)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando EJEMPLO 490B en lugar de tetrahidro-2H-piran-4-ilmetanol y EJEMPLO 387A en lugar de EJEMPLO 329A en EJEMPLO 329B.

EJEMPLO 490D

N-({5-cloro-6-[(4,4-difluoro-1-hidroxiciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

Una mezcla de 4-dimetilaminopiridina (28 mg), clorhidrato de 1-etil-3-[3-(dimetilamino)propil]-carbodiimida (62 mg), EJEMPLO 435D (108 mg) y EJEMPLO 490C (55 mg) en diclorometano (4 mL) se agitó durante la noche. La mezcla se cromatografió sobre gel de sílice usando 50-100% acetato de etilo en hexanos, y luego metanol al 5% en acetato de etilo como eluyente para dar el producto protegido. Este material se colocó en fluoruro de tetrabutilamonio 1M (8 mL) y la mezcla resultante se agitó por 4 días a 50°C y se concentró. El residuo se neutralizó con $NaHCO_3$ y se extrajo con diclorometano. La capa de

diclorometano se concentró y se cromatografió sobre gel de sílice usando 50-100% acetato de etilo en hexanos, y luego metanol al 5% en acetato de etilo como eluyente para dar el producto. ^{1}H NMR (300MHz, sulfóxido de dimetilo-d_6) δ 13,05 (br s, 1H), 8,24 (s, 1H), 7,83 (d, 1H), 7,60 (m, 3H), 7,35 (d, 2H), 7,06 (d, 2H), 7,05 (d, 1H), 6,75 (d, 1H), 6,47 (s, 1H), 6,12 (dd, 1H), 4,87 (s, 1H), 4,23 (s, 2H), 3,13 (m, 2H), 3,02 (m, 2H), 2,77 (m, 1H), 2,27 (m, 2H), 2,17 (m, 4H), 1,97 (s, 2H), 1,91 (m, 2H), 1,74 (m, 4H), 1,60 (m, 2H), 1,40 (m, 2H), 1,31 (m, 1H), 0,94 (s, 3H), 0,91 (m, 2H).

EJEMPLO 491

N-({5-cloro-6-[(2,2-difluorociclopropil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 491A

5-cloro-6-((2,2-difluorociclopropil)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando (2,2-difluorociclopropil)metanol en lugar de (tetrahidro-2H-piran-4-il)metanol y EJEMPLO 387A en lugar de EJEMPLO 329A en EJEMPLO 329B.

EJEMPLO 491B

N-(5-cloro-6-((2,2-difluorociclopropil)metoxi)piridin-3-ilsulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-2-(1-((2-(trimetilsilil)etoxi)metil)-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 435D en lugar de EJEMPLO 1E y EJEMPLO 491A en lugar de EJEMPLO 1F en EJEMPLO 1G.

EJEMPLO 491C

N-({5-cloro-6-[(2,2-difluorociclopropil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

Se trató EJEMPLO 491B (0,196 g) con fluoruro de tetrabutilamonio (1M en tetrahidrofurano) (2,000 mL), se calentó a 50 ºC durante la noche, se enfrió a temperatura ambiente y luego se trató con solución acuosa 1N de NaOH (2,0 mL). La mezcla se agitó por 5 horas a temperatura ambiente y luego se extrajo con CH_2Cl_2. Los extractos se combinaron, se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró. El residuo se purificó mediante HPLC de fase inversa en una columna C18 usando un gradiente de 20-80%

acetonitrilo/ácido trifluoroacético al 0,1% en agua para dar el compuesto del título como la sal trifluoroacetato. La sal de ácido trifluoroacético se disolvió en diclorometano, se lavó con $NaHCO_3$ acuoso saturado solución y salmuera, se secó (Na_2SO_4), se filtró, se concentró, se formó una lechada en CH_3CN, se concentró nuevamente y se secó durante la noche en un horno de vacío a 80 ºC para dar el compuesto del título. ^{1}H NMR (400 MHz, piridin-d_5) δ 14,62 (s, 1H), 8,88 (d, 1H), 8,37 (m, 2H), 8,06 (d, 1H), 7,46 (d, 2H), 7,34 (d, 1H), 7,11 (m, 3H), 6,87 (m, 2H), 6,48 (d, 1H), 4,53 (m, 1H), 4,43 (m, 1H), 3,17 (m, 4H), 2,82 (s, 2H), 2,27 (m, 7H), 1,99 (s, 2H), 1,56 (m, 1H), 1,38 (m, 3H), 0,96 (s, 6H).

EJEMPLO 492

N-({5-cloro-6-[(trans-4-cianociclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

Una solución de EJEMPLO 483D (50 mg) en dioxano (12 mL) y piridina (1,2 mL) se enfrió en un baño de agua-hielo. La mezcla se calentó ligeramente eliminando el baño de hielo y luego se agregó ácido trifluoroacético (0,3 mL). La reacción se agitó por 1 hora y se detuvo con metanol y NaOH acuoso. La mezcla resultante se agitó por 1 hora y se concentró. El residuo se purificó mediante HPLC de fase inversa, y se eluyó con 40% - 70% acetonitrilo en ácido trifluoroacético al 0,1% agua a lo largo de 40 minutos. Las fracciones deseadas se concentraron para eliminar acetonitrilo, se neutralizó con $NaHCO_3$ y se extrajo con diclorometano. La capa de diclorometano se secó sobre Na_2SO_4, se filtró, se concentró y se secó para dar el compuesto del título. ^{1}H NMR (400 MHz, sulfóxido de dimetilo-d_6) δ 13,10 (s, 1H), 8,27 (d, 1H), 7,85 (d, 1H), 7,80 (s, 1H), 7,58 (d, 1H), 7,37 (d, 2H), 7,02 - 7,11 (m, 4H), 6,80 (dd, 1H), 6,54 (d, 1H), 6,14 (d, 1H), 4,19 (d, 2H), 3,22 (s, 4H), 2,97 (s, 2H), 2,59 - 2,71 (m, 1H), 2,41 (s, 2H), 2,18 (s, 2H), 2,05 (dd, 2H), 1,98 (s, 2H), 1,79 - 1,90 (m, 3H), 1,47 - 1,62 (m, 2H), 1,42 (t, 2H), 1,04 - 1,19 (m, 2H), 0,94 (s, 6H).

EJEMPLO 493

N-({5-cloro-6-[(cis-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 493A

4-(hidroximetil)-1-metilciclohexanol

4-(Hidroximetil)ciclohexanona (800 mg) en tetrahidrofurano (15 mL) se trató con cloruro de metilmagnesio 3 M en tetrahidrofurano (6,24 mL) a 0°C. La reacción se calentó a temperatura ambiente durante 2 horas y se detuvo con metanol y agua. La mezcla resultante se concentró y el residuo se suspendió en acetato de etilo. Los precipitados se retiraron por filtración y el material filtrado se concentró. El residuo se purificó mediante cromatografía, eluyendo con 0-100% acetato de etilo en hexano para dar el compuesto del título.

EJEMPLO 493B

5-cloro-6-((trans-4-hidroxi-4-metilciclohexil)metoxi)piridin-3-sulfonamida

Se trató EJEMPLO 493A (970 mg) y EJEMPLO 387A (1,6 g) en N,N-dimetilformamida (8 mL) con hidruro de sodio (1,8 g, 60%) a temperatura ambiente por 2 días. La reacción se detuvo con agua. La mezcla resultante se neutralizó con HCl acuoso diluido, y se extrajo con acetato de etilo. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se purificó mediante una cromatografía de fase inversa, y se eluyó con 30-45% acetonitrilo en ácido trifluoroacético acuoso al 0,1% para dar el compuesto del título.

EJEMPLO 493C

5-cloro-6-((cis-4-hidroxi-4-metilciclohexil)metoxi)piridin-3-sulfonamida

Se trató EJEMPLO 493A (970 mg) y EJEMPLO 387A (1,6 g) en N,N-dimetilformamida (8 mL) con hidruro de sodio (1,8 g, 60%) a temperatura ambiente por 2 días. La reacción se detuvo con agua. La mezcla resultante se neutralizó con HCl acuoso diluido, y se extrajo con acetato de etilo. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se purificó mediante una cromatografía de fase inversa, y se eluyó con 30-45% acetonitrilo en ácido trifluoroacético acuoso al 0,1% para dar el compuesto del título.

EJEMPLO 493D

N-({5-cloro-6-[(cis-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

Una mezcla de 4-dimetilaminopiridina (175,0 mg), clorhidrato de 1-etil-3-[3-(dimetilamino)propil]-carbodiimida (82 mg), EJEMPLO 435D (251 mg) y EJEMPLO 493C (120 mg) en diclorometano (6 mL) se agitó durante la noche y se concentró. El residuo se disolvió en una solución 1 M de monohidrato de tetrabutilamonio en tetrahidrofurano (11 mL) y la solución resultante se sometió a reflujo por 9 horas y se concentró. El residuo se

purificó mediante HPLC de fase inversa, se eluyó con 40% - 70% acetonitrilo en ácido trifluoroacético acuoso al 0,1% a lo largo de 40 minutos. Las fracciones deseadas se concentraron para eliminar acetonitrilo, se neutralizó con $NaHCO_3$ y se extrajo con diclorometano. La capa de diclorometano se secó sobre Na_2SO_4, se filtró, se concentró y se secó para dar el compuesto del título. ^{1}H NMR (400 MHz, sulfóxido de dimetilo-d_6) δ 13,11 (s, 1H), 8,27 (d, 1H), 7,85 (d, 1H), 7,81 (s, 1H), 7,59 (d, 1H), 7,36 (d, 2H), 7,03 - 7,11 (m, 4H), 6,80 (dd, 1H), 6,54 (d, 1H), 6,14 (d, 1H), 4,20 (d, 2H), 3,96 (s, 1H), 3,21 (s, 4H), 2,86 - 3,05 (m, 1H), 2,40 (s, 2H), 2,18 (s, 2H), 1,98 (s, 2H), 1,63 - 1,78 (m, 1H), 1,50 - 1,62 (m, 4H), 1,36 - 1,49 (m, 4H), 1,20 - 1,34 (m, 2H), 1,10 (s, 3H), 0,94 (s, 6H).

EJEMPLO 494

N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 494A

Éster tert-butílico del ácido 4-hidroxi-indazol-1-carboxílico y éster tert-butílico del ácido 4-hidroxi-indazol-2-carboxílico

Se agregó 4-hidroxiindazol (3,94 g) a tetrahidrofurano (250 mL) y se enfrió a 0°C usando un baño de hielo. Se agregó hidruro de sodio (dispersión al 60% en aceite mineral, 1,23 g), y la mezcla se agitó a 0°C por cinco minutos. La mezcla se dejó calentar a temperatura ambiente y se agitó por otros 20 minutos. La mezcla se enfrió nuevamente a 0°C usando un baño de hielo, y se agregó tert-butildimetilclorosilano (4,65 g). La mezcla se dejó calentar a temperatura ambiente y se agitó por 16 horas. El volumen del solvente se redujo bajo vacío, el residuo se filtró al vacío a través de una almohadilla de gel de sílice y se lavó con acetato de etilo, y el solvente se eliminó bajo vacío. Al residuo se agregó acetonitrilo (200 mL), dicarbonato de di-tert-butilo (7,06 g), y 4-(dimetilamino)piridina (0,359 g). La mezcla se agitó a temperatura ambiente por tres horas, y el solvente se eliminó bajo vacío. Al residuo se agregó tetrahidrofurano (200 mL) y fluoruro de tetrabutilamonio (1M en tetrahidrofurano, 82 mL). La mezcla se agitó a temperatura ambiente por cuatro días, el solvente se eliminó bajo vacío, y el residuo se recogió con acetato de etilo. La mezcla se extrajo con cloruro de amonio acuoso saturado, se extrajo con salmuera, y se secó sobre sulfato de sodio anhidro. La mezcla se filtró al vacío a través de gel de sílice, y el solvente se

eliminó bajo vacío para dar una mezcla de los dos productos, la cual se usó en el siguiente paso sin purificación adicional.

EJEMPLO 494B

éster metílico del ácido 4-fluoro-2-(1H-indazol-4-iloxi)-benzoico

Se agregó EJEMPLO 494A (5,56 g) a diglima (200 mL), y se agregó tert-butóxido de potasio (1M en tetrahidrofurano, 30,8 mL). La mezcla se agitó a temperatura ambiente por 15 minutos, se agregó 2,4-difluorobenzoato de metilo, y la mezcla se calentó a 115°C por 16 horas. La mezcla se enfrió, el solvente se eliminó bajo vacío, el residuo se colocó en diclorometano (100 mL), y se agregó ácido trifluoroacético (22,6 mL). La mezcla se agitó a temperatura ambiente por 16 horas, el solvente se eliminó bajo vacío, el residuo se colocó en acetato de etilo y se lavó con una mezcla acuosa saturada de bicarbonato de sodio, y la capa orgánica se secó con sulfato de sodio anhidro. El material se purificó mediante columna flash cromatografía sobre gel de sílice usando acetato de etilo al 30% (en hexanos) elevando a acetato de etilo al 40% (en hexanos).

EJEMPLO 494C

éster metílico del ácido 2-(1H-Indazol-4-iloxi)-4-piperazin-1-il-benzoico

Se agregó EJEMPLO 494B (2,00 g) y piperazina (2,71 g) a sulfóxido de dimetilo (60 mL) y se calentó a 100°C por una hora. La mezcla se enfrió, se agregó a diclorometano, se lavó con agua dos veces, se lavó con una mezcla acuosa saturada de bicarbonato de sodio, y se secó sobre sulfato de sodio anhidro. Luego de la filtración, el solvente se eliminó bajo vacío.

EJEMPLO 494D

4,4-dimetil-2-(trifluorometilsulfoniloxi)ciclohex-1-encarboxilato de metilo

A una suspensión de NaH lavado con hexano (17 g) en diclorometano (700 mL), se agregó 5,5-dimetil-2-metoxicarbonilciclohexanona (38,5 g) por goteo a 0°C. Luego de agitar por 30 minutos, la mezcla se enfrió a -78°C y se agregó anhídrido trifluorometansulfónico (40 mL). La mezcla de la reacción se calentó a temperatura ambiente y se agitó por 24 horas. La capa orgánica se lavó con salmuera, se secó (Na_2SO_4), se filtró, y se concentró para dar el producto.

EJEMPLO 494E

2-(4-clorofenil)-4,4-dimetilciclohex-1-encarboxilato de metilo

Se calentó EJEMPLO 494D (62,15g), ácido 4-clorofenilborónico (32,24 g), CsF (64 g) y tetrakis(trifenilfosfin)paladio(0) (2g) en 2:1 1,2-dimetoxietano/metanol (600 mL) a 70^0C por 24 horas. La mezcla se concentró. Se agregó éter (4x 200 mL) y la mezcla se filtró. La solución de éter combinada se concentró para dar el producto.

EJEMPLO 494F

(2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metanol

A una mezcla de $LiBH_4$ (13g), EJEMPLO 494E (53,8 g) y éter (400 mL), se agregó metanol (25 mL) lentamente mediante una jeringa. La mezcla se agitó a temperatura ambiente por 24 horas. La reacción se detuvo con HCl acuoso 1N enfriando con hielo. La mezcla se diluyó con agua y se extrajo con éter (3x 100mL). Los extractos se secaron (Na_2SO_4), y se concentró. El producto crudo se cromatografió sobre gel de sílice con acetato de etilo al 0-30%/hexanos.

EJEMPLO 494G

2-(4-clorofenil)-4,4-dimetilciclohex-1-encarbaldehido

A una solución de EJEMPLO 494F en diclorometano (120 mL) a 0^oC se agregó Periodinano de Dess-Martin (17,7 g) y la reacción se dejó calentar a temperatura ambiente. La reacción se diluyó con diclorometano (200 mL), se lavó dos veces con Solución acuosa saturada de $NaHCO_3$ y salmuera, se secó sobre Na_2SO_4, se filtró, y se concentró. El producto crudo se filtró a través de un tapón de gel de sílice para dar el compuesto del título.

EJEMPLO 494H

éster metílico del ácido 4-{4-[2-(4-Cloro-fenil)-4,4-dimetil-ciclohex-1-enilmetil]-piperazin-1-il}-2-(1H-indazol-4-iloxi)-benzoico

A diclorometano (60 mL) se agregó EJEMPLO 494C (2,500 g) y EJEMPLO 494G (2,029 g). La solución se agitó a temperatura ambiente por 30 minutos, se agregó triacetoxiborhidruro de sodio (1,804 g), y la solución se agitó a temperatura ambiente por 16 horas. La solución se diluyó con acetato de etilo, se lavó con una solución acuosa saturada de bicarbonato de sodio, se lavó con salmuera, y la capa orgánica se secó sobre sulfato de sodio anhidro. Luego de la filtración, la solución se concentró y se purificó mediante columna flash cromatografía sobre gel de sílice usando acetato de etilo al 20-50% en hexanos.

EJEMPLO 494I

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-2-(1-tritil-1H-indazol-4-iloxi)benzoato de metilo

Se disolvió EJEMPLO 494H (300 mg) en diclorometano (1,5 mL), se enfrió a 0 °C, luego se agregó trietilamina (0,22 mL) y cloruro de tritilo (145 mg). La reacción se dejó calentar a temperatura ambiente durante la noche. La mezcla de la reacción se colocó directamente en una columna de gel de sílice y se eluyó con 1acetato de etilo al 0-30% en hexanos para dar el compuesto del título.

EJEMPLO 494J

ácido 4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-2-(1-tritil-1H-indazol-4-iloxi)benzoico

Se disolvió EJEMPLO 494I (0,591 g) en tetrahidrofurano (6 mL) y metanol (2 mL) y a la solución resultante se agregó solución acuosa 1M de LiOH (2,14 mL) y la reacción se calentó a 60°C por 5 horas. La reacción se enfrió y se diluyó con diclorometano (100 mL) y agua (10 mL), y luego se detuvo con HCl acuoso 1N (2 mL). La capa orgánica se separó, se lavó con salmuera (25 mL) y se concentró. La cromatografía sobre gel de sílice (Reveleris 40 g) eluyendo con un gradiente de 1% a 4% metanol/diclorometano a lo largo de 30 minutos dio el compuesto del título.

EJEMPLO 494K

4-(hidroximetil)-1-metilciclohexanol

4-(Hidroximetil)ciclohexanona (800 mg) en tetrahidrofurano (15 mL) se trató con cloruro de metilmagnesio 3 M en tetrahidrofurano (6,24 mL) a 0°C. La reacción se calentó a temperatura ambiente durante 2 horas y se detuvo con metanol y agua. La mezcla resultante se concentró y el residuo se suspendió en acetato de etilo. Los precipitados se retiraron por filtración y el material filtrado se concentró. El residuo se purificó mediante cromatografía, eluyendo con 0-100% acetato de etilo en hexano para dar el compuesto del título.

EJEMPLO 494L

5,6-dicloropiridin-3-sulfonamida

A una solución de cloruro de 5,6-dicloropiridin-3-sulfonilo (32,16 g) en alcohol isopropílico (300 mL) a 0 ºC se agregó una solución acuosa al 30% de NH_4OH (50,8

mL). Luego de agitar durante la noche, el solvente se redujo a 1/3 del volumen original. Luego se particionó entre agua y acetato de etilo. La capa acuosa se extrajo con acetato de etilo adicional. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre $MgSO_4$, se filtró, y se concentró. El residuo se cromatografió sobre gel de sílice. Luego se formó una lechada con el material en 1:9 acetato de etilo/hexanos, se filtró y se secó bajo vacío para dar el compuesto del título.

EJEMPLO 494M

5-cloro-6-((trans-4-hidroxi-4-metilciclohexil)metoxi)piridin-3-sulfonamida

Se trató EJEMPLO 494K (970 mg) y EJEMPLO 494L (1,6 g) en N,N-dimetilformamida (8 mL) con hidruro de sodio (1,8 g, 60%) a temperatura ambiente por 2 días. La reacción se detuvo con agua. La mezcla resultante se neutralizó con HCl acuoso diluido, y se extrajo con acetato de etilo. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se purificó mediante una cromatografía de fase inversa, y se eluyó con 30-45% acetonitrilo en ácido trifluoroacético al 0,1%/agua para dar el compuesto del título.

EJEMPLO 494N

N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

Una mezcla de EJEMPLO 494J (3,4 g), EJEMPLO 494M (1,539 g), N, N-dimetilpiridin-4-amina (2,043 g) y clorhidrato de N^1-((etilimino)metilen)-N^3,N^3-dimetilpropan-1,3-diamina (1,042 g) en diclorometano (65 mL) se agitó durante la noche. Se agregó agua (5 mL). La mezcla resultante se enfrió en un baño de hielo y luego ácido trifluoroacético (5 mL) se agregó lentamente. La mezcla se agitó mientras se calentaba de 0ºC a temperatura ambiente y luego se agitó a temperatura ambiente por 2 horas. La mezcla de la reacción se concentró sin calentar y el residuo se suspendió en una mezcla de sulfóxido de dimetilo y metanol (1:1, 40 mL). Los precipitados se retiraron por filtración. El material filtrado se cargó sobre una columna C18, se eluyó con 40%-70% acetonitrilo en ácido trifluoroacético acuoso al 0,1%. Las fracciones deseadas se concentraron para eliminar acetonitrilo, se neutralizó con $NaHCO_3$ y se extrajo con diclorometano. La capa orgánica se secó sobre Na_2SO_4, se filtró, se concentró y se secó para dar el compuesto del título. ^{1}H NMR (500 MHz, sulfóxido de dimetilo-d_6) δ 13,11 (s, 1H), 8,28 (d, 1H), 7,85 (d, 1H), 7,81 (s, 1H),

7,59 (d, 1H), 7,37 (d, 2H), 7,03 - 7,12 (m, 4H), 6,80 (dd, 1H), 6,54 (d, 1H), 6,14 (d, 1H), 4,18 - 4,31 (m, 3H), 3,15 - 3,26 (m, 4H), 2,96 (s, 2H), 2,28 - 2,48 (m, 3H), 2,18 (s, 2H), 1,98 (s, 2H), 1,69 - 1,82 (m, 3H), 1,56 (d, 2H), 1,34 - 1,45 (m, 4H), 1,16 - 1,27 (m, 2H), 1,11 (s, 3H), 0,94 (s, 6H).

EJEMPLO 496

N-({3-cloro-4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]fenil}sulfonil)-4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 496A

3-cloro-4-((4-fluorotetrahidro-2H-piran-4-il)metoxi)bencenosulfonamida

El compuesto del título se preparó utilizando EJEMPLO 306C en lugar de (tetrahidro-2H-piran-4-il)metanol y 3-cloro-4-fluorobencenosulfonamida en lugar de EJEMPLO 329A en EJEMPLO 329B.

EJEMPLO 496B

N-(3-cloro-4-((4-fluorotetrahidro-2H-piran-4-il)metoxi)fenilsulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-2-(1-((2-(trimetilsilil)etoxi)metil)-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 496A en lugar de EJEMPLO 1F y EJEMPLO 435D en lugar de EJEMPLO 27G en EJEMPLO 27H.

EJEMPLO 496C

N-({3-cloro-4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]fenil}sulfonil)-4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 496B en lugar de EJEMPLO 435E en EJEMPLO 435F. ^{1}H NMR (400MHz, sulfóxido de dimetilo-d_6) δ 13,16 (s, 1H), 11,62 (v br s, 1H), 7,86 (s, 1H), 7,67 (d, 1H), 7,59 (dd, 1H), 7,55 (d, 1H), 7,39 (d, 2H), 7,15 (m, 5H), 6,80 (dd, 1H), 6,52 (d, 1H), 6,22 (d, 1H), 4,25 (d, 2H), 4,14 (s, 2H), 3,80 (m, 2H), 3,60 (m, 2H), 3,17 (br m, 4H), 2,88 (s, 2H), 2,25 (br m, 4H), 2,16 (s, 2H), 1,90 (m, 4H), 1,20 (s, 6H).

EJEMPLO 497

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]-3-(trifluorometil)fenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 497A

4-((4-fluorotetrahidro-2H-piran-4-il)metoxi)-3-(trifluorometil)bencenosulfonamida

El compuesto del título se preparó utilizando EJEMPLO 306C en lugar de (tetrahidro-2H-piran-4-il)metanol y 4-fluoro-3-(trifluorometil)bencenosulfonamida en lugar de EJEMPLO 329A en EJEMPLO 329B.

EJEMPLO 497B

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-N-(4-((4-fluorotetrahidro-2H-piran-4-il)metoxi)-3-(trifluorometil)fenilsulfonil)-2-(1-tritil-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 498C en lugar de EJEMPLO 1E y EJEMPLO 497A en lugar de EJEMPLO 1F en EJEMPLO 1G.

EJEMPLO 497C

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]-3-(trifluorometil)fenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida

Se trató EJEMPLO 497B (0,1557 g) en diclorometano (1,5 mL) a 0 °C por goteo con ácido trifluoroacético (1,041 mL), se agitó por 1 hora, se diluyó con CH_2Cl_2 y se basificó con solución saturada de $NaHCO_3$. Las capas se separaron y la capa orgánica se lavó con agua y salmuera, se secó (Na_2SO_4), se filtró y se concentró. El material concentrado se cromatografió sobre gel de sílice con metanol entre 0 y 4% en CH_2Cl_2 como eluyente. ^1H NMR (500 MHz, piridina -d_5) δ 14,59 (s, 1H), 8,58 (d, 1H), 8,39 (dd, 1H), 8,36 (s, 1H), 8,07 (d, 1H), 7,46 (m, 2H), 7,37 (d, 1H), 7,17 (t, 1H), 7,09 (m, 3H), 6,85 (dd, 1H), 6,82 (d, 1H), 6,55 (d, 1H), 4,21 (d, 2H), 3,86 (m, 2H), 3,78 (td, 2H), 3,15 (m, 4H), 2,81 (s, 2H), 2,29 (t, 2H), 2,21 (m, 4H), 1,95 (m, 6H), 1,41 (t, 2H), 0,95 (s, 6H).

EJEMPLO 498

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-cloro-4-(tetrahidro-2H-piran-4-ilmetoxi)fenil]sulfonil}-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 498A

3-cloro-4-((tetrahidro-2H-piran-4-il)metoxi)bencenosulfonamida

El compuesto del título se preparó utilizando 3-cloro-4-fluorobencenosulfonamida en lugar de EJEMPLO 329A en EJEMPLO 329B.

EJEMPLO 498B

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-2-(1-tritil-1H-indazol-4-iloxi)benzoato de metilo

Se disolvió EJEMPLO 400D (300 mg) en diclorometano (1,5 mL), se enfrió a 0° C, luego se agregó trietilamina (0,22 mL) y cloruro de tritilo (145 mg). La reacción se dejó alcanzar temperatura ambiente durante la noche. La mezcla de la reacción se colocó directamente en una columna de gel de sílice y se eluyó con acetato de etilo al 10-30% en hexanos para dar el compuesto del título.

EJEMPLO 498C

ácido 4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-2-(1-tritil-1H-indazol-4-iloxi)benzoico

El compuesto del título se preparó utilizando EJEMPLO 498B en lugar de EJEMPLO 175D en EJEMPLO 175E.

EJEMPLO 498D

N-(3-cloro-4-((tetrahidro-2H-piran-4-il)metoxi)fenilsulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-2-(1-tritil-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 498C en lugar de EJEMPLO 1E y EJEMPLO 498A en lugar de EJEMPLO 1F en EJEMPLO 1G.

EJEMPLO 498E

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-cloro-4-(tetrahidro-2H-piran-4-ilmetoxi)fenil]sulfonil}-2-(1H-indazol-4-iloxi)benzamida

Se disolvió EJEMPLO 498D (150 mg) en diclorometano (3,5 mL) y ácido trifluoroacético (3,5 mL). Luego de agitar a temperatura ambiente por 30 minutos, la reacción se vertió en $NaHCO_3$ acuoso saturado y se extrajo con diclorometano. La capa orgánica se

lavó con salmuera y se secó sobre Na_2SO_4. Luego de la filtración y concentración el residuo se purificó mediante HPLC de fase inversa en una columna C18 usando un gradiente de 40-60% acetonitrilo/ácido trifluoroacético al 0,1% en agua para dar el compuesto del título como la sal trifluoroacetato. La sal de ácido trifluoroacético se disolvió en diclorometano (6 mL) y se lavó con $NaHCO_3$ acuoso al 50%. La capa orgánica se secó sobre Na_2SO_4 anhidro, se filtró, y se concentró para dar el compuesto del título. ^{1}H NMR (400MHz, sulfóxido de dimetilo-d_6) δ 13,16 (s, 1H), 7,85 (s, 1H), 7,64 (d, 1H), 7,57 (dd, 1H), 7,55 (d, 1H), 7,35 (d, 2H), 7,35 (m, 3H), 7,04 (d, 2H), 6,80 (dd, 1H), 6,53 (d, 1H), 6,22 (d, 1H), 3,97 (d, 2H), 3,88 (m, 2H), 3,35 (m, 2H), 3,18 (br m, 4H), 2,80 (s, 2H), 2,27 (br m, 4H), 2,18 (br m, 2H), 2,04 (m, 1H), 1,97 (s, 2H), 1,69 (m, 2H), 1,40 (m, 4H) 0,93 (s, 6H).

EJEMPLO 499

2-(1H-bencimidazol-4-iloxi)-N-({3-cloro-4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida

El compuesto del título se preparó utilizando EJEMPLO 496A en lugar de EJEMPLO 428D en EJEMPLO 428E. ^{1}H NMR (500MHz, piridin-d_5) δ 8,58 (s, 1H), 8,53 (d, 1H), 8,33 (dd, 1H), 7,96 (d, 1H), 7,54 (d, 1H), 7,43 (d, 2H), 7,26 (t, 1H), 7,20 (m, 2H), 7,07 (d, 2H), 7,04 (d, 1H), 6,72-6,68 (m, 2H), 4,17 (d, 2H), 3,89 (m, 2H), 3,83 (m, 2H), 3,03 (m, 4H), 2,76 (s, 2H), 2,26 (m, 2H), 2,14 (m, 4H), 2,03-1,95 (m, 6H), 1,38 (t, 2H), 0,94 (s, 6H).

EJEMPLO 500

2-(1H-bencimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[5-cloro-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil}benzamida

El compuesto del título se preparó utilizando EJEMPLO 387B en lugar de EJEMPLO 428D en EJEMPLO 428E. ^{1}H NMR (500MHz, piridin-d_5) δ 9,16 (d, 1H), 8,72 (d, 1H), 8,59 (s, 1H), 7,97 (d, 1H), 7,53 (d, 1H), 7,43 (d, 2H), 7,25 (t, 1H), 7,20 (m, 2H), 7,07 (d, 2H), 6,73-6,68 (m, 2H), 4,21 (d, 2H), 3,99 (dd, 2H), 3,33 (dt, 2H), 3,03 (m, 4H), 2,77 (s, 2H), 2,25 (m, 2H), 2,14 (m, 4H), 1,98 (m, 1H), 1,97 (s, 2H), 1,60 (d, 2H), 1,43 (m, 2H), 1,38 (t, 2H), 0,94 (s, 6H).

EJEMPLO 501

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-ciano-4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]fenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 501A

3-ciano-4-((4-fluorotetrahidro-2H-piran-4-il)metoxi)bencenosulfonamida

El compuesto del título se preparó utilizando (4-fluorotetrahidro-2H-piran-4-il)metanol en lugar de (tetrahidro-2H-piran-4-il)metanol y 3-ciano-4-fluorobencenosulfonamida en lugar de EJEMPLO 329A en EJEMPLO 329B.

EJEMPLO 501B

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-N-(3-ciano-4-((4-fluorotetrahidro-2H-piran-4-il)metoxi)fenilsulfonil)-2-(1-((2-(trimetilsilil)etoxi)metil)-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 501A en lugar de EJEMPLO 1F y EJEMPLO 435D en lugar de EJEMPLO 1E en EJEMPLO 1G.

EJEMPLO 501C

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-ciano-4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]fenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 501B en lugar de EJEMPLO 435E en EJEMPLO 435F. ^{1}H NMR (300 MHz, sulfóxido de dimetilo-d_6) δ 13,09 (s, 1H), 7,85 (m, 2H), 7,79 (s, 1H), 7,57 (d, 1H), 7,35 (d, 2H), 7,22 (m, 1H), 7,13 (m, 2H), 7,05 (d, 2H), 6,78 (dd, 1H), 6,50 (d, 1H), 6,17 (dd, 1H), 4,34 (d, 2H), 3,79 (m, 2H), 3,63 (m, 2H), 3,16 (m, 4H), 2,82 (m, 2H), 2,27 (m, 4H), 2,17 (m, 3H), 1,97 (m, 2H), 1,91 (m, 2H), 1,85 (m, 2H), 1,40 (t, 2H), 0,94 (s, 6H).

EJEMPLO 502

N-{[3-cloro-4-(1,4-dioxan-2-ilmetoxi)fenil]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 502A

4-((1,4-dioxan-2-il)metoxi)-3-clorobencenosulfonamida

El compuesto del título se preparó utilizando (1,4-dioxan-2-il)metanol en lugar de (tetrahidro-2H-piran-4-il)metanol y 3-cloro-4-fluorobencenosulfonamida en lugar de EJEMPLO 329A en EJEMPLO 329B.

EJEMPLO 502B

N-(4-((1,4-dioxan-2-il)metoxi)-3-clorofenilsulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-2-(1-((2-(trimetilsilil)etoxi)metil)-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 502A en lugar de EJEMPLO 1F y EJEMPLO 435D en lugar de EJEMPLO 1E en EJEMPLO 1G.

EJEMPLO 502C

N-{[3-cloro-4-(1,4-dioxan-2-ilmetoxi)fenil]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 502B en lugar de EJEMPLO 435E en EJEMPLO 435F. ^{1}H NMR (300 MHz, sulfóxido de dimetilo-d_6) δ 13,02 (s, 1H), 7,78 (m, 1H), 7,63 (m, 1H), 7,58 (m, 1H), 7,42 (m, 1H), 7,35 (d, 2H), 7,11 (d, 2H), 7,06 (d, 2H), 6,99 (m, 1H), 6,74 (m, 1H), 6,42 (m, 1H), 6,15 (m, 1H), 4,06 (m, 2H), 3,83 (m, 2H), 3,65 (m, 2H), 3,47 (m, 2H), 3,07 (m, 4H), 2,75 (m, 2H), 2,21 (m, 6H), 1,97 (m, 2H), 1,40 (t, 2H), 1,23 (m, 1H), 0,93 (s, 6H).

EJEMPLO 503

2-(1H-bencimidazol-4-iloxi)-N-[(5-cloro-6-{[(2S)-4-ciclopropilmorfolin-2-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida

EJEMPLO 503A

(S)-5-cloro-6-((4-ciclopropilmorfolin-2-il)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando EJEMPLO 423B en lugar de EJEMPLO 415B en EJEMPLO 432A.

EJEMPLO 503B

2-(1H-bencimidazol-4-iloxi)-N-[(5-cloro-6-{[(2S)-4-ciclopropilmorfolin-2-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida

El compuesto del título se preparó utilizando EJEMPLO 503A en lugar de EJEMPLO 428D en EJEMPLO 428E. ^{1}H NMR (400 MHz, piridin-d_5) δ 9,08 (d, 1H), 8,64 (m, 1H), 8,56 (s, 1H), 7,99 (d, 1H), 7,51 (d, 1H), 7,43 (d, 2H), 7,23 (d, 1H), 7,13 (m, 1H), 7,07 (d, 2H), 6,71 (m, 2H), 6,51 (m, 1H), 5,86 (m, 1H), 4,62 - 4,57 (m, 1H), 4,52 - 4,48 (m, 1H), 3,99 (m, 1 H), 3,84 (m, 1H), 3,57 (m, 1H), 3,04 (m, 5H), 2,77 (s, 2H), 2,69 (m, 1H), 2,40 - 2,32 (m, 2H), 2,29 - 2,23 (m, 2H), 2,15 (m, 4H), 1,97 (s, 2H), 1,59 (m, 1H), 1,39 (t, 2H), 0,94 (s, 6H), 0,48 - 0,36 (m, 4H).

EJEMPLO 504

N-[(5-cloro-6-{[(2S)-4-ciclopropilmorfolin-2-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 503A en lugar de EJEMPLO 1F y EJEMPLO 400E en lugar de EJEMPLO 26C en EJEMPLO 177. ^{1}H NMR (400 MHz, piridin-d_5) δ 8,86 (d, 1H), 8,38 (d, 2H), 8,14 (d, 1H), 7,47 (d, 2H), 7,34 (d, 1H), 7,13 - 7,10 (m, 3H), 6,88 - 6,85 (m, 2H), 6,49 (d, 1H), 5,41 (m, 2H), 4,62 - 4,57 (m, 1H), 4,51 - 4,47 (m, 1H), 3,98 (m, 1H), 3,84 (m, 1H), 3,57 (m, 1H), 3,16 (m, 4H), 3,02 (m, 1H), 2,83 (s, 2H), 2,69 (m, 1H), 2,38 - 2,27 (m, 4H), 2,24 (m, 4H), 1,99 (s, 2H), 1,58 (m, 1H), 1,41 (t, 2H), 0,96 (m, 6H), 0,48 - 0,36 (m, 4H).

EJEMPLO 505

2-{[(4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzoil]sulfamoil}-2-nitrofenil)amino]metil}morfolina-4-carboxilato de metilo

EJEMPLO 505A

2-((2-nitro-4-sulfamoilfenilamino)metil)morfolina-4-carboxilato de metilo

El compuesto del título se preparó utilizando cloroformato de metilo en lugar de cloruro de acetilo en EJEMPLO 457A.

EJEMPLO 505B

2-{[(4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzoil]sulfamoil}-2-nitrofenil)amino]metil}morfolina-4-carboxilato de metilo

El compuesto del título se preparó utilizando EJEMPLO 400E en lugar de EJEMPLO 26C y EJEMPLO 505A en lugar de EJEMPLO 1F en EJEMPLO 177. ^{1}H NMR (500MHz, piridin-d_5) δ 14,58 (bs, 1H), 9,05 (d, 1H), 8,82 (t, 1H), 8,36 (s, 1H), 8,18 (d, 1H), 8,12 (d, 1H), 7,45 (d, 2H), 7,34 (d, 1H), 7,15 (t, 1H), 7,10 (d, 2H), 6,87-6,82 (m, 3H), 6,53 (d, 1H), 4,29, 4,03 (bd, 1H), 3,86 (m, 1H), 3,73 (m, 2H), 3,71 (s, 3H), 3,54-3,40 (m, 3H), 3,14 (m, 4H), 2,96 (dt, 1H), 2,85 (m, 1H), 2,82 (s, 2H), 2,30 (m, 2H), 2,22 (m, 4H), 1,99 (s, 2H), 1,41 (t, 2H), 0,96 (s, 6H).

EJEMPLO 506

2-{[(4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzoil]sulfamoil}-2-nitrofenil)amino]metil}-N-etil-N-metilmorfolina-4-carboxamida

EJEMPLO 506A

N-etil-N-metil-2-((2-nitro-4-sulfamoilfenilamino)metil)morfolina-4-carboxamida

El compuesto del título se preparó utilizando cloruro de *N*-etil-*N*-metil-carbamoilo en lugar de cloruro de acetilo en EJEMPLO 457A.

EJEMPLO 506B

2-{[(4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzoil]sulfamoil}-2-nitrofenil)amino]metil}-N-etil-N-metilmorfolina-4-carboxamida

El compuesto del título se preparó utilizando EJEMPLO 400E en lugar de EJEMPLO 26C y EJEMPLO 506A en lugar de EJEMPLO 1F en EJEMPLO 177. ^{1}H NMR (500MHz, piridin-d_5) δ 14,58 (bs, 1H), 9,07 (d, 1H), 8,82 (t, 1H), 8,37 (s, 1H), 8,13 (m, 2H), 7,45 (d, 2H), 7,34 (d, 1H), 7,15 (t, 1H), 7,11 (d, 2H), 6,87 (d, 1H), 6,83-6,79 (m, 2H), 6,54 (d, 1H), 3,92-3,85 (m, 2H), 3,75 (m, 1H), 3,62 (dt, 1H), 3,50 (m, 1H), 3,40 (m, 2H), 3,21 (q, 2H), 3,14 (m, 4H), 3,00 (dt, 1H), 2,82 (s, 2H), 2,76 (s, 3H), 2,30 (m, 2H), 2,23 (m, 4H), 1,99 (s, 2H), 1,41 (t, 2H), 1,06 (t, 3H), 0,96 (s, 6H).

EJEMPLO 507

2-{[(4-{[2-(1H-bencimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzoil]sulfamoil}-2-nitrofenil)amino]metil}-N-etil-N-metilmorfolina-4-carboxamida

El compuesto del título se preparó utilizando EJEMPLO 506A en lugar de EJEMPLO 428D en EJEMPLO 428E. ^{1}H NMR (500MHz, piridin-d_5) δ 9,25 (d, 1H), 8,86 (t, 1H), 8,56 (s, 1H), 8,35 (dd, 1H), 8,01 (d, 1H), 7,52 (d, 1H), 7,43 (d, 2H), 7,25 (m, 1H), 7,13 (d, 1H), 7,07 (d, 2H), 6,94 (d, 1H), 6,73-6,68 (m, 2H), 3,96-3,85 (m, 2H), 3,87 (m, 1H), 3,64 (dt, 1H), 3,53 (m, 1H), 3,48-3,41 (m, 2H), 3,21 (q, 2H), 3,03 (m, 5H), 2,92 (dd, 1H), 2,90 (d, 1H), 2,76 (s, 5H), 2,25 (m, 2H), 2,14 (m, 4H), 1,97 (s, 2H), 1,38 (t, 2H), 1,06 (t, 3H), 0,94 (s, 6H).

EJEMPLO 508

N-({5-cloro-6-[(trans-4-etil-4-hidroxiciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 508A

1-etil-4-(hidroximetil)ciclohexanol

4-(Hidroximetil)ciclohexanona (1,22 g) en tetrahidrofurano (20 mL) se trató con bromuro de etilmagnesio 1M en tetrahidrofurano (28,6 mL) a 0°C. La reacción se calentó a temperatura ambiente durante 4 horas y se detuvo con metanol (2 mL) y agua (2 mL). La mezcla resultante se concentró y el residuo se suspendió en acetato de etilo. Los precipitados se retiraron por filtración y el material filtrado se concentró y se purificó mediante cromatografía flash, se eluyó con 0-100% acetato de etilo en hexano para dar el compuesto del título.

EJEMPLO 508B

5-cloro-6-((trans-4-etil-4-hidroxiciclohexil)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó como se describe en EJEMPLO 493B reemplazando EJEMPLO 493A con EJEMPLO 508A.

EJEMPLO 508C

5-cloro-6-((cis-4-etil-4-hidroxiciclohexil)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó como se describe en EJEMPLO 493B reemplazando EJEMPLO 493A con EJEMPLO 508A.

EJEMPLO 508D

N-({5-cloro-6-[(trans-4-etil-4-hidroxiciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó como se describe en EJEMPLO 177 reemplazando EJEMPLO 26C y EJEMPLO 1F con EJEMPLO 400E y EJEMPLO 508B, respectivamente. ^{1}H NMR (400 MHz, sulfóxido de dimetilo-d_6) δ 13,20 (s, 1H), 8,37 (d, 1H), 7,95 (d, 1H), 7,91 (s, 1H), 7,70 (d, 1H), 7,47 (d, 2H), 7,14 - 7,21 (m, 4H), 6,89 (dd, 1H), 6,63 (d, 1H), 6,25 (dd, 1H), 4,34 (d, 2H), 4,11 (s, 1H), 3,24 - 3,33 (m, 4H), 3,02 (d, 2H), 2,46 (s, 4H), 2,28 (s, 2H), 2,09 (s, 2H), 1,77 - 1,96 (m, 3H), 1,61 - 1,76 (m, 3H), 1,48 - 1,60 (m, 4H), 1,21 - 1,47 (m, 5H), 1,04 (s, 6H), 0,91 (t, 3H).

EJEMPLO 509

N-({5-cloro-6-[(cis-4-etil-4-hidroxiciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó como se describe en EJEMPLO 177 reemplazando EJEMPLO 26C y EJEMPLO 1F con EJEMPLO 400E y EJEMPLO 508C, respectivamente. ^{1}H NMR (400 MHz, sulfóxido de dimetilo-d_6) δ 13,10 (s, 1H), 8,26 (d, 1H), 7,84 (d, 1H), 7,80 (s, 1H), 7,59 (d, 1H), 7,36 (d, 2H), 7,03 - 7,11 (m, 4H), 6,79 (dd, 1H), 6,53 (s, 1H), 6,12 - 6,15 (m, 1H), 4,20 (d, 2H), 3,77 (s, 1H), 3,11 - 3,24 (m, 4H), 2,88 (s, 2H), 2,24 - 2,41 (m, 3H), 2,18 (s, 2H), 1,98 (s, 2H), 1,71 (s, 1H), 1,55 (d, 5H), 1,18 - 1,49 (m, 9H), 0,94 (s, 6H), 0,83 (t, 3H).

EJEMPLO 510

5-cloro-N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 510A

2-(1H-indazol-4-iloxi)-5-cloro-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoato de metilo

Una mezcla de EJEMPLO 400D (0,5 g) y 1-cloropirrolidin-2,5-diona (0,126 g) en acetonitrilo (10 mL) se agitó a temperatura ambiente por 4 horas. El solvente se eliminó, y el residuo se purificó mediante cromatografía flash de columna sobre gel de sílice para dar el compuesto del título.

EJEMPLO 510B

ácido 2-(1H-indazol-4-iloxi)-5-cloro-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoico

El compuesto del título se preparó utilizando EJEMPLO 435C en lugar de EJEMPLO 1D en EJEMPLO 1E.

EJEMPLO 510C

5-cloro-N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 404A en lugar de EJEMPLO 1F y EJEMPLO 510B en lugar de EJEMPLO 26C en EJEMPLO 177. ^{1}H NMR (500MHz, sulfóxido de dimetilo-d_6) δ 13,22 (s, 1H), 8,38 (d, 1H), 8,03 (d, 1H), 7,54 (d, 2H), 7,19-7,26 (m, 4H), 6,83 (s, 1H), 6,34 (d, 1H), 4,60 (d, 2H), 3,88-3,93 (m, 2H), 3,70-3,73 (m, 2H), 3,15 (br s, 4H), 2,86 (br s, 2H), 2,30 (bs, 2H), 2,13 (s, 2H), 1,94-2,05 (m, 4H), 1,55 (t, 2H), 1,06 (s, 6H).

EJEMPLO 511

5-cloro-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4-fluorotetrahidro-2H-piran-4-il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 409D en lugar de EJEMPLO 1F y EJEMPLO 510B en lugar de EJEMPLO 26C en EJEMPLO 177. ^{1}H NMR (500MHz, sulfóxido de dimetilo-d_6) δ 13,07 (s, 1H), 8,46 (s, 1H), 8,33 (s, 1H), 8,03 (d, 1H), 7,75 (s, 1H), 7,68 (s, 1H), 7,60-7,62 (m, 1H), 7,38 (d, 2H), 7,06-7,11 (m, 5H), 6,69 (d, 1H), 6,20 (d,

1H), 3,67-3,77 (m, 4H), 3,50-3,55 (m, 2H), 2,89 (br s, 6H), 2,14 (bs, 2H), 1,97 (s, 2H), 1,76-1,82 (m, 4H), 1,39 (t, 2H), 0,92 (s, 6H).

EJEMPLO 512

N-({5-cloro-6-[(cis-1-fluoro-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 512A

Una solución en sulfóxido de dimetilo (40 mL) de 1,4-dioxaespiro[4,5]decan-8-ona (6,25 g) se agregó por goteo a una solución de yoduro de trifenilsulfoxonio (8,8 g) y t-butóxido de potasio (4,5 g) en sulfóxido de dimetilo (50 mL). La mezcla se agitó a temperatura ambiente durante la noche. La mezcla luego se vertió sobre hielo-agua y se extrajo con éter etílico (3x 200 mL). Los extractos orgánicos combinados se lavaron con agua y salmuera, se secó sobre Na_2SO_4. El filtrado y la evaporación del solvente dio el producto crudo.

EJEMPLO 512B

(8-fluoro-1,4-dioxaespiro[4,5]decan-8-il)metanol

Una solución de fluorhidrato de piridina (4 g) en diclorometano (10 mL) se agregó por goteo a una solución de EJEMPLO 512A (1,7 g) en diclorometano (20 mL) en una botella de polietileno a 0°C. La mezcla se agitó a temperatura ambiente durante la noche. TLC mostró que la reacción se había completado. La mezcla se vertió cuidadosamente sobre una mezcla de hielo-agua y Na_2CO_3 y se extrajo con acetato de etilo (2x 300mL). Luego de lavar con agua y salmuera, la capa orgánica se secó sobre Na_2SO_4. El filtrado y la evaporación del solvente dio el producto crudo.

EJEMPLO 512C

5-cloro-6-((8-fluoro-1,4-dioxaespiro[4,5]decan-8-il)metoxi)piridin-3-sulfonamida

A una solución de EJEMPLO 512B (500 mg) en N,N-dimetilformamida (5 mL) se agregó NaH (65% en aceite mineral, 252 mg) a temperatura ambiente. La mezcla se agitó por 30 minutos, y luego se agregó 5,6-dicloropiridin-3-sulfonamida (0,6 g). La mezcla se agitó a temperatura ambiente durante la noche. La mezcla se vertió sobre NH_4Cl acuoso y se extrajo

con acetato de etilo (3x 100 mL). Las capas orgánicas combinadas se lavaron con agua, salmuera y se secó sobre Na_2SO_4. Luego de la filtración y evaporación del solvente, el residuo se cargó en un cartucho de gel de sílice y se eluyó con acetato de etilo al 30% en hexano para dar el producto puro.

EJEMPLO 512D

5-cloro-6-((1-fluoro-4-oxociclohexil)metoxi)piridin-3-sulfonamida

A una solución de EJEMPLO 512C (1,6 g) y p-toluensulfonato de piridinio (1,2 g) en acetona (10 mL) se agregó agua (2 mL) y la mezcla se agitó en un reactor de microondas CEM Discover a 100^{oC} por 10 minutos. La mezcla se diluyó con diclorometano (300 mL) y se lavó con $NaHCO_3$ acuoso, agua, salmuera y se secó sobre Na_2SO_4. El filtrado y la evaporación del solvente dio el producto crudo.

EJEMPLO 512E

5-cloro-6-((cis-1-fluoro-4-hidroxi-4-metilciclohexil)metoxi)piridin-3-sulfonamida

A una solución de EJEMPLO 512D (1,2 g) en tetrahidrofurano (30 mL) se agregó por goteo una solución de bromuro de metilmagnesio (5 mL, 3,0M en éter) a 0°C. Luego de la adición, la mezcla de la reacción solidificó. Se agregó más tetrahidrofurano (10 mL) a la mezcla y la agitación se continuó por 1 hora. La mezcla se vertió sobre NH_4Cl acuoso y se extrajo con acetato de etilo (3x 300mL). Las capas orgánicas combinadas se lavaron con agua, salmuera y se secó sobre Na_2SO_4. La mezcla se filtró y el solvente se evaporó, y el residuo crudo se disolvió en sulfóxido de dimetilo/metanol (20 mL, 1:1) y se cargó sobre HPLC (Gilson, C18 (100A) 250 x 121,2 mm (10 micron), condiciones: 20% acetonitrilo a 45% acetonitrilo en 40 minutos) para separar los dos isómeros, de los cuales EJEMPLO 512E es el isómero cis.

EJEMPLO 512F

N-({5-cloro-6-[(cis-1-fluoro-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 512E en lugar de EJEMPLO 493C en EJEMPLO 493D. ^{1}H NMR (300 MHz, sulfóxido de dimetilo-d_6) δ 13,04 (s, 1H),

8,26 (d, 1H), 7,87 (d, 1H), 7,78 (s, 1H), 7,61 (d, 1H), 7,36 (d, 2H), 7,06 (m, 5H), 6,77 (dd, 1H), 6,49 (s, 1H), 4,49 (d, 2H), 4,35 (s, 1H), 3,16 (m, 5H), 2,88 (m, 2H), 2,26 (m, 4H), 1,95 (m, 4H), 1,68 (m, 4H), 1,43 (m, 4H), 1,12 (s, 3H), 0,94 (s, 6H).

EJEMPLO 513

N-({5-cloro-6-[(trans-1-fluoro-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 513A

5-cloro-6-((trans-1-fluoro-4-hidroxi-4-metilciclohexil)metoxi)piridin-3-sulfonamida

Este compuesto también se aisló como un producto de EJEMPLO 512E.

EJEMPLO 513B

N-({5-cloro-6-[(trans-1-fluoro-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 400E en lugar de EJEMPLO 1E y EJEMPLO 513A en lugar de EJEMPLO 1F en EJEMPLO 1G. ^{1}H NMR (300 MHz, sulfóxido de dimetilo-d_6) δ 13,06 (s, 1H), 8,24 (d, 1H), 7,87 (d, 1H), 7,79 (s, 1H), 7,60 (d, 1H), 7,36 (d, 2H), 7,06 (m, 5H), 6,78 (dd, 1H), 6,51 (d, 1H), 6,13 (dd, 1H), 4,45 (d, 2H), 4,15 (s, 1H), 3,18 (m, 4H), 2,86 (m, 2H), 2,27 (m, 4H), 1,85 (m, 6H), 1,48 (m, 7H), 1,15 (s, 3H), 0,94 (s, 6H).

EJEMPLO 514

2-(1H-benzotriazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4-fluorotetrahidro-2H-piran-4-il)metil]amino}-3-nitrofenil)sulfonil]benzamida

EJEMPLO 514A

4-(tert-butildimetilsililoxi)-1H-benzo[d][1,2,3]triazol

Se trató 1H-benzo[d][1,2,3]triazol-4-ol (2,0 g) en tetrahidrofurano (30 mL) con hidruro de sodio al 60% (0,622 g). Luego de 10 minutos, se agregó tert-

butilclorodimetilsilano (2,454 g). La solución se agitó por 16 horas. El solvente se eliminó, y el residuo se purificó mediante cromatografía flash de columna sobre gel de sílice usando acetato de etilo al 10-50% en hexanos como eluyente para dar el compuesto del título.

EJEMPLO 514B

4-(tert-butildimetilsililoxi)-1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d][1,2,3]triazol

Se trató EJEMPLO 514A (1,5 g) en tetrahidrofurano (30 mL) con hidruro de sodio al 60% (0,253 g). Luego de 10 minutos, se agregó (2-(clorometoxi)etil)trimetilsilano (1,1 g). La solución se agitó por 2 horas. La mezcla de la reacción se particionó entre agua y acetato de etilo. La capa orgánica se separó, y la capa acuosa se extrajo con acetato de etilo adicional. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre $MgSO_4$, se filtró, y se concentró. El residuo se purificó mediante cromatografía flash sobre gel de sílice usando acetato de etilo al 5% en hexanos como eluyente para dar el producto deseado.

EJEMPLO 514C

1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d][1,2,3]triazol-4-ol

Una mezcla de EJEMPLO 514B (1,32 g) y 1,0 N fluoruro de tetrabutilamonio (10,4 mL) en tetrahidrofurano (15 mL) se agitó por 2 horas. El solvente se eliminó, y el residuo se particionó entre agua y acetato de etilo. La capa orgánica se separó, y la capa acuosa se extrajo con acetato de etilo adicional. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre $MgSO_4$, se filtró, y se concentró. El residuo se purificó mediante cromatografía flash sobre gel de sílice usando acetato de etilo al 10% en hexanos como eluyente para dar el compuesto del título.

EJEMPLO 514D

4-fluoro-2-(1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d][1,2,3]triazol-4-iloxi)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 514C en lugar de 1H-indazol-5-ol y 2,4-difluorobenzoato de metilo en lugar de 2,4-difluorobenzoato de etilo en EJEMPLO 20A.

EJEMPLO 514E

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-2-(1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d][1,2,3]triazol-4-iloxi)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 514D en lugar de EJEMPLO 20A en EJEMPLO 20D.

EJEMPLO 514F

ácido 4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-2-(1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d][1,2,3]triazol-4-iloxi)benzoico

El compuesto del título se preparó utilizando EJEMPLO 514E en lugar de EJEMPLO 1D en EJEMPLO 1E.

EJEMPLO 514G

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-N-(4-((4-fluorotetrahidro-2H-piran-4-il)metilamino)-3-nitrofenilsulfonil)-2-(1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d][1,2,3]triazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 514F en lugar de EJEMPLO 1E y EJEMPLO 409D en lugar de EJEMPLO 1F en EJEMPLO 1G.

EJEMPLO 514H

2-(1H-benzotriazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4-fluorotetrahidro-2H-piran-4-il)metil]amino}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 514G en lugar de EJEMPLO 498D en EJEMPLO 498E. ^{1}H NMR (500MHz, sulfóxido de dimetilo-d_6) δ 8,58 (s, 1H), 8,33 (d, 1H), 7,62 (d, 1H), 7,56 (d, 1H), 7,34-7,38 (m, 3H), 7,04-7,10 (m, 4H), 6,80 (dd, 1H), 6,53 (s, 1H), 6,41 (d, 1H), 3,70-3,80 (m, 3H), 3,52-3,58 (m, 2H), 3,17 (br s, 4H), 2,81 (br s, 6H), 2,17-2,32 (m, 6H), 1,97 (s, 2H), 1,78-1,87 (m, 4H), 1,40 (t, 2H), 0,94 (s, 6H).

EJEMPLO 515

2-(1H-benzotriazol-4-iloxi)-N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida

EJEMPLO 515A

N-(5-cloro-6-((4-fluorotetrahidro-2H-piran-4-il)metoxi)piridin-3-ilsulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-2-(1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d][1,2,3]triazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 514F en lugar de EJEMPLO 1E y EJEMPLO 404A en lugar de EJEMPLO 1F en EJEMPLO 1G.

EJEMPLO 515B

2-(1H-benzotriazol-4-iloxi)-N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida

El compuesto del título se preparó utilizando EJEMPLO 515A en lugar de EJEMPLO 498D en EJEMPLO 498E. ^{1}H NMR (500MHz, sulfóxido de dimetilo-d_6) δ 8,21 (s, 1H), 7,86 (d, 1H), 7,65 (d, 1H), 7,36-7,38 (m, 3H), 7,06-7,10 (m, 3H), 6,79 (dd, 1H), 6,56 (s, 1H), 6,30 (s, 1H), 4,48 (d, 2H), 3,77-3,81 (m, 3H), 3,59-3,64 (m, 3H), 3,23 (br s, 4H), 2,19 (s, 2H), 1,87-1,99 (m, 6H), 1,42 (t, 2H), 0,94 (s, 6H).

EJEMPLO 516

2-(1H-bencimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-cloro-4-(tetrahidro-2H-piran-4-ilmetoxi)fenil]sulfonil}benzamida

El compuesto del título se preparó utilizando EJEMPLO 498A en lugar de EJEMPLO 428D y en EJEMPLO 428E. ^{1}H NMR (500 MHz, piridin-d_5) δ 9,27 (d, 1H), 8,59 (s, 1H), 8,55 (d, 1H), 8,40 (dd, 1H), 7,99 (d, 1H), 7,54 (m, 1H), 7,43 (d, 2H), 7,25 (m, 1H), 7,16 (m, 1H), 7,07 (d, 2H), 6,86 (d, 1H), 6,69 (m, 2H), 5,73 (m, 2H), 4,15 (m, 1H), 3,90 (s, 2H), 3,03 (m, 4H), 2,96 - 287. (m, 2H), 2,81 - 2,76 (m, 3H), 2,58 (m, 1H), 2,32 - 2,23 (m, 3H), 2,14 (m, 4H), 1,97 (s, 2H), 1,73 (m, 1H), 1,38 (t, 2H), 0,94 (s, 6H).

EJEMPLO 517

N-[(3-cloro-4-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}fenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 517A

4-fluoro-1-(oxetan-3-il)piperidin-4-carboxilato de etilo

A 4-fluoropiperidin-1,4-dicarboxilato de 1-tert-butilo 4-etilo (1,0 g) se agregó HCl (4,0M en dioxano, 4,5 mL). Luego de 1 hora la reacción se concentró y se secó bajo alto vacío. El sólido resultante se disolvió en diclorometano (5 mL) y se trató con triacetoxiborhidruro de sodio (1,2 g) y oxetan-3-ona (0,26 g) y se agitó durante la noche. La reacción se detuvo con solución acuosa saturada de $NaHCO_3$ (20 mL) y se extrajo con diclorometano (2 x 25 mL). La capa orgánica se secó sobre sulfato de magnesio, se filtró, y se concentró. La cromatografía sobre gel de sílice (Reveleris 80 g) eluyendo con un gradiente de metanol entre 0,5% y 3,75%/diclorometano a lo largo de 40 minutos (velocidad de flujo = 30 mL/minutos) dio el compuesto del título.

EJEMPLO 517B

(4-fluoro-1-(oxetan-3-il)piperidin-4-il)metanol

A una solución de EJEMPLO 517A (0,59 g) en tetrahidrofurano (5 mL) se agregó hidruro de litio y aluminio (1,8 mL) a 0°C. La reacción se retiró del baño de hielo y se dejó calentar a temperatura ambiente. La reacción se detuvo mediante la adición por goteo de 0,6 mL de agua seguido por 0,2 ml de NaOH 2N acuoso. La reacción se filtró a través de tierra diatomea, se enjuagó con acetato de etilo (50 mL) y se concentró. La cromatografía sobre gel de sílice (Reveleris 40 g) eluyendo con un gradiente de metanol entre 0,75% y 7,5%/diclorometano a lo largo de 30 minutos (velocidad de flujo = 40 ml/minutos) dio el compuesto del título.

EJEMPLO 517C

3-cloro-N,N-bis(2,4-dimetoxibencil)-4-fluorobencenosulfonamida

A una solución de bis(2,4-dimetoxibencil)amina (12 g) y cloruro de 3-cloro-4-fluorobencen-1-sulfonilo (8,66 g) en diclorometano (120 mL) se agregó N,N-diisopropiletilamina (13,5 mL) y una cantidad catalítica de 4-dimetilaminopiridina. La mezcla se agitó a temperatura ambiente durante la noche. La mezcla se diluyó con acetato de etilo (600 mL) y se lavó con HCl acuoso al 5%, agua y salmuera. Luego de secar sobre Na_2SO_4, la mezcla se filtró y el material filtrado se concentró bajo vacío para dar producto crudo el cual se cargó en una columna de gel de sílice de 400 g y se eluyó con acetato de etilo al 30% en hexano para dar el compuesto del título.

EJEMPLO 517D

3-cloro-N,N-bis(2,4-dimetoxibencil)-4-((4-fluoro-1-(oxetan-3-il)piperidin-4-il)metoxi)bencenosulfonamida

A una solución de EJEMPLO 517B (0,100 g) en tetrahidrofurano (3 mL) se agregó hidruro de sodio (0,042 g). Luego de agitar por 15 minutos, se agregó EJEMPLO 517C (0,270 g) en una porción y la reacción se agitó a temperatura ambiente por 16 horas luego se calentó a 50°C por 2 horas. La reacción se enfrió y se detuvo con agua (20 mL) y se extrajo con diclorometano (2 x 30 mL). Los orgánicos se combinaron, se lavó con salmuera (25 mL), se secó sobre sulfato de magnesio, se filtró y se concentró. El aceite resultante se cargó sobre gel de sílice (Reveleris 40 g) y se eluyó usando un gradiente de metanol al 0,5%-5%/diclorometano a lo largo de 30 minutos (velocidad de flujo = 40 ml/minuto) para dar el compuesto del título.

EJEMPLO 517E

3-cloro-4-((4-fluoro-1-(oxetan-3-il)piperidin-4-il)metoxi)bencenosulfonamida

A una solución de EJEMPLO 517D (0,258 g) en diclorometano (3 mL) se agregó ácido trifluoroacético (2 mL) por goteo. La reacción se agitó por 1 hora luego se detuvo mediante la adición de solución saturada de $NaHCO_3$ (20 mL). La reacción se extrajo con diclorometano (2 x 50 mL), la capa de diclorometano se concentró, se agregó acetato de etilo (20 mL) y el sólido resultante se filtró. La capa orgánica se diluyó a 50 ml, se lavó con salmuera (25 mL), se secó sobre sulfato de magnesio, se filtró y se concentró. El aceite resultante se trató con diclorometano y se concentró, y el sólido se trituró con acetato de etilo y se filtró para dar el compuesto del título.

EJEMPLO 517F

El compuesto del título se preparó utilizando EJEMPLO 498C en lugar de EJEMPLO 1E y EJEMPLO 517E en lugar de EJEMPLO 1F en EJEMPLO 1G.

EJEMPLO 517G

N-[(3-cloro-4-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}fenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 517F en lugar de EJEMPLO 497B en EJEMPLO 497C. ^{1}H NMR (300 MHz, sulfóxido de dimetilo-d_6) δ 13,14 (d, 1H), 11,61 – 11,29 (m, 1H), 7,84 (d, 1H), 7,67 (d, 1H), 7,61 – 7,56 (m, 1H), 7,54 (d, 1H), 7,38 –

7,31 (m, 2H), 7,21 – 7,09 (m, 3H), 7,08 – 7,01 (m, 2H), 6,87 – 6,72 (m, 1H), 6,52 (d, 1H), 6,23 (dd, 1H), 4,55 (t, 2H), 4,45 (t, 2H), 4,24 (d, 2H), 3,55 – 3,41 (m, 1H), 3,16 (s, 4H), 2,80 (s, 2H), 2,69 – 2,54 (m, 2H), 2,38 – 1,67 (m, 14H), 1,40 (s, 2H), 0,93 (s, 6H).

EJEMPLO 518

N-({5-cloro-6-[(cis-1-fluoro-4-hidroxiciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 518A

5-cloro-6-((cis-1-fluoro-4-hidroxiciclohexil)metoxi)piridin-3-sulfonamida

A una solución de EJEMPLO 512D (336 mg) en tetrahidrofurano (10 mL) se agregó $NaBH_4$ (75 mg). La mezcla se agitó a temperatura ambiente por 45 minutos. La mezcla se diluyó con acetato de etilo (300 mL) y se lavó con NaOH 2N acuoso, agua, y salmuera. Luego de secar sobre Na_2SO_4, la mezcla se filtró, y el solvente se evaporó para dar el producto crudo.

EJEMPLO 518B

N-({5-cloro-6-[(cis-1-fluoro-4-hidroxiciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 518A en lugar de EJEMPLO 493C en EJEMPLO 493D. ^{1}H NMR (300 MHz, sulfóxido de dimetilo-d_6) δ 12,94 (s, 1H), 8,17 (d, 1H), 7,82 (d, 1H), 7,71 (s, 1H), 7,66 (d, 1H), 7,35 (d, 2H), 7,04 (m, 5H), 6,71 (dd, 1H), 6,40 (d, 1H), 6,09 (m, 1H), 4,61 (d, 1H), 4,38 (d, 2H), 3,47 (m, 1H), 3,17 (d, 1H), 3,06 (m, 4H), 2,74 (m, 2H), 2,24 (m, 5H), 1,99 (m, 5H), 1,56 (m, 7H), 0,92 (m, 6H)

EJEMPLO 519

2-(1H-benzotriazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]-3-nitrofenil}sulfonil)benzamida

EJEMPLO 519A

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-N-(4-((4-fluorotetrahidro-2H-piran-4-il)metoxi)-3-nitrofenilsulfonil)-2-(1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d][1,2,3]triazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 514F en lugar de EJEMPLO 1E y EJEMPLO 306D en lugar de EJEMPLO 1F en EJEMPLO 1G.

EJEMPLO519B

2-(1H-benzotriazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]-3-nitrofenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 519A en lugar de EJEMPLO 498D en EJEMPLO 498E. ^{1}H NMR (500MHz, sulfóxido de dimetilo-d_6) δ 8,04 (d, 1H), 7,73 (d, 1H), 7,65 (d, 1H), 7,35-7,38 (m, 3H), 7,18-7,19 (m, 1H), 7,05-7,09 (m, 3H), 6,78 (dd, 1H), 6,52 (s, 1H), 6,32 (s, 1H), 4,34 (d, 2H), 3,78-3,82 (m, 2H), 3,59-3,64 (m, 2H), 3,23 (br s, 4H), 2,83 (br s, 2H), 2,18-2,30 (m, 6H), 1,82-1,98 (m, 6H), 1,41 (t, 2H), 0,94 (s, 6H).

EJEMPLO 520

N-[(5-cloro-6-{[(1R,2R,4R,5R)-5-hidroxi-5-metilbiciclo[2,2,1]hept-2-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 520A

(1R,4S)-espiro[biciclo[2,2,1]heptan-2,2'-[1,3]dioxolan]-5-carboxilato de metilo

Una mezcla de 1,4-dioxaespiro[4,4]non-6-eno (5 g), acrilato de metilo (10,24 g), e hidroquinona (0,13 g) se calentó en un autoclave a 100 °C en acetonitrilo (12 mL) por tres días. Luego de enfriar, el solvente se eliminó, y el residuo se purificó mediante cromatografía flash sobre gel de sílice eluyendo con 4:1 hexano/acetato de etilo para dar el compuesto del título como una mezcla de dos 5-isómeros.

EJEMPLO 520B

(1R,4S)-espiro[biciclo[2,2,1]heptan-2,2'-[1,3]dioxolan]-5-ilmetanol

Se enfrió EJEMPLO 520A (1,0 g) en tetrahidrofurano a 0 ºC. A esta solución se agregó hidruro de litio y aluminio 1,0 N (2,8 mL) por goteo. La mezcla de la reacción se

agitó por 2 horas. Se agregó agua (0,4 mL) seguido por NaOH acuoso 2 N (0,2 mL). El sólido se retiró por filtración, y el material filtrado se concentró. Se agregó tolueno, y destiló para eliminar cantidades residuales de agua. El compuesto del título se usó para la siguiente reacción sin purificación adicional.

EJEMPLO 520C

5-cloro-6-(((1S,2R,4R)-5-oxobiciclo[2,2,1]heptan-2-il)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando EJEMPLO 520B en lugar de (tetrahidro-2H-piran-4-il)metanol y EJEMPLO 387A en lugar de EJEMPLO 329A en EJEMPLO 329B. Los dos isómeros se aislaron mediante HPLC de fase inversa preparativa. Las fracciones deseadas se recogieron, y los solventes se eliminaron bajo vacío reducido a 60°C. Durante este proceso, se formó una gran cantidad de sólido. Luego se particionó entre agua y acetato de etilo. La capa orgánica se separó, y la capa acuosa se extrajo con acetato de etilo adicional. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre $MgSO_4$, se filtró y se concentró para dar la cetona deseada.

EJEMPLO 520D

5-cloro-6-(((1S,2R,4R,5R)-5-hidroxi-5-metilbiciclo[2,2,1]heptan-2-il)metoxi)piridin-3-sulfonamida

Se trató EJEMPLO 520C (0,44 g) en tetrahidrofurano (15 mL) con bromuro de metilmagnesio 3,0 M (5,3 mL) a 0 ºC. La mezcla se agitó por 16 horas. La mezcla de la reacción luego se particionó entre acetato de etilo y HCl acuoso 0,05 N (20 mL). La capa orgánica se separó, y la capa acuosa se extrajo con acetato de etilo adicional tres veces. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre $MgSO_4$, se filtró, y se concentró. El residuo se purificó mediante cromatografía flash de columna sobre gel de sílice usando acetato de etilo al 10-50% en hexanos como eluyente para dar el compuesto del título.

EJEMPLO 520E

N-[(5-cloro-6-{[(1R,2R,4R,5R)-5-hidroxi-5-metilbiciclo[2,2,1]hept-2-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 400E en lugar de EJEMPLO 1E y EJEMPLO 520D en lugar de EJEMPLO 1F en EJEMPLO 1G. ^{1}H NMR (500MHz, sulfóxido de dimetilo-d_6) δ 13,10 (s, 1H), 8,28 (d, 1H), 7,84 (d, 1H), 7,82 (s, 1H),

7,59 (d, 1H), 7,36 (d, 2H), 7,04-7,11 (m, 4H), 6,80 (dd, 1H), 6,54 (d, 1H), 6,14 (d, 1H), 4,41-4,46 (m, 2H), 4,35 (s, 1H), 3,20 (br s, 4H), 2,93 (br s, 2H), 2,31-2,37 (m, 4H), 2,17-2,02 (m, 4H), 1,98-1,99 (m, 2H), 1,89 (d, 1H), 1,68-1,71 (m, 1H), 1,56 (d, 1H), 1,31-1,48 (m, 7H), 1,20 (s, 6H), 0,94 (s, 6H).

EJEMPLO 521

N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 521A

5,5-difluoro-2-oxociclohexanocarboxilato de etilo

A una solución de 4,4-difluoroheptandioato de dietilo (4,3 g) en tolueno (50 mL) se agregó 2-metilpropan-2-olato de potasio (2,87 g) y la reacción se agitó durante la noche a temperatura ambiente. La reacción se detuvo con HCl acuoso 1N (100 mL) y se extrajo con éter dietílico (150 mL). La capa de éter se lavó con salmuera (50 mL), se secó sobre sulfato de magnesio, se filtró, y se concentró. La cromatografía sobre gel de sílice (Reveleris 40 g) eluyendo con un gradiente de acetato de etilo entre 1% y 5%/hexanos dio el compuesto del título.

EJEMPLO 521B

5,5-difluoro-2-(trifluorometilsulfoniloxi)ciclohex-1-encarboxilato de etilo

A una solución de EJEMPLO 521A (2,37 g) en diclorometano (40 mL) a 0°C se agregó N,N-diisopropiletilamina (5,02 mL) seguido por anhídrido trifluorometansulfónico (2,33 mL) y la reacción se dejó calentar lentamente a temperatura ambiente. Luego de agitar durante la noche la reacción se detuvo con 10 ml de agua luego HCl acuoso 1N (100 mL). La reacción se extrajo con diclorometano (3 x 75 mL), los orgánicos combinados se lavaron con salmuera (50 mL) y se concentró. La cromatografía sobre gel de sílice (Reveleris 40 g) eluyendo con un gradiente de acetato de etilo entre 1% y 25%/hexanos dio el compuesto del título.

EJEMPLO 521C

2-(4-clorofenil)-5,5-difluorociclohex-1-encarboxilato de etilo

Una solución de EJEMPLO 521B (3,47 g), ácido 4-clorofenilborónico (1,925 g) y fluoruro de cesio (3,43 g) en 30 ml de dimetoxietano y 15 ml de etanol se desgasificó con nitrógeno por 5 minutos. Se agregó tetrakis(trifenilfosfin)paladio(0) (0,237 g) y la reacción se calentó a 70°C. La reacción se diluyó con éter (200 mL) y se lavó con HCl acuoso 1N (100 mL), salmuera (100 mL), se secó sobre sulfato de magnesio, se filtró y se concentró. La cromatografía sobre gel de sílice (Reveleris 40 g) eluyendo con un gradiente de acetato de etilo entre 1% y 8%/hexanos a lo largo de 40 minutos dio el compuesto del título.

EJEMPLO 521D

(2-(4-clorofenil)-5,5-difluorociclohex-1-enil)metanol

A una solución de EJEMPLO 521C (1,84 g) en éter dietílico (25 mL) a 0°C se agregó hidruro de litio y aluminio (1,0M, 4,28 mL). La reacción se detuvo con la adición por goteo de agua, luego se agregó HCl acuoso 1N (50 mL) y la reacción se diluyó con éter dietílico (100 mL). La capa orgánica se separó, se lavó con salmuera (50 mL), se secó sobre sulfato de magnesio, se filtró, y se concentró para dar el compuesto del título.

EJEMPLO 521E

2-(4-clorofenil)-5,5-difluorociclohex-1-encarbaldehido

A una solución de EJEMPLO 521D (1,38 g) en diclorometano (25 mL) se agregó Periodinano de Dess-Martin (2,489 g) y la reacción se agitó por 1 hora a temperatura ambiente. La reacción se detuvo con solución acuosa 1N de NaOH (75 mL) y el producto se extrajo con diclorometano (2 x 100 mL). Los orgánicos combinados se lavaron con salmuera (75 mL), se secó sobre sulfato de magnesio, se filtró y se concentró. La cromatografía sobre gel de sílice (Reveris 80 g) eluyendo con un gradiente de acetato de etilo entre 1% y 10%/hexanos a lo largo de 40 minutos dio el compuesto del título.

EJEMPLO 521F

2-(1H-indazol-4-iloxi)-4-(4-((2-(4-clorofenil)-5,5-difluorociclohex-1-enil)metil)piperazin-1-il)benzoato de metilo

A una solución de EJEMPLO 521E (1,05 g) en diclorometano (10 mL) se agregó EJEMPLO 400C (1,31 g) seguido por triacetoxihidroborato de sodio (1,18 g) y la reacción se agitó durante la noche a temperatura ambiente. La reacción se detuvo con $NaHCO_3$ saturado

(50 mL) y se extrajo con diclorometano (2 x 100 mL). Las capas orgánicas combinadas se secaron sobre sulfato de magnesio, se filtró, y se concentró. La cromatografía sobre gel de sílice (Reveleris 80 g) eluyendo con un gradiente de metanol al 0,5%-5%/diclorometano a lo largo de 40 minutos dio el compuesto del título.

EJEMPLO 521G

4-(4-((2-(4-clorofenil)-5,5-difluorociclohex-1-enil)metil)piperazin-1-il)-2-(1-tritil-1H-indazol-4-iloxi)benzoato de metilo

A una solución de EJEMPLO 521F (1,81 g) y trietilamina (0,85 mL) en diclorometano (10 mL) se agregó cloruro de tritilo (1,06 g) y la reacción se agitó a temperatura ambiente. Luego de agitar por 16 horas la reacción se cargó sobre gel de sílice (Reveleris 80 g) y se eluyó usando un gradiente de metanol al 0,1%-1,5%/diclorometano a lo largo de 40 minutos (velocidad de flujo = 40 ml/min) para dar el compuesto del título.

EJEMPLO 521H

ácido 4-(4-((2-(4-clorofenil)-5,5-difluorociclohex-1-enil)metil)piperazin-1-il)-2-(1-tritil-1H-indazol-4-iloxi)benzoico

A una solución de EJEMPLO 521G (2,51 g) en tetrahidrofurano (30 mL) y metanol (10 mL) se agregó hidróxido de litio (1,0M, 10 mL) y la solución se calentó a 60°C. Luego de 4 horas la reacción se enfrió, se diluyó con diclorometano (150 mL) y se detuvo con HCl acuoso 1N (10 mL) y agua (30 mL). La capa orgánica se lavó con salmuera (50 mL), se secó sobre sulfato de magnesio, se filtró, y se concentró. La cromatografía sobre gel de sílice (Reveleris 120 g) eluyendo con un gradiente de metanol al 0,25%-2,5%/diclorometano a lo largo de 40 minutos dio el compuesto del título.

EJEMPLO 521I

N-(5-cloro-6-((4-fluorotetrahidro-2H-piran-4-il)metoxi)piridin-3-ilsulfonil)-4-(4-((2-(4-clorofenil)-5,5-difluorociclohex-1-enil)metil)piperazin-1-il)-2-(1-tritil-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 521H en lugar de EJEMPLO 1E y EJEMPLO 404A en lugar de EJEMPLO 1F en EJEMPLO 1G.

EJEMPLO 521J

2-(1H-indazol-4-iloxi)-N-(5-cloro-6-((4-fluorotetrahidro-2H-piran-4-il)metoxi)piridin-3-ilsulfonil)-4-(4-((2-(4-clorofenil)-5,5-difluorociclohex-1-enil)metil)piperazin-1-il)benzamida

A una solución de EJEMPLO 521I (0,24 g) diclorometano (1 mL) se agregó ácido trifluoroacético (0,5 mL). Luego de agitar por 1 hora, la reacción se concentró, se disolvió en diclorometano (5 mL) y se detuvo con $NaHCO_3$ saturado (5 mL). La reacción se diluyó con agua (10 mL) y $NaHCO_3$ saturado (15 mL) y el producto se extrajo con diclorometano (2 x 25 mL). Los orgánicos combinados se lavaron con salmuera (25 mL), se secó sobre sulfato de magnesio, se filtró, y se concentró. El residuo se cargó sobre gel de sílice (Reveleris 40 g) y se eluyó usando un gradiente de metanol al 0,5%-3%/diclorometano a lo largo de 30 minutos (velocidad de flujo = 40 ml/minutos). El producto se recogió, se concentró, se disolvió en acetonitrilo y se concentró, y se secó en un horno de vacío a 75°C durante la noche para dar el compuesto del título. ^{1}H NMR (300 MHz, sulfóxido de dimetilo-d_6) δ 13,12 (s, 1H), 12,24 - 11,44 (m, 1H), 8,31 (d, 1H), 7,91 (d, 1H), 7,83 (s, 1H), 7,57 (d, 1H), 7,40 (d, 2H), 7,13 (d, 4H), 6,81 (dd, 1H), 6,56 (d, 1H), 6,16 (dd, 1H), 4,52 (d, 2H), 3,79 (dt, 2H), 3,70 - 3,51 (m, 2H), 3,20 (s, 4H), 2,76 (dd, 4H), 2,49 (m, 8H), 2,02 - 1,71 (m, 4H).

EJEMPLO 522

N-[(5-cloro-6-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 522A

5-cloro-6-((4-fluoro-1-(oxetan-3-il)piperidin-4-il)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando EJEMPLO 387A en lugar de EJEMPLO 329A y EJEMPLO 517B en lugar de (tetrahidro-2H-piran-4-il)metanol en EJEMPLO 329B.

EJEMPLO 522B

N-(5-cloro-6-((4-fluoro-1-(oxetan-3-il)piperidin-4-il)metoxi)piridin-3-ilsulfonil)-4-(4-((2-(4-clorofenil)-5,5-difluorociclohex-1-enil)metil)piperazin-1-il)-2-(1-tritil-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 521H en lugar de EJEMPLO 1E y EJEMPLO 522A en lugar de EJEMPLO 1F en EJEMPLO 1G.

EJEMPLO 522C

2-(1H-indazol-4-iloxi)-N-(5-cloro-6-((4-fluoro-1-(oxetan-3-il)piperidin-4-il)metoxi)piridin-3-ilsulfonil)-4-(4-((2-(4-clorofenil)-5,5-difluorociclohex-1-enil)metil)piperazin-1-il)benzamida

El compuesto del título se preparó utilizando EJEMPLO 522B en lugar de EJEMPLO 521I en EJEMPLO 521J. ^{1}H NMR (300 MHz, sulfóxido de dimetilo-d_6) δ 13,10 (s, 1H), 11,54 (s, 1H), 8,29 (d, 1H), 7,90 (d, 1H), 7,81 (s, 1H), 7,58 (d, 1H), 7,40 (d, 2H), 7,13 (d, 4H), 6,80 (dd, 1H), 6,53 (d, 1H), 6,15 (dd, 1H), 4,53 (d, 6H), 3,60 (s, 1H), 3,18 (s, 4H), 2,74 (dd, 8H), 2,41 - 1,70 (m, 12H).

EJEMPLO 523

2-(1H-benzotriazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 523A

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-N-(3-nitro-4-((tetrahidro-2H-piran-4-il)metilamino)fenilsulfonil)-2-(1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d][1,2,3]triazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 514F en lugar de EJEMPLO 1E en EJEMPLO 1G.

EJEMPLO 523B

2-(1H-benzotriazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 523A en lugar de EJEMPLO 498D en EJEMPLO 498E. ^{1}H NMR (500MHz, sulfóxido de dimetilo-d_6) δ 8,51 (s, 1H), 8,30 (d, 1H), 7,57-7,59 (m, 2H), 7,33-7,38 (m, 3H), 7,04-7,10 (m, 3H), 6,90 (d, 1H), 6,79 (dd, 1H), 6,52 (d, 1H), 6,39 (d, 1H), 3,87 (dd, 2H), 3,143 (br s, 4H), 2,78 (br s, 2H), 2,17-2,23 (m, 6H), 1,88-1,97 (m, 3H), 1,63-1,66 (m, 2H), 1,40 (t, 2H), 1,23-1,32 (m, 2H), 0,93 (s, 6H).

EJEMPLO 524

4-(4-{[2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)benzamida

EJEMPLO 524A

4-(4-((2-(4-clorofenil)-5,5-difluorociclohex-1-enil)metil)piperazin-1-il)-N-(3-nitro-4-((tetrahidro-2H-piran-4-il)metilamino)fenilsulfonil)-2-(1-tritil-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 521H en lugar de EJEMPLO 1E en EJEMPLO 1G.

EJEMPLO 524B

2-(1H-indazol-4-iloxi)-4-(4-((2-(4-clorofenil)-5,5-difluorociclohex-1-enil)metil)piperazin-1-il)-N-(3-nitro-4-((tetrahidro-2H-piran-4-il)metilamino)fenilsulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 524A en lugar de EJEMPLO 521I en EJEMPLO 521J. ^{1}H NMR (300 MHz, sulfóxido de dimetilo-d_6) δ 13,10 (d, 1H), 11,63 (s, 1H), 8,57 (t, 1H), 8,38 (d, 1H), 7,81 (d, 1H), 7,52 (d, 2H), 7,39 (d, 2H), 7,11 (dd, 4H), 7,00 (d, 1H), 6,80 (dd, 1H), 6,52 (d, 1H), 6,20 (dd, 1H), 3,86 (dd, 2H), 3,29 (d, 4H), 3,16 (s, 4H), 2,83 - 2,60 (m, 4H), 2,49 (s, 2H), 2,34 - 2,01 (m, 6H), 1,89 (dd, 1H), 1,63 (d, 2H), 1,27 (qd, 2H).

EJEMPLO 525

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(trans-4-hidroxi-4-metilciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 525A

(4-hidroxi-4-metilciclohexil)metilcarbamato de tert-butilo

A una solución en agitación enérgica de (4-oxociclohexil)metilcarbamato de tert-butilo (1,7 g) en tetrahidrofurano (40 mL) a -78°C se agregó por goteo metillitio 1,6 M (14,02 mL) en éter. Luego de completarse la adición, la mezcla se agitó a -78°C por 1,2 horas y se vertió en una solución acuosa fría de NH_4Cl. La mezcla resultante se extrajo con diclorometano (3x 100 mL) y la capa orgánica se secó sobre Na_2SO_4, se filtró, y se concentró. El residuo se disolvió en diclorometano y se cargó en un sistema de purificación Analogix, y se eluyó con acetato de etilo al 0 - 50% en diclorometano para dar el compuesto del título.

EJEMPLO 525B

4-(aminometil)-1-metilciclohexanol

Se trató EJEMPLO 525A (1,3 g) en diclorometano (5 mL) a 0°C con ácido trifluoroacético (2,1 mL) y unas pocas gotas de agua por 1 horas. La mezcla de la reacción se concentró y el residuo se usó directamente para el siguiente paso.

EJEMPLO 525C

4-((trans-4-hidroxi-4-metilciclohexil)metilamino)-3-nitrobencenosulfonamida

Se trató EJEMPLO 525B (732 mg) y 4-fluoro-3-nitrobencenosulfonamida (1,1 g) en tetrahidrofurano (15 mL) con trietilamina durante la noche. La mezcla de la reacción se concentró y el residuo se purificó mediante una cromatografía de fase inversa, eluyendo con 30% - 50% acetonitrilo en solución acuosa de ácido trifluoroacético al 0,1% para dar el compuesto del título.

EJEMPLO 525D

4-((cis-4-hidroxi-4-metilciclohexil)metilamino)-3-nitrobencenosulfonamida

Se trató EJEMPLO 525B (732 mg) y 4-fluoro-3-nitrobencenosulfonamida (1,1 g) en tetrahidrofurano (15 mL) con trietilamina durante la noche. La mezcla de la reacción se concentró y el residuo se purificó mediante una cromatografía de fase inversa, eluyendo con 30% - 50% acetonitrilo en solución acuosa de ácido trifluoroacético al 0,1% para dar el compuesto del título.

EJEMPLO 525E

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(trans-4-hidroxi-4-metilciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó como se describe en EJEMPLO 177 reemplazando EJEMPLO 26C y EJEMPLO 1F por EJEMPLO 400E y EJEMPLO 525C, respectivamente. ^{1}H NMR (400 MHz, sulfóxido de dimetilo-d_6) δ 13,10 (s, 1H), 11,54 (s, 1H), 8,53 (t, 1H), 8,37 (d, 1H), 7,82 (s, 1H), 7,48 - 7,58 (m, 2H), 7,32 - 7,39 (m, 2H), 7,02 - 7,11 (m, 4H), 6,95 (d, 1H), 6,80 (dd, 1H), 6,52 (d, 1H), 6,17 (dd, 1H), 4,25 (s, 1H), 3,26 - 3,31 (m, 2H), 3,17 (s, 4H), 2,80 (s, 2H), 2,21 (d, 6H), 1,97 (s, 2H), 1,60 - 1,75 (m, 3H), 1,56 (d, 2H), 1,30 - 1,43 (m, 4H), 1,08 - 1,19 (m, 5H), 0,93 (s, 6H).

EJEMPLO 526

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(cis-4-hidroxi-4-metilciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó como se describe en EJEMPLO 177 reemplazando EJEMPLO 26C y EJEMPLO 1F por EJEMPLO 400E y EJEMPLO 525D, respectivamente. ^{1}H NMR (400 MHz, sulfóxido de dimetilo-d_6) δ 13,11 (d, 1H), 11,55 (s, 1H), 8,56 (t, 1H), 8,37 (d, 1H), 7,81 (s, 1H), 7,50 - 7,55 (m, 2H), 7,33 - 7,38 (m, 2H), 7,04 - 7,13 (m, 4H), 6,95 (d, 1H), 6,80 (dd, 1H), 6,52 (d, 1H), 6,17 (d, 1H), 3,97 (s, 1H), 3,26 (t, 2H), 3,16 (s, 4H), 2,79 (s, 2H), 2,20 (d, 6H), 1,97 (s, 2H), 1,46 - 1,61 (m, 5H), 1,35 - 1,45 (m, 4H), 1,19 - 1,30 (m, 2H), 1,09 (s, 3H), 0,93 (s, 6H).

EJEMPLO 527

2-(1H-benzotriazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({[(2S)-4-ciclopropilmorfolin-2-il]metil}amino)-3-nitrofenil]sulfonil}benzamida

EJEMPLO 527A

(S)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-N-(4-((4-ciclopropilmorfolin-2-il)metilamino)-3-nitrofenilsulfonil)-2-(1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d][1,2,3]triazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 514F en lugar de EJEMPLO 1E y EJEMPLO 529A en lugar de EJEMPLO 1F en EJEMPLO 1G.

EJEMPLO 527B

2-(1H-benzotriazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({[(2S)-4-ciclopropilmorfolin-2-il]metil}amino)-3-nitrofenil]sulfonil}benzamida

El compuesto del título se preparó utilizando EJEMPLO 527A en lugar de EJEMPLO 498D en EJEMPLO 498E. ^{1}H NMR (500MHz, sulfóxido de dimetilo-d_6) δ 8,56 (s, 1H), 8,31 (s, 1H), 7,55-7,60 (m, 2H), 7,34-7,38 (m, 3H), 7,04-7,10 (m, 3H), 6,92 (d, 1H), 6,80 (dd, 1H), 6,53 (d, 1H), 6,38 (d, 1H), 3,84 (d, 1H), 3,55 (m, 1H), 3,41-3,54 (m, 6H), 3,17 (m, 4H), 2,74-2,94 (m, 6H), 2,15-2,36 (m, 10H), 1,97 (s, 2H), 1,69 (t, 2H), 1,40 (t, 2H), 0,94 (s, 6H), 0,35-0,44 (m, 4H).

EJEMPLO 528

N-[(5-cloro-6-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 528A

N-(5-cloro-6-((4-fluoro-1-(oxetan-3-il)piperidin-4-il)metoxi)piridin-3-ilsulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-2-(1-tritil-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 522A en lugar de EJEMPLO 1F y EJEMPLO 498C en lugar de EJEMPLO 1E en EJEMPLO 1G.

EJEMPLO 528B

N-[(5-cloro-6-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 528A en lugar de EJEMPLO 542E en EJEMPLO 542F. ^{1}H NMR (400 MHz, sulfóxido de dimetilo-d_6) δ 13,08 (s, 1H), 8,26 (d, 1H), 7,88 (d, 1H), 7,79 (m, 1H), 7,60 (d, 1H), 7,37 (d, 2H), 7,07 (m, 4H), 6,79 (dd, 1H), 6,53 (d, 1H), 6,13 (d, 1H), 4,57 (t, 2H), 4,52 (s, 1H), 4,47 (m, 3H), 3,55 (m, 2H), 3,18 (m, 4H), 2,94 (m, 2H), 2,67 (m, 2H), 2,38 (m, 3H), 2,18 (m, 4H), 1,97 (m, 5H), 1,80 (m, 1H), 1,41 (t, 2H), 0,94 (s, 6H).

EJEMPLO 529

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({[(2S)-4-ciclopropilmorfolin-2-il]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 529A

(S)-4-((4-ciclopropilmorfolin-2-il)metilamino)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando EJEMPLO 438B en lugar de EJEMPLO 415B en EJEMPLO 432A.

EJEMPLO 529B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({[(2S)-4-ciclopropilmorfolin-2-il]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 400E en lugar de EJEMPLO 26C y EJEMPLO 529A en lugar de EJEMPLO 1F en EJEMPLO 177. ^{1}H NMR (500MHz, piridin-d_5) δ 14,58 (bs, 1H), 9,05 (d, 1H), 8,87 (t, 1H), 8,37 (s, 1H), 8,16 (dd, 1H), 8,08 (d, 1H), 7,45 (d, 2H), 7,34 (d, 1H), 7,15 (t, 1H), 7,10 (d, 2H), 6,90-6,80 (m, 3H), 6,52 (d, 1H), 3,90-3,81 (m, 2H), 3,57 (dt, 1H), 3,50-3,42 (m, 2H), 3,15 (m, 4H), 2,93 (m, 1H), 2,82 (s, 2H), 2,71 (m, 1H), 2,31 (dt, 1H), 2,30 (m, 2H), 2,22 (m, 4H), 2,21 (m, 1H), 1,99 (s, 2H), 1,58 (m, 1H), 1,41 (t, 2H), 0,96 (s, 6H), 0,40 (m, 4H).

EJEMPLO 530

2-(1H-bencimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({[(2S)-4-ciclopropilmorfolin-2-il]metil}amino)-3-nitrofenil]sulfonil}benzamida

El compuesto del título se preparó utilizando EJEMPLO 529A en lugar de EJEMPLO 428D en EJEMPLO 428E. ^{1}H NMR (500MHz, piridin-d_5) δ 9,25 (d, 1H), 8,90 (t, 1H), 8,57 (s, 1H), 8,37 (dd, 1H), 7,99 (d, 1H), 7,53 (d, 1H), 7,43 (d, 2H), 7,24 (d, 1H), 7,17 (d, 1H), 7,07 (d, 2H), 6,97 (d, 1H), 6,73-6,68 (m, 2H), 3,92-3,85 (m, 2H), 3,59 (dt, 1H), 3,50-3,40 (m, 2H), 3,02 (m, 4H), 2,95 (d, 1H), 2,76 (s, 2H), 2,69 (d, 1H), 2,36 (dt, 1H), 2,20-2,20 (m, 3H), 2,14 (m, 4H), 1,97 (s, 2H), 1,59 (m, 1H), 1,38 (t, 2H), 0,93 (s, 6H), 0,41 (m, 4H).

EJEMPLO 531

N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 531A

1,4-dioxaespiro[4,5]decan-8-carboxilato de etilo

A una solución de 4-oxociclohexanocarboxilato de etilo (31,8 g) en tolueno (100 mL) se agregó etilenglicol (36,5 mL) y ácido p-toluenosulfónico monohidratado (0,426 g). La mezcla bifásica se agitó rápidamente a temperatura ambiente por 72 horas. La reacción se

diluyó con agua (900 mL) y se extrajo con éter (900 mL). La capa orgánica se lavó con solución saturada de bicarbonato de sodio y salmuera, y luego se secó sobre sulfato de sodio anhidro. Luego de la filtración, el compuesto del título se obtuvo mediante la concentración del material filtrado bajo alto vacío.

EJEMPLO 531B

1,4-dioxaespiro[4,5]decan-8-ilmetanol

A una suspensión de hidruro de litio y aluminio (8,19 g) en tetrahidrofurano (400 mL) se agregó lentamente por goteo una solución de EJEMPLO 531A (37,8 g) en tetrahidrofurano (75 mL). La mezcla luego se calentó a reflujo por 2 horas. La mezcla de la reacción se enfrió en un baño de hielo y se detuvo muy lentamente con agua (8 mL). Luego se agregó en forma secuencial hidróxido de sodio acuoso 4N (8 mL), éter (200 mL), agua (24 mL), éter (500 mL) y sulfato de sodio anhidro (250 g). La mezcla resultante se agitó rápidamente por 2 horas y luego se filtró. El compuesto del título se aisló mediante la concentración del material filtrado.

EJEMPLO 531C

8-(benciloximetil)-1,4-dioxaespiro[4,5]decano

A una suspensión de hidruro de sodio (dispersión de aceite al 60%) (8,86 g) en tetrahidrofurano (170 mL) se agregó una solución de EJEMPLO 531B (30,52 g) en tetrahidrofurano (100 mL). Esta mezcla se agitó por 30 minutos y se agregó bromuro de bencilo (24 mL). Luego de agitar por 72 horas, la reacción se detuvo con solución acuosa saturada de cloruro de amonio (400 mL) y se diluyó con éter (500 mL). Las capas se separaron y la capa acuosa se extrajo con éter (2 X 150 mL). Los orgánicos combinados se secaron sobre sulfato de sodio, se filtró y se concentró. El producto crudo se purificó sobre gel de sílice eluyendo con un gradiente escalonado de acetato de etilo al 0, 10, 15, 75% para dar el compuesto del título.

EJEMPLO 531D

4-(benciloximetil)ciclohexanona

A una solución de EJEMPLO 531C (43,02 g) en dioxano (500 mL) se agregó agua (125 mL) y ácido clorhídrico 2M (90 mL). La mezcla se calentó a 85 ºC por 18 horas. Luego de enfriar, la mezcla de la reacción se diluyó con salmuera (1500 mL), solución saturada de bicarbonato de sodio (300 mL) y éter (1000 mL). La capa orgánica se secó sobre sulfato de

sodio, se filtró y se concentró. El producto crudo se purificó sobre gel de sílice eluyendo con un gradiente escalonado de acetato de etilo al 5, 15, 25, 50% para dar el compuesto del título.

EJEMPLO 531E

trans-4-(benciloximetil)-1-metilciclohexanol

A 2,6-di-t-butil-4-metilfenol (83,4 g) en tolueno (1100 mL) se agregó $(CH_3)_3Al$ 2,0M (en hexanos) (95 mL) para de algún modo cuidadosamente controlar la evolución de metano y una pequeña reacción exotérmica. La mezcla de la reacción se agitó a temperatura ambiente bajo N_2 por 75 minutos y luego se enfrió a -77º C. Se agregó una solución de EJEMPLO 531D (14 g) en tolueno (15 mL) por goteo, manteniendo la temperatura bajo -74 ºC. Luego se agregó metillitio (1,6M en éter dietílico) (120 mL) por goteo, manteniendo la temperatura bajo -65 ºC. La mezcla resultante se agitó a -77 °C bajo N_2 por 2 horas. La mezcla de la reacción luego se vertió en HCl acuoso 1N (1600 mL), enjuagando el recipiente con tolueno. La capa orgánica se lavó con salmuera y las capas acuosas combinadas se extrajeron con éter dietílico. Las capas orgánicas combinadas se secaron (Na_2SO_4), se filtró y se concentró. El material concentrado se cromatografió sobre 650 g de gel de sílice esférico usando 2,5 L de 80/20 hexanos/acetato de etilo, luego 3,0 L de 75/25 hexanos/acetato de etilo, y finalmente 4,0 L de 70/30 hexanos/acetato de etilo como eluyentes para dar el compuesto del título.

EJEMPLO 531F

trans-4-(hidroximetil)-1-metilciclohexanol

Se agregó EJEMPLO 531E (12,6 g) y etanol (120 mL) a $Pd(OH)_2/C$ al 20% húmedo (1,26 g) en una botella de presión SS de 500 mL. La mezcla de la reacción se agitó a temperatura ambiente bajo 30 psi de gas hidrógeno. La toma de hidrógeno se detuvo a los 5 minutos. La mezcla se filtró a través de una membrana de nylon enjuagando con etanol. El material filtrado se concentró y luego se azeotropeó con tolueno (100 mL) para eliminar el etanol restante. El material concentrado se secó bajo alto vacío por 40 minutos para dar el compuesto del título.

EJEMPLO 531G

5-cloro-6-((trans-4-hidroxi-4-metilciclohexil)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando EJEMPLO 387A en lugar de 4-fluoro-3-nitrobencenosulfonamida y EJEMPLO 531F en lugar de (tetrahidro-2H-piran-4-il)metanol en EJEMPLO 279A.

EJEMPLO 531H

N-(5-cloro-6-((trans-4-hidroxi-4-metilciclohexil)metoxi)piridin-3-ilsulfonil)-4-(4-((2-(4-clorofenil)-5,5-difluorociclohex-1-enil)metil)piperazin-1-il)-2-(1-tritil-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 521H en lugar de EJEMPLO 1E y EJEMPLO 531G en lugar de EJEMPLO 1F en EJEMPLO 1G.

EJEMPLO 531I

2-(1H-indazol-4-iloxi)-N-(5-cloro-6-((trans-4-hidroxi-4-metilciclohexil)metoxi)piridin-3-ilsulfonil)-4-(4-((2-(4-clorofenil)-5,5-difluorociclohex-1-enil)metil)piperazin-1-il)benzamida

El compuesto del título se preparó utilizando EJEMPLO 531H en lugar de EJEMPLO 521I en EJEMPLO 521J. ^{1}H NMR (300 MHz, sulfóxido de dimetilo-d_6) δ 13,13 (s, 1H), 12,05 - 11,55 (m, 1H), 8,29 (d, 1H), 7,92 - 7,78 (m, 2H), 7,56 (d, 1H), 7,47 - 7,33 (m, 2H), 7,19 - 6,98 (m, 4H), 6,82 (dd, 1H), 6,56 (d, 1H), 6,16 (dd, 1H), 4,25 (d, 3H), 3,20 (s, 4H), 2,72 (s, 4H), 2,48 - 2,40 (m, 2H), 2,41 - 2,03 (m, 6H), 1,76 (s, 3H), 1,54 (s, 2H), 1,38 (m, 2H), 1,21 (m, 2H), 1,11 (s, 3H).

EJEMPLO 532

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(cis-4-hidroxi-4-metilciclohexil)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 532A

4-((cis-4-hidroxi-4-metilciclohexil)metoxi)-3-nitrobencenosulfonamida

Se trató EJEMPLO 493A (732 mg) y 4-fluoro-3-nitrobencenosulfonamida (1,2 g) en tetrahidrofurano (40 mL) con hidruro de sodio al 60% (1,6 g) por 3 días. La reacción se detuvo con agua. La mezcla resultante se neutralizó con HCl acuoso diluido, y se extrajo con acetato de etilo. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se purificó mediante una cromatografía de fase inversa, eluyendo con 30-50% acetonitrilo en ácido trifluoroacético acuoso al 0,1% para dar el compuesto del título.

EJEMPLO 532B

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-N-(4-((cis-4-hidroxi-4-metilciclohexil)metoxi)-3-nitrofenilsulfonil)-2-(1-tritil-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 532A en lugar de EJEMPLO 1F y EJEMPLO 498C en lugar de EJEMPLO 1E en EJEMPLO 1G.

EJEMPLO 532C

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(cis-4-hidroxi-4-metilciclohexil)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 532B en lugar de EJEMPLO 542E en EJEMPLO 542F. ^{1}H NMR (400 MHz, sulfóxido de dimetilo-d_6) δ 13,09 (s, 1H), 8,10 (m, 1H), 7,81 (s, 1H), 7,78 (dd, 1H), 7,56 (d, 1H), 7,36 (d, 2H), 7,28 (d, 1H), 7,11 (m, 2H), 7,06 (d, 2H), 6,80 (dd, 1H), 6,52 (d, 1H), 6,17 (dd, 1H), 4,02 (d, 2H), 3,96 (s, 1H), 3,18 (m, 4H), 2,86 (m, 2H), 2,17 (m, 2H), 1,98 (m, 3H), 1,69 (m, 2H), 1,55 (m, 4H), 1,41 (m, 5H), 1,29 (m, 3H), 1,11 (s, 3H), 0,94 (m, 6H).

EJEMPLO 533

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(trans-4-hidroxi-4-metilciclohexil)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 533A

4-((trans-4-hidroxi-4-metilciclohexil)metoxi)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando EJEMPLO 531F en lugar de (tetrahidro-2H-piran-4-il)metanol y 4-fluoro-3-nitrobencenosulfonamida en lugar de EJEMPLO 329A en EJEMPLO 329B.

EJEMPLO 533B

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-N-(4-((trans-4-hidroxi-4-metilciclohexil)metoxi)-3-nitrofenilsulfonil)-2-(1-tritil-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 533A en lugar de EJEMPLO 1F y EJEMPLO 498C en lugar de EJEMPLO 1E en EJEMPLO 1G.

EJEMPLO 533C

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(trans-4-hidroxi-4-metilciclohexil)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 533B en lugar de EJEMPLO 542E en EJEMPLO 542F. ^{1}H NMR (400 MHz, sulfóxido de dimetilo-d_6) δ 13,11 (s, 1H), 8,11 (m, 1H), 7,81 (m, 2H), 7,57 (dd, 1H), 7,36 (d, 2H), 7,28 (m, 1H), 7,11 (m, 2H), 7,06 (d, 2H), 6,80 (dd, 1H), 6,52 (d, 1H), 6,18 (d, 1H), 4,27 (s, 1H), 4,06 (d, 2H), 3,16 (m, 4H), 2,81 (m, 2H), 2,20 (m, 4H), 1,98 (m, 2H), 1,74 (m, 3H), 1,57 (m, 2H), 1,40 (m, 4H), 1,24 (m, 3H), 1,11 (s, 3H), 0,94 (s, 6H).

EJEMPLO 534

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-ciano-4-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}fenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 534A

3-ciano-4-((4-fluoro-1-(oxetan-3-il)piperidin-4-il)metoxi)bencenosulfonamida

A una solución de EJEMPLO 517B (0,185 g) en tetrahidrofurano (5 mL) se agregó hidruro de sodio (0,090 g). Luego de 30 minutos, se agregó 3-ciano-4-fluorobencenosulfonamida (0,178 g) en una porción. La reacción se agitó a temperatura ambiente por 2 horas. La reacción se detuvo con HCl acuoso 1N (4 mL), se diluyó con diclorometano (30 mL) y $NaHCO_3$ acuoso saturado (25 mL). La capa orgánica se secó sobre sulfato de magnesio, se filtró y se concentró. El sólido resultante material se trituró con diclorometano y se filtró para dar el compuesto del título.

EJEMPLO 534B

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-N-(3-ciano-4-((4-fluoro-1-(oxetan-3-il)piperidin-4-il)metoxi)fenilsulfonil)-2-(1-tritil-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 521H en lugar de EJEMPLO 1E y EJEMPLO 534A en lugar de EJEMPLO 1F en EJEMPLO 1G.

EJEMPLO 534C

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-ciano-4-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}fenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 534B en lugar de EJEMPLO 521I en EJEMPLO 521J. ^{1}H NMR (300 MHz, sulfóxido de dimetilo-d_6) δ 13,11 (s, 1H), 11,64 - 11,28 (m, 1H), 7,95 - 7,75 (m, 3H), 7,56 (d, 1H), 7,44 - 7,26 (m, 2H), 7,22 (d, 1H), 7,09 (ddd, 4H), 6,81 (s, 1H), 6,52 (d, 1H), 6,18 (dd, 1H), 4,51 (dt, 4H), 4,33 (d, 2H), 3,50 (s, 1H), 3,18 (s, 8H), 2,49 - 1,68 (m, 14H), 1,42 (d, 2H), 0,94 (s, 6H).

EJEMPLO 535

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-{[3-nitro-4-(2-oxaespiro[3,5]non-7-ilmetoxi)fenil]sulfonil}benzamida

EJEMPLO 535A

1,4-dioxaespiro[4,5]decan-8,8-dicarboxilato de dietilo

Un balón de 500 mL se cargó con diisopropilamina (16 mL) y tetrahidrofurano (311 mL). La solución se enfrió a -78°C bajo N_2 y n-BuLi (2,5 M en hexanos, 44,8 mL) se agregó. La reacción se agitó por 30 minutos a -78 °C y 1,4-dioxaespiro[4,5]decan-8-carboxilato de etilo (20 g) se agregó como una solución de tetrahidrofurano (aprox. 10 mL). La solución se agitó a -78 °C por 1 hora y se agregó cloroformato de etilo (9 mL) límpido. Luego de agitar a -78 °C por 10 minutos, la reacción se calentó a temperatura ambiente durante 2 horas. La reacción se detuvo con NH_4Cl acuoso saturado y se diluyó con éter dietílico. Las capas se separaron, la capa acuosa se extrajo con éter dietílico y los orgánicos combinados se secaron (Na_2SO_4), se filtró y se concentró por evaporación por rotación. El residuo se purificó mediante cromatografía flash de columna de fase normal (Analogix, 0-65% hexanos / acetato de etilo).

EJEMPLO 535B

1,4-dioxaespiro[4,5]decan-8,8-diildimetanol

A un balón de 1 L se agregó EJEMPLO 535A (26,6 g) y tetrahidrofurano (310 mL). La solución se enfrió a 0°C y se agregó hidruro de litio y aluminio (2M en tetrahidrofurano, 62 mL) mediante una jeringa. La reacción se dejó calentar a temperatura ambiente y se agitó durante la noche. La mezcla se enfrió nuevamente a 0°C, se detuvo lentamente con 4,7 mL de agua, 4,7 ml de NaOH acuoso al 10% y 14 mL de agua, y se dejó agitar hasta que se formaron sales y luego la mezcla se filtró a través de un embudo Buchner de gel de sílice Supelco de 90 mm. El material filtrado se concentró por evaporación por rotación y el residuo

se purificó mediante cromatografía flash de columna de fase normal (Analogix, 0-80% hexanos / acetato de etilo).

EJEMPLO 535C

2,8,11-trioxadiespiro[3,2,4,2]tridecano

A un balón de 1 L se agregó EJEMPLO 535B (13 g) en tetrahidrofurano (321 mL). La solución se enfrió a -78°C bajo N_2 y se agregó n-butillitio (25,7 mL) por goteo mediante una jeringa. Luego de completarse la adición, la reacción se agitó por 30 minutos y se agregó una solución en tetrahidrofurano de cloruro de tolueno-2-sulfonilo (12,25 g) a través de un embudo de adición. La reacción se dejó agitar durante la noche, calentando gradualmente a temperatura ambiente. La reacción se enfrió nuevamente a -78 °C y se agregó n-butillitio (25,7mL). La reacción se dejó calentar a temperatura ambiente y se agitó por 3 horas. La reacción se detuvo con NH_4Cl acuoso saturado y se diluyó con éter dietílico. Las capas se separaron, la capa acuosa se extrajo con éter dietílico y los orgánicos combinados se secaron (Na_2SO_4), se filtró y se concentró por evaporación por rotación. El residuo se purificó mediante cromatografía flash de columna de fase normal (Analogix, 0-20% acetona / hexanos).

EJEMPLO 535D

2-oxaespiro[3,5]nonan-7-ona

A un balón de 500 mL se agregó EJEMPLO 535C (11 g) en ácido acético al 80 % (200 mL). La reacción se calentó a 65°C y se agitó por aproximadamente 4 horas. La mayor parte del ácido acético y el agua se eliminaron por evaporación por rotación y el residuo se purificó mediante cromatografía flash de columna de fase normal (Analogix, 0-65% hexanos/acetato de etilo).

EJEMPLO 535E

7-metilen-2-oxaespiro[3,5]nonano

A un balón de 250 mL se agregó yoduro de metiltrifenilfosfonio (4,33 g) en tetrahidrofurano (35,7 mL). La suspensión se enfrió a -15°C. Se agregó n-Butillitio (2,5 M en hexanos, 4,28 mL) por goteo. La mezcla se agitó a -15°C por 40 minutos y se agregó EJEMPLO 535D (1 g) como una solución en tetrahidrofurano (aprox. 5 mL). La mezcla se agitó a -15°C por aproximadamente 15 minutos y se calentó a temperatura ambiente. Luego de 1,5 horas la reacción se había completado y se detuvo con NH_4Cl acuoso saturado y se

diluyó con éter dietílico. Las capas se separaron y la capa acuosa se extrajo (2x) con éter dietílico. Los orgánicos combinados se lavaron con salmuera, se secó (Na_2SO_4), se filtró y se concentró por evaporación por rotación. El residuo se purificó mediante cromatografía de fase normal (Analogix, hexanos al 0-50%/acetato de etilo).

EJEMPLO 535F

2-oxaespiro[3,5]nonan-7-ilmetanol

A un balón de 25 mL se agregó EJEMPLO 535E (568 mg) y tetrahidrofurano (4,11 mL). Se agregó 9-borabiciclo[3,3,1]nonano (0,5 M en tetrahidrofurano, 24,7 mL) y la reacción se dejó agitar por 2 horas a temperatura ambiente. Se agregó etanol (11 mL) seguido por NaOH acuoso (5M, 4,11 mL) y luego se agregó peróxido de hidrógeno al 30% (2,1 mL). La reacción se calentó a 50°C por 2 horas. La mayor parte del etanol y el tetrahidrofurano se retiró por evaporación por rotación y el residuo se diluyó con agua y acetato de etilo. La capa acuosa se extrajo con acetato de etilo (3x) y los orgánicos combinados se secaron (Na_2SO_4), se filtró y se concentró por evaporación por rotación. El residuo se purificó mediante cromatografía flash de columna de fase normal (Analogix, 0-70 % hexanos / acetato de etilo).

EJEMPLO 535G

4-(2-oxaespiro[3,5]nonan-7-ilmetoxi)-3-nitrobencenosulfonamida

EJEMPLO 535G se preparó utilizando EJEMPLO 535F en lugar de (tetrahidro-2H-piran-4-il)metanol en EJEMPLO 279A.

EJEMPLO 535H

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-{[3-nitro-4-(2-oxaespiro[3,5]non-7-ilmetoxi)fenil]sulfonil}benzamida

En un vial de 4 mL se agregó EJEMPLO 498C (171 mg) y EJEMPLO 535G (75 mg) en diclorometano (1052 µl) para dar una solución incolora. Se agregó clorhidrato de 1-etil-3-[3-(dimetilamino)propil]-carbodiimida (64,5 mg) y 4-dimetilaminopiridina (77 mg) y la solución se agitó durante la noche a temperatura ambiente. La reacción se cargó directamente sobre gel de sílice y se cromatografió mediante cromatografía flash de columna de fase normal (Analogix, 0-100% hexanos / acetato de etilo). Las fracciones se combinaron, se concentró, se trató con ácido trifluoroacético al 50% en diclorometano (2 mL) y se agitó por 2 horas. Los volátiles se eliminaron mediante una corriente de nitrógeno, el residuo se colocó en diclorometano, se cargó directamente sobre gel de sílice y se purificó mediante columna

cromatografía flash de columna (Analogix, 0,4 - 4% diclorometano / metanol). ^{1}H NMR (300 MHz, sulfóxido de dimetilo-d_6) δ 13,10 (s, 1H) 8,11 (d, 1H) 7,76 - 7,84 (m, 2H) 7,55 (d, 1H) 7,36 (d, 2H) 7,27 (d, 1H) 7,02 - 7,15 (m, 4H) 6,79 (dd, 1H) 6,52 (d, 1H) 6,18 (dd, 1H) 4,30 (s, 2H) 4,21 (s, 2H) 4,00 (d , 2H) 3,11 - 3,26 (m, 4H) 2,85 (s, 3H) 2,70 - 2,75 (m, 1H) 2,22 - 2,46 (m, 3H) 2,13 - 2,22 (m, 3H) 2,07 (d, 2H) 1,98 (s, 2H) 1,66 - 1,77 (m, 3H) 1,36 - 1,50 (m, 4H) 0,98 - 1,16 (m, 2H) 0,94 (s, 6H).

EJEMPLO 536

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[5-cloro-6-(5,6,7,8-tetrahidroimidazo[1,2-a]piridin-6-ilmetoxi)piridin-3-il]sulfonil}-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 536A

5,6,7,8-tetrahidroimidazo[1,2-a]piridin-6-carboxilato de metilo

En una botella de presión de 50 mL se colocó imidazo[1,2-a]piridin-6-carboxilato de metilo (0,26 g), ácido acético (10 mL), y paladio sobre carbono al 5% húmedo (0,052 g). La mezcla de la reacción se agitó por 16 horas a 30 psi y 50 °C. El sólido se retiró por filtración, y el material filtrado se concentró. El residuo se disolvió en acetato de etilo. Luego se lavó con bicarbonato de sodio saturado, salmuera, se secó sobre $MgSO_4$, se filtró, y se concentró. El residuo se purificó mediante cromatografía flash de columna sobre gel de sílice para dar el compuesto del título.

EJEMPLO 536B

(5,6,7,8-tetrahidroimidazo[1,2-a]piridin-6-il)metanol

El compuesto del título se preparó utilizando EJEMPLO 536A en lugar de EJEMPLO 339A en EJEMPLO 339B.

EJEMPLO 536C

5-cloro-6-((5,6,7,8-tetrahidroimidazo[1,2-a]piridin-6-il)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando EJEMPLO 536B en lugar de (tetrahidro-2H-piran-4-il)metanol y EJEMPLO 387A en lugar de EJEMPLO 329A en EJEMPLO 329B.

EJEMPLO 536D

N-(5-cloro-6-((5,6,7,8-tetrahidroimidazo[1,2-a]piridin-6-il)metoxi)piridin-3-ilsulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-2-(1-((2-(trimetilsilil)etoxi)metil)-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 435D en lugar de EJEMPLO 1E y EJEMPLO 536C en lugar de EJEMPLO 1F en EJEMPLO 1G.

EJEMPLO 536E

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[5-cloro-6-(5,6,7,8-tetrahidroimidazo[1,2-a]piridin-6-ilmetoxi)piridin-3-il]sulfonil}-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 536D en lugar de EJEMPLO 435E en EJEMPLO 435F. ^{1}H NMR (500MHz, sulfóxido de dimetilo-d_6) δ 12,97 (s, 1H), 8,20 (d, 1H), 7,84 (d, 1H), 7,72 (s, 1H), 7,66 (d, 1H), 7,35 (d, 2H), 7,29 (s, 1H), 7,15 (s, 1H), 7,03-7,07 (m, 4H), 6,72 (dd, 1H), 6,40 (d, 1H), 6,09 (dd, 1H), 4,35-4,48 (m, 2H), 4,24-4,28 (m, 1H), 3,84-3,90 (m, 1H), 3,06 (br s, 4H), 2,83-2,92 (m, 2H), 2,76 (s, 2H), 2,09-2,23 (m, 8H), 1,97 (s, 2H), 1,76 (m, 1H), 1,40 (t, 2H), 0,93 (s, 6H).

EJEMPLO 537

2-(1H-bencimidazol-4-iloxi)-N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida

El compuesto del título se preparó utilizando EJEMPLO 493B en lugar de EJEMPLO 428D y en EJEMPLO 428E. ^{1}H NMR (500 MHz, piridin-d_5) δ 9,17 (d, 1H), 8,70 (d, 1H), 8,57 - 8,58 (s, 1H), 7,98 (d, 1H), 7,53 (d, 1H), 7,43 (d, 2H), 7,24 (t, 1H), 7,16 (d, 1H), 7,07 (d, 2H), 6,70 (m, 2H), 5,94 (m, 3H), 4,30 (d, 2H), 3,03 (m, 4H), 2,77 (s, 2H), 2,25 (m, 2H), 2,13 (m, 4H), 1,97 (s, 2H), 1,94 - 1,87 (m, 5H), 1,76 (m, 2H), 1,43 - 1,28 (m, 7H), 0,94 (m, 6H).

EJEMPLO 538

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(5-ciano-6-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}piridin-3-il)sulfonil]-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 538A

5-bromo-6-((4-fluoro-1-(oxetan-3-il)piperidin-4-il)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando EJEMPLO 517B en lugar de (tetrahidro-2H-piran-4-il)metanol en EJEMPLO 329B.

EJEMPLO 538B

5-ciano-6-((4-fluoro-1-(oxetan-3-il)piperidin-4-il)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando EJEMPLO 538A en lugar de EJEMPLO 329B en EJEMPLO 333A.

EJEMPLO 538C

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-N-(5-ciano-6-((4-fluoro-1-(oxetan-3-il)piperidin-4-il)metoxi)piridin-3-ilsulfonil)-2-(1-tritil-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 498C en lugar de EJEMPLO 1E y EJEMPLO 538B en lugar de EJEMPLO 1F en EJEMPLO 1G.

EJEMPLO 538D

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(5-ciano-6-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}piridin-3-il)sulfonil]-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 538C en lugar de EJEMPLO 521I en EJEMPLO 521J. ^{1}H NMR (300 MHz, sulfóxido de dimetilo-d_6) δ 13,03 (s, 1H), 8,49 (d, 1H), 8,19 (s, 1H), 7,74 (s, 1H), 7,62 (d, 1H), 7,37 (d, 2H), 7,14 - 6,94 (m, 3H), 6,77 (dd, 1H), 6,51 (s, 1H), 6,09 (dd, 1H), 4,53 (dt, 6H), 3,60 (s, 3H), 2,84 (dd, 8H), 2,46 - 1,71 (m, 12H), 1,44 (d, 2H), 0,94 (s, 6H).

EJEMPLO 539

N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-5-(metoximetil)-5-metilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 539A

8-metil-1,4-dioxaespiro[4,5]decan-8-carboxilato de etilo

A un balón de 500 mL se agregó diisopropilamina (7,98 mL) en tetrahidrofurano (233 mL). La mezcla se enfrió a -78°C bajo N_2 y se agregó n-butillitio (2,5 M en hexanos, 22,40 mL). La reacción se agitó por 30 minutos y se agregó 1,4-dioxaespiro[4,5]decan-8-carboxilato de etilo (10 g). La reacción se dejó agitar por 1,5 horas luego de las cuales se agregó CH_3I (4,38 mL). La reacción se dejó calentar a temperatura ambiente durante la noche con agitación. Se agregó agua y la capa acuosa se extrajo con acetato de etilo. Los orgánicos combinados se secaron (Na_2SO_4), se filtró y se concentró por evaporación por rotación. El residuo se purificó mediante cromatografía flash de columna de fase normal (Analogix, hexanos al 0-50% / acetato de etilo).

EJEMPLO 539B

(8-metil-1,4-dioxaespiro[4,5]decan-8-il)metanol

A un balón de 500 mL se agregó hidruro de litio y aluminio (1,772 g) en tetrahidrofurano (234 mL). La mezcla se enfrió a 0°C y se agregó EJEMPLO 539A (10,66 g) a través de un embudo de adición. La reacción se agitó durante la noche a temperatura ambiente y luego se enfrió nuevamente a 0°C. El exceso hidruro de litio y aluminio se detuvo lentamente con 1,8 mL de agua, 1,8 mL de NaOH acuoso (5N) y 5,6 mL de agua. La suspensión se agitó hasta que las sales se volvieron blancas y luego se filtró a través de un tapón de gel de sílice. El material filtrado se concentró por evaporación por rotación y el residuo se purificó mediante cromatografía flash de columna de fase normal (Analogix, 0-75% hexanos / acetato de etilo).

EJEMPLO 539C

8-(metoximetil)-8-metil-1,4-dioxaespiro[4,5]decano

A un balón de 250 mL se agregó NaH (0,902 g) y tetrahidrofurano (37,6 mL). Se agregó EJEMPLO 539B (3,8 g) como una solución de tetrahidrofurano a temperatura ambiente. La suspensión se agitó por 30 minutos y luego se agregó CH_3I (0,611 mL). La reacción se agitó bajo N_2 durante la noche, se detuvo cuidadosamente con salmuera y se diluyó con agua y éter. La capa acuosa se extrajo con éter (2x) y los orgánicos combinados se secaron (Na_2SO_4), se filtró y se concentró por evaporación por rotación. El residuo se purificó mediante cromatografía flash de columna (Analogix, 0-60% hexanos / acetato de etilo).

EJEMPLO 539D

4-(metoximetil)-4-metilciclohexanona

El compuesto del título se preparó utilizando EJEMPLO 539C en lugar de EJEMPLO 535C en EJEMPLO 535D.

EJEMPLO 539E

2-cloro-5-(metoximetil)-5-metilciclohex-1-encarbaldehido

A un balón de 25 mL se agregó N,N-dimetilformamida (0,70 mL) y diclorometano (3,31 mL). La solución se enfrió a 0°C y se agregó $POCl_3$ (0,772 mL) por goteo bajo nitrógeno. Luego de completarse la adición, la solución se calentó a temperatura ambiente y se agitó por 35 minutos. Luego se agregó EJEMPLO 539D (1,035 g) como una solución de diclorometano y la mezcla se dejó agitar durante la noche a temperatura ambiente. La reacción se vertió en hielo y $NaHCO_3$, se calentó a temperatura ambiente, y se extrajo con diclorometano (2x). La capa acuosa combinada se extrajo con éter dietílico y luego los orgánicos combinados se secaron (Na_2SO_4), se filtró y se concentró por evaporación por rotación. El residuo se purificó mediante cromatografía flash de columna de fase normal (Analogix, 0-45% hexanos / acetato de etilo).

EJEMPLO 539F

2-(4-clorofenil)-5-(metoximetil)-5-metilciclohex-1-encarbaldehido

A un vial de 20 mL se agregó EJEMPLO 539E (700 mg) y ácido 4-clorofenilborónico (648 mg) en agua (3,8 mL). Se agregó bromuro de tetrabutilamonio (1,1 g) y carbonato de potasio (1,2 g) seguido por acetato de paladio (II) (23,3mg). La mezcla se desgasificó con nitrógeno por 2 minutos, el vial se tapó y la reacción se calentó a 45°C durante la noche. La mezcla de la reacción se diluyó con acetato de etilo y agua y la capa acuosa se extrajo con acetato de etilo (3x). Los orgánicos combinados se secaron ($NaSO_4$), se filtró y se concentró por evaporación por rotación. El residuo se purificó mediante cromatografía flash de columna de fase normal (Analogix, 0-60% hexanos / acetato de etilo).

EJEMPLO 539G

2-(1H-indazol-4-iloxi)-4-(4-((2-(4-clorofenil)-5-(metoximetil)-5-metilciclohex-1-enil)metil)piperazin-1-il)benzoato de metilo

A un vial de 20 mL se agregó EJEMPLO 400C (531 mg) y EJEMPLO 539F (420 mg) en diclorometano (8 mL). Se agregó triacetoxiborhidruro de sodio (415 mg). La reacción se agitó por 2 días a temperatura ambiente y luego se detuvo con $NaHCO_3$ acuoso saturado. La capa acuosa se extrajo con diclorometano (3x), se secó ($MgSO_4$), se filtró y se concentró por

evaporación por rotación. El residuo se purificó mediante cromatografía flash de columna de fase normal (Analogix, 0,4% - 4% diclorometano/metanol).

EJEMPLO 539H

4-(4-((2-(4-clorofenil)-5-(metoximetil)-5-metilciclohex-1-enil)metil)piperazin-1-il)-2-(1-tritil-1H-indazol-4-iloxi)benzoato de metilo

A un balón de 25 mL se agregó EJEMPLO 539G (704 mg) en diclorometano (5 mL). Se agregó trietilamina (319 µl) seguido por cloruro de tritilo (399 mg). La reacción se agitó durante la noche y se diluyó con agua y diclorometano. La capa acuosa se extrajo con diclorometano (2x) y los orgánicos combinados se secaron ($MgSO_4$), se filtró y se concentró por evaporación por rotación. El residuo se colocó en diclorometano y se pasó por un embudo buchner de gel de sílice Supelco preempaquetado y las impurezas no polares se retiraron enjuagando con diclorometano. El producto se eluyó con metanol al 5% en diclorometano. El residuo se concentró por evaporación por rotación y el residuo se usó en el siguiente paso sin purificación adicional.

EJEMPLO 539I

ácido 4-(4-((2-(4-clorofenil)-5-(metoximetil)-5-metilciclohex-1-enil)metil)piperazin-1-il)-2-(1-tritil-1H-indazol-4-iloxi)benzoico

El compuesto del título se preparó utilizando EJEMPLO 539H en lugar de EJEMPLO 175D en EJEMPLO 175E.

EJEMPLO 539J

N-(5-cloro-6-((trans-4-hidroxi-4-metilciclohexil)metoxi)piridin-3-ilsulfonil)-4-(4-((2-(4-clorofenil)-5-(metoximetil)-5-metilciclohex-1-enil)metil)piperazin-1-il)-2-(1-tritil-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 539I en lugar de EJEMPLO 1E y EJEMPLO 493B en lugar de EJEMPLO 1F en EJEMPLO 1G.

EJEMPLO 539K

N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-5-(metoximetil)-5-metilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 539J en lugar de EJEMPLO 542E en EJEMPLO 542F. 1H NMR (300 MHz, sulfóxido de dimetilo-d_6) δ 13,10 (s, 1H) 8,28 (d, 1H) 7,77 - 7,91 (m, 2H) 7,58 (d, 1H) 7,37 (d, 2H) 6,99 - 7,19 (m, 4H) 6,80 (dd, 1H) 6,54 (s, 1H) 6,15 (dd, 1H) 4,10 - 4,34 (m, 3H) 3,26 (s, 3H) 3,05 - 3,21 (m, 6H) 2,12 - 2,29 (m, 4H) 2,09 (s, 1H) 1,85 - 1,98 (m, 1H) 1,68 - 1,81 (m, 4H) 1,50 - 1,63 (m, 4H) 1,31 - 1,45 (m, 3H) 1,13 - 1,30 (m, 2H) 1,11 (s, 3H) 0,94 (s, 3H).

EJEMPLO 540

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-{[3-nitro-4-({[(2S)-4-(oxetan-3-il)morfolin-2-il]metil}amino)fenil]sulfonil}benzamida

EJEMPLO 540A

(S)-3-nitro-4-((4-(oxetan-3-il)morfolin-2-il)metilamino)bencenosulfonamida

Un balón se cargó con EJEMPLO 438B (1,012 g), metanol anhidro (15 mL) y ácido acético (2,75 mL). Se agregó oxetan-3-ona (0,461 g) y la mezcla se agitó a temperatura ambiente por 30 minutos. Luego se agregó cianoborohidruro de sodio (0,603 g) y la mezcla se agitó a temperatura ambiente durante la noche. La mezcla se concentró y el residuo se recogió en una solución acuosa al 5% de Na_2CO_3 (15 mL). La mezcla se extrajo con acetato de etilo, y las capas orgánicas combinadas se concentraron. El producto crudo se purificó en una columna de gel de sílice eluyendo con 5% y 10% metanol en CH_2Cl_2 para dar el compuesto del título.

EJEMPLO 540B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-{[3-nitro-4-({[(2S)-4-(oxetan-3-il)morfolin-2-il]metil}amino)fenil]sulfonil}benzamida

El compuesto del título se preparó utilizando EJEMPLO 400E en lugar de EJEMPLO 26C y EJEMPLO 540A en lugar de EJEMPLO 1F en EJEMPLO 177. ^{1}H NMR (500MHz, piridin-d_5) δ 14,58 (bs, 1H), 9,05 (d, 1H), 8,85 (t, 1H), 8,37 (s, 1H), 8,17 (dd, 1H), 8,02 (d, 1H), 7,45 (d, 2H), 7,34 (d, 1H), 7,15 (t, 1H), 7,10 (d, 2H), 6,90-6,80 (m, 3H), 6,53 (d, 1H), 4,67-4,61 (m, 4H), 3,94-3,90 (m, 2H), 3,68 (dt, 1H), 3,47 (m, 1H), 3,44-3,34 (m, 2H), 3,14 (m, 4H), 2,82 (s, 2H), 2,71 (d, 1H), 2,44 (d, 1H), 2,30 (m, 2H), 2,22 (m, 4H), 1,99 (s, 2H), 1,95 (dt, 1H), 1,84 (t, 1H), 1,41 (t, 2H), 0,96 (s, 6H).

EJEMPLO 541

2-(1H-bencimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-nitro-4-({[(2S)-4-(oxetan-3-il)morfolin-2-il]metil}amino)fenil]sulfonil}benzamida

El compuesto del título se preparó utilizando EJEMPLO 540A en lugar de EJEMPLO 428D en EJEMPLO 428E. ^{1}H NMR (500MHz, piridin-d_5) δ 9,25 (d, 1H), 8,87 (t, 1H), 8,57 (s, 1H), 8,38 (dd, 1H), 8,01 (d, 1H), 7,52 (d, 1H), 7,43 (d, 2H), 7,24 (d, 1H), 7,14 (d, 1H), 7,07 (d, 2H), 6,97 (d, 1H), 6,73-6,68 (m, 2H), 4,69-4,62 (m, 4H), 3,97-3,89 (m, 2H), 3,69 (dt, 1H), 3,51 (m, 1H), 3,47-3,35 (m, 2H), 3,03 (m, 4H), 2,77 (s, 2H), 2,74 (d, 1H), 2,43 (d, 1H), 2,25 (m, 2H), 2,14 (m, 4H), 1,97 (s, 2H), 1,95 (m, 1H), 1,86 (t, 1H), 1,38 (t, 2H), 0,94 (s, 6H).

EJEMPLO 542

N-[(5-cloro-6-{[trans-4-(2-hidroxipropan-2-il)ciclohexil]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 542A

trans-4-((tert-butildimetilsililoxi)metilo) ciclohexanocarboxilato de metilo

Se disolvió Trans-4-(hidroximetil)ciclohexanocarboxilato de metilo se disolvió en diclorometano (30 mL), luego se agregó imidazol (1,0 g) y tert-butilclorodimetilsilano (1,6 g). La reacción se agitó a temperatura ambiente durante la noche. La mezcla de la reacción luego se concentró, se disolvió en acetato de etilo y se lavó con HCl acuoso 1N, agua, y salmuera. La capa orgánica se secó sobre Na_2SO_4. El compuesto del título se obtuvo luego de la filtración y concentración.

EJEMPLO 542B

2-(trans-4-((tert-butildimetilsililoxi)metil)ciclohexil)propan-2-ol

Se disolvió EJEMPLO 542A (1,4 g) en tetrahidrofurano (15 mL), luego se agregó una solución de cloruro de metilmagnesio 3,0*M* en tetrahidrofurano (3,4 mL) cuidadosamente y la reacción se dejó agitar a temperatura ambiente bajo nitrógeno durante la noche. La reacción luego se vertió en NH_4Cl acuoso saturado y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre Na_2SO_4. Luego de la filtración y concentración el

producto se purificó mediante cromatografía de columna sobre gel de sílice usando 9/1 hexanos/acetato de etilo.

EJEMPLO 542C

2-(trans-4-(hidroximetil)ciclohexil)propan-2-ol

Se disolvió EJEMPLO 542B en tetrahidrofurano (10 mL), luego se agregó una solución 1,0*M* de fluoruro de tetrabutilamonio en tetrahidrofurano (17,5 mL) y la reacción se agitó a temperatura ambiente durante la noche. La reacción se concentró y el residuo se purificó mediante cromatografía de columna sobre gel de sílice usando 50-70% acetato de etilo en hexanos.

EJEMPLO 542D

5-cloro-6-((trans-4-(2-hidroxipropan-2-il)ciclohexil)metoxi) piridin-3-sulfonamida

El compuesto del título se preparó utilizando EJEMPLO 542C en lugar de (tetrahidro-2H-piran-4-il)metanol y 5,6-dicloropiridin-3-sulfonamida en lugar de EJEMPLO 329A en EJEMPLO 329B, excepto que aquí dimetilformamida se usó en lugar de tetrahidrofurano.

EJEMPLO 542E

N-(5-cloro-6-((trans-4-(2-hidroxipropan-2-il)ciclohexil)metoxi)piridin-3-ilsulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-2-(2-tritil-2H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 498C en lugar de EJEMPLO 1E y EJEMPLO 542D en lugar de EJEMPLO 1F en EJEMPLO 1G.

EJEMPLO 542F

N-[(5-cloro-6-{[trans-4-(2-hidroxipropan-2-il)ciclohexil]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 542E (310 mg) se disolvió en diclorometano (2,5 mL), y se agregó ácido p-toluenosulfónico monohidratado (27 mg). Luego de agitar a temperatura ambiente por 30 minutos, la reacción se vertió en $NaHCO_3$ acuoso saturado y se extrajo con diclorometano. La capa orgánica se lavó con salmuera y se secó sobre Na_2SO_4. Luego de la filtración y concentración el residuo se purificó mediante cromatografía de columna sobre gel de sílice usando metanol al 2-10% en diclorometano. ^{1}H NMR (500MHz, sulfóxido de dimetilo-d_6) δ

13,10 (s, 1H), 8,27 (d, 1H), 7,85 (d, 1H), 7,81 (s, 1H), 7,58 (d, 1H), 7,37 (d, 2H), 7,06 (m, 4H), 6,80 (dd, 1H), 6,54 (d, 1H), 6,13 (d, 1H), 4,19 (d, 2H), 4,00 (s, 1H), 3,21 (br s, 4H), 2,96 (v br s, 2H), 2,40 (br s, 4H), 2,19 (br m, 2H), 1,98 (s, 2H), 1,83 (br m, 4H), 1,70 (br m, 1H), 1,42 (t, 2H), 1,18 (br m, 1H), 1,02 (br m, 4H), 1,02 (s, 6H), 0,93 (s, 6H).

EJEMPLO 543

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-ciano-4-[(trans-4-hidroxi-4-metilciclohexil)metoxi]fenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 543A

3-ciano-4-((trans-4-hidroxi-4-metilciclohexil)metoxi)bencenosulfonamida

El compuesto del título se preparó utilizando EJEMPLO 531F en lugar de EJEMPLO 517B en EJEMPLO 534A.

EJEMPLO 543B

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-N-(3-ciano-4-((trans-4-hidroxi-4-metilciclohexil)metoxi)fenilsulfonil)-2-(1-tritil-1H-indazol-4-iloxi)benzamida

Este EJEMPLO se preparó utilizando EJEMPLO 498C en lugar de EJEMPLO 1E y EJEMPLO 543A en lugar de EJEMPLO 1F en EJEMPLO 1G.

EJEMPLO 543C

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-ciano-4-[(trans-4-hidroxi-4-metilciclohexil)metoxi]fenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 543B en lugar de EJEMPLO 521I en EJEMPLO 521J. ^{1}H NMR (300 MHz, sulfóxido de dimetilo-d_6) δ 13,12 (s, 1H), 11,70 - 11,35 (m, 1H), 7,87 (d, 1H), 7,81 (t, 2H), 7,55 (d, 1H), 7,39 - 7,33 (m, 2H), 7,20 - 7,10 (m, 3H), 7,09 - 7,03 (m, 2H), 6,80 (dd, 1H), 6,53 (d, *J* = 2,1 Hz, 1H), 6,18 (dd, 1H), 4,26 (s, 1H), 4,05 (d, 2H), 3,19 (s, 4H), 2,86 (s, 2H), 2,17 (m, 6H), 1,98 (s, 2H), 1,77 (m, 3H), 1,56 (m, 2H), 1,42 (m, 6H), 1,12 (s, 3H), 0,94 (s, 6H).

EJEMPLO 544

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({5-ciano-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 544A

5-bromo-6-((trans-4-hidroxi-4-metilciclohexil)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando EJEMPLO 531F en lugar de (tetrahidro-2H-piran-4-il)metanol en EJEMPLO 329B.

EJEMPLO 544B

5-ciano-6-((trans-4-hidroxi-4-metilciclohexil)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando EJEMPLO 544A en lugar de EJEMPLO 329B en EJEMPLO 333A.

EJEMPLO 544C

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-N-(5-ciano-6-((trans-4-hidroxi-4-metilciclohexil)metoxi)piridin-3-ilsulfonil)-2-(1-tritil-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 498C en lugar de EJEMPLO 1E y EJEMPLO 544B en lugar de EJEMPLO 1F en EJEMPLO 1G.

EJEMPLO 544D

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({5-ciano-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 544C en lugar de EJEMPLO 521I en EJEMPLO 521J. ^{1}H NMR (300 MHz, sulfóxido de dimetilo-d_6) δ 13,07 (s, 1H), 8,50 (d, 1H), 8,23 - 8,12 (m, 1H), 7,76 (s, 1H), 7,60 (d, 1H), 7,37 (d, 2H), 7,07 (dd, 4H), 6,87 - 6,72 (m, 1H), 6,54 (d, 1H), 6,17 - 6,03 (m, 1H), 4,29 (d, 3H), 3,25 - 3,11 (m, 4H), 2,19 (s, 4H), 2,00 (s, 2H), 1,76 (s, 4H), 1,55 (s, 3H), 1,48 - 1,31 (m, 4H), 1,31 - 1,14 (m, 4H), 1,12 (s, 3H), 0,94 (s, 6H).

EJEMPLO 545

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-({5-nitro-6-[(tetrahidro-2H-piran-4-ilmetil)amino]piridin-3-il}sulfonil)benzamida

EJEMPLO 545A

ácido 6-amino-5-nitropiridin-3-sulfónico

Se calentó ácido 6-aminopiridin-3-sulfónico (20 g) en H_2SO_4 concentrado (80 mL) a 50 ºC hasta que se disolvió completamente. A esta solución se agregó HNO_3 fumante por goteo a lo largo de 20 minutos. La velocidad de adición se mantuvo baja de manera tal que temperatura interna no excediera los 55 ºC. Luego de completarse la adición, la mezcla de la reacción se calentó a 50 ºC por 1 hora. Luego de enfriar la mezcla a temperatura ambiente, se vertió en 150 g de hielo. La mezcla se agitó por otra 1 hora. El recipiente completo se enfrió a 0 ºC, y se mantuvo a 0 ºC por otras 2 horas. El sólido se recogió mediante filtración, y se lavó con 1:1 agua/etanol frío (20 mL), seguido por éter dietílico (10 mL). El sólido se secó en un horno de vacío durante la noche para dar el compuesto del título.

EJEMPLO 545B

ácido 6-hidroxi-5-nitropiridin-3-sulfónico

Se trató EJEMPLO 545A (4,0 g) en HCl (37%, 12 mL) y agua (50 mL) con nitrito de sodio (1,19 g) en agua (8 mL) por goteo a 0 ºC. Luego de completarse la adición, la mezcla de la reacción se agitó a 0 ºC por 1 hora. La mezcla luego se calentó bajo reflujo por 2 horas. Se retiró el agua por destilación para dar un residuo casi seco. Luego de enfriar a temperatura ambiente, se agregó una solución de 1:1 etanol/agua (20 mL). La suspensión resultante se enfrió a 0 ºC, y se mantuvo a 0 ºC por 1 hora. El sólido se recogió mediante filtración para dar el compuesto del título.

EJEMPLO 545C

cloruro de 6-cloro-5-nitropiridin-3-sulfonilo

Una mezcla de EJEMPLO 545B (2,6 g), PCl_5 (5,91 g), y $POCl_3$ (10 mL) se calentó a 120 ºC por 4 horas. La suspensión inicial se volvió una solución traslúcida. El exceso de $POCl_3$ se retiró por destilación. Luego de enfriar a temperatura ambiente, el residuo se vertió en 50 g de hielo triturado. El sólido se extrajo con acetato de etilo. La capa acuosa se extrajo con acetato de etilo adicional. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre $MgSO_4$, se filtró, y se concentró para dar el producto crudo que se usó para la siguiente reacción sin purificación adicional.

EJEMPLO 545D

6-cloro-5-nitropiridin-3-sulfonamida

Se enfrió EJEMPLO 545C en tetrahidrofurano (10 mL) a -10 ºC. A esta solución se agregó hidróxido de amonio concentrado (0,82 mL) por goteo. La solución se agitó a -10 ºC por 10 minutos. El solvente se eliminó bajo presión a temperatura ambiente. El residuo se particionó entre agua y acetato de etilo. La capa acuosa se extrajo con acetato de etilo adicional. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre $MgSO_4$, se filtró, y se concentró. El residuo se purificó mediante cromatografía flash de columna sobre gel de sílice para dar el compuesto del título.

EJEMPLO 545E

5-nitro-6-((tetrahidro-2H-piran-4-il)metilamino)piridin-3-sulfonamida

El compuesto del título se preparó utilizando EJEMPLO 545D en lugar de 4-fluoro-3-nitrobencenosulfonamida en EJEMPLO 1F.

EJEMPLO 545F

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-N-(5-nitro-6-((tetrahidro-2H-piran-4-il)metilamino)piridin-3-ilsulfonil)-2-(1-tritil-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 498C en lugar de EJEMPLO 1E y EJEMPLO 545E en lugar de EJEMPLO 1F en EJEMPLO 1G.

EJEMPLO 545G

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-({5-nitro-6-[(tetrahidro-2H-piran-4-ilmetil)amino]piridin-3-il}sulfonil)benzamida

El compuesto del título se preparó utilizando EJEMPLO 545F en lugar de EJEMPLO 542E EJEMPLO 542F. ^{1}H NMR (500MHz, sulfóxido de dimetilo-d_6) δ 13,03 (s, 1H), 8,66 (br s, 1H), 8,49 (d, 1H), 8,45 (d, 1H), 7,78 (s, 1H), 7,57 (d, 1H), 7,36 (d, 2H), 7,01-7,07 (m, 4H), 6,79 (dd, 1H), 6,52 (s, 1H), 6,11 (dd, 1H), 3,84 (dd, 2H), 3,51 (t, 1H), 3,23-3,29 (m, 2H), 3,17 (br s, 4H), 2,84 (br s, 2H), 2,16-2,34 (m, 6H), 1,98 (s, 2H), 1,58-1,61 (m, 2H), 1,41 (t, 2H), 0,94 (s, 6H).

EJEMPLO 546

2-(1H-benzotriazol-4-iloxi)-N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida

EJEMPLO 546A

N-(5-cloro-6-(((1r,4r)-4-hidroxi-4-metilciclohexil)metoxi)piridin-3-ilsulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-2-(1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d][1,2,3]triazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 514F en lugar de EJEMPLO 1E y EJEMPLO 493B en lugar de EJEMPLO 1F en EJEMPLO 1G.

EJEMPLO 546B

2-(1H-benzotriazol-4-iloxi)-N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida

Se trató EJEMPLO 546A (0,22 g) en tetrahidrofurano (10 mL) con fluoruro de tetrabutilamonio 1,0 N (4,3 M). La mezcla de la reacción se calentó a 50 ºC por 3 horas. El solvente se eliminó, y el residuo se particionó entre agua y acetato de etilo. La capa orgánica se separó, y la capa acuosa se extrajo con acetato de etilo adicional tres veces. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre $MgSO_4$, se filtró, y se concentró. El residuo se purificó mediante Sistema de HPLC Gilson preparativa de fase inversa con una columna Fenomenex prep (Luna, 5 μ, C18(2), 250X21,20 mm, 5 Å) eluyendo con 20-80% acetonitrilo en agua con ácido trifluoroacético al 0,1% para dar el compuesto del título. ^{1}H NMR (500MHz, sulfóxido de dimetilo-d_6) δ 8,24 (s, 1H), 7,86 (d, 1H), 7,63 (d, 1H), 7,36-7,38 (m, 3H), 7,06-7,09 (m, 3H), 6,81 (dd, 1H), 6,57 (d, 1H), 6,33 (d, 1H), 4,32 (s, 1H), 4,22 (d, 2H), 3,00 (br s, 4H), 2,41 (br s, 2H), 2,19 (s, 2H), 1,99 (s, 2H), 1,73-1,77 (m, 2H), 1,56-1,59 (m, 2H), 1,36-1,43 (m, 4H), 1,12-1,27 (m, 6H), 0,94 (s, 6H).

EJEMPLO 547

N-({3-cloro-4-[(cis-4-ciano-1-fluorociclohexil)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 547A

1-oxaespiro[2,5]octan-6-carbonitrilo

Una solución de 4-oxociclohexanocarbonitrilo (1,90 g) en sulfóxido de dimetilo (8 mL) se agregó por goteo a una solución de t-butóxido de potasio (2,60 g) y yoduro de trifenilsulfoxonio (5,09 g) en sulfóxido de dimetilo (30 mL) a temperatura ambiente. La mezcla se agitó durante la noche, se diluyó con salmuera al 20%, y se extrajo con 3x acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera al 20%, se secó sobre Na_2SO_4, y se concentró. El crudo se purificó en una columna de 40 g usando un sistema flash ISCO Companion eluyendo con hexano/acetato de etilo (6:4 a 5:5) para dar el producto deseado.

EJEMPLO 547B

cis-4-fluoro-4-(hidroximetil)ciclohexanocarbonitrilo

Una solución de fluorhidrato de piridina (2,25 g) en diclorometano (8 mL) se agregó por goteo a una solución de EJEMPLO 547A (0,780 g) en diclorometano (8 mL) en una botella de polietileno a 0°C. La reacción se calentó lentamente a temperatura ambiente y se agitó por 43 horas. La mezcla de la reacción se agregó lentamente a una Na_2CO_3 acuoso saturado enfriado con hielo hasta alcanzar pH=8-9 y se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se concentró, y se purificó en una columna de sílice de 80g usando un sistema flash ISCO Companion eluyendo con hexano/acetato de etilo (65:35 a 55:45) para dar el producto deseado. También se aisló EJEMPLO 548A a partir de esta reacción.

EJEMPLO 547C

3-cloro-4-((cis-4-ciano-1-fluorociclohexil)metoxi)-N,N-bis(2,4-dimetoxibencil)bencenosulfonamida

El compuesto del título se preparó como se describe en EJEMPLO 329B reemplazando EJEMPLO 329A con EJEMPLO 517C y (tetrahidro-2H-piran-4-il)metanol con EJEMPLO 547B.

EJEMPLO 547D

3-cloro-4-((cis-4-ciano-1-fluorociclohexil)metoxi)bencenosulfonamida

El compuesto del título se preparó como se describe en EJEMPLO 517E reemplazando EJEMPLO 517D con EJEMPLO 547C.

EJEMPLO 547E

N-(3-cloro-4-((cis-4-ciano-1-fluorociclohexil)metoxi)fenilsulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-2-(1-tritil-1H-indazol-4-iloxi)benzamida.

El compuesto del título se preparó como se describe en EJEMPLO 1G reemplazando EJEMPLO 1E con EJEMPLO 498C y EJEMPLO 1F con EJEMPLO 547D.

EJEMPLO 547F

2-(1H-indazol-4-iloxi)-N-(3-cloro-4-((cis-4-ciano-1-fluorociclohexil)metoxi)fenilsulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzamida.

El compuesto del título se preparó como se describe en EJEMPLO 497C reemplazando EJEMPLO 497B con EJEMPLO 547E**.** ^{1}H NMR (300 MHz, sulfóxido de dimetilo-d_6) δ 13,14 (s, 1H), 11,18-12,10 (bs, 1H), 7,84 (s, 1H), 7,66 (d, 1H), 7,48-7,63 (m, 2H), 7,28-7,42 (m, 2H), 7,09-7,24 (m, 3H), 7,05 (m, 2H), 6,80 (dd, 1H), 6,52 (d, 1H), 6,14-6,31 (m, 1H), 4,20 (d, 2H), 3,05-3,26 (m, 4H), 2,69-2,93 (m, 3H), 2,10-2,37 (m, 6H), 1,89-2,11 (m, 7H), 1,50-1,85 (m, 4H), 1,40 (t, 1H), 0,94 (s, 6H).

EJEMPLO 548

N-({3-cloro-4-[(trans-4-ciano-1-fluorociclohexil)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 548A

trans-4-fluoro-4-(hidroximetil)ciclohexanocarbonitrilo

El compuesto del título se preparó y se aisló como se describe en EJEMPLO 547B.

EJEMPLO 548B

3-cloro-4-((trans-4-ciano-1-fluorociclohexil)metoxi)-N,N-bis(2,4-dimetoxibencil)bencenosulfonamida

El compuesto del título se preparó como se describe en EJEMPLO 329B reemplazando EJEMPLO 329A con EJEMPLO 517C y (tetrahidro-2H-piran-4-ilo) metanol con EJEMPLO 548A.

EJEMPLO 548C

3-cloro-4-((trans-4-ciano-1-fluorociclohexil)metoxi)bencenosulfonamida

El compuesto del título se preparó como se describe en EJEMPLO 517E reemplazando EJEMPLO 517D con EJEMPLO 548B.

EJEMPLO 548D

N-(3-cloro-4-((trans-4-ciano-1-fluorociclohexil)metoxi)fenilsulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-2-(1-tritil-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó como se describe en EJEMPLO 1G reemplazando EJEMPLO 1E con EJEMPLO 498C y EJEMPLO 1F con EJEMPLO 548C.

EJEMPLO 548E

N-(3-cloro-4-((trans-4-ciano-1-fluorociclohexil)metoxi)fenilsulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-2-(1-tritil-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó como se describe en EJEMPLO 497C reemplazando EJEMPLO 497B con EJEMPLO 548D. ^{1}H NMR (300 MHz, sulfóxido de dimetilo-d_6) δ 13,15 (s, 1H), 11,50 (s, 1H), 7,85 (s, 1H), 7,67 (d, 1H), 7,46-7,64 (m, 2H), 7,35 (d, 2H), 7,11-7,23 (m, 3H), 7,05 (d, 2H), 6,80 (dd, 1H), 6,52 (d, 1H), 6,23 (d, 1H), 4,30 (d, 2H), 3,10-3,25 (m, 5H), 2,81 (s, 2H), 2,09-2,35 (m, 6H), 1,70-2,07 (m, 10H), 1,40 (t, 2H), 0,83-1,02 (m, 6H).

EJEMPLO 549

N-({5-cloro-6-[(cis-4-ciano-1-fluorociclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 549A

5-cloro-6-((cis-4-ciano-1-fluorociclohexil)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó como se describe en EJEMPLO 329B reemplazando EJEMPLO 329A con EJEMPLO 387A y (tetrahidro-2H-piran-4-il)metanol con EJEMPLO 547B.

EJEMPLO 549B

N-(5-cloro-6-((cis-4-ciano-1-fluorociclohexil)metoxi)piridin-3-ilsulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-2-(1-tritil-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó como se describe en EJEMPLO 1G reemplazando EJEMPLO 1E con EJEMPLO 498C y EJEMPLO 1F con EJEMPLO 549A.

EJEMPLO 549C

2-(1H-indazol-4-iloxi)-N-(5-cloro-6-((cis-4-ciano-1-fluorociclohexil)metoxi)piridin-3-ilsulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzamida

El compuesto del título se preparó como se describe en EJEMPLO 497C reemplazando EJEMPLO 497B con EJEMPLO 549B**.** ^{1}H NMR (400 MHz, piridin-d_5) δ 8,92 (d, 1H), 8,39 (bs, 2H), 8,07 (d, 1H), 7,46 (d, 2H), 7,36 (d, 1H), 7,13 (m, 2H), 6,86 (m, 3H), 6,50 (d, 1H), 4,50 (m, 2H), 3,17 (m, 3H), 3,01 (m, 1H), 2,82 (s, 2H), 2,30 (m, 2H), 2,24 (m, 3H), 2,23 (m, 4H), 1,97-2,04 (m, 4H), 1,83-1,90 (m, 2H), 1,77 (m, 2H), 1,41 (t, 2H), 0,96 (s, 6H).

EJEMPLO 550

N-({5-cloro-6-[(trans-4-ciano-1-fluorociclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 550A

5-cloro-6-((trans-4-ciano-1-fluorociclohexil)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó como se describe en EJEMPLO 329B reemplazando EJEMPLO 329A con EJEMPLO 387A y (tetrahidro-2H-piran-4-il)metanol con EJEMPLO 548A.

EJEMPLO 550B

N-(5-cloro-6-((trans-4-ciano-1-fluorociclohexil)metoxi)piridin-3-ilsulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-2-(1-tritil-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó como se describe en EJEMPLO 1G reemplazando EJEMPLO 1E con EJEMPLO 498C y EJEMPLO 1F con EJEMPLO 550A.

EJEMPLO 550C

2-(1H-indazol-4-iloxi)-N-(5-cloro-6-((trans-4-ciano-1-fluorociclohexil)metoxi)piridin-3-ilsulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzamida

El compuesto del título se preparó como se describe en EJEMPLO 497C reemplazando EJEMPLO 497B con EJEMPLO 550B**.** ^{1}H NMR (400 MHz, piridin-d_5) δ 8,92 (d, 1H), 8,39 (bs, 2H), 8,07 (d, 1H), 7,46 (d, 2H), 7,36 (d, 1H), 7,13 (m, 2H), 6,86 (m, 3H), 6,50 (d, 1H), 4,50 (m, 2H), 3,17 (m, 3H), 3,01 (m, 1H), 2,82 (s, 2H), 2,30 (m, 2H), 2,24 (m, 3H), 2,23 (m, 4H), 1,97-2,04 (m, 4H), 1,83-1,90 (m, 2H), 1,77 (m, 2H), 1,41 (t, 2H), 0,96 (s, 6H).

EJEMPLO 551

N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 551A

4-(4-((4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il)metil)piperazin-1-il)-2-(1-tritil-1H-indazol-4-iloxi)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 465A en lugar de EJEMPLO 400D en EJEMPLO 498B.

EJEMPLO 551B

ácido 4-(4-((4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il)metil)piperazin-1-il)-2-(1-tritil-1H-indazol-4-iloxi)benzoico

El compuesto del título se preparó utilizando EJEMPLO 551A en lugar de EJEMPLO 175D en EJEMPLO 175E.

EJEMPLO 551C

N-(5-cloro-6-((trans-4-hidroxi-4-metilciclohexil)metoxi)piridin-3-ilsulfonil)-4-(4-((4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il)metil)piperazin-1-il)-2-(1-tritil-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 551B en lugar de EJEMPLO 1E y EJEMPLO 493B en lugar de EJEMPLO 1F en EJEMPLO 1G.

EJEMPLO 551D

N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 551C en lugar de EJEMPLO 542E en EJEMPLO 542F. ^{1}H NMR (400MHz, sulfóxido de dimetilo-d_6) δ 13,13 (s, 1H), 8,27 (d, 1H), 7,85 (d, 1H), 7,81 (s, 1H), 7,57 (d, 1H), 7,38 (d, 2H), 7,15 (d, 2H), 7,08 (m, 2H), 6,80 (dd, 1H), 6,56 (d, 1H), 6,14 (d, 1H), 4,26 (s, 1H), 4,25 (d, 2H), 4,15 (s, 2H), 3,20 (br s, 4H), 2,95 (v br s, 2H), 2,31 (br s, 4H), 1,98 (s, 2H), 1,77 (m, 3H), 1,58 (m, 2H), 1,39 (m, 2H), 1,22 (m, 2H), 1,20 (s, 6H), 1,10 (s, 3H).

EJEMPLO 552

2-(1H-bencimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(trans-4-hidroxi-4-metilciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 525C en lugar de EJEMPLO 428D y en EJEMPLO 428E. ^{1}H NMR (500 MHz, piridin-d_5) δ 9,30 (m, 1H), 8,69 (t, 1H), 8,59 (s, 1H), 8,41 (dd, 1H), 7,99 (d, 1H), 7,53 (d, 1H), 7,43 (d, 2H), 7,25 (t, 1H), 7,18 (d, 1H), 7,07 (d, 2H), 6,94 (d, 1H), 6,72 - 6,68 (m, 2H), 5,85 (m, 3H), 3,22 (t, 2H), 3,02 (m, 4H), 2,76 (s, 2H), 2,25 (m, 2H), 2,13 (m, 4H), 1,97 (s, 2H), 1,92 - 1,85 (m, 4H), 1,78 - 1,71 (m, 3H), 1,43 - 1,36 (m, 5H), 1,33 - 1,21 (m, 2H), 0,94 (s, 6H).

EJEMPLO 553

N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-5-metoxi-5-metilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 553A

2-cloro-5-metoxi-5-metilciclohex-1-encarbaldehido

Se trató N,N-dimetilformamida (1,298 mL) en diclorometano (2,0 mL) a -10 °C por goteo con $POCl_3$ (1,426 mL). La mezcla se agitó por 5 minutos y luego se calentó a temperatura ambiente y se agitó 30 minutos. La solución se enfrió a -10 °C, se trató por goteo con una solución de 4-metoxi-4-metilciclohexanona (1,74 g) en diclorometano (2,5 mL) y se agitó por 4 horas a temperatura ambiente. La mezcla de la reacción se vertió sobre una mezcla de hielo y solución al 25% de acetato de sodio. Cuando el hielo se derritió, la mezcla de la reacción se vertió en un embudo de separación y se extrajo con éter dietílico (4 x 125 mL). Los extractos de éter dietílico se lavaron con Solución acuosa de $NaHCO_3$ y salmuera, se secó ($MgSO_4$), se filtró y se concentró. El material concentrado se cromatografió sobre gel de sílice con acetato de etilo al 0-5% en hexanos como eluyente.

EJEMPLO 553B

2-(4-clorofenil)-5-metoxi-5-metilciclohex-1-encarbaldehido

Se combinó EJEMPLO 553A (1,55 g), ácido 4-clorofenilborónico (1,542 g), acetato de paladio(II) (0,055 g), K_2CO_3 (2,84 g) y bromuro de tetrabuilamonio (2,65 g) en un balón de 50 mL equipado con una barra de agitación magnética. Se agregó agua (9,13 mL). Se hizo pasar nitrógeno por el vial, se tapó y se agitó a 45 °C por 14 horas. La mezcla de la reacción se enfrió a temperatura ambiente y se particionó entre salmuera y éter dietílico. La capa orgánica se lavó con salmuera, se secó ($MgSO_4$), se filtró a través de un tapón de tierra diatomea, se concentró y se cromatografió sobre gel de sílice con acetato de etilo entre 5 y 20 % en hexanos como eluyente.

EJEMPLO 553C

2-(1H-indazol-4-iloxi)-4-(4-((2-(4-clorofenil)-5-metoxi-5-metilciclohex-1-enil)metil)piperazin-1-il)benzoato de metilo

El compuesto del título se preparó utilizando EJEMPLO 553B en lugar de 4-clorobifenil-2-carboxaldehido y EJEMPLO 400C en lugar de piperazin-1-carboxilato de tert-butilo en EJEMPLO 1A excepto que una pequeña cantidad de sulfóxido de dimetilo se agregó a la mezcla de la reacción para disolver los reactivos.

EJEMPLO 553D

4-(4-((2-(4-clorofenil)-5-metoxi-5-metilciclohex-1-enil)metil)piperazin-1-il)-2-(1-tritil-1H-indazol-4-iloxi)benzoato de metilo

Se trató EJEMPLO 553C (1,46 g) en diclorometano (11,84 mL) en forma secuencial con cloruro de tritilo (0,667 g) y trietilamina (0,990 mL) y se agitó por 7 días a temperatura ambiente. La mezcla de la reacción se concentró y se cromatografió sobre gel de sílice con metanol entre 0 y 4% en CH_2Cl_2 como eluyente.

EJEMPLO 553E

ácido 4-(4-((2-(4-clorofenil)-5-metoxi-5-metilciclohex-1-enil)metil)piperazin-1-il)-2-(1-tritil-1H-indazol-4-iloxi)benzoico

El compuesto del título se preparó utilizando EJEMPLO 553D en lugar de EJEMPLO 175D en EJEMPLO 175E.

EJEMPLO 553F

N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi)piridin-3-il}sulfonil)-4-(4-((2-(4-clorofenil)-5-metoxi-5-metilciclohex-1-enil)metil)piperazin-1-il)-2-(1-tritil-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 553E en lugar de EJEMPLO 1E y EJEMPLO 531G en lugar de EJEMPLO 1F en EJEMPLO 1G.

EJEMPLO 553G

N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-5-metoxi-5-metilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 553F en lugar de EJEMPLO 542E en EJEMPLO 542F. ^{1}H NMR (500 MHz, piridina -d_5) δ 14,62 (s, 1H), 8,95 (d, 1H), 8,39 (d, 1H), 8,38 (d, 1H), 8,06 (d, 1H), 7,44 (m, 2H), 7,37 (d, 1H), 7,14 (m, 3H), 6,86 (m, 2H), 6,50 (d, 1H), 4,29 (d, 2H), 3,24 (s, 3H), 3,17 (t, 4H), 2,82 (m, 2H), 2,62 (d, 1H), 2,52 (m, 1H), 2,25 (m, 6H), 1,88 (m, 6H), 1,75 (m, 2H), 1,64 (m, 1H), 1,41 (s, 3H), 1,32 (m, 2H), 1,24 (s, 3H).

EJEMPLO 554

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(5-cloro-6-{[1-(1,3-tiazol-2-il)piperidin-4-il]metoxi}piridin-3-il)sulfonil]-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 554A

1-(tiazol-2-il)piperidin-4-carboxilato de metilo

Una mezcla de piperidin-4-carboxilato de metilo (2,045 g), 2-bromotiazol (1,64 g), y Cs_2CO_3 (5,86 g) en N,N-dimetilformamida (15 mL) se calentó a 100 ºC durante la noche. Luego de enfriar la mezcla a temperatura ambiente, la mezcla de la reacción se particionó entre agua y acetato de etilo. La capa orgánica se separó, y la capa acuosa se extrajo con acetato de etilo adicional tres veces. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre $MgSO_4$, se filtró, y se concentró. El residuo se purificó mediante cromatografía flash sobre gel de sílice para dar el compuesto del título.

EJEMPLO 554B

(1-(tiazol-2-il)piperidin-4-il)metanol

El compuesto del título se preparó utilizando EJEMPLO 554A en lugar de EJEMPLO 520A en EJEMPLO 520B.

EJEMPLO 554C

5-cloro-6-((1-(tiazol-2-il)piperidin-4-il)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando EJEMPLO 554B en lugar de (tetrahidro-2H-piran-4-il)metanol y EJEMPLO 387A en lugar de EJEMPLO 329A en EJEMPLO 329B.

EJEMPLO 554D

N-(5-cloro-6-((1-(tiazol-2-il)piperidin-4-il)metoxi)piridin-3-ilsulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-2-(1-tritil-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 498C en lugar de EJEMPLO 1E y EJEMPLO 554C en lugar de EJEMPLO 1F en EJEMPLO 1G.

EJEMPLO 554E

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(5-cloro-6-{[1-(1,3-tiazol-2-il)piperidin-4-il]metoxi}piridin-3-il)sulfonil]-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 554D en lugar de EJEMPLO 542E en EJEMPLO 545F. ^{1}H NMR (500MHz, sulfóxido de dimetilo-d_6) δ 13,17 (s, 1H), 9,50 (s, 1H), 8,32 (d, 1H), 7,88 (d, 1H), 7,83 (s, 1H), 7,59 (d, 1H), 7,40 (d, 2H), 7,18 (d, 1H), 7,04-7,13 (m, 4H), 6,87 (d, 1H), 6,84 (d, 1H), 6,66 (d, 1H), 6,14 (d, 1H), 4,30 (d, 2H), 3,94-3,99

(m, 2H), 3,80-3,82 (m, 2H), 3,05-3,12 (m, 6H), 2,78 (br s, 2H), 2,25 (s, 2H), 2,04-2,12 (m 4H), 1,86-1,89 (m, 2H), 1,41-1,49 (m, 5H), 0,96 (s, 6H).

EJEMPLO 555

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(6-{[(cis-4-hidroxi-4-metilciclohexil)metil]amino}-5-nitropiridin-3-il)sulfonil]-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 555A

(4-hidroxi-4-metilciclohexil)metilcarbamato de tert-butilo

Una solución de (4-oxociclohexil)metilcarbamato de tert-butilo (1,00 g) se disolvió en tetrahidrofurano (20 mL) y se enfrió a -78°C. Se agregó bromuro de metilmagnesio (4,40 mL) por goteo. La reacción se agitó por 2 horas a -78°C luego se dejó calentar a 0°C y se agitó por 30 minutos. La suspensión resultante se detuvo con agua (10 mL), se diluyó con éter (50 mL) y se lavó con cloruro de amonio (25 mL) y salmuera (25 mL), se secó sobre sulfato de magnesio, se filtró, y se concentró. La cromatografía sobre gel de sílice (Reveleris 80 g) eluyendo usando un gradiente de acetato de etilo entre 5% y 50%/diclorometano a lo largo de 30 minutos (velocidad de flujo = 60 ml/min) dio el compuesto del título como una mezcla ~2:1 de isómeros cis y trans.

EJEMPLO 555B

sal trifluoroacetato de 4-(aminometil)-1-metilciclohexanol

A una solución de EJEMPLO 555A (0,75 g) en diclorometano (3 mL) se agregó unas pocas gotas de agua seguido por ácido trifluoroacético (1,19 mL) y la reacción se agitó a temperatura ambiente. Luego de agitar por 2 horas, se agregó más ácido trifluoroacético (0,5 mL). Luego de 4 horas adicionales, la mezcla de la reacción se concentró y se secó bajo alto vacío. El sólido oleoso resultante se trituró con éter dietílico con sonicación. El filtrado y el lavado con éter dietílico dio el compuesto del título como una mezcla de isómeros cis y trans.

EJEMPLO 555C

6-((cis-4-hidroxi-4-metilciclohexil)metilamino)-5-nitropiridin-3-sulfonamida

El compuesto del título se preparó utilizando EJEMPLO 545D en lugar de EJEMPLO 387A y EJEMPLO 555B en lugar de (4-fluorotetrahidro-2H-piran-4-il)metanamina en EJEMPLO 413A. Se aislaron dos isómeros mediante un sistema de HPLC Gilson preparativa de fase inversa con una columna Fenomenex prep (Luna, 5 μ, C18(2), 250X21,20 mm, 5 Å) eluyendo con 20-80% acetonitrilo en agua con ácido trifluoroacético al 0,1%.

EJEMPLO 555D

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-N-(6-(((1s,4s)-4-hidroxi-4-metilciclohexil)metilamino)-5-nitropiridin-3-ilsulfonil)-2-(1-tritil-1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 498C en lugar de EJEMPLO 1E y EJEMPLO 555C en lugar de EJEMPLO 1F en EJEMPLO 1G.

EJEMPLO 555E

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(6-{[(cis-4-hidroxi-4-metilciclohexil)metil]amino}-5-nitropiridin-3-il)sulfonil]-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 555D en lugar de EJEMPLO 542E en EJEMPLO 542F. ^{1}H NMR (500MHz, sulfóxido de dimetilo-d_6) δ 13,04 (s, 1H), 8,85 (s, 1H), 8,48 (d, 1H), 8,44 (d, 1H), 7,79 (s, 1H), 7,57 (d, 1H), 7,36 (d, 2H), 6,96-7,07 (m, 4H), 6,80 (dd, 1H), 6,54 (d, 1H), 6,11 (dd, 1H), 3,95 (s, 1H), 3,48 (t, 2H), 3,19 (s, 4H), 2,87 (br s, 2H), 2,30-2,34 (m, 4H), 2,18 (m 2H), 1,97-1,99 (m, 2H), 1,35-1,55 (m, 10H), 1,20-1,26 (m, 4H), 1,08 (s, 3H), 0,94 (s, 6H).

EJEMPLO 556

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]-5-(trifluorometil)piridin-3-il}sulfonil)-2-(1H-indazol-4-iloxi)benzamida

EJEMPLO 556A

6-((trans-4-hidroxi-4-metilciclohexil)metoxi)-5-(trifluorometil)piridin-3-sulfonamida

Este EJEMPLO se preparó utilizando EJEMPLO 493A en lugar de (tetrahidro-2H-piran-4-il)metanol y EJEMPLO 410E en lugar de EJEMPLO 329A en EJEMPLO 329B. Los productos de la reacción crudos se purificaron mediante un sistema de HPLC Gilson

preparativa de fase inversa con una columna Fenomenex prep (Luna, 5 µ, C18(2), 250X21,20 mm, 5 Å) eluyendo con 20-80% acetonitrilo en agua con ácido trifluoroacético al 0,1% para dar el compuesto del título.

EJEMPLO 556B

El compuesto del título se preparó utilizando EJEMPLO 498C en lugar de EJEMPLO 1E y EJEMPLO 556A en lugar de EJEMPLO 1F en EJEMPLO 1G.

EJEMPLO 556C

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]-5-(trifluorometil)piridin-3-il}sulfonil)-2-(1H-indazol-4-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 556B en lugar de EJEMPLO 542E en EJEMPLO 542F. ^{1}H NMR (500MHz, sulfóxido de dimetilo-d_6) δ 13,06 (s, 1H), 8,49 (s, 1H), 8,13 (d, 1H), 7,77 (s, 1H), 7,61 (d, 1H), 7,37 (d, 2H), 7,01-7,08 (m, 4H), 6,78 (dd, 1H), 6,51 (s, 1H), 6,12 (dd, 1H), 4,26-4,30 (m, 3H), 3,18 (s, 4H), 2,91 (br s, 2H), 2,31-2,35 (m, 2H), 2,16-2,18 (m 2H), 1,97-1,99 (m, 2H), 1,68-1,75 (m, 4H), 1,55-1,58 (m, 2H), 1,26 (m, 2H), 1,10 (s, 3H), 0,94 (s, 6H).

EJEMPLO 557

2-(1H-bencimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(cis-4-hidroxi-4-metilciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó utilizando EJEMPLO 525D en lugar de EJEMPLO 428D en EJEMPLO 428E. ^{1}H NMR (500MHz, piridin-d_5) δ 9,29 (d, 1H), 8,58 (s, 1H), 8,40 (dd, 1H), 8,00 (d, 1H), 7,53 (d, 1H), 7,43 (d, 2H), 7,25 (m, 2H), 7,18 (d, 1H), 7,07 (d, 2H), 6,91 (d, 1H), 6,73-6,68 (m, 2H), 3,21 (t, 2H), 3,02 (m, 4H), 2,76 (s, 2H), 2,25 (m, 2H), 2,13 (m, 4H), 1,97 (s, 2H), 1,90-1,79 (m, 4H), 1,70-1,60 (m, 3H), 1,45-1,30 (m, 8H), 0,94 (s, 6H).

EJEMPLO 558

N-(4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzoil]sulfamoil}-2-nitrofenil)-4-cianopiperidin-1-carboxamida

EJEMPLO 558A

4-cianopiperidin-1-carboxamida

Un balón con fosgeno (20% en peso en tolueno, 3,16 mL) y diclorometano (10 mL) se enfrió con un baño de hielo. Se agregó una solución de N-etil-N-isopropilpropan-2-amina (1,393 mL) y piperidin-4-carbonitrilo (0,441 g) en diclorometano (5 mL) con una jeringa por goteo. La mezcla se agitó a temperatura ambiente durante la noche y luego se concentró hasta secar. El residuo se disolvió en metanol (10 mL) y 2 mL de NH_3 7 N en metanol. La mezcla se agitó a 50 °C durante la noche. La mezcla se concentró y el sólido residual se mezcló con salmuera (5 mL) y se extrajo con acetato de etilo (8x 25 mL). La solución orgánica se secó ($MgSO_4$), se filtró y se concentró. El material crudo se purificó en una columna de gel de sílice eluyendo con 5-10% metanol en CH_2Cl_2.

EJEMPLO 558B

4-ciano-N-(2-nitro-4-sulfamoilfenil)piperidin-1-carboxamida

El compuesto del título se preparó utilizando EJEMPLO 558A en lugar de (tetrahidro-2H-piran-4-il)metanol en EJEMPLO 279A.

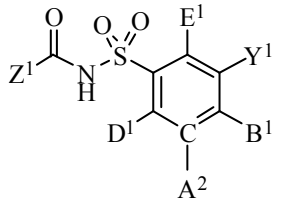
EJEMPLO 558C

N-(4-(N-(2-(1H-indazol-4-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoil)sulfamoil)-2-nitrofenil)-4-cianopiperidin-1-carboxamida

El compuesto del título se preparó utilizando EJEMPLO 400E en lugar de EJEMPLO 26C y EJEMPLO 558B en lugar de EJEMPLO 1F en EJEMPLO 177. ^{1}H NMR (500MHz, piridin-d_5) δ 14,58 (bs, 1H), 10,43 (s, 1H), 9,05 (d, 1H), 8,56 (d, 1H), 8,36 (s, 1H), 8,16 (d, 1H), 8,10 (d, 1H), 7,45 (d, 2H), 7,35 (d, 1H), 7,14 (d, 1H), 7,11 (d, 2H), 6,85 (m, 2H), 6,49 (d, 1H), 3,79 (m, 2H), 3,46 (m, 2H), 3,16 (m, 4H), 2,98 (m, 1H), 2,82 (s, 2H), 2,30 (t, 2H), 2,24 (m, 4H), 1,99 (s, 2H), 1,85 (m, 2H), 1,79 (m, 2H), 1,41 (t, 2H), 0,96 (s, 6H).

REIVINDICACIONES:

1. Un compuesto CARACTERIZADO PORQUE tiene la Fórmula I



(I),

o una sal, profármaco o sal de profármaco terapéuticamente aceptable del mismo ,

A^1 es N o $C(A^2)$;

uno o dos o tres o cada uno de A^2, B^1, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes se seleccionan en forma independiente entre H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$; y

Y^1 es H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ o $NHSO_2R^{17}$;

o

B^1 y Y^1, junto con los átomos a los cuales están unidos , son imidazol o triazol; y

uno o dos o cada uno de A^2, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes se seleccionan en forma independiente entre H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$;

R^1 es R^2, R^3, R^4 o R^5;

R^{1A} es C_1-C_6-alquilo, C_3-C_6-alquenilo o C_3-C_6-alquinilo;

R^2 es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{2A}; R^{2A} es cicloalcano o heterocicloalcano;

R^3 es heteroarilo que no está fusionado o está fusionado con benceno, heteroareno o R^{3A}; R^{3A} es cicloalcano o heterocicloalcano;

R^4 es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{4A}; R^{4A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^5 es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^6 es C_2-C_5-espiroalquilo, cada uno de los cuales no esta sustituido o está sustituido con OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ o $N(CH_3)_2$;

R^{6A} y R^{6B} se seleccionan en forma independiente entre alquilo o, junto con el N al cual están unidos, R^{6C};

R^{6C} es aziridin-1–ilo, azetidin-1–ilo, pirrolidin-1–ilo o piperidin-1–ilo, teniendo cada uno una unidad CH_2 no reemplazada o reemplazada con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH;

R^7 es R^8, R^9, R^{10} o R^{11};

R^8 es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{8A};

R^{8A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^9 es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{9A}; R^{9A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{10} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{10A}; R^{10A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{11} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I;

R^{12} es R^{13}, R^{14}, R^{15} o R^{16};

R^{13} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{13A}; R^{13A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{14} es heteroarilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{14A}; R^{14A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{15} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{15A}; R^{15A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{16} es alquilo, alquenilo o alquinilo;

R^{17} es R^{18}, R^{19}, R^{20} o R^{21};

R^{18} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{18A}; R^{18A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{19} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{19A}; R^{19A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{20} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{20A}; R^{20A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{21} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{22} es R^{23}, R^{24} o R^{25};

R^{23} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{23A}; R^{23A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{24} es heteroareno que no está fusionado o está fusionado con areno, heteroareno o R^{24A}; R^{24A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{25} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{25A}; R^{25A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

Z^1 es R^{26} o R^{27}, cada uno de los cuales está sustituido con R^{28}, R^{29} o R^{30}, cada uno de los cuales está sustituido con F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} o $N(R^{32})R^{37}$;

R^{26} es fenilo que no está fusionado o está fusionado con areno o heteroareno;

R^{27} es heteroareno que no está fusionado o está fusionado con areno o heteroareno;

R^{28} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{28A}; R^{28A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno

R^{29} es heteroarilo o R^{29A}; R^{29A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{30} es cicloalquilo o cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{30A}; R^{30A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{31} y R^{31A} son en forma independiente F, Cl, Br o alquilo o se toman juntos y son C_2-C_5-espiroalquilo;

R^{32} es R^{33}, $C(O)R^{33}$ o $C(O)OR^{33}$;

R^{33} es R^{34} o R^{35};

R^{34} es fenilo que no está fusionado o está fusionado con arilo, heteroarilo o R^{34A}; R^{34A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{35} es alquilo que no está sustituido o está sustituido con R^{36};

R^{36} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{36A}; R^{36A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{37} es R^{38}, R^{39} o R^{40}, cada uno de los cuales está sustituido con F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ o SO_2R^{41};

R^{38} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{38A}; R^{38A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{39} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{39A}; R^{39A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{40} es C_3-C_8-cicloalquilo o C_4-C_8-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{40A}; R^{40A} cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{41} es R^{42}, R^{43}, R^{44} o R^{45};

R^{42} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{42A}; R^{42A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{43} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{43A}; R^{43A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{44} es C_3-C_9-cicloalquilo o C_4-C_7-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{44A}; R^{44A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{45} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos sustituyentes seleccionados en forma independiente entre: R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{46} es R^{47}, R^{48} o R^{49};

R^{47} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{47A}; R^{47A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{48} es heteroarilo o R^{48A}; R^{48A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{49} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{49A}; R^{49A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

en donde las unidades representadas por R^{26} y R^{27} se sustituyen adicionalmente con uno o dos o tres sustituyentes seleccionados en forma independiente entre: R^{50A}, OR^{50A}, SR^{50A}, $S(O)R^{50A}$, SO_2R^{50A} o NHR^{50A},

R^{50A} es R^{51A}, R^{52A}, R^{53A} o R^{54A};

R^{51A} es fenilo que no está fusionado o está fusionado con benceno, heteroareno o R^{51AA},

en donde R^{51AA} es cicloalcano, cicloalqueno o heterocicloalcano heterocicloalqueno,

R^{52A} es heteroarilo;

R^{53A} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo; donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{53AA};

en donde R^{53AA} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{54A} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre: R^{55AA}, OR^{55AA}, SR^{55AA}, $S(O)R^{55AA}$, SO_2R^{55AA}, NHR^{55AA}, $N(R^{55AA})_2$, $C(O)R^{55AA}$, $C(O)NH_2$, $C(O)NHR^{55AA}$, $NHC(O)R^{55AA}$, $NHSO_2R^{55AA}$, $NHC(O)OR^{55AA}$, SO_2NH_2, SO_2NHR^{55AA}, $SO_2N(R^{55AA})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55AA}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{55AA} es alquilo, alquenilo, alquinilo, fenilo o heteroarilo, o R^{56A};

R^{56A} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N;

en donde las unidades representadas por R^2 R^3 R^4, R^6, R^{6C}, R^8, R^{8A} R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{18}, R^{19}, R^{20}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{34}, R^{36}, R^{38}, R^{39}, R^{40}, R^{42}, R^{43}, R^{44}, R^{47}, R^{48}, y R^{49} son en forma independiente no sustituidas, adicionalmente no sustituidas, sustituidas o adicionalmente sustituidas con uno o dos o tres o cuatro o cinco sustituyentes seleccionados en forma independiente entre $R^{50\,AA}$, R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{50AA} es espirociclilo;

R^{50} es R^{51}, R^{52}, R^{53} o R^{54};

R^{51} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{51B};

R^{51B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{52} es heteroarilo;

R^{53} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{53B};

en donde R^{53B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{54} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$,

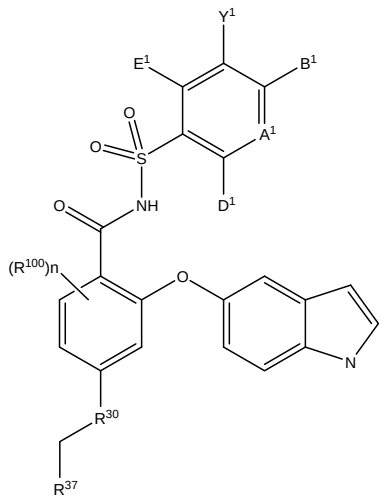
$C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{55} es alquilo, alquenilo, alquinilo, fenilo, heteroarilo o R^{56};

en donde el alquilo, alquenilo, alquinilo no están sustituidos o están sustituidos con OCH_3; y

R^{56} es C_3-C_8-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N.

2. Un compuesto CARACTERIZADO PORQUE tiene la Fórmula II



(II),

o una sal, profármaco o sal de profármaco terapéuticamente aceptable del mismo ,

en donde

R^{100} tiene los valores que se definen para los sustituyentes de R^{26};

n es 0, 1, 2, o 3;

A^1 es N o $C(A^2)$;

uno o dos o tres o cada uno de A^2, B^1, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1,

$SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes se seleccionan en forma independiente entre H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$; y

Y^1 es H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ o $NHSO_2R^{17}$;

o

B^1 y Y^1, junto con los átomos a los cuales están unidos , son imidazol o triazol; y

uno o dos o cada uno de A^2, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes se seleccionan en forma independiente entre H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$;

R^1 es R^2, R^3, R^4 o R^5;

R^{1A} es C_1-C_6-alquilo, C_3-C_6-alquenilo o C_3-C_6-alquinilo;

R^2 es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{2A}; R^{2A} es cicloalcano o heterocicloalcano;

R^3 es heteroarilo que no está fusionado o está fusionado con benceno, heteroareno o R^{3A}; R^{3A} es cicloalcano o heterocicloalcano;

R^4 es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{4A}; R^{4A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^5 es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^6 es C_2-C_5-espiroalquilo, cada uno de los cuales no esta sustituido o está sustituido con OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ o $N(CH_3)_2$;

R^{6A} y R^{6B} se seleccionan en forma independiente entre alquilo o, junto con el N al cual están unidos, R^{6C};

R^{6C} es aziridin-1–ilo, azetidin-1–ilo, pirrolidin-1–ilo o piperidin-1–ilo, teniendo cada uno una unidad CH_2 no reemplazada o reemplazada con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH;

R^7 es R^8, R^9, R^{10} o R^{11};

R^8 es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{8A};

R^{8A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^9 es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{9A}; R^{9A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{10} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{10A}; R^{10A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{11} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{12} es R^{13}, R^{14}, R^{15} o R^{16};

R^{13} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{13A}; R^{13A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{14} es heteroarilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{14A}; R^{14A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{15} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{15A}; R^{15A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{16} es alquilo, alquenilo o alquinilo;

R^{17} es R^{18}, R^{19}, R^{20} o R^{21};

R^{18} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{18A}; R^{18A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{19} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{19A}; R^{19A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{20} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH,

$CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{20A}; R^{20A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{21} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{22} es R^{23}, R^{24} o R^{25};

R^{23} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{23A}; R^{23A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{24} es heteroareno que no está fusionado o está fusionado con areno, heteroareno o R^{24A}; R^{24A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{25} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{25A}; R^{25A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{30} es cicloalquilo o cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{30A}; R^{30A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; cada uno de los cuales está sustituido con F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} o $N(R^{32})R^{37}$;

R^{31} y R^{31A} son en forma independiente F, Cl, Br o alquilo o se toman juntos y son C_2-C_5-espiroalquilo;

R^{32} es R^{33}, $C(O)R^{33}$ o $C(O)OR^{33}$;

R^{33} es R^{34} o R^{35};

R^{34} es fenilo que no está fusionado o está fusionado con arilo, heteroarilo o R^{34A}; R^{34A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{35} es alquilo que no está sustituido o está sustituido con R^{36};

R^{36} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{36A}; R^{36A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{37} es R^{38}, R^{39} o R^{40}, cada uno de los cuales está sustituido con F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ o SO_2R^{41};

R^{38} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{38A}; R^{38A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{39} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{39A}; R^{39A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{40} es C_3-C_8-cicloalquilo o C_4-C_8-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{40A}; R^{40A} cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{41} es R^{42}, R^{43}, R^{44} o R^{45};

R^{42} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{42A}; R^{42A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{43} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{43A}; R^{43A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{44} es C_3-C_9-cicloalquilo o C_4-C_7-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{44A}; R^{44A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{45} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos sustituyentes seleccionados en forma independiente entre: R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{46} es R^{47}, R^{48} o R^{49};

R^{47} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{47A}; R^{47A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{48} es heteroarilo o R^{48A}; R^{48A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{49} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con

N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{49A}; R^{49A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

en donde las unidades representadas por R^2 R^3 R^4, R^6, R^{6C}, R^8, R^{8A} R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{18}, R^{19}, R^{20}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{34}, R^{36}, R^{38}, R^{39}, R^{40}, R^{42}, R^{43}, R^{44}, R^{47}, R^{48}, y R^{49} son en forma independiente no sustituidas, adicionalmente no sustituidas, sustituidas o adicionalmente sustituidas con uno o dos o tres o cuatro o cinco sustituyentes seleccionados en forma independiente entre R^{50AA}, R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{50AA} es espirociclilo;

R^{50} es R^{51}, R^{52}, R^{53} o R^{54};

R^{51} es fenil que no está fusionado o está fusionado con areno, heteroareno o R^{51B}; R^{51B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{52} es heteroarilo;

R^{53} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, teniendo cada uno una o dos unidades CH_2 no reemplazadas o reemplazadas con O, C(O), CNOH, CNOCH#3, S, S(O), SO_2 o NH seleccionados en forma independiente y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{53B};

donde R^{53B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

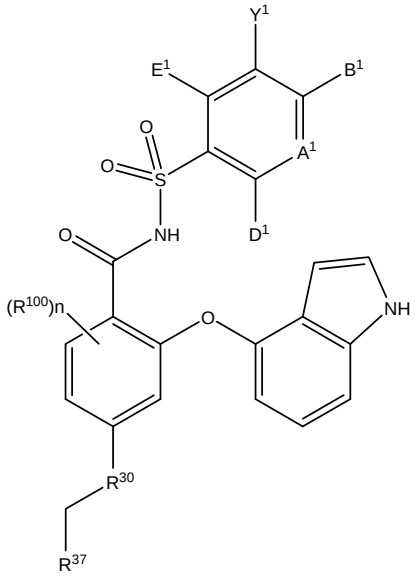
R^{54} es alquilo, alquenilo o alquinilo, cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados entre R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{55} es alquilo, alquenilo, alquinilo, fenilo, heteroarilo o R^{56};

donde el alquilo, alquenilo, alquinilo no están sustituidos o están sustituidos con OCH_3; y

R^{56} es C_3-C_8-cicloalquilo o C_4-C_6-cicloalquenilo, teniendo cada uno una o dos unidades CH_2 no reemplazadas o reemplazadas con O, C(O), CNOH, CNOCH#3, S, S(O), SO_2 o NH seleccionados en forma independiente y una o dos unidades CH no reemplazadas o reemplazadas con N.

3. Un compuesto CARACTERIZADO PORQUE tiene la fórmula III



(III),

o una sal terapéuticamente aceptable, profármaco o sal de profármaco del mismo ,

en donde

R^{100} tiene los valores descritos para los sustituyentes en R^{26};

n es 0, 1, 2, o 3;

A^1 es N o $C(A^2)$;

uno o dos o tres o cada uno de A^2, B^1, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes son sustituyentes seleccionados en forma independiente entre H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$ y ; y

Y^1 es H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ o $NHSO_2R^{17}$;

or

B^1 y Y^1, junto con los átomos a los cuales están unidos, son imidazol o triazol y ; y

uno o dos o cada uno de A^2, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1,

$SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes son sustituyentes seleccionados en forma independiente entre H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$;

R^1 es R^2, R^3, R^4 o R^5;

R^{1A} es C_1-C_6-alquilo, C_3-C_6-alquenilo o C_3-C_6-alquinil;

R^2 es fenil que no está fusionado o está fusionado con areno, heteroareno o R^{2A}; R^{2A} es cicloalcano o heterocicloalcano;

R^3 es heteroarilo que no está fusionado o está fusionado con benceno, heteroareno o R^{3A}; R^{3A} es cicloalcano o heterocicloalcano;

R^4 es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{4A}; R^{4A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^5 es alquilo, alquenilo o alquinilo, cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados entre R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^6 es C_2-C_5-espiroalquilo, cada uno de los cuales no está sustituido o está sustituido con OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ o $N(CH_3)_2$;

R^{6A} y R^{6B} se seleccionan en forma independiente entre alquilo o, junto con el N al cual están unidos, R^{6C};

R^{6C} es aziridin-1-ilo, azetidin-1-ilo, pirrolidin-1-il o piperidin-1-ilo, teniendo cada uno una unidad CH_2 no reemplazada o reemplazada con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH;

R^7 es R^8, R^9, R^{10} o R^{11};

R^8 es fenil que no está fusionado o está fusionado con areno, heteroareno o R^{8A};

R^{8A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^9 es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{9A}; R^{9A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{10} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, teniendo cada uno una o dos unidades CH_2 no reemplazadas o reemplazadas con O, C(O), CNOH, CNOCH#3, S, S(O), SO_2 o NH seleccionados en forma independiente y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno,

heteroareno o R^{10A}; R^{10A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{11} es alquilo, alquenilo o alquinilo, cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados entre R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{12} es R^{13}, R^{14}, R^{15} o R^{16};

R^{13} es fenil que no está fusionado o está fusionado con areno, heteroareno o R^{13A}; R^{13A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{14} es heteroarilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{14A}; R^{14A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{15} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{15A}; R^{15A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{16} es alquilo, alquenilo o alquinil;

R^{17} es R^{18}, R^{19}, R^{20} o R^{21};

R^{18} es fenil que no está fusionado o está fusionado con areno, heteroareno o R^{18A}; R^{18A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{19} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{19A}; R^{19A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{20} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, teniendo cada uno una o dos unidades CH_2 no reemplazadas o reemplazadas con O, C(O), CNOH, CNOCH#3, S, S(O), SO_2 o NH seleccionados en forma independiente y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{20A}; R^{20A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{21} es alquilo, alquenilo o alquinilo, cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados entre R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{22} es R^{23}, R^{24} o R^{25};

R^{23} es fenil que no está fusionado o está fusionado con areno, heteroareno o R^{23A}; R^{23A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{24} es heteroareno que no está fusionado o está fusionado con areno, heteroareno o R^{24A}; R^{24A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{25} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, teniendo cada uno una o dos unidades CH_2 no reemplazadas o reemplazadas con O, C(O), CNOH, CNOCH#3, S, S(O), SO_2 o NH seleccionados en forma independiente y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{25A}; R^{25A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{30} es cicloalquilo o cicloalquenilo, teniendo cada uno una o dos unidades CH_2 no reemplazadas o reemplazadas con O, C(O), CNOH, CNOCH#3, S, S(O), SO_2 o NH seleccionados en forma independiente y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{30A}; R^{30A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; cada uno de los cuales está sustituido con F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} o $N(R^{32})R^{37}$;

R^{31} y R^{31A} son en forma independiente F, Cl, Br o alquilo o son taken togeter y son C_2-C_5-espiroalquilo;

R^{32} es R^{33}, $C(O)R^{33}$ o $C(O)OR^{33}$;

R^{33} es R^{34} o R^{35};

R^{34} es fenil que no está fusionado o está fusionado con arilo, heteroarilo o R^{34A}; R^{34A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{35} es alquilo which no está sustituido o está sustituido con R^{36};

R^{36} es fenil que no está fusionado o está fusionado con areno, heteroareno o R^{36A}; R^{36A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{37} es R^{38}, R^{39} o R^{40}, cada uno de los cuales está sustituido con F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ o SO_2R^{41};

R^{38} es fenil que no está fusionado o está fusionado con areno, heteroareno o R^{38A}; R^{38A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{39} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{39A}; R^{39A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{40} es C_3-C_8-cicloalquilo o C_4-C_8-cicloalquenilo, teniendo cada uno una o dos unidades CH_2 no reemplazadas o reemplazadas con O, C(O), CNOH, CNOCH#3, S, S(O), SO_2 o NH seleccionados en forma independiente y una o dos unidades CH no reemplazadas o

reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{40A}; R^{40A} cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{41} es R^{42}, R^{43}, R^{44} o R^{45};

R^{42} es fenil que no está fusionado o está fusionado con areno, heteroareno o R^{42A}; R^{42A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{43} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{43A}; R^{43A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{44} es C_3-C_9-cicloalquilo o C_4-C_7-cicloalquenilo, teniendo cada uno una o dos unidades CH_2 no reemplazadas o reemplazadas con O, C(O), CNOH, CNOCH#3, S, S(O), SO_2 o NH seleccionados en forma independiente y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{44A}; R^{44A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{45} es alquilo, alquenilo o alquinilo, cada uno de los cuales no está sustituido o está sustituido con uno o dos sustituyentes seleccionados en forma independiente entre R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{46} es R^{47}, R^{48} o R^{49};

R^{47} es fenil que no está fusionado o está fusionado con areno, heteroareno o R^{47A}; R^{47A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{48} es heteroarilo o R^{48A}; R^{48A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{49} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, teniendo cada uno una o dos unidades CH_2 no reemplazadas o reemplazadas con O, C(O), CNOH, CNOCH#3, S, S(O), SO_2 o NH seleccionados en forma independiente y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{49A}; R^{49A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

donde las unidades representadas por R^2 R^3 R^4, R^6, R^{6C}, R^8, R^{8A} R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{18}, R^{19}, R^{20}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{34}, R^{36}, R^{38}, R^{39}, R^{40}, R^{42}, R^{43}, R^{44}, R^{47}, R^{48}, y R^{49} en forma independiente no están sustituidas , no están adicionalmente sustituidas, están sustituidas o adicionalmente sustituidas con uno o dos o tres o cuatro o cinco sustituyentes seleccionados en forma independiente entre R^{50AA}, R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$,

$C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{50AA} es espirociclilo;

R^{50} es R^{51}, R^{52}, R^{53} o R^{54};

R^{51} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{51B};

R^{51B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{52} es heteroarilo;

R^{53} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{53B};

en donde R^{53B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

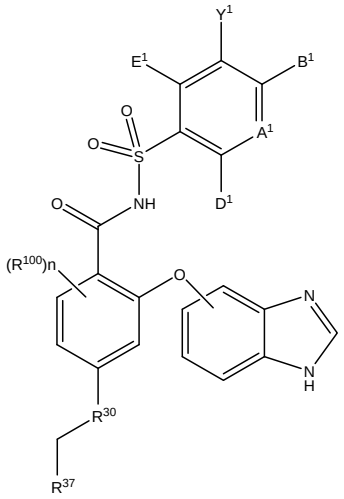
R^{54} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{55} es alquilo, alquenilo, alquinilo, fenilo, heteroarilo o R^{56};

en donde el alquilo, alquenilo, alquinilo no están sustituidos o están sustituidos con OCH_3; y

R^{56} es C_3-C_8-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N.

4. Un compuesto CARACTERIZADO PORQUE tiene la Fórmula IV



(IV),

o una sal, profármaco o sal de profármaco terapéuticamente aceptable del mismo ,

en donde

R^{100} tiene los valores que se definen para los sustituyentes de R^{26};

n es 0, 1, 2, o 3;

A^1 es N o $C(A^2)$;

uno o dos o tres o cada uno de A^2, B^1, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes se seleccionan en forma independiente entre H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$; y

Y^1 es H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ o $NHSO_2R^{17}$;

o

B^1 y Y^1, junto con los átomos a los cuales están unidos , son imidazol o triazol; y

uno o dos o cada uno de A^2, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes se seleccionan en forma independiente entre H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$;

R^1 es R^2, R^3, R^4 o R^5;

R^{1A} es C_1-C_6-alquilo, C_3-C_6-alquenilo o C_3-C_6-alquinilo;

R^2 es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{2A}; R^{2A} es cicloalcano o heterocicloalcano;

R^3 es heteroarilo que no está fusionado o está fusionado con benceno, heteroareno o R^{3A}; R^{3A} es cicloalcano o heterocicloalcano;

R^4 es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{4A}; R^{4A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^5 es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^6 es C_2-C_5-espiroalquilo, cada uno de los cuales no esta sustituido o está sustituido con OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ o $N(CH_3)_2$;

R^{6A} y R^{6B} se seleccionan en forma independiente entre alquilo o, junto con el N al cual están unidos, R^{6C};

R^{6C} es aziridin-1–ilo, azetidin-1–ilo, pirrolidin-1–ilo o piperidin-1–ilo, teniendo cada uno una unidad CH_2 no reemplazada o reemplazada con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH;

R^7 es R^8, R^9, R^{10} o R^{11};

R^8 es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{8A};

R^{8A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^9 es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{9A}; R^{9A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{10} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{10A}; R^{10A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{11} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma

independiente: R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{12} es R^{13}, R^{14}, R^{15} o R^{16};

R^{13} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{13A}; R^{13A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{14} es heteroarilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{14A}; R^{14A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{15} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{15A}; R^{15A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{16} es alquilo, alquenilo o alquinilo;

R^{17} es R^{18}, R^{19}, R^{20} o R^{21};

R^{18} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{18A}; R^{18A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{19} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{19A}; R^{19A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{20} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{20A}; R^{20A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{21} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{22} es R^{23}, R^{24} o R^{25};

R^{23} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{23A}; R^{23A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{24} es heteroareno que no está fusionado o está fusionado con areno, heteroareno o R^{24A}; R^{24A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{25} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con

N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{25A}; R^{25A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{30} es cicloalquilo o cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{30A}; R^{30A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; cada uno de los cuales está sustituido con F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} o $N(R^{32})R^{37}$;

R^{31} y R^{31A} son en forma independiente F, Cl, Br o alquilo o se toman juntos y son C_2-C_5-espiroalquilo;

R^{32} es R^{33}, $C(O)R^{33}$ o $C(O)OR^{33}$;

R^{33} es R^{34} o R^{35};

R^{34} es fenilo que no está fusionado o está fusionado con arilo, heteroarilo o R^{34A}; R^{34A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{35} es alquilo que no está sustituido o está sustituido con R^{36};

R^{36} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{36A}; R^{36A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{37} es R^{38}, R^{39} o R^{40}, cada uno de los cuales está sustituido con F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ o SO_2R^{41};

R^{38} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{38A}; R^{38A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{39} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{39A}; R^{39A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{40} es C_3-C_8-cicloalquilo o C_4-C_8-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{40A}; R^{40A} cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{41} es R^{42}, R^{43}, R^{44} o R^{45};

R^{42} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{42A}; R^{42A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{43} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{43A}; R^{43A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{44} es C_3-C_9-cicloalquilo o C_4-C_7-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{44A}; R^{44A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{45} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos sustituyentes seleccionados en forma independiente entre: R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{46} es R^{47}, R^{48} o R^{49};

R^{47} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{47A}; R^{47A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{48} es heteroarilo o R^{48A}; R^{48A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{49} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{49A}; R^{49A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

en donde las unidades representadas por R^2 R^3 R^4, R^6, R^{6C}, R^8, R^{8A} R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{18}, R^{19}, R^{20}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{34}, R^{36}, R^{38}, R^{39}, R^{40}, R^{42}, R^{43}, R^{44}, R^{47}, R^{48}, y R^{49} son en forma independiente no sustituidas, adicionalmente no sustituidas, sustituidas o adicionalmente sustituidas con uno o dos o tres o cuatro o cinco sustituyentes seleccionados en forma independiente entre $R^{50\,AA}$, R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{50AA} es espirociclilo;

R^{50} es R^{51}, R^{52}, R^{53} o R^{54};

R^{51} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{51B}; R^{51B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{52} es heteroarilo;

R^{53} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{53B};

en donde R^{53B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

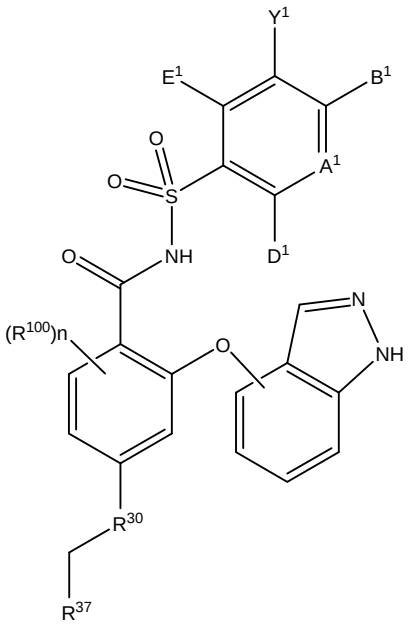
R^{54} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{55} es alquilo, alquenilo, alquinilo, fenilo, heteroarilo o R^{56};

en donde el alquilo, alquenilo, alquinilo no están sustituidos o están sustituidos con OCH_3; y

R^{56} es C_3-C_8-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N.

5. Un compuesto CARACTERIZADO PORQUE tiene la Fórmula V



(V),

o una sal, profármaco o sal de profármaco terapéuticamente aceptable del mismo ,

en donde

R^{100} tiene los valores que se definen para los sustituyentes de R^{26};

n es 0, 1, 2, o 3;

A^1 es N o $C(A^2)$;

uno o dos o tres o cada uno de A^2, B^1, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes se seleccionan en forma independiente entre H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$; y

Y^1 es H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ o $NHSO_2R^{17}$;

o

B^1 y Y^1, junto con los átomos a los cuales están unidos , son imidazol o triazol; y

uno o dos o cada uno de A^2, D^1 y E^1 se seleccionan en forma independiente entre R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NHC(O)NHR^1$, $N(CH_3)C(O)N(CH_3)R^1$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ o $N(CH_3)SO_2N(CH_3)R^1$, y los restantes se seleccionan en forma independiente entre H, F, Cl, Br, I, CF_3, C(O)OH, $C(O)NH_2$ o $C(O)OR^{1A}$;

R^1 es R^2, R^3, R^4 o R^5;

R^{1A} es C_1-C_6-alquilo, C_3-C_6-alquenilo o C_3-C_6-alquinilo;

R^2 es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{2A}; R^{2A} es cicloalcano o heterocicloalcano;

R^3 es heteroarilo que no está fusionado o está fusionado con benceno, heteroareno o R^{3A}; R^{3A} es cicloalcano o heterocicloalcano;

R^4 es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{4A}; R^{4A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^5 es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^6, $NC(R^{6A})(R^{6B})$, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$,

$NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^6 es C_2-C_5-espiroalquilo, cada uno de los cuales no esta sustituido o está sustituido con OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ o $N(CH_3)_2$;

R^{6A} y R^{6B} se seleccionan en forma independiente entre alquilo o, junto con el N al cual están unidos, R^{6C};

R^{6C} es aziridin-1–ilo, azetidin-1–ilo, pirrolidin-1–ilo o piperidin-1–ilo, teniendo cada uno una unidad CH_2 no reemplazada o reemplazada con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH;

R^7 es R^8, R^9, R^{10} o R^{11};

R^8 es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{8A};

R^{8A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^9 es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{9A}; R^{9A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{10} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{10A}; R^{10A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{11} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{12} es R^{13}, R^{14}, R^{15} o R^{16};

R^{13} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{13A}; R^{13A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{14} es heteroarilo, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{14A}; R^{14A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{15} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno, cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{15A}; R^{15A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{16} es alquilo, alquenilo o alquinilo;

R^{17} es R^{18}, R^{19}, R^{20} o R^{21};

R^{18} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{18A}; R^{18A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{19} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{19A}; R^{19A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{20} es C_3-C_{10}-cicloalquilo o C_4-C_{10}-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{20A}; R^{20A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{21} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{22} es R^{23}, R^{24} o R^{25};

R^{23} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{23A}; R^{23A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{24} es heteroareno que no está fusionado o está fusionado con areno, heteroareno o R^{24A}; R^{24A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{25} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{25A}; R^{25A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{30} es cicloalquilo o cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{30A}; R^{30A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; cada uno de los cuales está sustituido con F, Cl, Br, I, CH_2R^{37}, $CH(R^{31})(R^{37})$, $C(R^{31})(R^{31A})(R^{37})$, $C(O)R^{37}$, OR^{37}, SR^{37}, $S(O)R^{37}$, SO_2R^{37}, NHR^{37} o $N(R^{32})R^{37}$;

R^{31} y R^{31A} son en forma independiente F, Cl, Br o alquilo o se toman juntos y son C_2-C_5-espiroalquilo;

R^{32} es R^{33}, $C(O)R^{33}$ o $C(O)OR^{33}$;

R^{33} es R^{34} o R^{35};

R^{34} es fenilo que no está fusionado o está fusionado con arilo, heteroarilo o R^{34A}; R^{34A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{35} es alquilo que no está sustituido o está sustituido con R^{36};

R^{36} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{36A}; R^{36A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{37} es R^{38}, R^{39} o R^{40}, cada uno de los cuales está sustituido con F, Cl, Br, I, R^{41}, OR^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$, SR^{41}, $S(O)R^{41}$ o SO_2R^{41};

R^{38} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{38A}; R^{38A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{39} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{39A}; R^{39A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{40} es C_3-C_8-cicloalquilo o C_4-C_8-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{40A}; R^{40A} cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{41} es R^{42}, R^{43}, R^{44} o R^{45};

R^{42} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{42A}; R^{42A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{43} es heteroarilo que no está fusionado o está fusionado con areno, heteroareno o R^{43A}; R^{43A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{44} es C_3-C_9-cicloalquilo o C_4-C_7-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{44A}; R^{44A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{45} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos sustituyentes seleccionados en forma independiente entre: R^{46}, OR^{46}, NHR^{46}, $N(R^{46})_2$, $C(O)NH_2$, $C(O)NHR^{46}$, $C(O)N(R^{46})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br o I ;

R^{46} es R^{47}, R^{48} o R^{49};

R^{47} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{47A}; R^{47A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{48} es heteroarilo o R^{48A}; R^{48A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{49} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{49A}; R^{49A} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

en donde las unidades representadas por R^2 R^3 R^4, R^6, R^{6C}, R^8, R^{8A} R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{18}, R^{19}, R^{20}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{34}, R^{36}, R^{38}, R^{39}, R^{40}, R^{42}, R^{43}, R^{44}, R^{47}, R^{48}, y R^{49} son en forma independiente no sustituidas, adicionalmente no sustituidas, sustituidas o adicionalmente sustituidas con uno o dos o tres o cuatro o cinco sustituyentes seleccionados en forma independiente entre $R^{50\,AA}$, R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{50}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{50AA} es espirociclilo;

R^{50} es R^{51}, R^{52}, R^{53} o R^{54};

R^{51} es fenilo que no está fusionado o está fusionado con areno, heteroareno o R^{51B}; R^{51B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{52} es heteroarilo;

R^{53} es C_3-C_6-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N, y cada uno de los cuales no está fusionado o está fusionado con areno, heteroareno o R^{53B};

en donde R^{53B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{54} es alquilo, alquenilo o alquinilo, cada uno de los cuales no esta sustituido o está sustituido con uno o dos o tres de los siguientes sustituyentes, seleccionados en forma independiente: R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, (O), N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br o I ;

R^{55} es alquilo, alquenilo, alquinilo, fenilo, heteroarilo o R^{56};

en donde el alquilo, alquenilo, alquinilo no están sustituidos o están sustituidos con OCH_3; y

R^{56} es C_3-C_8-cicloalquilo o C_4-C_6-cicloalquenilo, donde cada uno tiene una o dos unidades CH_2 no reemplazadas o reemplazadas en forma independiente con O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 o NH y una o dos unidades CH no reemplazadas o reemplazadas con N.

6. El compuesto de la reivindicación 1, la reivindicación 2, la reivindicación 3, la reivindicación 4, o la reivindicación 5, CARACTERIZADO PORQUE

A^1 es $C(A^2)$; y

A^2 es H.

7. El compuesto de la reivindicación 1, la reivindicación 2, la reivindicación 3, la reivindicación 4, o la reivindicación 5, CARACTERIZADO PORQUE

A^1 es $C(A^2)$ o N;

A^2 es H; y

B^1 es NHR^1.

8. El compuesto de la reivindicación 1, la reivindicación 2, la reivindicación 3, la reivindicación 4, o la reivindicación 5, CARACTERIZADO PORQUE

A^1 es $C(A^2)$;

A^2 es H;

B^1 es NHR^1; y

D^1 es H.

9. El compuesto de la reivindicación 1, la reivindicación 2, la reivindicación 3, la reivindicación 4, o la reivindicación 5, CARACTERIZADO PORQUE

A^1 es $C(A^2)$ o N;

A^2 es H;

B^1 es NHR^1;

D^1 es H; y

E^1 es H.

10. El compuesto de la reivindicación 1, la reivindicación 2, la reivindicación 3, la reivindicación 4, o la reivindicación 5, CARACTERIZADO PORQUE

A^1 es $C(A^2)$ o N;

A^2 es H;

B^1 es NHR^1;

D^1 es H;

E^1 es H; y

Y^1 es NO_2.

11. Un compuesto de la reivindicación 1, CARACTERIZADO PORQUE el compuesto se selecciona entre:

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;

benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

2-(benciloxi)-4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(2-feniletoxi)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(feniltio)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(feniltio)-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)-2-(feniltio)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(fenilsulfonil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(fenilsulfinil)benzamida;

2-bencil-4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

2-bencil-4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

2-bencil-4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(2-feniletil)benzamida;
2-(bencilamino)-4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
2-anilino-4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
2-anilino-4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-metoxi-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indazol-5–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indazol-5–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)-2-(1,2,3,4-tetrahidroquinolin-6–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)-2-(1,2,3,4-tetrahidroquinolin-6–iloxi)benzamida;
4-(4-((4'-cloro-4-(pirrolidin-1–ilmetil)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(2-pirrolidin-1–iletil)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((1-ciclopentilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)-3-isobutilpiperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-(2,4-dioxo-3-azabiciclo(3.2.0)hept-3–il)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-(4-metil-6-oxo-1,4,5,6-tetrahidropiridazin-3–il)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-(3,3-dimetil-2-oxoazetidin-1–il)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-(4-nitro-2H-1,2,3-triazol-2–il)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((2-(2-piperidin-1–iletoxi)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-((((1-etilpirrolidin-2–il)metil)amino)carbonil)-4-metoxifenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1-naftiloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(2-naftiloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)-2-(2-naftiloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(2-naftiloxi)-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(quinolin-7–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(quinolin-6–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(isoquinolin-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(isoquinolin-5–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(quinolin-6–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-4–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-6–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(isoquinolin-7–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(isoquinolin-7–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-4–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-4–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-metoxifenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-metilfenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((3-morfolin-4–ilpropil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
N-((3-((cloro(difluoro)metil)sulfonil)-4-((3-(dimetilamino)propil)amino)fenil)sulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;
2-(1H-indol-4–iloxi)-4-(4-((2-(4-metoxifenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((4,4-dimetil-2-(4-(trifluorometil)fenil)ciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((4,4-dimetil-2-(4-(trifluorometoxi)fenil)ciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((4,4-dimetil-2-(3-(trifluorometil)fenil)ciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((2-(3-fluorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-fluorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
N-((3-((cloro(difluoro)metil)sulfonil)-4-((1-metilpiperidin-4–il)amino)fenil)sulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;
4-(4-((2-(4-clorofenil)ciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(fenoximetil)benzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(piridin-3–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(piridin-3–iloxi)-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-(((1R)-3-(dimetilamino)-1-((feniltio)metil)propil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-(piridin-4–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)-2-(piridin-3–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)-2-(piridin-4–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((2-(4-metilpiperazin-1–il)etil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(4-metilpiperazin-1–il)propil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)(metil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-(((1-metilpiperidin-4–il)metil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-ciano-4-((3-(dimetilamino)propil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-(trifluorometil)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(isopropil(metil)amino)propil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-(3-(dimetilamino)propoxi)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;

4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((2-(4-metilpiperazin-1–il)etil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((3-(4-metilpiperazin-1–il)propil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((3-(4-metilpiperazin-1–il)propil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-(3-(dimetilamino)propoxi)-3-nitrofenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((2-(4-metilpiperazin-1–il)etil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-(((1-metilpiperidin-4–il)metil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-(((1-metilpiperidin-4–il)metil)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-(3-(dimetilamino)propoxi)-3-nitrofenil)sulfonil)-2-(1H-indol-4–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-(4-metilpiperazin-1–il)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((1-(2,2,2-trifluoroetil)piperidin-4–il)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-(((4-(dimetilamino)-1-metilpiperidin-4–il)metil)amino)-3-nitrofenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(2,3-dihidro-1,4-benzodioxin-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

5-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-1,1'-bifenil-2-carboxamida;
5-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-1,1'-bifenil-2-carboxamida;
4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-4-(3-piperidin-1–ilpropoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-4-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-4-(3-(dimetilamino)propoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-4-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(3-piperidin-1–ilpropoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(3-(dimetilamino)propoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;

4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-3-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-3-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-3-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(2-morfolin-4–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-4-(2-(dimetilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((1-(2,2,2-trifluoroetil)piperidin-4–il)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-4-(2-pirrolidin-1–iletoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-4-(2-(diisopropilamino)etoxi)-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-(2,3-dihidro-1H-indol-5–iloxi)-N-((3-nitro-4-((tetrahidro-2H-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)ciclohept-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;

4-(4-((2-(4-clorofenil)ciclooct-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)ciclopent-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((3-nitro-4-((3-pirrolidin-1–ilpropil)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclopent-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)ciclooct-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)ciclohept-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)ciclopent-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)ciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-4–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)ciclohept-1-en-1–il)metil)piperazin-1–il)-2-(1H-indol-5–iloxi)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((1-metilpiperidin-4–il)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((2-(dimetilamino)etil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-morfolin-4–ilpropil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((4-(dimetilamino)butil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((1-(fenilsulfonil)piperidin-4–il)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((1-(quinolin-8–ilsulfonil)piperidin-4–il)amino)fenil)sulfonil)-2-fenoxibenzamida;

4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((1-(fenilsulfonil)piperidin-4–il)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((1-(quinolin-8–ilsulfonil)piperidin-4–il)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-(((1S)-3-(dimetilamino)-1-tien-2–ilpropil)amino)-3-nitrofenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((tien-2–ilmetil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-2-fenoxi-N-((4-((tetrahidro-2H-piran-4–ilmetil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((2-(1H-1,2,3-triazol-1–il)etil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((2-(2H-1,2,3-triazol-2–il)etil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-nitrofenil)sulfonil)-2-(2-naftiloxi)benzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((2-(2-oxopiridin-1(2H)–il)etil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((2-(piridin-2–iloxi)etil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((4'-cloro-1,1'-bifenil-2–il)metil)piperazin-1–il)-N-((3-nitro-4-((2-piridin-4–iletil)amino)fenil)sulfonil)-2-fenoxibenzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-((trifluorometil)sulfonil)fenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((4-((3-(dimetilamino)propil)amino)-3-(trifluorometil)fenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-N-((3-ciano-4-((3-(dimetilamino)propil)amino)fenil)sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1*H*-indol-5–iloxi)-*N*-((3-nitro-4-((1-tetrahidro-2*H*-piran-4–ilpiperidin-4–il)amino)fenil)sulfonil)benzamida;
4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1*H*-indol-5–iloxi)-*N*-((4-((4-metilpiperazin-1–il)amino)-3-nitrofenil)sulfonil)benzamida;

4-(4-(1-(4'-cloro-1,1'-bifenil-2–il)etil)piperazin-1–il)-2-(1*H*-indol-4–iloxi)-*N*-((3-nitro-4-((tetrahidro-2*H*-piran-4–ilmetil)amino)fenil)sulfonil)benzamida;

N-((4-(((4-aminotetrahidro-2*H*-piran-4–il)metil)amino)-3-nitrofenil)sulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il)metil)piperazin-1–il)-2-(1*H*-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-morfolin-4–ilciclohexil)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(2-metoxietil)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[(3S)-tetrahidro-2H-piran-3–ilmetil]amino}fenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[(3R)-tetrahidro-2H-piran-3–ilmetil]amino}fenil)sulfonil]benzamida;

4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-hidroxi-1-metilpiperidin-4–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-3-fluoro-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-3-fluoro-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-hidroxi-1-metilpiperidin-4–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;

N-[(4-{[(3S,4R)-1-bencil-3-hidroxipiperidin-4–il]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

N-[(4-{[(4-aminotetrahidro-2H-piran-4–il)metil]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[1-(2-metoxietil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(2-hidroxietil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[1-(2-metoxietil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(3-hidroxipropil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;
4-[4-({4'-cloro-3-[3-(dimetilamino)propil]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(3-hidroxipropil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-{4-[(4'-cloro-4-morfolin-4–il-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-[4-({4'-cloro-3-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(dietilamino)ciclohexil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(dimetilamino)ciclohexil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(dietilamino)ciclohexil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(4-morfolin-4–ilciclohexil)amino]-3-nitrofenil}sulfonil)benzamida;
4-[4-({4'-cloro-3-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;
4-{4-[1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[4-(dimetilamino)tetrahidro-2H-piran-4–il]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida;

N-({4-[(2-aminociclohexil)amino]-3-nitrofenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;
4-[4-({4'-cloro-4-[3-(dimetilamino)prop-1-ynil]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(3-nitro-4-{[1-(4,4,4-trifluorobutil)piperidin-4–il]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[2-(4-hidroxi-1-metilpiperidin-4–il)etil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[1-(1,3-tiazol-2–il)piperidin-4–il]amino}fenil)sulfonil]benzamida;
4-(4-{[4'-cloro-4-(2-hidroxietoxi)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(ciclopropilmetil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[1-(4,4,4-trifluorobutil)piperidin-4–il]amino}fenil)sulfonil]benzamida;
4-{4-[1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida;
4-[4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}-3-(hidroximetil)piperazin-1–il]-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;
4-[4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}-3-(hidroximetil)piperazin-1–il]-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
4-(4-{[4'-cloro-4-(2-hidroxietoxi)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[3-(3-oxopiperazin-1–il)propil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(3-nitro-4-{[3-(3-oxopiperazin-1–il)propil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-5-hidroxiciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-5-hidroxiciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-5-hidroxiciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(2,3-dihidro-1H-inden-2–il)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(2,3-dihidro-1H-inden-2–il)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(1-morfolin-4–ilciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[1-(1,3-tiazol-2–ilmetil)piperidin-4–il]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[1-(1,3-tiazol-4–ilmetil)piperidin-4–il]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[4-(hidroximetil)tetrahidro-2H-piran-4–il]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(2-hidroxietil)piperazin-1–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(3S)-1-metilpirrolidin-3–il]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[1-(3-fluoropropil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-[4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}-3-(hidroximetil)piperazin-1–il]-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

N-[(4-{[(4-aminotetrahidro-2H-piran-4–il)metil]amino}-3-nitrofenil)sulfonil]-4-[4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}-3-(hidroximetil)piperazin-1–il]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1-hidroxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(2-metoxietil)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(hidroximetil)tetrahidro-2H-piran-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[4-(hidroximetil)tetrahidro-2H-piran-4–il]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2-hidroxi-1-tetrahidro-2H-piran-4–iletil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-({1-[2-(1H-pirazol-1–il)etil]piperidin-4–il}amino)fenil]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(metilamino)-3-nitrofenil]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[4-(metilamino)-3-nitrofenil]sulfonil}benzamida;

4-{4-[1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-5-hidroxiciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-5-morfolin-4–ilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

N-[(4-{[(1-aminociclohexil)metil]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[2-(2-oxopirrolidin-1–il)etil]amino}fenil)sulfonil]benzamida;
4-{4-[1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{1-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]etil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{1-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]etil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida;
4-{4-[(1R)-1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-{4-[(1S)-1-(4'-cloro-1,1'-bifenil-2–il)etil]piperazin-1–il}-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{1-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]etil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{1-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]etil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(ciclohexilmetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(morfolin-4–ilamino)-3-nitrofenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-3–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[4-(morfolin-4–ilamino)-3-nitrofenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(tetrahidro-2H-piran-4–ilamino)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(3-metiloxetan-3–il)metil]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-metoxiciclohexil)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[3-(1,1-dioxidotiomorfolin-4–il)propil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[2-(2-oxopiperidin-1–il)etil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[2-(2-oxoimidazolidin-1–il)etil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(2-piridin-4–iletil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-morfolin-4–il-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(4-metoxipiperidin-1–il)-3-nitrofenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-5-pirrolidin-1–ilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[2-(3-oxopiperazin-1–il)etil]amino}fenil)sulfonil]benzamida;
4-[4-({4'-cloro-4-[2-(dimetilamino)etoxi]-1,1'-bifenil-2–il}metil)piperazin-1–il]-2-(1H-indol-4–iloxi)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1,1-dioxidotetrahidrotien-3–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1,1-dioxidotetrahidrotien-3–il)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-[(tetrahidro-2H-piran-4–ilmetil)amino]-3-(trifluorometil)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[2-(1,3-dioxolan-2–il)etil]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(tetrahidro-2H-piran-4–ilmetoxi)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(3-nitro-4-{[2-(3-oxopiperazin-1–il)etil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metil-5-oxopirrolidin-3–il)amino]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metil-6-oxopiperidin-3–il)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[3-nitro-4-(piperidin-1–ilamino)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(piperidin-1–ilamino)fenil]sulfonil}benzamida;
4-(4-{[4-(4-clorofenil)-1-metil-1H-pirazol-5–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(3-metiloxetan-3–il)metoxi]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[(1-oxidotetrahidro-2H-tiopiran-4–il)metil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1,3-tiazol-5–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[3-nitro-4-(tetrahidro-2H-piran-4–ilmetoxi)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(2-tetrahidro-2H-piran-4–iletil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(3-nitro-4-{[2-(trifluorometoxi)etil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[2-(2-metoxietoxi)etil]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[3-(metilsulfonil)propil]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[3-(1,1-dioxidotiomorfolin-4–il)propil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(2-tetrahidro-2H-piran-4–iletil)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-(1,4-dioxan-2–ilmetoxi)-3-nitrofenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[2-(2-metoxietoxi)etil]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1,1-dioxidotetrahidrotien-3–il)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[2-(trifluorometoxi)etil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1,1-dioxidotetrahidro-2H-tiopiran-4–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2,2-difluoroetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4,4-difluorociclohexil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[4-(4-clorofenil)-1-isopropil-6-oxo-1,6-dihidropiridin-3–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(tetrahidro-2H-piran-4–ilmetil)amino]carbonil}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(2-metoxietil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-hidroxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(4-metoxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-hidroxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(4-metoxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[3-nitro-4-(2-tetrahidro-2H-piran-4–iletoxi)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(2-metoxietil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[3-(metilsulfonil)propoxi]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(3-metoxipropil)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(3-metoxipropil)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2-cianoetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2-cianoetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[(3R)-4-hidroxi-1-adamantil]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[Cis-4-hidroxi-1-adamantil]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(3,3,3-trifluoropropil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(3,3,3-trifluoropropil)amino]fenil}sulfonil)benzamida;
N-({5-bromo-6-[(tetrahidro-2H-piran-4–ilmetil)amino]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1,1-dioxidotetrahidrotien-3–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-(metilamino)-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;

N-{[5-bromo-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[4-(4-clorofenil)-6-isopropoxipiridin-3–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[6-(tetrahidro-2H-piran-4–ilmetoxi)-5-(1,3-tiazol-2–il)piridin-3–il]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(2-metoxietil)amino]carbonil}fenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-ciano-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indol-5–iloxi)benzamida;

N-({4-[(1-acetilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[1-(metilsulfonil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1,4-dioxan-2–ilmetil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;

N-({4-[(1-acetilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[1-(metilsulfonil)piperidin-4–il]amino}-3-nitrofenil)sulfonil]benzamida;

4-(4-{[4'-cloro-5-(trifluorometil)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[4'-cloro-5-(trifluorometil)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(tetrahidro-2H-piran-4–ilmetoxi)fenil]sulfonil}benzamida;

4-{4-[(5-tert-butil-4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

4-{4-[(5-tert-butil-4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-5–iloxi)-N-{[3-nitro-4-(tetrahidro-2H-piran-4–ilmetoxi)fenil]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(2,2,2-trifluoroetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(2,2,2-trifluoroetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-{[(tetrahidro-2H-piran-4–ilmetil)amino]carbonil}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2R)-1,4-dioxan-2–ilmetoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2S)-1,4-dioxan-2–ilmetoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({4-[(3-morfolin-4–ilpropil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
N-({5-bromo-6-[(tetrahidro-2H-piran-4–ilmetil)amino]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(2-morfolin-4–iletil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-ciano-6-[(tetrahidro-2H-piran-4–ilmetil)amino]piridin-3–il}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)oxi]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(1-metilpiperidin-4–il)metoxi]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[4-(4-clorofenil)-1-(3-hidroxipropil)-1,2,5,6-tetrahidropiridin-3–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-({[4-({[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzoil]amino}sulfonil)-2-nitrofenil]amino}metil)piperidin-1-carboxilato de bencilo ;
N-{[3-(aminocarbonil)-4-(tetrahidro-2H-piran-4–ilmetoxi)fenil]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[4'-cloro-5-(trifluorometil)-1,1'-bifenil-2–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;
4-{4-[(5-tert-butil-4'-cloro-1,1'-bifenil-2–il)metil]piperazin-1–il}-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(1-metil-1H-imidazol-5–il)metil]amino}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(morfolin-4–ilsulfonil)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1,1-dioxidotiomorfolin-4–il)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-morfolin-4–ilciclohexil)amino]-3-nitrofenil}sulfonil)benzamida;
N-{[5-bromo-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[6-[(tetrahidro-2H-piran-4–ilmetil)amino]-5-(1,3-tiazol-2–il)piridin-3–il]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-ciano-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-ciano-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(3,3-dimetilbutil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1S)-1-(hidroximetil)-3-metilbutil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[(2R)-tetrahidrofuran-2–ilmetil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1R)-1-(hidroximetil)-2-metilpropil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-metoxifenil)amino]-3-nitrofenil}sulfonil)benzamida;
N-[(4-{[2-(1,3-benzodioxol-5–il)etil]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[3-(2-oxopirrolidin-1–il)propil]amino}fenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-hidroxifenil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
N-{[4-({2-[4-(aminosulfonil)fenil]etil}amino)-3-nitrofenil]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[3-(1H-imidazol-1–il)propil]amino}-3-nitrofenil)sulfonil]-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(3-nitro-4-{[(1S)-1-feniletil]amino}fenil)sulfonil]benzamida;
N-({2-cloro-5-fluoro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[2-(2-metoxietoxi)etil]tio}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-[(4-{[2-(2-metoxietoxi)etil]tio}-3-nitrofenil)sulfonil]benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-{[4-(metilsulfonil)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)-N-{[4-(metilsulfonil)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(2,2-dimetiltetrahidro-2H-piran-4–il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-ciano-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-ciano-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-cloro-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-ciano-6-(2-morfolin-4–iletoxi)piridin-3–il]sulfonil}-2-(1H-indol-5–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)oxi]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-({4-[(4-morfolin-4–ilbut-2-ynil)oxi]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-etinil-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-ciano-6-(2-morfolin-4–iletoxi)piridin-3–il]sulfonil}-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-ciano-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-2-(1H-indol-4–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(3-hidroxi-4-metoxifenil)amino]-3-nitrofenil}sulfonil)-2-(1H-indol-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(2,3-dihidro-1H-indol-4–iloxi)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)-2-(piridin-3–ilamino)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)-2-(piridin-3–ilamino)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)-2-(piridin-3–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-(1,2,3,4-tetrahidroisoquinolin-5–iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;
Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)-N-({4-[(4-morfolin-4–ilciclohexil)amino]-3-nitrofenil}sulfonil)benzamida;
2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;

N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-ciano-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-2-(1H-indazol-4–iloxi)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(3R)-1-(2,2-difluoroetil)pirrolidin-3–il]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]-3-nitrofenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-fluorotetrahidro-2H-piran-4–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]-5-(trifluorometil)piridin-3–il]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-ciclopropilmorfolin-2–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4,4-difluorociclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4–iloxi)benzamida;

N-[(5-cloro-6-{[(4-fluorotetrahidro-2H-piran-4–il)metil]amino}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

Trans-N-({5-cloro-6-[(4-metoxiciclohexil)metoxi]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[4-(2,2-difluoroetil)morfolin-2–il]metil}amino)-3-nitrofenil]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-fluoro-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-2-(1H-indazol-4–iloxi)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(1-tetrahidro-2H-piran-4–ilpiperidin-4–il)amino]fenil}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1-metilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;

N-[(5-cloro-6-{[1-(cianometil)-4-fluoropiperidin-4–il]metoxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-cloro-6-(tetrahidrofuran-3–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;

Trans-N-({5-cloro-6-[(4-hidroxiciclohexil)metoxi]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

N-[(5-cloro-6-{[(3R)-1-(2,2-difluoroetil)pirrolidin-3–il]oxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

2-(1H-benzimidazol-4–iloxi)-N-[(5-cloro-6-{[(2S)-4-(N,N-dimetilglicil)morfolin-2–il]metoxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)benzamida;

2-(1H-benzimidazol-4–iloxi)-N-[(5-cloro-6-{[(2R)-4-(N,N-dimetilglicil)morfolin-2–il]metoxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)benzamida;

N-[(5-cloro-6-{[(2S)-4-(N,N-dimetilglicil)morfolin-2–il]metoxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

N-[(5-cloro-6-{[(2R)-4-(N,N-dimetilglicil)morfolin-2–il]metoxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-cloro-6-(tetrahidro-2H-piran-4–ilmetoxi)piridin-3–il]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(3R)-1-(cianometil)pirrolidin-3–il]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({(3R)-1-[2-(2-metoxietoxi)etil]pirrolidin-3–il}amino)-3-nitrofenil]sulfonil}benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(3R)-1-(N,N-dimetilglicil)pirrolidin-3–il]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[4-(cianometil)morfolin-2–il]metil}amino)-3-nitrofenil]sulfonil}benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-ciclopropilmorfolin-2–il)metil]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(3-nitro-4-{[(4-oxetan-3–ilmorfolin-2–il)metil]amino}fenil)sulfonil]benzamida;

N-{[5-cloro-6-({(3R)-1-[2-fluoro-1-(fluorometil)etil]pirrolidin-3–il}oxi)piridin-3–il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({(3R)-1-[2-fluoro-1-(fluorometil)etil]pirrolidin-3–il}amino)-3-nitrofenil]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1-ciclopropilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)-2-(1H-indazol-4–iloxi)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[(2R)-4-(N,N-dimetilglicil)morfolin-2–il]metil}amino)-3-nitrofenil]sulfonil}benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[(2S)-4-(N,N-dimetilglicil)morfolin-2–il]metil}amino)-3-nitrofenil]sulfonil}benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(tetrahidrofuran-3–ilmetil)amino]fenil}sulfonil)benzamida;

Trans-2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-metoxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-fluorotetrahidro-2H-piran-4–il)metil]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({5-fluoro-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)benzamida;

N-{[5-cloro-6-({(3R)-1-[2-fluoro-1-(fluorometil)etil]pirrolidin-3–il}metoxi)piridin-3–il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

N-[(5-cloro-6-{[(3R)-1-(2,2-difluoroetil)pirrolidin-3–il]metoxi}piridin-3–il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)-N-[(4-{[(4-metoxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-(1,4-dioxan-2–ilmetoxi)-3-nitrofenil]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;

N-({5-cloro-6-[(1-ciclopropilpiperidin-4–il)amino]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

2-(1H-benzimidazol-4–iloxi)-N-({5-cloro-6-[(1-ciclopropilpiperidin-4–il)amino]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1,4-dioxan-2–ilmetil)amino]-3-nitrofenil}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(1-ciclopropilpiperidin-4–il)amino]-3-nitrofenil}sulfonil)benzamida;

Trans-2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-morfolin-4–ilciclohexil)amino]-3-nitrofenil}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[(4-metilpiperazin-1–il)amino]-3-nitrofenil}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(1-metilpiperidin-4–il)metil]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({4-[({(2R)-4-[2-(2-metoxietoxi)etil]morfolin-2–il}metil)amino]-3-nitrofenil}sulfonil)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4,4-difluorociclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;

N-[(4-{[(4-acetilmorfolin-2–il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)benzamida;

2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[4-({[4-(metilsulfonil)morfolin-2–il]metil}amino)-3-nitrofenil]sulfonil}benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[6-({4-fluoro-1-[2-fluoro-1-(fluorometil)etil]piperidin-4–il}metoxi)-5-(trifluorometil)piridin-3–il]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-{[5-cloro-6-(2-tetrahidrofuran-2–iletoxi)piridin-3–il]sulfonil}-2-(1H-indazol-4–iloxi)benzamida;

Trans-2-(1H-benzimidazol-4–iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-N-[(4-{[(4-cianociclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzimidazol-4–iloxi)-N-({5-cloro-6-[(4,4-difluorociclohexil)metoxi]piridin-3–il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)benzamida;

N-({3-cloro-4-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4–il)metoxi]piridin-3–il}sulfonil)-4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3–il]metil}piperazin-1–il)-2-(1H-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-*N*-{[5-ciano-6-(2-tetrahidro-2*H*-piran-4–iletoxi)piridin-3–il]sulfonil}-2-(1*H*-indazol-4–iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1–il]metil}piperazin-1–il)-2-(1H-indol-5–iloxi)-N-[(4-{[(1R,5S)-8-metil-8-azabiciclo[3.2.1]oct-3–il]amino}-3-nitrofenil)sulfonil]benzamida;

N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxi-4-(4-{(3-fenilpropanoil)[(1S,2S,3S,5R)-2,6,6-trimetilbiciclo[3.1.1]hept-3–il]amino}piperidin-1–il)benzamida;

N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)-2-fenoxi-4-(4-{(3-fenilpropanoil)[(1S,2S,3S,5R)-2,6,6-trimetilbiciclo[3.1.1]hept-3–il]amino}piperidin-1–il)benzamida;

N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxi-4-(4-{(3-fenilpropil)[(1S,2S,3S,5R)-2,6,6-trimetilbiciclo[3.1.1]hept-3–il]amino}piperidin-1–il)benzamida;

N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)-2-fenoxi-4-(4-{(3-fenilpropil)[(1S,2S,3S,5R)-2,6,6-trimetilbiciclo[3.1.1]hept-3–il]amino}piperidin-1–il)benzamida;

4-[4-(2-{[(1R,5S)-8-metil-8-azabiciclo[3.2.1]oct-3–il]amino}bencil)piperazin-1–il]-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)-2-fenoxibenzamida;

4-[4-(2-{[(1R,5S)-8-metil-8-azabiciclo[3.2.1]oct-3–il]amino}bencil)piperazin-1–il]-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida;

4-{4-[2-(3-azabiciclo[3.2.2]non-3–il)bencil]piperazin-1–il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida;
4-{4-[2-(3-azabiciclo[3.2.2]non-3–il)bencil]piperazin-1–il}-2-fenoxi-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
4-{4-[2-(3-azabiciclo[3.2.2]non-3–il)bencil]piperazin-1–il}-2-fenoxi-N-({4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)benzamida;
4-{4-[2-(3-azabiciclo[3.2.2]non-3–il)bencil]piperazin-1–il}-N-({4-[(3-morfolin-4–ilpropil)amino]-3-nitrofenil}sulfonil)-2-fenoxibenzamida;
4-(4-{2-[(4R,7S)-2,3,3a,4,7,7a-hexahidro-1H-4,7-metanoinden-5–il]bencil}piperazin-1–il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida;
4-[4-(2-{5-[(1R,5S)-8-azabiciclo[3.2.1]oct-8–ilmetil]tien-2–il}bencil)piperazin-1–il]-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida;
4-[4-(2-{5-[(1R,5S)-8-azabiciclo[3.2.1]oct-8–ilmetil]tien-2–il}benciliden)piperidin-1–il]-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida;
4-[4-(3-{5-[(1R,5S)-8-azabiciclo[3.2.1]oct-8–ilmetil]tien-2–il}bencil)piperazin-1–il]-N-({3-nitro-4-[(tetrahidro-2H-piran-4–ilmetil)amino]fenil}sulfonil)-2-fenoxibenzamida;
N-({5-cloro-6-[(4,4-difluorociclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
N-({6-[(trans-4-carbamoilciclohexil)metoxi]-5-cloropiridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(trans-4-cianociclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;
N-({5-cloro-6-[2-(1H-imidazol-1-il)etoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
N-({5-cloro-6-[(1-metil-1H-imidazol-5-il)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[5-fluoro-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil}-2-(1H-indazol-4-iloxi)benzamida;
N-{[5-cloro-6-(1,4-dioxan-2-ilmetoxi)piridin-3-il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(4,4-difluoro-1-hidroxiciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
N-({5-cloro-6-[(2,2-difluorociclopropil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
N-({5-cloro-6-[(trans-4-cianociclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
N-({5-cloro-6-[(cis-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
N-({3-cloro-4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]fenil}sulfonil)-4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]-3-(trifluorometil)fenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-cloro-4-(tetrahidro-2H-piran-4-ilmetoxi)fenil]sulfonil}-2-(1H-indazol-4-iloxi)benzamida;
2-(1H-benzimidazol-4-iloxi)-N-({3-cloro-4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida;
2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[5-cloro-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-ciano-4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]fenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida;
N-{[3-cloro-4-(1,4-dioxan-2-ilmetoxi)fenil]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
2-(1H-benzimidazol-4-iloxi)-N-[(5-cloro-6-{[(2S)-4-ciclopropilmorfolin-2-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida;

N-[(5-cloro-6-{[(2S)-4-ciclopropilmorfolin-2-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

2-{[(4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzoil]sulfamoil}-2-nitrofenil)amino]metil}morfolin-4-carboxilato de metilo ;

2-{[(4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzoil]sulfamoil}-2-nitrofenil)amino]metil}-N-etil-N-metilmorfolin-4-carboxamida;

2-{[(4-{[2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzoil]sulfamoil}-2-nitrofenil)amino]metil}-N-etil-N-metilmorfolin-4-carboxam
ide;

N-({5-cloro-6-[(trans-4-etil-4-hidroxiciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(cis-4-etil-4-hidroxiciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

5-cloro-N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamid
e;

5-cloro-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4-fluorotetrahidro-2H-piran-4-il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(cis-1-fluoro-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamid
e;

N-({5-cloro-6-[(trans-1-fluoro-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzam
ide;

2-(1H-benzotriazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4-fluorotetrahidro-2H-piran-4-il)metil]amino}-3-nitrofenil)sulfonil]benzamida;

2-(1H-benzotriazol-4-iloxi)-N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida;

2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-cloro-4-(tetrahidro-2H-piran-4-ilmetoxi)fenil]sulfonil}benzamida;

N-[(3-cloro-4-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}fenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(cis-1-fluoro-4-hidroxiciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

2-(1H-benzotriazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]-3-nitrofenil}sulfonil)benzamida;

N-[(5-cloro-6-{[(1R,2R,4R,5R)-5-hidroxi-5-metilbiciclo[2.2.1]hept-2-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-[(5-cloro-6-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

2-(1H-benzotriazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(trans-4-hidroxi-4-metilciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(cis-4-hidroxi-4-metilciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;
2-(1H-benzotriazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({[(2S)-4-ciclopropilmorfolin-2-il]metil}amino)-3-nitrofenil]sulfonil}benzamida;
N-[(5-cloro-6-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({[(2S)-4-ciclopropilmorfolin-2-il]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-indazol-4-iloxi)benzamida;
2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({[(2S)-4-ciclopropilmorfolin-2-il]metil}amino)-3-nitrofenil]sulfonil}benzamida;
N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(cis-4-hidroxi-4-metilciclohexil)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(trans-4-hidroxi-4-metilciclohexil)metoxi]-3-nitrofenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-ciano-4-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}fenil)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-{[3-nitro-4-(2-oxaspiro[3.5]non-7-ilmetoxi)fenil]sulfonil}benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[5-cloro-6-(5,6,7,8-tetrahidroimidazo[1,2-a]piridin-6-ilmetoxi)piridin-3-il]sulfonil}-2-(1H-indazol-4-iloxi)benzami
de;

2-(1H-benzimidazol-4-iloxi)-N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(5-ciano-6-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}piridin-3-il)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;
N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-5-(metoximetil)-5-metilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)b
enzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-{[3-nitro-4-({[(2S)-4-(oxetan-3-il)morfolin-2-il]metil}amino)fenil]sulfonil}benzamida;
2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-nitro-4-({[(2S)-4-(oxetan-3-il)morfolin-2-il]metil}amino)fenil]sulfonil}benzamida;
N-[(5-cloro-6-{[trans-4-(2-hidroxipropan-2-il)ciclohexil]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-ciano-4-[(trans-4-hidroxi-4-metilciclohexil)metoxi]fenil}sulfonil)-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({5-ciano-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)-N-({5-nitro-6-[(tetrahidro-2H-piran-4-ilmetil)amino]piridin-3-il}sulfonil)benzamida;
2-(1H-benzotriazol-4-iloxi)-N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)benzamida;
N-({3-cloro-4-[(cis-4-ciano-1-fluorociclohexil)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
N-({3-cloro-4-[(trans-4-ciano-1-fluorociclohexil)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;

N-({5-cloro-6-[(cis-4-ciano-1-fluorociclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
N-({5-cloro-6-[(trans-4-ciano-1-fluorociclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzami
de;
2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(trans-4-hidroxi-4-metilciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;
N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-5-metoxi-5-metilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(5-cloro-6-{[1-(1,3-tiazol-2-il)piperidin-4-il]metoxi}piridin-3-il)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(6-{[(cis-4-hidroxi-4-metilciclohexil)metil]amino}-5-nitropiridin-3-il)sulfonil]-2-(1H-indazol-4-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]-5-(trifluorometil)piridin-3-il}sulfonil)-2-(1H-indazol-4-iloxi)benz
amida;
2-(1H-benzimidazol-4-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(cis-4-hidroxi-4-metilciclohexil)metil]amino}-3-nitrofenil)sulfonil]benzamida;
N-(4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-indazol-4-iloxi)benzoil]sulfamoil}-2-nitrofenil)-4-cianopiperidin-1-carboxamida;y sus sales, profármacos, sales de profármacos y metabolitos terapéuticamente aceptables.

12. Una composición para tratar cáncer de vejiga, cáncer de cerebro, cáncer de mamas, cáncer de médula ósea, cáncer cervical, leucemia linfocítica crónica, cáncer colorrectal, cáncer de esófago, cáncer hepatocelular, leucemia linfoblástica, linfoma folicular,

malignidades linfoides originadas en células T o células B, melanoma, leucemia mielógena, mieloma, cáncer oral, cáncer de ovarios, cáncer de pulmón de células no pequeñas, leucemia linfocítica crónica, mieloma, cáncer de próstata, cáncer de pulmón o cáncer de bazo de células pequeñas, CARACTERIZADA PORQUE dicha composición comprende un excipiente y una cantidad terapéuticamente efectiva del compuesto de la reivindicación 1.

13. Un método para tratar cáncer de vejiga, cáncer de cerebro, cáncer de mamas, cáncer de médula ósea, cáncer cervical, leucemia linfocítica crónica, cáncer colorrectal, cáncer de esófago, cáncer hepatocelular, leucemia linfoblástica, linfoma folicular, malignidades linfoides originadas en células T o células B, melanoma, leucemia mielógena, mieloma, cáncer oral, cáncer de ovarios, cáncer de pulmón de células no pequeñas, leucemia linfocítica crónica, mieloma, cáncer de próstata, cáncer de pulmón o cáncer de bazo de células pequeñas en un paciente, CARACTERIZADO PORQUE dicho método comprende administrar al paciente una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1.

14. Un método para tratar cáncer de vejiga, cáncer de cerebro, cáncer de mamas, cáncer de médula ósea, cáncer cervical, leucemia linfocítica crónica, cáncer colorrectal, cáncer de esófago, cáncer hepatocelular, leucemia linfoblástica, linfoma folicular, malignidades linfoides originadas en células T o células B, melanoma, leucemia mielógena, mieloma, cáncer oral, cáncer de ovarios, cáncer de pulmón de células no pequeñas, leucemia linfocítica crónica, mieloma, cáncer de próstata, cáncer de pulmón o cáncer de bazo de células pequeñas en un paciente, CARACTERIZADO PORQUE dicho método comprende administrar al paciente una cantidad terapéuticamente efectiva del compuesto de la reivindicación 1 y una cantidad terapéuticamente efectiva de un agente terapéutico adicional o más de un agente terapéutico adicional.

AGENTES INDUCTORES DE APOPTOSIS CON SELECTIVIDAD POR Bcl-2 PARA EL TRATAMIENTO DE CÁNCER Y ENFERMEDADES INMUNES

RESUMEN

Compuestos que inhiben la actividad de las proteínas anti-apoptóticas Bcl-2 o Bcl-X_L, composiciones que contienen dichos compuestos y métodos para tratar enfermedades durante las cuales se expresa la proteína anti-apoptótica Bcl-2.