



No. 11-178424- -00000-0000

Fecha: 2011-12-26 14:15:48 Dep. 2020 DIR.NUEVASCR

Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI

Act. 411 PRESENTACION Folios: 1307

Act. 411 PRESENTACION Folios: 1302



Industria y Comercio

SUPERINTENDENCIA

República de Colombia
Ministerio de Comercio, Industria y Turismo

**PROPIEDAD
INDUSTRIAL**



Delegatura de Propiedad Industrial
División de Nuevas Creaciones

SOLICITUD DE

**PATENTE DE INVENCION
PCT ENTRADA EN FASE NACIONAL
(PARTE I)**

21. EXPEDIENTE No. _____

54. TITULO: AGENTES INDUCTORES DE APOPTOSIS PARA EL
TRATAMIENTO DE CANCER Y ENFERMEDADES
INMUNES Y AUTOINMUNES

52. CLASIFICACION INTERNACIONAL: C07D 471/04

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., _____

No. 11-178424- -00000-0000
Fecha: 2011-12-26 14:15:48 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1307
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ORIO

Espacio reservado para el adhesivo de radicación

SUPERINTENDENCIA

FORMULARIO UNICO DE SOLICITUD DE PATENTES
PCT
ENTRADA EN FASE NACIONAL

SOLICITUD DE:

1

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.
☒ Capítulo I ☐ Capítulo II

2

SOLICITANTE (71)

Nombre: ABBOTT LABORATORIES
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Lugar de Constitución: ESTADOS UNIDOS DE
AMERICA

Teléfono: Fax:
E-mail:

IDENTIFICACIÓN

C.C. ☐ NIT ☐
C.E. ☐ Otro ☐
Número Cual

3

REPRESENTANTE
O APODERADO

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Número 39'779.654 TPA 70.819

4

INVENTOR (ES) (72)

VER ANEXO # 1

5

PCT (86)

Solicitud Internacional No. PCT/US2010/036198 Fecha 26/05/2010
Publicación Internacional No. WO 2010/138588 A2 Fecha 02/12/2010

6

Título (54) AGENTES INDUCTORES DE APOPTOSIS PARA EL TRATAMIENTO DE CANCER Y
ENFERMEDADES INMUNES Y AUTOINMUNES

7

Clasificación Internacional (51) C07D 471/04

8

Prioridad

(33) País de Origen

(32) Fecha

(31) Número de Solicitud

SI ☒ NO ☐

US

26/05/2009

61/181,203

9

Comprobantes de pago Nos. 11-114415 y 11-114416 Fecha Noviembre 24 de 2011

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

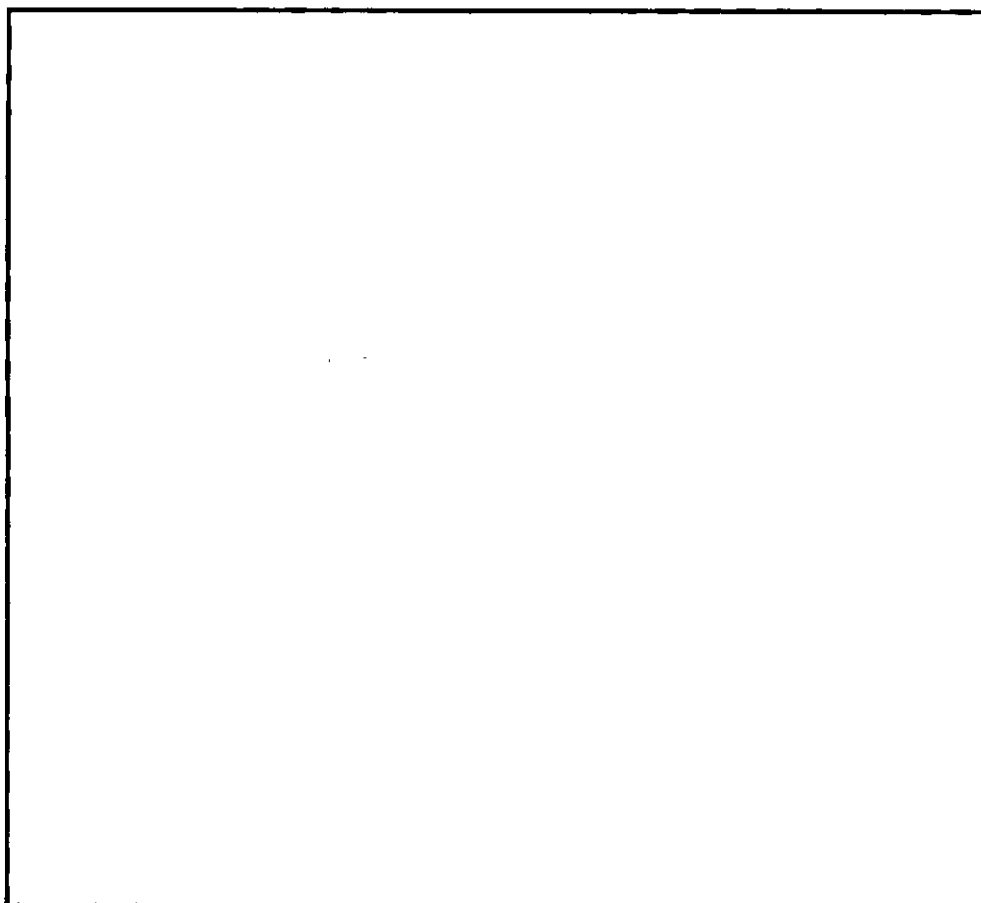
10

Anexos

- ☒ Comprobante de pago de la tasa de presentación de la solicitud.
☒ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica.
☒ Poderes, si fuere el caso, junto con la sustitución del mismo a mi favor
☐ Documento de cesión del inventor al solicitante o a su causante.
☐ Declaraciones.
☒ Copia de la solicitud internacional (Resumen, descripción, reivindicaciones, dibujos).
☒ Traducción de la solicitud internacional al castellano (Resumen, descripción, reivindicaciones, dibujos).
☐ Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
☐ Traducción del examen preliminar internacional efectuado por la IPEA.
☐ De ser el caso, copia del contrato de acceso.
☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
☐ De ser el caso, certificado de depósito del material biológico.
☐ Arte final 12x12
☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
☐ De ser el caso, modificaciones efectuadas a la solicitud internacional.
☒ Otros Tarjeta Propietario y Extracto para la Publicación

11

FIGURA CARACTERISTICA:



12

Solicito la concesión de la patente,

NOMBRE: MARGARITA CASTELLANOS ABONDANO

FIRMA:

C.C. No. 89'779.654 Usaquén - TPA 70.819 C.S.J.

20 DIC. 2011

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RECIBO DE CAJA

No. 11 - 114415

Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C., Noviembre 24 de 2011 - 11:04:43

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	387647632	24/11/2011	8.623.750.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	VR. UNIDITARIO	VR. CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCIÓN	571.000.00	571.000.00
				\$571.000.00

SON: **QUINIENTOS SETENTA Y UN MIL PESOS MONEDA CORRIENTE**

Responsable:

Recibo de Caja Aplicado al Expediente No.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 11-178424- -00000-0000

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

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RECIBO DE CAJA

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Bogotá D.C., Noviembre 24 de 2011 - 11:04:43

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	387647632	24/11/2011	8.623.750.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	VR. UNDITARIO	VR. CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD INDUSTRIAL	99 OTROS SERVICIOS ADMINISTRATIVOS	594.000.00	594.000.00
				\$594.000.00

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

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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PCT

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61/181,203 26 May 2009 (26.05.2009) US(71) Applicant (for all designated States except US): **ABBOTT LABORATORIES** [US/US]; 100 Abbott Park Road, Abbott Park, Illinois 60064 (US).

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(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, 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:

- without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) Title: APOPTOSIS-INDUCING AGENTS FOR THE TREATMENT OF CANCER AND IMMUNE AND AUTOIMMUNE DISEASES

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

APOPTOSIS-INDUCING AGENTS FOR THE TREATMENT OF CANCER AND
IMMUNE AND AUTOIMMUNE DISEASES

This application claims priority to United States Provisional Application Serial No.
5 61/181,203 filed May 26, 2009, which is incorporated by reference in its entirety.

FIELD OF THE INVENTION

This invention pertains to compounds which inhibit the activity of Bcl-2
anti-apoptotic proteins, compositions containing the compounds, and methods of treating
10 diseases during which anti-apoptotic Bcl-2 proteins are expressed.

BACKGROUND OF THE INVENTION

Anti-apoptotic Bcl-2 proteins are associated with a number of diseases. There is
therefore an existing need in the therapeutic arts for compounds which inhibit the activity of
15 anti-apoptotic Bcl-2 proteins.

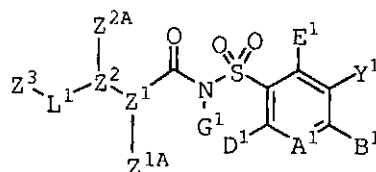
Overexpression of Bcl-2 proteins correlates with resistance to chemotherapy, clinical
outcome, disease progression, overall prognosis or a combination thereof in various cancers
and disorders of the immune system.

Involvement of Bcl-2 proteins in bladder cancer, brain cancer, breast cancer, bone
20 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,
spleen cancer, and the like is described in commonly-owned PCT US 2004/36770, published
25 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 proteins in arthritis is disclosed in commonly-
30 owned United States Provisional Patent Application Serial No. 60/988,479. Involvement of
Bcl-2 proteins in bone marrow transplant rejection is disclosed in commonly-owned United
States Patent Application Serial No. 11/941,196.

SUMMARY OF THE INVENTION

One embodiment of this invention, therefore, pertains to compounds or therapeutically acceptable salts, which are useful as inhibitors of anti-apoptotic Bcl-2 proteins, the compounds having Formula (I)



(I),

wherein

A¹ is N or C(A²);

A² is H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR¹A; 15

B¹ is H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR¹A; 20

D¹ is H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR¹A; 25

E¹ is H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, 30

NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂,
 SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹,
 NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹,
 C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂,
 5 N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR^{1A}; and

Y¹ is H, CN, NO₂, C(O)OH, F, Cl, Br, I, CF₃, OCF₃, CF₂CF₃, OCF₂CF₃, R¹⁷, OR¹⁷,
 C(O)R¹⁷, C(O)OR¹⁷, SR¹⁷, SO₂R¹⁷, NH₂, NHR¹⁷, N(R¹⁷)₂, NHC(O)R¹⁷, C(O)NH₂,
 C(O)NHR¹⁷, C(O)N(R¹⁷)₂, NHS(O)R¹⁷ or NHSO₂R¹⁷; or

E¹ and Y¹, together with the atoms to which they are attached, are benzene,
 10 naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
 and

A², B¹, and D¹ are independently selected H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹,
 C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹,
 NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹,
 15 NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹,
 NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹,
 C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹,
 N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃,
 C(O)OH, C(O)NH₂ or C(O)OR^{1A}; or

Y¹ and B¹, together with the atoms to which they are attached, are benzene,
 20 naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
 and

A², D¹, and E¹ are independently selected H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹,
 C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹,
 25 NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹,
 NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹,
 NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹,
 C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹,
 N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃,
 30 C(O)OH, C(O)NH₂ or C(O)OR^{1A}; or

A² and B¹, together with the atoms to which they are attached, are benzene,
 naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
 and

D¹, E¹, and Y¹ are independently selected H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR^{1A}; or

A² and D¹, together with the atoms to which they are attached, are benzene,
 10 naphthalene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
 and

B¹, E¹, and Y¹ are independently selected H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹,
 15 NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR^{1A};

20 G¹ is H, or C(O)OR;

R is alkyl;

R¹ is R², R³, R⁴ or R⁵;

R^{1A} is cycloalkyl, cycloalkenyl or cycloalkynyl;

R² is phenyl, which is unfused or fused with R^{2A}; R^{2A} is benzene, heteroarene,
 25 cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R³ is heteroaryl, which is unfused or fused with R^{3A}; R^{3A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R⁴ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{4A}; R^{4A} is benzene, heteroarene, cycloalkane, cycloalkene,
 30 heterocycloalkane or heterocycloalkene;

R⁵ is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R⁶, NC(R^{6A})(R^{6B}), R⁷, OR⁷, SR⁷, S(O)R⁷, SO₂R⁷, NHR⁷, N(R⁷)₂, C(O)R⁷, C(O)NH₂, C(O)NHR⁷, C(O)N(R⁷)₂, NHC(O)R⁷, NR⁷C(O)R⁷, NHSO₂R⁷, NHC(O)OR⁷, SO₂NH₂, SO₂NHR⁷, SO₂N(R⁷)₂, NHC(O)NH₂, NHC(O)NHR⁷,

NHC(O)CH(CH₃)NHC(O)CH(CH₃)NH₂, NHC(O)CH(CH₃)NHC(O)CH(CH₃)NHR⁷, OH, (O), C(O)OH, N₃, CN, NH₂, CF₃, CF₂CF₃, F, Cl, Br or I;

R⁶ is C₂-C₅-spiroalkyl, each of which is unsubstituted or substituted with OH, (O), N₃, CN, CF₃, CF₂CF₃, F, Cl, Br, I, NH₂, NH(CH₃) or N(CH₃)₂;

5 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 CH₂ moiety unreplaced or replaced with O, C(O), CNOH, CNOCH₃, S, S(O), SO₂ or NH;

R⁷ is R⁸, R⁹, R¹⁰ or R¹¹;

10 R⁸ is phenyl, which is unfused or fused with R^{8A}; R^{8A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R⁹ is heteroaryl, which is unfused or fused with R^{9A}; R^{9A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

15 R¹⁰ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{10A}; R^{10A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R¹¹ is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R¹², OR¹², SR¹², S(O)R¹², SO₂R¹², C(O)R¹², CO(O)R¹², OC(O)R¹², OC(O)OR¹², NH₂, NHR¹², N(R¹²)₂, NHC(O)R¹², NR¹²C(O)R¹², NHS(O)₂R¹², NR¹²S(O)₂R¹², NHC(O)OR¹², NR¹²C(O)OR¹², NHC(O)NH₂, NHC(O)NHR¹², NHC(O)N(R¹²)₂, NR¹²C(O)NHR¹², NR¹²C(O)N(R¹²)₂, C(O)NH₂, C(O)NHR¹², C(O)N(R¹²)₂, C(O)NHOH, C(O)NHOR¹², C(O)NHSO₂R¹², C(O)NR¹²SO₂R¹², SO₂NH₂, SO₂NHR¹², SO₂N(R¹²)₂, C(O)H, C(O)OH, C(N)NH₂, C(N)NHR¹², C(N)N(R¹²)₂, CNOH, CNOCH₃, OH, (O), CN, N₃, NO₂, CF₃, CF₂CF₃, OCF₃, OCF₂CF₃, F, Cl, Br or I;

25 R¹² is R¹³, R¹⁴, R¹⁵ or R¹⁶;

R¹³ is phenyl, which is unfused or fused with R^{13A}; R^{13A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R¹⁴ is heteroaryl, which is unfused or fused with R^{14A}; R^{14A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

30 R¹⁵ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene, each of which is unfused or fused with R^{15A}; R^{15A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R¹⁶ is alkyl, alkenyl or alkynyl;

R¹⁷ is R¹⁸, R¹⁹, R²⁰ or R²¹;

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

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

5 R^{20} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl each of which is unfused or fused with R^{20A} ; R^{20A} is benzene, heteroarene, 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 of independently selected R^{22} , OR^{22} , SR^{22} , $S(O)R^{22}$, SO_2R^{22} , $C(O)R^{22}$,
 10 $CO(O)R^{22}$, $OC(O)R^{22}$, $OC(O)OR^{22}$, NH_2 , NHR^{22} , $N(R^{22})_2$, $NHC(O)R^{22}$, $NR^{22}C(O)R^{22}$, $NHS(O)_2R^{22}$, $NR^{22}S(O)_2R^{22}$, $NHC(O)OR^{22}$, $NR^{22}C(O)OR^{22}$, $NHC(O)NH_2$, $NHC(O)NHR^{22}$, $NHC(O)N(R^{22})_2$, $NR^{22}C(O)NHR^{22}$, $NR^{22}C(O)N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, $C(O)NHOH$, $C(O)NHOR^{22}$, $C(O)NHSO_2R^{22}$, $C(O)NR^{22}SO_2R^{22}$, SO_2NH_2 , SO_2NHR^{22} , $SO_2N(R^{22})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{22}$, $C(N)N(R^{22})_2$, $CNOH$, $CNOCH_3$, OH ,
 15 (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br or I ;

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

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

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

R^{25} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{25A} ; R^{25A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

Z^1 is R^{26} or R^{27} ;

25 Z^2 is R^{28} , R^{29} or R^{30} ;

Z^{1A} and Z^{2A} are both absent or are taken together to form CH_2 , CH_2CH_2 or Z^{12A} ;

Z^{12A} is C_2 - C_6 -alkylene having one or two CH_2 moieties replaced by NH , $N(CH_3)$, S , $S(O)$ or SO_2 ;

L^1 is a R^{37} , OR^{37} , SR^{37} , $S(O)R^{37}$, SO_2R^{37} , $C(O)R^{37}$, $CO(O)R^{37}$, $OC(O)R^{37}$,
 30 $OC(O)OR^{37}$, NHR^{37} , $C(O)NH$, $C(O)NR^{37}$, $C(O)NHOR^{37}$, $C(O)NHSO_2R^{37}$, SO_2NH , SO_2NHR^{37} , $C(N)NH$, $C(N)NHR^{37}$;

R^{26} is phenylene, which is unfused or fused with R^{26A} ; R^{26A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{27} is heteroarylene, which is unfused or fused with R^{27A} ; R^{27A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

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

5 R^{29} is heteroarylene, which is unfused or fused with R^{29A} ; R^{29A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{30} is cycloalkylene, cycloalkenylene, heterocycloalkylene or heterocycloalkenylene, each of which is unfused or fused with R^{30A} ; R^{30A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

10 R^{37} is a bond or R^{37A} ;

R^{37A} is alkylene, alkenylene, or alkynylene, each of which is unsubstituted or substituted with one or two or three independently selected R^{37B} , OR^{37B} , SR^{37B} , $S(O)R^{37B}$, SO_2R^{37B} , $C(O)R^{37B}$, $CO(O)R^{37B}$, $OC(O)R^{37B}$, $OC(O)OR^{37B}$, NH_2 , NHR^{37B} , $N(R^{37B})_2$, $NHC(O)R^{37B}$, $NR^{37B}C(O)R^{37B}$, $NHS(O)_2R^{37B}$, $NR^{37B}S(O)_2R^{37B}$, $NHC(O)OR^{37B}$, $NR^{37B}C(O)OR^{37B}$, $NHC(O)NH_2$, $NHC(O)NHR^{37B}$, $NHC(O)N(R^{37B})_2$, $NR^{37B}C(O)NHR^{37B}$, $NR^{37B}C(O)N(R^{37B})_2$, $C(O)NH_2$, $C(O)NHR^{37B}$, $C(O)N(R^{37B})_2$, $C(O)NHOH$, $C(O)NHOR^{37B}$, $C(O)NHSO_2R^{37B}$, $C(O)NR^{37B}SO_2R^{37B}$, SO_2NH_2 , SO_2NHR^{37B} , $SO_2N(R^{37B})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{37B}$, $C(N)N(R^{37B})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br and I substituents;

20 R^{37B} is alkyl, alkenyl, alkynyl, or R^{37C} ;

R^{37C} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

Z^3 is R^{38} , R^{39} or R^{40} ;

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

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

30 R^{40} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{40A} ; R^{40A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein the moieties represented by R^{26} and R^{27} are substituted (i.e., if Z^{1A} and Z^{2A} are absent) or further substituted (i.e., if Z^{1A} and Z^{2A} are present) with R^{41} , OR^{41} , SR^{41} , $S(O)R^{41}$, SO_2R^{41} , $C(O)R^{41}$, $CO(O)R^{41}$, $OC(O)R^{41}$, $OC(O)OR^{41}$, NHR^{41} , $N(R^{41})_2$, $NHC(O)R^{41}$, $NR^{41}C(O)R^{41}$, $NHS(O)_2R^{41}$, $NR^{41}S(O)_2R^{41}$, $NHC(O)OR^{41}$, $NR^{41}C(O)OR^{41}$, $NHC(O)NHR^{41}$,

NHC(O)N(R⁴¹)₂, NR⁴¹C(O)NHR⁴¹, NR⁴¹C(O)N(R⁴¹)₂, C(O)NHR⁴¹, C(O)N(R⁴¹)₂,
C(O)NHR⁴¹, C(O)NHSO₂R⁴¹, C(O)NR⁴¹SO₂R⁴¹, SO₂NHR⁴¹, SO₂N(R⁴¹)₂, C(N)NHR⁴¹, or
C(N)N(R⁴¹)₂;

5 R⁴¹ is heteroaryl, which is fused with R^{43A}; R^{43A} is benzene, heteroarene, cycloalkane,
cycloalkene, heterocycloalkane or heterocycloalkene; which is unfused or fused with
benzene, heteroarene or R^{43B}; R^{43B} is cycloalkane, cycloalkene, heterocycloalkane or
heterocycloalkene;

wherein the cyclic moieties represented by E¹ and Y¹ together, Y¹ and B¹ together, A²
and B¹ together, A² and D¹ together, R^{1A}, R², R^{2A}, R³, R^{3A}, R⁴, R^{4A}, R⁶, R^{6C}, R⁸, R^{8A}, R⁹, R^{9A},
10 R¹⁰, R^{10A}, R¹³, R^{13A}, R¹⁴, R^{14A}, R¹⁵, R^{15A}, R¹⁸, R^{18A}, R¹⁹, R^{19A}, R²⁰, R^{20A}, R²³, R^{23A}, R²⁴, R^{24A},
R²⁵, R^{25A}, R²⁶, R^{26A}, R²⁷, R^{27A}, R²⁸, R^{28A}, R²⁹, R^{29A}, R³⁰, R^{30A}, R^{37B}, R³⁸, R^{38A}, R³⁹, R^{39A},
R⁴⁰, and R^{40A} are independently unsubstituted, further unsubstituted, substituted or further
substituted with one or two or three or four or five of independently selected R^{57A}, R⁵⁷, OR⁵⁷,
SR⁵⁷, S(O)R⁵⁷, SO₂R⁵⁷, C(O)R⁵⁷, CO(O)R⁵⁷, OC(O)R⁵⁷, OC(O)OR⁵⁷, NH₂, NHR⁵⁷, N(R⁵⁷)₂,
15 NHC(O)R⁵⁷, NR⁵⁷C(O)R⁵⁷, NHS(O)₂R⁵⁷, NR⁵⁷S(O)₂R⁵⁷, NHC(O)OR⁵⁷, NR⁵⁷C(O)OR⁵⁷,
NHC(O)NH₂, NHC(O)NHR⁵⁷, NHC(O)N(R⁵⁷)₂, NR⁵⁷C(O)NHR⁵⁷, NR⁵⁷C(O)N(R⁵⁷)₂,
C(O)NH₂, C(O)NHR⁵⁷, C(O)N(R⁵⁷)₂, C(O)NHOH, C(O)NHR⁵⁷, C(O)NHSO₂R⁵⁷,
C(O)NR⁵⁷SO₂R⁵⁷, SO₂NH₂, SO₂NHR⁵⁷, SO₂N(R⁵⁷)₂, C(O)H, C(O)OH, C(N)NH₂,
C(N)NHR⁵⁷, C(N)N(R⁵⁷)₂, CNOH, CNOCH₃, OH, (O), CN, N₃, NO₂, CF₃, CF₂CF₃, OCF₃,
20 OCF₂CF₃, F, Cl, Br or I;

R^{57A} is spiroalkyl, or spiroheteroalkyl;

R⁵⁷ is R⁵⁸, R⁵⁹, R⁶⁰ or R⁶¹;

R⁵⁸ is phenyl, which is unfused or fused with R^{58A}; R^{58A} is benzene, heteroarene,
cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

25 R⁵⁹ is heteroaryl, which is unfused or fused with R^{59A}; R^{59A} is benzene, heteroarene,
cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R⁶⁰ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which
is unfused or fused with R^{60A}; R^{60A} is benzene, heteroarene, cycloalkane, cycloalkene,
heterocycloalkane or heterocycloalkene;

30 R⁶¹ is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one
or two or three of independently selected R⁶², OR⁶², SR⁶², S(O)R⁶², SO₂R⁶², C(O)R⁶²,
CO(O)R⁶², OC(O)R⁶², OC(O)OR⁶², NH₂, NHR⁶², N(R⁶²)₂, NHC(O)R⁶², NR⁶²C(O)R⁶²,
NHS(O)₂R⁶², NR⁶²S(O)₂R⁶², NHC(O)OR⁶², NR⁶²C(O)OR⁶², NHC(O)NH₂, NHC(O)NHR⁶²,
NHC(O)N(R⁶²)₂, NR⁶²C(O)NHR⁶², NR⁶²C(O)N(R⁶²)₂, C(O)NH₂, C(O)NHR⁶², C(O)N(R⁶²)₂,

C(O)NHOH, C(O)NHOR⁶², C(O)NHSO₂R⁶², C(O)NR⁶²SO₂R⁶², SO₂NH₂, SO₂NHR⁶², SO₂N(R⁶²)₂, C(O)H, C(O)OH, C(N)NH₂, C(N)NHR⁶², C(N)N(R⁶²)₂, CNOH, CNOCH₃, OH, (O), CN, N₃, NO₂, CF₃, CF₂CF₃, OCF₃, OCF₂CF₃, F, Cl, Br or I;

R⁶² is R⁶³, R⁶⁴, R⁶⁵ or R⁶⁶;

5 R⁶³ is phenyl, which is unfused or fused with R^{63A}; R^{63A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R⁶⁴ is heteroaryl, which is unfused or fused with R^{64A}; R^{64A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

10 R⁶⁵ is cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, each of which is unfused or fused with R^{65A}; R^{65A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R⁶⁶ is alkyl, alkenyl or alkenyl, each of which is unsubstituted or substituted with one or two or three of independently selected R⁶⁷, OR⁶⁷, SR⁶⁷, S(O)R⁶⁷, SO₂R⁶⁷, C(O)R⁶⁷, CO(O)R⁶⁷, OC(O)R⁶⁷, OC(O)OR⁶⁷, NH₂, NHR⁶⁷, N(R⁶⁷)₂, NHC(O)R⁶⁷, NR⁶⁷C(O)R⁶⁷,
15 NHS(O)₂R⁶⁷, NR⁶⁷S(O)₂R⁶⁷, NHC(O)OR⁶⁷, NR⁶⁷C(O)OR⁶⁷, NHC(O)NH₂, NHC(O)NHR⁶⁷, NHC(O)N(R⁶⁷)₂, NR⁶⁷C(O)NHR⁶⁷, NR⁶⁷C(O)N(R⁶⁷)₂, C(O)NH₂, C(O)NHR⁶⁷, C(O)N(R⁶⁷)₂, C(O)NHOH, C(O)NHOR⁶⁷, C(O)NHSO₂R⁶⁷, C(O)NR⁶⁷SO₂R⁶⁷, SO₂NH₂, SO₂NHR⁶⁷, SO₂N(R⁶⁷)₂, C(O)H, C(O)OH, C(N)NH₂, C(N)NHR⁶⁷, C(N)N(R⁶⁷)₂, CNOH, CNOCH₃, OH, (O), CN, N₃, NO₂, CF₃, CF₂CF₃, OCF₃, OCF₂CF₃, F, Cl, Br or I substituents;

20 R⁶⁷ is alkyl, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl;

wherein the cyclic moieties represented by R^{57A}, R⁵⁸, R⁵⁹, R⁶⁰, R⁶³, R⁶⁴, R⁶⁵, and R⁶⁷ are unsubstituted or substituted with one or two or three or four of independently selected R⁶⁸, OR⁶⁸, SR⁶⁸, S(O)R⁶⁸, SO₂R⁶⁸, C(O)R⁶⁸, CO(O)R⁶⁸, OC(O)R⁶⁸, OC(O)OR⁶⁸, NH₂,
25 NHR⁶⁸, N(R⁶⁸)₂, NHC(O)R⁶⁸, NR⁶⁸C(O)R⁶⁸, NHS(O)₂R⁶⁸, NR⁶⁸S(O)₂R⁶⁸, NHC(O)OR⁶⁸, NR⁶⁸C(O)OR⁶⁸, NHC(O)NH₂, NHC(O)NHR⁶⁸, NHC(O)N(R⁶⁸)₂, NR⁶⁸C(O)NHR⁶⁸, NR⁶⁸C(O)N(R⁶⁸)₂, C(O)NH₂, C(O)NHR⁶⁸, C(O)N(R⁶⁸)₂, C(O)NHOH, C(O)NHOR⁶⁸, C(O)NHSO₂R⁶⁸, C(O)NR⁶⁸SO₂R⁶⁸, SO₂NH₂, SO₂NHR⁶⁸, SO₂N(R⁶⁸)₂, C(O)H, C(O)OH, C(N)NH₂, C(N)NHR⁶⁸, C(N)N(R⁶⁸)₂, CNOH, CNOCH₃, OH, (O), CN, N₃, NO₂, CF₃,
30 CF₂CF₃, OCF₃, OCF₂CF₃, F, Cl, Br or I;

R⁶⁸ is R⁶⁹, R⁷⁰, R⁷¹ or R⁷²;

R⁶⁹ is phenyl, which is unfused or fused with R^{69A}; R^{69A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{70} is heteroaryl, which is unfused or fused with R^{70A} ; R^{70A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{71} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{71A} ; R^{71A} is benzene, heteroarene, cycloalkane, cycloalkene,

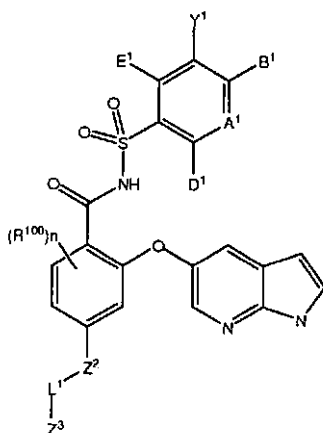
5 heterocycloalkane or heterocycloalkene;

R^{72} is alkyl, alkenyl or alkenyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{73} , OR^{73} , SR^{73} , $S(O)R^{73}$, SO_2R^{73} , $C(O)R^{73}$, $CO(O)R^{73}$, $OC(O)R^{73}$, $OC(O)OR^{73}$, NH_2 , NHR^{73} , $N(R^{73})_2$, $NHC(O)R^{73}$, $NR^{73}C(O)R^{73}$, $NHS(O)_2R^{73}$, $NR^{73}S(O)_2R^{73}$, $NHC(O)OR^{73}$, $NR^{73}C(O)OR^{73}$, $NHC(O)NH_2$, $NHC(O)NHR^{73}$, $NHC(O)N(R^{73})_2$, $NR^{73}C(O)NHR^{73}$, $NR^{73}C(O)N(R^{73})_2$, $C(O)NH_2$, $C(O)NHR^{73}$, $C(O)N(R^{73})_2$, $C(O)NHOH$, $C(O)NHOR^{73}$, $C(O)NHSO_2R^{73}$, $C(O)NR^{73}SO_2R^{73}$, SO_2NH_2 , SO_2NHR^{73} , $SO_2N(R^{73})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{73}$, $C(N)N(R^{73})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br or I ;

R^{73} is alkyl, alkenyl, alkenyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, 15 heterocycloalkyl or heterocycloalkenyl; and

wherein the moieties represented by R^{69} , R^{70} , and R^{71} are unsubstituted or substituted with one or two or three or four of independently selected NH_2 , $C(O)NH_2$, $C(O)NHOH$, SO_2NH_2 , CF_3 , CF_2CF_3 , $C(O)H$, $C(O)OH$, $C(N)NH_2$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br or I .

20 Another embodiment of this invention pertains to compounds or therapeutically acceptable salts, which are useful as inhibitors of anti-apoptotic Bcl-2 proteins, the compounds having Formula (II)



(II),

25 or a therapeutically acceptable salt thereof, wherein

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

n is 0, 1, 2, or 3;

A¹ is N or C(A²);

A² is H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹,
 5 NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR^{1A};

10 B¹ is H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹,
 15 C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR^{1A};

D¹ is H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂,
 20 SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR^{1A};

E¹ is H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂,
 25 SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR^{1A}; and
 30

Y¹ is H, CN, NO₂, C(O)OH, F, Cl, Br, I, CF₃, OCF₃, CF₂CF₃, OCF₂CF₃, R¹⁷, OR¹⁷, C(O)R¹⁷, C(O)OR¹⁷, SR¹⁷, SO₂R¹⁷, NH₂, NHR¹⁷, N(R¹⁷)₂, NHC(O)R¹⁷, C(O)NH₂, C(O)NHR¹⁷, C(O)N(R¹⁷)₂, NHC(O)R¹⁷ or NHSO₂R¹⁷; or

E^1 and Y^1 , together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

A^2 , B^1 , and D^1 are independently selected H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$, $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 , $C(O)OH$, $C(O)NH_2$ or $C(O)OR^{1A}$; or

Y^1 and B^1 , together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

A^2 , D^1 , and E^1 are independently selected H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$, $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 , $C(O)OH$, $C(O)NH_2$ or $C(O)OR^{1A}$; or

A^2 and B^1 , together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

D^1 , E^1 , and Y^1 are independently selected H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$, $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 , $C(O)OH$, $C(O)NH_2$ or $C(O)OR^{1A}$; or

A² and D¹, together with the atoms to which they are attached, are benzene, naphthalene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

B¹, E¹, and Y¹ are independently selected H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹,
 5 C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹,
 NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹,
 NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹,
 NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹,
 C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹,
 10 N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃,
 C(O)OH, C(O)NH₂ or C(O)OR^{1A};

R¹ is R², R³, R⁴ or R⁵;

R^{1A} is cycloalkyl, cycloalkenyl or cycloalkynyl;

R² is phenyl, which is unfused or fused with R^{2A}; R^{2A} is benzene, heteroarene,
 15 cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R³ is heteroaryl, which is unfused or fused with R^{3A}; R^{3A} is benzene, heteroarene,
 cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R⁴ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which
 is unfused or fused with R^{4A}; R^{4A} is benzene, heteroarene, cycloalkane, cycloalkene,
 20 heterocycloalkane or heterocycloalkene;

R⁵ is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one
 or two or three of independently selected R⁶, NC(R^{6A})(R^{6B}), R⁷, OR⁷, SR⁷, S(O)R⁷, SO₂R⁷,
 NHR⁷, N(R⁷)₂, C(O)R⁷, C(O)NH₂, C(O)NHR⁷, C(O)N(R⁷)₂, NHC(O)R⁷, NR⁷C(O)R⁷,
 NHSO₂R⁷, NHC(O)OR⁷, SO₂NH₂, SO₂NHR⁷, SO₂N(R⁷)₂, NHC(O)NH₂, NHC(O)NHR⁷,
 25 NHC(O)CH(CH₃)NHC(O)CH(CH₃)NH₂, NHC(O)CH(CH₃)NHC(O)CH(CH₃)NHR⁷, OH,
 (O), C(O)OH, N₃, CN, NH₂, CF₃, CF₂CF₃, F, Cl, Br or I;

R⁶ is C₂-C₅-spiroalkyl, each of which is unsubstituted or substituted with OH, (O), N₃,
 CN, CF₃, CF₂CF₃, F, Cl, Br, I, NH₂, NH(CH₃) or N(CH₃)₂;

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

R^{6C} is aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, each having one
 CH₂ moiety unreplaced or replaced with O, C(O), CNOH, CNOCH₃, S, S(O), SO₂ or NH;

R⁷ is R⁸, R⁹, R¹⁰ or R¹¹;

R^8 is phenyl, which is unfused or fused with R^{8A} ; R^{8A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

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

5 R^{10} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{10A} ; R^{10A} is benzene, heteroarene, 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 of independently selected R^{12} , OR^{12} , SR^{12} , $S(O)R^{12}$, SO_2R^{12} , $C(O)R^{12}$,
 10 $CO(O)R^{12}$, $OC(O)R^{12}$, $OC(O)OR^{12}$, NH_2 , NHR^{12} , $N(R^{12})_2$, $NHC(O)R^{12}$, $NR^{12}C(O)R^{12}$, $NHS(O)_2R^{12}$, $NR^{12}S(O)_2R^{12}$, $NHC(O)OR^{12}$, $NR^{12}C(O)OR^{12}$, $NHC(O)NH_2$, $NHC(O)NHR^{12}$, $NHC(O)N(R^{12})_2$, $NR^{12}C(O)NHR^{12}$, $NR^{12}C(O)N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, $C(O)NHOH$, $C(O)NHOR^{12}$, $C(O)NHSO_2R^{12}$, $C(O)NR^{12}SO_2R^{12}$, SO_2NH_2 , SO_2NHR^{12} , $SO_2N(R^{12})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{12}$, $C(N)N(R^{12})_2$, $CNOH$, $CNOCH_3$, OH ,
 15 (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br or I ;

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

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

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

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

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

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

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

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

30 R^{20} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl each of which is unfused or fused with R^{20A} ; R^{20A} is benzene, heteroarene, 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 of independently selected R^{22} , OR^{22} , SR^{22} , $S(O)R^{22}$, SO_2R^{22} , $C(O)R^{22}$,

- CO(O)R²², OC(O)R²², OC(O)OR²², NH₂, NHR²², N(R²²)₂, NHC(O)R²², NR²²C(O)R²²,
 NHS(O)₂R²², NR²²S(O)₂R²², NHC(O)OR²², NR²²C(O)OR²², NHC(O)NH₂, NHC(O)NHR²²,
 NHC(O)N(R²²)₂, NR²²C(O)NHR²², NR²²C(O)N(R²²)₂, C(O)NH₂, C(O)NHR²², C(O)N(R²²)₂,
 C(O)NHOH, C(O)NHOR²², C(O)NHSO₂R²², C(O)NR²²SO₂R²², SO₂NH₂, SO₂NHR²²,
 5 SO₂N(R²²)₂, C(O)H, C(O)OH, C(N)NH₂, C(N)NHR²², C(N)N(R²²)₂, CNOH, CNOCH₃, OH,
 (O), CN, N₃, NO₂, CF₃, CF₂CF₃, OCF₃, OCF₂CF₃, F, Cl, Br or I;
 R²² is R²³, R²⁴ or R²⁵;
 R²³ is phenyl, which is unfused or fused with R^{23A}; R^{23A} is benzene, heteroarene,
 cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
 10 R²⁴ is heteroarene, which is unfused or fused with R^{24A}; R^{24A} is benzene, heteroarene,
 cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
 R²⁵ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which
 is unfused or fused with R^{25A}; R^{25A} is benzene, heteroarene, cycloalkane, cycloalkene,
 heterocycloalkane or heterocycloalkene;
 15 Z² is R²⁸, R²⁹ or R³⁰;
 L¹ is a R³⁷, OR³⁷, SR³⁷, S(O)R³⁷, SO₂R³⁷, C(O)R³⁷, CO(O)R³⁷, OC(O)R³⁷,
 OC(O)OR³⁷, NHR³⁷, C(O)NH, C(O)NR³⁷, C(O)NHOR³⁷, C(O)NHSO₂R³⁷, SO₂NH,
 SO₂NHR³⁷, C(N)NH, C(N)NHR³⁷;
 R²⁸ is phenylene, which is unfused or fused with R^{28A}; R^{28A} is benzene, heteroarene,
 20 cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
 R²⁹ is heteroarylene, which is unfused or fused with R^{29A}; R^{29A} is benzene,
 heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
 R³⁰ is cycloalkylene, cycloalkenylene, heterocycloalkylene or heterocycloalkenylene,
 each of which is unfused or fused with R^{30A}; R^{30A} is benzene, heteroarene, cycloalkane,
 25 cycloalkene, heterocycloalkane or heterocycloalkene;
 R³⁷ is a bond or R^{37A};
 R^{37A} is alkylene, alkenylene, or alkynylene, each of which is unsubstituted or
 substituted with one or two or three independently selected R^{37B}, OR^{37B}, SR^{37B}, S(O)R^{37B},
 SO₂R^{37B}, C(O)R^{37B}, CO(O)R^{37B}, OC(O)R^{37B}, OC(O)OR^{37B}, NH₂, NHR^{37B}, N(R^{37B})₂,
 30 NHC(O)R^{37B}, NR^{37B}C(O)R^{37B}, NHS(O)₂R^{37B}, NR^{37B}S(O)₂R^{37B}, NHC(O)OR^{37B},
 NR^{37B}C(O)OR^{37B}, NHC(O)NH₂, NHC(O)NHR^{37B}, NHC(O)N(R^{37B})₂, NR^{37B}C(O)NHR^{37B},
 NR^{37B}C(O)N(R^{37B})₂, C(O)NH₂, C(O)NHR^{37B}, C(O)N(R^{37B})₂, C(O)NHOH, C(O)NHOR^{37B},
 C(O)NHSO₂R^{37B}, C(O)NR^{37B}SO₂R^{37B}, SO₂NH₂, SO₂NHR^{37B}, SO₂N(R^{37B})₂, C(O)H,

C(O)OH, C(N)NH₂, C(N)NHR^{37B}, C(N)N(R^{37B})₂, CNOH, CNOCH₃, OH, (O), CN, N₃, NO₂, CF₃, CF₂CF₃, OCF₃, OCF₂CF₃, F, Cl, Br and I substituents;

R^{37B} is alkyl, alkenyl, alkynyl, or R^{37C};

R^{37C} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or
5 heterocycloalkenyl;

Z³ is R³⁸, R³⁹ or R⁴⁰;

R³⁸ is phenyl, which is unfused or fused with R^{38A}; R^{38A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R³⁹ is heteroaryl, which is unfused or fused with R^{39A}; R^{39A} is benzene, heteroarene,
10 cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R⁴⁰ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{40A}; R^{40A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein the cyclic moieties represented by E¹ and Y¹ together, Y¹ and B¹ together, A²
15 and B¹ together, A² and D¹ together, R^{1A}, R², R^{2A}, R³, R^{3A}, R⁴, R^{4A}, R⁶, R^{6C}, R⁸, R^{8A}, R⁹, R^{9A}, R¹⁰, R^{10A}, R¹³, R^{13A}, R¹⁴, R^{14A}, R¹⁵, R^{15A}, R¹⁸, R^{18A}, R¹⁹, R^{19A}, R²⁰, R^{20A}, R²³, R^{23A}, R²⁴, R^{24A}, R²⁵, R^{25A}, R²⁶, R^{26A}, R²⁷, R^{27A}, R²⁸, R^{28A}, R²⁹, R^{29A}, R³⁰, R^{30A}, R^{37B}, R³⁸, R^{38A}, R³⁹, R^{39A}, R⁴⁰, and R^{40A} are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five of independently selected R^{57A}, R⁵⁷, OR⁵⁷,
20 SR⁵⁷, S(O)R⁵⁷, SO₂R⁵⁷, C(O)R⁵⁷, CO(O)R⁵⁷, OC(O)R⁵⁷, OC(O)OR⁵⁷, NH₂, NHR⁵⁷, N(R⁵⁷)₂, NHC(O)R⁵⁷, NR⁵⁷C(O)R⁵⁷, NHS(O)₂R⁵⁷, NR⁵⁷S(O)₂R⁵⁷, NHC(O)OR⁵⁷, NR⁵⁷C(O)OR⁵⁷, NHC(O)NH₂, NHC(O)NHR⁵⁷, NHC(O)N(R⁵⁷)₂, NR⁵⁷C(O)NHR⁵⁷, NR⁵⁷C(O)N(R⁵⁷)₂, C(O)NH₂, C(O)NHR⁵⁷, C(O)N(R⁵⁷)₂, C(O)NHOH, C(O)NHOR⁵⁷, C(O)NHSO₂R⁵⁷, C(O)NR⁵⁷SO₂R⁵⁷, SO₂NH₂, SO₂NHR⁵⁷, SO₂N(R⁵⁷)₂, C(O)H, C(O)OH, C(N)NH₂,
25 C(N)NHR⁵⁷, C(N)N(R⁵⁷)₂, CNOH, CNOCH₃, OH, (O), CN, N₃, NO₂, CF₃, CF₂CF₃, OCF₃, OCF₂CF₃, F, Cl, Br or I;

R^{57A} is spiroalkyl or heterospiroalkyl;

R⁵⁷ is R⁵⁸, R⁵⁹, R⁶⁰ or R⁶¹;

R⁵⁸ is phenyl, which is unfused or fused with R^{58A}; R^{58A} is benzene, heteroarene,
30 cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R⁵⁹ is heteroaryl, which is unfused or fused with R^{59A}; R^{59A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{60} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{60A} ; R^{60A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{61} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{62} , OR^{62} , SR^{62} , $S(O)R^{62}$, SO_2R^{62} , $C(O)R^{62}$, $CO(O)R^{62}$, $OC(O)R^{62}$, $OC(O)OR^{62}$, NH_2 , NHR^{62} , $N(R^{62})_2$, $NHC(O)R^{62}$, $NR^{62}C(O)R^{62}$, $NHS(O)_2R^{62}$, $NR^{62}S(O)_2R^{62}$, $NHC(O)OR^{62}$, $NR^{62}C(O)OR^{62}$, $NHC(O)NH_2$, $NHC(O)NHR^{62}$, $NHC(O)N(R^{62})_2$, $NR^{62}C(O)NHR^{62}$, $NR^{62}C(O)N(R^{62})_2$, $C(O)NH_2$, $C(O)NHR^{62}$, $C(O)N(R^{62})_2$, $C(O)NHOH$, $C(O)NHOR^{62}$, $C(O)NHSO_2R^{62}$, $C(O)NR^{62}SO_2R^{62}$, SO_2NH_2 , SO_2NHR^{62} , $SO_2N(R^{62})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{62}$, $C(N)N(R^{62})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br or I ;

R^{62} is R^{63} , R^{64} , R^{65} or R^{66} ;

R^{63} is phenyl, which is unfused or fused with R^{63A} ; R^{63A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{64} is heteroaryl, which is unfused or fused with R^{64A} ; R^{64A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{65} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{65A} ; R^{65A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{66} is alkyl, alkenyl or alkenyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{67} , OR^{67} , SR^{67} , $S(O)R^{67}$, SO_2R^{67} , $C(O)R^{67}$, $CO(O)R^{67}$, $OC(O)R^{67}$, $OC(O)OR^{67}$, NH_2 , NHR^{67} , $N(R^{67})_2$, $NHC(O)R^{67}$, $NR^{67}C(O)R^{67}$, $NHS(O)_2R^{67}$, $NR^{67}S(O)_2R^{67}$, $NHC(O)OR^{67}$, $NR^{67}C(O)OR^{67}$, $NHC(O)NH_2$, $NHC(O)NHR^{67}$, $NHC(O)N(R^{67})_2$, $NR^{67}C(O)NHR^{67}$, $NR^{67}C(O)N(R^{67})_2$, $C(O)NH_2$, $C(O)NHR^{67}$, $C(O)N(R^{67})_2$, $C(O)NHOH$, $C(O)NHOR^{67}$, $C(O)NHSO_2R^{67}$, $C(O)NR^{67}SO_2R^{67}$, SO_2NH_2 , SO_2NHR^{67} , $SO_2N(R^{67})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{67}$, $C(N)N(R^{67})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br or I substituents;

R^{67} is alkyl, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl;

wherein the cyclic moieties represented by R^{57A} , R^{58} , R^{59} , R^{60} , R^{63} , R^{64} , R^{65} , and R^{67} are unsubstituted or substituted with one or two or three or four of independently selected R^{68} , OR^{68} , SR^{68} , $S(O)R^{68}$, SO_2R^{68} , $C(O)R^{68}$, $CO(O)R^{68}$, $OC(O)R^{68}$, $OC(O)OR^{68}$, NH_2 , NHR^{68} , $N(R^{68})_2$, $NHC(O)R^{68}$, $NR^{68}C(O)R^{68}$, $NHS(O)_2R^{68}$, $NR^{68}S(O)_2R^{68}$, $NHC(O)OR^{68}$, $NR^{68}C(O)OR^{68}$, $NHC(O)NH_2$, $NHC(O)NHR^{68}$, $NHC(O)N(R^{68})_2$, $NR^{68}C(O)NHR^{68}$,

NR⁶⁸C(O)N(R⁶⁸)₂, C(O)NH₂, C(O)NHR⁶⁸, C(O)N(R⁶⁸)₂, C(O)NHOH, C(O)NHOR⁶⁸,
C(O)NH₂SO₂R⁶⁸, C(O)NR⁶⁸SO₂R⁶⁸, SO₂NH₂, SO₂NHR⁶⁸, SO₂N(R⁶⁸)₂, C(O)H, C(O)OH,
C(N)NH₂, C(N)NHR⁶⁸, C(N)N(R⁶⁸)₂, CNOH, CNOCH₃, OH, (O), CN, N₃, NO₂, CF₃,
CF₂CF₃, OCF₃, OCF₂CF₃, F, Cl, Br or I;

5 R⁶⁸ is R⁶⁹, R⁷⁰, R⁷¹ or R⁷²;

R⁶⁹ is phenyl, which is unfused or fused with R^{69A}; R^{69A} is benzene, heteroarene,
cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R⁷⁰ is heteroaryl, which is unfused or fused with R^{70A}; R^{70A} is benzene, heteroarene,
cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

10 R⁷¹ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which
is unfused or fused with R^{71A}; R^{71A} is benzene, heteroarene, cycloalkane, cycloalkene,
heterocycloalkane or heterocycloalkene;

R⁷² is alkyl, alkenyl or alkenyl, each of which is unsubstituted or substituted with one
or two or three of independently selected R⁷³, OR⁷³, SR⁷³, S(O)R⁷³, SO₂R⁷³, C(O)R⁷³,
15 CO(O)R⁷³, OC(O)R⁷³, OC(O)OR⁷³, NH₂, NHR⁷³, N(R⁷³)₂, NHC(O)R⁷³, NR⁷³C(O)R⁷³,
NHS(O)₂R⁷³, NR⁷³S(O)₂R⁷³, NHC(O)OR⁷³, NR⁷³C(O)OR⁷³, NHC(O)NH₂, NHC(O)NHR⁷³,
NHC(O)N(R⁷³)₂, NR⁷³C(O)NHR⁷³, NR⁷³C(O)N(R⁷³)₂, C(O)NH₂, C(O)NHR⁷³, C(O)N(R⁷³)₂,
C(O)NHOH, C(O)NHOR⁷³, C(O)NH₂SO₂R⁷³, C(O)NR⁷³SO₂R⁷³, SO₂NH₂, SO₂NHR⁷³,
SO₂N(R⁷³)₂, C(O)H, C(O)OH, C(N)NH₂, C(N)NHR⁷³, C(N)N(R⁷³)₂, CNOH, CNOCH₃, OH,
20 (O), CN, N₃, NO₂, CF₃, CF₂CF₃, OCF₃, OCF₂CF₃, F, Cl, Br or I;

R⁷³ is alkyl, alkenyl, alkenyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl,
heterocycloalkyl or heterocycloalkenyl; and

wherein the moieties represented by R⁶⁹, R⁷⁰, and R⁷¹ are unsubstituted or substituted
with one or two or three or four of independently selected NH₂, C(O)NH₂, C(O)NHOH,
25 SO₂NH₂, CF₃, CF₂CF₃, C(O)H, C(O)OH, C(N)NH₂, OH, (O), CN, N₃, NO₂, CF₃, CF₂CF₃,
OCF₃, OCF₂CF₃, F, Cl, Br or I.

Another embodiment pertains to compounds of Formula (I) wherein A¹ is N or C(A²);
A² is H, and G¹ is H.

Another embodiment pertains to compounds of Formula (I) wherein A¹ is N or C(A²);
30 A² is H; G¹ is H, and B¹ is NHR¹.

Another embodiment pertains to compounds of Formula (I) wherein A¹ is N or C(A²);
A² is H; G¹ is H, B¹ is NHR¹; and D¹ is H.

Another embodiment pertains to compounds of Formula (I) wherein A¹ is N or C(A²);
A² is H; G¹ is H, B¹ is NHR¹; D¹ is H; and E¹ is H.

Another embodiment pertains to compounds of Formula (I) wherein A¹ is N or C(A²); A² is H; G¹ is H, B¹ is NHR¹; D¹ is H; E¹ is H; and Y¹ is NO₂.

Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are

- 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-(1H-pyrrolo[2,3-b]pyridin-5-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-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 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-yl)piperidin-4-yl]amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 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-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 Trans-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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-methoxyethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(3S)-tetrahydro-2H-pyran-3-ylmethyl]amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3R)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-(2-naphthylsulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-[(2-methoxyethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-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-[(3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(3,3,3-trifluoropropyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Cis-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]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 Trans-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({[5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Cis-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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-{[4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl]sulfonyl}benzamide;
- 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;
- 10 Trans-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 5-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino}sulfonyl)-2-(tetrahydro-2H-pyran-4-ylmethoxy)nicotinamide;
- N-({5-bromo-6-[(1-methylpiperidin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 N-({5-bromo-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- N-({3-chloro-5-cyano-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 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-pyrrolo[2,3-b]pyridin-5-yloxy)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-morpholin-4-yl)propyl]amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(3-chloro-4-{[2-(2-methoxyethoxy)ethyl]sulfonyl}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[2-(2-methoxyethoxy)ethyl]sulfonyl}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-yl)cyclohexyl]oxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-({5-bromo-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- Cis-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-N-({4-({4-[bis(cyclopropylmethyl)amino]cyclohexyl)amino)-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 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]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(morpholin-3-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-yl)but-2-ynyl]oxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-oxo-3,4-dihydroquinazolin-6-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Cis-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- Trans-4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 tert-butyl 3-{{4-([4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino)sulfonyl)-2-nitrophenoxy)methyl}morpholine-4-carboxylate;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-(morpholin-3-ylmethoxy)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(methylsulfonyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 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)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 N-[(4-chloro-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[1-(2,2,2-trifluoroethyl)piperidin-4-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]oxy}pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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

N-({3-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

and therapeutically acceptable salts, and metabolites thereof.

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-({1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl}amino)-3-nitrophenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yl oxy)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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

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

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

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

N-({5-bromo-6-[(4-ethylmorpholin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-ethylmorpholin-3-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(4-tetrahydro-2H-pyran-4-ylmorpholin-3-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(3S)-1-tetrahydro-2H-pyran-4-ylpiperidin-3-yl]amino)phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-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-ylmethyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)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-pyrrolo[2,3-b]pyridin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-morpholin-4-ylcyclohexyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1S,3R)-3-morpholin-4-ylcyclopentyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1R,3S)-3-morpholin-4-ylcyclopentyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(morpholin-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({1-[cis-3-fluorotetrahydro-2H-pyran-4-yl]piperidin-4-yl}amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)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-ylazetidin-3-yl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydrofuran-3-ylazetidin-3-yl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-({[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl}amino)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(4-((trans-4-hydroxycyclohexyl)methoxy)-3-nitrophenylsulfonyl)benzamide;
- 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(4-((cis-4-methoxycyclohexyl)methoxy)-3-nitrophenylsulfonyl)benzamide;
- Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(cyclopropylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(tetrahydro-2H-pyran-4-ylamino)cyclohexyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-N-({5-bromo-6-[(4-morpholin-4-ylcyclohexyl)oxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- tert-butyl 4-{[4-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino}sulfonyl)-2-nitrophenoxy]methyl}-4-fluoropiperidine-1-carboxylate;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(4-tetrahydro-2H-pyran-4-yl)piperazin-1-yl]cyclohexyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl}methoxy)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3R)-1-tetrahydro-2H-pyran-4-yl]pyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-1-tetrahydro-2H-pyran-4-yl]pyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({[4-(2-methoxyethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- N-[(4-[(4-acetylmorpholin-2-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(4-
5 {[(trans-4-(fluoromethyl)-1-oxetan-3-yl]pyrrolidin-3-yl)methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-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)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(3-nitro-4-[(1-oxetan-3-yl)piperidin-4-yl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(4-
[(1-cyclobutyl)piperidin-4-yl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-
15 yloxy)benzamide;
- 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(4-
{[1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(4-
20 {[(3S)-1-cyclopropylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(3-nitro-4-[(1-tetrahydrofuran-3-yl)piperidin-4-yl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(4-
{[(3R)-1-cyclopropylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(3-nitro-4-[(3S)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl]amino]phenyl)sulfonyl]-
30 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(4-
[(3-hydroxy-2,2-dimethylpropyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
 ({[1-(methylsulfonyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 N-[(4-{[(1-acetyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl]sulfonyl]-4-(4-{[2-(4-
 chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
 {[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-
 nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
 ({[1-(2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl]amino)-3-nitrophenyl]sulfonyl}-2-(1H-
 15 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
 ({[1-(methylsulfonyl)pyrrolidin-3-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 N-[(4-{[(1-acetyl)pyrrolidin-3-yl]methyl}amino)-3-nitrophenyl]sulfonyl]-4-(4-{[2-(4-
 chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- N-[(4-{[(3R)-1-acetylpyrrolidin-3-yl]amino}-3-nitrophenyl]sulfonyl)-4-(4-{[2-(4-
 chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
 [(3-methoxy-2,2-dimethylpropyl)amino]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
 ({[(1R,3R)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-
 30 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
 ({[(1S,3S)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-
 ({[(1S,3R)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl}sulfonyl}-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-
 5 ({[(1R,3S)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl}sulfonyl}-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-
 nitro-4-{[(3S)-2-oxopiperidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-
 yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
 [({1-[2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl]methyl}amino)-3-nitrophenyl}sulfonyl)-2-
 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-
 nitro-4-{[(1-oxetan-3-ylazetidin-3-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
 15 b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-
 nitro-4-{[(1-oxetan-3-ylpiperidin-4-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
 20 {[(1-cyclopropylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-
 ({[4-(2-fluoroethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl}sulfonyl}-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 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}-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
 [(4-fluoro-1-oxetan-3-ylpiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-
 30 b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
 {[(2S)-4,4-difluoro-1-oxetan-3-ylpyrrolidin-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(4-tetrahydro-2H-pyran-4-yl)morpholin-3-yl]methyl}amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyclobutyl)morpholin-3-yl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(4-tetrahydrofuran-3-yl)morpholin-3-yl]methyl}amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-cyclopropyl-4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxybenzyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[3-(trifluoromethoxy)benzyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3-methoxybenzyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-(difluoromethoxy)benzyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1,4-dioxaspiro[4.5]dec-8-ylamino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-N-[(4-{[4-(acetylamino)cyclohexyl]amino)-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 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]-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-[(4-
 {[(3S)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- 4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-[(4-
 {[(3S)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-[(4-
 {[(3R)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- 4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-[(3-
 nitro-4-{{(3S)-1-oxetan-3-ylpyrrolidin-3-yl}methoxy}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
 15 b]pyridin-5-yloxy)benzamide;
- 4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-[(4-
 {(4-hydroxybenzyl)amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-
 yloxy)benzamide;
- 4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-[(4-
 20 [(3-hydroxybenzyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-
 yloxy)benzamide;
- 4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-[(4-
 {[3-(difluoromethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-
 yloxy)benzamide;
- 25 4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-[(4-
 {[cis-3-morpholin-4-ylcyclopentyl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-
 {[4-((4-[(methylsulfonyl)amino]cyclohexyl)amino)-3-nitrophenyl)sulfonyl]-2-(1H-
 30 pyrrolo[2,3-b]pyridin-5-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-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-tetrahydrofuran-3-yl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[[4-fluoro-1-(methylsulfonyl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-([[(3R)-1-oxetan-3-ylpyrrolidin-3-yl]methyl]amino)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-hydroxycyclohexyl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-([3-(dimethylamino)propoxy]benzyl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-morpholin-4-ylethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-([[(E)-4-hydroxy-1-adamantyl]methyl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-([[(Z)-4-hydroxy-1-adamantyl]methyl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-({4-[(1S,4S)-bicyclo[2.2.1]hept-5-en-2-ylmethoxy]-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methyl-5-oxopyrrolidin-3-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-5 {[(1R,4R,5R,6S)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1R,4R,5S,6R)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3-oxocyclohexyl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohexa-1,3-dien-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-20 [(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-({[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methyl}amino)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Cis-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
 [({4-[2-(2-methoxyethoxy)ethyl]morpholin-2-yl]methyl)amino]-3-nitrophenyl}sulfonyl)-2-
 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
 5 ({4-(cyanomethyl)morpholin-2-yl]methyl)amino)-3-nitrophenyl}sulfonyl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
 ({4-(N,N-dimethylglycyl)morpholin-2-yl]methyl)amino)-3-nitrophenyl}sulfonyl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 (2-({4-({4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-
 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl}sulfamoyl)-2-
 nitrophenyl)amino[methyl]morpholin-4-yl)acetic acid;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-
 nitro-4-({4-(oxetan-3-yl)morpholin-2-yl]methyl)amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-
 15 b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
 ({4-(cyclopropyl)morpholin-2-yl]methyl)amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-
 20 (methylsulfonyl)-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-
 pyrrolo[2,3-b]pyridin-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-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-
 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
 [(4-methyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- ethyl 4-(4-{[4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-
 yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl}sulfamoyl)-2-nitrophenyl)piperazine-1-
 30 carboxylate;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[4-
 (morpholin-4-yl)piperidin-1-yl]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-
 yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3R)-1-(oxetan-3-yl)pyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-isopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 N-[(4-{[1-(tert-butylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-(2-methoxyethyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-(cyanomethyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluoro-1-methylpiperidin-4-yl)methoxy]-3-{(trifluoromethyl)sulfonyl}phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 N-[(5-chloro-6-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 tert-butyl 4-[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]-2-nitrophenyl)amino]piperazine-1-carboxylate;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-(pentafluoro- λ^6 -sulfanyl)-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(oxetan-3-yl)piperazin-1-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(3R)-tetrahydrofuran-3-ylamino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(4-{[(1-tert-butylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(5-chloro-6-{[(2S)-4-(cyanomethyl)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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- N-[(5-chloro-6-[(2R)-4-(cyanomethyl)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-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 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-pyrrolo[2,3-b]pyridin-5-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-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 N-({5-chloro-6-[3-hydroxy-2-(hydroxymethyl)-2-methylpropoxy]pyridin-3-yl)sulfonyl)-4-
 (4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-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]pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-
 15 b]pyridin-5-yloxy)benzamide;
- 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-{{4-
 ([4-(1,3-difluoropropan-2-yl)morpholin-2-yl]methyl)amino}-3-nitrophenyl)sulfonyl}-2-
 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(5-chloro-6-[[1-(cyanomethyl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-[[2-(4-
 20 chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- 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}-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 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]-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(3-
 nitro-4-[[1-(oxetan-3-yl)azetidin-3-yl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-
 30 5-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-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 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]-2-
 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
 5 (((2S)-4-(N,N-dimethylglycyl)morpholin-2-yl)methyl)amino]-3-nitrophenyl}sulfonyl]-2-
 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(5-chloro-6-{[1-(N,N-dimethylglycyl)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-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 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-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 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]-2-(1H-pyrrolo[2,3-
 15 b]pyridin-5-yloxy)benzamide;
- 4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-methoxypiperidin-1-yl}-N-({5-chloro-6-[(4-
 fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- 4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-methoxypiperidin-1-yl}-N-({3-nitro-4-[(tetrahydro-
 20 2H-pyran-4-yl)methyl]amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-
 yloxy)benzamide;
- 4-(4-{[9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-
 yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-
 ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-
 yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl}sulfonyl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-
 yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-
 30 yl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-
 yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl]-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- N-({5-chloro-6-[(4-fluoro-1-methylpiperidin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 N-[(5-chloro-6-{[1-(N,N-dimethylglycyl)-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-fluoropiperidin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-fluoropiperidin-1-yl}-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-
- 15 (trifluoromethyl)phenyl}sulfonyl)benzamide;
- N-[(5-chloro-6-{[(3R)-1-(1,3-difluoropropan-2-yl)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-
- 20 nitro-4-[2-(tetrahydrofuran-3-yloxy)ethoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-
- 30 cyano-6-[2-(tetrahydro-2H-pyran-4-yl)ethoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-(3-furylmethoxy)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- N-[(5-chloro-6-[(3R)-1-(1,3-difluoropropan-2-yl)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(5-chloro-6-{[1-(1,3-difluoropropan-2-yl)-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 N-({3-chloro-4-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-yl)methoxy}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 N-[(5-chloro-6-{[1-(2,2-difluoroethyl)-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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-{[1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl]methoxy}-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-chloro-6-[2-(tetrahydrofuran-2-yl)ethoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-methylpiperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(cyclopropylamino)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 N-[(5-chloro-6-(2-methoxyethoxy)pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 N-[(3-chloro-4-{[1-(methoxyacetyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(3-chloro-4-{[1-(N,N-dimethylglycyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohexyl]methyl}piperidin-1-yl)-N-[(3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-[(6-(tetrahydro-2H-pyran-4-ylmethoxy)-5-(trifluoromethyl)pyridin-3-yl)sulfonyl]benzamide;
- 20 N-[(5-chloro-6-[(trans-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(6-[(trans-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(6-[(cis-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-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}piperidin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 N-[(3-chloro-4-{[trans-4-(morpholin-4-yl)cyclohexyl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({3-[cyclopropyl(1,3-thiazol-5-ylmethyl)amino]propyl)amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 N-({3-chloro-4-[(trans-4-hydroxycyclohexyl)methoxy]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({3-[cyclopropyl(2,2,2-trifluoroethyl)amino]propyl)amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 N-[(3-chloro-4-{[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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3,5-difluoro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({3-[cyclopropyl(oxetan-3-yl)amino]propyl)amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 N-[(3-chloro-4-{[1-(1-methyl-L-prolyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3,4-difluoro-5-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-N-({3-chloro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- methyl 2-[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl]morpholine-4-carboxylate;
- 15 2-[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide;
- 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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-((3-[cyclobutyl(cyclopropyl)amino]propyl)amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-chloro-4-(tetrahydrofuran-3-ylmethoxy)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl)sulfonyl)-4-(4-{[9-(4-chlorophenyl)-3-(oxetan-3-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([(2R)-4-cyclopropylmorpholin-2-yl]methyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-([5-chloro-6-([4-(cyclopropyl(oxetan-3-yl)amino)cyclohexyl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-N-([4-([(4-cyclopropylmorpholin-2-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-({3-chloro-4-[(4-cyclopropylmorpholin-2-yl)methoxy]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-([3-chloro-4-([(4-cyclopropylmorpholin-2-yl)methyl]amino)phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 2-([(2-chloro-4-([4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]phenyl)amino)methyl]-N-ethyl-N-methylmorpholine-4-carboxamide;
- (2S)-2-([(3-chloro-5-([4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]pyridin-2-yl)oxy)methyl]-N-ethyl-N-methylmorpholine-4-carboxamide;

- N-[(5-chloro-6-{{(4-cyclopropylmorpholin-2-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-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 2-{{(3-chloro-5-{{4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-
 5 yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl}sulfamoyl}pyridin-
 2-yl)amino]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide;
- 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-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 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-
 pyrrolo[2,3-b]pyridin-5-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-
 15 yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-
 ((4-[(2-cyanoethyl)(cyclopropyl)amino]cyclohexyl)amino)-3-nitrophenyl}sulfonyl}-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-((5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-
 20 {[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 N-[(5-chloro-6-{{(1R,2S,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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-
 30 b]pyridin-5-yloxy)benzamide;
- N-[(5-chloro-6-{{4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-
 (4-{{5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(3,3-difluoropyrrolidin-1-yl)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(2,2-difluorocyclopropyl)amino]cyclohexyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-(2-oxaspiro[3.5]non-7-ylmethoxy)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 4-(4-{[2-(4-chlorophenyl)-5,5-bis(fluoromethyl)cyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(cyclopropylmorpholin-2-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-ethyl-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(cis-4-ethyl-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 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]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 N-[(3-chloro-4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-[(2-cyanoethyl)(cyclopropyl)amino]-1-fluorocyclohexyl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-nitro-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(2-oxaspiro[3.5]non-7-ylmethyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyano-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 {[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]([4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)amino)methyl pivalate;

- {[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl}amino)methyl butyrate;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-{[3-(tetrahydro-2H-pyran-4-ylmethyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-6-yl)sulfonyl}benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(6-[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino)-5-nitropyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)morpholine-4-carboxamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-([4-(methoxymethyl)cyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and therapeutically acceptable salts, and metabolites thereof.

Another embodiment pertains to the compound 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-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound Trans-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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

5 Another embodiment pertains to the compound Cis-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]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

10 Another embodiment pertains to the compound Trans-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]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

15 Another embodiment pertains to the compound 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

20 Another embodiment pertains to the compound 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

25 Another embodiment pertains to the compound 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

30 Another embodiment pertains to the compound N-({5-bromo-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-

(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-({3-[cyclopropyl(oxetan-3-yl)amino]propyl}amino)-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-({3-[cyclopropyl(oxetan-3-yl)amino]propyl}amino)-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are N-[(5-chloro-6-{[1-(cyanomethyl)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-({3-[cyclopropyl(oxetan-3-yl)amino]propyl}amino)-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are 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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({3-[cyclopropyl(oxetan-3-yl)amino]propyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

5 Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{3-nitro-4-({[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl}amino)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{{(3S)-tetrahydro-2H-pyran-3-ylmethyl}amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

15 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

20 N-({5-bromo-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-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-pyrrolo[2,3-b]pyridin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{3-nitro-4-({[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl}amino)phenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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

30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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

5 N-[(5-chloro-6-{{1-(cyanomethyl)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-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide;

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

10 N-[(5-chloro-6-{{(1R,2S,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-pyrrolo[2,3-b]pyridin-5-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-
15 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound N-[(5-chloro-6-{{1-
20 (cyanomethyl)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-pyrrolo[2,3-b]pyridin-5-
yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Still another embodiment pertains to compounds having Formula (I) or Formula (II),
which are N-[(4-{{(4-aminotetrahydro-2H-pyran-4-yl)methyl}amino}-3-
25 nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-
yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-
chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-
methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

30 Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-4,4-
dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxytetrahydro-2H-pyran-
4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a
pharmaceutically acceptable salt 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 a compound of Formula (I) or Formula(II).

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 a compound of Formula (I) or Formula(II).

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) or Formula(II) 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 "C₃-C₆ 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 alkenylene" 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 -CH₂CH=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 "C₁-C₆ 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 "C₂-C₆ 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, -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -CH₂CH₂CH₂CH₂-, and -CH₂CH(CH₃)CH₂-.

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 "C₃-C₆ 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.

5 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,
10 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
15 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
20 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[3.2.2]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
25 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
30 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, 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, 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, imidazoliny, isothiazoliny, oxadiazoliny, isoxazoliny, oxazoliny, pyranyl, pyrazoliny, pyrroliny, thiadiazoliny, thiazoliny, and thiopyranyl.

The term "phenyl," as used herein, means a monovalent radical formed by removal of a hydrogen atom from benzene.

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 C₂-spiroalkyl, C₃-spiroalkyl, C₄-spiroalkyl, C₅-spiroalkyl, C₆-spiroalkyl, C₇-spiroalkyl, C₈-spiroalkyl, C₉-spiroalkyl and the like.

The term "spiroheteroalkyl," as used herein, means spiroalkyl having one or two CH₂ moieties replaced with independently selected O, C(O), CNOH, CNOCH₃, S, S(O), SO₂ 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 CH₂ moieties replaced with independently selected O, C(O), CNOH, CNOCH₃, S, S(O), SO₂ or NH and one or two CH moieties unreplaced or replaced with N and also means spiroalkenyl having one or two CH₂ moieties unreplaced or replaced with independently selected O, C(O), CNOH, CNOCH₃, S, S(O), SO₂ or NH and one or two CH moieties replaced with N.

The term "C₂-C₅-spiroalkyl," as used herein, means C₂-spiroalkyl, C₃-spiroalkyl, C₄-spiroalkyl, and C₅-spiroalkyl.

The term "C₂-spiroalkyl," as used herein, means eth-1,2-ylene, both ends of which replace hydrogen atoms of the same CH₂ moiety.

The term "C₃-spiroalkyl," as used herein, means prop-1,3-ylene, both ends of which replace hydrogen atoms of the same CH₂ moiety.

5 The term "C₄-spiroalkyl," as used herein, means but-1,4-ylene, both ends of which replace hydrogen atoms of the same CH₂ moiety.

The term "C₅-spiroalkyl," as used herein, means pent-1,5-ylene, both ends of which replace hydrogen atoms of the same CH₂ moiety.

10 The term "C₆-spiroalkyl," as used herein, means hex-1,6-ylene, both ends of which replace hydrogen atoms of the same CH₂ 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-amylloxycarbonyl, tert-butoxycarbonyl, 15 para-methoxybenzyloxycarbonyl, 3,4-dimethoxybenzyl-oxycarbonyl, 4-(phenylazo)benzyloxycarbonyl, 2-furfuryl-oxycarbonyl, diphenylmethoxycarbonyl, 1,1-dimethylpropoxy-carbonyl, isopropoxycarbonyl, phthaloyl, succinyl, alanyl, leucyl, 1-adamantylloxycarbonyl, 8-quinolyloxycarbonyl, benzyl, diphenylmethyl, triphenylmethyl, 2-nitrophenylthio, methanesulfonyl, para-toluenesulfonyl, N,N-dimethylaminomethylene, 20 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, 25 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- 30 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-butyl dimethylsilyl, tert-butyl diphenylsilyl, diphenylmethylsilyl, and
 5 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,
 10 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,
 15 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,
 20 2-(trimethylsilyl)ethoxymethyl, 1-ethoxyethyl, methanesulfonyl, para-toluenesulfonyl, trimethylsilyl, triethylsilyl, triisopropylsilyl, diethylisopropylsilyl, tert-butyl dimethylsilyl, tert-butyl diphenylsilyl, diphenylmethylsilyl, and tert-butylmethoxyphenylsilyl.

Compounds

Geometric isomers may exist in the present compounds. Compounds of this invention
 25 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
 30 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.

Compounds of this invention may 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
5 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
10 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.

Isotope Enriched or Labeled Compounds

Compounds of the invention can exist in isotope-labeled or -enriched form containing
15 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, ^2H , ^3H , ^{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
20 within the scope of this invention.

In another embodiment, the isotope-labeled compounds contain deuterium (^2H), tritium (^3H) 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
25 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 deuterio acid such as $\text{D}_2\text{SO}_4/\text{D}_2\text{O}$. In addition to the above, relevant procedures and intermediates are disclosed, for instance, in
30 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).

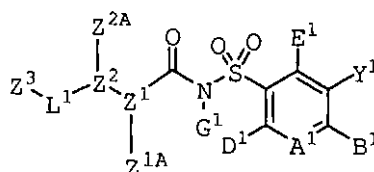
In addition, non-radio active isotope containing drugs, such as deuterated drugs called "heavy drugs," can be used for the treatment of diseases and conditions related to Bcl-2 activity. Increasing the amount of an isotope present in a compound above its natural abundance is called enrichment. Examples 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; Czajka 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.

Suitable groups for A^1 , B^1 , D^1 , E^1 , G^1 , Y^1 , L^1 , Z^{1A} , Z^{2A} , Z^1 , Z^2 , and Z^3 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 , G^1 , Y^1 , L^1 , Z^{1A} , Z^{2A} , Z^1 , Z^2 , and Z^3 can be combined with embodiments defined for any other of A^1 , B^1 , D^1 , E^1 , G^1 , Y^1 , L^1 , Z^{1A} , Z^{2A} , Z^1 , Z^2 , and Z^3 .

One embodiment of this invention, therefore, pertains to compounds or therapeutically acceptable salts, which are useful as inhibitors of anti-apoptotic Bcl-2 proteins, the compounds having Formula (I)



(I),

wherein

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

A^2 is H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$, $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 , $C(O)OH$, $C(O)NH_2$ or $C(O)OR^{1A}$;

B^1 is H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$, $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 , $C(O)OH$, $C(O)NH_2$ or $C(O)OR^{1A}$;

D^1 is H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$, $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 , $C(O)OH$, $C(O)NH_2$ or $C(O)OR^{1A}$;

E^1 is H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$, $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, 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} , SO_2R^{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

E^1 and Y^1 , together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

A^2 , B^1 , and D^1 are independently selected H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$, $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 , $C(O)OH$, $C(O)NH_2$ or $C(O)OR^{1A}$; or

Y^1 and B^1 , together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

A^2 , D^1 , and E^1 are independently selected H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$,

NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹,
 NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹,
 C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹,
 N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃,
 5 C(O)OH, C(O)NH₂ or C(O)OR^{1A}; or

A² and B¹, together with the atoms to which they are attached, are benzene,
 naphthylene, heteroarene cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
 and

D¹, E¹, and Y¹ are independently selected H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹,
 10 C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹,
 NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹,
 NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹,
 NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹,
 C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹,
 15 N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃,
 C(O)OH, C(O)NH₂ or C(O)OR^{1A}; or

A² and D¹, together with the atoms to which they are attached, are benzene,
 naphthalene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
 and

B¹, E¹, and Y¹ are independently selected H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹,
 20 C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹,
 NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹,
 NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹,
 NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹,
 25 C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹,
 N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃,
 C(O)OH, C(O)NH₂ or C(O)OR^{1A};

G¹ is H, or C(O)OR;

R is alkyl;

30 R¹ is R², R³, R⁴ or R⁵;

R^{1A} is cycloalkyl, cycloalkenyl or cycloalkynyl;

R² is phenyl, which is unfused or fused with R^{2A}; R^{2A} is benzene, heteroarene,
 cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

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

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

5 heterocycloalkane or heterocycloalkene;

R^5 is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^6 , $NC(R^{6A})(R^{6B})$, R^7 , OR^7 , SR^7 , $S(O)R^7$, SO_2R^7 , NHR^7 , $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $C(O)N(R^7)_2$, $NHC(O)R^7$, $NR^7C(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2 , SO_2NHR^7 , $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$,
10 $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^7$, OH , (O) , $C(O)OH$, N_3 , CN , NH_2 , CF_3 , CF_2CF_3 , F , Cl , Br or I ;

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
15 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 R^{8A} ; R^{8A} is benzene, heteroarene,
20 cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

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

R^{10} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{10A} ; R^{10A} is benzene, heteroarene, cycloalkane, cycloalkene,

25 heterocycloalkane or heterocycloalkene;

R^{11} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{12} , OR^{12} , SR^{12} , $S(O)R^{12}$, SO_2R^{12} , $C(O)R^{12}$, $CO(O)R^{12}$, $OC(O)R^{12}$, $OC(O)OR^{12}$, NH_2 , NHR^{12} , $N(R^{12})_2$, $NHC(O)R^{12}$, $NR^{12}C(O)R^{12}$, $NHS(O)_2R^{12}$, $NR^{12}S(O)_2R^{12}$, $NHC(O)OR^{12}$, $NR^{12}C(O)OR^{12}$, $NHC(O)NH_2$, $NHC(O)NHR^{12}$,
30 $NHC(O)N(R^{12})_2$, $NR^{12}C(O)NHR^{12}$, $NR^{12}C(O)N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, $C(O)NHOH$, $C(O)NHOR^{12}$, $C(O)NHSO_2R^{12}$, $C(O)NR^{12}SO_2R^{12}$, SO_2NH_2 , SO_2NHR^{12} , $SO_2N(R^{12})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{12}$, $C(N)N(R^{12})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br or I ;

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

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

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

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

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

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

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

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

15 R^{20} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl each of which is unfused or fused with R^{20A} ; R^{20A} is benzene, heteroarene, 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 of independently selected R^{22} , OR^{22} , SR^{22} , $S(O)R^{22}$, SO_2R^{22} , $C(O)R^{22}$, $CO(O)R^{22}$, $OC(O)R^{22}$, $OC(O)OR^{22}$, NH_2 , NHR^{22} , $N(R^{22})_2$, $NHC(O)R^{22}$, $NR^{22}C(O)R^{22}$, $NHS(O)_2R^{22}$, $NR^{22}S(O)_2R^{22}$, $NHC(O)OR^{22}$, $NR^{22}C(O)OR^{22}$, $NHC(O)NH_2$, $NHC(O)NHR^{22}$, $NHC(O)N(R^{22})_2$, $NR^{22}C(O)NHR^{22}$, $NR^{22}C(O)N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, $C(O)NHOH$, $C(O)NHOR^{22}$, $C(O)NHSO_2R^{22}$, $C(O)NR^{22}SO_2R^{22}$, SO_2NH_2 , SO_2NHR^{22} , $SO_2N(R^{22})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{22}$, $C(N)N(R^{22})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br or I ;

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

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

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

30 R^{25} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{25A} ; R^{25A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

Z^1 is R^{26} or R^{27} ;

Z^2 is R^{28} , R^{29} or R^{30} ;

Z^{1A} and Z^{2A} are both absent or are taken together to form CH_2 , CH_2CH_2 or Z^{12A} ;

Z^{12A} is C_2 - C_6 -alkylene having one or two CH_2 moieties replaced by NH , $N(CH_3)$, S , $S(O)$ or SO_2 ;

L^1 is a R^{37} , OR^{37} , SR^{37} , $S(O)R^{37}$, SO_2R^{37} , $C(O)R^{37}$, $CO(O)R^{37}$, $OC(O)R^{37}$,
 5 $OC(O)OR^{37}$, NHR^{37} , $C(O)NH$, $C(O)NR^{37}$, $C(O)NHR^{37}$, $C(O)NHSO_2R^{37}$, SO_2NH ,
 SO_2NHR^{37} , $C(N)NH$, $C(N)NHR^{37}$;

R^{26} is phenylene, which is unfused or fused with R^{26A} ; R^{26A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{27} is heteroarylene, which is unfused or fused with R^{27A} ; R^{27A} is benzene,
 10 heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

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

R^{29} is heteroarylene, which is unfused or fused with R^{29A} ; R^{29A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

15 R^{30} is cycloalkylene, cycloalkenylene, heterocycloalkylene or heterocycloalkenylene, each of which is unfused or fused with R^{30A} ; R^{30A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{37} is a bond or R^{37A} ;

R^{37A} is alkylene, alkenylene, or alkynylene, each of which is unsubstituted or
 20 substituted with one or two or three independently selected R^{37B} , OR^{37B} , SR^{37B} , $S(O)R^{37B}$,
 SO_2R^{37B} , $C(O)R^{37B}$, $CO(O)R^{37B}$, $OC(O)R^{37B}$, $OC(O)OR^{37B}$, NH_2 , NHR^{37B} , $N(R^{37B})_2$,
 $NHC(O)R^{37B}$, $NR^{37B}C(O)R^{37B}$, $NHS(O)_2R^{37B}$, $NR^{37B}S(O)_2R^{37B}$, $NHC(O)OR^{37B}$,
 $NR^{37B}C(O)OR^{37B}$, $NHC(O)NH_2$, $NHC(O)NHR^{37B}$, $NHC(O)N(R^{37B})_2$, $NR^{37B}C(O)NHR^{37B}$,
 $NR^{37B}C(O)N(R^{37B})_2$, $C(O)NH_2$, $C(O)NHR^{37B}$, $C(O)N(R^{37B})_2$, $C(O)NHOH$, $C(O)NHR^{37B}$,
 25 $C(O)NHSO_2R^{37B}$, $C(O)NR^{37B}SO_2R^{37B}$, SO_2NH_2 , SO_2NHR^{37B} , $SO_2N(R^{37B})_2$, $C(O)H$,
 $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{37B}$, $C(N)N(R^{37B})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 ,
 CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br and I substituents;

R^{37B} is alkyl, alkenyl, alkynyl, or R^{37C} ;

R^{37C} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or
 30 heterocycloalkenyl;

Z^3 is R^{38} , R^{39} or R^{40} ;

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

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

R^{40} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{40A} ; R^{40A} is benzene, heteroarene, cycloalkane, cycloalkene,

5 heterocycloalkane or heterocycloalkene;

wherein the moieties represented by R^{26} and R^{27} are substituted (i.e., if Z^{1A} and Z^{2A} are absent) or further substituted (i.e., if Z^{1A} and Z^{2A} are present) with R^{41} , OR^{41} , SR^{41} , $S(O)R^{41}$, SO_2R^{41} , $C(O)R^{41}$, $CO(O)R^{41}$, $OC(O)R^{41}$, $OC(O)OR^{41}$, NHR^{41} , $N(R^{41})_2$, $NHC(O)R^{41}$, $NR^{41}C(O)R^{41}$, $NHS(O)_2R^{41}$, $NR^{41}S(O)_2R^{41}$, $NHC(O)OR^{41}$, $NR^{41}C(O)OR^{41}$, $NHC(O)NHR^{41}$,
 10 $NHC(O)N(R^{41})_2$, $NR^{41}C(O)NHR^{41}$, $NR^{41}C(O)N(R^{41})_2$, $C(O)NHR^{41}$, $C(O)N(R^{41})_2$, $C(O)NHOR^{41}$, $C(O)NHSO_2R^{41}$, $C(O)NR^{41}SO_2R^{41}$, SO_2NHR^{41} , $SO_2N(R^{41})_2$, $C(N)NHR^{41}$, or $C(N)N(R^{41})_2$;

R^{41} is heteroaryl, which is fused with R^{43A} ; R^{43A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; which is unfused or fused with
 15 benzene, heteroarene or R^{43B} ; R^{43B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein the cyclic moieties represented by E^1 and Y^1 together, Y^1 and B^1 together, A^2 and B^1 together, A^2 and D^1 together, R^{1A} , R^2 , R^{2A} , R^3 , R^{3A} , R^4 , R^{4A} , R^6 , R^{6C} , R^8 , R^{8A} , R^9 , R^{9A} , 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} ,
 20 R^{25} , R^{25A} , R^{26} , R^{26A} , R^{27} , R^{27A} , R^{28} , R^{28A} , R^{29} , R^{29A} , R^{30} , R^{30A} , R^{37B} , R^{38} , R^{38A} , R^{39} , R^{39A} , R^{40} , and R^{40A} are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five of independently selected R^{57A} , R^{57} , OR^{57} , SR^{57} , $S(O)R^{57}$, SO_2R^{57} , $C(O)R^{57}$, $CO(O)R^{57}$, $OC(O)R^{57}$, $OC(O)OR^{57}$, NH_2 , NHR^{57} , $N(R^{57})_2$, $NHC(O)R^{57}$, $NR^{57}C(O)R^{57}$, $NHS(O)_2R^{57}$, $NR^{57}S(O)_2R^{57}$, $NHC(O)OR^{57}$, $NR^{57}C(O)OR^{57}$,
 25 $NHC(O)NH_2$, $NHC(O)NHR^{57}$, $NHC(O)N(R^{57})_2$, $NR^{57}C(O)NHR^{57}$, $NR^{57}C(O)N(R^{57})_2$, $C(O)NH_2$, $C(O)NHR^{57}$, $C(O)N(R^{57})_2$, $C(O)NHOH$, $C(O)NHOR^{57}$, $C(O)NHSO_2R^{57}$, $C(O)NR^{57}SO_2R^{57}$, SO_2NH_2 , SO_2NHR^{57} , $SO_2N(R^{57})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{57}$, $C(N)N(R^{57})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br or I ;

30 R^{57A} is spiroalkyl, or spiroheteroalkyl;

R^{57} is R^{58} , R^{59} , R^{60} or R^{61} ;

R^{58} is phenyl, which is unfused or fused with R^{58A} ; R^{58A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{59} is heteroaryl, which is unfused or fused with R^{59A} ; R^{59A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{60} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{60A} ; R^{60A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{61} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{62} , OR^{62} , SR^{62} , $S(O)R^{62}$, SO_2R^{62} , $C(O)R^{62}$, $CO(O)R^{62}$, $OC(O)R^{62}$, $OC(O)OR^{62}$, NH_2 , NHR^{62} , $N(R^{62})_2$, $NHC(O)R^{62}$, $NR^{62}C(O)R^{62}$, $NHS(O)_2R^{62}$, $NR^{62}S(O)_2R^{62}$, $NHC(O)OR^{62}$, $NR^{62}C(O)OR^{62}$, $NHC(O)NH_2$, $NHC(O)NHR^{62}$, $NHC(O)N(R^{62})_2$, $NR^{62}C(O)NHR^{62}$, $NR^{62}C(O)N(R^{62})_2$, $C(O)NH_2$, $C(O)NHR^{62}$, $C(O)N(R^{62})_2$, $C(O)NHOH$, $C(O)NHOR^{62}$, $C(O)NHSO_2R^{62}$, $C(O)NR^{62}SO_2R^{62}$, SO_2NH_2 , SO_2NHR^{62} , $SO_2N(R^{62})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{62}$, $C(N)N(R^{62})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br or I ;

R^{62} is R^{63} , R^{64} , R^{65} or R^{66} ;

R^{63} is phenyl, which is unfused or fused with R^{63A} ; R^{63A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{64} is heteroaryl, which is unfused or fused with R^{64A} ; R^{64A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{65} is cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, each of which is unfused or fused with R^{65A} ; R^{65A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{66} is alkyl, alkenyl or alkenyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{67} , OR^{67} , SR^{67} , $S(O)R^{67}$, SO_2R^{67} , $C(O)R^{67}$, $CO(O)R^{67}$, $OC(O)R^{67}$, $OC(O)OR^{67}$, NH_2 , NHR^{67} , $N(R^{67})_2$, $NHC(O)R^{67}$, $NR^{67}C(O)R^{67}$, $NHS(O)_2R^{67}$, $NR^{67}S(O)_2R^{67}$, $NHC(O)OR^{67}$, $NR^{67}C(O)OR^{67}$, $NHC(O)NH_2$, $NHC(O)NHR^{67}$, $NHC(O)N(R^{67})_2$, $NR^{67}C(O)NHR^{67}$, $NR^{67}C(O)N(R^{67})_2$, $C(O)NH_2$, $C(O)NHR^{67}$, $C(O)N(R^{67})_2$, $C(O)NHOH$, $C(O)NHOR^{67}$, $C(O)NHSO_2R^{67}$, $C(O)NR^{67}SO_2R^{67}$, SO_2NH_2 , SO_2NHR^{67} , $SO_2N(R^{67})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{67}$, $C(N)N(R^{67})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br or I substituents;

R^{67} is alkyl, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl;

wherein the cyclic moieties represented by R^{57A} , R^{58} , R^{59} , R^{60} , R^{63} , R^{64} , R^{65} , and R^{67} are unsubstituted or substituted with one or two or three or four of independently selected R^{68} , OR^{68} , SR^{68} , $S(O)R^{68}$, SO_2R^{68} , $C(O)R^{68}$, $CO(O)R^{68}$, $OC(O)R^{68}$, $OC(O)OR^{68}$, NH_2 ,

- NHR^{68} , $\text{N(R}^{68})_2$, NHC(O)R^{68} , $\text{NR}^{68}\text{C(O)R}^{68}$, $\text{NHS(O)}_2\text{R}^{68}$, $\text{NR}^{68}\text{S(O)}_2\text{R}^{68}$, NHC(O)OR^{68} ,
 $\text{NR}^{68}\text{C(O)OR}^{68}$, NHC(O)NH_2 , NHC(O)NHR^{68} , $\text{NHC(O)N(R}^{68})_2$, $\text{NR}^{68}\text{C(O)NHR}^{68}$,
 $\text{NR}^{68}\text{C(O)N(R}^{68})_2$, C(O)NH_2 , C(O)NHR^{68} , $\text{C(O)N(R}^{68})_2$, C(O)NHOH , C(O)NHOR^{68} ,
 $\text{C(O)NHSO}_2\text{R}^{68}$, $\text{C(O)NR}^{68}\text{SO}_2\text{R}^{68}$, SO_2NH_2 , $\text{SO}_2\text{NHR}^{68}$, $\text{SO}_2\text{N(R}^{68})_2$, C(O)H , C(O)OH ,
5 C(N)NH_2 , C(N)NHR^{68} , $\text{C(N)N(R}^{68})_2$, CNOH , CNOCH_3 , OH , (O) , CN , N_3 , NO_2 , CF_3 ,
 CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br or I ;
 R^{68} is R^{69} , R^{70} , R^{71} or R^{72} ;
 R^{69} is phenyl, which is unfused or fused with $\text{R}^{69\text{A}}$; $\text{R}^{69\text{A}}$ is benzene, heteroarene,
cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
10 R^{70} is heteroaryl, which is unfused or fused with $\text{R}^{70\text{A}}$; $\text{R}^{70\text{A}}$ is benzene, heteroarene,
cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
 R^{71} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which
is unfused or fused with $\text{R}^{71\text{A}}$; $\text{R}^{71\text{A}}$ is benzene, heteroarene, cycloalkane, cycloalkene,
heterocycloalkane or heterocycloalkene;
15 R^{72} is alkyl, alkenyl or alkenyl, each of which is unsubstituted or substituted with one
or two or three of independently selected R^{73} , OR^{73} , SR^{73} , S(O)R^{73} , SO_2R^{73} , C(O)R^{73} ,
 CO(O)R^{73} , OC(O)R^{73} , OC(O)OR^{73} , NH_2 , NHR^{73} , $\text{N(R}^{73})_2$, NHC(O)R^{73} , $\text{NR}^{73}\text{C(O)R}^{73}$,
 $\text{NHS(O)}_2\text{R}^{73}$, $\text{NR}^{73}\text{S(O)}_2\text{R}^{73}$, NHC(O)OR^{73} , $\text{NR}^{73}\text{C(O)OR}^{73}$, NHC(O)NH_2 , NHC(O)NHR^{73} ,
 $\text{NHC(O)N(R}^{73})_2$, $\text{NR}^{73}\text{C(O)NHR}^{73}$, $\text{NR}^{73}\text{C(O)N(R}^{73})_2$, C(O)NH_2 , C(O)NHR^{73} , $\text{C(O)N(R}^{73})_2$,
20 C(O)NHOH , C(O)NHOR^{73} , $\text{C(O)NHSO}_2\text{R}^{73}$, $\text{C(O)NR}^{73}\text{SO}_2\text{R}^{73}$, SO_2NH_2 , $\text{SO}_2\text{NHR}^{73}$,
 $\text{SO}_2\text{N(R}^{73})_2$, C(O)H , C(O)OH , C(N)NH_2 , C(N)NHR^{73} , $\text{C(N)N(R}^{73})_2$, CNOH , CNOCH_3 , OH ,
 (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br or I ;
 R^{73} is alkyl, alkenyl, alkenyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl,
heterocycloalkyl or heterocycloalkenyl; and
25 wherein the moieties represented by R^{69} , R^{70} , and R^{71} are unsubstituted or substituted
with one or two or three or four of independently selected NH_2 , C(O)NH_2 , C(O)NHOH ,
 SO_2NH_2 , CF_3 , CF_2CF_3 , C(O)H , C(O)OH , C(N)NH_2 , OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 ,
 OCF_3 , OCF_2CF_3 , F , Cl , Br or I .

Another embodiment of this invention pertains to compounds of Formula (I), wherein
 30 A^1 is N or $\text{C(A}^2)$;

A^2 is H , 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 , $\text{N(R}^1)_2$,
 C(O)NHR^1 , $\text{C(O)N(R}^1)_2$, NHC(O)R^1 , $\text{NR}^1\text{C(O)R}^1$, NHC(O)OR^1 , $\text{NR}^1\text{C(O)OR}^1$,
 NHC(O)NH_2 , NHC(O)NHR^1 , $\text{NHC(O)N(R}^1)_2$, $\text{NR}^1\text{C(O)NHR}^1$, $\text{NR}^1\text{C(O)N(R}^1)_2$, SO_2NH_2 ,
 SO_2NHR^1 , $\text{SO}_2\text{N(R}^1)_2$, NHSO_2R^1 , $\text{NR}^1\text{SO}_2\text{R}^1$, $\text{NHSO}_2\text{NHR}^1$, $\text{NHSO}_2\text{N(R}^1)_2$, $\text{NR}^1\text{SO}_2\text{NHR}^1$,

NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHOSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR^{1A};

B¹ is H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂,
5 C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹,
NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂,
SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹,
NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹,
C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂,
10 N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR^{1A};

D¹ is H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR^{1A};

E¹ is H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹,
 20 NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂,
 SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹,
 NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹,
 C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂,
 N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR^{1A}; and

25 Y¹ is H, CN, NO₂, C(O)OH, F, Cl, Br, I, CF₃, OCF₃, CF₂CF₃, OCF₂CF₃, R¹⁷, OR¹⁷, C(O)R¹⁷, C(O)OR¹⁷, SR¹⁷, SO₂R¹⁷, NH₂, NHR¹⁷, N(R¹⁷)₂, NHC(O)R¹⁷, C(O)NH₂, C(O)NHR¹⁷, C(O)N(R¹⁷)₂, NHS(O)R¹⁷ or NHSO₂R¹⁷; or

E¹ and Y¹, together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

A², B¹, and D¹ are independently selected H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹,

NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹,
C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂ NHSO₂NHR¹, NHSO₂N(CH₃)R¹,
N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃,
C(O)OH, C(O)NH₂ or C(O)OR^{1A}; or

- 5 Y¹ and B¹, together with the atoms to which they are attached, are benzene,
naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
and

- A², D¹, and E¹ are independently selected H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹,
C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹,
10 NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹,
NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹,
NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹,
C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂ NHSO₂NHR¹, NHSO₂N(CH₃)R¹,
N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃,
15 C(O)OH, C(O)NH₂ or C(O)OR^{1A}; or

A² and B¹, together with the atoms to which they are attached, are benzene,
naphthylene, heteroarene cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
and

- D¹, E¹, and Y¹ are independently selected H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹,
20 C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹,
NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹,
NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹,
NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹,
C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂ NHSO₂NHR¹, NHSO₂N(CH₃)R¹,
25 N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃,
C(O)OH, C(O)NH₂ or C(O)OR^{1A}; or

A² and D¹, together with the atoms to which they are attached, are benzene,
naphthalene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
and

- 30 B¹, E¹, and Y¹ are independently selected H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹,
C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹,
NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹,
NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹,
NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹,

C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂ NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR^{1A};

G¹ is H, or C(O)OR;

5 R is alkyl;

R¹ is R², R³, R⁴ or R⁵;

R^{1A} is cycloalkyl, cycloalkenyl or cycloalkynyl;

R² is phenyl, which is unfused or fused with R^{2A}; R^{2A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

10 R³ is heteroaryl, which is unfused or fused with R^{3A}; R^{3A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R⁴ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{4A}; R^{4A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

15 R⁵ is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R⁶, NC(R^{6A})(R^{6B}), R⁷, OR⁷, SR⁷, S(O)R⁷, SO₂R⁷, NHR⁷, N(R⁷)₂, C(O)R⁷, C(O)NH₂, C(O)NHR⁷, C(O)N(R⁷)₂, NHC(O)R⁷, NR⁷C(O)R⁷, NHSO₂R⁷, NHC(O)OR⁷, SO₂NH₂, SO₂NHR⁷, SO₂N(R⁷)₂, NHC(O)NH₂, NHC(O)NHR⁷, NHC(O)CH(CH₃)NHC(O)CH(CH₃)NH₂, NHC(O)CH(CH₃)NHC(O)CH(CH₃)NHR⁷, OH, (O), C(O)OH, N₃, CN, NH₂, CF₃, CF₂CF₃, F, Cl, Br or I;

R⁶ is C₂-C₅-spiroalkyl, each of which is unsubstituted or substituted with OH, (O), N₃, CN, CF₃, CF₂CF₃, F, Cl, Br, I, NH₂, NH(CH₃) or N(CH₃)₂;

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

25 R^{6C} is aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, each having one CH₂ moiety unreplaced or replaced with O, C(O), CNOH, CNOCH₃, S, S(O), SO₂ or NH;

R⁷ is R⁸, R⁹, R¹⁰ or R¹¹;

R⁸ is phenyl, which is unfused or fused with R^{8A}; R^{8A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

30 R⁹ is heteroaryl, which is unfused or fused with R^{9A}; R^{9A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R¹⁰ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{10A}; R^{10A} is benzene, heteroarene, 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 of independently selected R^{12} , OR^{12} , SR^{12} , $S(O)R^{12}$, SO_2R^{12} , $C(O)R^{12}$, $CO(O)R^{12}$, $OC(O)R^{12}$, $OC(O)OR^{12}$, NH_2 , NHR^{12} , $N(R^{12})_2$, $NHC(O)R^{12}$, $NR^{12}C(O)R^{12}$, $NHS(O)_2R^{12}$, $NR^{12}S(O)_2R^{12}$, $NHC(O)OR^{12}$, $NR^{12}C(O)OR^{12}$, $NHC(O)NH_2$, $NHC(O)NHR^{12}$, $NHC(O)N(R^{12})_2$, $NR^{12}C(O)NHR^{12}$, $NR^{12}C(O)N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, $C(O)NHOH$, $C(O)NHOR^{12}$, $C(O)NHSO_2R^{12}$, $C(O)NR^{12}SO_2R^{12}$, SO_2NH_2 , SO_2NHR^{12} , $SO_2N(R^{12})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{12}$, $C(N)N(R^{12})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br or I ;

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

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

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

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

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

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

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

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

25 R^{20} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl each of which is unfused or fused with R^{20A} ; R^{20A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

30 R^{21} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{22} , OR^{22} , SR^{22} , $S(O)R^{22}$, SO_2R^{22} , $C(O)R^{22}$, $CO(O)R^{22}$, $OC(O)R^{22}$, $OC(O)OR^{22}$, NH_2 , NHR^{22} , $N(R^{22})_2$, $NHC(O)R^{22}$, $NR^{22}C(O)R^{22}$, $NHS(O)_2R^{22}$, $NR^{22}S(O)_2R^{22}$, $NHC(O)OR^{22}$, $NR^{22}C(O)OR^{22}$, $NHC(O)NH_2$, $NHC(O)NHR^{22}$, $NHC(O)N(R^{22})_2$, $NR^{22}C(O)NHR^{22}$, $NR^{22}C(O)N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, $C(O)NHOH$, $C(O)NHOR^{22}$, $C(O)NHSO_2R^{22}$, $C(O)NR^{22}SO_2R^{22}$, SO_2NH_2 , SO_2NHR^{22} , $SO_2N(R^{22})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{22}$, $C(N)N(R^{22})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br or I ;

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

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

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

5 R^{25} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{25A} ; R^{25A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

Z^1 is R^{26} or R^{27} ;

Z^2 is R^{28} , R^{29} or R^{30} ;

10 Z^{1A} and Z^{2A} are both absent or are taken together to form CH_2 , CH_2CH_2 or Z^{12A} ;

Z^{12A} is C_2 - C_6 -alkylene having one or two CH_2 moieties replaced by NH , $N(CH_3)$, S , $S(O)$ or SO_2 ;

L^1 is a R^{37} , OR^{37} , SR^{37} , $S(O)R^{37}$, SO_2R^{37} , $C(O)R^{37}$, $CO(O)R^{37}$, $OC(O)R^{37}$, $OC(O)OR^{37}$, NHR^{37} , $C(O)NH$, $C(O)NR^{37}$, $C(O)NHR^{37}$, $C(O)NHSO_2R^{37}$, SO_2NH ,
15 SO_2NHR^{37} , $C(N)NH$, $C(N)NHR^{37}$;

R^{26} is phenylene, which is unfused or fused with R^{26A} ; R^{26A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{27} is heteroarylene, which is unfused or fused with R^{27A} ; R^{27A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

20 R^{28} is phenylene, which is unfused or fused with R^{28A} ; R^{28A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{29} is heteroarylene, which is unfused or fused with R^{29A} ; R^{29A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{30} is cycloalkylene, cycloalkenylene, heterocycloalkylene or heterocycloalkenylene,
25 each of which is unfused or fused with R^{30A} ; R^{30A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{37} is a bond or R^{37A} ;

R^{37A} is alkylene, alkenylene, or alkynylene, each of which is unsubstituted or substituted with one or two or three independently selected R^{37B} , OR^{37B} , SR^{37B} , $S(O)R^{37B}$,
30 SO_2R^{37B} , $C(O)R^{37B}$, $CO(O)R^{37B}$, $OC(O)R^{37B}$, $OC(O)OR^{37B}$, NH_2 , NHR^{37B} , $N(R^{37B})_2$, $NHC(O)R^{37B}$, $NR^{37B}C(O)R^{37B}$, $NHS(O)_2R^{37B}$, $NR^{37B}S(O)_2R^{37B}$, $NHC(O)OR^{37B}$, $NR^{37B}C(O)OR^{37B}$, $NHC(O)NH_2$, $NHC(O)NHR^{37B}$, $NHC(O)N(R^{37B})_2$, $NR^{37B}C(O)NHR^{37B}$, $NR^{37B}C(O)N(R^{37B})_2$, $C(O)NH_2$, $C(O)NHR^{37B}$, $C(O)N(R^{37B})_2$, $C(O)NHOH$, $C(O)NHR^{37B}$, $C(O)NHSO_2R^{37B}$, $C(O)NR^{37B}SO_2R^{37B}$, SO_2NH_2 , SO_2NHR^{37B} , $SO_2N(R^{37B})_2$, $C(O)H$,

C(O)OH, C(N)NH₂, C(N)NHR^{37B}, C(N)N(R^{37B})₂, CNOH, CNOCH₃, OH, (O), CN, N₃, NO₂, CF₃, CF₂CF₃, OCF₃, OCF₂CF₃, F, Cl, Br and I substituents;

R^{37B} is alkyl, alkenyl, alkynyl, or R^{37C};

R^{37C} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or
5 heterocycloalkenyl;

Z³ is R³⁸, R³⁹ or R⁴⁰;

R³⁸ is phenyl, which is unfused or fused with R^{38A}; R^{38A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R³⁹ is heteroaryl, which is unfused or fused with R^{39A}; R^{39A} is benzene, heteroarene,
10 cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R⁴⁰ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{40A}; R^{40A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein the moieties represented by R²⁶ and R²⁷ are substituted (i.e., if Z^{1A} and Z^{2A}
15 are absent) or further substituted (i.e., if Z^{1A} and Z^{2A} are present) with R⁴¹, OR⁴¹, SR⁴¹, S(O)R⁴¹, SO₂R⁴¹, C(O)R⁴¹, CO(O)R⁴¹, OC(O)R⁴¹, OC(O)OR⁴¹, NHR⁴¹, N(R⁴¹)₂, NHC(O)R⁴¹, NR⁴¹C(O)R⁴¹, NHS(O)₂R⁴¹, NR⁴¹S(O)₂R⁴¹, NHC(O)OR⁴¹, NR⁴¹C(O)OR⁴¹, NHC(O)NHR⁴¹, NHC(O)N(R⁴¹)₂, NR⁴¹C(O)NHR⁴¹, NR⁴¹C(O)N(R⁴¹)₂, C(O)NHR⁴¹, C(O)N(R⁴¹)₂, C(O)NHOR⁴¹, C(O)NHSO₂R⁴¹, C(O)NR⁴¹SO₂R⁴¹, SO₂NHR⁴¹, SO₂N(R⁴¹)₂, C(N)NHR⁴¹, or
20 C(N)N(R⁴¹)₂;

R⁴¹ is heteroaryl, which is fused with R^{43A}; R^{43A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; which is unfused;

wherein the cyclic moieties represented by E¹ and Y¹ together, Y¹ and B¹ together, A² and B¹ together, A² and D¹ together, R^{1A}, R², R^{2A}, R³, R^{3A}, R⁴, R^{4A}, R⁶, R^{6C}, R⁸, R^{8A}, R⁹, R^{9A},
25 R¹⁰, R^{10A}, R¹³, R^{13A}, R¹⁴, R^{14A}, R¹⁵, R^{15A}, R¹⁸, R^{18A}, R¹⁹, R^{19A}, R²⁰, R^{20A}, R²³, R^{23A}, R²⁴, R^{24A}, R²⁵, R^{25A}, R²⁶, R^{26A}, R²⁷, R^{27A}, R²⁸, R^{28A}, R²⁹, R^{29A}, R³⁰, R^{30A}, R^{37B}, R³⁸, R^{38A}, R³⁹, R^{39A}, R⁴⁰, and R^{40A} are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five of independently selected R^{57A}, R⁵⁷, OR⁵⁷, SR⁵⁷, S(O)R⁵⁷, SO₂R⁵⁷, C(O)R⁵⁷, CO(O)R⁵⁷, OC(O)R⁵⁷, OC(O)OR⁵⁷, NH₂, NHR⁵⁷, N(R⁵⁷)₂, NHC(O)R⁵⁷, NR⁵⁷C(O)R⁵⁷, NHS(O)₂R⁵⁷, NR⁵⁷S(O)₂R⁵⁷, NHC(O)OR⁵⁷, NR⁵⁷C(O)OR⁵⁷,
30 NHC(O)NH₂, NHC(O)NHR⁵⁷, NHC(O)N(R⁵⁷)₂, NR⁵⁷C(O)NHR⁵⁷, NR⁵⁷C(O)N(R⁵⁷)₂, C(O)NH₂, C(O)NHR⁵⁷, C(O)N(R⁵⁷)₂, C(O)NHOH, C(O)NHOR⁵⁷, C(O)NHSO₂R⁵⁷, C(O)NR⁵⁷SO₂R⁵⁷, SO₂NH₂, SO₂NHR⁵⁷, SO₂N(R⁵⁷)₂, C(O)H, C(O)OH, C(N)NH₂,

C(N)NHR⁵⁷, C(N)N(R⁵⁷)₂, CNOH, CNOCH₃, OH, (O), CN, N₃, NO₂, CF₃, CF₂CF₃, OCF₃, OCF₂CF₃, F, Cl, Br or I;

R^{57A} is spiroalkyl, or spiroheteroalkyl;

R⁵⁷ is R⁵⁸, R⁵⁹, R⁶⁰ or R⁶¹;

5 R⁵⁸ is phenyl, which is unfused or fused with R^{58A}; R^{58A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R⁵⁹ is heteroaryl, which is unfused or fused with R^{59A}; R^{59A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

10 R⁶⁰ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{60A}; R^{60A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R⁶¹ is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R⁶², OR⁶², SR⁶², S(O)R⁶², SO₂R⁶², C(O)R⁶², CO(O)R⁶², OC(O)R⁶², OC(O)OR⁶², NH₂, NHR⁶², N(R⁶²)₂, NHC(O)R⁶², NR⁶²C(O)R⁶²,
15 NHS(O)₂R⁶², NR⁶²S(O)₂R⁶², NHC(O)OR⁶², NR⁶²C(O)OR⁶², NHC(O)NH₂, NHC(O)NHR⁶², NHC(O)N(R⁶²)₂, NR⁶²C(O)NHR⁶², NR⁶²C(O)N(R⁶²)₂, C(O)NH₂, C(O)NHR⁶², C(O)N(R⁶²)₂, C(O)NHOH, C(O)NHOR⁶², C(O)NHSO₂R⁶², C(O)NR⁶²SO₂R⁶², SO₂NH₂, SO₂NHR⁶², SO₂N(R⁶²)₂, C(O)H, C(O)OH, C(N)NH₂, C(N)NHR⁶², C(N)N(R⁶²)₂, CNOH, CNOCH₃, OH, (O), CN, N₃, NO₂, CF₃, CF₂CF₃, OCF₃, OCF₂CF₃, F, Cl, Br or I;

20 R⁶² is R⁶³, R⁶⁴, R⁶⁵ or R⁶⁶;

R⁶³ is phenyl, which is unfused or fused with R^{63A}; R^{63A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R⁶⁴ is heteroaryl, which is unfused or fused with R^{64A}; R^{64A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

25 R⁶⁵ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{65A}; R^{65A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R⁶⁶ is alkyl, alkenyl or alkenyl, each of which is unsubstituted or substituted with one or two or three of independently selected R⁶⁷, OR⁶⁷, SR⁶⁷, S(O)R⁶⁷, SO₂R⁶⁷, C(O)R⁶⁷,
30 CO(O)R⁶⁷, OC(O)R⁶⁷, OC(O)OR⁶⁷, NH₂, NHR⁶⁷, N(R⁶⁷)₂, NHC(O)R⁶⁷, NR⁶⁷C(O)R⁶⁷, NHS(O)₂R⁶⁷, NR⁶⁷S(O)₂R⁶⁷, NHC(O)OR⁶⁷, NR⁶⁷C(O)OR⁶⁷, NHC(O)NH₂, NHC(O)NHR⁶⁷, NHC(O)N(R⁶⁷)₂, NR⁶⁷C(O)NHR⁶⁷, NR⁶⁷C(O)N(R⁶⁷)₂, C(O)NH₂, C(O)NHR⁶⁷, C(O)N(R⁶⁷)₂, C(O)NHOH, C(O)NHOR⁶⁷, C(O)NHSO₂R⁶⁷, C(O)NR⁶⁷SO₂R⁶⁷, SO₂NH₂, SO₂NHR⁶⁷,

SO₂N(R⁶⁷)₂, C(O)H, C(O)OH, C(N)NH₂, C(N)NHR⁶⁷, C(N)N(R⁶⁷)₂, CNOH, CNOCH₃, OH, (O), CN, N₃, NO₂, CF₃, CF₂CF₃, OCF₃, OCF₂CF₃, F, Cl, Br or I substituents;

R⁶⁷ is alkyl, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl;

5 wherein the cyclic moieties represented by R^{57A}, R⁵⁸, R⁵⁹, R⁶⁰, R⁶³, R⁶⁴, R⁶⁵, and R⁶⁷ are unsubstituted or substituted with one or two or three or four of independently selected R⁶⁸, OR⁶⁸, SR⁶⁸, S(O)R⁶⁸, SO₂R⁶⁸, C(O)R⁶⁸, CO(O)R⁶⁸, OC(O)R⁶⁸, OC(O)OR⁶⁸, NH₂, NHR⁶⁸, N(R⁶⁸)₂, NHC(O)R⁶⁸, NR⁶⁸C(O)R⁶⁸, NHS(O)₂R⁶⁸, NR⁶⁸S(O)₂R⁶⁸, NHC(O)OR⁶⁸, NR⁶⁸C(O)OR⁶⁸, NHC(O)NH₂, NHC(O)NHR⁶⁸, NHC(O)N(R⁶⁸)₂, NR⁶⁸C(O)NHR⁶⁸,
10 NR⁶⁸C(O)N(R⁶⁸)₂, C(O)NH₂, C(O)NHR⁶⁸, C(O)N(R⁶⁸)₂, C(O)NHOH, C(O)NHOR⁶⁸, C(O)NHSO₂R⁶⁸, C(O)NR⁶⁸SO₂R⁶⁸, SO₂NH₂, SO₂NHR⁶⁸, SO₂N(R⁶⁸)₂, C(O)H, C(O)OH, C(N)NH₂, C(N)NHR⁶⁸, C(N)N(R⁶⁸)₂, CNOH, CNOCH₃, OH, (O), CN, N₃, NO₂, CF₃, CF₂CF₃, OCF₃, OCF₂CF₃, F, Cl, Br or I;

R⁶⁸ is R⁶⁹, R⁷⁰, R⁷¹ or R⁷²;

15 R⁶⁹ is phenyl, which is unfused or fused with R^{69A}; R^{69A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R⁷⁰ is heteroaryl, which is unfused or fused with R^{70A}; R^{70A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R⁷¹ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which
20 is unfused or fused with R^{71A}; R^{71A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R⁷² is alkyl, alkenyl or alkenyl, each of which is unsubstituted or substituted with one or two or three of independently selected R⁷³, OR⁷³, SR⁷³, S(O)R⁷³, SO₂R⁷³, C(O)R⁷³, CO(O)R⁷³, OC(O)R⁷³, OC(O)OR⁷³, NH₂, NHR⁷³, N(R⁷³)₂, NHC(O)R⁷³, NR⁷³C(O)R⁷³,
25 NHS(O)₂R⁷³, NR⁷³S(O)₂R⁷³, NHC(O)OR⁷³, NR⁷³C(O)OR⁷³, NHC(O)NH₂, NHC(O)NHR⁷³, NHC(O)N(R⁷³)₂, NR⁷³C(O)NHR⁷³, NR⁷³C(O)N(R⁷³)₂, C(O)NH₂, C(O)NHR⁷³, C(O)N(R⁷³)₂, C(O)NHOH, C(O)NHOR⁷³, C(O)NHSO₂R⁷³, C(O)NR⁷³SO₂R⁷³, SO₂NH₂, SO₂NHR⁷³, SO₂N(R⁷³)₂, C(O)H, C(O)OH, C(N)NH₂, C(N)NHR⁷³, C(N)N(R⁷³)₂, CNOH, CNOCH₃, OH, (O), CN, N₃, NO₂, CF₃, CF₂CF₃, OCF₃, OCF₂CF₃, F, Cl, Br or I;

30 R⁷³ is alkyl, alkenyl, alkenyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; and

wherein the moieties represented by R⁶⁹, R⁷⁰, and R⁷¹ are unsubstituted or substituted with one or two or three or four of independently selected NH₂, C(O)NH₂, C(O)NHOH,

SO₂NH₂, CF₃, CF₂CF₃, C(O)H, C(O)OH, C(N)NH₂, OH, (O), CN, N₃, NO₂, CF₃, CF₂CF₃, OCF₃, OCF₂CF₃, F, Cl, Br or I.

Another embodiment of this invention pertains to compounds of Formula (I), wherein

A¹ is N or C(A²);

5 A² is H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹,
10 C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR^{1A};

B¹ is H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂,
15 SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR^{1A};

D¹ is H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂,
20 SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR^{1A};

E¹ is H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂,
30 SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ 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} , SO_2R^{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

E^1 and Y^1 , together with the atoms to which they are attached, are benzene,
5 naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
and

A^2 , B^1 , and D^1 are independently selected H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$,
10 $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$, $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 , $C(O)OH$, $C(O)NH_2$ or $C(O)OR^{1A}$; or

Y^1 and B^1 , together with the atoms to which they are attached, are benzene,
15 naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
and

A^2 , D^1 , and E^1 are independently selected H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$,
20 $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$, $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 ,
25 $C(O)OH$, $C(O)NH_2$ or $C(O)OR^{1A}$; or

A^2 and B^1 , together with the atoms to which they are attached, are benzene,
naphthylene, heteroarene cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
and

D^1 , E^1 , and Y^1 are independently selected H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$,
30 $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$, $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$,

$N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 , $C(O)OH$, $C(O)NH_2$ or $C(O)OR^{1A}$; or

A^2 and D^1 , together with the atoms to which they are attached, are benzene, naphthalene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
5 and

B^1 , E^1 , and Y^1 are independently selected H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$,
10 $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$, $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 , $C(O)OH$, $C(O)NH_2$ or $C(O)OR^{1A}$;

G^1 is H, or $C(O)OR$;

15 R is alkyl;

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

R^{1A} is cycloalkyl, cycloalkenyl or cycloalkynyl;

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

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

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

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

R^6 is C₂-C₅-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, CNOCH₃, S, S(O), SO₂ or NH;

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 benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

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

R^{10} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{10A} ; R^{10A} is benzene, heteroarene, 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 of independently selected R^{12} , OR¹², SR¹², S(O)R¹², SO₂R¹², C(O)R¹², CO(O)R¹², OC(O)R¹², OC(O)OR¹², NH₂, NHR¹², N(R¹²)₂, NHC(O)R¹², NR¹²C(O)R¹², NHS(O)₂R¹², NR¹²S(O)₂R¹², NHC(O)OR¹², NR¹²C(O)OR¹², NHC(O)NH₂, NHC(O)NHR¹², NHC(O)N(R¹²)₂, NR¹²C(O)NHR¹², NR¹²C(O)N(R¹²)₂, C(O)NH₂, C(O)NHR¹², C(O)N(R¹²)₂, C(O)NHOH, C(O)NHOR¹², C(O)NHSO₂R¹², C(O)NR¹²SO₂R¹², SO₂NH₂, SO₂NHR¹², SO₂N(R¹²)₂, C(O)H, C(O)OH, C(N)NH₂, C(N)NHR¹², C(N)N(R¹²)₂, CNOH, CNOCH₃, OH, (O), CN, N₃, NO₂, CF₃, CF₂CF₃, OCF₃, OCF₂CF₃, F, Cl, Br or I;

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

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

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

R^{15} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene, each of which is unfused or fused with R^{15A} ; R^{15A} is benzene, heteroarene, 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 R^{18A} ; R^{18A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

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

R^{20} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl each of which is unfused or fused with R^{20A} ; R^{20A} is benzene, heteroarene, 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 of independently selected R^{22} , OR^{22} , SR^{22} , $S(O)R^{22}$, SO_2R^{22} , $C(O)R^{22}$, $CO(O)R^{22}$, $OC(O)R^{22}$, $OC(O)OR^{22}$, NH_2 , NHR^{22} , $N(R^{22})_2$, $NHC(O)R^{22}$, $NR^{22}C(O)R^{22}$, $NHS(O)_2R^{22}$, $NR^{22}S(O)_2R^{22}$, $NHC(O)OR^{22}$, $NR^{22}C(O)OR^{22}$, $NHC(O)NH_2$, $NHC(O)NHR^{22}$, $NHC(O)N(R^{22})_2$, $NR^{22}C(O)NHR^{22}$, $NR^{22}C(O)N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, $C(O)NHOH$, $C(O)NHOR^{22}$, $C(O)NHSO_2R^{22}$, $C(O)NR^{22}SO_2R^{22}$, SO_2NH_2 , SO_2NHR^{22} , $SO_2N(R^{22})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{22}$, $C(N)N(R^{22})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br or I ;

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

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

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

R^{25} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{25A} ; R^{25A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

Z^1 is R^{26} or R^{27} ;

Z^2 is R^{28} , R^{29} or R^{30} ;

Z^{1A} and Z^{2A} are both absent or are taken together to form CH_2 , CH_2CH_2 or Z^{12A} ;

Z^{12A} is C_2 - C_6 -alkylene having one or two CH_2 moieties replaced by NH , $N(CH_3)$, S , $S(O)$ or SO_2 ;

L^1 is a R^{37} , OR^{37} , SR^{37} , $S(O)R^{37}$, SO_2R^{37} , $C(O)R^{37}$, $CO(O)R^{37}$, $OC(O)R^{37}$, $OC(O)OR^{37}$, NHR^{37} , $C(O)NH$, $C(O)NR^{37}$, $C(O)NHOR^{37}$, $C(O)NHSO_2R^{37}$, SO_2NH , SO_2NHR^{37} , $C(N)NH$, $C(N)NHR^{37}$;

R^{26} is phenylene, which is unfused or fused with R^{26A} ; R^{26A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{27} is heteroarylene, which is unfused or fused with R^{27A} ; R^{27A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

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

R^{29} is heteroarylene, which is unfused or fused with R^{29A} ; R^{29A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{30} is cycloalkylene, cycloalkenylene, heterocycloalkylene or heterocycloalkenylene, each of which is unfused or fused with R^{30A} ; R^{30A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{37} is a bond or R^{37A} ;

R^{37A} is alkylene, alkenylene, or alkynylene, each of which is unsubstituted or substituted with one or two or three independently selected R^{37B} , OR^{37B} , SR^{37B} , $S(O)R^{37B}$, SO_2R^{37B} , $C(O)R^{37B}$, $CO(O)R^{37B}$, $OC(O)R^{37B}$, $OC(O)OR^{37B}$, NH_2 , NHR^{37B} , $N(R^{37B})_2$, $NHC(O)R^{37B}$, $NR^{37B}C(O)R^{37B}$, $NHS(O)_2R^{37B}$, $NR^{37B}S(O)_2R^{37B}$, $NHC(O)OR^{37B}$, $NR^{37B}C(O)OR^{37B}$, $NHC(O)NH_2$, $NHC(O)NHR^{37B}$, $NHC(O)N(R^{37B})_2$, $NR^{37B}C(O)NHR^{37B}$, $NR^{37B}C(O)N(R^{37B})_2$, $C(O)NH_2$, $C(O)NHR^{37B}$, $C(O)N(R^{37B})_2$, $C(O)NHOH$, $C(O)NHOR^{37B}$, $C(O)NHSO_2R^{37B}$, $C(O)NR^{37B}SO_2R^{37B}$, SO_2NH_2 , SO_2NHR^{37B} , $SO_2N(R^{37B})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{37B}$, $C(N)N(R^{37B})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br and I substituents;

R^{37B} is alkyl, alkenyl, alkynyl, or R^{37C} ;

R^{37C} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

Z^3 is R^{38} , R^{39} or R^{40} ;

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

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

R^{40} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{40A} ; R^{40A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein the moieties represented by R^{26} and R^{27} are substituted (i.e., if Z^{1A} and Z^{2A} are absent) or further substituted (i.e., if Z^{1A} and Z^{2A} are present) with R^{41} , OR^{41} , SR^{41} , $S(O)R^{41}$, SO_2R^{41} , $C(O)R^{41}$, $CO(O)R^{41}$, $OC(O)R^{41}$, $OC(O)OR^{41}$, NHR^{41} , $N(R^{41})_2$, $NHC(O)R^{41}$, $NR^{41}C(O)R^{41}$, $NHS(O)_2R^{41}$, $NR^{41}S(O)_2R^{41}$, $NHC(O)OR^{41}$, $NR^{41}C(O)OR^{41}$, $NHC(O)NHR^{41}$, $NHC(O)N(R^{41})_2$, $NR^{41}C(O)NHR^{41}$, $NR^{41}C(O)N(R^{41})_2$, $C(O)NHR^{41}$, $C(O)N(R^{41})_2$, $C(O)NHOR^{41}$, $C(O)NHSO_2R^{41}$, $C(O)NR^{41}SO_2R^{41}$, SO_2NHR^{41} , $SO_2N(R^{41})_2$, $C(N)NHR^{41}$, or $C(N)N(R^{41})_2$;

R^{41} is heteroaryl, which is fused with R^{43A} ; R^{43A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; which is fused with benzene, heteroarene or R^{43B} ; R^{43B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

- 5 wherein the cyclic moieties represented by E^1 and Y^1 together, Y^1 and B^1 together, A^2 and B^1 together, A^2 and D^1 together, R^{1A} , R^2 , R^{2A} , R^3 , R^{3A} , R^4 , R^{4A} , R^6 , R^{6C} , R^8 , R^{8A} , R^9 , R^{9A} , 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^{26A} , R^{27} , R^{27A} , R^{28} , R^{28A} , R^{29} , R^{29A} , R^{30} , R^{30A} , R^{37B} , R^{38} , R^{38A} , R^{39} , R^{39A} , R^{40} , and R^{40A} are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five of independently selected R^{57A} , R^{57} , OR^{57} , SR^{57} , $S(O)R^{57}$, SO_2R^{57} , $C(O)R^{57}$, $CO(O)R^{57}$, $OC(O)R^{57}$, $OC(O)OR^{57}$, NH_2 , NHR^{57} , $N(R^{57})_2$, $NHC(O)R^{57}$, $NR^{57}C(O)R^{57}$, $NHS(O)_2R^{57}$, $NR^{57}S(O)_2R^{57}$, $NHC(O)OR^{57}$, $NR^{57}C(O)OR^{57}$, $NHC(O)NH_2$, $NHC(O)NHR^{57}$, $NHC(O)N(R^{57})_2$, $NR^{57}C(O)NHR^{57}$, $NR^{57}C(O)N(R^{57})_2$, $C(O)NH_2$, $C(O)NHR^{57}$, $C(O)N(R^{57})_2$, $C(O)NHOH$, $C(O)NHOR^{57}$, $C(O)NHSO_2R^{57}$, $C(O)NR^{57}SO_2R^{57}$, SO_2NH_2 , SO_2NHR^{57} , $SO_2N(R^{57})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{57}$, $C(N)N(R^{57})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br or I ;

R^{57A} is spiroalkyl, or spiroheteroalkyl;

R^{57} is R^{58} , R^{59} , R^{60} or R^{61} ;

- 20 R^{58} is phenyl, which is unfused or fused with R^{58A} ; R^{58A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{59} is heteroaryl, which is unfused or fused with R^{59A} ; R^{59A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

- 25 R^{60} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{60A} ; R^{60A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

- 30 R^{61} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{62} , OR^{62} , SR^{62} , $S(O)R^{62}$, SO_2R^{62} , $C(O)R^{62}$, $CO(O)R^{62}$, $OC(O)R^{62}$, $OC(O)OR^{62}$, NH_2 , NHR^{62} , $N(R^{62})_2$, $NHC(O)R^{62}$, $NR^{62}C(O)R^{62}$, $NHS(O)_2R^{62}$, $NR^{62}S(O)_2R^{62}$, $NHC(O)OR^{62}$, $NR^{62}C(O)OR^{62}$, $NHC(O)NH_2$, $NHC(O)NHR^{62}$, $NHC(O)N(R^{62})_2$, $NR^{62}C(O)NHR^{62}$, $NR^{62}C(O)N(R^{62})_2$, $C(O)NH_2$, $C(O)NHR^{62}$, $C(O)N(R^{62})_2$, $C(O)NHOH$, $C(O)NHOR^{62}$, $C(O)NHSO_2R^{62}$, $C(O)NR^{62}SO_2R^{62}$, SO_2NH_2 , SO_2NHR^{62} , $SO_2N(R^{62})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{62}$, $C(N)N(R^{62})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br or I ;

R^{62} is R^{63} , R^{64} , R^{65} or R^{66} ;

R^{63} is phenyl, which is unfused or fused with R^{63A} ; R^{63A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{64} is heteroaryl, which is unfused or fused with R^{64A} ; R^{64A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{65} is cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, each of which is unfused or fused with R^{65A} ; R^{65A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{66} is alkyl, alkenyl or alkenyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{67} , OR^{67} , SR^{67} , $S(O)R^{67}$, SO_2R^{67} , $C(O)R^{67}$, $CO(O)R^{67}$, $OC(O)R^{67}$, $OC(O)OR^{67}$, NH_2 , NHR^{67} , $N(R^{67})_2$, $NHC(O)R^{67}$, $NR^{67}C(O)R^{67}$, $NHS(O)_2R^{67}$, $NR^{67}S(O)_2R^{67}$, $NHC(O)OR^{67}$, $NR^{67}C(O)OR^{67}$, $NHC(O)NH_2$, $NHC(O)NHR^{67}$, $NHC(O)N(R^{67})_2$, $NR^{67}C(O)NHR^{67}$, $NR^{67}C(O)N(R^{67})_2$, $C(O)NH_2$, $C(O)NHR^{67}$, $C(O)N(R^{67})_2$, $C(O)NHOH$, $C(O)NHOR^{67}$, $C(O)NHSO_2R^{67}$, $C(O)NR^{67}SO_2R^{67}$, SO_2NH_2 , SO_2NHR^{67} , $SO_2N(R^{67})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{67}$, $C(N)N(R^{67})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br or I substituents;

R^{67} is alkyl, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl;

wherein the cyclic moieties represented by R^{57A} , R^{58} , R^{59} , R^{60} , R^{63} , R^{64} , R^{65} , and R^{67} are unsubstituted or substituted with one or two or three or four of independently selected R^{68} , OR^{68} , SR^{68} , $S(O)R^{68}$, SO_2R^{68} , $C(O)R^{68}$, $CO(O)R^{68}$, $OC(O)R^{68}$, $OC(O)OR^{68}$, NH_2 , NHR^{68} , $N(R^{68})_2$, $NHC(O)R^{68}$, $NR^{68}C(O)R^{68}$, $NHS(O)_2R^{68}$, $NR^{68}S(O)_2R^{68}$, $NHC(O)OR^{68}$, $NR^{68}C(O)OR^{68}$, $NHC(O)NH_2$, $NHC(O)NHR^{68}$, $NHC(O)N(R^{68})_2$, $NR^{68}C(O)NHR^{68}$, $NR^{68}C(O)N(R^{68})_2$, $C(O)NH_2$, $C(O)NHR^{68}$, $C(O)N(R^{68})_2$, $C(O)NHOH$, $C(O)NHOR^{68}$, $C(O)NHSO_2R^{68}$, $C(O)NR^{68}SO_2R^{68}$, SO_2NH_2 , SO_2NHR^{68} , $SO_2N(R^{68})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{68}$, $C(N)N(R^{68})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br or I ;

R^{68} is R^{69} , R^{70} , R^{71} or R^{72} ;

R^{69} is phenyl, which is unfused or fused with R^{69A} ; R^{69A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{70} is heteroaryl, which is unfused or fused with R^{70A} ; R^{70A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{71} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{71A} ; R^{71A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{72} is alkyl, alkenyl or alkenyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{73} , OR^{73} , SR^{73} , $S(O)R^{73}$, SO_2R^{73} , $C(O)R^{73}$, $CO(O)R^{73}$, $OC(O)R^{73}$, $OC(O)OR^{73}$, NH_2 , NHR^{73} , $N(R^{73})_2$, $NHC(O)R^{73}$, $NR^{73}C(O)R^{73}$, $NHS(O)_2R^{73}$, $NR^{73}S(O)_2R^{73}$, $NHC(O)OR^{73}$, $NR^{73}C(O)OR^{73}$, $NHC(O)NH_2$, $NHC(O)NHR^{73}$, $NHC(O)N(R^{73})_2$, $NR^{73}C(O)NHR^{73}$, $NR^{73}C(O)N(R^{73})_2$, $C(O)NH_2$, $C(O)NHR^{73}$, $C(O)N(R^{73})_2$, $C(O)NHOH$, $C(O)NHOR^{73}$, $C(O)NHSO_2R^{73}$, $C(O)NR^{73}SO_2R^{73}$, SO_2NH_2 , SO_2NHR^{73} , $SO_2N(R^{73})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{73}$, $C(N)N(R^{73})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br or I ;

R^{73} is alkyl, alkenyl, alkenyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; and

wherein the moieties represented by R^{69} , R^{70} , and R^{71} are unsubstituted or substituted with one or two or three or four of independently selected NH_2 , $C(O)NH_2$, $C(O)NHOH$, SO_2NH_2 , CF_3 , CF_2CF_3 , $C(O)H$, $C(O)OH$, $C(N)NH_2$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br or I .

In one embodiment of Formula (I), A^1 is N , and G^1 is H . In another embodiment of Formula (I), A^1 is $C(A^2)$ and G^1 is H . In another embodiment of Formula (I), A^1 is $C(A^2)$; A^2 is H , F , Cl , Br , or I ; and G^1 is H . In another embodiment of Formula (I), A^1 is $C(A^2)$; A^2 is H ; and G^1 is H .

In one embodiment of Formula (I), B^1 is R^1 , OR^1 , NHR^1 , $NHC(O)R^1$, F , Cl , Br , or I . In another embodiment of Formula (I), A^1 is $C(A^2)$; A^2 is H ; B^1 is NHR^1 , and G^1 is H . In another embodiment of Formula (I), A^1 is $C(A^2)$; A^2 is H ; B^1 is OR^1 , and G^1 is H . In another embodiment of Formula (I), A^1 is $C(A^2)$; A^2 is H ; B^1 is Cl ; and G^1 is H . In another embodiment of Formula (I), A^1 is $C(A^2)$; A^2 is H ; B^1 is R^1 ; and G^1 is H . In another embodiment of Formula (I), A^1 is N ; B^1 is NHR^1 , and G^1 is H . In another embodiment of Formula (I), A^1 is N ; B^1 is OR^1 ; and G^1 is H . In another embodiment of Formula (I), A^1 is N ; B^1 is Cl ; and G^1 is H . In another embodiment of Formula (I), A^1 is N ; B^1 is R^1 ; and G^1 is H .

In one embodiment of Formula (I), D^1 is H or Cl . In another embodiment of Formula (I), A^1 is $C(A^2)$; A^2 is H ; B^1 is NHR^1 ; D^1 is H ; and G^1 is H . In another embodiment of Formula (I), A^1 is $C(A^2)$; A^2 is H ; B^1 is NHR^1 ; D^1 is Cl ; and G^1 is H . In another embodiment of Formula (I), A^1 is $C(A^2)$; A^2 is H ; B^1 is OR^1 ; D^1 is H ; and G^1 is H . In another embodiment of Formula (I), A^1 is $C(A^2)$; A^2 is H ; B^1 is Cl ; D^1 is H ; and G^1 is H . In another embodiment

of Formula (I), A¹ is C(A²); A² is H; B¹ is R¹; D¹ is H; and G¹ is H. In another embodiment of Formula (I), A¹ is N; B¹ is NHR¹; D¹ is H; and G¹ is H. In another embodiment of Formula (I), A¹ is N; B¹ is NHR¹; D¹ is Cl; and G¹ is H. In another embodiment of Formula (I), A¹ is N; B¹ is OR¹; D¹ is H; and G¹ is H. In another embodiment of Formula (I), A¹ is N; B¹ is Cl; D¹ is H; and G¹ is H. In another embodiment of Formula (I), A¹ is N; B¹ is R¹; D¹ is H; and G¹ is H.

In one embodiment of Formula (I), E¹ is H. In another embodiment of Formula (I), A¹ is C(A²); A² is H; B¹ is NHR¹; D¹ is H; E¹ is H; and G¹ is H. In another embodiment of Formula (I), A¹ is C(A²); A² is H; B¹ is NHR¹; E¹ is H; D¹ is Cl; and G¹ is H. In another embodiment of Formula (I), A¹ is C(A²); A² is H; B¹ is OR¹; D¹ is H; E¹ is H; and G¹ is H. In another embodiment of Formula (I), A¹ is C(A²); A² is H; B¹ is Cl; D¹ is H; E¹ is H; and G¹ is H. In another embodiment of Formula (I), A¹ is C(A²); A² is H; B¹ is R¹; D¹ is H; E¹ is H; and G¹ is H. In another embodiment of Formula (I), A¹ is N; B¹ is NHR¹; D¹ is H; E¹ is H; and G¹ is H. In another embodiment of Formula (I), A¹ is N; B¹ is NHR¹; E¹ is H; D¹ is Cl; and G¹ is H. In another embodiment of Formula (I), A¹ is N; B¹ is OR¹; D¹ is H; E¹ is H; and G¹ is H. In another embodiment of Formula (I), A¹ is N; B¹ is Cl; D¹ is H; E¹ is H; and G¹ is H. In another embodiment of Formula (I), A¹ is N; B¹ is R¹; D¹ is H; E¹ is H; and G¹ is H.

In one embodiment of Formula (I), Y¹ is H, CN, NO₂, F, Cl, Br, I, CF₃, R¹⁷, OR¹⁷, SR¹⁷, SO₂R¹⁷, or C(O)NH₂. In another embodiment of Formula (I), Y¹ is H. In another embodiment of Formula (I), Y¹ is CN. In another embodiment of Formula (I), Y¹ is F, Cl, Br, or I. In another embodiment of Formula (I), Y¹ is CF₃. In another embodiment of Formula (I), Y¹ is SR¹⁷. In another embodiment of Formula (I), Y¹ is OR¹⁷. In another embodiment of Formula (I), Y¹ is NO₂. In another embodiment of Formula (I), Y¹ is SO₂R¹⁷; wherein R¹⁷ is as defined herein. In another embodiment of Formula (I), Y¹ is SO₂R¹⁷; wherein R¹⁷ is alkyl. In another embodiment of Formula (I), Y¹ is R¹⁷; wherein R¹⁷ is alkynyl. In another embodiment of Formula (I), A¹ is C(A²); A² is H; B¹ is NHR¹; D¹ is H; E¹ is H; G¹ is H; and Y¹ is NO₂ or SO₂R¹⁷; wherein R¹⁷ is alkyl or alkynyl. In another embodiment of Formula (I), A¹ is C(A²); A² is H; B¹ is NHR¹; D¹ is H; E¹ is H; G¹ is H; and Y¹ is NO₂. In another embodiment of Formula (I), A¹ is C(A²); A² is H; B¹ is NHR¹; D¹ is H; E¹ is H; G¹ is H; and Y¹ is SO₂R¹⁷; wherein R¹⁷ is alkyl substituted with three F. In another embodiment of Formula (I), A¹ is N; B¹ is NHR¹; D¹ is H; E¹ is H; G¹ is H; and Y¹ is NO₂ or SO₂R¹⁷; wherein R¹⁷ is alkyl or alkynyl. In another embodiment of Formula (I), A¹ is N; B¹ is NHR¹; D¹ is H; E¹ is H; G¹ is H; and Y¹ is NO₂. In another embodiment of Formula (I), A¹ is N; B¹

is NHR^1 ; D^1 is H; E^1 is H; G^1 is H; and Y^1 is SO_2R^{17} ; wherein R^{17} is alkyl substituted with three F.

In one embodiment of Formula (I), G^1 is H; A^1 is N or $\text{C}(\text{A}^2)$; and A^2 is H. In another embodiment of Formula (I), G^1 is H; A^1 is N or $\text{C}(\text{A}^2)$; A^2 is H; and B^1 is NHR^1 . In another embodiment of Formula (I), G^1 is H; A^1 is N or $\text{C}(\text{A}^2)$; A^2 is H; B^1 is NHR^1 ; and D^1 is H. In another embodiment of Formula (I), G^1 is H; A^1 is N or $\text{C}(\text{A}^2)$; A^2 is H; B^1 is NHR^1 ; D^1 is H; and E^1 is H. In another embodiment of Formula (I), G^1 is H; A^1 is N or $\text{C}(\text{A}^2)$; A^2 is H; B^1 is NHR^1 ; D^1 is H; E^1 is H; and Y^1 is NO_2 .

In one embodiment of Formula (I), Y^1 and B^1 , together with the atoms to which they are attached, are benzene. In another embodiment of Formula (I), Y^1 and B^1 , together with the atoms to which they are attached, are heteroarene. In another embodiment of Formula (I), A^1 is $\text{C}(\text{A}^2)$; A^2 , G^1 , E^1 , and D^1 are independently selected H; and Y^1 and B^1 , together with the atoms to which they are attached, are benzene. In another embodiment of Formula (I), A^1 is $\text{C}(\text{A}^2)$; A^2 , G^1 , E^1 , and D^1 are independently selected H; and Y^1 and B^1 , together with the atoms to which they are attached, are heteroarene.

In one embodiment of Formula (I), R^1 is R^4 or R^5 . In one embodiment of Formula (I), R^1 is R^4 . In one embodiment of Formula (I), R^1 is R^5 . In one embodiment of Formula (I), R^1 is R^4 ; and R^4 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl. In one embodiment of Formula (I), R^1 is R^4 ; and R^4 is cycloalkyl or heterocycloalkyl. In one embodiment of Formula (I), R^1 is R^4 ; and R^4 is cycloalkyl. In one embodiment of Formula (I), R^1 is R^4 ; and R^4 is heterocycloalkyl.

In one embodiment of Formula (I), R^1 is R^4 ; and R^4 is cycloalkyl; wherein R^4 is unsubstituted or substituted as defined herein. In another embodiment of Formula (I), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is substituted as defined herein. In another embodiment of Formula (I), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is substituted with R^{57} or $\text{N}(\text{R}^{57})_2$. In another embodiment of Formula (I), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R^{57} ; and R^{57} is R^{60} . In another embodiment of Formula (I), R^1 is R^4 ; R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R^{57} ; R^{57} is R^{60} ; and R^{60} is heterocycloalkyl. In another embodiment of Formula (I), R^1 is R^4 ; R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R^{57} ; R^{57} is R^{60} ; R^{60} is heterocycloalkyl; wherein the heterocycloalkyl ring is morpholinyl. In another embodiment of Formula (I), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is substituted with $\text{N}(\text{R}^{57})_2$. In

another embodiment of Formula (I), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with $N(R^{57})_2$. In another embodiment of Formula (I), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with $N(R^{57})_2$; R^{57} is R^{61} ; and R^{61} is alkyl which is unsubstituted or substituted with R^{62} . In another embodiment of Formula (I), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R^{57} ; R^{57} is R^{61} ; and R^{61} is alkyl which is unsubstituted or substituted with R^{62} ; R^{62} is R^{65} ; and R^{65} is cycloalkyl. In another embodiment of Formula (I), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R^{57} ; R^{57} is R^{61} ; and R^{61} is alkyl which is substituted with R^{62} ; R^{62} is R^{65} ; and R^{65} is cyclopropyl.

In one embodiment of Formula (I), R^1 is R^4 ; and R^4 is heterocycloalkyl; wherein R^4 is unsubstituted or substituted as defined herein. In another embodiment of Formula (I), R^1 is R^4 ; and R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted as defined herein. In another embodiment of Formula (I), R^1 is R^4 ; and R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted with R^{57} . In another embodiment of Formula (I), R^1 is R^4 ; and R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is piperdinyl or piperizinyl; and wherein the heterocycloalkyl ring is substituted with R^{57} ; and R^{57} is R^{60} or R^{61} . In another embodiment of Formula (I), R^1 is R^4 ; R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is piperdinyl or piperizinyl; and wherein the piperdinyl or piperizinyl ring is substituted with R^{57} ; R^{57} is R^{60} or R^{61} ; R^{60} is heterocycloalkyl; and R^{61} is alkyl. In another embodiment of Formula (I), R^1 is R^4 ; R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is piperdinyl or piperizinyl; and wherein the piperdinyl or piperizinyl ring is substituted with R^{57} ; R^{57} is R^{60} ; R^{60} is heterocycloalkyl; wherein the heterocycloalkyl is tetrahydropyranyl. In another embodiment of Formula (I), R^1 is R^4 ; R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is piperdinyl or piperizinyl; and wherein the piperdinyl or piperizinyl ring is substituted with R^{57} ; R^{57} is R^{61} ; R^{61} is alkyl; and the alkyl is methyl. In another embodiment of Formula (I), R^1 is R^4 ; R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is piperdinyl or piperizinyl; and wherein the piperdinyl or piperizinyl ring is substituted with $C(O)OR^{57}$; R^{57} is R^{61} ; R^{61} is alkyl; and the alkyl is methyl.

In one embodiment of Formula (I), R^1 is R^5 ; and R^5 is alkyl which is unsubstituted or substituted. In one embodiment of Formula (I), R^1 is R^5 ; and R^5 is alkyl which is unsubstituted or substituted with R^7 , OR^7 , OH , CN , or F . In another embodiment of Formula (I), R^1 is R^5 ; and R^5 is alkyl which is substituted with R^7 , OR^7 , NHR^7 , or $N(R^7)_2$.

In one embodiment of Formula (I), R^7 is R^8 , R^9 , R^{10} or R^{11} which are unsubstituted or substituted as defined herein. In another embodiment of Formula (I), R^7 is R^8 which is unsubstituted or substituted as defined herein. In another embodiment of Formula (I), R^7 is R^9 which is unsubstituted or substituted as defined herein. In another embodiment of
5 Formula (I), R^7 is R^{10} which is unsubstituted or substituted as defined herein. In another embodiment of Formula (I), R^7 is R^{11} which is unsubstituted or substituted as defined herein.

In one embodiment of Formula (I), R^8 is phenyl which is unsubstituted or substituted as defined herein.

In one embodiment of Formula (I), R^9 is heteroaryl which is unsubstituted or
10 substituted as defined herein. In another embodiment of Formula (I), R^9 is furanyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (I), R^9 is furanyl; which is unsubstituted.

In one embodiment of Formula (I), R^{10} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, heterocycloalkyl which are unsubstituted or substituted as defined
15 herein. In another embodiment of Formula (I), R^{10} is heterocycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (I), R^{10} is tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, dioxanyl, oxetanyl, piperdiny, or pyrrolidinyl, which are unsubstituted or substituted as defined herein. In another embodiment of Formula (I), R^{10} is tetrahydropyranyl; which is unsubstituted or substituted as defined
20 herein. In another embodiment of Formula (I), R^{10} is morpholinyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (I), R^{10} is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (I), R^{10} is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (I), R^{10} is cyclohexyl, cyclopropyl, cyclobutyl, or bicyclo[2.2.1]heptanyl, which is
25 unsubstituted or substituted as defined herein. In another embodiment of Formula (I), R^{10} is heterocycloalkyl which is fused with R^{10A} ; and R^{10A} is heteroarene. In another embodiment of Formula (I), R^{10} is 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl.

In one embodiment of Formula (I), R^{11} is alkyl, alkenyl or alkynyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (I), R^{11} is
30 alkyl. In another embodiment of Formula (I), R^{11} is methyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (I), R^{11} is alkyl; which is substituted as defined herein. In another embodiment of Formula (I), R^{11} is alkyl; which is substituted with R^{12} , OR^{12} , or CF_3 . In another embodiment of Formula (I), R^{11} is alkyl; which is substituted with OR^{12} , R^{12} is R^{16} ; and R^{16} is alkyl. In another embodiment of Formula (I),

R^{11} is alkyl; which is substituted with CF_3 . In another embodiment of Formula (I), R^{11} is alkyl; which is substituted with R^{12} ; R^{12} is R^{14} ; and R^{14} is heteroaryl.

In one embodiment of Formula (I), A^1 is N or $C(A^2)$;

A^2 is H, F, Br, I, or Cl;

5 B^1 is R^1 , OR^1 , NHR^1 , $NHC(O)R^1$, F, Br, I or Cl;

D^1 is H, F, Br, I, or Cl;

E^1 is H; and

Y^1 is H, CN, NO_2 , F, Cl, Br, I, CF_3 , R^{17} , OR^{17} , SR^{17} , SO_2R^{17} , or $C(O)NH_2$; or

10 Y^1 and B^1 , together with the atoms to which they are attached, are benzene, heteroarene, or heterocycloalkene; and

A^2 , D^1 , and E^1 are independently selected H;

G^1 is H, or $C(O)OR$;

R is alkyl;

R^1 is R^4 or R^5 ;

15 R^4 is cycloalkyl, or heterocycloalkyl;

R^5 is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^7 , OR^7 , NHR^7 , $N(R^7)_2$, CN, OH, F, Cl, Br or I;

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

R^8 is phenyl;

20 R^9 is heteroaryl;

R^{10} is cycloalkyl, cycloalkenyl, or heterocycloalkyl; each of which is unfused or fused with R^{10A} , R^{10A} is heteroarene;

R^{11} is alkyl each of which is unsubstituted or substituted with one or two or three of independently selected R^{12} , OR^{12} or CF_3 ;

25 R^{12} is R^{14} or R^{16} ;

R^{14} is heteroaryl;

R^{16} is alkyl;

R^{17} is R^{21} ;

30 R^{21} is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{22} , F, Cl, Br or I;

R^{22} is R^{25} ;

R^{25} is heterocycloalkyl;

Z^1 is R^{26} ;

Z^2 is R^{30} ;

- Z^{1A} and Z^{2A} are both absent;
 L^1 is a R^{37} ;
 R^{26} is phenylene;
 R^{30} is heterocycloalkylene;
5 R^{37} is R^{37A} ;
 R^{37A} is alkylene;
 Z^3 is R^{38} , or R^{40} ;
 R^{38} is phenyl;
 R^{40} is cycloalkyl, cycloalkenyl, or heterocycloalkenyl;
10 wherein the moiety represented by R^{26} is substituted with OR^{41} ;
 R^{41} is heteroaryl, which is fused with R^{43A} ; R^{43A} is heteroarene; which is unfused or fused with benzene;
wherein the cyclic moieties represented by Y^1 and B^1 together, R^4 , R^8 , R^{10} , R^{25} , R^{30} , R^{38} , and R^{40} are independently unsubstituted, further unsubstituted, substituted or further
15 substituted with one or two or three or four or five of independently selected R^{57A} , R^{57} , OR^{57} , SO_2R^{57} , $C(O)R^{57}$, $CO(O)R^{57}$, $C(O)N(R^{57})_2$, NH_2 , NHR^{57} , $N(R^{57})_2$, $NHC(O)R^{57}$, $NHS(O)_2R^{57}$, OH , CN , (O) , F , Cl , Br or I ;
 R^{57A} is spiroalkyl, or spiroheteroalkyl;
 R^{57} is R^{58} , R^{59} , R^{60} or R^{61} ;
20 R^{58} is phenyl;
 R^{59} is heteroaryl;
 R^{60} is cycloalkyl, or heterocycloalkyl;
 R^{61} is alkyl which is unsubstituted or substituted with one or two or three of
independently selected R^{62} , OR^{62} , $N(R^{62})_2$, $C(O)OH$, CN , F , Cl , Br or I ;
25 R^{62} is R^{65} , or R^{66} ;
 R^{65} is cycloalkyl, or heterocycloalkyl;
 R^{66} is alkyl which is unsubstituted or substituted with OR^{67} ;
 R^{67} is alkyl;
wherein the cyclic moieties represented by R^{57A} , R^{58} , and R^{60} are unsubstituted or
30 substituted with one or two or three or four of independently selected R^{68} , F , Cl , Br or I ;
 R^{68} is R^{71} or R^{72} ;
 R^{71} is heterocycloalkyl; and
 R^{72} is alkyl, which is unsubstituted or substituted with one or two F .
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-(1H-pyrrolo[2,3-b]pyridin-5-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-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 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-yl)piperidin-4-yl]amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 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-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 2-(9H-carbazol-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-(9H-carbazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)benzamide;
- 20 Trans-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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-methoxyethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(3S)-tetrahydro-2H-pyran-3-ylmethyl]amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3R)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-(2-naphthylsulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{(2-methoxyethyl)amino}-3-{(trifluoromethyl)sulfonyl}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-[(4-{[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-{(trifluoromethyl)sulfonyl}phenyl)sulfonyl]benzamide;
- 15 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(3,3,3-trifluoropropyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 Cis-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]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 Trans-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Cis-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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-{[4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl]sulfonyl}benzamide;
- 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;
- 10 Trans-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 5-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino}sulfonyl)-2-(tetrahydro-2H-pyran-4-ylmethoxy)nicotinamide;
- N-({5-bromo-6-[(1-methylpiperidin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-({5-bromo-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- N-({3-chloro-5-cyano-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 N-({4-[(1-acetyl)piperidin-4-yl]amino]-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 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-(1H-pyrrolo[2,3-b]pyridin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(3-chloro-4-{[2-(2-methoxyethoxy)ethyl]sulfonyl}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[2-(2-methoxyethoxy)ethyl]sulfonyl}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)oxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-({5-bromo-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Cis-4-(4-([4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl)piperazin-1-yl)-N-([4-([4-morpholin-4-ylcyclohexyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-N-([4-([4-([bis(cyclopropylmethyl)amino]cyclohexyl)amino)-3-nitrophenyl]sulfonyl]-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([morpholin-3-ylmethyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl)piperazin-1-yl)-N-([4-([4-methylpiperazin-1-yl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([4-morpholin-4-ylbut-2-ynyl]oxy)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-oxo-3,4-dihydroquinazolin-6-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-([8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl)piperazin-1-yl)-N-([4-([4-morpholin-4-ylcyclohexyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Cis-4-(4-([4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl)piperazin-1-yl)-N-([4-([4-methoxycyclohexyl]methyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl)piperazin-1-yl)-N-([4-([4-fluorotetrahydro-2H-pyran-4-yl]methoxy)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- Trans-4-(4-([8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl)piperazin-1-yl)-N-[(4-([4-methoxycyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-([2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-([2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 tert-butyl 3-([4-([4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino)sulfonyl)-2-nitrophenoxymethyl)morpholine-4-carboxylate;
- 4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({4-(morpholin-3-ylmethoxy)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 4-(4-([8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl)piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([1-(methylsulfonyl)piperidin-4-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 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)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 N-[(4-chloro-3-nitrophenyl)sulfonyl]-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(3-nitro-4-([1-(2,2,2-trifluoroethyl)piperidin-4-yl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({5-cyano-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]oxy]pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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

N-({3-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

and therapeutically acceptable salts, and metabolites thereof.

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yl oxy)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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

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

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

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

N-({5-bromo-6-[(4-ethylmorpholin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-
[(4-ethylmorpholin-3-yl)methoxy]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-
yloxy)benzamide;
- 4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([3-
5 nitro-4-[(4-tetrahydro-2H-pyran-4-ylmorpholin-3-yl)methoxy]phenyl]sulfonyl)-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([3-
nitro-4-[(3S)-1-tetrahydro-2H-pyran-4-ylpiperidin-3-yl]amino]phenyl)sulfonyl)-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 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-pyrrolo[2,3-
b]pyridin-5-yloxy)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-pyrrolo[2,3-
15 b]pyridin-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-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide;
- Trans-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-
20 ([5-cyano-6-[(4-morpholin-4-ylcyclohexyl)amino]pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-
b]pyridin-5-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-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide;
- 25 4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-
[(1S,3R)-3-morpholin-4-ylcyclopentyl]amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide;
- 4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-
[(1R,3S)-3-morpholin-4-ylcyclopentyl]amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-
30 b]pyridin-5-yloxy)benzamide;
- 4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-
[(morpholin-2-ylmethyl)amino]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-
yloxy)benzamide;

- 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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
5 ({1-[cis-3-fluorotetrahydro-2H-pyran-4-yl]piperidin-4-yl}amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)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-ylazetidin-3-yl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydrofuran-3-ylazetidin-3-yl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-({[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl}amino)phenyl}sulfonyl)-
15 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(4-((trans-4-hydroxycyclohexyl)methoxy)-3-nitrophenylsulfonyl)benzamide;
- 20 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(4-((cis-4-methoxycyclohexyl)methoxy)-3-nitrophenylsulfonyl)benzamide;
- 25 Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(cyclopropylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(tetrahydro-2H-pyran-4-ylamino)cyclohexyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 Trans-N-({5-bromo-6-[(4-morpholin-4-ylcyclohexyl)oxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-((4-[(4-methoxycyclohexyl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

tert-butyl 4-{[4-([4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-

5 yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino}sulfonyl)-2-nitrophenoxymethyl]-4-fluoropiperidine-1-carboxylate;

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

10 Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(4-tetrahydro-2H-pyran-4-yl)piperazin-1-yl]cyclohexyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl}methoxy)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

15 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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

25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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

30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[4-(2-methoxyethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- N-[(4-{[(4-acetylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[trans-4-(fluoromethyl)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-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)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(1-oxetan-3-yl)piperidin-4-yl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-[(1-cyclobutyl)piperidin-4-yl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-cyclopropylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-cyclopropylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(1-tetrahydrofuran-3-yl)piperidin-4-yl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3-hydroxy-2,2-dimethylpropyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-
 ({[1-(methylsulfonyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl]sulfonyl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 N-[(4-{[(1-acetyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl]sulfonyl]-4-(4-{[2-(4-
 chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-
 {[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-
 nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-
 ({1-[2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-
 15 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-
 ({[1-(methylsulfonyl)pyrrolidin-3-yl]methyl}amino)-3-nitrophenyl]sulfonyl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 N-[(4-{[(1-acetylpyrrolidin-3-yl]methyl}amino)-3-nitrophenyl]sulfonyl]-4-(4-{[2-(4-
 chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- N-[(4-{[(3R)-1-acetylpyrrolidin-3-yl]amino}-3-nitrophenyl]sulfonyl)-4-(4-{[2-(4-
 chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-
 25 b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-
 [(3-methoxy-2,2-dimethylpropyl)amino]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-
 30 {[(1R,3R)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-
 {[(1S,3S)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
 ({[(1S,3R)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl)sulfonyl}-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
 5 ({[(1R,3S)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl)sulfonyl}-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-
 nitro-4-{[(3S)-2-oxopiperidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-
 yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
 [({1-[2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl}methyl)amino]-3-nitrophenyl)sulfonyl)-2-
 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-
 nitro-4-{[(1-oxetan-3-ylazetidin-3-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
 15 b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-
 nitro-4-{[(1-oxetan-3-ylpiperidin-4-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
 20 {[(1-cyclopropyl)piperidin-4-yl]methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
 ({[4-(2-fluoroethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl)sulfonyl}-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 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}-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
 [(4-fluoro-1-oxetan-3-ylpiperidin-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-
 30 b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
 {[(2S)-4,4-difluoro-1-oxetan-3-ylpyrrolidin-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(4-tetrahydro-2H-pyran-4-yl)morpholin-3-yl]methyl}amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyclobutyl)morpholin-3-yl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(4-tetrahydrofuran-3-yl)morpholin-3-yl]methyl}amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-cyclopropyl-4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxybenzyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[3-(trifluoromethoxy)benzyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3-methoxybenzyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-(difluoromethoxy)benzyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1,4-dioxaspiro[4.5]dec-8-ylamino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 Trans-N-[(4-{[4-(acetylamino)cyclohexyl]amino)-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 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]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-hydroxybenzyl)amino]-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3-hydroxybenzyl)amino]-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3-(difluoromethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(cis-3-morpholin-4-ylcyclopentyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-{[(methylsulfonyl)amino]cyclohexyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-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-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-oxetan-3-ylpiperidin-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-tetrahydrofuran-3-ylpiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-(methylsulfonyl)piperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-([[(3R)-1-oxetan-3-ylpyrrolidin-3-yl]methyl]amino)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-hydroxycyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-[3-(dimethylamino)propoxy]benzyl]amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-(2-morpholin-4-ylethoxy)benzyl]amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(*(E)*-4-hydroxy-1-adamantyl]methyl]amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(*(Z)*-4-hydroxy-1-adamantyl]methyl]amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-({4-[(1S,4S)-bicyclo[2.2.1]hept-5-en-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methyl-5-oxopyrrolidin-3-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-5 {[(1R,4R,5R,6S)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-10 {[(1R,4R,5S,6R)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-10 nitro-4-[(3-oxocyclohexyl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohexa-1,3-dien-1-yl]methyl}piperazin-1-yl)-N-15 ({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-15 ({(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl}amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-20 [(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-25 nitro-4-({[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methyl}amino)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-N-({5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-25 chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Cis-N-({5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-30 chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-30 nitro-4-[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
 [({4-[2-(2-methoxyethoxy)ethyl]morpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-
 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
 5 ({4-(cyanomethyl)morpholin-2-yl)methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
 ({4-(N,N-dimethylglycyl)morpholin-2-yl)methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 (2-{{4-({4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-
 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl)sulfamoyl}-2-
 nitrophenyl)amino)methyl}morpholin-4-yl)acetic acid;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-
 nitro-4-({4-(oxetan-3-yl)morpholin-2-yl)methyl}amino)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-
 15 b]pyridin-5-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-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-
 20 (methylsulfonyl)-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl)sulfonyl)-2-(1H-
 pyrrolo[2,3-b]pyridin-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-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-
 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
 [(4-methyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- ethyl 4-(4-{[4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-
 yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl)sulfamoyl}-2-nitrophenyl)piperazine-1-
 30 carboxylate;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[4-
 (morpholin-4-yl)piperidin-1-yl]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-
 yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3R)-1-(oxetan-3-yl)pyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-isopropylpiperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 N-[(4-{[1-tert-butylpiperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(2-methoxyethyl)piperidin-3-yl]methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(cyanomethyl)piperidin-3-yl]methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-fluoro-1-methylpiperidin-4-yl]methoxy}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 N-[(5-chloro-6-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 tert-butyl 4-[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]-2-nitrophenyl)amino]piperazine-1-carboxylate;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-(pentafluoro- λ^6 -sulfanyl)-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-methoxytetrahydro-2H-pyran-4-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(oxetan-3-yl)piperazin-1-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{(3R)-tetrahydrofuran-3-ylamino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(4-{[(1-tert-butylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(oxetan-3-yl)morpholin-2-yl]methyl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(5-chloro-6-{[(2S)-4-(cyanomethyl)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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- N-[(5-chloro-6-[[2R]-4-(cyanomethyl)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-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 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-pyrrolo[2,3-b]pyridin-5-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-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 N-({5-chloro-6-[3-hydroxy-2-(hydroxymethyl)-2-methylpropoxy]pyridin-3-yl}sulfonyl)-4-
 (4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-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]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-
 15 b]pyridin-5-yloxy)benzamide;
- 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-({4-
 ([4-(1,3-difluoropropan-2-yl)morpholin-2-yl]methyl)amino)-3-nitrophenyl)sulfonyl)-2-
 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(5-chloro-6-[[1-(cyanomethyl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-[[2-(4-
 20 chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- 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)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 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]-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(3-
 nitro-4-[[1-(oxetan-3-yl)azetidin-3-yl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-
 30 5-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-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 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}-2-
 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
 5 ({[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-
 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(5-chloro-6-{[1-(N,N-dimethylglycyl)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-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 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-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 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]-2-(1H-pyrrolo[2,3-
 15 b]pyridin-5-yloxy)benzamide;
- 4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-methoxypiperidin-1-yl}-N-({5-chloro-6-[(4-
 fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- 4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-methoxypiperidin-1-yl}-N-({3-nitro-4-[(tetrahydro-
 20 2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-
 yloxy)benzamide;
- 4-(4-{[9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-
 yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-
 ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-
 yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-
 yl]methyl}piperazin-1-yl)-N-({5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-
 30 yl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-
 yl)-N-({5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl)sulfonyl}-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- N-({5-chloro-6-[(4-fluoro-1-methylpiperidin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 N-[(5-chloro-6-{[1-(N,N-dimethylglycyl)-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-fluoropiperidin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-fluoropiperidin-1-yl}-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-
- 15 (trifluoromethyl)phenyl}sulfonyl)benzamide;
- N-[(5-chloro-6-{[(3R)-1-(1,3-difluoropropan-2-yl)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-
- 20 nitro-4-[2-(tetrahydrofuran-3-yloxy)ethoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-
- 30 cyano-6-[2-(tetrahydro-2H-pyran-4-yl)ethoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-(3-furylmethoxy)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- N-[(5-chloro-6-[(3R)-1-(1,3-difluoropropan-2-yl)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(5-chloro-6-[1-(1,3-difluoropropan-2-yl)-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 N-({3-chloro-4-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-ylmethoxy)phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 N-[(5-chloro-6-[1-(2,2-difluoroethyl)-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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([6-{1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl]methoxy}-5-(trifluoromethyl)pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-yl)ethoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-methylpiperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(cyclopropylamino)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 N-[[5-chloro-6-(2-methoxyethoxy)pyridin-3-yl]sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 N-[(3-chloro-4-{[1-(methoxyacetyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(3-chloro-4-{[1-(N,N-dimethylglycyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohexyl]methyl}piperidin-1-yl)-N-[(3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-[[6-(tetrahydro-2H-pyran-4-ylmethoxy)-5-(trifluoromethyl)pyridin-3-yl]sulfonyl]benzamide;
- 20 N-[(5-chloro-6-[(trans-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(6-[(trans-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(6-[(cis-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-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}piperidin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 N-[(3-chloro-4-{[trans-4-(morpholin-4-yl)cyclohexyl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({3-[cyclopropyl(1,3-thiazol-5-ylmethyl)amino]propyl)amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 N-({3-chloro-4-[(trans-4-hydroxycyclohexyl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 b]pyridin-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-(trifluoromethyl)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({3-[cyclopropyl(2,2,2-trifluoroethyl)amino]propyl)amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 N-[(3-chloro-4-{[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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3,5-difluoro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({3-[cyclopropyl(oxetan-3-yl)amino]propyl)amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 N-[(3-chloro-4-{[1-(1-methyl-L-prolyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3,4-difluoro-5-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-N-({3-chloro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- methyl 2-{{[4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl]amino]methyl}morpholine-4-carboxylate;
- 15 2-{{[4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl]amino]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide;
- 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}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{[4-({[3-(cyclobutyl(cyclopropyl)amino]propyl)amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-chloro-4-(tetrahydrofuran-3-ylmethoxy)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl)sulfonyl)-4-(4-{[9-(4-chlorophenyl)-3-(oxetan-3-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-(((2R)-4-cyclopropylmorpholin-2-yl)methyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-([5-chloro-6-({4-[cyclopropyl(oxetan-3-yl)amino]cyclohexyl)methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-N-([4-({4-cyclopropylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-({3-chloro-4-[(4-cyclopropylmorpholin-2-yl)methoxy]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(3-chloro-4-({4-cyclopropylmorpholin-2-yl)methyl]amino}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 2-({[2-chloro-4-({4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}phenyl)amino)methyl}-N-ethyl-N-methylmorpholine-4-carboxamide;
- (2S)-2-({[3-chloro-5-({4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}pyridin-2-yl)oxy)methyl}-N-ethyl-N-methylmorpholine-4-carboxamide;

- N-[(5-chloro-6-[[4-(cyclopropylmorpholin-2-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-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 2-[[[3-chloro-5-{[4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-
 5 yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}pyridin-
 2-yl)amino]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide;
- 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-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 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-
 pyrrolo[2,3-b]pyridin-5-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-
 15 yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-
 ({4-[(2-cyanoethyl)(cyclopropyl)amino]cyclohexyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-
 20 {[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)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-yl)methoxy}pyridin-3-yl)sulfonyl)-2-
 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 N-[(5-chloro-6-[[[(1R,2S,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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-
 30 b]pyridin-5-yloxy)benzamide;
- N-[(5-chloro-6-[[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-
 (4-[[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(3,3-difluoropyrrolidin-1-yl)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(2,2-difluorocyclopropyl)amino]cyclohexyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-(2-oxaspiro[3.5]non-7-yl)methoxy)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 4-(4-{[2-(4-chlorophenyl)-5,5-bis(fluoromethyl)cyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-cyclopropylmorpholin-2-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-ethyl-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(cis-4-ethyl-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-({3-chloro-4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({4-[(2-cyanoethyl)(cyclopropyl)amino]-1-fluorocyclohexyl)methoxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-nitro-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(2-oxaspiro[3.5]non-7-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyano-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- {[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)amino}methyl pivalate;

- {[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl}amino)methyl butyrate;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-{[3-(tetrahydro-2H-pyran-4-ylmethyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-6-yl]sulfonyl}benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(6-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-5-nitropyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl)sulfamoyl]-2-nitrophenyl)morpholine-4-carboxamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-({[4-(methoxymethyl)cyclohexyl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-({[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and therapeutically acceptable salts, and metabolites thereof.

Still another embodiment pertains to 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-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and therapeutically acceptable salts, and metabolites thereof.

Still another embodiment pertains to Trans-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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and therapeutically acceptable salts, and metabolites thereof.

5 Still another embodiment pertains to Cis-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]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and therapeutically acceptable salts, and metabolites thereof.

10 Still another embodiment pertains to Trans-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]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and therapeutically acceptable salts, and metabolites thereof.

15 Still another embodiment pertains to 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and therapeutically acceptable salts, and metabolites thereof.

20 Another embodiment pertains to the compound 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

25 Another embodiment pertains to the compound 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

30 Another embodiment pertains to the compound 4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}(²H₈)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound N-({5-bromo-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(4-{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-{[4-({3-[cyclopropyl(oxetan-3-yl)amino]propyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(4-{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-{[4-({3-[cyclopropyl(oxetan-3-yl)amino]propyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are N-[(5-chloro-6-{[1-(cyanomethyl)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-{[4-({3-[cyclopropyl(oxetan-3-yl)amino]propyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are 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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

5 Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-{[3-(cyclopropyl(oxetan-3-yl)amino]propyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Still another embodiment pertains to compounds having Formula (I) or Formula (II),
 10 which are 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-({[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl}amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-
 15 5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 20 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 N-({5-bromo-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 25 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-({[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl}amino)phenyl)sulfonyl]-
 30 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-((4-
 5 [(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-([1-(cyanomethyl)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-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;

10 4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-((4-
 ((3-[cyclopropyl(oxetan-3-yl)amino]propyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-([(1R,2S,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-
 15 yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-
 20 N-((3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

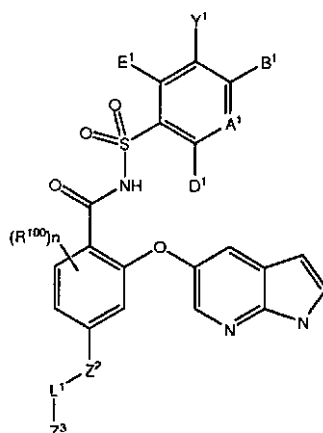
Another embodiment pertains to the compound N-[(5-chloro-6-([1-
 (cyanomethyl)piperidin-4-yl]methoxy)pyridin-3-yl)sulfonyl]-4-(4-([2-(4-chlorophenyl)-4,4-
 dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-
 25 yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Still another embodiment pertains to compounds having Formula (I) or Formula (II),
 which are 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-([2-(4-
 30 chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-((4-[(4-
 methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-([2-(4-chlorophenyl)-4,4-
 dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-((4-[(4-methoxytetrahydro-2H-pyran-

4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention provides compounds of Formula (II)



(II)

and therapeutically acceptable salts, and metabolites thereof,

wherein A^1 , B^1 , D^1 , E^1 , Y^1 , Z^2 , L^1 , and Z^3 are as described herein for Formula (II); n is 0, 1, 2, or 3; describing the number of substituents on Z^1 ; and R^{100} is as described for substituents on R^{26} .

In one embodiment of Formula (II), n is 0 or 1. In another embodiment of Formula (II), n is 0.

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, F, Cl, Br, or I. 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 , NHR^1 , $NHC(O)R^1$, F, Cl, Br, or I. In another embodiment of Formula (II), A^1 is $C(A^2)$; A^2 is H; and B^1 is NHR^1 . In another embodiment of Formula (II), A^1 is $C(A^2)$; A^2 is H; and B^1 is OR^1 . In another embodiment of Formula (II), A^1 is $C(A^2)$; A^2 is H; and B^1 is Cl. In another embodiment of Formula (II), A^1 is $C(A^2)$; A^2 is H; and B^1 is R^1 . In another embodiment of Formula (II), A^1 is N; and B^1 is NHR^1 . In another embodiment of Formula (II), A^1 is N; and B^1 is OR^1 . In another embodiment of Formula (II), A^1 is N; and B^1 is Cl. In another embodiment of Formula (II), A^1 is N; and B^1 is R^1 .

In one embodiment of Formula (II), D^1 is H or Cl. In another embodiment of Formula (II), A^1 is $C(A^2)$; A^2 is H; B^1 is NHR^1 ; and D^1 is H. In another embodiment of Formula (II), A^1 is $C(A^2)$; A^2 is H; B^1 is NHR^1 ; and D^1 is Cl. In another embodiment of Formula (II), A^1 is $C(A^2)$; A^2 is H; B^1 is OR^1 ; and D^1 is H. In another embodiment of Formula (II), A^1 is $C(A^2)$; A^2 is H; B^1 is OR^1 ; and D^1 is H. In another embodiment of Formula (II), A^1 is $C(A^2)$;

A^2 is H; B^1 is Cl; and D^1 is H. In another embodiment of Formula (II), A^1 is $C(A^2)$; A^2 is H; B^1 is R^1 ; and D^1 is H. In another embodiment of Formula (II), A^1 is N; B^1 is NHR^1 ; and D^1 is H. In another embodiment of Formula (II), A^1 is N; B^1 is NHR^1 ; and D^1 is Cl. In another embodiment of Formula (II), A^1 is N; B^1 is OR^1 ; and D^1 is H. In another embodiment of Formula (II), A^1 is N; B^1 is Cl; and D^1 is H. In another embodiment of Formula (II), A^1 is N; B^1 is R^1 ; and D^1 is H.

In one embodiment of Formula (II), E^1 is H. In another embodiment of Formula (II), A^1 is $C(A^2)$; A^2 is H; B^1 is NHR^1 ; D^1 is H; and E^1 is H. In another embodiment of Formula (II), A^1 is $C(A^2)$; A^2 is H; B^1 is NHR^1 ; E^1 is H; and D^1 is Cl. In another embodiment of Formula (II), A^1 is $C(A^2)$; A^2 is H; B^1 is OR^1 ; D^1 is H; and E^1 is H. In another embodiment of Formula (II), A^1 is $C(A^2)$; A^2 is H; B^1 is Cl; D^1 is H; and E^1 is H. In another embodiment of Formula (II), A^1 is $C(A^2)$; A^2 is H; B^1 is R^1 ; D^1 is H; and E^1 is H. In another embodiment of Formula (II), A^1 is N; B^1 is NHR^1 ; D^1 is H; and E^1 is H. In another embodiment of Formula (II), A^1 is N; B^1 is NHR^1 ; E^1 is H; and D^1 is Cl. In another embodiment of Formula (II), A^1 is N; B^1 is OR^1 ; D^1 is H; and E^1 is H. In another embodiment of Formula (II), A^1 is N; B^1 is Cl; D^1 is H; and E^1 is H. In another embodiment of Formula (II), A^1 is N; B^1 is R^1 ; D^1 is H; and E^1 is H.

In one embodiment of Formula (II), Y^1 is H, CN, NO_2 , F, Cl, Br, I, CF_3 , R^{17} , OR^{17} , SR^{17} , SO_2R^{17} , or $C(O)NH_2$. In another embodiment of Formula (II), Y^1 is H. In another embodiment of Formula (II), Y^1 is CN. In another embodiment of Formula (II), Y^1 is F, Cl, Br, or I. In another embodiment of Formula (II), Y^1 is CF_3 . In another embodiment of Formula (II), Y^1 is SR^{17} . In another embodiment of Formula (II), Y^1 is OR^{17} . In another embodiment of Formula (II), Y^1 is NO_2 . In another embodiment of Formula (II), Y^1 is SO_2R^{17} ; wherein R^{17} is as defined herein. In another embodiment of Formula (II), Y^1 is SO_2R^{17} ; wherein R^{17} is alkyl. In another embodiment of Formula (II), Y^1 is R^{17} ; wherein R^{17} is alkynyl. In another embodiment of Formula (II), A^1 is $C(A^2)$; A^2 is H; B^1 is NHR^1 ; D^1 is H; E^1 is H; and Y^1 is NO_2 or SO_2R^{17} ; wherein R^{17} is alkyl or alkynyl. In another embodiment of Formula (II), A^1 is $C(A^2)$; A^2 is H; B^1 is NHR^1 ; D^1 is H; E^1 is H; and Y^1 is NO_2 . In another embodiment of Formula (II), A^1 is $C(A^2)$; A^2 is H; B^1 is NHR^1 ; D^1 is H; E^1 is H; and Y^1 is SO_2R^{17} ; wherein R^{17} is alkyl substituted with three F. In another embodiment of Formula (II), A^1 is N; B^1 is NHR^1 ; D^1 is H; E^1 is H; and Y^1 is NO_2 or SO_2R^{17} ; wherein R^{17} is alkyl or alkynyl. In another embodiment of Formula (II), A^1 is N; B^1 is NHR^1 ; D^1 is H; E^1 is H; and Y^1 is NO_2 . In another embodiment of Formula (II), A^1 is N; B^1 is NHR^1 ; D^1 is H; E^1 is H; and Y^1 is SO_2R^{17} ; wherein R^{17} is alkyl substituted with three F.

In one embodiment of Formula (II), G^1 is H; A^1 is N or $C(A^2)$; and A^2 is H. In another embodiment of Formula (II), G^1 is H; A^1 is N or $C(A^2)$; A^2 is H; and B^1 is NHR^1 . In another embodiment of Formula (II), G^1 is H; A^1 is N or $C(A^2)$; A^2 is H; B^1 is NHR^1 ; and D^1 is H. In another embodiment of Formula (II), G^1 is H; A^1 is N or $C(A^2)$; A^2 is H; B^1 is NHR^1 ; D^1 is H; and E^1 is H. In another embodiment of Formula (II), G^1 is H; A^1 is N or $C(A^2)$; A^2 is H; B^1 is NHR^1 ; D^1 is H; E^1 is H; and Y^1 is NO_2 .

In one embodiment of Formula (II), Y^1 and B^1 , together with the atoms to which they are attached, are benzene. In another embodiment of Formula (II), Y^1 and B^1 , together with the atoms to which they are attached, are heteroarene. In another embodiment of Formula (II), A^1 is $C(A^2)$; A^2 , G^1 , E^1 , and D^1 are independently selected H; and Y^1 and B^1 , together with the atoms to which they are attached, are benzene. In another embodiment of Formula (II), A^1 is $C(A^2)$; A^2 , G^1 , E^1 , and D^1 are independently selected H; and Y^1 and B^1 , together with the atoms to which they are attached, are heteroarene.

In one embodiment of Formula (II), R^1 is R^4 or R^5 . In one embodiment of Formula (II), R^1 is R^4 . In one embodiment of Formula (II), R^1 is R^5 . In one embodiment of Formula (II), R^1 is R^4 ; and R^4 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl. In one embodiment of Formula (II), R^1 is R^4 ; and R^4 is cycloalkyl or heterocycloalkyl. In one embodiment of Formula (II), R^1 is R^4 ; and R^4 is cycloalkyl. In one embodiment of Formula (II), R^1 is R^4 ; and R^4 is heterocycloalkyl.

In one embodiment of Formula (II), R^1 is R^4 ; and R^4 is cycloalkyl; wherein R^4 is unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is substituted as defined herein. In another embodiment of Formula (II), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is substituted with R^{57} or $N(R^{57})_2$. In another embodiment of Formula (II), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R^{57} ; and R^{57} is R^{60} . In another embodiment of Formula (II), R^1 is R^4 ; R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R^{57} ; R^{57} is R^{60} ; and R^{60} is heterocycloalkyl. In another embodiment of Formula (II), R^1 is R^4 ; R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R^{57} ; R^{57} is R^{60} ; R^{60} is heterocycloalkyl; wherein the heterocycloalkyl ring is morpholinyl. In another embodiment of Formula (II), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is substituted with $N(R^{57})_2$. In another embodiment of Formula (II), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with $N(R^{57})_2$. In another

embodiment of Formula (II), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with $N(R^{57})_2$; R^{57} is R^{61} ; and R^{61} is alkyl which is unsubstituted or substituted with R^{62} . In another embodiment of Formula (II), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R^{57} ; R^{57} is R^{61} ; and R^{61} is alkyl which is unsubstituted or substituted with R^{62} ; R^{62} is R^{65} ; and R^{65} is cycloalkyl. In another embodiment of Formula (II), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R^{57} ; R^{57} is R^{61} ; and R^{61} is alkyl which is substituted with R^{62} ; R^{62} is R^{65} ; and R^{65} is cyclopropyl

10 In one embodiment of Formula (II), R^1 is R^4 ; and R^4 is heterocycloalkyl; wherein R^4 is unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R^1 is R^4 ; and R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted as defined herein. In another embodiment of Formula (II), R^1 is R^4 ; and R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted with R^{57} . In another embodiment of Formula (II), R^1 is R^4 ; and R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is piperdinyl or piperizinyl; and wherein the heterocycloalkyl ring is substituted with R^{57} ; and R^{57} is R^{60} or R^{61} . In another embodiment of Formula (II), R^1 is R^4 ; R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is piperdinyl or piperizinyl; and wherein the piperdinyl or piperizinyl ring is substituted with R^{57} ; R^{57} is R^{60} or R^{61} ; R^{60} is heterocycloalkyl; and R^{61} is alkyl. In 15 another embodiment of Formula (II), R^1 is R^4 ; R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is piperdinyl or piperizinyl; and wherein the piperdinyl or piperizinyl ring is substituted with R^{57} ; R^{57} is R^{60} ; R^{60} is heterocycloalkyl; wherein the heterocycloalkyl is tetrahydropyranyl. In another embodiment of Formula (II), R^1 is R^4 ; R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is piperdinyl or piperizinyl; and wherein the piperdinyl or piperizinyl ring is substituted with R^{57} ; R^{57} is R^{61} ; R^{61} is alkyl; and the alkyl is methyl. In another embodiment of Formula (II), R^1 is R^4 ; R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is piperdinyl or piperizinyl; and wherein the piperdinyl or piperizinyl ring is substituted with $C(O)OR^{57}$; R^{57} is R^{61} ; R^{61} is alkyl; and the alkyl is methyl.

25 In one embodiment of Formula (II), R^1 is R^5 ; and R^5 is alkyl which is unsubstituted or substituted. In one embodiment of Formula (II), R^1 is R^5 ; and R^5 is alkyl which is unsubstituted or substituted with R^7 , OR^7 , OH , CN , or F . In another embodiment of Formula (II), R^1 is R^5 ; and R^5 is alkyl which is substituted with R^7 , OR^7 , NHR^7 , or $N(R^7)_2$.

In one embodiment of Formula (II), R^7 is R^8 , R^9 , R^{10} or R^{11} which are unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R^7 is R^8 which is

unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R^7 is R^9 which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R^7 is R^{10} which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R^7 is R^{11} which is unsubstituted or substituted as defined herein.

5 In one embodiment of Formula (II), R^8 is phenyl which is unsubstituted or substituted as defined herein.

In one embodiment of Formula (II), R^9 is heteroaryl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R^9 is furanyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R^9 is furanyl; which is unsubstituted.

10 In one embodiment of Formula (II), R^{10} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, heterocycloalkyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R^{10} is heterocycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R^{10} is tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, dioxanyl, oxetanyl, piperdiny, or pyrrolidinyl, which are unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R^{10} is tetrahydropyranyl, which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R^{10} is morpholinyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R^{10} is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R^{10} is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R^{10} is cyclohexyl, cyclopropyl, cyclobutyl, or bicyclo[2.2.1]heptanyl, which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R^{10} is heterocycloalkyl which is fused with R^{10A} ; and R^{10A} is heteroarene. In another embodiment of Formula (II), R^{10} is 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl.

25 In one embodiment of Formula (II), R^{11} is alkyl, alkenyl or alkynyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R^{11} is alkyl. In another embodiment of Formula (II), R^{11} is methyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R^{11} is alkyl; which is substituted as defined herein. In another embodiment of Formula (II), R^{11} is alkyl; which is substituted with R^{12} , OR^{12} , or CF_3 . In another embodiment of Formula (II), R^{11} is alkyl; which is substituted with OR^{12} ; R^{12} is R^{16} ; and R^{16} is alkyl. In another embodiment of

Formula (II), R^{11} is alkyl; which is substituted with CF_3 . In another embodiment of Formula (II), R^{11} is alkyl; which is substituted with R^{12} , R^{12} is R^{14} , and R^{14} is heteroaryl.

In one embodiment of Formula (II),

n is 0;

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

A^2 is H, F, Br, I, or Cl;

B^1 is R^1 , OR^1 , NHR^1 , $NHC(O)R^1$, F, Br, I or Cl;

D^1 is H, F, Br, I, or Cl;

E^1 is H; and

10 Y^1 is H, CN, NO_2 , F, Cl, Br, I, CF_3 , R^{17} , OR^{17} , SR^{17} , SO_2R^{17} , or $C(O)NH_2$; or

Y^1 and B^1 , together with the atoms to which they are attached, are benzene,

heteroarene, or heterocycloalkene; and

A^2 , D^1 , and E^1 are independently selected H;

R^1 is R^4 or R^5 ;

15 R^4 is cycloalkyl, or heterocycloalkyl;

R^5 is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^7 , OR^7 , NHR^7 , $N(R^7)_2$, CN, OH, F, Cl, Br or I;

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

R^8 is phenyl;

20 R^9 is heteroaryl;

R^{10} is cycloalkyl, cycloalkenyl, or heterocycloalkyl; each of which is unfused or fused with R^{10A} , R^{10A} is heteroarene;

R^{11} is alkyl each of which is unsubstituted or substituted with one or two or three of independently selected R^{12} , OR^{12} or CF_3 ;

25 R^{12} is R^{14} or R^{16} ;

R^{14} is heteroaryl;

R^{16} is alkyl;

R^{17} is R^{21} ;

30 R^{21} is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{22} , F, Cl, Br or I;

R^{22} is R^{25} ;

R^{25} is heterocycloalkyl;

Z^2 is R^{30} ;

Z^{1A} and Z^{2A} are both absent;

L^1 is a R^{37} ;

R^{30} is heterocycloalkylene;

R^{37} is R^{37A} ;

R^{37A} is alkylene;

5 Z^3 is R^{38} , or R^{40} ;

R^{38} is phenyl;

R^{40} is cycloalkyl, cycloalkenyl, or heterocycloalkenyl;

wherein the cyclic moieties represented by Y^1 and B^1 together, R^4 , R^8 , R^{10} , R^{25} , R^{30} , R^{38} , and R^{40} are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five of independently selected R^{57A} , R^{57} , OR^{57} , SO_2R^{57} , $C(O)R^{57}$, $CO(O)R^{57}$, $C(O)N(R^{57})_2$, NH_2 , NHR^{57} , $N(R^{57})_2$, $NHC(O)R^{57}$, $NHS(O)_2R^{57}$, OH , CN , (O) , F , Cl , Br or I ;

R^{57A} is spiroalkyl, or spiroheteroalkyl;

R^{57} is R^{58} , R^{60} or R^{61} ;

15 R^{58} is phenyl;

R^{60} is cycloalkyl, or heterocycloalkyl;

R^{61} is alkyl which is unsubstituted or substituted with one or two or three of independently selected R^{62} , OR^{62} , $N(R^{62})_2$, $C(O)OH$, CN , F , Cl , Br or I ;

R^{62} is R^{65} , or R^{66} ;

20 R^{65} is cycloalkyl, or heterocycloalkyl;

R^{66} is alkyl which is unsubstituted or substituted with OR^{67} ;

R^{67} is alkyl;

wherein the cyclic moieties represented by R^{57A} , R^{58} , and R^{60} are unsubstituted or substituted with one or two or three or four of independently selected R^{68} , F , Cl , Br or I ;

25 R^{68} is R^{71} or R^{72} ;

R^{71} is heterocycloalkyl; and

R^{72} is alkyl, which is unsubstituted or substituted with one or two F .

Still another embodiment pertains to compounds having Formula (II), which are
 4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-
 30 pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)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-yl)piperidin-4-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-(1H-pyrrolo[2,3-b]pyridin-5-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-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-methoxyethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3S)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3R)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-(2-naphthylsulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-methoxyethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-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-({3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3,3,3-trifluoropropyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Cis-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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- Trans-4-(4-([4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl)piperazin-1-yl)-N-([4-([4-(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([4-(4-methoxycyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-([4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl)piperazin-1-yl)-N-([5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-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-pyrrolo[2,3-b]pyridin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Cis-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([4-(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-([4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl)piperazin-1-yl)-N-([5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-([4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-([4-([4-(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl]sulfonyl)benzamide;
- 4-(4-([4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-([4-([4-(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)sulfonyl]phenyl)sulfonyl)benzamide;

- Trans-4-(4-([4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl)piperazin-1-yl)-N-([4-([4-morpholin-4-ylcyclohexyl]amino)-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-([4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl)piperazin-1-yl)-N-([4-([1-methylpiperidin-4-yl]amino)-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5-(4-([4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino)sulfonyl)-2-(tetrahydro-2H-pyran-4-ylmethoxy)nicotinamide;
- 10 N-([5-bromo-6-([1-methylpiperidin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([1-methylpiperidin-4-yl]methoxy)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([5-cyano-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-([5-bromo-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 N-([3-chloro-5-cyano-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-([4-([1-acetyl]piperidin-4-yl)amino]-3-nitrophenyl)sulfonyl)-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-morpholin-4-yl)propyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-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-pyrrolo[2,3-b]pyridin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 N-[(3-chloro-4-{[2-(2-methoxyethoxy)ethyl]sulfonyl}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-{[2-(2-methoxyethoxy)ethyl]sulfonyl}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-yl)cyclohexyl]oxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-({5-bromo-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 Cis-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-yl)cyclohexyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-N-([4-({4-[bis(cyclopropylmethyl)amino]cyclohexyl}amino)-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(morpholin-3-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-
 5 N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylbut-2-ynyl)oxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-oxo-3,4-dihydroquinazolin-6-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 Trans-4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Cis-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- tert-butyl 3-([4-([4-(4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino)sulfonyl)-2-nitrophenoxymethyl)morpholine-4-carboxylate;
- 4-(4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-(morpholin-3-ylmethoxy)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([1-(methylsulfonyl)piperidin-4-yl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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)amino]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-([4-chloro-3-nitrophenyl]sulfonyl)-4-(4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-([1-(2,2,2-trifluoroethyl)piperidin-4-yl]amino)phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([5-cyano-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]oxy]pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([5-isopropyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-([3-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- and therapeutically acceptable salts, and metabolites thereof.
- 4-(4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yl oxy)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-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{ [2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
 5 { [1-(2,2-difluoroethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
 b]pyridin-5-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-pyrrolo[2,3-b]pyridin-
 5-yloxy)benzamide;
- 10 4-(4-{ [2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
 { [(1-morpholin-4-yl)cyclohexyl]methyl}amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- Trans-4-(4-{ [2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 [(4-{ [4-(dicyclopropylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
 15 b]pyridin-5-yloxy)benzamide;
- 4-(4-{ [2-(4-chlorophenyl)-6,6-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-
 nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- N-({5-bromo-6-[(4-ethylmorpholin-3-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{ [2-(4-
 20 chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- 4-(4-{ [2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
 [(4-ethylmorpholin-3-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-
 yloxy)benzamide;
- 25 4-(4-{ [2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-
 nitro-4-[(4-tetrahydro-2H-pyran-4-ylmorpholin-3-yl)methoxy]phenyl}sulfonyl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{ [2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-
 nitro-4-{ [(3S)-1-tetrahydro-2H-pyran-4-ylpiperidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-
 30 pyrrolo[2,3-b]pyridin-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-ylmethyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)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-pyrrolo[2,3-b]pyridin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-morpholin-4-ylcyclohexyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1S,3R)-3-morpholin-4-ylcyclopentyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1R,3S)-3-morpholin-4-ylcyclopentyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(morpholin-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-[cis-3-fluorotetrahydro-2H-pyran-4-yl]piperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)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-ylazetidin-3-yl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydrofuran-3-ylazetidin-3-yl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-({[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl}amino)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(4-((trans-4-hydroxycyclohexyl)methoxy)-3-nitrophenylsulfonyl)benzamide;
- 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(4-((cis-4-methoxycyclohexyl)methoxy)-3-nitrophenylsulfonyl)benzamide;
- Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(cyclopropylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(tetrahydro-2H-pyran-4-ylamino)cyclohexyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-N-({5-bromo-6-[(4-morpholin-4-ylcyclohexyl)oxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- tert-butyl 4-([4-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino)sulfonyl]-2-nitrophenoxy)methyl)-4-fluoropiperidine-1-carboxylate;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(4-tetrahydro-2H-pyran-4-ylpiperazin-1-yl)cyclohexyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
 ((1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl)methoxy)-3-nitrophenyl]sulfonyl}-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-
 5 nitro-4-{[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
 {[(3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-
 nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-
 nitro-4-{[(3S)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
 {[(3S)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-
 15 nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
 {[(4-methylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
 20 {[(4-(2-methoxyethyl)morpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(4-{[(4-acetylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-
 chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
 {[trans-4-(fluoromethyl)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-
 (1H-pyrrolo[2,3-b]pyridin-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)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-
 30 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-
 nitro-4-[(1-oxetan-3-ylpiperidin-4-yl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-
 yloxy)benzamide;

- 4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-({4-[(1-cyclobutylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-[(4-
5 {{1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)piperidin-4-yl}amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-[(4-
{{(3S)-1-cyclopropylpyrrolidin-3-yl}amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydrofuran-3-yl)piperidin-4-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-[(4-
{{(3R)-1-cyclopropylpyrrolidin-3-yl}amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
15 b]pyridin-5-yloxy)benzamide;
- 4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-({3-nitro-4-({[(3S)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl}amino)phenyl}sulfonyl)-
2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-({4-
20 [(3-hydroxy-2,2-dimethylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-({4-
({[1-(methylsulfonyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl}sulfonyl)-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 N-[(4-{{1-(1-acetylpiperidin-3-yl)methyl}amino}-3-nitrophenyl)sulfonyl]-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-[(4-
{{(3R)-1-(methylsulfonyl)pyrrolidin-3-yl}amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
30 b]pyridin-5-yloxy)benzamide;
- 4-(4-{{2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
 ({1-[2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yl)oxy)benzamide;
- 5 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
 ({[1-(methylsulfonyl)pyrrolidin-3-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yl)oxy)benzamide;
 N-[(4-{[(1-acetylpyrrolidin-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-
 chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-
 10 b]pyridin-5-yl)oxy)benzamide;
 N-[(4-{[(3R)-1-acetylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-
 chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yl)oxy)benzamide;
- 15 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
 [(3-methoxy-2,2-dimethylpropyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yl)oxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
 ({[(1R,3R)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yl)oxy)benzamide;
- 20 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
 ({[(1S,3S)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yl)oxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
 ({[(1S,3R)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yl)oxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
 ({[(1R,3S)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yl)oxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-
 30 nitro-4-{[(3S)-2-oxopiperidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-
 yl)oxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
 ({[1-[2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-
 (1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(1-oxetan-3-ylazetidin-3-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(1-oxetan-3-ylpiperidin-4-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-cyclopropylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-({[4-(2-fluoroethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 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]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-[(4-fluoro-1-oxetan-3-ylpiperidin-4-yl)methoxy]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(2S)-4,4-difluoro-1-oxetan-3-ylpyrrolidin-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(4-tetrahydro-2H-pyran-4-yl)morpholin-3-yl]methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyclobutyl)morpholin-3-yl]methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(4-tetrahydrofuran-3-yl)morpholin-3-yl]methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-[(1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl]methyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropyl-4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxybenzyl)amino]-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[3-(trifluoromethoxy)benzyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-methoxybenzyl)amino]-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(difluoromethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-(1,4-dioxaspiro[4.5]dec-8-ylamino)-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-N-[(4-{[4-(acetyl)amino]cyclohexyl}amino)-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 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]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-1-oxetan-3-yl]pyrrolidin-3-yl}methoxy)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-hydroxybenzyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-hydroxybenzyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-{[3-(difluoromethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[cis-3-morpholin-4-ylcyclopentyl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({4-[(methylsulfonyl)amino]cyclohexyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-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-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-oxetan-3-ylpiperidin-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-tetrahydrofuran-3-ylpiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-fluoro-1-(methylsulfonyl)piperidin-4-yl]methoxy)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{3-nitro-4-({[(3R)-1-oxetan-3-ylpyrrolidin-3-yl]methyl}amino)phenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 5 ((4-[(4-hydroxycyclohexyl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-({4-[3-(dimethylamino)propoxy]benzyl}amino)-3-nitrophenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(2-morpholin-4-ylethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-({[(E)-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-({[(Z)-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-({4-[(1S,4S)-bicyclo[2.2.1]hept-5-en-2-ylmethoxy]-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-[(1-methyl-5-oxopyrrolidin-3-yl)amino]-3-nitrophenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{{[(1R,4R,5R,6S)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy}-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{{[(1R,4R,5S,6R)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy}-3-nitrophenyl}sulfonyl]-2-
 30 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3-oxocyclohexyl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohexa-1,3-dien-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{3-nitro-4-(((3S)-1-oxetan-3-ylpyrrolidin-3-yl)methyl)amino}phenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Cis-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[[4-(2-(2-methoxyethoxy)ethyl)morpholin-2-yl]methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[[4-(N,N-dimethylglycyl)morpholin-2-yl]methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- (2-[[4-([4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]-2-nitrophenyl)amino]methyl)morpholin-4-yl)acetic acid;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{3-nitro-4-({[4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)phenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-{{[(4-cyclopropyl)morpholin-2-yl]methyl}amino}-3-nitrophenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{5-(methylsulfonyl)-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 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)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-[(4-methyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 ethyl 4-(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)piperazine-1-carboxylate;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-[4-(morpholin-4-yl)piperidin-1-yl]-3-nitrophenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{3-nitro-4-{{[(3R)-1-(oxetan-3-yl)pyrrolidin-3-yl]amino}phenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-{{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-[(1-isopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 N-{{4-[(1-tert-butylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-
 ([1-(2-methoxyethyl)piperidin-3-yl]methyl)amino)-3-nitrophenyl)sulfonyl]-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-
 ([1-(cyanomethyl)piperidin-3-yl]methyl)amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-
 [(4-fluoro-1-methylpiperidin-4-yl)methoxy]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-
 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 N-[(5-chloro-6-[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino)pyridin-3-
 yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-
 yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- tert-butyl 4-[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-
 yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]-2-
 15 nitrophenyl)amino]piperazine-1-carboxylate;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-
 (pentafluoro- λ^6 -sulfanyl)-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl]-2-
 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-
 [(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
 20 b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-
 {[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy}-3-nitrophenyl)sulfonyl]-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-
 nitro-4-{[4-(oxetan-3-yl)piperazin-1-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-
 5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-
 nitro-4-{[4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl]amino}phenyl)sulfonyl]-2-(1H-
 30 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-
 nitro-4-[(3R)-tetrahydrofuran-3-ylamino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-
 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-({4-[(1-tert-butylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-(oxetan-3-yl)morpholin-2-yl)methyl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 b]pyridin-5-yloxy)benzamide;
- N-[(5-chloro-6-{[(2S)-4-(cyanomethyl)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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(5-chloro-6-{[(2R)-4-(cyanomethyl)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-({5-chloro-6-[3-hydroxy-2-(hydroxymethyl)-2-methylpropoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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]pyridin-3-yl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-((4-(1,3-difluoropropan-2-yl)morpholin-2-yl)methyl)amino]-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 N-[(5-chloro-6-{[1-(cyanomethyl)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 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}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 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]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[1-(oxetan-3-yl)azetidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 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}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 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}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(5-chloro-6-{[1-(N,N-dimethylglycyl)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 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]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-methoxypiperidin-1-yl}-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-methoxypiperidin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-({5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-({5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-({5-chloro-6-[(4-fluoro-1-methylpiperidin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(5-chloro-6-{[1-(N,N-dimethylglycyl)-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-fluoropiperidin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-fluoropiperidin-1-yl}-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl}sulfonyl)benzamide;
- 5 N-[(5-chloro-6-{[(3R)-1-(1,3-difluoropropan-2-yl)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[2-(tetrahydrofuran-3-yloxy)ethoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[2-(tetrahydro-2H-pyran-4-yl)ethoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-(3-furylmethoxy)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 N-[(5-chloro-6-{[(3R)-1-(1,3-difluoropropan-2-yl)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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(5-chloro-6-{[1-(1,3-difluoropropan-2-yl)-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 N-({3-chloro-4-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-ylmethoxy)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 N-[(5-chloro-6-{[1-(2,2-difluoroethyl)-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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[6-{[1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl]methoxy}-5-(trifluoromethyl)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-chloro-6-[2-(tetrahydrofuran-2-yl)ethoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-methylpiperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-{[3-(cyclopropylamino)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 N-([5-chloro-6-(2-methoxyethoxy)pyridin-3-yl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 N-[(3-chloro-4-{[1-(methoxyacetyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- N-[(3-chloro-4-{{1-(N,N-dimethylglycyl)piperidin-4-yl}methoxy}phenyl)sulfonyl]-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohexyl}methyl}piperidin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-{{6-[(tetrahydro-2H-pyran-4-ylmethoxy)-5-(trifluoromethyl)pyridin-3-yl}sulfonyl}benzamide;
- 10 N-({5-chloro-6-[(trans-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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-({6-[(trans-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-({6-[(cis-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 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}piperidin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 N-[(3-chloro-4-{{trans-4-(morpholin-4-yl)cyclohexyl}methoxy}phenyl)sulfonyl]-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-{{4-({3-[cyclopropyl(1,3-thiazol-5-ylmethyl)amino]propyl}amino)-3-nitrophenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 N-({3-chloro-4-[(trans-4-hydroxycyclohexyl)methoxy]phenyl}sulfonyl)-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-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-(trifluoromethyl)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({3-[cyclopropyl(2,2,2-trifluoroethyl)amino]propyl)amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 N-[(3-chloro-4-{[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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3,5-difluoro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({3-[cyclopropyl(oxetan-3-yl)amino]propyl)amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(3-chloro-4-{[1-(1-methyl-L-prolyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3,4-difluoro-5-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-N-({3-chloro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- methyl 2-{{(4-{{(4-{{(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl}sulfamoyl)-2-nitrophenyl)amino)methyl}morpholine-4-carboxylate;
- 2-{{(4-{{(4-{{(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl}sulfamoyl)-2-nitrophenyl)amino)methyl}-N-ethyl-N-methylmorpholine-4-carboxamide;
- 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}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{{(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-{{(4-((3-(cyclobutyl(cyclopropyl)amino)propyl)amino)-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{{(2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-{{(3-nitro-4-((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{{(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-{{(3-chloro-4-(tetrahydrofuran-3-ylmethoxy)phenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{{(2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-{{(4-(((trans-4-hydroxycyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-((3-chloro-4-{{(4-fluorotetrahydro-2H-pyran-4-yl)methoxy}phenyl)sulfonyl)-4-(4-{{(9-(4-chlorophenyl)-3-(oxetan-3-yl)-3-azaspiro[5.5]undec-8-en-8-yl)methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{{(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-{{(4-(((2R)-4-cyclopropylmorpholin-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-({5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl)methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-chloro-6-({4-[cyclopropyl(oxetan-3-yl)amino]cyclohexyl}methoxy)pyridin-3-

5 yl)sulfonyl)-4-(4-({2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-({5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl)methyl}piperazin-1-yl)-N-[(4-({4-cyclopropylmorpholin-2-yl)methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

10 N-({3-chloro-4-[(4-cyclopropylmorpholin-2-yl)methoxy]phenyl)sulfonyl)-4-(4-({2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(3-chloro-4-[(4-cyclopropylmorpholin-2-yl)methyl]amino}phenyl)sulfonyl]-4-(4-({2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-

15 b]pyridin-5-yloxy)benzamide;

2-({[(2-chloro-4-({4-(4-({2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-

yloxy)benzoyl]sulfamoyl}phenyl)amino)methyl}-N-ethyl-N-methylmorpholine-4-carboxamide;

20 (2S)-2-({[(3-chloro-5-({4-(4-({2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}pyridin-2-yl)oxy)methyl}-N-ethyl-N-methylmorpholine-4-carboxamide;

N-[(5-chloro-6-[(4-cyclopropylmorpholin-2-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-

25 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

2-({[(3-chloro-5-({4-(4-({2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-

yl)methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}pyridin-2-yl)amino)methyl}-N-ethyl-N-methylmorpholine-4-carboxamide;

4-(4-({2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-[(4-

30 {[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
 5 ({4-[(2-cyanoethyl)(cyclopropyl)amino]cyclohexyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 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-yl)methoxy}pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(5-chloro-6-[(1R,2S,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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(5-chloro-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[[4-(3,3-difluoropyrrolidin-1-yl)cyclohexyl]amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({4-[(2,2-difluorocyclopropyl)amino]cyclohexyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-(2-oxaspiro[3.5]non-7-ylmethoxy)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-5,5-bis(fluoromethyl)cyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-cyclopropylmorpholin-2-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-ethyl-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(cis-4-ethyl-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 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}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 N-({3-chloro-4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({4-[(2-cyanoethyl)(cyclopropyl)amino]-1-fluorocyclohexyl}methoxy)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-nitro-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(2-oxaspiro[3.5]non-7-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[(4-cyano-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({[3-(tetrahydro-2H-pyran-4-ylmethyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-6-yl]sulfonyl}benzamide;
- 20 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([6-({[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-5-nitropyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-(4-([4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl)-2-nitrophenyl)morpholine-4-
- 30 carboxamide;
- 4-(4-([4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[4-(methoxymethyl)cyclohexyl]methyl}amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

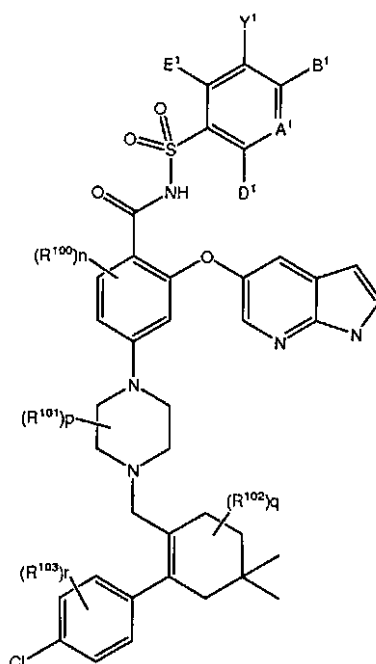
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-chloro-6-{[1-(1,3-thiazol-2-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(6-
5 {[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-5-nitropyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-
N-[(4-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-
(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

10 4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-
N-[(3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide; and therapeutically acceptable salts, and metabolites thereof.

In another aspect, the present invention provides compounds of Formula (III)



(III);

and therapeutically acceptable salts, and metabolites thereof,

wherein A^1 , B^1 , D^1 , E^1 , and Y^1 are as described herein for Formula (I); R^{100} is as described for substituents on R^{26} ; n is 0, 1, 2, or 3; R^{101} is as described for substituents on R^{30} ; p is 0, 1, 2, 3, 4, 5, or 6; R^{102} is as described for substituents on R^{40} ; q is 0, 1, 2, 3, 4, 5, or 6; R^{103} is as
20 described for substituents on R^{58} ; and r is 0, 1, 2, 3, or 4.

In one embodiment of Formula (III), n , p , r , and q are each 0.

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, F, Cl, Br, or I. 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 , NHR^1 , $NHC(O)R^1$, F, Cl, Br, or I.
 5 In another embodiment of Formula (III), A^1 is $C(A^2)$; A^2 is H; and B^1 is NHR^1 . In another embodiment of Formula (III), A^1 is $C(A^2)$; A^2 is H; and B^1 is OR^1 . In another embodiment of Formula (III), A^1 is $C(A^2)$; A^2 is H; and B^1 is Cl. In another embodiment of Formula (III), A^1 is $C(A^2)$; A^2 is H; and B^1 is R^1 . In another embodiment of Formula (III), A^1 is N; and B^1 is NHR^1 . In another embodiment of Formula (III), A^1 is N; and B^1 is OR^1 . In another
 10 embodiment of Formula (III), A^1 is N; and B^1 is Cl. In another embodiment of Formula (III), A^1 is N; and B^1 is R^1 .

In one embodiment of Formula (III), D^1 is H or Cl. In another embodiment of Formula (III), A^1 is $C(A^2)$; A^2 is H; B^1 is NHR^1 ; and D^1 is H. In another embodiment of Formula (III), A^1 is $C(A^2)$; A^2 is H; B^1 is NHR^1 ; and D^1 is Cl. In another embodiment of
 15 Formula (III), A^1 is $C(A^2)$; A^2 is H; B^1 is OR^1 ; and D^1 is H. In another embodiment of Formula (III), A^1 is $C(A^2)$; A^2 is H; B^1 is Cl; and D^1 is H. In another embodiment of Formula (III), A^1 is $C(A^2)$; A^2 is H; B^1 is R^1 ; and D^1 is H. In another embodiment of Formula (III), A^1 is N; B^1 is NHR^1 ; and D^1 is H. In another embodiment of Formula (III), A^1 is N; B^1 is NHR^1 ; and D^1 is Cl. In another embodiment of Formula (III), A^1 is N; B^1 is OR^1 ; and D^1 is H. In
 20 another embodiment of Formula (III), A^1 is N; B^1 is Cl; and D^1 is H. In another embodiment of Formula (III), A^1 is N; B^1 is R^1 ; and D^1 is H.

In one embodiment of Formula (III), E^1 is H. In another embodiment of Formula (III), A^1 is $C(A^2)$; A^2 is H; B^1 is NHR^1 ; D^1 is H; and E^1 is H. In another embodiment of Formula (III), A^1 is $C(A^2)$; A^2 is H; B^1 is NHR^1 ; E^1 is H; and D^1 is Cl. In another
 25 embodiment of Formula (III), A^1 is $C(A^2)$; A^2 is H; B^1 is OR^1 ; D^1 is H; and E^1 is H. In another embodiment of Formula (III), A^1 is $C(A^2)$; A^2 is H; B^1 is Cl; D^1 is H; and E^1 is H. In another embodiment of Formula (III), A^1 is $C(A^2)$; A^2 is H; B^1 is R^1 ; D^1 is H; and E^1 is H. In another embodiment of Formula (III), A^1 is N; B^1 is NHR^1 ; D^1 is H; and E^1 is H. In another embodiment of Formula (III), A^1 is N; B^1 is NHR^1 ; E^1 is H; and D^1 is Cl. In another
 30 embodiment of Formula (III), A^1 is N; B^1 is OR^1 ; D^1 is H; and E^1 is H. In another embodiment of Formula (III), A^1 is N; B^1 is Cl; D^1 is H; and E^1 is H. In another embodiment of Formula (III), A^1 is N; B^1 is R^1 ; D^1 is H; and E^1 is H.

In one embodiment of Formula (III), Y^1 is H, CN, NO_2 , F, Cl, Br, I, CF_3 , R^{17} , OR^{17} , SR^{17} , SO_2R^{17} , or $C(O)NH_2$. In another embodiment of Formula (III), Y^1 is H. In another

embodiment of Formula (III), Y^1 is CN. In another embodiment of Formula (III), Y^1 is F, Cl, Br, or I. In another embodiment of Formula (III), Y^1 is CF_3 . In another embodiment of Formula (III), Y^1 is SR^{17} . In another embodiment of Formula (III), Y^1 is OR^{17} . In another embodiment of Formula (III), Y^1 is NO_2 . In another embodiment of Formula (III), Y^1 is SO_2R^{17} ; wherein R^{17} is as defined herein. In another embodiment of Formula (III), Y^1 is SO_2R^{17} ; wherein R^{17} is alkyl. In another embodiment of Formula (III), Y^1 is R^{17} ; wherein R^{17} is alkynyl. In another embodiment of Formula (III), A^1 is $C(A^2)$; A^2 is H; B^1 is NHR^1 ; D^1 is H; E^1 is H; and Y^1 is NO_2 or SO_2R^{17} ; wherein R^{17} is alkyl or alkynyl. In another embodiment of Formula (III), A^1 is $C(A^2)$; A^2 is H; B^1 is NHR^1 ; D^1 is H; E^1 is H; and Y^1 is NO_2 . In another embodiment of Formula (III), A^1 is $C(A^2)$; A^2 is H; B^1 is NHR^1 ; D^1 is H; E^1 is H; and Y^1 is SO_2R^{17} ; wherein R^{17} is alkyl substituted with three F. In another embodiment of Formula (III), A^1 is N; B^1 is NHR^1 ; D^1 is H; E^1 is H; and Y^1 is NO_2 or SO_2R^{17} ; wherein R^{17} is alkyl or alkynyl. In another embodiment of Formula (III), A^1 is N; B^1 is NHR^1 ; D^1 is H; E^1 is H; and Y^1 is NO_2 . In another embodiment of Formula (III), A^1 is N; B^1 is NHR^1 ; D^1 is H; E^1 is H; and Y^1 is SO_2R^{17} ; wherein R^{17} is alkyl substituted with three F.

In one embodiment of Formula (III), Y^1 and B^1 , together with the atoms to which they are attached, are benzene. In another embodiment of Formula (III), Y^1 and B^1 , together with the atoms to which they are attached, are heteroarene. In another embodiment of Formula (III), A^1 is $C(A^2)$; A^2 , G^1 , E^1 , and D^1 are independently selected H; and Y^1 and B^1 , together with the atoms to which they are attached, are benzene. In another embodiment of Formula (III), A^1 is $C(A^2)$; A^2 , G^1 , E^1 , and D^1 are independently selected H; and Y^1 and B^1 , together with the atoms to which they are attached, are heteroarene.

In one embodiment of Formula (III), R^1 is R^4 or R^5 . In one embodiment of Formula (III), R^1 is R^4 . In one embodiment of Formula (III), R^1 is R^5 . In one embodiment of Formula (III), R^1 is R^4 ; and R^4 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl. In one embodiment of Formula (III), R^1 is R^4 ; and R^4 is cycloalkyl or heterocycloalkyl. In one embodiment of Formula (III), R^1 is R^4 ; and R^4 is cycloalkyl. In one embodiment of Formula (III), R^1 is R^4 ; and R^4 is heterocycloalkyl.

In one embodiment of Formula (III), R^1 is R^4 ; and R^4 is cycloalkyl; wherein R^4 is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is substituted as defined herein. In another embodiment of Formula (III), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is substituted with R^{57} or $N(R^{57})_2$. In another embodiment of Formula (III), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring

is substituted with R^{57} ; and R^{57} is R^{60} . In another embodiment of Formula (III), R^1 is R^4 ; R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R^{57} ; R^{57} is R^{60} ; and R^{60} is heterocycloalkyl. In another embodiment of Formula (III), R^1 is R^4 ; R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and
 5 wherein the cyclohexyl ring is substituted with R^{57} ; R^{57} is R^{60} ; R^{60} is heterocycloalkyl; wherein the heterocycloalkyl ring is morpholinyl. In another embodiment of Formula (III), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is substituted with $N(R^{57})_2$. In another embodiment of Formula (III), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with $N(R^{57})_2$. In another
 10 embodiment of Formula (III), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with $N(R^{57})_2$; R^{57} is R^{61} ; and R^{61} is alkyl which is unsubstituted or substituted with R^{62} . In another embodiment of Formula (III), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R^{57} ; R^{57} is R^{61} ; and R^{61} is alkyl which is unsubstituted or
 15 substituted with R^{62} ; R^{62} is R^{65} ; and R^{65} is cycloalkyl. In another embodiment of Formula (III), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R^{57} ; R^{57} is R^{61} ; and R^{61} is alkyl which is substituted with R^{62} ; R^{62} is R^{65} ; and R^{65} is cyclopropyl.

In one embodiment of Formula (III), R^1 is R^4 ; and R^4 is heterocycloalkyl; wherein R^4
 20 is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R^1 is R^4 ; and R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted as defined herein. In another embodiment of Formula (III), R^1 is R^4 ; and R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted with R^{57} . In another embodiment of Formula (III), R^1 is R^4 ; and R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is piperdinyl or
 25 piperizinyl; and wherein the heterocycloalkyl ring is substituted with R^{57} ; and R^{57} is R^{60} or R^{61} . In another embodiment of Formula (III), R^1 is R^4 ; R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is piperdinyl or piperizinyl; and wherein the piperdinyl or piperizinyl ring is substituted with R^{57} ; R^{57} is R^{60} or R^{61} ; R^{60} is heterocycloalkyl; and R^{61} is alkyl. In another embodiment of Formula (III), R^1 is R^4 ; R^4 is heterocycloalkyl; wherein the
 30 heterocycloalkyl ring is piperdinyl or piperizinyl; and wherein the piperdinyl or piperizinyl ring is substituted with R^{57} ; R^{57} is R^{60} ; R^{60} is heterocycloalkyl; wherein the heterocycloalkyl is tetrahydropyranyl. In another embodiment of Formula (III), R^1 is R^4 ; R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is piperdinyl or piperizinyl; and wherein the piperdinyl or piperizinyl ring is substituted with R^{57} ; R^{57} is R^{61} ; R^{61} is alkyl; and the alkyl

is methyl. In another embodiment of Formula (III), R^1 is R^4 ; R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is piperdinyl or piperizinyl; and wherein the piperdinyl or piperizinyl ring is substituted with $C(O)OR^{57}$; R^{57} is R^{61} ; R^{61} is alkyl; and the alkyl is methyl.

In one embodiment of Formula (III), R^1 is R^5 ; and R^5 is alkyl which is unsubstituted or substituted. In one embodiment of Formula (III), R^1 is R^5 ; and R^5 is alkyl which is unsubstituted or substituted with R^7 , OR^7 , OH , CN , or F . In another embodiment of Formula (III), R^1 is R^5 ; and R^5 is alkyl which is substituted with R^7 , OR^7 , NHR^7 , or $N(R^7)_2$.

In one embodiment of Formula (III), R^7 is R^8 , R^9 , R^{10} or R^{11} which are unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R^7 is R^8 which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R^7 is R^9 which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R^7 is R^{10} which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R^7 is R^{11} which is unsubstituted or substituted as defined herein.

In one embodiment of Formula (III), R^8 is phenyl which is unsubstituted or substituted as defined herein.

In one embodiment of Formula (III), R^9 is heteroaryl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R^9 is furanyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R^9 is furanyl; which is unsubstituted.

In one embodiment of Formula (III), R^{10} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, heterocycloalkyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R^{10} is heterocycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R^{10} is tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, dioxanyl, oxetanyl, piperdinyl, or pyrrolidinyl, which are unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R^{10} is tetrahydropyranyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R^{10} is morpholinyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R^{10} is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R^{10} is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R^{10} is cyclohexyl, cyclopropyl, cyclobutyl, or bicyclo[2.2.1]heptanyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R^{10} is heterocycloalkyl which is fused with R^{10A} ; and R^{10A} is

heteroarene. In another embodiment of Formula (III), R¹⁰ is 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl.

In one embodiment of Formula (III), R¹¹ is alkyl, alkenyl or alkynyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R¹¹ is alkyl. In another embodiment of Formula (III), R¹¹ is methyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R¹¹ is alkyl; which is substituted as defined herein. In another embodiment of Formula (III), R¹¹ is alkyl; which is substituted with R¹², OR¹², or CF₃. In another embodiment of Formula (III), R¹¹ is alkyl; which is substituted with OR¹²; R¹² is R¹⁶; and R¹⁶ is alkyl. In another embodiment of Formula (III), R¹¹ is alkyl; which is substituted with CF₃. In another embodiment of Formula (III), R¹¹ is alkyl; which is substituted with R¹²; R¹² is R¹⁴; and R¹⁴ is heteroaryl.

In one embodiment of Formula (III),

n, p, r, and q are each 0;

A¹ is N or C(A²);

A² is H, F, Br, I, or Cl;

B¹ is R¹, OR¹, NHR¹, NHC(O)R¹, F, Br, I or Cl;

D¹ is H, F, Br, I, or Cl;

E¹ is H; and

Y¹ is H, CN, NO₂, F, Cl, Br, I, CF₃, R¹⁷, OR¹⁷, SR¹⁷, SO₂R¹⁷, or C(O)NH₂; or

Y¹ and B¹, together with the atoms to which they are attached, are benzene,

heteroarene, or heterocycloalkene; and

A², D¹, and E¹ are independently selected H;

R¹ is R⁴ or R⁵;

R⁴ is cycloalkyl, or heterocycloalkyl;

R⁵ is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R⁷, OR⁷, NHR⁷, N(R⁷)₂, CN, OH, F, Cl, Br or I;

R⁷ is R⁸, R⁹, R¹⁰, or R¹¹;

R⁸ is phenyl;

R⁹ is heteroaryl;

R¹⁰ is cycloalkyl, cycloalkenyl, or heterocycloalkyl; each of which is unfused or fused with R^{10A}, R^{10A} is heteroarene;

R¹¹ is alkyl each of which is unsubstituted or substituted with one or two or three of independently selected R¹², OR¹² or CF₃;

R¹² is R¹⁴ or R¹⁶;

R^{14} is heteroaryl;

R^{16} is alkyl;

R^{17} is R^{21} ;

R^{21} is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two
5 or three of independently selected R^{22} , F, Cl, Br or I;

R^{22} is R^{25} ;

R^{25} is heterocycloalkyl;

wherein the cyclic moieties represented by Y^1 and B^1 together, R^4 , R^8 , R^{10} , and R^{25} ,
are independently unsubstituted, further unsubstituted, substituted or further substituted with
10 one or two or three or four or five of independently selected R^{57A} , R^{57} , OR^{57} , SO_2R^{57} ,
 $C(O)R^{57}$, $CO(O)R^{57}$, $C(O)N(R^{57})_2$, NH_2 , NHR^{57} , $N(R^{57})_2$, $NHC(O)R^{57}$, $NHS(O)_2R^{57}$, OH, CN,
(O), F, Cl, Br or I;

R^{57A} is spiroalkyl, or spiroheteroalkyl;

R^{57} is R^{58} , R^{60} or R^{61} ;

15 R^{58} is phenyl;

R^{60} is cycloalkyl, or heterocycloalkyl;

R^{61} is alkyl which is unsubstituted or substituted with one or two or three of
independently selected R^{62} , OR^{62} , $N(R^{62})_2$, $C(O)OH$, CN, F, Cl, Br or I;

R^{62} is R^{65} , or R^{66} ;

20 R^{65} is cycloalkyl, or heterocycloalkyl;

R^{66} is alkyl which is unsubstituted or substituted with OR^{67} ;

R^{67} is alkyl;

wherein the cyclic moieties represented by R^{57A} , R^{58} , and R^{60} are unsubstituted or
substituted with one or two or three or four of independently selected R^{68} , F, Cl, Br or I;

25 R^{68} is R^{71} or R^{72} ;

R^{71} is heterocycloalkyl; and

R^{72} is alkyl, which is unsubstituted or substituted with one or two F.

Still another embodiment pertains to compounds having Formula (III), which are
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-
30 nitro-4-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}phenyl)sulfonyl)-2-(1H-
pyrrolo[2,3-b]pyridin-5-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-(1H-pyrrolo[2,3-b]pyridin-5-
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-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-methoxyethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(3S)-tetrahydro-2H-pyran-3-ylmethyl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(3R)-tetrahydro-2H-pyran-3-ylmethyl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-(2-naphthylsulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-methoxyethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-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-({3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3,3,3-trifluoropropyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Cis-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]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 b]pyridin-5-yloxy)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-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]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 b]pyridin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 b]pyridin-5-yloxy)benzamide;
- Cis-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)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino)sulfonyl)-2-(tetrahydro-2H-pyran-4-ylmethoxy)nicotinamide;
- N-({5-bromo-6-[(1-methylpiperidin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 N-({5-bromo-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-pyrrolo[2,3-b]pyridin-5-yloxy)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 N-({3-chloro-5-cyano-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 N-({4-[(1-acetyl)pyridin-4-yl]amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 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-(1H-pyrrolo[2,3-b]pyridin-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-pyrrolo[2,3-b]pyridin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(3-chloro-4-{[2-(2-methoxyethoxy)ethyl]sulfonyl}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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

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

N-({5-bromo-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-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-pyrrolo[2,3-b]pyridin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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

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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylbut-2-ynyl)oxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-oxo-3,4-dihydroquinazolin-6-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- tert-butyl 3-{{4-{{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino}sulfonyl}-2-nitrophenoxy)methyl}morpholine-4-carboxylate;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-(morpholin-3-ylmethoxy)-3-nitrophenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{{1-(methylsulfonyl)piperidin-4-yl}amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 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}amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(4-chloro-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{{1-(2,2,2-trifluoroethyl)piperidin-4-yl}amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-((5-cyano-6-{{1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl}oxy}pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{5-isopropyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-((3-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-((1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl)amino)-3-nitrophenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yl

oxy)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

5 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(2,2-difluoroethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-10 5-yloxy)benzamide;

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

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-15 [(4-{[4-(dicyclopropylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-bromo-6-[(4-ethylmorpholin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

20 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-ethylmorpholin-3-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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

25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-1-tetrahydro-2H-pyran-4-yl]piperidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-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-ylmethyl)amino]pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

30 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-pyrrolo[2,3-b]pyridin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-
 5 ((5-cyano-6-[(4-morpholin-4-ylcyclohexyl)amino]pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(4-[(1S,3R)-3-morpholin-4-ylcyclopentyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(4-[(1R,3S)-3-morpholin-4-ylcyclopentyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-((4-[(morpholin-2-ylmethyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-((4-[(1-cis-3-fluorotetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 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-ylazetidin-3-yl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-((3-nitro-4-[(1-tetrahydrofuran-3-ylazetidin-3-yl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-((3-nitro-4-[(1-(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl)methyl]amino)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(4-(((trans-4-hydroxycyclohexyl)methoxy)-3-nitrophenylsulfonyl)benzamide;
- 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(4-(((cis-4-methoxycyclohexyl)methoxy)-3-nitrophenylsulfonyl)benzamide;
- 5 Cis-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([4-(cyclopropylamino)cyclohexyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 Trans-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([(3-nitro-4-([4-(tetrahydro-2H-pyran-4-ylamino)cyclohexyl]amino)phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-N-([5-bromo-6-[(4-morpholin-4-yl)cyclohexyl]oxy]pyridin-3-yl)sulfonyl)-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 Trans-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([4-(4-methoxycyclohexyl)methoxy]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- tert-butyl 4-([4-([4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino)sulfonyl)-2-nitrophenoxymethyl]-4-fluoropiperidine-1-carboxylate;
- 20 4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([4-(4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 Trans-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([(3-nitro-4-([4-(4-tetrahydro-2H-pyran-4-yl)piperazin-1-yl)cyclohexyl]amino)phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl]methoxy)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([(3-nitro-4-([(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]amino)phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-(2-methoxyethyl)morpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 N-[(4-{[(4-acetylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-(fluoromethyl)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(1-oxetan-3-ylpiperidin-4-yl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-cyclobutylpiperidin-4-yl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-cyclopropylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydrofuran-3-yl)piperidin-4-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-cyclopropylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-(3S)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-hydroxy-2,2-dimethylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-(methylsulfonyl)piperidin-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(4-{[(1-acetylpiperidin-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-[2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-(methylsulfonyl)pyrrolidin-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(4-{[(1-acetylpyrrolidin-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(4-[[[(3R)-1-acetylpyrrolidin-3-yl]amino]-3-nitrophenyl]sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-([4-[(3-methoxy-2,2-dimethylpropyl)amino]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-([4-([[(1R,3R)-3-hydroxycyclopentyl]methyl]amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

10 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-([4-([[(1S,3S)-3-hydroxycyclopentyl]methyl]amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-([4-([[(1S,3R)-3-hydroxycyclopentyl]methyl]amino)-3-nitrophenyl]sulfonyl]-2-(1H-

15 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-([4-([[(1R,3S)-3-hydroxycyclopentyl]methyl]amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

20 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(3-nitro-4-[[[(3S)-2-oxopiperidin-3-yl]amino]phenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-([4-[[[1-[2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl]methyl]amino]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

25 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(3-nitro-4-[[[(1-oxetan-3-ylazetidin-3-yl)methyl]amino]phenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(3-nitro-4-[[[(1-oxetan-3-ylpiperidin-4-yl)methyl]amino]phenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

30 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(4-[[[(1-cyclopropylpiperidin-4-yl)methyl]amino]-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-
 ({[4-(2-fluoroethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-
 5 ({[4-(2,2-difluoroethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-
 [(4-fluoro-1-oxetan-3-yl)piperidin-4-yl]methoxy]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-
 {[2S]-4,4-difluoro-1-oxetan-3-ylpyrrolidin-2-yl]methoxy}-3-nitrophenyl]sulfonyl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-
 nitro-4-{[(4-tetrahydro-2H-pyran-4-yl)morpholin-3-yl]methyl}amino]phenyl]sulfonyl)-2-(1H-
 15 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-
 {[4-(cyclobutyl)morpholin-3-yl]methyl}amino]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-
 20 nitro-4-{[(4-tetrahydrofuran-3-yl)morpholin-3-yl]methyl}amino]phenyl]sulfonyl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-
 [(1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl]methyl)amino]-3-nitrophenyl]sulfonyl)-
 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-
 [(1-cyclopropyl-4-fluoropiperidin-4-yl]methoxy]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-
 [(4-methoxybenzyl)amino]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-
 30 yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-
 nitro-4-{[3-(trifluoromethoxy)benzyl]amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-
 5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-methoxybenzyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
5 {4-(difluoromethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{4-(1,4-dioxaspiro[4.5]dec-8-ylamino)-3-nitrophenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 Trans-N-[(4-{[4-(acetylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
15 {[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
20 {[(3S)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
25 {[(3S)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
30 {[(3R)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-hydroxybenzyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-hydroxybenzyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(difluoromethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-
5 ([cis-3-morpholin-4-ylcyclopentyl]methyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
{[4-([4-(methylsulfonyl)amino]cyclohexyl)amino]-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-[(1-cyclopropylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-[(1-oxetan-3-ylpiperidin-4-yl)methoxy]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-
15 b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-[(4-fluoro-1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-
20 [(4-fluoro-1-tetrahydrofuran-3-ylpiperidin-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-{[4-fluoro-1-(methylsulfonyl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-([[(3R)-1-oxetan-3-ylpyrrolidin-3-yl]methyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
([4-[(4-hydroxycyclohexyl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-
30 5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-[3-(dimethylamino)propoxy]benzyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(2-morpholin-4-ylethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-
5 (([(*E*)-4-hydroxy-1-adamantyl]methyl)amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-
(([(*Z*)-4-hydroxy-1-adamantyl]methyl)amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 N-({4-[(1*S*,4*S*)-bicyclo[2.2.1]hept-5-en-2-ylmethoxy}-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
[(1-methyl-5-oxopyrrolidin-3-yl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-
15 b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
{[(1*R*,4*R*,5*R*,6*S*)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-
(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
20 {[(1*R*,4*R*,5*S*,6*R*)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-
(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-
nitro-4-[(3-oxocyclohexyl)methoxy]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-
yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-
({(3*R*)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-2-
(1H-pyrrolo[2,3-b]pyridin-5-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-
30 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[3-
nitro-4-({[(3*S*)-1-oxetan-3-ylpyrrolidin-3-yl]methyl)amino]phenyl)sulfonyl]-2-(1H-
pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Cis-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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

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

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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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

2-({4-([4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl)-2-nitrophenyl}amino)methyl)morpholin-4-yl)acetic acid;

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

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

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

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
[(4-methyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide;
- ethyl 4-(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-
5 yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)piperazine-1-
carboxylate;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[4-
(morpholin-4-yl)piperidin-1-yl]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-
yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-
nitro-4-{[(3R)-1-(oxetan-3-yl)pyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino}-3-
15 [(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
[(1-isopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-
yloxy)benzamide;
- N-({4-[(1-tert-butylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-
20 4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-
yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
([1-(2-methoxyethyl)piperidin-3-yl]methyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
([1-(cyanomethyl)piperidin-3-yl]methyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
[(4-fluoro-1-methylpiperidin-4-yl)methoxy]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-2-
30 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(5-chloro-6-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino}pyridin-3-
yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-
yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- tert-butyl 4-[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]piperazine-1-carboxylate;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-(pentafluoro- λ^6 -sulfanyl)-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(oxetan-3-yl)piperazin-1-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3R)-tetrahydrofuran-3-ylamino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-({4-[(1-tert-butylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-(oxetan-3-yl)morpholin-2-yl)methyl]amino)-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(2S)-4-(cyanomethyl)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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(2R)-4-(cyanomethyl)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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-chloro-6-[3-hydroxy-2-(hydroxymethyl)-2-methylpropoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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

N-[(5-chloro-6-{[1-(cyanomethyl)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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})-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 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]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[1-(oxetan-3-yl)azetidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 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]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 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]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(5-chloro-6-{[1-(N,N-dimethylglycyl)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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 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]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(5-chloro-6-{[4-fluoro-1-methylpiperidin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(5-chloro-6-{[1-(N,N-dimethylglycyl)-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(5-chloro-6-{[(3R)-1-(1,3-difluoropropan-2-yl)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[2-(tetrahydrofuran-3-yloxy)ethoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
5 {[(trans-4-cyanocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[2-(tetrahydro-2H-pyran-4-yl)ethoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[4-(3-furylmethoxy)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 N-[(5-chloro-6-{[(3R)-1-(1,3-difluoropropan-2-yl)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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 N-[(5-chloro-6-{[1-(1,3-difluoropropan-2-yl)-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-({3-chloro-4-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 N-({3-chloro-4-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-yl)methoxy}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 N-[(5-chloro-6-{[1-(2,2-difluoroethyl)-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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{6-[[1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl]methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-chloro-6-[2-(tetrahydrofuran-2-yl)ethoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(cyclopropylamino)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-
- 15 5-yloxy)benzamide;
- N-[[5-chloro-6-(2-methoxyethoxy)pyridin-3-yl]sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-yl)methoxy}pyridin-3-yl}sulfonyl]-2-(1H-pyrrolo[2,3-
- 20 b]pyridin-5-yloxy)benzamide;
- N-[(3-chloro-4-{{1-(methoxyacetyl)piperidin-4-yl}methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 N-[(3-chloro-4-{{1-(N,N-dimethylglycyl)piperidin-4-yl}methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-{{6-(tetrahydro-2H-pyran-4-yl)methoxy)-5-
- 30 (trifluoromethyl)pyridin-3-yl}sulfonyl}benzamide;
- N-({5-chloro-6-[(trans-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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(trans-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(cis-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 N-[(3-chloro-4-{[trans-4-(morpholin-4-yl)cyclohexyl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({3-[cyclopropyl(1,3-thiazol-5-ylmethyl)amino]propyl}amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 N-({3-chloro-4-[(trans-4-hydroxycyclohexyl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({3-[cyclopropyl(2,2,2-trifluoroethyl)amino]propyl}amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(3-chloro-4-{[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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3,5-difluoro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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

5 N-[(3-chloro-4-{[1-(1-methyl-L-prolyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-
chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide;

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

10 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-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

methyl 2-{[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-
yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-
15 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}-N-
ethyl-N-methylmorpholine-4-carboxamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-
20 ({[4-(methylsulfonyl)morpholin-2-yl]methyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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

25 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-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-
chloro-4-(tetrahydrofuran-3-ylmethoxy)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-
30 yloxy)benzamide;

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

4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-
 5 {[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-
 yloxy)benzamide;

N-{[5-chloro-6-({4-[cyclopropyl(oxetan-3-yl)amino]cyclohexyl}methoxy)pyridin-3-
 yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-
 yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

10 4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-N-([4-({(4-
 cyclopropylmorpholin-2-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;

N-({3-chloro-4-[(4-cyclopropylmorpholin-2-yl)methoxy]phenyl)sulfonyl)-4-(4-{[2-(4-
 chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-
 15 b]pyridin-5-yloxy)benzamide;

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

2-({[(2-chloro-4-({4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-
 20 yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-
 yloxy)benzoyl]sulfamoyl}phenyl)amino]methyl}-N-ethyl-N-methylmorpholine-4-
 carboxamide;

(2S)-2-({[(3-chloro-5-({4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-
 yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}pyridin-
 25 2-yl)oxy]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide;

N-[(5-chloro-6-({(4-cyclopropylmorpholin-2-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-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

2-({[(3-chloro-5-({4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-
 30 yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}pyridin-
 2-yl)amino]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide;

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-
 pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(2-cyanoethyl)(cyclopropyl)amino]cyclohexyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(5-chloro-6-{[(1R,2S,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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(5-chloro-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(3,3-difluoropyrrolidin-1-yl)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
({4-[(2,2-difluorocyclopropyl)amino]cyclohexyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 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-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-
nitro-4-(2-oxaspiro[3.5]non-7-ylmethoxy)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-
yloxy)benzamide;
- 10 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-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
[(4-cyclopropylmorpholin-2-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-
15 b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-({5-chloro-6-[(cis-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-
20 yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-
yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
{[(trans-4-ethyl-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
{[(cis-4-ethyl-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-
30 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 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}-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({3-chloro-4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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

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

10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(2-oxaspiro[3.5]non-7-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-[(4-cyano-4-methylcyclohexyl)methyl]amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

15 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-([3-(tetrahydro-2H-pyran-4-ylmethyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-6-yl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([6-([(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino)-5-nitropyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

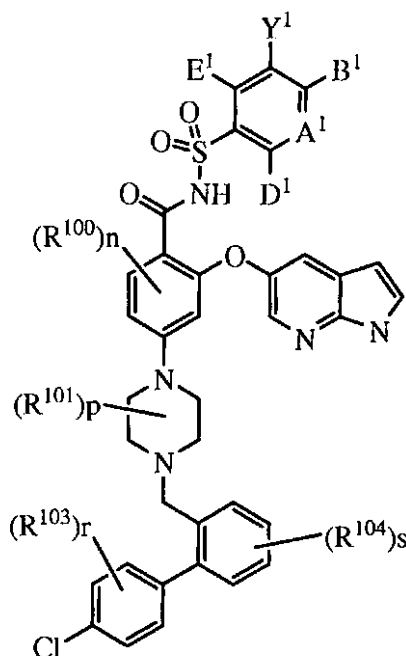
25 N-(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)morpholine-4-carboxamide;

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

30 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-pyrrolo[2,3-b]pyridin-5-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-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and therapeutically acceptable salts, and
 metabolites thereof.

5 In another aspect, the present invention provides compounds of Formula (IV)



(IV);

and therapeutically acceptable salts, and metabolites thereof,

wherein A¹, B¹, D¹, E¹, and Y¹ are as described herein for Formula (I); R¹⁰⁰ is as described
 10 for substituents on R²⁶; n is 0, 1, 2, or 3; R¹⁰¹ is as described for substituents on R³⁰; p is 0, 1,
 2, 3, 4, 5, or 6; R¹⁰⁴ is as described for substituents on R³⁸; s is 0, 1, 2, 3, 4, 5, or 6; R¹⁰³ is as
 described for substituents on R⁵⁸; and r is 0, 1, 2, 3, or 4.

In one embodiment of Formula (IV), n, p, r, and s are each 0.

In one embodiment of Formula (IV), A¹ is N. In another embodiment of Formula
 15 (IV), A¹ is C(A²). In another embodiment of Formula (IV), A¹ is C(A²); and A² is H, F, Cl,
 Br, or I. In another embodiment of Formula (IV), A¹ is C(A²); and A² is H.

In one embodiment of Formula (IV), B¹ is R¹, OR¹, NHR¹, NHC(O)R¹, F, Cl, Br, or I.
 In another embodiment of Formula (IV), A¹ is C(A²); A² is H; and B¹ is NHR¹. In another
 embodiment of Formula (IV), A¹ is C(A²); A² is H; and B¹ is OR¹. In another embodiment of
 20 Formula (IV), A¹ is C(A²); A² is H; and B¹ is Cl. In another embodiment of Formula (IV), A¹
 is C(A²); A² is H; and B¹ is R¹. In another embodiment of Formula (IV), A¹ is N; and B¹ is
 NHR¹. In another embodiment of Formula (IV), A¹ is N; and B¹ is OR¹. In another

embodiment of Formula (IV), A¹ is N; and B¹ is Cl. In another embodiment of Formula (IV), A¹ is N; and B¹ is R¹.

In one embodiment of Formula (IV), D¹ is H or Cl. In another embodiment of Formula (IV), A¹ is C(A²); A² is H; B¹ is NHR¹; and D¹ is H. In another embodiment of Formula (IV), A¹ is C(A²); A² is H; B¹ is NHR¹; and D¹ is Cl. In another embodiment of Formula (IV), A¹ is C(A²); A² is H; B¹ is OR¹; and D¹ is H. In another embodiment of Formula (IV), A¹ is C(A²); A² is H; B¹ is Cl; and D¹ is H. In another embodiment of Formula (IV), A¹ is C(A²); A² is H; B¹ is R¹; and D¹ is H. In another embodiment of Formula (IV), A¹ is N; B¹ is NHR¹; and D¹ is H. In another embodiment of Formula (IV), A¹ is N; B¹ is NHR¹; and D¹ is Cl. In another embodiment of Formula (IV), A¹ is N; B¹ is OR¹; and D¹ is H. In another embodiment of Formula (IV), A¹ is N; B¹ is Cl; and D¹ is H. In another embodiment of Formula (IV), A¹ is N; B¹ is R¹; and D¹ is H.

In one embodiment of Formula (IV), E¹ is H. In another embodiment of Formula (IV), A¹ is C(A²); A² is H; B¹ is NHR¹; D¹ is H; and E¹ is H. In another embodiment of Formula (IV), A¹ is C(A²); A² is H; B¹ is NHR¹; E¹ is H; and D¹ is Cl. In another embodiment of Formula (IV), A¹ is C(A²); A² is H; B¹ is OR¹; D¹ is H; and E¹ is H. In another embodiment of Formula (IV), A¹ is C(A²); A² is H; B¹ is Cl; D¹ is H; and E¹ is H. In another embodiment of Formula (IV), A¹ is C(A²); A² is H; B¹ is R¹; D¹ is H; and E¹ is H. In another embodiment of Formula (IV), A¹ is N; B¹ is NHR¹; D¹ is H; and E¹ is H. In another embodiment of Formula (IV), A¹ is N; B¹ is NHR¹; E¹ is H; and D¹ is Cl. In another embodiment of Formula (IV), A¹ is N; B¹ is OR¹; D¹ is H; and E¹ is H. In another embodiment of Formula (IV), A¹ is N; B¹ is Cl; D¹ is H; and E¹ is H. In another embodiment of Formula (IV), A¹ is N; B¹ is R¹; D¹ is H; and E¹ is H.

In one embodiment of Formula (IV), Y¹ is H, CN, NO₂, F, Cl, Br, I, CF₃, R¹⁷, OR¹⁷, SR¹⁷, SO₂R¹⁷, or C(O)NH₂. In another embodiment of Formula (IV), Y¹ is H. In another embodiment of Formula (IV), Y¹ is CN. In another embodiment of Formula (IV), Y¹ is F, Cl, Br, or I. In another embodiment of Formula (IV), Y¹ is CF₃. In another embodiment of Formula (IV), Y¹ is SR¹⁷. In another embodiment of Formula (IV), Y¹ is OR¹⁷. In another embodiment of Formula (IV), Y¹ is NO₂. In another embodiment of Formula (IV), Y¹ is SO₂R¹⁷; wherein R¹⁷ is as defined herein. In another embodiment of Formula (IV), Y¹ is SO₂R¹⁷; wherein R¹⁷ is alkyl. In another embodiment of Formula (IV), Y¹ is R¹⁷; wherein R¹⁷ is alkynyl. In another embodiment of Formula (IV), A¹ is C(A²); A² is H; B¹ is NHR¹; D¹ is H; E¹ is H; and Y¹ is NO₂ or SO₂R¹⁷; wherein R¹⁷ is alkyl or alkynyl. In another embodiment of Formula (IV), A¹ is C(A²); A² is H; B¹ is NHR¹; D¹ is H; E¹ is H; and Y¹ is NO₂. In

another embodiment of Formula (IV), A^1 is $C(A^2)$; A^2 is H; B^1 is NHR^1 ; D^1 is H; E^1 is H; and Y^1 is SO_2R^{17} ; wherein R^{17} is alkyl substituted with three F. In another embodiment of Formula (IV), A^1 is N; B^1 is NHR^1 ; D^1 is H; E^1 is H; and Y^1 is NO_2 or SO_2R^{17} ; wherein R^{17} is alkyl or alkynyl. In another embodiment of Formula (IV), A^1 is N; B^1 is NHR^1 ; D^1 is H; E^1 is H; and Y^1 is NO_2 . In another embodiment of Formula (IV), A^1 is N; B^1 is NHR^1 ; D^1 is H; E^1 is H; and Y^1 is SO_2R^{17} ; wherein R^{17} is alkyl substituted with three F.

In one embodiment of Formula (IV), Y^1 and B^1 , together with the atoms to which they are attached, are benzene. In another embodiment of Formula (IV), Y^1 and B^1 , together with the atoms to which they are attached, are heteroarene. In another embodiment of Formula (IV), A^1 is $C(A^2)$; A^2 , G^1 , E^1 , and D^1 are independently selected H; and Y^1 and B^1 , together with the atoms to which they are attached, are benzene. In another embodiment of Formula (IV), A^1 is $C(A^2)$; A^2 , G^1 , E^1 , and D^1 are independently selected H; and Y^1 and B^1 , together with the atoms to which they are attached, are heteroarene.

In one embodiment of Formula (IV), R^1 is R^4 or R^5 . In one embodiment of Formula (IV), R^1 is R^4 . In one embodiment of Formula (IV), R^1 is R^5 . In one embodiment of Formula (IV), R^1 is R^4 ; and R^4 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl. In one embodiment of Formula (IV), R^1 is R^4 ; and R^4 is cycloalkyl or heterocycloalkyl. In one embodiment of Formula (IV), R^1 is R^4 ; and R^4 is cycloalkyl. In one embodiment of Formula (IV), R^1 is R^4 ; and R^4 is heterocycloalkyl.

In one embodiment of Formula (IV), R^1 is R^4 ; and R^4 is cycloalkyl; wherein R^4 is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is substituted as defined herein. In another embodiment of Formula (IV), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is substituted with R^{57} or $N(R^{57})_2$. In another embodiment of Formula (IV), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R^{57} ; and R^{57} is R^{60} . In another embodiment of Formula (IV), R^1 is R^4 ; R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R^{57} ; R^{57} is R^{60} ; and R^{60} is heterocycloalkyl. In another embodiment of Formula (IV), R^1 is R^4 ; R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R^{57} ; R^{57} is R^{60} ; R^{60} is heterocycloalkyl; wherein the heterocycloalkyl ring is morpholinyl. In another embodiment of Formula (IV), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is substituted with $N(R^{57})_2$. In another embodiment of Formula (IV), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with $N(R^{57})_2$. In another

embodiment of Formula (IV), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with $N(R^{57})_2$; R^{57} is R^{61} ; and R^{61} is alkyl which is unsubstituted or substituted with R^{62} . In another embodiment of Formula (IV), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R^{57} ; R^{57} is R^{61} ; and R^{61} is alkyl which is unsubstituted or substituted with R^{62} , R^{62} is R^{65} ; and R^{65} is cycloalkyl. In another embodiment of Formula (IV), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R^{57} ; R^{57} is R^{61} ; and R^{61} is alkyl which is substituted with R^{62} ; R^{62} is R^{65} ; and R^{65} is cyclopropyl

In one embodiment of Formula (IV), R^1 is R^4 ; and R^4 is heterocycloalkyl; wherein R^4 is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV), R^1 is R^4 ; and R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted as defined herein. In another embodiment of Formula (IV), R^1 is R^4 ; and R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted with R^{57} . In another embodiment of Formula (IV), R^1 is R^4 ; and R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is piperdinyl or piperizinyl; and wherein the heterocycloalkyl ring is substituted with R^{57} ; and R^{57} is R^{60} or R^{61} . In another embodiment of Formula (IV), R^1 is R^4 ; R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is piperdinyl or piperizinyl; and wherein the piperdinyl or piperizinyl ring is substituted with R^{57} ; R^{57} is R^{60} or R^{61} ; R^{60} is heterocycloalkyl; and R^{61} is alkyl. In another embodiment of Formula (IV), R^1 is R^4 ; R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is piperdinyl or piperizinyl; and wherein the piperdinyl or piperizinyl ring is substituted with R^{57} ; R^{57} is R^{60} ; R^{60} is heterocycloalkyl; wherein the heterocycloalkyl is tetrahydropyranyl. In another embodiment of Formula (IV), R^1 is R^4 ; R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is piperdinyl or piperizinyl; and wherein the piperdinyl or piperizinyl ring is substituted with R^{57} ; R^{57} is R^{61} ; R^{61} is alkyl; and the alkyl is methyl. In another embodiment of Formula (IV), R^1 is R^4 ; R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is piperdinyl or piperizinyl; and wherein the piperdinyl or piperizinyl ring is substituted with $C(O)OR^{57}$; R^{57} is R^{61} ; R^{61} is alkyl; and the alkyl is methyl.

In one embodiment of Formula (IV), R^1 is R^5 ; and R^5 is alkyl which is unsubstituted or substituted. In one embodiment of Formula (IV), R^1 is R^5 ; and R^5 is alkyl which is unsubstituted or substituted with R^7 , OR^7 , OH , CN , or F . In another embodiment of Formula (IV), R^1 is R^5 ; and R^5 is alkyl which is substituted with R^7 , OR^7 , NHR^7 , or $N(R^7)_2$.

In one embodiment of Formula (IV), R^7 is R^8 , R^9 , R^{10} or R^{11} which are unsubstituted or substituted as defined herein. In another embodiment of Formula (IV), R^7 is R^8 which is

unsubstituted or substituted as defined herein. In another embodiment of Formula (IV), R⁷ is R⁹ which is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV), R⁷ is R¹⁰ which is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV), R⁷ is R¹¹ which is unsubstituted or substituted as defined
5 herein.

In one embodiment of Formula (IV), R⁸ is phenyl which is unsubstituted or substituted as defined herein.

In one embodiment of Formula (IV), R⁹ is heteroaryl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV), R⁹ is furanyl; which
10 is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV), R⁹ is furanyl; which is unsubstituted.

In one embodiment of Formula (IV), R¹⁰ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, heterocycloalkyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (IV), R¹⁰ is heterocycloalkyl which is
15 unsubstituted or substituted as defined herein. In another embodiment of Formula (IV), R¹⁰ is tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, dioxanyl, oxetanyl, piperdiny, or pyrrolidinyl, which are unsubstituted or substituted as defined herein. In another embodiment of Formula (IV), R¹⁰ is tetrahydropyranyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV), R¹⁰ is morpholinyl; which is unsubstituted
20 or substituted as defined herein. In another embodiment of Formula (IV), R¹⁰ is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV), R¹⁰ is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV), R¹⁰ is cyclohexyl, cyclopropyl, cyclobutyl, or bicyclo[2.2.1]heptanyl, which is unsubstituted or substituted as defined herein. In another
25 embodiment of Formula (IV), R¹⁰ is heterocycloalkyl which is fused with R^{10A}; and R^{10A} is heteroarene. In another embodiment of Formula (IV), R¹⁰ is 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl.

In one embodiment of Formula (IV), R¹¹ is alkyl, alkenyl or alkynyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (IV), R¹¹ is
30 alkyl. In another embodiment of Formula (IV), R¹¹ is methyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV), R¹¹ is alkyl; which is substituted as defined herein. In another embodiment of Formula (IV), R¹¹ is alkyl; which is substituted with R¹², OR¹², or CF₃. In another embodiment of Formula (IV), R¹¹ is alkyl; which is substituted with OR¹²; R¹² is R¹⁶; and R¹⁶ is alkyl. In another embodiment of

Formula (IV), R^{11} is alkyl; which is substituted with CF_3 . In another embodiment of Formula (IV), R^{11} is alkyl; which is substituted with R^{12} , R^{12} is R^{14} , and R^{14} is heteroaryl.

In one embodiment of Formula (IV),

$n, p, r,$ and s are each 0;

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

A^2 is H, F, Br, I, or Cl;

B^1 is R^1 , OR^1 , NHR^1 , $NHC(O)R^1$, F, Br, I or Cl;

D^1 is H, F, Br, I, or Cl;

E^1 is H; and

10 Y^1 is H, CN, NO_2 , F, Cl, Br, I, CF_3 , R^{17} , OR^{17} , SR^{17} , SO_2R^{17} , or $C(O)NH_2$; or

Y^1 and B^1 , together with the atoms to which they are attached, are benzene,

heteroarene, or heterocycloalkene; and

A^2 , D^1 , and E^1 are independently selected H;

R^1 is R^4 or R^5 ;

15 R^4 is cycloalkyl, or heterocycloalkyl;

R^5 is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^7 , OR^7 , NHR^7 , $N(R^7)_2$, CN, OH, F, Cl, Br or I;

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

R^8 is phenyl;

20 R^9 is heteroaryl;

R^{10} is cycloalkyl, cycloalkenyl, or heterocycloalkyl; each of which is unfused or fused with R^{10A} , R^{10A} is heteroarene;

R^{11} is alkyl each of which is unsubstituted or substituted with one or two or three of independently selected R^{12} , OR^{12} or CF_3 ;

25 R^{12} is R^{14} or R^{16} ;

R^{14} is heteroaryl;

R^{16} is alkyl;

R^{17} is R^{21} ;

30 R^{21} is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{22} , F, Cl, Br or I;

R^{22} is R^{25} ;

R^{25} is heterocycloalkyl;

wherein the cyclic moieties represented by Y^1 and B^1 together, R^4 , R^8 , R^{10} , and R^{25} , are independently unsubstituted, further unsubstituted, substituted or further substituted with

one or two or three or four or five of independently selected R^{57A} , R^{57} , OR^{57} , SO_2R^{57} , $C(O)R^{57}$, $CO(O)R^{57}$, $C(O)N(R^{57})_2$, NH_2 , NHR^{57} , $N(R^{57})_2$, $NHC(O)R^{57}$, $NHS(O)_2R^{57}$, OH , CN , (O) , F , Cl , Br or I ;

R^{57A} is spiroalkyl, or spiroheteroalkyl;

5 R^{57} is R^{58} , R^{60} or R^{61} ;

R^{58} is phenyl;

R^{60} is cycloalkyl, or heterocycloalkyl;

R^{61} is alkyl which is unsubstituted or substituted with one or two or three of independently selected R^{62} , OR^{62} , $N(R^{62})_2$, $C(O)OH$, CN , F , Cl , Br or I ;

10 R^{62} is R^{65} , or R^{66} ;

R^{65} is cycloalkyl, or heterocycloalkyl;

R^{66} is alkyl which is unsubstituted or substituted with OR^{67} ;

R^{67} is alkyl;

15 wherein the cyclic moieties represented by R^{57A} , R^{58} , and R^{60} are unsubstituted or substituted with one or two or three or four of independently selected R^{68} , F , Cl , Br or I ;

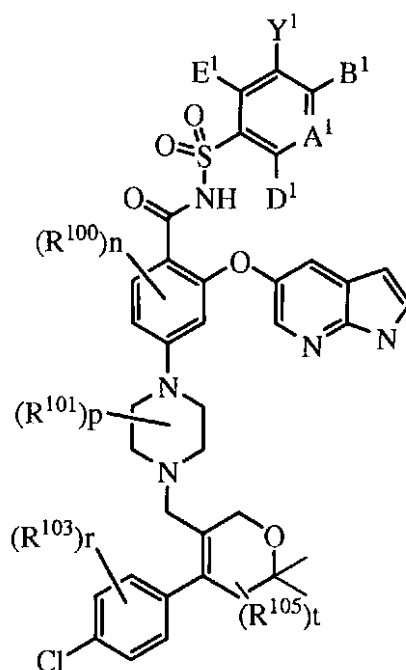
R^{68} is R^{71} or R^{72} ;

R^{71} is heterocycloalkyl; and

R^{72} is alkyl, which is unsubstituted or substituted with one or two F .

20 Still another embodiment pertains to compounds having Formula (IV), 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-(1H-pyrrolo[2,3-b]pyridin-5-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-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and therapeutically acceptable salts, and metabolites thereof.

25 In another aspect, the present invention provides compounds of Formula (V)



(V);

and therapeutically acceptable salts, and metabolites thereof,

wherein A^1 , B^1 , D^1 , E^1 , and Y^1 are as described herein for Formula (I); R^{100} is as described

- 5 for substituents on R^{26} ; n is 0, 1, 2, or 3; R^{101} is as described for substituents on R^{30} ; p is 0, 1, 2, 3, 4, 5, or 6; R^{105} is as described for substituents on R^{40} ; t is 0, 1, 2, 3, or 4; R^{103} is as described for substituents on R^{58} ; and r is 0, 1, 2, 3, or 4.

In one embodiment of Formula (V), n , p , r , and t are each 0.

- In one embodiment of Formula (V), A^1 is N. In another embodiment of Formula (V),
 10 A^1 is $C(A^2)$. In another embodiment of Formula (V), A^1 is $C(A^2)$; and A^2 is H, F, Cl, Br, or I. 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 , NHR^1 , $NHC(O)R^1$, F, Cl, Br, or I. In another embodiment of Formula (V), A^1 is $C(A^2)$; A^2 is H; and B^1 is NHR^1 . In another embodiment of Formula (V), A^1 is $C(A^2)$; A^2 is H; and B^1 is OR^1 . In another embodiment of
 15 Formula (V), A^1 is $C(A^2)$; A^2 is H; and B^1 is Cl. In another embodiment of Formula (V), A^1 is $C(A^2)$; A^2 is H; and B^1 is R^1 . In another embodiment of Formula (V), A^1 is N; and B^1 is NHR^1 . In another embodiment of Formula (V), A^1 is N; and B^1 is OR^1 . In another embodiment of Formula (V), A^1 is N; and B^1 is Cl. In another embodiment of Formula (V), A^1 is N; and B^1 is R^1 .

- 20 In one embodiment of Formula (V), D^1 is H or Cl. In another embodiment of Formula (V), A^1 is $C(A^2)$; A^2 is H; B^1 is NHR^1 ; and D^1 is H. In another embodiment of Formula (V), A^1 is $C(A^2)$; A^2 is H; B^1 is NHR^1 ; and D^1 is Cl. In another embodiment of

Formula (V), A^1 is $C(A^2)$; A^2 is H; B^1 is OR^1 ; and D^1 is H. In another embodiment of Formula (V), A^1 is $C(A^2)$; A^2 is H; B^1 is Cl; and D^1 is H. In another embodiment of Formula (V), A^1 is $C(A^2)$; A^2 is H; B^1 is R^1 ; and D^1 is H. In another embodiment of Formula (V), A^1 is N; B^1 is NHR^1 ; and D^1 is H. In another embodiment of Formula (V), A^1 is N; B^1 is NHR^1 ; and D^1 is Cl. In another embodiment of Formula (V), A^1 is N; B^1 is OR^1 ; and D^1 is H. In another embodiment of Formula (V), A^1 is N; B^1 is Cl; and D^1 is H. In another embodiment of Formula (V), A^1 is N; B^1 is R^1 ; and D^1 is H.

In one embodiment of Formula (V), E^1 is H. In another embodiment of Formula (V), A^1 is $C(A^2)$; A^2 is H; B^1 is NHR^1 ; D^1 is H; and E^1 is H. In another embodiment of Formula (V), A^1 is $C(A^2)$; A^2 is H; B^1 is NHR^1 ; E^1 is H; and D^1 is Cl. In another embodiment of Formula (V), A^1 is $C(A^2)$; A^2 is H; B^1 is OR^1 ; D^1 is H; and E^1 is H. In another embodiment of Formula (V), A^1 is $C(A^2)$; A^2 is H; B^1 is Cl; D^1 is H; and E^1 is H. In another embodiment of Formula (V), A^1 is $C(A^2)$; A^2 is H; B^1 is R^1 ; D^1 is H; and E^1 is H. In another embodiment of Formula (V), A^1 is N; B^1 is NHR^1 ; D^1 is H; and E^1 is H. In another embodiment of Formula (V), A^1 is N; B^1 is NHR^1 ; E^1 is H; and D^1 is Cl. In another embodiment of Formula (V), A^1 is N; B^1 is OR^1 ; D^1 is H; and E^1 is H. In another embodiment of Formula (V), A^1 is N; B^1 is Cl; D^1 is H; and E^1 is H. In another embodiment of Formula (V), A^1 is N; B^1 is R^1 ; D^1 is H; and E^1 is H.

In one embodiment of Formula (V), Y^1 is H, CN, NO_2 , F, Cl, Br, I, CF_3 , R^{17} , OR^{17} , SR^{17} , SO_2R^{17} , or $C(O)NH_2$. In another embodiment of Formula (V), Y^1 is H. In another embodiment of Formula (V), Y^1 is CN. In another embodiment of Formula (V), Y^1 is F, Cl, Br, or I. In another embodiment of Formula (V), Y^1 is CF_3 . In another embodiment of Formula (V), Y^1 is SR^{17} . In another embodiment of Formula (V), Y^1 is OR^{17} . In another embodiment of Formula (V), Y^1 is NO_2 . In another embodiment of Formula (V), Y^1 is SO_2R^{17} ; wherein R^{17} is as defined herein. In another embodiment of Formula (V), Y^1 is SO_2R^{17} ; wherein R^{17} is alkyl. In another embodiment of Formula (V), Y^1 is R^{17} ; wherein R^{17} is alkynyl. In another embodiment of Formula (V), A^1 is $C(A^2)$; A^2 is H; B^1 is NHR^1 ; D^1 is H; E^1 is H; and Y^1 is NO_2 or SO_2R^{17} ; wherein R^{17} is alkyl or alkynyl. In another embodiment of Formula (V), A^1 is $C(A^2)$; A^2 is H; B^1 is NHR^1 ; D^1 is H; E^1 is H; and Y^1 is NO_2 . In another embodiment of Formula (V), A^1 is $C(A^2)$; A^2 is H; B^1 is NHR^1 ; D^1 is H; E^1 is H; and Y^1 is SO_2R^{17} ; wherein R^{17} is alkyl substituted with three F. In another embodiment of Formula (V), A^1 is N; B^1 is NHR^1 ; D^1 is H; E^1 is H; and Y^1 is NO_2 or SO_2R^{17} ; wherein R^{17} is alkyl or alkynyl. In another embodiment of Formula (V), A^1 is N; B^1 is NHR^1 ; D^1 is H; E^1 is H; and

Y^1 is NO_2 . In another embodiment of Formula (V), A^1 is N; B^1 is NHR^1 ; D^1 is H; E^1 is H; and Y^1 is SO_2R^{17} ; wherein R^{17} is alkyl substituted with three F.

In one embodiment of Formula (V), Y^1 and B^1 , together with the atoms to which they are attached, are benzene. In another embodiment of Formula (V), Y^1 and B^1 , together with the atoms to which they are attached, are heteroarene. In another embodiment of Formula (V), A^1 is $C(A^2)$; A^2 , G^1 , E^1 , and D^1 are independently selected H; and Y^1 and B^1 , together with the atoms to which they are attached, are benzene. In another embodiment of Formula (V), A^1 is $C(A^2)$; A^2 , G^1 , E^1 , and D^1 are independently selected H; and Y^1 and B^1 , together with the atoms to which they are attached, are heteroarene.

In one embodiment of Formula (V), R^1 is R^4 or R^5 . In one embodiment of Formula (V), R^1 is R^4 . In one embodiment of Formula (V), R^1 is R^5 . In one embodiment of Formula (V), R^1 is R^4 ; and R^4 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl. In one embodiment of Formula (V), R^1 is R^4 ; and R^4 is cycloalkyl or heterocycloalkyl. In one embodiment of Formula (V), R^1 is R^4 ; and R^4 is cycloalkyl. In one embodiment of Formula (V), R^1 is R^4 ; and R^4 is heterocycloalkyl.

In one embodiment of Formula (V), R^1 is R^4 ; and R^4 is cycloalkyl; wherein R^4 is unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is substituted as defined herein. In another embodiment of Formula (V), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is substituted with R^{57} or $N(R^{57})_2$. In another embodiment of Formula (V), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R^{57} ; and R^{57} is R^{60} . In another embodiment of Formula (V), R^1 is R^4 ; R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R^{57} ; R^{57} is R^{60} ; and R^{60} is heterocycloalkyl. In another embodiment of Formula (V), R^1 is R^4 ; R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R^{57} ; R^{57} is R^{60} ; R^{60} is heterocycloalkyl; wherein the heterocycloalkyl ring is morpholinyl. In another embodiment of Formula (V), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is substituted with $N(R^{57})_2$. In another embodiment of Formula (V), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with $N(R^{57})_2$. In another embodiment of Formula (V), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with $N(R^{57})_2$; R^{57} is R^{61} ; and R^{61} is alkyl which is unsubstituted or substituted with R^{62} . In another embodiment of Formula (V), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the

cyclohexyl ring is substituted with R^{57} ; R^{57} is R^{61} ; and R^{61} is alkyl which is unsubstituted or substituted with R^{62} ; R^{62} is R^{65} ; and R^{65} is cycloalkyl. In another embodiment of Formula (V), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R^{57} ; R^{57} is R^{61} ; and R^{61} is alkyl which is substituted with R^{62} ; R^{62} is R^{65} ; and R^{65} is cyclopropyl

In one embodiment of Formula (V), R^1 is R^4 ; and R^4 is heterocycloalkyl; wherein R^4 is unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R^1 is R^4 ; and R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted as defined herein. In another embodiment of Formula (V), R^1 is R^4 ; and R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted with R^{57} . In another embodiment of Formula (V), R^1 is R^4 ; and R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is piperdinyl or piperizinyll; and wherein the heterocycloalkyl ring is substituted with R^{57} ; and R^{57} is R^{60} or R^{61} . In another embodiment of Formula (V), R^1 is R^4 ; R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is piperdinyl or piperizinyll; and wherein the piperdinyl or piperizinyll ring is substituted with R^{57} ; R^{57} is R^{60} or R^{61} ; R^{60} is heterocycloalkyl; and R^{61} is alkyl. In another embodiment of Formula (V), R^1 is R^4 ; R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is piperdinyl or piperizinyll; and wherein the piperdinyl or piperizinyll ring is substituted with R^{57} ; R^{57} is R^{60} ; R^{60} is heterocycloalkyl; wherein the heterocycloalkyl is tetrahydropyranyl. In another embodiment of Formula (V), R^1 is R^4 ; R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is piperdinyl or piperizinyll; and wherein the piperdinyl or piperizinyll ring is substituted with R^{57} ; R^{57} is R^{61} ; R^{61} is alkyl; and the alkyl is methyl. In another embodiment of Formula (V), R^1 is R^4 ; R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is piperdinyl or piperizinyll; and wherein the piperdinyl or piperizinyll ring is substituted with $C(O)OR^{57}$; R^{57} is R^{61} ; R^{61} is alkyl; and the alkyl is methyl.

In one embodiment of Formula (V), R^1 is R^5 ; and R^5 is alkyl which is unsubstituted or substituted. In one embodiment of Formula (V), R^1 is R^5 ; and R^5 is alkyl which is unsubstituted or substituted with R^7 , OR^7 , OH , CN , or F . In another embodiment of Formula (V), R^1 is R^5 ; and R^5 is alkyl which is substituted with R^7 , OR^7 , NHR^7 , or $N(R^7)_2$.

In one embodiment of Formula (V), R^7 is R^8 , R^9 , R^{10} or R^{11} which are unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R^7 is R^8 which is unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R^7 is R^9 which is unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R^7 is R^{10} which is unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R^7 is R^{11} which is unsubstituted or substituted as defined herein.

In one embodiment of Formula (V), R⁸ is phenyl which is unsubstituted or substituted as defined herein.

In one embodiment of Formula (V), R⁹ is heteroaryl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R⁹ is furanyl; which is
 5 unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R⁹ is furanyl; which is unsubstituted.

In one embodiment of Formula (V), R¹⁰ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, heterocycloalkyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R¹⁰ is heterocycloalkyl which is
 10 unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R¹⁰ is tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, dioxanyl, oxetanyl, piperdinyl, or pyrrolidinyl, which are unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R¹⁰ is tetrahydropyranyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R¹⁰ is morpholinyl; which is unsubstituted or
 15 substituted as defined herein. In another embodiment of Formula (V), R¹⁰ is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R¹⁰ is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R¹⁰ is cyclohexyl, cyclopropyl, cyclobutyl, or bicyclo[2.2.1]heptanyl; which is unsubstituted or substituted as defined herein. In another
 20 embodiment of Formula (V), R¹⁰ is heterocycloalkyl which is fused with R^{10A}; and R^{10A} is heteroarene. In another embodiment of Formula (V), R¹⁰ is 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl.

In one embodiment of Formula (V), R¹¹ is alkyl, alkenyl or alkynyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R¹¹ is
 25 alkyl. In another embodiment of Formula (V), R¹¹ is methyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R¹¹ is alkyl; which is substituted as defined herein. In another embodiment of Formula (V), R¹¹ is alkyl; which is substituted with R¹², OR¹², or CF₃. In another embodiment of Formula (V), R¹¹ is alkyl; which is substituted with OR¹²; R¹² is R¹⁶; and R¹⁶ is alkyl. In another embodiment of
 30 Formula (V), R¹¹ is alkyl; which is substituted with CF₃. In another embodiment of Formula (V), R¹¹ is alkyl; which is substituted with R¹²; R¹² is R¹⁴; and R¹⁴ is heteroaryl.

In one embodiment of Formula (V),

n, p, r, and t are each 0;

A¹ is N or C(A²);

- A^2 is H, F, Br, I, or Cl;
 B^1 is R^1 , OR^1 , NHR^1 , $NHC(O)R^1$, F, Br, I or Cl;
 D^1 is H, F, Br, I, or Cl;
 E^1 is H; and
5 Y^1 is H, CN, NO_2 , F, Cl, Br, I, CF_3 , R^{17} , OR^{17} , SR^{17} , SO_2R^{17} , or $C(O)NH_2$; or
 Y^1 and B^1 , together with the atoms to which they are attached, are benzene,
heteroarene, or heterocycloalkene; and
 A^2 , D^1 , and E^1 are independently selected H;
 R^1 is R^4 or R^5 ;
10 R^4 is cycloalkyl, or heterocycloalkyl;
 R^5 is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two
or three of independently selected R^7 , OR^7 , NHR^7 , $N(R^7)_2$, CN, OH, F, Cl, Br or I;
 R^7 is R^8 , R^9 , R^{10} , or R^{11} ;
 R^8 is phenyl;
15 R^9 is heteroaryl;
 R^{10} is cycloalkyl, cycloalkenyl, or heterocycloalkyl; each of which is unfused or fused
with R^{10A} , R^{10A} is heteroarene;
 R^{11} is alkyl each of which is unsubstituted or substituted with one or two or three of
independently selected R^{12} , OR^{12} or CF_3 ;
20 R^{12} is R^{14} or R^{16} ;
 R^{14} is heteroaryl;
 R^{16} is alkyl;
 R^{17} is R^{21} ;
 R^{21} is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two
25 or three of independently selected R^{22} , F, Cl, Br or I;
 R^{22} is R^{25} ;
 R^{25} is heterocycloalkyl;
wherein the cyclic moieties represented by Y^1 and B^1 together, R^4 , R^8 , R^{10} , and R^{25} ,
are independently unsubstituted, further unsubstituted, substituted or further substituted with
30 one or two or three or four or five of independently selected R^{57A} , R^{57} , OR^{57} , SO_2R^{57} ,
 $C(O)R^{57}$, $CO(O)R^{57}$, $C(O)N(R^{57})_2$, NH_2 , NHR^{57} , $N(R^{57})_2$, $NHC(O)R^{57}$, $NHS(O)_2R^{57}$, OH, CN,
(O), F, Cl, Br or I;
 R^{57A} is spiroalkyl, or spiroheteroalkyl;
 R^{57} is R^{58} , R^{60} or R^{61} ;

R^{58} is phenyl;

R^{60} is cycloalkyl, or heterocycloalkyl;

R^{61} is alkyl which is unsubstituted or substituted with one or two or three of independently selected R^{62} , OR^{62} , $N(R^{62})_2$, $C(O)OH$, CN , F , Cl , Br or I ;

5 R^{62} is R^{65} , or R^{66} ;

R^{65} is cycloalkyl, or heterocycloalkyl;

R^{66} is alkyl which is unsubstituted or substituted with OR^{67} ;

R^{67} is alkyl;

10 wherein the cyclic moieties represented by R^{57A} , R^{58} , and R^{60} are unsubstituted or substituted with one or two or three or four of independently selected R^{68} , F , Cl , Br or I ;

R^{68} is R^{71} or R^{72} ;

R^{71} is heterocycloalkyl; and

R^{72} is alkyl, which is unsubstituted or substituted with one or two F .

Still another embodiment pertains to a compound having Formula (V), which is

15 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

20 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

25 Trans-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

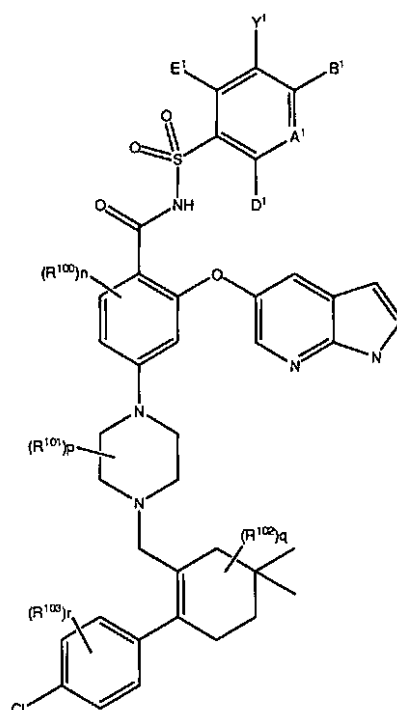
4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

30 ide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-
2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-{[4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-
(trifluoromethyl)phenyl]sul
fonyl}benzamide;
- 5 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-
2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-{[4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-
[(trifluoromethyl)sulfonyl]
phenyl]sulfonyl}benzamide;
- 10 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-
N-{[4-[(4-morpholin-4-ylcyclohexyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl]sulfonyl)-
2-(1H-pyrrolo[2,3-b]pyri
din-5-yloxy)benzamide;
- 15 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-
N-{[4-[(1-methylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl]sulfonyl)-2-(1H-
pyrrolo[2,3-b]pyridin-
5-yloxy)benzamide;
- Cis-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-
yl)-N-{[4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide;
- 20 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-
N-{[4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide;
- 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-
N-{[4-[(4-methoxycyclohexyl)methyl]amino]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-
25 b]pyridin-5-yloxy)benzamide;
- and therapeutically acceptable salts, and metabolites thereof.

In another aspect, the present invention provides compounds of Formula (VI)



(VI);

and therapeutically acceptable salts, and metabolites thereof,

wherein A^1 , B^1 , D^1 , E^1 , and Y^1 are as described herein for Formula (I); R^{100} is as described

- 5 for substituents on R^{26} ; n is 0, 1, 2, or 3; R^{101} is as described for substituents on R^{30} ; p is 0, 1, 2, 3, 4, 5, or 6; R^{102} is as described for substituents on R^{40} ; q is 0, 1, 2, 3, 4, 5, or 6; R^{103} is as described for substituents on R^{58} ; and r is 0, 1, 2, 3, or 4.

In one embodiment of Formula (VI), n , p , r , and q are each 0.

- 10 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, F, Cl, Br, or I. 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 , NHR^1 , $NHC(O)R^1$, F, Cl, Br, or I. In another embodiment of Formula (VI), A^1 is $C(A^2)$; A^2 is H; and B^1 is NHR^1 . In another embodiment of Formula (VI), A^1 is $C(A^2)$; A^2 is H; and B^1 is OR^1 . In another embodiment of Formula (VI), A^1 is $C(A^2)$; A^2 is H; and B^1 is Cl. In another embodiment of Formula (VI), A^1 is $C(A^2)$; A^2 is H; and B^1 is R^1 . In another embodiment of Formula (VI), A^1 is N; and B^1 is NHR^1 . In another embodiment of Formula (VI), A^1 is N; and B^1 is OR^1 . In another embodiment of Formula (VI), A^1 is N; and B^1 is Cl. In another embodiment of Formula (VI), A^1 is N; and B^1 is R^1 .

- 20 In one embodiment of Formula (VI), D^1 is H or Cl. In another embodiment of Formula (VI), A^1 is $C(A^2)$; A^2 is H; B^1 is NHR^1 ; and D^1 is H. In another embodiment of

Formula (VI), A^1 is $C(A^2)$; A^2 is H; B^1 is NHR^1 ; and D^1 is Cl. In another embodiment of Formula (VI), A^1 is $C(A^2)$; A^2 is H; B^1 is OR^1 ; and D^1 is H. In another embodiment of Formula (VI), A^1 is $C(A^2)$; A^2 is H; B^1 is Cl; and D^1 is H. In another embodiment of Formula (VI), A^1 is $C(A^2)$; A^2 is H; B^1 is R^1 ; and D^1 is H. In another embodiment of Formula (VI), A^1 is N; B^1 is NHR^1 ; and D^1 is H. In another embodiment of Formula (VI), A^1 is N; B^1 is NHR^1 ; and D^1 is Cl. In another embodiment of Formula (VI), A^1 is N; B^1 is OR^1 ; and D^1 is H. In another embodiment of Formula (VI), A^1 is N; B^1 is Cl; and D^1 is H. In another embodiment of Formula (VI), A^1 is N; B^1 is R^1 ; and D^1 is H.

In one embodiment of Formula (VI), E^1 is H. In another embodiment of Formula (VI), A^1 is $C(A^2)$; A^2 is H; B^1 is NHR^1 ; D^1 is H; and E^1 is H. In another embodiment of Formula (VI), A^1 is $C(A^2)$; A^2 is H; B^1 is NHR^1 ; E^1 is H; and D^1 is Cl. In another embodiment of Formula (VI), A^1 is $C(A^2)$; A^2 is H; B^1 is OR^1 ; D^1 is H; and E^1 is H. In another embodiment of Formula (VI), A^1 is $C(A^2)$; A^2 is H; B^1 is Cl; D^1 is H; and E^1 is H. In another embodiment of Formula (VI), A^1 is $C(A^2)$; A^2 is H; B^1 is R^1 ; D^1 is H; and E^1 is H. In another embodiment of Formula (VI), A^1 is N; B^1 is NHR^1 ; D^1 is H; and E^1 is H. In another embodiment of Formula (VI), A^1 is N; B^1 is NHR^1 ; E^1 is H; and D^1 is Cl. In another embodiment of Formula (VI), A^1 is N; B^1 is OR^1 ; D^1 is H; and E^1 is H. In another embodiment of Formula (VI), A^1 is N; B^1 is Cl; D^1 is H; and E^1 is H. In another embodiment of Formula (VI), A^1 is N; B^1 is R^1 ; D^1 is H; and E^1 is H.

In one embodiment of Formula (VI), Y^1 is H, CN, NO_2 , F, Cl, Br, I, CF_3 , R^{17} , OR^{17} , SR^{17} , SO_2R^{17} , or $C(O)NH_2$. In another embodiment of Formula (VI), Y^1 is H. In another embodiment of Formula (VI), Y^1 is CN. In another embodiment of Formula (VI), Y^1 is F, Cl, Br, or I. In another embodiment of Formula (VI), Y^1 is CF_3 . In another embodiment of Formula (VI), Y^1 is SR^{17} . In another embodiment of Formula (VI), Y^1 is OR^{17} . In another embodiment of Formula (VI), Y^1 is NO_2 . In another embodiment of Formula (VI), Y^1 is SO_2R^{17} ; wherein R^{17} is as defined herein. In another embodiment of Formula (VI), Y^1 is SO_2R^{17} ; wherein R^{17} is alkyl. In another embodiment of Formula (VI), Y^1 is R^{17} ; wherein R^{17} is alkynyl. In another embodiment of Formula (VI), A^1 is $C(A^2)$; A^2 is H; B^1 is NHR^1 ; D^1 is H; E^1 is H; and Y^1 is NO_2 or SO_2R^{17} ; wherein R^{17} is alkyl or alkynyl. In another embodiment of Formula (VI), A^1 is $C(A^2)$; A^2 is H; B^1 is NHR^1 ; D^1 is H; E^1 is H; and Y^1 is NO_2 . In another embodiment of Formula (VI), A^1 is $C(A^2)$; A^2 is H; B^1 is NHR^1 ; D^1 is H; E^1 is H; and Y^1 is SO_2R^{17} ; wherein R^{17} is alkyl substituted with three F. In another embodiment of Formula (VI), A^1 is N; B^1 is NHR^1 ; D^1 is H; E^1 is H; and Y^1 is NO_2 or SO_2R^{17} ; wherein R^{17} is alkyl or alkynyl. In another embodiment of Formula (VI), A^1 is N; B^1 is NHR^1 ; D^1 is H; E^1 is

H; and Y^1 is NO_2 . In another embodiment of Formula (VI), A^1 is N; B^1 is NHR^1 ; D^1 is H; E^1 is H; and Y^1 is SO_2R^{17} ; wherein R^{17} is alkyl substituted with three F.

In one embodiment of Formula (IV), Y^1 and B^1 , together with the atoms to which they are attached, are benzene. In another embodiment of Formula (IV), Y^1 and B^1 , together with the atoms to which they are attached, are heteroarene. In another embodiment of Formula (IV), A^1 is $C(A^2)$; A^2 , G^1 , E^1 , and D^1 are independently selected H; and Y^1 and B^1 , together with the atoms to which they are attached, are benzene. In another embodiment of Formula (IV), A^1 is $C(A^2)$; A^2 , G^1 , E^1 , and D^1 are independently selected H; and Y^1 and B^1 , together with the atoms to which they are attached, are heteroarene.

In one embodiment of Formula (VI), R^1 is R^4 or R^5 . In one embodiment of Formula (VI), R^1 is R^4 . In one embodiment of Formula (VI), R^1 is R^5 . In one embodiment of Formula (VI), R^1 is R^4 ; and R^4 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl. In one embodiment of Formula (VI), R^1 is R^4 ; and R^4 is cycloalkyl or heterocycloalkyl. In one embodiment of Formula (VI), R^1 is R^4 ; and R^4 is cycloalkyl. In one embodiment of Formula (VI), R^1 is R^4 ; and R^4 is heterocycloalkyl.

In one embodiment of Formula (VI), R^1 is R^4 ; and R^4 is cycloalkyl; wherein R^4 is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is substituted as defined herein. In another embodiment of Formula (VI), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is substituted with R^{57} or $N(R^{57})_2$. In another embodiment of Formula (VI), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R^{57} ; and R^{57} is R^{60} . In another embodiment of Formula (VI), R^1 is R^4 ; R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R^{57} ; R^{57} is R^{60} ; and R^{60} is heterocycloalkyl. In another embodiment of Formula (VI), R^1 is R^4 ; R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R^{57} ; R^{57} is R^{60} ; R^{60} is heterocycloalkyl; wherein the heterocycloalkyl ring is morpholinyl. In another embodiment of Formula (VI), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is substituted with $N(R^{57})_2$. In another embodiment of Formula (VI), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with $N(R^{57})_2$. In another embodiment of Formula (VI), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with $N(R^{57})_2$; R^{57} is R^{61} ; and R^{61} is alkyl which is unsubstituted or substituted with R^{62} . In another embodiment of Formula (VI), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the

cyclohexyl ring is substituted with R^{57} ; R^{57} is R^{61} ; and R^{61} is alkyl which is unsubstituted or substituted with R^{62} ; R^{62} is R^{65} ; and R^{65} is cycloalkyl. In another embodiment of Formula (VI), R^1 is R^4 ; and R^4 is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R^{57} ; R^{57} is R^{61} ; and R^{61} is alkyl which is substituted with R^{62} ; R^{62} is R^{65} ; and R^{65} is cyclopropyl.

In one embodiment of Formula (VI), R^1 is R^4 ; and R^4 is heterocycloalkyl; wherein R^4 is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R^1 is R^4 ; and R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted as defined herein. In another embodiment of Formula (VI), R^1 is R^4 ; and R^4 is heterocycloalkyl;

wherein the heterocycloalkyl ring is substituted with R^{57} . In another embodiment of Formula (VI), R^1 is R^4 ; and R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is piperdinyll or piperizinyll; and wherein the heterocycloalkyl ring is substituted with R^{57} ; and R^{57} is R^{60} or R^{61} . In another embodiment of Formula (VI), R^1 is R^4 ; R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is piperdinyll or piperizinyll; and wherein the piperdinyll or piperizinyll ring is substituted with R^{57} ; R^{57} is R^{60} or R^{61} ; R^{60} is heterocycloalkyl; and R^{61} is alkyl. In another embodiment of Formula (VI), R^1 is R^4 ; R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is piperdinyll or piperizinyll; and wherein the piperdinyll or piperizinyll ring is substituted with R^{57} ; R^{57} is R^{60} ; R^{60} is heterocycloalkyl; wherein the heterocycloalkyl is tetrahydropyranyll. In another embodiment of Formula (VI), R^1 is R^4 ; R^4 is

heterocycloalkyl; wherein the heterocycloalkyl ring is piperdinyll or piperizinyll; and wherein the piperdinyll or piperizinyll ring is substituted with R^{57} ; R^{57} is R^{61} ; R^{61} is alkyl; and the alkyl is methyl. In another embodiment of Formula (VI), R^1 is R^4 ; R^4 is heterocycloalkyl; wherein the heterocycloalkyl ring is piperdinyll or piperizinyll; and wherein the piperdinyll or piperizinyll ring is substituted with $C(O)OR^{57}$; R^{57} is R^{61} ; R^{61} is alkyl; and the alkyl is methyl.

In one embodiment of Formula (VI), R^1 is R^5 ; and R^5 is alkyl which is unsubstituted or substituted. In one embodiment of Formula (VI), R^1 is R^5 ; and R^5 is alkyl which is unsubstituted or substituted with R^7 , OR^7 , OH , CN , or F . In another embodiment of Formula (VI), R^1 is R^5 ; and R^5 is alkyl which is substituted with R^7 , OR^7 , NHR^7 , or $N(R^7)_2$.

In one embodiment of Formula (VI), R^7 is R^8 , R^9 , R^{10} or R^{11} which are unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R^7 is R^8 which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R^7 is R^9 which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R^7 is R^{10} which is unsubstituted or substituted as defined herein. In another

embodiment of Formula (VI), R^7 is R^{11} which is unsubstituted or substituted as defined herein.

In one embodiment of Formula (VI), R^8 is phenyl which is unsubstituted or substituted as defined herein.

5 In one embodiment of Formula (VI), R^9 is heteroaryl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R^9 is furanyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R^9 is furanyl; which is unsubstituted.

10 In one embodiment of Formula (VI), R^{10} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, heterocycloalkyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R^{10} is heterocycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R^{10} is tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, dioxanyl, oxetanyl, piperdiny, or pyrrolidinyl; which are unsubstituted or substituted as defined herein. In another
15 embodiment of Formula (VI), R^{10} is tetrahydropyranyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R^{10} is morpholinyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R^{10} is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R^{10} is cycloalkyl which is unsubstituted or substituted as defined herein. In
20 another embodiment of Formula (VI), R^{10} is cyclohexyl, cyclopropyl, cyclobutyl, or bicyclo[2.2.1]heptanyl, which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R^{10} is heterocycloalkyl which is fused with R^{10A} ; and R^{10A} is heteroarene. In another embodiment of Formula (VI), R^{10} is 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl.

25 In one embodiment of Formula (VI), R^{11} is alkyl, alkenyl or alkynyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R^{11} is alkyl. In another embodiment of Formula (VI), R^{11} is methyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R^{11} is alkyl; which is substituted as defined herein. In another embodiment of Formula (VI), R^{11} is alkyl; which is
30 substituted with R^{12} , OR^{12} , or CF_3 . In another embodiment of Formula (VI), R^{11} is alkyl, which is substituted with OR^{12} ; R^{12} is R^{16} ; and R^{16} is alkyl. In another embodiment of Formula (VI), R^{11} is alkyl; which is substituted with CF_3 . In another embodiment of Formula (VI), R^{11} is alkyl, which is substituted with R^{12} ; R^{12} is R^{14} ; and R^{14} is heteroaryl.

In one embodiment of Formula (VI),

- n, p, r, and q are each 0;
 A^1 is N or $C(A^2)$;
 A^2 is H, F, Br, I, or Cl;
 B^1 is R^1 , OR^1 , NHR^1 , $NHC(O)R^1$, F, Br, I or Cl;
5 D^1 is H, F, Br, I, or Cl;
 E^1 is H; and
 Y^1 is H, CN, NO_2 , F, Cl, Br, I, CF_3 , R^{17} , OR^{17} , SR^{17} , SO_2R^{17} , or $C(O)NH_2$; or
 Y^1 and B^1 , together with the atoms to which they are attached, are benzene,
heteroarene, or heterocycloalkene; and
10 A^2 , D^1 , and E^1 are independently selected H;
 R^1 is R^4 or R^5 ;
 R^4 is cycloalkyl, or heterocycloalkyl;
 R^5 is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two
or three of independently selected R^7 , OR^7 , NHR^7 , $N(R^7)_2$, CN, OH, F, Cl, Br or I;
15 R^7 is R^8 , R^9 , R^{10} , or R^{11} ;
 R^8 is phenyl;
 R^9 is heteroaryl;
 R^{10} is cycloalkyl, cycloalkenyl, or heterocycloalkyl; each of which is unfused or fused
with R^{10A} , R^{10A} is heteroarene;
20 R^{11} is alkyl each of which is unsubstituted or substituted with one or two or three of
independently selected R^{12} , OR^{12} or CF_3 ;
 R^{12} is R^{14} or R^{16} ;
 R^{14} is heteroaryl;
 R^{16} is alkyl;
25 R^{17} is R^{21} ;
 R^{21} is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two
or three of independently selected R^{22} , F, Cl, Br or I;
 R^{22} is R^{25} ;
 R^{25} is heterocycloalkyl;
30 wherein the cyclic moieties represented by Y^1 and B^1 together, R^4 , R^8 , R^{10} , and R^{25} ,
are independently unsubstituted, further unsubstituted, substituted or further substituted with
one or two or three or four or five of independently selected R^{57A} , R^{57} , OR^{57} , SO_2R^{57} ,
 $C(O)R^{57}$, $CO(O)R^{57}$, $C(O)N(R^{57})_2$, NH_2 , NHR^{57} , $N(R^{57})_2$, $NHC(O)R^{57}$, $NHS(O)_2R^{57}$, OH, CN,
(O), F, Cl, Br or I;

R^{57A} is spiroalkyl, or spiroheteroalkyl;

R^{57} is R^{58} , R^{60} or R^{61} ;

R^{58} is phenyl;

R^{60} is cycloalkyl, or heterocycloalkyl;

5 R^{61} is alkyl which is unsubstituted or substituted with one or two or three of independently selected R^{62} , OR^{62} , $N(R^{62})_2$, $C(O)OH$, CN , F , Cl , Br or I ;

R^{62} is R^{65} , or R^{66} ;

R^{65} is cycloalkyl, or heterocycloalkyl;

R^{66} is alkyl which is unsubstituted or substituted with OR^{67} ;

10 R^{67} is alkyl;

wherein the cyclic moieties represented by R^{57A} , R^{58} , and R^{60} are unsubstituted or substituted with one or two or three or four of independently selected R^{68} , F , Cl , Br or I ;

R^{68} is R^{71} or R^{72} ;

R^{71} is heterocycloalkyl; and

15 R^{72} is alkyl, which is unsubstituted or substituted with one or two F .

Still another embodiment pertains to a compound having Formula (VI), which is 4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

20 4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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

25 and therapeutically acceptable salts, and metabolites thereof.

Pharmaceutical Compositions, Combination Therapies, Methods of Treatment, and Administration

Another embodiment comprises pharmaceutical compositions comprising a
30 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).

5 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).

10 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
15 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
20 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
25 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
30 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 proteins.

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 proteins.

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, camphorsulfonate, 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 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.

5 The compounds having Formula (I) may be administered, for example, buccally, 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
10 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
15 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,
20 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
25 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,
30 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, proteasome 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'-OCH₃-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 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.

5 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,
10 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
15 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), capecitabine, LEUSTAT[®] (cladribine), clofarabine,
20 cytarabine, cytarabine ocfosfate, cytosine arabinoside, decitabine, deferoxamine, doxifluridine, eflornithine, EICAR (5-ethynyl-1- β -D-ribofuranosylimidazole-4-carboxamide), enocitabine, ethynylcytidine, fludarabine, 5-fluorouracil alone or in combination with leucovorin, GEMZAR[®] (gemcitabine), hydroxyurea, ALKERAN[®] (melphalan), mercaptopurine, 6-mercaptopurine riboside, methotrexate,
25 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
30 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.

5 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.

10 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.

15 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, pertuzumab), 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 bispecific antibodies, mAB AR-209, mAB 2B-1 and the like.

25 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.

30 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
5 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.

10 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),
15 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.

20 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,
25 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,
30 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) and the like.

Antibiotics include intercalating antibiotics aclarubicin, actinomycin D, amrubicin, annamycin, adriamycin, BLENOXANE[®] (bleomycin), daunorubicin, CAELYX[®] or MYOCET[®] (liposomal doxorubicin), elsamitrucin, epirubicin, glarubicin, 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, pirarubicin, 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 seocalcitrol (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, 5 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 10 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, tecceleukin, THERACYS[®] (Bacillus Calmette-Guerin), ubenimex, VIRULIZIN[®] (immunotherapeutic, Lorus Pharmaceuticals), Z-100 15 (Specific Substance of Maruyama (SSM)), WF-10 (Tetrachlorodccaoxide (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 20 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 25 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 30 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
 5 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 (combrestatin derivative) BEC2 (mitumomab),
 10 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
 15 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
 20 (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
 25 (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, PANDIMEXT™ (aglycone saponins from ginseng
 30 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
 5 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- α v β 3 antibody), XCYTRIN[®] (motexafin gadolinium), XINLAY[™] (atrasentan), XYOTAX[™] (paclitaxel poliglumex), YONDELIS[®] (trabectedin), ZD-6126, ZINECARD[®] (dexrazoxane), ZOMETA[®] (zoledronic acid),
 10 zorubicin and the like.

Data

Determination of the utility of compounds having Formula (I) as binders to and inhibitors of anti-apoptotic Bcl-2 proteins was performed using the Time Resolved-Fluorescence Resonance Energy Transfer (TR-FRET) Assay. Tb-anti-GST antibody was
 15 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
 20 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-
 25 OH, Fmoc-Asn(Trt)-OH, Fmoc-Pro-OH, Fmoc-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
 30 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 μ mol preloaded Wang resin/vessel on an
5 ABI 433A peptide synthesizer using 250 μ mol 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.

10 *Removal Of 4-Methyltrityl (Mtt) From Lysine*

The resin from the synthesizer was washed thrice with DCM 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
15 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 $\times$ DCM and 1 $\times$ methanol) and dried to provide an orange
20 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
25 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
30 Unipoint® analysis software (Gilson, Inc., Middleton, WI) on a radial compression column
containing two 25 $\times$ 100 mm segments packed with Delta-Pak™ C18 15 μ m 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

5 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
10 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-NH₂

Fmoc-Rink amide MBHA resin was extended using the general peptide synthesis
15 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
20 (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-NH₂

The protected peptide was assembled on 0.25 mmol Fmoc-Rink amide MBHA resin (Novabiochem) on an Applied Biosystems 433A automated peptide synthesizer running
25 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
30 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 μ M (2 $\times$ starting concentration; 10% DMSO) and 10 μ L were transferred into a 384-well plate. Then 10 μ L of a protein/probe/antibody mix was added to each well at final concentrations listed in TABLE 1. The samples are 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. Dissociation constants (K_i) are shown in TABLE 2 below and 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 1. Protein, Probe And Antibody Used For TR-FRET Assays

Protein	Probe	Protein (nM)	Probe (nM)	Antibody	Antibody (nM)
GST-Bcl-2	F-Bak Peptide Probe Acetyl-(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 are shown in TABLE 2 below. 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

5 Wang's equation (Wang Zx., 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 Bcl-2 Binding K_i (μ M)

EXAMPLE #	K_i	EXAMPLE #	K_i
1	0.000225	190	0.000026
2	< 0.000010	191	< 0.000010
3	0.000013	192	< 0.000010
4	< 0.000010	193	< 0.000010
5	< 0.000010	194	< 0.000010
6	0.000018	195	< 0.000010
7	0.00492	196	< 0.000010
8	0.000153	197	< 0.000010
9	< 0.000010	198	< 0.000010
10	< 0.000010	199	< 0.000010
11	0.000016	200	< 0.000010
12	< 0.000010	201	0.000014
13	< 0.000010	202	< 0.000010
14	0.002798	203	< 0.000010
15	< 0.000010	204	< 0.000010
16	0.000219	205	< 0.000010
17	0.00009	206	0.000036
18	0.000017	207	0.00003
19	0.000226	208	0.000104
20	0.000181	209	< 0.000010
21	0.000912	210	0.000011
22	0.000291	211	0.000058
23	0.000083	212	0.0001330
24	< 0.000010	213	< 0.000010

25	< 0.000010	214	< 0.000010
26	0.000011	215	< 0.000010
27	0.000134	216	< 0.000010
28	< 0.000010	217	< 0.000010
29	< 0.000010	218	0.000013
30	< 0.000010	219	0.001192
31	< 0.000010	220	0.000988
32	< 0.000010	221	0.000049
33	< 0.000010	222	0.000938
34	0.00001	223	0.000053
35	< 0.000010	224	< 0.000010
36	0.000017	225	0.000196
37	< 0.000010	226	0.000139
38	0.0003	227	< 0.000010
39	0.000012	228	0.026761
40	< 0.000010	229	0.002109
41	< 0.000010	230	0.000031
42	0.000439	231	0.000770
43	0.000012	232	0.001631
44	< 0.000010	233	0.001654
45	< 0.000010	234	0.000115
46	0.000935	235	0.000023
47	< 0.000010	236	0.000033
48	< 0.000010	237	0.000024
49	0.000074	238	< 0.000010
50	0.000021	239	0.000026
51	< 0.000010	240	< 0.000010
52	0.000114	241	< 0.000010
53	< 0.000010	242	0.000057
54	0.002071	243	0.000546
55	< 0.000010	244	0.000281
56	0.000037	245	0.000015

57	0.000063	246	0.000144
58	< 0.000010	247	0.000019
59	0.000203	248	0.000029
60	< 0.000010	250	0.000412
61	0.000091	251	0.000571
62	< 0.000010	252	< 0.000010
63	< 0.000010	253	0.000052
64	< 0.000010	254	< 0.000010
65	< 0.000010	255	< 0.000010
66	< 0.000010	256	< 0.000010
67	< 0.000010	257	0.000052
68	0.000012	258	< 0.000010
69	0.001157	259	< 0.000010
70	0.003964	260	0.000016
71	0.00001	261	0.000134
72	< 0.000010	262	< 0.000010
73	< 0.000010	263	0.000156
74	0.000029	264	0.000036
75	< 0.000010	265	< 0.000010
76	0.000196	266	< 0.000010
77	0.000213	267	0.000035
78	< 0.000010	268	< 0.000010
79	< 0.000010	269	0.000016
80	< 0.000010	270	< 0.000010
81	< 0.000010	271	0.000039
82	0.000328	272	0.000031
83	0.000071	273	0.000035
84	0.000123	274	0.000040
85	0.000391	275	< 0.000010
86	0.000498	276	< 0.000010
87	0.000618	277	< 0.000010
88	0.000672	278	0.000252

89	0.000073	279	0.000035
90	0.000013	280	0.000071
91	0.000487	281	0.000145
92	0.000128	282	< 0.000010
93	0.003461	283	< 0.000010
94	0.000678	284	0.000024
95	0.000014	285	< 0.000010
96	0.000014	286	< 0.000010
97	0.000017	287	0.000081
98	< 0.000010	288	0.000251
99	0.000233	289	0.000090
100	< 0.000010	290	< 0.000010
101	0.000021	291	< 0.000010
102	0.000094	292	0.000190
103	< 0.000010	293	0.000093
104	0.000016	294	0.000046
105	< 0.000010	295	< 0.000010
106	0.000895	296	0.000512
107	0.000035	297	0.000174
108	< 0.000010	298	< 0.000010
109	0.000127	299	0.000039
110	0.000557	300	0.001627
111	< 0.000010	301	0.002065
112	< 0.000010	302	0.000332
113	< 0.000010	303	0.000044
114	< 0.000010	304	nd
115	< 0.000010	305	0.000033
116	< 0.000010	306	0.002067
117	< 0.000010	307	0.000130
118	< 0.000010	308	0.000141
119	< 0.000010	309	0.000023
120	< 0.000010	310	0.000165

121	< 0.000010	311	< 0.000010
122	< 0.000010	312	< 0.000010
123	< 0.000010	313	0.001102
124	< 0.000010	314	0.000042
125	< 0.000010	315	0.000052
126	< 0.000010	316	0.000601
127	< 0.000010	317	< 0.000010
128	< 0.000010	318	< 0.000010
129	0.000002	319	< 0.000010
130	< 0.000010	320	< 0.000010
131	< 0.000010	321	< 0.000010
132	< 0.000010	322	< 0.000010
133	< 0.000010	323	0.000104
134	< 0.000010	324	< 0.000010
135	< 0.000010	325	< 0.000010
136	< 0.000010	326	< 0.000010
137	< 0.000010	327	< 0.000010
138	< 0.000010	328	< 0.000010
139	< 0.000010	329	0.000030
140	< 0.000010	330	< 0.000010
141	< 0.000010	331	0.001086
142	0.00013	332	0.000621
143	< 0.000010	333	0.000511
144	< 0.000010	334	0.000572
145	< 0.000010	335	0.000150
146	< 0.000010	336	0.000198
147	< 0.000010	337	< 0.000010
148	< 0.000010	338	0.000013
149	< 0.000010	339	0.000036
150	< 0.000010	340	< 0.000010
151	0.000017	341	< 0.000010
152	< 0.000010	342	< 0.000010

153	< 0.000010	343	< 0.000010
154	< 0.000010	344	< 0.000010
155	0.000059	345	< 0.000010
156	< 0.000010	346	0.000042
157	< 0.000010	347	0.000013
158	< 0.000010	348	0.000034
159	< 0.000010	349	0.000023
160	< 0.000010	350	< 0.000010
161	< 0.000010	351	< 0.000010
162	< 0.000010	352	0.000014
163	< 0.000010	353	< 0.000010
164	< 0.000010	354	0.000010
165	< 0.000010	355	0.000014
166	< 0.000010	356	0.000039
167	< 0.000010	357	< 0.000010
168	< 0.000010	358	< 0.000010
169	0.000021	359	< 0.000010
170	0.000022	360	< 0.000010
171	< 0.000010	361	< 0.000010
172	< 0.000010	362	0.000016
173	< 0.000010	363	0.000017
174	< 0.000010	364	< 0.000010
175	0.000119	365	< 0.000010
176	0.000023	366	0.000024
177	0.000111	367	nd
178	0.000076	368	nd
179	< 0.000010	369	< 0.000010
180	< 0.000010	370	0.000285
181	0.000017	371	< 0.0000010
182	0.000068	372	nd
183	< 0.000010	373	< 0.0000010
184	< 0.000010	374	< 0.0000010

185	0.000022	375	0.00010999
186	0.000047	376	< 0.0000010
187	0.00008	377	< 0.0000010
188	< 0.000010	378	< 0.0000010
189	0.000018		

nd = not determined

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. So a large K_i value indicates a low binding affinity and a small K_i value indicates a high binding affinity.

TABLE 2 shows inhibition constants for the inhibition of a Bak BH3 peptide probe to Bcl-2 protein and indicate that compounds according to the invention have high binding affinities for anti-apoptotic Bcl-2 protein. The compounds are therefore expected to have utility in treatment of diseases during which anti-apoptotic Bcl-2 protein is expressed.

RS4;11 Cell Viability Assay

The acute lymphoblastic leukemia (ALL) cell line RS4;11 was used as the primary human cell line to assess the cellular activity of Bcl-2 selective agents in vitro and their efficacy in vivo. Previous studies have shown by BH3 profiling, a mitochondrial assay that classifies blocks in the intrinsic apoptotic pathway, that RS4;11 cells were highly dependant on BCL-2 for survival and sensitive to the Bcl-2 family member inhibitor ABT-737 (Blood, 2008, Vol. 111, 2300-2309). The prevalence of Bcl-2 complexed to the proapoptotic BH3 protein Bim in RS4;11 suggests that these cells are "primed" or more susceptible to cell death by antagonism of the antiapoptotic protein Bcl-2 for which they depend on for survival.

RS4;11 cells were cultured in RPMI-1640 supplemented with 2 mM L-glutamine, 10% FBS, 1 mM sodium pyruvate, 2 mM HEPES, 1% penicillin/streptomycin (Invitrogen), 4.5 g/L glucose and maintained at 37 C containing 5% CO₂. To test for the cellular activity of compounds in vitro, cells were treated at 50,000 cells per well in 96-well microtiter plates in the presence of 10% human serum for 48 hours in a humidified chamber with 5% CO₂. Cell cytotoxicity EC₅₀ values were assessed using CellTiter Glo (Promega) according to the manufacturer's recommendations. The EC₅₀ values were determined as a percentage of viable cells following treatment compared to the untreated control cells.

Table 3. RS4;11 EC₅₀ Values (μM)

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PCT/US2010/036198

EXAMPLE #	EC50	EXAMPLE #	EC50
1	0.712	190	0.55068
2	0.783	191	0.00691
3	0.0142	192	0.00241
4	0.01854	193	0.00076
5	0.01241	194	0.00819
6	0.03487	195	0.00207
7	0.192	196	0.00172
8	0.158	197	0.0125
9	0.01476	198	0.03619
10	0.05202	199	0.00506
11	0.01393	200	0.01099
12	0.03471	201	0.59132
13	0.0232	202	0.0438
14	3.8947	203	0.02208
15	0.01276	204	0.16475
16	1.2098	205	0.01059
17	0.475	206	0.05291
18	0.086	207	0.00376
19	0.465	208	0.12121
20	0.191	209	0.0045
21	0.062	210	0.06022
22	0.085	211	0.3073
23	0.045	212	0.01283
24	0.00983	213	0.0060976
25	0.007	214	0.0043751
26	0.05888	215	0.00056038
27	0.33237	216	0.68263
28	0.0419	217	0.0015528
29	0.02047	218	0.0072907
30	0.01529	219	> 1

31	0.01565	220	> 1
32	0.08147	221	0.094771
33	0.00711	222	> 1
34	0.00748	223	0.18208
35	0.29147	224	0.013887
36	0.18137	225	0.56001
37	0.00118	226	0.1178
38	3.5092	227	0.0073566
39	0.01974	228	> 1
40	0.09974	229	> 1
41	0.05801	230	0.052821
42	0.53412	231	0.52301
43	0.27208	232	> 1
44	0.05309	233	> 1
45	0.00992	234	0.13532
46	> 5	235	0.03232
47	0.03265	236	0.04292
48	0.00333	237	0.05316
49	0.35161	238	0.10303
50	0.31264	239	0.023699
51	0.02308	240	0.017266
52	0.19964	241	0.11377
53	0.06674	242	0.22275
54	1.9158	243	0.80718
55	0.0132	244	0.79378
56	0.08654	245	0.083614
57	0.42611	246	0.40218
58	> 5	247	0.092976
59	0.7215	248	0.099588
60	0.05948	250	> 1
61	0.18337	251	0.91782
62	0.02506	252	0.003475

63	0.00751	253	0.049586
64	0.00025	254	0.019908
65	0.00025	255	0.009004
66	0.01893	256	0.017997
67	0.04954	257	0.026002
68	0.10846	258	0.00055345
69	1.7243	259	0.00038795
70	> 5	260	0.0054323
71	0.09165	261	0.18366
72	0.00751	262	0.016346
73	0.02369	263	> 1
74	0.057	264	0.68866
75	0.01509	265	0.0071718
76	0.51131	266	0.0072924
77	0.76196	267	0.06944
78	0.01252	268	0.048792
79	0.0649	269	0.0072346
80	0.06863	270	0.0025216
81	0.04814	271	0.43657
82	0.68383	272	0.84006
83	0.197	273	0.20925
84	0.158	274	0.21418
85	1.95	275	0.14303
86	1.02	276	0.0035006
87	1.18	277	0.0081845
88	0.447	278	0.79393
89	0.06446	279	0.22492
90	0.06299	280	0.45923
91	0.18296	281	0.65371
92	0.08089	282	0.032187
93	> 5	283	0.013096
94	1.6946	284	0.16213

95	0.02954	285	0.057413
96	0.04356	286	0.034464
97	0.05557	287	0.59312
98	0.0229	288	0.39042
99	1.3923	289	0.6687
100	0.13666	290	0.10663
101	0.2991	291	0.016079
102	0.62178	292	0.88938
103	0.03917	293	0.28715
104	0.07125	294	0.12525
105	0.05357	295	0.014803
106	0.82639	296	0.76869
107	0.06117	297	0.59157
108	0.02407	298	0.070305
109	0.18339	299	0.067981
110	0.53638	300	0.76334
111	0.01451	301	> 1
112	0.02063	302	0.38106
113	0.00136	303	0.04776
114	0.01078	304	0.29755
115	0.01184	305	0.032539
116	0.02853	306	0.55348
117	0.0182	307	0.12767
118	0.01294	308	0.257
119	0.01138	309	0.052421
120	0.00147	310	> 1
121	0.05972	311	0.035835
122	0.00185	312	0.016178
123	0.00333	313	> 1
124	0.21224	314	0.66006
125	0.00838	315	0.21027
126	0.05359	316	> 1

127	0.00975	317	0.013313
128	0.00589	318	0.011566
129	0.01484	319	0.0044972
130	0.01059	320	0.050974
131	0.01266	321	0.0188
132	0.02209	322	0.012367
133	0.03186	323	0.71689
134	0.00251	324	0.0045254
135	0.00237	325	0.012319
136	0.00296	326	0.023133
137	0.01272	327	0.0027224
138	0.00152	328	0.0098808
139	0.01681	329	0.42369
140	0.01275	330	0.0097843
141	0.02044	331	0.92638
142	0.34531	332	0.45738
143	0.01914	333	0.46292
144	0.0212	334	> 1
145	0.004	335	0.26951
146	0.01916	336	0.35134
147	0.02618	337	0.001759
148	0.00938	338	0.003399
149	0.01347	339	0.45016
150	0.05103	340	0.05646
151	0.03372	341	0.031652
152	0.02037	342	0.050891
153	0.01723	343	0.12664
154	0.02647	344	0.0066616
155	0.59421	345	0.0092536
156	0.00805	346	0.19003
157	0.01086	347	0.018849
158	0.01793	348	0.050263

159	0.01179	349	0.023086
160	0.08363	350	0.0058378
161	0.03465	351	0.0020618
162	0.01297	352	0.0011961
163	0.00432	353	0.0050512
164	0.01476	354	0.053231
165	0.0051	355	0.018771
166	0.01185	356	0.026623
167	0.00093	357	0.013235
168	0.08867	358	0.0038131
169	0.07626	359	0.0059243
170	0.12515	360	0.0098968
171	0.05272	361	0.00053755
172	0.02053	362	0.031726
173	0.00516	363	0.02643
174	0.12621	364	0.011244
175	> 1	365	0.0030168
176	0.13353	366	0.016548
177	0.15936	367	nd
178	0.20234	368	nd
179	0.04273	369	0.0079974
180	0.0118	370	nd
181	0.10612	371	0.007165
182	0.1234	372	nd
183	0.01753	373	nd
184	0.02323	374	0.015475
185	0.02747	375	0.56013
186	0.06443	376	0.008765
187	0.21494	377	0.002377
188	0.01638	378	0.006764
189	0.14397		

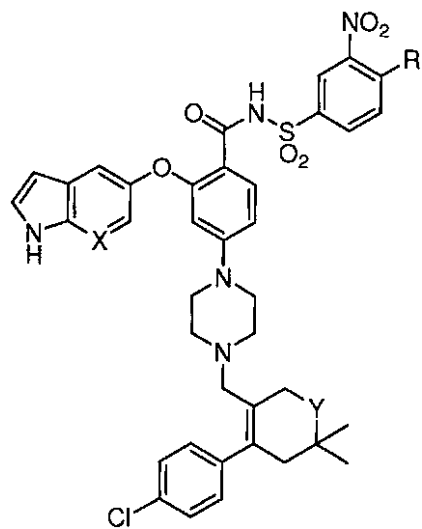
nd = not determined

TABLE 3 shows the utility of compounds having Formula I to functionally inhibit anti-apoptotic Bcl-2 protein in a cellular context. The acute lymphoblastic leukemia (ALL) cell line RS4;11 has been shown by BH3 profiling, a mitochondrial assay that classifies blocks in the intrinsic apoptotic pathway, to be highly dependant on Bcl-2 for survival and is sensitive to the Bcl-2 family member inhibitor ABT-737 (*Blood*, **2008**, Vol. 111, 2300-2309). The ability of compounds to kill RS4;11 cells 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 RS4;11 cells as demonstrated by low EC₅₀ values.

Compounds taught in U.S. Patent Application No. 12/631404, entitled "BCL-2-SELECTIVE APOPTOSIS-INDUCING AGENTS FOR THE TREATMENT OF CANCER AND IMMUNE DISEASES," filed on December 4, 2009, have utility for the treatment of various cancers and auto-immune diseases due to their activity against Bcl-2 family proteins, and more specifically Bcl-2. These compounds bind to Bcl-2 with high affinity in a FRET based assay described in 12/631404. The administration of a one or more of these compounds to cells that are dependant on Bcl-2 or Bcl-2 family proteins for survival, such as the RS4;11 B-cell leukemia human tumor cell line, results in apoptosis, also known as programmed cell death. The amount of apoptosis caused by administration of the compound is represented by the EC₅₀ in the cell viability assay, which is a measure of the number of living cells after administration of compound.

TABLE 4 identifies certain compounds (described below in Examples in 19, 20, 23 and 92 and described more fully in 12/631404, the disclosure of which is incorporated herein by reference) with the various substituents being defined by R, X and Y as set forth. As can be seen from TABLE 4, these compounds exhibit a trend of increasing binding affinity (K_i) for Bcl-2 with increasing levels of apoptosis, or cell death, in the Bcl-2 dependant tumor cell line RS4;11. On this basis, the inventors expect that compounds with even greater affinity towards Bcl-2 than those compounds shown in Table 4 will exhibit a similar trend, potentially eliciting even greater levels of apoptosis, when administered to cells dependent on Bcl-2 for survival.

Table 4. Selected compounds in US Patent Application No. 12/631404



EXAMPLE	R	X	Y	Bcl-2 FRET K _i (μM)	RS4;11 EC50 (μM)
(23)		C	O	0.000083	0.045
(92)		C	C	0.000128	0.081
(20)		C	C	0.000181	0.191
(19)		C	C	0.000226	0.465

To this end, binding affinity and cellular activity for compounds according to the present invention were compared with structurally similar indole compounds. In particular, the compounds of the present invention, in which a nitrogen is contained at a specific position within the heteroarene fused to the heteroaryl ring were compared with the corresponding indole compounds, which latter compounds lack only the specific nitrogen substitution included in the compounds of the present invention.

As can be seen in TABLE 5, compounds of the present invention having the specific nitrogen substitutions shown (i.e., compounds of Examples 1, 2, 3, 4, 5, 6, 9, 10, 11, 12, 13, 15, 16, and 17, where Z = N) in fact achieve relatively greater levels of apoptosis when administered to cells that depend on Bcl-2 for survival and have increased affinity towards Bcl-2 relative to the corresponding structural analogs lacking the specific nitrogen

substitution (i.e., compounds of Examples 87, 88, 89, 90, 91, 19, 20, 21, 92, 22, 23, 93, and 94, respectively, where Z = C, taught in 9696USL2, the disclosure of which is incorporated herein by reference).

Specifically, the seventh column of TABLE 5 compares binding affinity of
5 compounds of the present invention (the compound identified by the designated substituents in the uppermost row in each pair of rows set apart by blank rows) to corresponding compounds lacking the described nitrogen substitution. In each comparison, compounds of the present application (upper row of each pair of rows separated by a blank row) bind Bcl-2 with greater affinity to Bcl-2 than the corresponding analogs (lower row of each pair of rows
10 separated by a blank row).

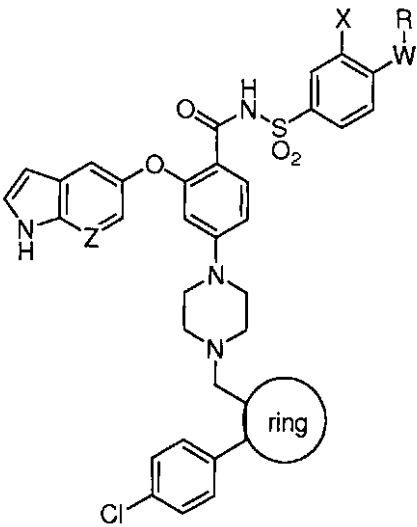
Further, column 8 of TABLE 5 compares the amount of apoptosis in the Bcl-2 dependant RS4;11 cell line achieved using compounds of the present invention (again the compound identified by the designated substituents in the uppermost row in each pair of rows set apart by blank rows) to that achieved using compounds of Examples 87, 88, 89, 90, 91,
15 19, 20, 21, 92, 22, 23, 93, and 94, where Z = C. In each comparison, compounds of the present invention (upper row of each pair of rows separated by a blank row) achieve greater extent of apoptosis in Bcl-2 dependent RS4;11 cells than the corresponding analogs (lower row of each pair of rows separated by a blank row).

The increase in binding affinity between the compounds of the present invention and
20 corresponding analogs ranges from 2.7x to greater than 100x, and the increased potency in RS4;11 cells ranges from a 1.65x increase to greater than 10x increase.

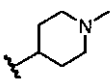
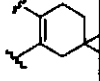
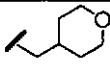
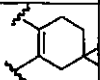
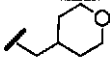
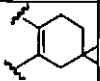
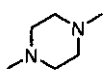
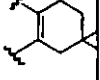
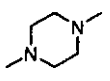
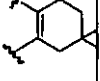
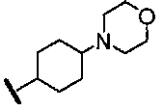
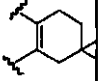
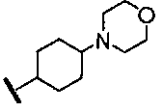
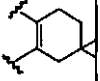
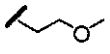
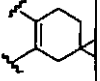
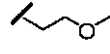
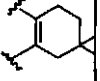
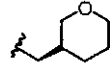
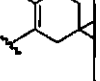
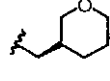
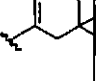
As detailed below, a specific substitution of a nitrogen atom for a carbon atom leads to unexpected increase in binding affinity to antiapoptotic Bcl-2 and increase in potency in cell viability assays assessing apoptosis in Bcl-2 dependent cell lines.

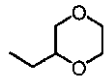
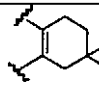
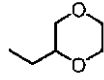
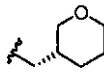
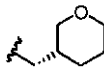
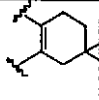
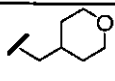
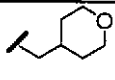
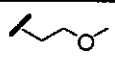
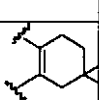
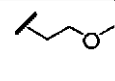
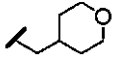
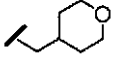
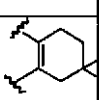
25 This invention therefore comprises a series of compounds that demonstrate unexpected properties with respect to their binding to and inhibiting the activity of anti-apoptotic Bcl-2 protein to a significantly greater extent than corresponding analog compounds.

TABLE 5. Direct comparison of compounds of the present invention with corresponding
30 analogs.

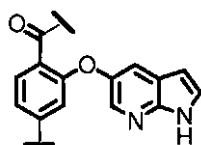


EXAMPLE	R	W	X	Ring	Z	Bcl-2 FRET ki (μM)	RS4;11 EC50 (μM)
(1)		NH	NO ₂		N	0.000225	0.712
(87)		NH	NO ₂		C	0.000618	1.180
(2)		NH	NO ₂		N	< 0.000010	0.783
(88)		NH	NO ₂		C	0.672	0.447
(3)		NH	NO ₂		N	0.000013	0.0142
(89)		NH	NO ₂		C	0.000074	0.064
(4)		NH	NO ₂		N	< 0.00001	0.019

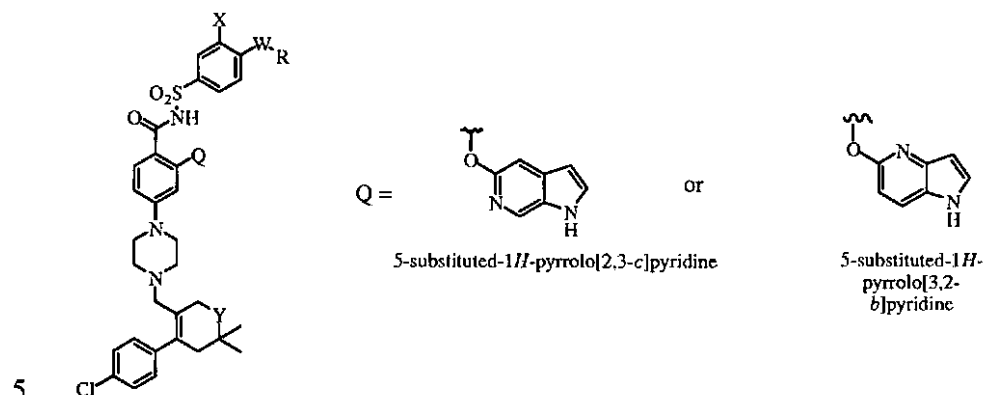
(90)		NH	NO ₂		C	0.000013	0.063
(5)		NH	NO ₂		N	< 0.00001	0.012
(18)		NH	NO ₂		C	0.000017	0.086
(6)		NH	NO ₂		N	0.000018	0.035
(91)		NH	NO ₂		C	0.000487	0.183
(9)		NH	NO ₂		N	< 0.00001	0.015
(19)		NH	NO ₂		C	0.000226	0.465
(10)		NH	NO ₂		N	< 0.00001	0.052
(20)		NH	NO ₂		C	0.000181	0.191
(11)		NH	NO ₂		N	0.000016	0.014
(21)		NH	NO ₂		C	0.000912	0.062

(12)		O	NO ₂		N	< 0.00001	0.035
(92)		O	NO ₂		C	0.000128	0.081
(13)		NH	NO ₂		N	< 0.00001	0.023
(22)		NH	NO ₂		C	0.000291	0.085
(15)		NH	NO ₂		N	< 0.00001	0.013
(23)		NH	NO ₂		C	0.000083	0.045
(16)		NH	SO ₂ CF ₃		N	0.000219	1.210
(93)		NH	SO ₂ CF ₃		C	0.035	> 5.000
(17)		NH	SO ₂ CF ₃		N	0.000090	0.475
(94)		NH	SO ₂ CF ₃		C	0.000678	1.690

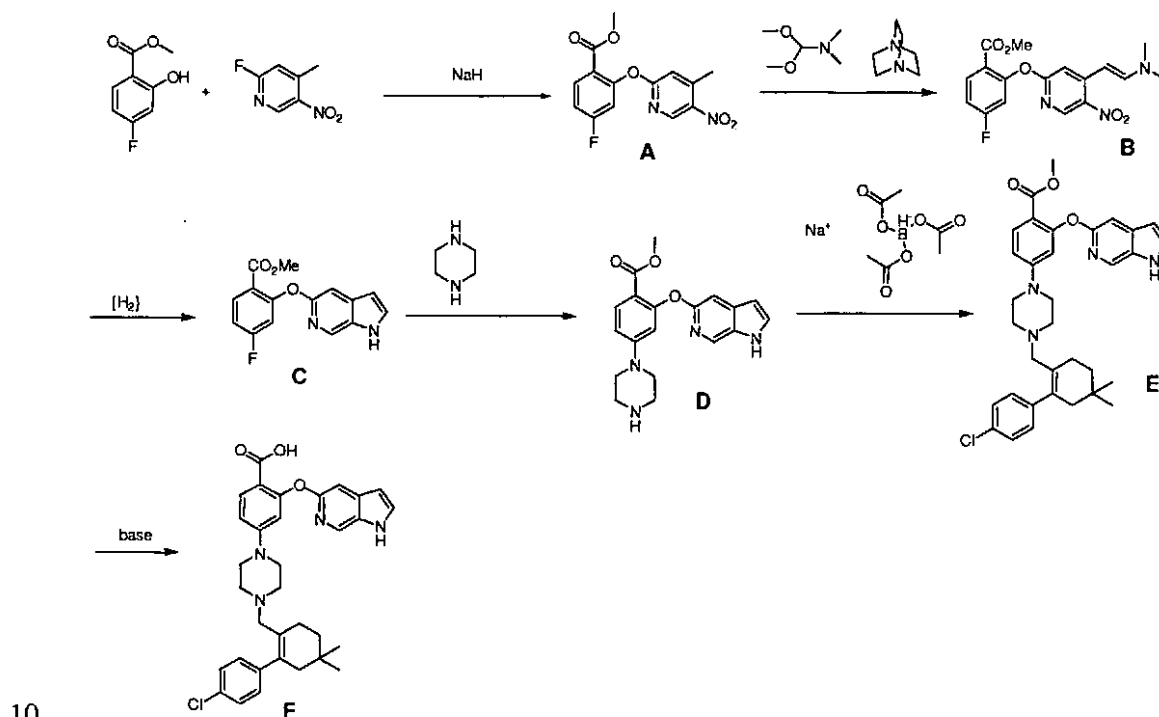
More specifically, compounds of the present invention contain a substitution pattern shown in the diagram below.



Other compounds that contain isomeric ring systems to that shown above, such as those rings systems containing a nitrogen adjacent to the oxygenated carbon within the ring, as shown below, are compromised by instability.

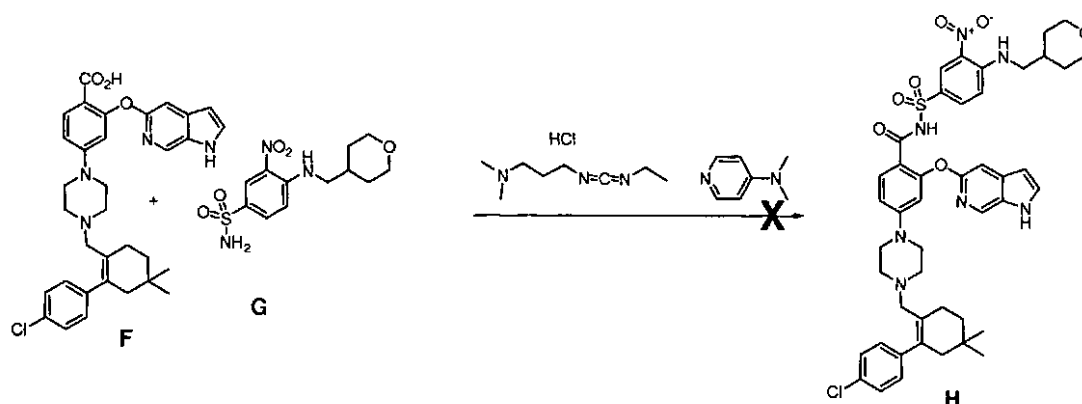


Specifically, this was discovered by the inventors in the following compound preparation. The intermediate structure F, that directly precedes the final product of the unstable compound, was prepared according to the route below. All intermediates A-F were stable and isolable using techniques known to those skilled in the art.

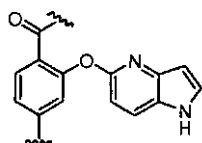


Intermediate F, shown in the scheme above, was reacted with intermediate G using standard coupling conditions that are known to those skilled in the art. The reaction mixture

was analyzed via HPLC/MS to monitor the formation of a peak corresponding to the compound **H**. While this peak formed within hours of initiating the reaction below, the peak progressively disappeared during workup and chromatography, until it no longer was present. The lack of stability of the putative compound originates from the position of the nitrogen within the fused ring-system described above. This position, which is adjacent to the oxygen-bearing carbon in the 5-substituted-1H-pyrrolo[2,3-c]pyridine ring system shown below and described above, makes the compound **H** unstable.



It is expected that a compound containing the fused 5-substituted-1H-pyrrolo[3,2-b]pyridine ring system below would be similarly unstable, since the position of the nitrogen is adjacent to the oxygen-bearing carbon within the ring.



Therefore, compounds with the 5-substituted-1H-pyrrolo[2,3-b]pyridines are preferred over the isomeric compounds.

It is expected that, because compounds having Formula (I) bind to Bcl-2, they would also have utility as binders to anti-apoptotic proteins having close structural homology to Bcl-2, such as, for example, anti-apoptotic Bcl-X_L, Bcl-w, Mcl-1 and Bfl-1/A1 proteins.

Involvement of Bcl-2 proteins 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.

5 Involvement of Bcl-2 proteins in arthritis is disclosed in commonly-owned United States Provisional Patent Application Serial No. 60/988,479.

Involvement of Bcl-2 proteins in bone marrow transplant rejection is disclosed in commonly-owned United States Patent Application Serial No. 11/941,196.

Overexpression of Bcl-2 proteins correlates with resistance to chemotherapy, clinical
 10 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
 15 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,
 20 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,
 25 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
 30 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 proteins 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 tumors, 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, abetalipoproteinemia, 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-1- 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
 5 (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
 10 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, choleosatis,
 chronic alcoholism, chronic active hepatitis, chronic fatigue syndrome, chronic immune
 15 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
 20 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
 25 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,
 30 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
 5 cell leukemia, Hallerorden-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 purpura, Hepatitis A, Hepatitis B, Hepatitis C, HIV infection/HIV neuropathy, Hodgkin's disease, hypoparathyroidism, Huntington's chorea,
 10 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
 15 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, lymphedema,
 20 lymphocytic infiltrative lung disease, malaria, male infertility idiopathic or NOS, malignant histiocytosis, malignant melanoma, meningitis, meningococemia, microscopic vasculitis of the kidneys, migraine headache, mitochondrial multisystem 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
 25 Machado-Joseph), myalgic encephalitis/Royal Free Disease, myasthenia gravis, microscopic vasculitis of the kidneys, mycobacterium avium intracellulare, mycobacterium tuberculosis, myelodysplastic syndrome, myocardial infarction, myocardial ischemic disorders, nasopharyngeal carcinoma, neonatal chronic lung disease, nephritis, nephrosis, nephrotic syndrome, neurodegenerative diseases, neurogenic I muscular atrophies, neutropenic fever,
 30 Non-alcoholic Steatohepatitis, occlusion of the abdominal aorta and its branches, occlusive arterial disorders, organ transplant rejection, orchitis/epididymitis, orchitis/vasectomy reversal procedures, organomegaly, osteoarthritis, 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 atherosclerotic 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 cardiomyopathy 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 supranuclear 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, Raynaud's 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, Sjögren's syndrome, skin allograft rejection, skin changes syndrome, small bowel transplant rejection, sperm autoimmunity, multiple sclerosis (all subtypes), spinal ataxia, spinocerebellar degenerations, spondyloarthropathy, 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, viral 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

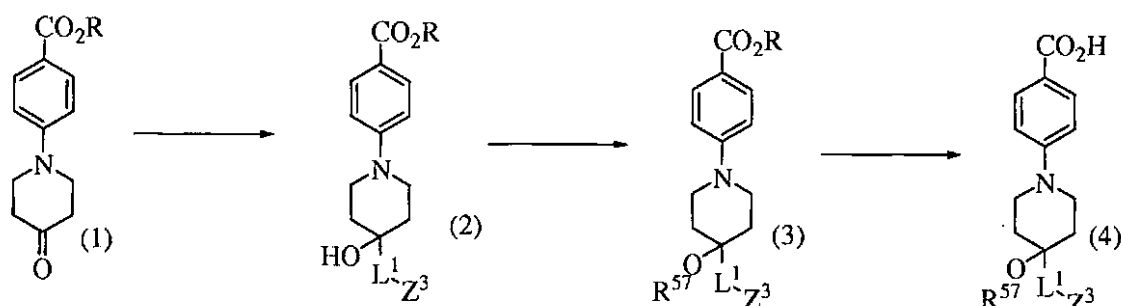
The following abbreviations have the meanings indicated. ADDP means

- 5 1,1'-(azodicarbonyl)dipiperidine; AD-mix- β means a mixture of (DHQD)₂PHAL, K₃Fe(CN)₆, K₂CO₃, and K₂SO₄; 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;
- 10 DMF means N,N-dimethylformamide; dmpe means 1,2-bis(dimethylphosphino)ethane; DMSO means dimethylsulfoxide; 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
- 15 fluorenylmethoxycarbonyl; HATU means O-(7-azabenzotriazol-1-yl)-N,N',N'-tetramethyluronium hexafluorophosphate; HMPA means hexamethylphosphoramide; IPA means isopropyl alcohol; MP-BH₃ means macroporous triethylammonium methylpolystyrene cyanoborohydride; TEA means triethylamine; TFA means trifluoroacetic acid; THF means tetrahydrofuran; NCS means N-chlorosuccinimide; NMM means N-methylmorpholine; NMP
- 20 means N-methylpyrrolidine; PPh₃ means triphenylphosphine.

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

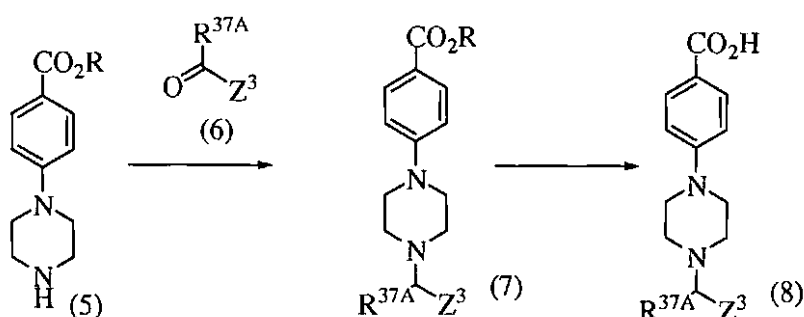
- 25 processes may be varied, that reagents, solvents and reaction conditions may be substituted for those specifically mentioned, and that vulnerable moieties may be protected and deprotected, as necessary.

SCHEME 1



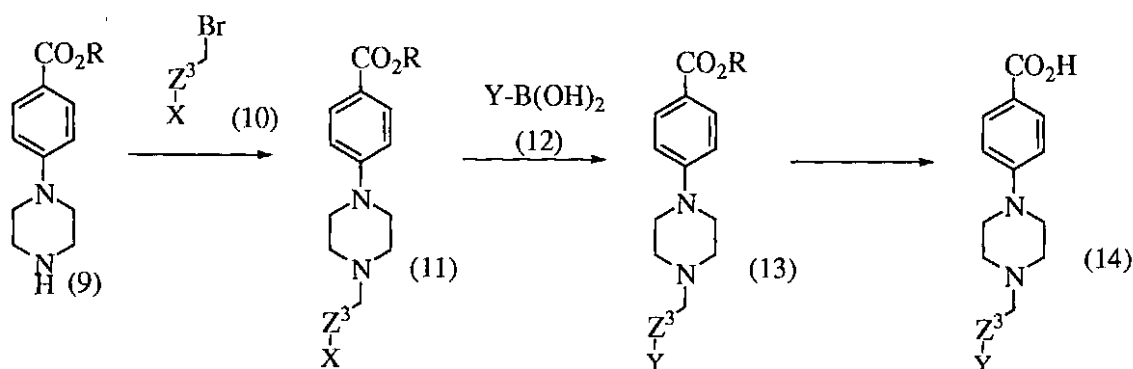
Compounds of Formula (4) can be prepared as shown in SCHEME 1, and can be used as described in SCHEME 8 to prepare compounds of Formula (I), which are representative of the compounds of the present invention. Compounds of Formula (1) wherein R is alkyl, can be converted to compounds of Formula (2) using $\text{Z}^3\text{L}^1\text{MgX}^1$, 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^{57}X^2 , wherein X^2 is a halide and R^{57} is as described herein. Compounds of Formula (3), when treated with aqueous NaOH or LiOH, will provide compounds of Formula (4).

SCHEME 2



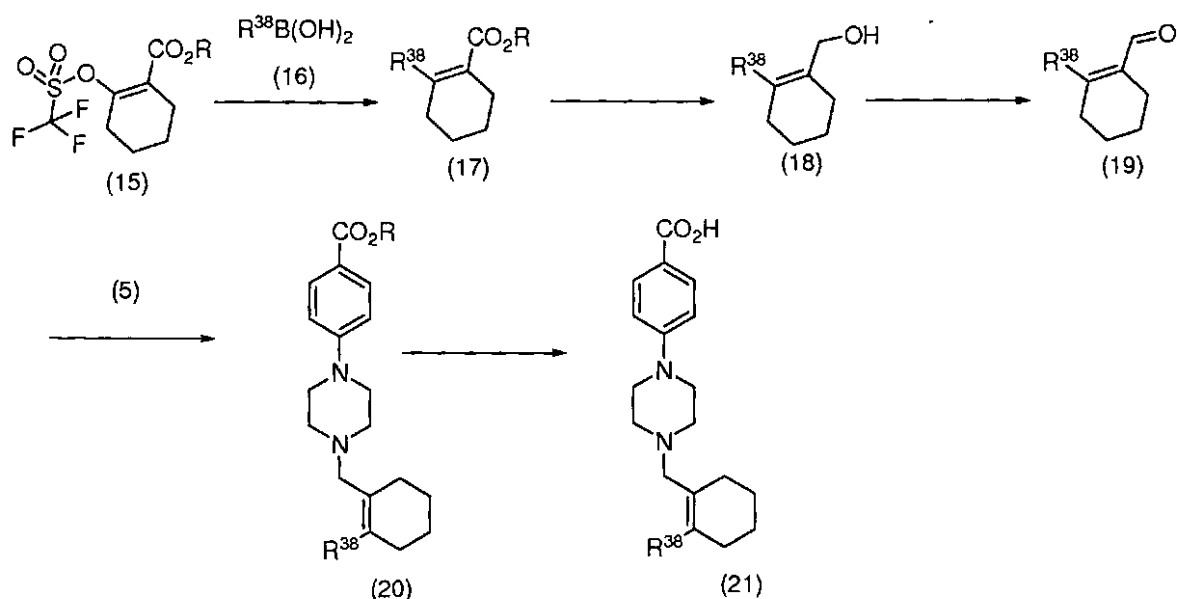
As shown in SCHEME 2, compounds of Formula (5) can be reacted with compounds of Formula (6) and a reducing agent to provide compounds of Formula (7). Examples of reducing agents include sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, polymer supported cyanoborohydride, and 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 8 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 Y is as described herein for substituents on Z^3 , 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 8 to prepare compounds of Formula (I).

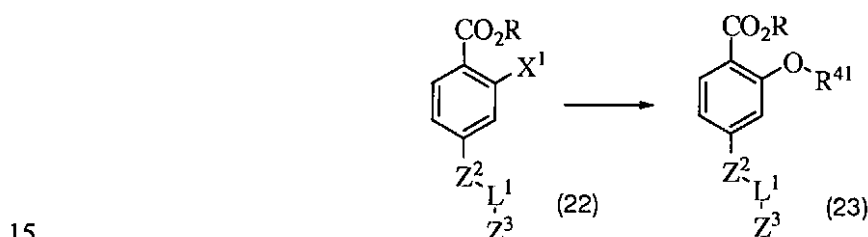
SCHEME 4



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^{38} 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
 5 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
 10 Formula (21) can be prepared from compounds of Formula (20) as described in SCHEME 1, and can be used as described in SCHEME 8 to prepare compounds of Formula (I).

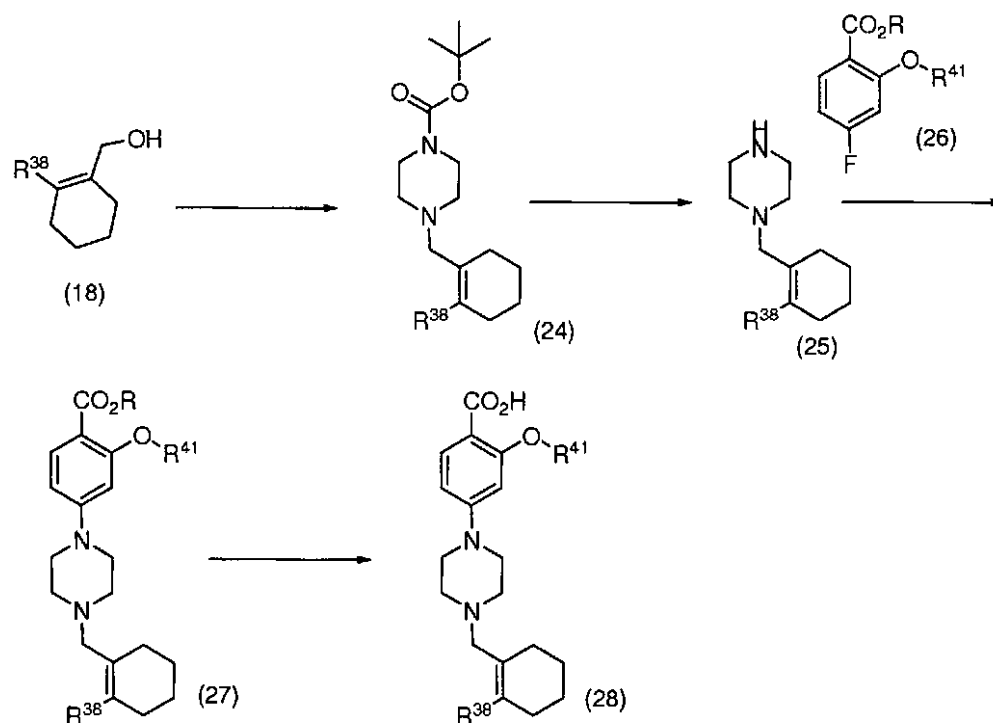
SCHEME 5



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 $\text{R}^{41}\text{-OH}$ and a catalyst, with or without a first base. Examples of catalysts include copper(I) trifluoromethanesulfonate toluene complex, PdCl_2 ,
 20 $\text{Pd}(\text{OAc})_2$, and $\text{Pd}_2(\text{dba})_3$. Examples of first bases include triethylamine, N,N-diisopropylethylamine, Cs_2CO_3 , Na_2CO_3 , K_3PO_4 , and mixtures thereof.

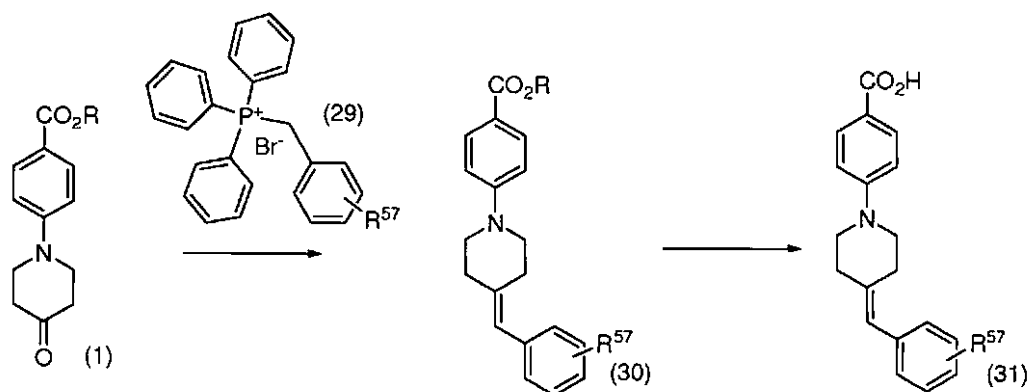
Compounds of Formula (22) may also be converted to compounds of Formula (23) by reacting the former, when X^1 is Cl, F, or NO_2 , and compounds of Formula $\text{R}^{41}\text{-OH}$ with a first base. Examples of first bases include triethylamine, N,N-diisopropylethylamine,
 25 Cs_2CO_3 , Na_2CO_3 , K_3PO_4 , and mixtures thereof.

SCHEME 6



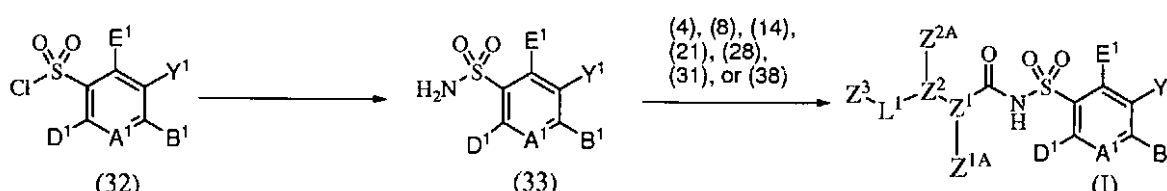
- Compounds of Formula (18) can be reacted with mesyl chloride and a base such as but not limited to triethylamine, followed by N-t-butoxycarbonylpiperazine, to provide compounds of Formula (24). Compounds of Formula (25) can be prepared by reacting compounds of Formula (24) with triethylsilane and trifluoroacetic acid. Compounds of Formula (25) can be reacted with compounds of Formula (26) and HK₂PO₄ 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 8 to prepare compounds of Formula (I).

SCHEME 7



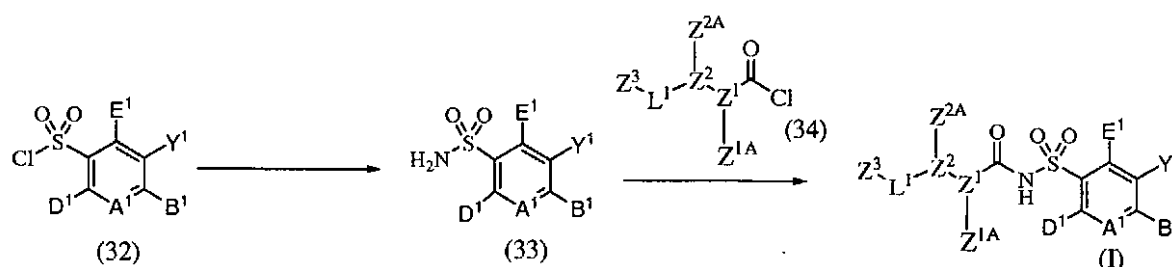
As shown in SCHEME 7, compounds of Formula (1) can be reacted with an appropriate triphenylphosphonium bromide of Formula (29) and a base such as but not limited to sodium hydride or n-butyllithium to provide compounds of Formula (30). The reaction is typically performed in a solvent such as THF or DMSO. Compounds of Formula (31) can be prepared from compounds of Formula (30) as described in SCHEME 1, and can be used as described in SCHEME 8 to prepare compounds of Formula (I).

SCHEME 8



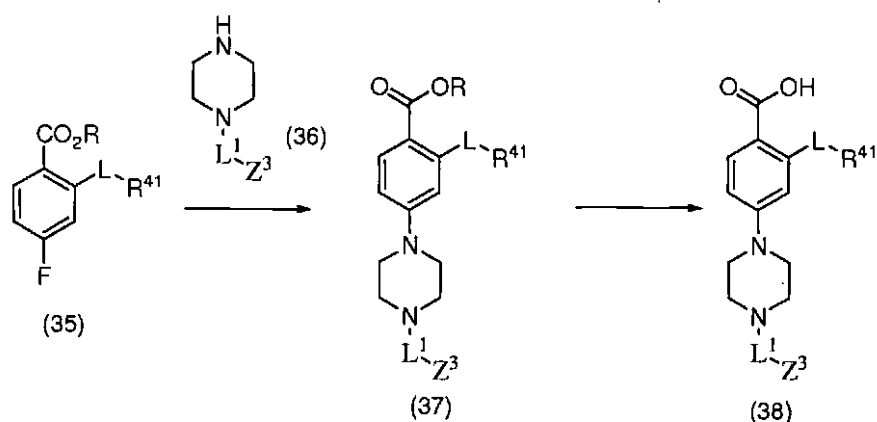
As shown in SCHEME 8, compounds of Formula (32), which can be prepared as described herein, may be converted to compounds of Formula (33) by reacting the former with ammonia. Compounds of Formula (33) may be converted to compounds of Formula (I) by reacting the former and compounds of Formula (4), (8), (14), (21), (28), (31), 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 9



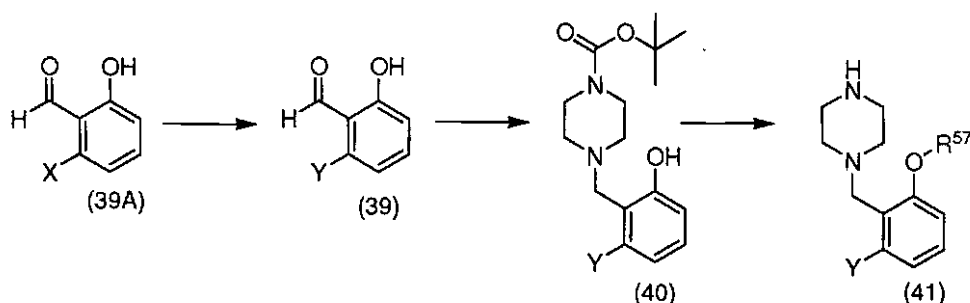
Compounds of Formula (33), prepared as described in SCHEME 8, may also be converted to compounds of Formula (I) by reacting the former and compounds of Formula (34) and a first base. Examples of first bases include but are not limited to sodium hydride, triethylamine, N,N-diisopropylethylamine, 4-(dimethylamino)pyridine, and mixtures thereof.

SCHEME 10



As shown in SCHEME 10, 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 8 to prepare compounds of Formula (I).

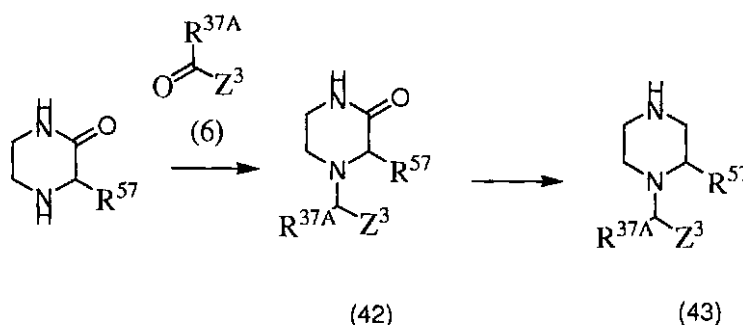
SCHEME 11



Compounds of Formula (39), wherein Y is as described herein for substituents on Z³, 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 R⁵⁷X, 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 10 wherein L^1-Z^3 is as shown in Formula (41).

SCHEME 12



As shown in SCHEME 12, substituted piperazin-2-ones wherein R^{57} is alkyl, can be reacted with compounds of Formula (6) 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 10 wherein L^1-Z^3 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), Advanced Chemistry Development Inc., Toronto, Ontario), 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-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 1A

tert-butyl 4-((4'-chlorobiphenyl-2-yl)methyl)piperazine-1-carboxylate

4'-Chlorobiphenyl-2-carboxaldehyde (4.1 g), tert-butyl piperazine-1-carboxylate (4.23 g), and sodium triacetoxyborohydride (5.61 g) in CH_2Cl_2 (60 mL) were 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.

5

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 material was taken up in dichloromethane (200 mL) and NaHCO_3 solution (100 mL), and partitioned. The organic layer was dried over Na_2SO_4 , and condensed to give the title compound.

10

EXAMPLE 1C

tert-butyl 4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-fluorobenzoate

15

Tert-butyl 4-bromo-2-fluorobenzoate (14.0 g), EXAMPLE 1B (16.05 g), $\text{Pd}_2(\text{dba})_3$ (tris(dibenzylideneacetone)dipalladium(0)) (1.40 g), 2-(di-tert-butylphosphino)biphenyl (1.82 g), and K_3PO_4 (16.2 g) were stirred in 1,2-dimethoxyethane (300 mL) at 80°C for 24 hours. The reaction was cooled and concentrated. The crude product was chromatographed on silica gel with 10-20% ethyl acetate/hexanes.

20

EXAMPLE 1D

tert-butyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)benzoate

1H-Pyrrolo[2,3-B]pyridine-5-ol (167 mg), EXAMPLE 1C (500 mg), and Cs_2CO_3 (508 mg) were stirred in dimethylsulfoxide (5 mL) at 130°C for 24 hours. The mixture was cooled, diluted with ethyl acetate, washed three times with water, and brine, and dried (Na_2SO_4), filtered and concentrated. The crude product was chromatographed on silica gel with 25% ethyl acetate/hexanes.

25

30

EXAMPLE 1E

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)benzoic acid

EXAMPLE 1D (200 mg) and triethylsilane (1 mL) were stirred in dichloromethane (15 mL) and trifluoroacetic acid (15 mL) for 1 hour. The mixture was concentrated, taken up in ethyl acetate, washed twice with NaH₂PO₄, and brine, and dried (Na₂SO₄), filtered and concentrated.

5

EXAMPLE 1F

3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

4-Fluoro-3-nitrobenzenesulfonamide (2.18 g), 1-(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 NaH₂PO₄ solution and brine, and dried (Na₂SO₄), filtered and concentrated. The product was triturated from ethyl acetate.

10

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-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

15

EXAMPLE 1E (115 mg), EXAMPLE 1F (67 mg), 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (82 mg), and 4-dimethylaminopyridine (26 mg) were stirred in CH₂Cl₂ (3 mL) for 24 hours. The reaction was cooled and chromatographed on silica gel with 0-5% methanol/ethyl acetate. ¹H NMR (300MHz, dimethylsulfoxide-d₆) δ 11.48 (brs, 1H), 8.34 (br s, 1H), 8.31 (m, 1H), 7.90 (d, 1H), 7.68 (m, 1H), 7.58 (m, 2H), 7.46 (m, 4H), 7.35 (m, 2H), 7.21 (dd, 1H), 6.76 (m, 4H), 6.28 (m, 2H), 3.02 (m, 2H), 2.89 (m, 4H), 2.80 (m, 4H), 2.40 (m, 3H), 1.59 (m, 2H), 1.25 (m, 4H), 0.87 (m, 2H).

20

25

EXAMPLE 2

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 2A

30

4-(3-morpholinopropylamino)-3-nitrobenzenesulfonamide

This EXAMPLE was prepared by substituting 3-(N-morpholinyl)-propylamine for 1-(tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 2B

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 2A for EXAMPLE 1F in
 5 EXAMPLE 1G. ¹H NMR (300MHz, dimethylsulfoxide-d₆) δ 11.60 (brs, 1H), 8.60 (m, 1H), 8.43 (d, 1H), 7.94 (d, 1H), 7.64 (m, 2H), 7.54 (d, 1H), 7.45 (m, 4H), 7.33 (m, 2H), 7.23 (dd, 1H), 6.96 (d, 1H), 6.85 (m, 2H), 6.32 (d, 1H), 6.26 (d, 1H), 3.60 (m, 4H), 3.10 (m, 4H), 3.05 (m, 10H), 2.40 (m, 2H), 2.33 (m, 2H), 1.77 (m, 2H).

EXAMPLE 3

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-yl)piperidin-4-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 3A

methyl 4,4-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

To a suspension of hexane washed NaH (17 g) in dichloromethane (700 mL) was added 5,5-dimethyl-2-methoxycarbonylcyclohexanone (38.5 g) dropwise at 0°C. After stirring for 30 minutes, the mixture was cooled to -78°C and trifluoroacetic anhydride (40
 20 mL) was added. The reaction mixture was warmed to room temperature and stirred for 24 hours. The organic layer was washed with brine, dried (Na₂SO₄), filtered, and concentrated to give the product.

EXAMPLE 3B

methyl 2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enecarboxylate

EXAMPLE 3A (62.15g), 4-chlorophenylboronic acid (32.24 g), CsF (64 g) and tetrakis(triphenylphosphine)palladium(0) (2g) in 2:1 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
 30 product.

EXAMPLE 3C

(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methanol

To a mixture of LiBH_4 (13g), EXAMPLE 3B (53.8 g) and ether (400 mL), was added methanol (25 mL) slowly by syringe. The mixture was stirred at room temperature for 24
5 hours. The reaction was quenched with 1N HCl with ice-cooling. The mixture was diluted with water and extracted with ether (3x 100 mL). The extracts were dried (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 0-30% ethyl acetate/hexanes.

10 EXAMPLE 3D

tert-butyl 4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine-1-carboxylate

Mesyl Chloride (7.5 mL) was added via syringe to EXAMPLE 3C (29.3 g) and triethylamine (30 mL) in CH_2Cl_2 (500 mL) at 0°C , and the mixture was stirred for 1 minute.
15 N-t-butoxycarbonylpiperazine (25 g) was added and the mixture was stirred at room temperature for 24 hours. The suspension was washed with brine, dried, (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 10-20% ethyl acetate/hexanes.

20 EXAMPLE 3E

1-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine

EXAMPLE 3D (1 g) was stirred in dichloromethane (10 mL), trifluoroacetic acid (10 mL), and triethylsilane (1 mL) for 1 hour. The mixture was concentrated, taken up in a mixture of dichloromethane (100 mL) and saturated aqueous Na_2CO_3 solution (20 mL) and
25 stirred for 10 minutes. The layers were separated, and the organic layer was dried over Na_2SO_4 , filtered, and concentrated to give the product.

EXAMPLE 3F

5-bromo-1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridine

To a mixture of 5-bromo-1H-pyrrolo[2,3-b]pyridine (15.4 g) in tetrahydrofuran (250 mL) was added 1M lithium hexamethyldisilazide in tetrahydrofuran (86 mL), and after 10 minutes, TIPS-Cl (triisopropylchlorosilane) (18.2 mL) was added. The mixture was stirred at room temperature for 24 hours. The reaction was diluted with ether, and the resulting solution
30

was washed twice with water. The extracts were dried (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 10% ethyl acetate/hexanes.

EXAMPLE 3G

5 1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridin-5-ol

To a mixture of EXAMPLE 3F (24.3 g) in tetrahydrofuran (500 mL) at -78°C was added 2.5M BuLi (30.3 mL). After 2 minutes, trimethylborate (11.5 mL) was added, and the mixture was allowed to warm to room temperature over 1 hour. The reaction was poured into water, extracted three times with ethyl acetate, and the combined extracts were washed with
10 brine and concentrated. The crude product was taken up in tetrahydrofuran (200 mL) at 0°C , and 1M NaOH (69 mL) was added, followed by 30% H_2O_2 (8.43 mL), and the solution was stirred for 1 hour. $\text{Na}_2\text{S}_2\text{O}_3$ (10 g) was added, and the pH was adjusted to 4-5 with concentrated HCl and solid NaH_2PO_4 . The solution was extracted twice with ethyl acetate, and the combined extracts were washed with brine, dried (Na_2SO_4), filtered, and
15 concentrated. The crude product was chromatographed on silica gel with 5-25% ethyl acetate/hexanes.

EXAMPLE 3H

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-fluorobenzoate

20 A mixture of EXAMPLE 3G (8.5 g), methyl 2,4-difluorobenzoate (7.05 g), and K_3PO_4 (9.32 g) in diglyme (40 mL) at 115°C was stirred for 24 hours. The reaction was cooled, diluted with ether (600 mL), and washed twice with water, and brine, and concentrated. The crude product was chromatographed on silica gel with 2-50% ethyl acetate/hexanes.

25 EXAMPLE 3I

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

A mixture of EXAMPLE 3H (1.55 g), EXAMPLE 3E (2.42 g), and HK_2PO_4 (1.42 g) in dimethylsulfoxide (20 mL) at 135°C was stirred for 24 hours. The reaction was cooled,
30 diluted with ether (400 mL), and washed with 3x 1M NaOH, and brine, and concentrated. The crude product was chromatographed on silica gel with 10-50% ethyl acetate/hexanes.

EXAMPLE 3J

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

EXAMPLE 3I (200 mg) in dioxane (10 mL) and 1M NaOH (6 mL) at 50°C was stirred for 24 hours. The reaction was cooled, added to NaH₂PO₄ solution, and extracted three times with ethyl acetate. The combined extracts were washed with brine, and concentrated to give the pure product.

EXAMPLE 3K

tert-butyl 1-(tetrahydro-2H-pyran-4-yl)piperidin-4-ylcarbamate

Tert-butyl piperidin-4-ylcarbamate (45.00 g, 225 mmol) and dihydro-2H-pyran-4(3H)-one (24.74 g, 247 mmol) were added to dichloromethane (1000 mL). Sodium triacetoxyborohydride (61.90 g, 292 mmol) was added, and the solution was stirred at room temperature for 16 hours. The solution was extracted with 1M sodium hydroxide and dried over anhydrous sodium sulfate. The solution was filtered and concentrated and purified by flash column chromatography on silica gel with 10% methanol (in dichloromethane) increasing to 20% methanol (in dichloromethane).

EXAMPLE 3L

1-(tetrahydro-2H-pyran-4-yl)piperidin-4-amine dihydrochloride

A solution of EXAMPLE 3K (52.57 g, 185 mmol) in dichloromethane (900 mL) was treated with 4M aqueous HCl (462 mL), and the solution was mixed vigorously at room temperature for 16 hours. Solvent was removed under vacuum to give crude product as the dihydrochloride salt, which was used without further purification.

EXAMPLE 3M

3-nitro-4-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-ylamino)benzenesulfonamide

EXAMPLE 3L (22.12 g, 86 mmol) was added to 1,4-dioxane (300 mL) and water (43 mL). Triethylamine (43.6 mL, 31.6 g, 313 mmol) was added, and the mixture was stirred at room temperature until EXAMPLE 3L had completely dissolved. 4-chloro-3-nitrobenzenesulfonamide was added and the mixture was heated at 90°C for 16 hours. The mixture was cooled, and the solvents were removed under vacuum. 10% methanol (in dichloromethane) was added and the solution was stirred vigorously at room temperature

until a fine suspension was obtained. The solid was isolated by vacuum filtration and washed with dichloromethane to give pure product.

EXAMPLE 3N

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

This EXAMPLE was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and
EXAMPLE 3M for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300MHz,
dimethylsulfoxide-d₆) δ 11.65 (brs, 1H), 8.53 (br s, 1H), 8.18 (m, 1H), 8.00 (br s, 1H), 7.63
10 (m, 1H), 7.49 (m, 3H), 7.34 (d, 2H), 7.12 (m, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.37 (d, 1H),
6.20 (d, 1H), 3.95 (m, 2H), 3.05 (m, 10H), 2.73 (m, 4H), 2.17 (m, 10H), 1.95 (m, 2H), 1.80
(m, 2H), 1.63 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

EXAMPLE 4

15 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-(1H-pyrrolo[2,3-b]pyridin-5-
yloxy)benzamide

EXAMPLE 4A

20 4-(1-methylpiperidin-4-ylamino)-3-nitrobenzenesulfonamide

This EXAMPLE was prepared by substituting 4-amino-N-methylpiperidine for 1-
(tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 4B

25 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-(1H-pyrrolo[2,3-b]pyridin-5-
yloxy)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and
EXAMPLE 4A for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300MHz,
30 dimethylsulfoxide-d₆) δ 11.65 (brs, 1H), 8.55 (br s, 1H), 8.17 (m, 1H), 8.02 (d, 1H), 7.85
(dd, 1H), 7.51 (m, 3H), 7.35 (m, 2H), 7.18 (dd, 1H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.38 (d, 1H),
6.20 (d, 1H), 3.90 (m, 1H), 3.09 (m, 8H), 2.77 (m, 2H), 2.05-2.30 (m, 10H), 1.95 (s, 3H),
1.39 (t, 2H), 1.24 (m, 2H), 0.93 (s, 6H).

EXAMPLE 5

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-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5

EXAMPLE 5A

3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

A mixture of 4-fluoro-3-nitrobenzenesulfonamide (2.18 g), 1-(tetrahydropyran-4-yl)methylamine (1.14 g), and triethylamine (1 g) in tetrahydrofuran (30 mL) were stirred overnight, neutralized with concentrated HCl and concentrated. The residue was suspended in ethyl acetate and the precipitates were collected, washed with water and dried to provide the title compound.

10

EXAMPLE 5B

15 methyl 4,4-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

To a suspension of hexane washed NaH (17 g) in dichloromethane (700 mL) was added 5,5-dimethyl-2-methoxycarbonylcyclohexanone (38.5 g) dropwise at 0°C. After stirring for 30 minutes, the mixture was cooled to -78°C and trifluoroacetic 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 (Na₂SO₄), filtered, and concentrated to give the product.

20

EXAMPLE 5C

methyl 2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enecarboxylate

25 EXAMPLE 5B (62.15g), 4-chlorophenylboronic acid (32.24 g), CsF (64 g) and tetrakis(triphenylphosphine)palladium(0) (2g) in 2:1 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.

30

EXAMPLE 5D

(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methanol

To a mixture of LiBH_4 (13g), EXAMPLE 5C (53.8 g) and ether (400 mL), was added methanol (25 mL) slowly by syringe. The mixture was stirred at room temperature for 24
5 hours. The reaction was quenched with 1N HCl with ice-cooling. The mixture was diluted with water and extracted with ether (3x 100 mL). The extracts were dried (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 0-30% ethyl acetate/hexanes.

10

EXAMPLE 5E

tert-butyl 4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine-1-carboxylate

Mesyl Chloride (7.5 mL) was added via syringe to EXAMPLE 5D (29.3 g) and triethylamine (30 mL) in CH_2Cl_2 (500 mL) at 0°C , and the mixture was stirred for 1 minute.

15

N-t-butoxycarbonylpiperazine (25 g) was added and the mixture was stirred at room temperature for 24 hours. The suspension was washed with brine, dried, (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 10-20% ethyl acetate/hexanes.

20

EXAMPLE 5F

1-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine

EXAMPLE 5E (200 mg) and triethylsilane (1 mL) were stirred in dichloromethane (15 mL) and trifluoroacetic acid (15 mL) for 1 hour. The mixture was concentrated, taken up in ethyl acetate, washed twice with NaH_2PO_4 , and brine, and dried (Na_2SO_4), filtered and
25 concentrated.

EXAMPLE 5G

5-bromo-1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridine

To a mixture of 5-bromo-1H-pyrrolo[2,3-b]pyridine (15.4 g) in tetrahydrofuran (250
30 mL) was added 1M lithium hexamethyldisilazide in tetrahydrofuran (86 mL), and after 10 minutes, TIPS-Cl (triisopropylchlorosilane) (18.2 mL) was added. The mixture was stirred at room temperature for 24 hours. The reaction was diluted with ether, and the resulting solution was washed twice with water. The extracts were dried (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 10% ethyl acetate/hexanes.

EXAMPLE 5H

1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridin-5-ol

To a mixture of EXAMPLE 5G (24.3 g) in tetrahydrofuran (500 mL) at -78°C was
5 added 2.5M BuLi (30.3 mL). After 2 minutes, trimethylborate (11.5 mL) was added, and the
mixture was allowed to warm to room temperature over 1 hour. The reaction was poured into
water, extracted three times with ethyl acetate, and the combined extracts were washed with
brine and concentrated. The crude product was taken up in tetrahydrofuran (200 mL) at 0°C ,
and 1M NaOH (69 mL) was added, followed by 30% H_2O_2 (8.43 mL), and the solution was
10 stirred for 1 hour. $\text{Na}_2\text{S}_2\text{O}_3$ (10 g) was added, and the pH was adjusted to 4-5 with
concentrated HCl and solid NaH_2PO_4 . The solution was extracted twice with ethyl acetate,
and the combined extracts were washed with brine, dried (Na_2SO_4), filtered, and
concentrated. The crude product was chromatographed on silica gel with 5-25% ethyl
acetate/hexanes.

15

EXAMPLE 5I

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-fluorobenzoate

A mixture of EXAMPLE 5H (8.5 g), methyl 2,4-difluorobenzoate (7.05 g), and K_3PO_4
(9.32 g) in diglyme (40 mL) at 115°C was stirred for 24 hours. The reaction was cooled,
20 diluted with ether (600 mL), and washed twice with water, and brine, and concentrated. The
crude product was chromatographed on silica gel with 2-50% ethyl acetate/hexanes.

EXAMPLE 5J

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-
25 dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

A mixture of EXAMPLE 5I (1.55 g), EXAMPLE 5F (2.42 g), and HK_2PO_4 (1.42 g) in
dimethylsulfoxide (20 mL) at 135°C was stirred for 24 hours. The reaction was cooled,
diluted with ether (400 mL), and washed with 3x 1M NaOH, and brine, and concentrated.
The crude product was chromatographed on silica gel with 10-50% ethyl acetate/hexanes.

30

EXAMPLE 5K

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-
enyl)methyl)piperazin-1-yl)benzoic acid

EXAMPLE 5J (200 mg) in dioxane (10 mL) and 1M NaOH (6 mL) at 50°C was stirred for 24 hours. The reaction was cooled, added to NaH₂PO₄ solution, and extracted three times with ethyl acetate. The combined extracts were washed with brine, and concentrated to give the pure product.

5

EXAMPLE 5L

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-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

10 EXAMPLE 5K (3.39 g), EXAMPLE 5A (1.87 g), 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (2.39 g), and 4-dimethylaminopyridine (1.09 g) were stirred in CH₂Cl₂ (40 mL) for 24 hours. The reaction was cooled and chromatographed on silica gel with 25-100% ethyl acetate/hexanes, then 10% methanol/ethyl acetate with 1% acetic acid, to give the product (1.62 g, 32%) as a white solid. ¹H NMR
15 (300MHz, dimethylsulfoxide-d₆) 11.65 (brs, 1H), 8.55 (br s, 1H), 8.04 (d, 1H), 7.89 (dd, 1H), 7.51 (m, 3H), 7.33 (d, 2H), 7.08 (m, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (d, 1H), 6.19 (d, 1H), 3.84 (m, 1H), 3.30 (m, 4H), 3.07 (m, 4H), 2.73(m, 2H), 2.18 (m, 6H), 1.95 (m, 2H), 1.61 (dd, 2H), 1.38 (m, 2H), 1.24 (m, 4H), 0.92 (s, 6H).

20

EXAMPLE 6

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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

25

EXAMPLE 6A

4-(4-methylpiperazin-1-ylamino)-3-nitrobenzenesulfonamide

A 50 mL round-bottomed flask was charged with 4-chloro-3-nitrobenzenesulfonamide (1 g, 4.23 mmol), 4-methylpiperazin-1-amine dihydrochloride (1 g, 5.32 mmol), and N¹,N¹,N²,N²-tetramethylethane-1,2-diamine (3 mL, 20.01 mmol) in dioxane
30 (10 mL). The reaction mixture was refluxed for 12 hours. After this time, the reaction mixture was cooled to room temperature, the salt filtered off via a Buchner funnel, and the solvent removed in vacuo. The crude product was added to a silica gel column (Analogix, SF65-200g) and purified by eluting with 0-5% methanol in dichloromethane.

EXAMPLE 6B

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)-2-(1H-pyrrolo[2,3-b]pyridin-5-
yloxy)benzamide

5 This EXAMPLE was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and
EXAMPLE 6A for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300MHz,
dimethylsulfoxide-d₆) δ 11.65 (brs, 1H), 9.09 (br s, 1H), 8.47 (d, 1H), 8.24 (dd, 1H), 7.99
(d, 1H), 7.50 (m, 4H), 7.34 (d, 2H), 7.04 (d, 2H), 6.64 (dd, 1H), 6.35 (d, 1H), 6.20 (d, 1H),
3.04 (m, 4H), 2.89 (m, 4H), 2.73 (m, 2H), 2.34 (s, 3H), 2.17 (m, 6H), 1.95 (br s, 2H), 1.38 (t,
10 2H), 1.05 (m, 4H), 0.93 (s, 6H).

EXAMPLE 7

2-(9H-carbazol-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-
15 nitrophenyl}sulfonyl)benzamide

EXAMPLE 7A

ethyl 2-(9H-carbazol-4-yloxy)-4-fluorobenzoate

This EXAMPLE was prepared by substituting ethyl 2,4-difluorobenzoate for methyl
20 2,4-difluorobenzoate and 4-hydroxycarbazole for EXAMPLE 3G in EXAMPLE 3H.

EXAMPLE 7B

ethyl 2-(9H-carbazol-4-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-
enyl)methyl)piperazin-1-yl)benzoate

25 This EXAMPLE was prepared by substituting EXAMPLE 7A for EXAMPLE 3H in
EXAMPLE 3I.

EXAMPLE 7C

2-(9H-carbazol-4-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-
30 enyl)methyl)piperazin-1-yl)benzoic acid

This EXAMPLE was prepared by substituting EXAMPLE 7B for EXAMPLE 3I in
EXAMPLE 3J, except here upon completion of the reaction, water and 2N HCl were added
to adjust the pH to 2, and the HCl salt of the product was extracted using CHCl₃/CH₃OH.

EXAMPLE 7D

2-(9H-carbazol-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

5 This EXAMPLE was prepared by substituting EXAMPLE 7C for EXAMPLE 1E and EXAMPLE 4A for EXAMPLE 1F in EXAMPLE 1G, except here the purification was done by preparative HPLC using a C18 column, 250 x 50 mm, 10 μ , and eluting with a gradient of 20-100% CH₃CN vs. 0.1% trifluoroacetic acid in water, giving the product as a bistrifluoroacetate salt. ¹H NMR (300 MHz, dimethylsulfoxide -d₆) δ 11.82 (br s, 1H),
10 11.40 (s, 1H), 9.70, 9.40 (both v br s, total 2H), 8.40 (d, 1H), 8.10 (br d, 1H), 7.90 (br d, 1H), 7.72 (dd, 1H), 7.60 (d, 1H), 7.48 (d, 1H), 7.38 (m, 3H), 7.22 (m, 2H), 7.07 (m, 4H), 6.78 (dd, 1H), 6.43 (dd, 1H), 6.19 (s, 1H), 3.97 (m, 1H), 3.80 (m, 2H), 3.60, 3.30, 3.10, 2.80 (all br m, total 11H), 2.20, 2.10, 2.00 (all br m, total 8H), 1.78 (m, 2H), 1.42 (m, 2H), 1.25 (m, 2H), 0.92 (s, 6H).

EXAMPLE 8

2-(9H-carbazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)benzamide

EXAMPLE 8A

3-nitro-4-(3-(pyrrolidin-1-yl)propylamino)benzenesulfonamide

This EXAMPLE was prepared by substituting 3-(pyrrolidin-1-yl)propan-1-amine for 1-(tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 8B

2-(9H-carbazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)benzamide

30 This EXAMPLE was prepared by substituting EXAMPLE 7C for EXAMPLE 1E and EXAMPLE 8A for EXAMPLE 1F in EXAMPLE 1G, except here the purification was done by preparative HPLC using a C18 column, 250 x 50 mm, 10 μ , and eluting with a gradient of 20-100% CH₃CN vs. 0.1% trifluoroacetic acid in water, giving the product as a

bistrifluoroacetate salt.. ¹H NMR (300 MHz, dimethylsulfoxide -d₆) δ 11.80 (br s, 1H), 11.42 (s, 1H), 9.50, 9.25 (both v br s, total 2H), 8.58 (br t, 1H), 8.43 (d, 1H), 7.91 (d, 1H), 7.72 (dd, 1H), 7.60 (d, 1H), 7.50 (d, 1H), 7.38 (m, 3H), 7.23 (m, 2H), 7.07 (m, 3H), 6.93 (d, 1H), 6.78 (dd, 1H), 6.44 (dd, 1H), 6.18 (s, 1H), 3.70, 3.60, 3.20, 3.00 (all br m, total 18H), 2.18 (br m, 2H), 2.00-1.80 (envelope, 8H), 1.42 (m, 2H), 0.92 (s, 6H).

EXAMPLE 9

Trans-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)-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

EXAMPLE 9A

Trans-tert-butyl 4-morpholinocyclohexylcarbamate

A solution of tert-butyl-4-aminocyclohexylcarbamate (20.32 g, 95 mmol), bis(2-bromoethyl) ether (14.30 ml, 114 mmol) and triethylamine (33.0 ml, 237 mmol) in N,N-dimethylformamide (200 ml) was stirred for 16 hours at 70 °C. The reaction mixture was cooled down to room temperature, concentrated and the product was extracted with ethyl acetate. The organic layer was washed with sodium carbonate solution (15% aq.), dried and concentrated. The product was used in next step without purification.

EXAMPLE 9B

Trans-4-morpholinocyclohexanamine dihydrochloride

To a solution of trans-tert-butyl-4-morpholinocyclohexylcarbamate (19.2 g, 67.5 mmol) in dichloromethane (100 ml) was added HCl (100 ml, 400 mmol) (4M in dioxane) and the reaction mixture was stirred for 16 hours at room temperature. The reaction mixture was diluted with ether and solid salt was filtered off, and dried in an oven.

EXAMPLE 9C

Trans-4-(4-morpholinocyclohexylamino)-3-nitrobenzenesulfonamide

A solution of trans-4-morpholinocyclohexanamine dihydrochloride (5 g, 19.44 mmol), 4-fluoro-3-nitrobenzenesulfonamide (4.32 g, 19.63 mmol) and triethylamine (20 ml, 143 mmol) in tetrahydrofuran (60 ml) was stirred for 16 hours at room temperature. The

solid product was filtered off, washed with tetrahydrofuran, ether, dichloromethane (3 x) and dried under vacuum.

EXAMPLE 9D

5 Trans-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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 9C for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300MHz, dimethylsulfoxide-d₆) δ 11.61 (brs, 1H), 8.49 (br s, 1H), 8.12 (m, 1H), 7.99 (br s, 1H), 7.71 (m, 1H), 7.50 (m, 3H), 7.35 (d, 2H), 7.04 (d, 2H), 7.01 (m, 1H), 6.65 (dd, 1H), 6.36 (d, 1H), 6.21 (d, 1H), 3.60 (m, 4H), 3.04 (m, 4H), 2.73 (m, 2H), 2.57 (m, 2H), 2.42 (m, 1H), 2.18 (m, 6H), 2.05 (m, 2H), 1.95 (m, 2H), 1.90 (m, 2H), 1.38 (m, 6H), 1.15 (m, 3H), 0.92 (s, 6H).

15 EXAMPLE 10

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

20 EXAMPLE 10A

4-(2-methoxyethylamino)-3-nitrobenzenesulfonamide

This EXAMPLE was prepared by substituting 2-methoxyethylamine for 1-(tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

25 EXAMPLE 10B

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

This EXAMPLE was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 10A for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300MHz, dimethylsulfoxide-d₆) δ 11.65 (brs, 1H), 8.58-8.49 (m, 1H), 8.55 (d, 1H), 8.03 (d, 1H), 7.79 (m, 1H), 7.49 (m, 3H), 7.34 (m, 2H), 7.06 (m, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.38 (m, 1H),

6.20 (d, 1H), 3.61-3.51 (m, 4H), 3.31 (s, 3H), 3.07 (m, 4H), 2.74 (m, 2H), 2.17 (m, 6H), 1.95 (br s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 11

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

EXAMPLE 11A

10 (S)-3-nitro-4-((tetrahydro-2H-pyran-3-yl)methylamino)benzenesulfonamide and
(R)-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 1F.

15 EXAMPLE 11B

(S)-3-nitro-4-((tetrahydro-2H-pyran-3-yl)methylamino)benzenesulfonamide

The racemic mixture of EXAMPLE 11A 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 CO₂ over 15 minutes (oven temperature: 40°C; flow rate: 40 mL/minute) to
20 provide the title compound.

EXAMPLE 11C

(R)-3-nitro-4-((tetrahydro-2H-pyran-3-yl)methylamino)benzenesulfonamide

The racemic mixture of EXAMPLE 11A was resolved by chiral SFC on an AD
25 column (21mm i.d.x 250 mm in length) using a gradient of 10-30% 0.1% diethylamine methanol in CO₂ over 15 minutes (oven temperature: 40°C; flow rate: 40 mL/minute) to provide the title compound.

EXAMPLE 11D

30 4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-[(3-nitro-4-{{(3S)-tetrahydro-2H-pyran-3-ylmethyl}amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

To a mixture of EXAMPLE 3J (59.8 mg, 0.105 mmol), EXAMPLE 11B (33mg, 0.105 mmol) and N,N-dimethylpyridin-4-amine (38.4 mg, 0.314 mmol) in dichloromethane

(5 ml) was added 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (24.07 mg, 0.13 mmol). The reaction mixture was stirred at room temperature overnight and concentrated. 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 NaHCO₃. The organic layer was dried over anhydrous Na₂SO₄ and concentrated to give the title compound. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.68 (s, 1 H), 11.40 (s, br, 1 H), 8.53 - 8.58 (m, 2 H), 8.04 (d, 1 H), 7.80 (dd, 1 H), 7.47 - 7.54 (m, 3 H), 7.34 (d, 2 H), 7.02 - 7.09 (m, 3 H), 6.67 (dd, 1 H), 6.39 (dd, 1 H), 6.19 (d, 1 H), 3.79 (dd, 1 H), 3.69 - 3.73 (m, 1 H), 3.22 - 3.37 (m, 3 H), 3.16 - 3.21 (m, 1 H), 3.07 (s, 4 H), 2.74 (s, 2 H), 2.09 - 2.24 (m, 6 H), 1.95 (s, 2 H), 1.86 - 1.93 (m, 1 H), 1.79 - 1.85 (m, 1 H), 1.58 - 1.64 (m, 1 H), 1.42 - 1.51 (m, 1 H), 1.38 (t, 2 H), 1.25 - 1.34 (m, 1 H), 0.92 (s, 6 H).

EXAMPLE 12

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 12A

4-((1,4-dioxan-2-yl)methoxy)-3-nitrobenzenesulfonamide

(1,4-Dioxan-2-yl)methanol (380 mg, 3.22 mmol) in tetrahydrofuran (30 ml) was treated with sodium hydride (60%) (245 mg, 6.13 mmol) at room temperature for 30 minutes. The reaction mixture was cooled in an ice bath and 4-fluoro-3-nitrobenzenesulfonamide (675 mg, 3.06 mmol) was added. The resulting mixture was stirred at room temperature for 2 hours and another portion of sodium hydride (60%) (245 mg, 6.13 mmol) 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 12B

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5 The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 12A in place of EXAMPLE 11B. ¹H NMR (500 MHz, dimethylsulfoxide -d₆) δ 11.67 (s, 1 H), 11.42 (s, br, 1 H), 8.34 (s, 1 H), 8.03 (d, 2 H), 7.48 - 7.55 (m, 3 H), 7.41 (d, 1 H), 7.35 (d, 2 H), 7.04 (d, 2 H), 6.67 (dd, 1 H), 6.39 (dd, 1 H), 6.21 (d, 1 H), 4.20 - 4.28 (m, 2 H), 3.85 - 3.91 (m, 1 H), 3.82 (dd, 1 H), 3.74 - 3.78 (m, 1 H), 3.59 - 3.69 (m, 2 H), 3.41 - 3.51 (m, 2 H),
10 3.05 - 3.17 (m, 4 H), 2.83 (s, br, 2 H), 2.27 (s, br, 4 H), 2.15 (s, 2 H), 1.96 (s, 2 H), 1.39 (t, 2 H), 0.93 (s, 6 H).

EXAMPLE 13

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

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 11C in place of EXAMPLE 11B. The proton NMR spectra of EXAMPLE 13 and EXAMPLE 11D are identical. ¹H NMR (500 MHz, dimethylsulfoxide -d₆) δ 11.68 (s, 1 H),
20 11.40 (s, br, 1 H), 8.53 - 8.58 (m, 2 H), 8.04 (d, 1 H), 7.80 (dd, 1 H), 7.47 - 7.54 (m, 3 H), 7.34 (d, 2 H), 7.02 - 7.09 (m, 3 H), 6.67 (dd, 1 H), 6.39 (dd, 1 H), 6.19 (d, 1 H), 3.79 (dd, 1 H), 3.69 - 3.73 (m, 1 H), 3.22 - 3.37 (m, 3 H), 3.16 - 3.21 (m, 1 H), 3.07 (s, 4 H), 2.74 (s, 2 H), 2.09 - 2.24 (m, 6 H), 1.95 (s, 2 H), 1.86 - 1.93 (m, 1 H), 1.79 - 1.85 (m, 1 H), 1.58 - 1.64 (m, 1 H), 1.42 - 1.51 (m, 1 H), 1.38 (t, 2 H), 1.25 - 1.34 (m, 1 H), 0.92 (s, 6 H).

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EXAMPLE 14

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-(2-naphthylsulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using naphthalene-2-sulfonamide (47 mg, 0.227 mmol) in place of EXAMPLE 11B. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.82 (s, 1 H), 11.69 (s, 1 H), 8.51 (s, 1 H), 8.08 (d, 1 H), 8.05 (d, 1 H), 7.97 (dd, 2 H), 7.82 (dd, 1 H), 7.66 - 7.71 (m, 1 H), 7.63 (t, 1 H), 7.54 (d, 1 H), 7.47 -

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7.52 (m, 2 H), 7.34 (d, 2 H), 7.04 (d, 2 H), 6.65 (dd, 1 H), 6.39 (dd, 1 H), 6.18 (s, 1 H), 3.04 (s, 4 H), 2.72 (s, 2 H), 2.10 - 2.20 (m, 6 H), 1.95 (s, 2 H), 1.38 (t, 2 H), 0.92 (s, 6 H).

EXAMPLE 15

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

EXAMPLE 15A

10 methyl 6,6-dimethyl-4-oxotetrahydro-2H-pyran-3-carboxylate

To a suspension of hexane-washed NaH (0.72 g, 60% in mineral oil) 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 at room temperature for 30 minutes. The dimethylcarbonate (6.31 mL) was added dropwise by syringe. The mixture was
15 heated to reflux for 4h. LC/MS showed the expected product as the major product. The mixture was acidified with 5% HCl and extracted with dichloromethane (100 mL x 3) and washed with water, brine and dried over Na₂SO₄. After evaporation, the crude product was loaded on a column and eluted with 10% ethyl acetate in hexane to give the product.

20 EXAMPLE 15B

methyl 6,6-dimethyl-4-(trifluoromethylsulfonyloxy)-5,6-dihydro-2H-pyran-3-carboxylate

To a cooled (0°C) stirring suspension of NaH (0.983 g, 60% in mineral oil) in ether (50 mL) was added EXAMPLE 15A (3.2 g). The mixture was stirred at 0°C for 30 minutes before the addition of Tf₂O (4.2 mL). The mixture was then stirred at room temperature
25 overnight. The mixture was diluted with ether (200 mL) and washed with 5% HCl, water and brine. After drying over Na₂SO₄, evaporation of solvent gave the crude product which was used in the next step without further purification.

EXAMPLE 15C

30 methyl 4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-carboxylate

To a solution of EXAMPLE 15B (2.88 g), 4-chlorophenylboronic acid (1.88 g) and Pd(Ph₃P)₄ (0.578 g) in toluene (40 mL) and ethanol (10 mL) was added 2N Na₂CO₃ (10 mL). The mixture was stirred at reflux overnight. The mixture was diluted ether (300 mL) and

washed with water, brine and dried over Na_2SO_4 . After evaporation of solvent, the residue was loaded on a column and eluted with 3% ethyl acetate in hexane to give the product.

EXAMPLE 15D

5 (4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methanol

To a solution of EXAMPLE 15C (1.6 g) in ether (20 mL) was added LiAlH_4 (1.2 g). The mixture was stirred for 4 hours. The mixture was acidified carefully with 5% HCl and extracted with ethyl acetate (100 mL x 3) and washed with water, brine and dried over Na_2SO_4 . After concentration, the crude product was loaded on a column and eluted with 10% ethyl acetate in hexane to give the product.

EXAMPLE 15E

4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-carbaldehyde

To a solution of oxalyl chloride (1.1 g) in dichloromethane (30 mL) at -78°C was added dimethylsulfoxide (6.12 mL). The mixture was stirred at the temperature for 30 minutes, and then a solution of EXAMPLE 15D (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 . Concentration of the solvent and column purification (5% ethyl acetate in hexane) gave the product.

EXAMPLE 15F

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(piperazin-1-yl)benzoate

25 A mixture of EXAMPLE 3H (20.5 g) and piperazine (37.0 g) in dimethylsulfoxide (200 mL) was heated to 110°C for 24 hours, and the mixture was allowed to cool to room temperature. The mixture was poured into water (1 L), extracted three times with dichloromethane, and the combined extracts were washed with 2x water, and brine and filtered and concentrated to give the pure product.

30

EXAMPLE 15G

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)benzoate

To a solution of EXAMPLE 15E (100 mg) and EXAMPLE 15F (177 mg) in dichloromethane (10 mL) was added sodium triacetoxyborohydride (154 mg). 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 Na₂SO₄, the mixture was filtered and the solvent was evaporated under vacuum. The residue was loaded on a column and eluted with 30% ethyl acetate in hexane to give the pure product.

EXAMPLE 15H

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)benzoic acid

To a solution of EXAMPLE 15G (254 mg) in tetrahydrofuran (4 mL), methanol (2 mL) and water (2 mL) was added LiOH H₂O (126mg). 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 Na₂SO₄. Filtration and evaporation of solvent gave the product.

EXAMPLE 15I

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

The title compound was prepared as described in EXAMPLE 1G, substituting EXAMPLE 1E with EXAMPLE 15H. ¹H NMR (300 MHz, dimethylsulfoxide -d₆) δ 11.68 (br s, 1H), 11.42 (s, 1H), 8.60 (m, 1H), 8.57 (d, 1H), 8.05(d, 1H), 7.80 (dd, 1H), 7.48-7.54 (m, 3H), 7.38 (d, 2H), 7.12 (m, 3H), 6.68 (dd, 1H), 6.40 (dd, 1H), 6.20 (s, 1H), 4.11(s, 2H), 3.85(m, 2H), 3.27(m, 6H), 3.07 (m, 2H), 2.84 (m, 2H), 2.14 (m, 5H), 1.92(m, 1H), 1.42 (m, 2H), 1.24(m, 2H), 1.10 (s, 6H).

EXAMPLE 16

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

EXAMPLE 16A

4-(2-methoxyethylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

4-Fluoro-3-(trifluoromethylsulfonyl)benzenesulfonamide (1.536 g, 5 mmol), 2-methoxyethanamine (0.376 g, 5 mmol), and triethylamine (1.939 g, 15 mmol) in anhydrous tetrahydrofuran (30 mL) solution was heated at 55°C for 3 hours. The solution was diluted with ethyl acetate, washed with water and brine, and dried (Na₂SO₄), filtered and the filtrate was concentrated. The crude material was used in the next step without further purification.

EXAMPLE 16B

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

This EXAMPLE was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 16A for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (400MHz, dimethylsulfoxide-d₆) δ 11.67 (brs, 1H), 8.14 (m, 1H), 8.03 (d, 1H), 7.91 (d, 1H), 7.50 (m, 3H), 7.34 (d, 2H), 7.19 (s, 1H), 7.04 (m, 3H), 6.67 (dd, 1H), 6.39 (m, 1H), 6.19 (d, 1H), 3.51 (m, 4H), 3.28 (s, 3H), 3.06 (m, 4H), 2.75 (m, 2H), 2.17 (m, 6H), 1.95 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

EXAMPLE 17

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

EXAMPLE 17A

4-((tetrahydro-2H-pyran-4-yl)methylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

This EXAMPLE was prepared by substituting 1-(tetrahydropyran-4-yl)methylamine for 2-methoxyethanamine in EXAMPLE 16A.

EXAMPLE 17B

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

This EXAMPLE was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 17A for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (400MHz, dimethylsulfoxide-d₆) δ 11.70 (brs, 1H), 8.15 (m 1H), 8.04 (d, 1H), 7.92 (d, 1H), 7.51 (m, 3H), 7.34 (d, 2H), 7.19 (s, 1H), 7.05 (m, 3H), 6.68 (dd, 1H), 6.40 (m, 1H), 6.18 (d, 1H), 3.85 (m, 2H), 3.25 (m, 4H), 3.07 (m, 4H), 2.77 (m, 2H), 2.17 (m, 6H), 1.95 (m, 2H), 1.84 (m, 1H), 1.54 (m, 2H), 1.39 (t, 2H), 1.24 (m, 2H), 0.93 (s, 6H).

EXAMPLE 18

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

EXAMPLE 18A

methyl 2-(1H-indol-5-yloxy)-4-fluorobenzoate

A mixture of 5-hydroxyindole (8.5 g), methyl 2,4-difluorobenzoate (7.05 g), and K₃PO₄ (9.32 g) in diglyme (40 mL) at 115°C was stirred for 24 hours. The reaction was cooled, diluted with ether (600 mL), and washed twice with water, and brine, and concentrated. The crude product was chromatographed on silica gel with 2-50% ethyl acetate/hexanes.

EXAMPLE 18B

methyl 2-(1H-indol-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

A mixture of EXAMPLE 18A (1.7 g), EXAMPLE 3E (1.8 g), and HK₂PO₄ (1.21 g) in dimethylsulfoxide (20 mL) at 135°C was stirred for 24 hours. The reaction was cooled, diluted with ether (400 mL), and washed with 3x 1M NaOH, and brine, and concentrated. The crude product was chromatographed on silica gel with 10-50% ethyl acetate/hexanes.

EXAMPLE 18C

2-(1H-indol-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

EXAMPLE 18B (200 mg) in dioxane (10 mL) and 1M NaOH (6 mL) at 50°C was stirred for 24 hours. The reaction was cooled, added to NaH₂PO₄ solution, and extracted three

times with ethyl acetate. The combined extracts were washed with brine, and concentrated to give the pure product.

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EXAMPLE 18D

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

The title compound was prepared as described in EXAMPLE 11D by replacing
 10 EXAMPLE 3J with EXAMPLE 18C, and EXAMPLE 1F for EXAMPLE 11B. ¹H NMR (300MHz, dimethylsulfoxide-d₆) 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),
 15 0.92 (s, 6H).

EXAMPLE 19

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 described in EXAMPLE 11D by replacing
 EXAMPLE 11B with EXAMPLE 9B and EXAMPLE 3J with EXAMPLE 18C. ¹H NMR (500 MHz, pyridine-d₅) 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),
 25 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).

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EXAMPLE 20

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 described in EXAMPLE 11D by replacing EXAMPLE 11B with EXAMPLE 10A and EXAMPLE 3J with EXAMPLE 18C. ¹H NMR (400 MHz, dimethylsulfoxide - *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 21

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 described in EXAMPLE 11D by replacing EXAMPLE 3J with EXAMPLE 18C. ¹H NMR (400 MHz, dimethylsulfoxide -*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 22

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 described in EXAMPLE 11D using EXAMPLE 11C in place of EXAMPLE 11B, and EXAMPLE 18C in place of EXAMPLE 3J. ¹H NMR (400 MHz, dimethylsulfoxide -*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 23

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

5

EXAMPLE 23A

methyl 2-(1H-indol-5-yloxy)-4-(piperazin-1-yl)benzoate

The title compound was prepared as described in EXAMPLE 15F by replacing
EXAMPLE 3H with EXAMPLE 18A.

10

EXAMPLE 23B

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 as described in EXAMPLE 15G by replacing
EXAMPLE 15F with EXAMPLE 23A.

15

EXAMPLE 23C

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 as described in EXAMPLE 15H by replacing
EXAMPLE 15G with EXAMPLE 23B.

20

EXAMPLE 23D

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

25

The title compound was prepared as described in EXAMPLE 11D by replacing
EXAMPLE 11B with EXAMPLE 1F, and EXAMPLE 3J with EXAMPLE 23C. ¹H NMR
(400 MHz, dimethylsulfoxide -d₆) 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).

30

EXAMPLE 24

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

EXAMPLE 24A

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 solution was stirred for 20 minutes at the room temperature. To this solution 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 MgSO₄, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel eluting with 20-60% ethyl acetate in hexanes.

EXAMPLE 24B

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

The title compound was prepared by substituting EXAMPLE 24A for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.67 (s, 1H), 8.33 (s, 1H), 8.00-8.02 (m, 2H), 7.50-7.53 (m, 3H), 7.34-7.36 (m, 3H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.38 (d, 1H), 6.21 (s, 1H), 4.06 (d, 2H), 3.88 (dd, 2H), 3.08 (s, 4H), 2.80 (s, 2H), 2.25 (s, 4H), 2.15 (s, 2H), 1.96 (s, 2H), 1.63-1.66 (m, 2H), 1.52-1.55 (m, 1 H), 1.33-1.40 (m, 4H), 0.92 (s, 6H).

EXAMPLE 25

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 25A

4-((1,4-dioxan-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared as described in EXAMPLE 1F using (1,4-dioxan-2-yl)methanamine in place of (tetrahydropyran-4-yl)methanamine.

EXAMPLE 25B

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

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE
25A in place of EXAMPLE 11B. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.66 (s,
1H), 11.38 (s, 1H), 8.53 - 8.59 (m, 2H), 8.03 (d, 1H), 7.81 (dd, 1H), 7.46 - 7.54 (m, 3H), 7.34
10 (d, 2H), 7.09 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.38 (dd, 1H), 6.19 (d, 1H), 3.75 - 3.86 (m,
3H), 3.58 - 3.68 (m, 2H), 3.45 - 3.52 (m, 2H), 3.35 - 3.43 (m, 2H), 3.07 (s, 4H), 2.75 (s, 2H),
2.17 (d, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H)

EXAMPLE 26

15 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-
nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-
yloxy)benzamide

EXAMPLE 26A

20 3-nitro-4-(2,2,2-trifluoroethylamino)benzenesulfonamide

The title compound was prepared by substituting 2,2,2-trifluoroethanamine for
(tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 26B

25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-
nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-
yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 26A for EXAMPLE
11B in EXAMPLE 11D. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.48 (s, 1H), 8.40 (m,
30 2H), 7.90 (d, 1H), 7.71 (dd, 1H), 7.59 (d, 1H), 7.40 (t, 1H), 7.34 (d, 2H), 7.25 (d, 1H), 7.06
(m, 3H), 6.61 (dd, 1H), 6.26 (m, 2H), 4.32 (m, 2H), 3.00 (m, 4H), 2.73 (s, 2H), 2.19 (m, 6H),
1.96 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

EXAMPLE 27

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

5

EXAMPLE 27A

3-nitro-4-(3,3,3-trifluoropropylamino)benzenesulfonamide

The title compound was prepared by substituting 3,3,3-trifluoropropan-1-amine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

10

EXAMPLE 27B

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

15

The title compound was prepared by substituting EXAMPLE 27A for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.47 (s, 1H), 8.37 (d, 1H), 8.29 (m, 1H), 7.89 (d, 1H), 7.61 (m, 2H), 7.39 (t, 1H), 7.35 (d, 2H), 7.22 (d, 1H), 7.05 (d, 2H), 6.75 (d, 1H), 6.62 (dd, 1H), 6.27 (m, 2H), 3.59 (q, 2H), 3.00 (m, 4H), 2.73 (s, 2H), 2.66 (m, 2H), 2.18 (m, 6H), 1.96 (s, 2H), 1.39 (t, 2H), 0.93 (m, 6H).

20

EXAMPLE 28

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

25

EXAMPLE 28A

(S)-4-((1,4-dioxan-2-yl)methoxy)-3-nitrobenzenesulfonamide

The racemic mixture of EXAMPLE 12A was resolved on a SFC chiral AD column to provide the title compound.

30

EXAMPLE 28B

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 28A in place of EXAMPLE 11B. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.67 (s, 2H), 8.35 (s, 1H), 8.03 (d, 2H), 7.48 - 7.57 (m, 3H), 7.42 (d, 1H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.21 (s, 1H), 4.19 - 4.30 (m, 2H), 3.85 - 3.92 (m, 1H), 3.73 - 3.85 (m, 2H), 3.58 - 3.70 (m, 2H), 3.40 - 3.52 (m, 2H), 3.10 (s, 4H), 2.85 (s, 2H), 2.18 - 2.39 (m, 3H), 2.15 (s, 2H), 1.96 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

EXAMPLE 29

Cis-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]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 29A

Cis-4-((4-methoxycyclohexyl)methylamino)-3-nitrobenzenesulfonamide
4-Fluoro-3-nitrobenzenesulfonamide (1.098 g) and EXAMPLE 34A (1 g) in tetrahydrofuran (20 mL) was treated with N,N-diisopropylethylamine (0.871 mL) overnight. The reaction mixture was concentrated and the residue was purified by reverse phase chromatography, eluted with 40-55% acetonitrile in 0.1% trifluoroacetic acid in water over 25 min to give the *cis* isomer EXAMPLE 29A and *trans* isomer EXAMPLE 34B.

EXAMPLE 29B

Cis-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]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 29A in place of EXAMPLE 11B. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.69 (s, 1H), 11.36 (s, 1H), 8.53 - 8.63 (m, 2H), 8.04 (d, 1H), 7.79 (dd, 1H), 7.47 - 7.56 (m, 3H), 7.34 (d, 2H), 7.00 - 7.12 (m, 3H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.37 (s, 1H), 3.26 (t, 2H), 3.20 (s, 3H), 3.07 (s, 4H), 2.75 (s, 2H), 2.17 (d, 6H), 1.95 (s, 2H), 1.81 (dd, 2H), 1.64 - 1.74 (m, 1H), 1.48 (dd, 2H), 1.23 - 1.42 (m, 6H), 0.92 (s, 6H).

EXAMPLE 30

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-pyrrolo[2,3-b]pyridin-5-
yloxy)benzamide

EXAMPLE 30A

(R)-4-((1,4-dioxan-2-yl)methoxy)-3-nitrobenzenesulfonamide

The racemic mixture of EXAMPLE 12A was resolved on a SFC chiral AD column to
provide the title compound.

EXAMPLE 30B

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-pyrrolo[2,3-b]pyridin-5-
yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE
30A in place of EXAMPLE 11B. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.67 (s,
2H), 8.35 (s, 1H), 8.03 (d, 2H), 7.48 - 7.57 (m, 3H), 7.42 (d, 1H), 7.35 (d, 2H), 7.05 (d, 2H),
6.68 (dd, 1H), 6.39 (dd, 1H), 6.21 (s, 1H), 4.19 - 4.30 (m, 2H), 3.85 - 3.92 (m, 1H), 3.73 -
3.85 (m, 2H), 3.58 - 3.70 (m, 2H), 3.40 - 3.52 (m, 2H), 3.10 (s, 4H), 2.85 (s, 2H), 2.18 - 2.39
(m, 3H), 2.15 (s, 2H), 1.96 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

EXAMPLE 31

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-
N-({4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-
5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 1G by replacing
EXAMPLE 1E and EXAMPLE 1F with EXAMPLE 15H and EXAMPLE 25A, respectively.
¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.66 (s, 1H), 11.46 (m, 1H), 8.54 (m, 2H),
8.45 (m, 1H), 8.03 (d, 1H), 7.83 (m, 2H), 7.50 (m, 3H), 7.34 (m, 3H), 7.12 (m, 2H), 6.68 (dd,
1H), 6.38 (dd, 1H), 6.20 (d, 1H), 4.11 (s, 2H), 3.79 (m, 4H), 3.51 (m, 6H), 3.05 (m, 4H), 2.17
(m, 3H), 1.17 (s, 6H).

EXAMPLE 32

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-
N-{[4-(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-
yloxy)benzamide

5 The title compound was prepared as described in EXAMPLE 1G by replacing
EXAMPLE 1E and EXAMPLE 1F with EXAMPLE 15H and EXAMPLE 12A, respectively.
¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.67 (s, 1H), 8.37 (d, 1H), 8.03 (m, 2H), 7.50
(m, 3H), 7.37 (d, 2H), 7.13 (d, 2H), 6.68 (dd, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 4.25 (m, 2H),
4.12 (s, 2H), 3.84 (m, 3H), 3.63 (m, 2H), 3.45 (m, 2H), 3.06 (m, 4H), 2.86 (m, 2H), 2.24 (m,
10 6H), 1.20 (m, 6H).

EXAMPLE 33

Trans-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-
1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-
15 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 1G by replacing
EXAMPLE 1E and EXAMPLE 1F with EXAMPLE 15H and EXAMPLE 9C, respectively.
¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.63 (s, 1H), 8.51 (d, 1H), 8.15 (d, 1H), 8.01
(d, 1H), 7.76 (dd, 1H), 7.48 (m, 3H), 7.38 (d, 2H), 7.13 (d, 2H), 7.06 (d, 1H), 6.66 (dd, 1H),
20 6.36 (dd, 1H), 6.21 (d, 1H), 4.11 (s, 2H), 3.63 (m, 5H), 3.05 (m, 4H), 2.83 (s, 2H), 2.64 (m,
4H), 2.17 (m, 6H), 2.05 (m, 2H), 1.91 (s, 2H), 1.43 (m, 6H), 1.17 (m, 6H).

EXAMPLE 34

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
25 [(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

EXAMPLE 34A

(4-methoxycyclohexyl)methanamine

30 (4-Methoxyphenyl)methanamine (1 g, 1.29 mmol) in ethanol (10 ml) was treated with
5% Rh-Al₂O₃ (99.8 mg, 0.048 mmol) under H₂ atmosphere (500 psi) at 50°C for 16 hours.
Additional 5% Rh-Al₂O₃ (0.4 g) was added. The resulting mixture was stirred under H₂
atmosphere (500 psi) at 60°C for 2 hours. The insoluble material was filtered off and the

filtrate was concentrated to provide a mixture of *cis* and *trans* product as an oil, which was used in the next step without further purification.

EXAMPLE 34B

5 Trans-4-((4-methoxycyclohexyl)methylamino)-3-nitrobenzenesulfonamide
4-Fluoro-3-nitrobenzenesulfonamide (1.098 g) and EXAMPLE 34A (1 g) in tetrahydrofuran (20 mL) was treated with N,N-diisopropylethylamine (0.871 mL) overnight. The reaction mixture was concentrated and the residue was purified by reverse phase chromatography, and was eluted with 40-55% acetonitrile in 0.1% trifluoroacetic acid in
10 water over 25 minutes.

EXAMPLE 34C

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
15 [(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 34B in place of EXAMPLE 11B. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.69 (s, 1 H), 11.37 (s, 1 H), 8.52 - 8.62 (m, 2 H), 8.04 (d, 1 H), 7.79 (dd, 1 H), 7.47 - 7.55 (m, 3 H), 7.34 (d, 2 H), 7.02 - 7.09 (m, 3 H), 6.68 (dd, 1 H), 6.39 (dd, 1 H), 6.19 (d, 1 H), 3.21 - 3.27
20 (m, 5 H), 3.02 - 3.12 (m, 5 H), 2.75 (s, 2 H), 2.20 (s, 4 H), 2.14 (s, 2 H), 1.93 - 2.04 (m, 4 H), 1.79 (d, 2 H), 1.55 - 1.65 (m, 1 H), 1.38 (t, 2 H), 0.97 - 1.12 (m, 4 H), 0.92 (s, 6 H).

EXAMPLE 35

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-
25 N-{[5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 1G by replacing EXAMPLE 1E and EXAMPLE 1F with EXAMPLE 15H and EXAMPLE 36C, respectively. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.65 (s, 1H), 8.78 (s, 1H), 8.58 (s, 1H), 8.00
30 (d, 1H), 7.51 (m, 3H), 7.38 (d, 2H), 7.14 (d, 2H), 6.68 (dd, 1H), 6.37 (dd, 1H), 6.23 (d, 1H), 4.31 (d, 2H), 4.13 (s, 2H), 3.88 (dd, 2H), 3.11 (m, 5H), 2.16 (m, 6H), 1.65 (m, 2H), 1.35 (m, 2H), 1.19 (s, 6H).

EXAMPLE 36

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5

EXAMPLE 36A

5-Bromo-6-chloropyridine-3-sulfonyl chloride (8.2 g) in methanol (20 mL) was cooled to 0 °C. To this solution was added 7N NH₃ 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 (MgSO₄), filtered, and concentrated. The solid was purified by flash column chromatography on silica gel using 20-100% ethyl acetate in hexanes to give the title compound.

10

15

EXAMPLE 36B

The title compound was prepared by substituting EXAMPLE 36A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

EXAMPLE 36C

A mixture of EXAMPLE 36B (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 MgSO₄, 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.

20

25

EXAMPLE 36D

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

30

The title compound was prepared by substituting EXAMPLE 36C for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.56 (s, 1H), 8.66 (s,

1H), 8.44 (s, 1H), 7.94 (d, 1H), 7.55 (d, 1H), 7.44 (t, 1H), 7.34-7.35 (m, 3H), 7.04 (d, 2H), 6.65 (dd, 1H), 6.32 (s, 1H), 6.24 (s, 1H), 4.26 (d, 2H), 3.86 (dd, 2H), 3.10 (s, 4H), 2.75 (s, 2H), 2.31-2.35 (m, 2H), 2.01-2.05 (m, 1H), 2.15 (s, 2H), 1.96 (s, 2H), 1.63-1.66 (m, 2H), 1.33-1.40 (m, 4H), 0.92 (s, 6H).

5

EXAMPLE 37

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-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

10

EXAMPLE 37A

1,6-dioxaspiro[2.5]octane-2-carbonitrile

A mixture of tetrahydropyran-4-one (10 mL) and chloroacetonitrile (6.4 mL) in tert-butanol (10 mL) was stirred for 10 minutes. To this solution was added a solution of
15 potassium tert-butoxide (12.11 g) in 200 mL of tert-butanol at room temperature over 40 minutes. The reaction mixture was stirred for 16 hours, diluted with water and quenched slowly with 1 N HCl. The solvent was partially removed by rotary evaporation. It was then extracted with ether (5x 200 mL). The combined extracts was washed with brine, dried over MgSO₄, filtered, and the filtrate was concentrated and purified by flash chromatography on
20 silica with 3:7 to 1:1 ethyl acetate:hexanes to provide the title compound.

EXAMPLE 37B

2-(4-fluorotetrahydro-2H-pyran-4-yl)-2-hydroxyacetonitrile

EXAMPLE 37A (11.5 g) in dichloromethane (40 mL) in a polypropylene bottle was
25 treated with 70% hydrogen fluoride-pyridine (10.4 mL) dropwise at 0 °C. The solution was allowed to warm to room temperature over 3 hours, and stirred for an additional 1.5 hours. The reaction mixture was diluted with ethyl acetate (200 mL) and poured into saturated aqueous NaHCO₃. Additional solid NaHCO₃ was used carefully until bubbling ceased. The organic layer was isolated, and the aqueous layer was extracted with additional ethyl acetate
30 three times (150 mL each). The combined organic layers were washed with 5% HCl (50 mL each, twice), brine, dried over MgSO₄, filtered and concentrated to give the desired product which was used directly in the next step.

EXAMPLE 37C

(4-fluorotetrahydro-2H-pyran-4-yl)methanol

EXAMPLE 37B (11.7 g, 74 mmol) in 2-propanol (150 mL) and water (37.5 mL) was cooled to 0 °C. To this solution was added NaBH₄ (4.20 g, 111 mmol). The solution was stirred and allowed to warm to room temperature over 3 hours. It was quenched with acetone, and stirred for another 1 hour. The clear liquid was separated from solid by decanting. Additional ethyl acetate (2x 100 mL) was used to wash the solid, and the mixture was decanted. The combined organic solutions were concentrated. The residue was purified by flash chromatography, eluting with 1:1 ethyl acetate:hexanes to provide the title compound.

EXAMPLE 37D

4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 37C for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

EXAMPLE 37E

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 37D in place of EXAMPLE 11B. ¹H NMR (dimethylsulfoxide-d₆). 11.64 (s, 2H), 8.33 (s, 1H), 8.00-8.01 (m, 2H), 7.39-7.57 (m, 4H), 7.33 (d, J = 8.24 Hz, 2H), 7.03 (d, J = 8.54 Hz, 2H), 6.65 (dd, J = 9, 1.98 Hz, 1H), 6.37-6.38 (m, 1H), 6.19 (d, J = 1.53 Hz, 1H), 4.35 (d, J = 20.75 Hz, 2H), 3.74-3.78 (m, 2H), 3.55-3.60 (m, 2H), 3.07 (br, 4H), 2.80 (br, 2H), 2.25 (br, 4H), 2.13 (br, 2H), 1.81-1.94 (m, 6H), 1.38 (t, J = 6.26 Hz, 2H), 0.91 (s, 6H).

EXAMPLE 38

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 38A

3-cyano-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

The title compound was prepared by substituting 3-cyano-4-fluorobenzenesulfonamide for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

EXAMPLE 38B

5 5-sulfamoyl-2-((tetrahydro-2H-pyran-4-yl)methoxy)benzamide

To a solution of EXAMPLE 38A (0.455 g) in ethanol (3 mL) and tetrahydrofuran (1 mL) was added hydrogen peroxide (30% in water, 2 mL) followed by 1 N aqueous NaOH (1.024 mL) and heated to 35°C for 3 hours. The reaction was poured into dichloromethane (50 mL) and 1N aqueous HCl (25 mL). The aqueous layer was extracted with
10 dichloromethane (3 x 50 mL). The precipitate contained in the combined organic layers was collected by filtration to give the title compound.

EXAMPLE 38C

15 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 38B for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.79 - 11.70 (m, 1H), 11.66 - 11.54 (m, 1H), 9.29 - 9.08 (m, 1H),
20 8.27 (d, 1H), 8.08 (d, 1H), 7.97 - 7.90 (m, 1H), 7.76 - 7.72 (m, 1H), 7.62 (s, 1H), 7.54 (s, 1H), 7.50 (d, 1H), 7.39 (d, 1H), 7.23 (d, 1H), 7.08 (d, 1H), 6.74 - 6.67 (m, 1H), 6.44 (s, 1H), 6.22 (s, 1H), 4.03 (d, 6H), 3.74 - 3.52 (m, 4H), 3.33 (s, 4H), 3.11 - 2.90 (m, 2H), 2.01 (s, 4H), 1.79 - 1.58 (m, 2H), 1.24 (s, 5H), 0.94 (s, 6H).

25 EXAMPLE 39

Cis-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)-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

30 EXAMPLE 39A

Cis-tert-butyl-4-morpholinocyclohexylcarbamate

To a solution of morpholine (4.08 g) 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/NaOH solution, extracted with ether, dried over magnesium sulfate, filtered, and concentrated. The product was separated from the trans isomer and purified by flash chromatography (silica gel, 50% - 100% acetone in hexanes) to provide the title compound.

5

EXAMPLE 39B

cis-4-morpholinocyclohexanamine bis(2,2,2-trifluoroacetate)

To a solution of EXAMPLE 39A (2.43 g) in dichloromethane (15 ml) was added trifluoroacetic acid (5 ml) and the reaction mixture was stirred for 16 hours at room temperature. The reaction mixture was concentrated and the crude product was used without purification.

10

EXAMPLE 39C

4-(cis-4-morpholinocyclohexylamino)-3-nitrobenzenesulfonamide

A solution of EXAMPLE 39B (0.40 g), 4-fluoro-3-nitrobenzenesulfonamide (0.478 g) and triethylamine (2 mL) in tetrahydrofuran (10 mL) was stirred for 3 days at room temperature. The reaction mixture was concentrated and purified by flash chromatography (silica gel, 0-30% methanol / dichloromethane) providing the product.

15

20

EXAMPLE 39D

Cis-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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 39C for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500 MHz, pyridine-d₅) δ 13.07 (s, 1H), 9.30 (d, 1H), 8.64 (d, 1H), 8.43 (d, 1H), 8.38 (dd, 1H), 8.11 (d, 1H), 7.67 (t, 2H), 7.44 (d, 2H), 7.06 (d, 2H), 6.91 (d, 1H), 6.74 (dd, 1H), 6.48 - 6.55 (m, 2H), 3.65 - 3.73 (m, 5H), 3.02 - 3.09 (m, 4H), 2.76 (s, 2H), 2.41 - 2.48 (m, 4H), 2.25 (t, 2H), 2.09 - 2.16 (m, 5H), 1.97 (s, 2H), 1.77 - 1.86 (m, 2H), 1.55 - 1.63 (m, 6H), 1.39 (t, 2H), 0.93 (s, 6H).

25
30

EXAMPLE 40

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5

EXAMPLE 40A

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 36A.

10

EXAMPLE 40B

5-chloro-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

15

EXAMPLE 40C

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

20

The title compound was prepared by substituting EXAMPLE 40B for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.67 (s, 1H), 8.52 (s, 1H), 8.39 (d, 1H), 8.03 (d, 1H), 7.54 (d, 1H), 7.52 (d, 1H), 7.50 (dd, 1H), 7.35 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.39 (m, 1H), 6.21 (d, 1H), 4.25 (d, 2H), 3.87 (dd, 2H), 3.30 (m, 2H), 3.10 (v br s, 4H), 2.90 (v br s, 2H), 2.35 (v br s, 4H), 2.17 (br m, 2H), 2.05 (m, 1H), 1.96 (s, 2H), 1.64 (d, 2H), 1.40 (t, 2H), 1.35 (ddd, 2H), 0.93 (s, 6H).

25

EXAMPLE 41

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

30

The title compound was prepared by substituting EXAMPLE 15H for EXAMPLE 3J and EXAMPLE 40B for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.68 (s, 1H), 8.55 (d, 1H), 8.41 (d, 1H), 8.04 (d, 1H), 7.54 (m, 2H),

7.50 (dd, 1H), 7.38 (d, 2H), 7.14 (d, 2H), 6.68 (dd, 1H), 6.40 (m, 1H), 6.20 (d, 1H), 4.25 (d, 2H), 4.12 (s, 2H), 3.87 (dd, 2H), 3.30 (m, 2H), 3.10 (v br s, 4H), 2.90 (v br s, 2H), 2.27 (v br s, 4H), 2.17 (br m, 2H), 2.05 (m, 1H), 1.96 (s, 2H), 1.64 (d, 2H), 1.35 (ddd, 2H), 0.97 (s, 6H).

5

EXAMPLE 42

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

10

EXAMPLE 42A

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.

15

EXAMPLE 42B

20 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-{[4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl]sulfonyl}benzamide

The title compound was prepared as described in EXAMPLE 1G by replacing EXAMPLE 1E and EXAMPLE 1F with EXAMPLE 15H and EXAMPLE 42A, respectively.

25

¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.73 (s, 1H), 11.25 (s, 1H), 8.08 (d, 1H), 7.89 (d, 1H), 7.77 (m, 1H), 7.61 (d, 1H), 7.51 (m, 2H), 7.37 (d, 2H), 7.13 (d, 2H), 6.88 (d, 1H), 6.67 (dd, 1H), 6.53 (m, 1H), 6.43 (m, 1H), 6.15 (d, 1H), 4.11 (s, 2H), 3.82 (dd, 2H), 3.19 (m, 5H), 3.05 (m, 4H), 2.82 (s, 2H), 2.20 (m, 7H), 1.85 (m, 1H), 1.56 (m, 2H), 1.18 (s, 6H).

30

EXAMPLE 43

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

The title compound was prepared as described in EXAMPLE 1G by replacing EXAMPLE 1E and EXAMPLE 1F with EXAMPLE 15H and EXAMPLE 17A, respectively. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.69 (s, 1H), 11.48 (m, 1H), 8.16 (d, 1H), 8.05 (d, 1H), 7.92 (dd, 1H), 7.52 (m, 3H), 7.37 (d, 2H), 7.27 (m, 1H), 7.11 (m, 3H), 6.68 (dd, 1H), 6.41 (dd, 1H), 6.18 (d, 1H), 4.11 (s, 2H), 3.84 (dd, 2H), 3.25 (m, 4H), 3.07 (m, 4H), 2.84 (m, 2H), 2.23 (m, 5H), 1.84 (m, 1H), 1.55 (m, 2H), 1.25 (m, 3H), 1.18 (s, 6H).

EXAMPLE 44

Trans-4-(4-([4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl)piperazin-1-yl)-N-([4-[(4-morpholin-4-ylcyclohexyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 44A

Trans-4-(4-morpholinocyclohexylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

The title compound was prepared as described in EXAMPLE 16A by replacing 2-methoxyethanamine with EXAMPLE 9B.

EXAMPLE 44B

Trans-4-(4-([4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl)piperazin-1-yl)-N-([4-[(4-morpholin-4-ylcyclohexyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 1G by replacing EXAMPLE 1E and EXAMPLE 1F with EXAMPLE 15H and EXAMPLE 44A, respectively. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.62 (s, 1H), 8.08 (s, 1H), 8.00 (d, 1H), 7.85 (d, 1H), 7.47 (m, 3H), 7.38 (d, 2H), 7.14 (d, 2H), 6.98 (d, 1H), 6.65 (dd, 1H), 6.55 (m, 1H), 6.37 (m, 1H), 6.21 (d, 1H), 4.12 (s, 2H), 3.54 (m, 6H), 3.04 (m, 4H), 2.83 (s, 2H), 2.57 (m, 3H), 2.24 (m, 6H), 1.91 (m, 5H), 1.34 (m, 4H), 1.20 (s, 6H).

EXAMPLE 45

4-(4-([4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl)piperazin-1-yl)-N-([4-[(1-methylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 45A

4-(1-methylpiperidin-4-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

The title compound was prepared as described in EXAMPLE 16A by replacing 2-methoxyethanamine with 1-methyl-4-aminopiperidine.

5

EXAMPLE 45B

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

10 The title compound was prepared as described in EXAMPLE 1G by replacing EXAMPLE 1E and EXAMPLE 1F with EXAMPLE 15H and EXAMPLE 45A, respectively. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.59 (s, 1H), 8.10 (s, 1H), 7.98 (d, 1H), 7.90 (dd, 1H), 7.49 (m, 3H), 7.39 (m, 3H), 7.14 (d, 2H), 7.02 (d, 1H), 6.65 (dd, 2H), 6.36 (dd, 1H), 6.22 (d, 1H), 4.12 (s, 2H), 3.75 (m, 1H), 3.16 (m, 4H), 2.98 (m, 5H), 2.88 (m, 5H), 2.67 (s, 15 2H), 2.22 (m, 6H), 1.68 (m, 1H), 1.18 (s, 6H).

EXAMPLE 46

5-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino}sulfonyl)-2-(tetrahydro-2H-pyran-4-ylmethoxy)nicotinamide

20

5-sulfamoyl-2-((tetrahydro-2H-pyran-4-yl)methoxy)nicotinamide

To EXAMPLE 36C (0.025 g) in ethanol (1 mL) and tetrahydrofuran (1 mL) was added hydrogen peroxide (30% in water, 0.5 mL) followed by 1M aqueous sodium hydroxide (0.056 ml) then another 1 mL of tetrahydrofuran. The reaction was heated to 45°C for 2 25 hours, cooled, quenched with 1N aqueous HCl (5 mL), and the product extracted into dichloromethane (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated to give the title compound.

EXAMPLE 46B

30 5-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino}sulfonyl)-2-(tetrahydro-2H-pyran-4-ylmethoxy)nicotinamide

The title compound was prepared by substituting EXAMPLE 46A for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. ¹H NMR (300 MHz, CDCl₃) δ 10.31 – 10.09 (m, 1H), 9.09 (s, 2H), 8.93 – 8.81 (m, 1H), 8.28 – 8.18 (m, 1H), 8.03 – 7.87 (m, 1H), 7.77 – 7.68 (m, 1H), 7.59 – 7.51 (m, 1H), 7.48 – 7.41 (m, 1H), 6.91 (d, 2H), 6.59 – 6.48 (m, 2H), 5.97 (s, 2H), 4.50 (d, 2H), 4.08 – 3.98 (m, 2H), 3.45 (s, 4H), 3.13 – 2.99 (m, 4H), 2.82 – 2.68 (m, 2H), 2.19 (s, 4H), 1.86 (s, 5H), 1.61 – 1.35 (m, 4H), 0.94 (s, 6H).

EXAMPLE 47

N-({5-bromo-6-[(1-methylpiperidin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 47A

5-bromo-6-((1-methylpiperidin-4-yl)methoxy)pyridine-3-sulfonamide

To (1-methylpiperidin-4-yl)methanol (0.109 g) in tetrahydrofuran (2 mL) was added sodium hydride (0.136 g). After 30 minutes, EXAMPLE 36A (0.230 g) was added as a solution in tetrahydrofuran (1 mL) and the reaction was heated to 50°C. After 4 hours, the reaction was cooled, poured into water (10 mL) and dichloromethane (50 mL), and the pH was adjusted to pH~8. The aqueous layer was extracted with dichloromethane (3 x 50 mL), and the organic layers were combined, washed with brine (30 mL), dried over magnesium sulfate, filtered, and concentrated to give the title compound.

EXAMPLE 47B

N-({5-bromo-6-[(1-methylpiperidin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 47A for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.51 (s, 1H), 8.35 (d, 1H), 8.17 (d, 1H), 7.93 (d, 1H), 7.60 (d, 1H), 7.44 – 7.40 (m, 1H), 7.33 (dd, 3H), 7.05 (d, 2H), 6.61 (d, 1H), 6.31 (dd, 1H), 6.24 (s, 1H), 4.25 (d, 2H), 3.40 (s, 4H), 3.01 (s, 4H), 2.73 (d, *J* = 8.2, 5H), 2.20 (s, 6H), 1.93 (d, 4H), 1.54 (s, 1H), 1.39 (s, 2H), 1.24 (s, 2H), 0.93 (s, 6H).

EXAMPLE 48

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5

EXAMPLE 48A

4-((1-methylpiperidin-4-yl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting (1-methylpiperidin-4-yl)methanol for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

10

EXAMPLE 48B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

15

The title compound was prepared by substituting EXAMPLE 48A for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.54 (s, 1H), 8.17 (s, 1H), 7.92 (s, 1H), 7.87 – 7.77 (m, 1H), 7.58 (d, 1H), 7.43 (s, 1H), 7.40 – 7.00 (m, 7H), 6.70 – 6.56 (m, 1H), 6.31 (s, 1H), 6.24 (s, 1H), 4.05 (s, 2H), 3.46 – 3.33 (m, 2H), 3.02 (s, 6H), 2.72 (d, 5H), 2.21 (s, 6H), 1.96 (s, 5H), 1.70 – 1.48 (m, 2H), 1.39 (s, 2H), 0.93 (s, 6H).

20

EXAMPLE 49

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{5-cyano-6-(1,4-dioxan-2-yl)methoxy}pyridin-3-yl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

25

EXAMPLE 49A

6-((1, 4-dioxan-2-yl)methoxy)-5-bromopyridine-3-sulfonamide

The title compound was prepared by substituting (1, 4-dioxan-2-yl)methanol for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 36A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

30

EXAMPLE 49B

6-((1,4-dioxan-2-yl)methoxy)-5-cyanopyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 49A for EXAMPLE 36B in EXAMPLE 36C.

EXAMPLE 49C

5 4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([5-cyano-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 49B for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (400MHz, dimethylsulfoxide-d₆) δ 11.50 (s, 1H), 8.60 (s, 1H), 8.40 (s, 1H), 7.91 (d, 1H), 7.58 (d, 1H), 7.42 (t, 1H), 7.35 (d, 2H), 7.28 (s, 1H), 7.06 (d, 2H), 6.64 (dd, 1H), 6.29 (m, 2H), 4.40 (d, 2H), 3.90 (m, 1H), 3.79 (m, 2H), 3.63 (m, 2H), 3.46 (m, 4H), 3.07 (s, 4H), 2.85 (m, 2H), 2.34 (m, 4H), 2.16 (m, 2H), 1.40 (t, 2H), 0.93 (s, 6H).

15 EXAMPLE 50

N-([5-bromo-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 49A for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (400MHz, dimethylsulfoxide-d₆) δ 11.60 (s, 1H), 8.46 (s, 1H), 8.27 (s, 1H), 7.99 (d, 1H), 7.56 (d, 1H), 7.46 (m, 2H), 7.35 (d, 2H), 7.05 (d, 2H), 6.65 (dd, 1H), 6.36 (dd, 1H), 6.22 (d, 1H), 4.34 (m, 2H), 3.88 (m, 1H), 3.79 (m, 2H), 3.63 (m, 2H), 3.46 (m, 2H), 3.06 (s, 4H), 2.81 (s, 2H), 2.26 (m, 4H), 2.15 (s, 2H), 1.96 (s, 2H), 1.38 (m, 2H), 0.93 (s, 6H).

25

EXAMPLE 51

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

30

EXAMPLE 51A

The title compound was prepared as described in EXAMPLE 12A by replacing (1,4-dioxan-2-yl)methanol with (2,2-dimethyltetrahydro-2H-pyran-4-yl)methanol.

EXAMPLE 51B

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-
5 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE
51A in place of EXAMPLE 11B. ¹H NMR (400 MHz, dimethylsulfoxide-d₆) δ 11.69 (s,
2H), 8.35 (s, 2H), 8.03 (d, 4H), 7.47 - 7.58 (m, 6H), 7.31 - 7.42 (m, 6H), 7.04 (d, 4H), 6.68
(dd, 2H), 6.40 (s, 2H), 6.20 (d, 2H), 3.96 - 4.09 (m, 2H), 3.54 - 3.68 (m, 2H), 3.09 (s, 4H),
10 2.83 (s, 2H), 2.09 - 2.37 (m, 7H), 1.96 (s, 2H), 1.55 - 1.69 (m, 2H), 1.39 (t, 2H), 1.19 (m,
8H), 0.92 (s, 6H).

EXAMPLE 52

N-({3-chloro-5-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{[2-
15 (4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

EXAMPLE 52A

3-cyano-4-fluorobenzenesulfonamide

20 3-Cyano-4-fluorobenzene-1-sulfonyl chloride (1.1 g) in 1,4-dioxane (10 mL) at 0 °C
was treated dropwise with a 7 M ammonia solution in methanol (3.57 mL) and stirred for 30
minutes. A small amount of solid was removed by filtration and discarded. The filtrate was
concentrated, diluted with ethyl acetate, washed with water and brine, dried (MgSO₄),
filtered, concentrated and triturated with diethyl ether to give the product.

25

EXAMPLE 52B

3-cyano-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 52A for 4-chloro-3-
nitrobenzenesulfonamide and (tetrahydro-2H-pyran-4-yl)methanamine for 4-
30 methylpiperazin-1-amine dihydrochloride in EXAMPLE 6A.

EXAMPLE 52C

3-chloro-5-cyano-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

EXAMPLE 52B (0.148 g) in acetonitrile (5 mL) was treated with N-chlorosuccinimide (0.080 g), heated at 60 °C for 3 hours and filtered to remove a small amount of solid. The filtrate was concentrated and chromatographed on silica gel with 3-15% ethyl acetate in dichloromethane as eluent. The obtained solid was slurried in water,
5 filtered, rinsed with additional water and dried under vacuum to give the product.

EXAMPLE 52D

N-({3-chloro-5-cyano-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-pyrrolo[2,3-
10 b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 52C for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.70 (s, 1H), 11.41 (br s, 1H), 8.07 (d, 1H), 7.89 (s, 2H), 7.61 (m, 1H), 7.53 (m, 2H), 7.35 (d, 2H), 7.18 (m, 1H), 7.05 (d, 2H), 6.69 (m, 1H), 6.42 (dd, 1H), 6.18 (dd, 1H), 3.83 (m, 2H), 3.55 (t, 2H), 3.23 (m,
15 3H), 3.06 (m, 4H), 2.15 (m, 4H), 1.92 (m, 4H), 1.60 (m, 2H), 1.40 (m, 2H), 1.19 (m, 4H), 0.93 (s, 6H).

EXAMPLE 53

N-({4-[(1-acetylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-
20 4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 53A

N-[(4-chloro-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-
25 1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and 4-chloro-3-nitrobenzenesulfonamide for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 53B

N-({4-[(1-acetylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-
30 4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

A 5 mL round-bottomed flask was charged with EXAMPLE 53A (120 mg), 1-acetylpiperidin-4-amine (28 mg), and triethylamine (0.064 mL) in dioxane (2 mL). The reaction mixture was heated to 90°C for 24 hours. The reaction mixture was cooled to room temperature, and added to a silica gel column and purified by eluting with 0-5% methanol in dichloromethane. ¹H NMR (300MHz, dimethylsulfoxide-d₆) δ 11.66 (br s, 1H), 8.65 (d, 1H), 8.24 (d, 1H), 8.03 (d, 1H), 7.83 (dd, 1H), 7.54-7.46 (m, 3H), 7.35 (d, 2H), 7.19 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (m, 1H), 6.20 (d, 1H), 4.28 (d, 1H), 3.97-3.75 (m, 2H), 3.07 (br s, 4H), 2.87-2.70 (m, 4H), 2.29-2.10 (m, 6H), 2.02 (s, 3H), 2.00-1.89 (m, 4H), 1.66-1.54 (m, 2H), 1.39 (t, 2H), 0.92 (s, 6H).

EXAMPLE 54

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 54A

2-chloro-5-fluoro-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

The title compound was prepared by substituting 2-chloro-4,5-difluorobenzenesulfonamide for 4-chloro-3-nitrobenzenesulfonamide and (tetrahydro-2H-pyran-4-yl)methanamine for 4-methylpiperazin-1-amine dihydrochloride in EXAMPLE 6A.

EXAMPLE 54

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 54A for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.76 (s, 1H), 11.31 (s, 1H), 8.08 (d, 1H), 7.69 (d, 1H), 7.60 (d, 1H), 7.55 (m, 2H), 7.34 (d, 2H), 7.04 (d, 2H), 6.90 (s, 1H), 6.84 (d, 1H), 6.69 (dd, 1H), 6.45 (dd, 1H), 6.13 (d, 1H), 3.82 (dd, 2H), 3.24 (t, 2H), 3.05 (m, 6H), 2.73 (s, 2H), 2.14 (m, 6H), 1.95 (s, 2H), 1.81 (m, 1H), 1.61 (m, 2H), 1.38 (t, 2H), 1.17 (m, 2H), 0.92 (s, 6H).

EXAMPLE 55

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-(1H-pyrrolo[2,3-b]pyridin-5-
yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 2A for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300MHz, dimethylsulfoxide-d₆) δ 11.66 (br s, 1H), 8.75 (t, 1H), 8.54 (d, 1H), 8.03 (d, 1H), 7.79 (dd, 1H), 7.54-7.48 (m, 3H), 7.35 (d, 2H), 7.08-7.02 (m, 3H), 6.67 (dd, 1H), 6.38 (m, 1H), 6.20 (d, 1H), 3.61 (t, 4H), 3.43 (q, 2H), 3.29 (m, 2H), 3.06 (br s, 4H), 2.73 (br s, 2H), 2.47 (br s, 4H), 2.18 (m, 6H), 1.95 (br s, 2H), 1.80 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 56

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 56A

5-bromo-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 37C for tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 36A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

EXAMPLE 56B

The title compound was prepared by substituting EXAMPLE 56A for EXAMPLE 36B in EXAMPLE 36C.

EXAMPLE 56C

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 56B for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.58 (s,

1H), 8.70 (s, 1H), 8.51 (s, 1H), 7.96 (d, 1H), 7.57 (d, 1H), 7.45 (t, 1H), 7.35-7.37 (m, 3H), 7.06 (d, 2H), 6.67 (dd, 1H), 6.33 (d, 1H), 6.26 (s, 1H), 4.56 (d, 2H), 3.76-3.80 (s, 2H), 3.56-3.62 (m, 2H), 3.01-3.10 (m, 4H), 2.14-2.18 (m, 2H), 1.96 (s, 2H), 1.80-1.87 (m, 4H), 1.41 (t, 2H), 0.93 (s, 6H).

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EXAMPLE 57

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

10

EXAMPLE 57A

5-bromo-6-(2-morpholinoethoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting 2-morpholinoethanol for tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 36A for 4-fluoro-3-nitrobenzenesulfonamide in

15 EXAMPLE 24A.

EXAMPLE 57B

5-cyano-6-(2-morpholinoethoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 57A for EXAMPLE 36A in EXAMPLE 36B.

20

EXAMPLE 57C

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

25

The title compound was prepared by substituting EXAMPLE 57B for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.56 (s, 1H), 8.64 (s, 1H), 8.41 (s, 1H), 7.92 (d, 1H), 7.58 (d, 1H), 7.44 (t, 1H), 7.36 (d, 2H), 7.31 (s, 1H), 7.06 (d, 2H), 6.65 (dd, 1H), 6.31 (d, 1H), 6.27 (d, 1H), 4.59 (t, 2H), 3.59 (s, 4H), 3.08 (s, 4H), 2.89 (s, 2H), 2.65 (s, 4H), 2.16-2.18 (m, 2H), 1.97 (s, 2H), 1.41 (t, 2H), 0.93 (s, 6H).

30

EXAMPLE 58

N-[(3-chloro-4-{[2-(2-methoxyethoxy)ethyl]sulfonyl}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 58A

3-chloro-4-(2-(2-methoxyethoxy)ethylthio)benzenesulfonamide

In a 25 mL microwave tube 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 stirring for 30 minutes, 3-chloro-4-fluorobenzenesulfonamide (1.54 g) dissolved in 10 mL tetrahydrofuran was added slowly. The mixture was heated at 110°C for 30 minutes in a Biotage Initiator microwave reactor. Water was added, the product was extracted with ether (20 mL x3), dried over Na₂SO₄, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica eluting with 0-25% ethyl acetate in hexane.

EXAMPLE 58B

3-chloro-4-(2-(2-methoxyethoxy)ethylsulfonyl)benzenesulfonamide

EXAMPLE 58A (0.15 g) was suspended in acetic acid (3 mL). Peracetic acid (0.4 mL) was added slowly. The mixture was stirred at room temperature overnight, then poured into Na₂S₂O₃ solution, and the product precipitated. After filtration and washing with water, the product was dried under vacuum.

EXAMPLE 58C

N-[(3-chloro-4-{[2-(2-methoxyethoxy)ethyl]sulfonyl}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 58B for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.52 (s, 1H), 7.92 (d, 1H), 7.84 (m, 2H), 7.68 (m, 1H), 7.62 (d, 1H), 7.42 (t, 1H), 7.35 (d, 2H), 7.29 (m, 1H), 7.05 (d, 2H), 6.62 (dd, 1H), 6.32 (m, 1H), 6.26 (d, 1H), 3.74 (t, 2H), 3.68 (t, 2H), 3.24 (m, 2H), 3.06 (m, 5H), 3.01 (m, 4H), 2.74 (s, 2H), 2.19 (m, 6H), 1.96 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

EXAMPLE 59

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

EXAMPLE 59A

4-(2-(2-methoxyethoxy)ethylthio)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 4-fluoro-3-nitrobenzenesulfonamide
10 for 3-chloro-4-fluorobenzenesulfonamide in EXAMPLE 58A.

EXAMPLE 59B

4-(2-(2-methoxyethoxy)ethylsulfonyl)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 59A for EXAMPLE
15 58A in EXAMPLE 58B.

EXAMPLE 59C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
20 { [2-(2-methoxyethoxy)ethyl]sulfonyl }-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-
5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 59B for EXAMPLE
11B in EXAMPLE 11D. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.51 (s, 1H), 8.17 (m,
1H), 7.94 (m, 3H), 7.64 (d, 1H), 7.42 (m, 1H), 7.35 (d, 2H), 7.28 (d, 1H), 7.05 (d, 2H), 6.62
(m, 1H), 6.28 (m, 2H), 3.83 (m, 4H), 3.16 (m, 2H), 3.08 (s, 3H), 3.01 (m, 4H), 2.73 (s, 2H),
25 2.18 (m, 6H), 1.96 (m, 4H), 1.39 (t, 2H), 0.93 (s, 6H)

EXAMPLE 60

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
30 ({4-[(4-morpholin-4-ylcyclohexyl)oxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

EXAMPLE 60A

Trans-4-(4-aminocyclohexyloxy)-3-nitrobenzenesulfonamide

To a solution of *tert*-butyl 4-hydroxycyclohexylcarbamate (0.250 g) in tetrahydrofuran (5 mL) was added sodium hydride (0.186 g). After stirring for 15 minutes, 4-fluoro-3-nitrobenzenesulfonamide (0.256 g) was added as a solution in tetrahydrofuran (1 mL). The reaction was heated to 60°C for 1.5 hours, cooled, and poured into a mixture of dichloromethane (100 mL) and water (25 mL). The aqueous layer was adjusted to pH~4 with 1N aqueous HCl and the organic layer was separated, washed with brine (50 mL), dried over magnesium sulfate, filtered, and concentrated. The residue was loaded onto silica gel (GraceResolv 40 g) and eluted using a gradient of 0.5% to 7.5% methanol/dichloromethane over 30 minutes. This solid was treated with HCl (4.0M in dioxane, 5 mL) at room temperature for 1 hour and concentrated to give the title compound.

EXAMPLE 60B

4-(trans-4-morpholinocyclohexyloxy)-3-nitrobenzenesulfonamide

To EXAMPLE 60A (0.220 g) and 1-bromo-2-(2-bromoethoxy)ethane (0.177 g) in N,N-dimethylformamide (3 mL) was added triethylamine (0.338 mL) and the reaction heated to 70°C for 5 hours. The reaction was cooled and the resulting precipitate was removed by filtration. The reaction was concentrated and loaded onto silica gel and was eluted using a gradient of 0.5% to 7.5% methanol/dichloromethane to give the title compound.

EXAMPLE 60C

Trans-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-((4-[(4-morpholin-4-ylcyclohexyl)oxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 60B for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.62 (s, 1H), 8.23 (s, 1H), 7.99 (s, 1H), 7.96 – 7.88 (m, 1H), 7.54 (d, 1H), 7.48 (s, 2H), 7.34 (d, 3H), 7.04 (d, 2H), 6.72 – 6.58 (m, 1H), 6.37 (s, 1H), 6.21 (s, 1H), 4.69 – 4.47 (m, 1H), 3.66 (s, 4H), 3.05 (s, 4H), 2.76 (s, 6H), 2.22 (s, 9H), 1.96 (s, 4H), 1.39 (s, 6H), 0.92 (s, 6H).

EXAMPLE 61

N-([5-bromo-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 61A

5-bromo-6-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-ylamino)pyridine-3-sulfonamide

A mixture of EXAMPLE 36A (1.0 g), EXAMPLE 3L (0.95 g) and triethylamine (3.08 mL) in anhydrous dioxane (20 mL) was heated at 110°C overnight. The organic solvent was removed under vacuum. The residue was purified with flash column chromatography on silica gel eluting with 2%-8% methanol/dichloromethane to give the title compound.

EXAMPLE 61B

10 N-({5-bromo-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 61A for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (400MHz, dimethylsulfoxide-d₆) δ 11.59 (s, 1H), 8.35 (s, 1H), 8.00 (s, 2H), 7.55 (d, 1H), 7.46 (m, 2H), 7.34 (d, 2H), 7.04 (d, 2H), 6.63 (dd, 1H), 6.49 (m, 1H), 6.36 (s, 1H), 6.20 (s, 1H), 4.05 (m, 1H), 3.94 (d, 2H), 3.28 (m, 6H), 3.01 (s, 4H), 2.72 (s, 2H), 2.16 (m, 6H), 1.93 (m, 4H), 1.80 (m, 4H), 1.57 (m, 2H), 1.38 (t, 2H), 1.17 (t, 2H), 0.90 (s, 6H).

EXAMPLE 62

20 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 62A

4-(2-cyanoethylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 3-aminopropanenitrile for EXAMPLE 39B in EXAMPLE 39C.

EXAMPLE 62B

30 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 62A for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (501 MHz, pyridine-d₅) δ 13.04 (s, 1H), 9.24 (d, 1H), 9.04 (t, 1H), 8.43 (d, 1H), 8.38 (dd, 1H), 8.13 (d, 1H), 7.64 - 7.68 (m, 2H), 7.44 (ddd, 2H), 7.07 (ddd, 2H), 7.02 (d, 1H), 6.76 (dd, 1H), 6.55 (d, 1H), 6.48 (dd, 1H), 3.83 (q, 2H), 3.07 (d, 4H), 2.98 (t, 2H), 2.77 (s, 2H), 2.26 (s, 2H), 2.11 - 2.17 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

EXAMPLE 63

Cis-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-yl)cyclohexyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 15H for EXAMPLE 3J and EXAMPLE 39C for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (501 MHz, pyridine-d₅) δ 13.09 (s, 1H), 9.30 (d, 1H), 8.64 (d, 1H), 8.43 (d, 1H), 8.38 (dd, 1H), 8.10 (d, 1H), 7.68 (dt, 2H), 7.46 (ddd, 2H), 7.12 (ddd, 2H), 6.91 (d, 1H), 6.72 (dd, 1H), 6.51 (dd, 1H), 6.49 (d, 1H), 5.69 (s, 2H), 4.40 (s, 2H), 3.69 - 3.73 (m, 4H), 3.68 (s, 1H), 2.95 - 3.02 (m, 4H), 2.84 (s, 2H), 2.40 - 2.46 (m, 4H), 2.21 (s, 2H), 2.08 - 2.15 (m, 5H), 1.76 - 1.84 (m, 2H), 1.55 - 1.63 (m, 6H), 1.29 (s, 6H).

EXAMPLE 64

Trans-N-{{4-({4-[bis(cyclopropylmethyl)amino]cyclohexyl}amino)-3-nitrophenyl}sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 64A

tert-butyl (trans)-4-(bis(cyclopropylmethyl)amino)cyclohexylcarbamate

The title compound was prepared by substituting cyclopropanecarbaldehyde for 4'-chlorobiphenyl-2-carboxaldehyde and tert-butyl (trans)-4-aminocyclohexylcarbamate for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 64B

(trans)-N¹,N¹-bis(cyclopropylmethyl)cyclohexane-1,4-diamine dihydrochloride

To a solution of EXAMPLE 64A (1.4 g) in dichloromethane (10 ml) was added hydrogen chloride (10 ml, 4M in dioxane) and the reaction was stirred for 16 hours at room temperature. The reaction mixture was diluted with ether and pure product was filtered off.

5

EXAMPLE 64C

Trans-4-(4-(bis(cyclopropylmethyl)amino)cyclohexylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 64B for EXAMPLE 39B in EXAMPLE 39C.

10

EXAMPLE 64D

Trans-N-{{4-({4-[bis(cyclopropylmethyl)amino]cyclohexyl}amino)-3-nitrophenyl}sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 64C for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500 MHz, pyridine-d₅) δ 13.06 (s, 1H), 9.30 (d, 1H), 8.44 (d, 1H), 8.41 (dd, 1H), 8.37 (d, 1H), 8.12 (d, 1H), 7.67 (d, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 7.00 (d, 1H), 6.75 (dd, 1H), 6.53 (d, 1H), 6.49 (dd, 1H), 3.36 - 3.43 (m, 1H), 3.02 - 3.09 (m, 4H), 2.87 - 2.94 (m, 1H), 2.77 (s, 2H), 2.47 (d, 4H), 2.25 (t, 2H), 2.11 - 2.16 (m, 4H), 2.08 (d, 2H), 1.97 (s, 2H), 1.84 (d, 2H), 1.39 (t, 2H), 1.26 - 1.35 (m, 4H), 0.90 - 0.98 (m, 8H), 0.50 - 0.56 (m; 4H), 0.18 - 0.23 (m, 4H).

20

EXAMPLE 65

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]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

25

EXAMPLE 65A

4-((1-methylpiperidin-4-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 4-aminomethyl-1-methyl piperidine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

30

EXAMPLE 65B

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]-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

5 The title compound was prepared by substituting EXAMPLE 65A for EXAMPLE
130C in EXAMPLE 130D. ¹H NMR (500MHz, dichloromethane-d₂) δ 9.57 (bs, 1H), 8.78
(d, 1H), 8.41 (d, 1H), 8.14 (d, 1H), 7.90 (m, 2H), 7.64 (d, 1H), 7.45 (d, 1H), 7.23 (d, 2H),
6.95 (d, 2H), 6.76 (d, 1H), 6.59 (dd, 1H), 6.51 (d, 1H), 6.09 (d, 1H), 3.21 (m, 2H), 3.08 (m,
4H), 3.02 (m, 2H), 2.74 (s, 2H), 2.33 (s, 3H), 2.21-2.17 (m, 6H), 2.16-2.02 (m, 3H), 1.97
10 (br.s, 2H), 1.78 (m, 4H), 1.41 (t, 2H), 0.94 (s, 6H).

EXAMPLE 66

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
[(morpholin-3-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-
15 yloxy)benzamide

EXAMPLE 66A

tert-butyl 3-((2-nitro-4-sulfamoylphenylamino)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting tert-butyl 3-
20 (aminomethyl)morpholine-4-carboxylate for (tetrahydropyran-4-yl)methylamine in
EXAMPLE 1F.

EXAMPLE 66B

tert-butyl 3-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-
25 dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-
nitrophenylamino)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting EXAMPLE 66A for EXAMPLE 1F
and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1F, with the exception that the product
was purified on a silica gel column eluted with 4% methanol in dichloromethane.

30 EXAMPLE 66C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
[(morpholin-3-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-
yloxy)benzamide

A solution of EXAMPLE 66B in 50% trifluoroacetic acid and dichloromethane mixture was stirred at ambient temperature for 2 hours. The solvents were evaporated and the residue was purified on a reverse phase HPLC using a gradient of 20-80% acetonitrile in water containing 10 mM ammonium acetate. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.61 (s, 1H), 8.52 (bs, 1H), 8.49 (d, 1H), 7.98 (d, 1H), 7.78 (d, 1H), 7.54 (d, 1H), 7.46 (s, 1H), 7.42 (s, 1H), 7.34 (d, 2H), 7.04 (m, 3H), 6.65 (dd, 1H), 6.34 (s, 1H), 6.21 (d, 1H), 3.89 (d, 1H), 3.76 (d, 1H), 3.55-3.46 (m, 2H), 3.40-3.35 (m, 4H), 3.04 (m, 4H), 2.91 (t, 1H), 2.73 (s, 2H), 2.20-2.12 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

10

EXAMPLE 67

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 1G by replacing EXAMPLE 1E and EXAMPLE 1F with EXAMPLE 15H and EXAMPLE 6A, respectively. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.58 (s, 1H), 9.04 (s, 1H), 8.44 (d, 1H), 7.97 (d, 1H), 7.76 (dd, 1H), 7.49 (m, 4H), 7.38 (d, 2H), 7.14 (d, 2H), 6.64 (dd, 1H), 6.34 (d, 1H), 6.21 (d, 1H), 4.12 (s, 2H), 3.03 (m, 6H), 2.85 (m, 5H), 2.29 (m, 4H), 2.18 (m, 6H), 1.20 (s, 6H).

20

EXAMPLE 68

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylbut-2-ynyl)oxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

25

EXAMPLE 68A

4-morpholinobut-2-yn-1-ol

To a solution 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 solution was stirred at 85 °C for 3 hours. After cooling, the solid was filtered off. The filtrate was subjected to vacuum distillation to give the pure title compound.

30

EXAMPLE 68B

4-(4-morpholinobut-2-ynyloxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 68A for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

5

EXAMPLE 68C

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-[(4-morpholin-4-ylbut-2-ynyl)oxy]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

10

The title compound was prepared by substituting EXAMPLE 68B for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.68 (s, 1H), 8.36 (s, 1H), 8.08 (d, 1H), 8.03 (d, 1H), 7.47-7.53 (m, 4H), 7.35 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 5.15 (s, 2H), 3.52-3.55 (m, 4H), 3.09 (s, 4H), 2.84 (br s, 2H), 2.23-2.40 (m, 6H), 2.12-2.18 (m, 2H), 1.96 (s, 2H), 1.39 (t, 2H), 0.92 (s, 6H).

15

EXAMPLE 69

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

20

EXAMPLE 69A

6-((tetrahydro-2H-pyran-4-yl)methoxy)-5-((triisopropylsilyl)ethynyl)pyridine-3-sulfonamide

EXAMPLE 36B (0.176 g), bis(triphenylphosphine)palladium(II) chloride (0.176 g), copper(I) iodide (0.010 g), N,N-dimethylacetamide (2.5 mL) and triethylamine (0.105 mL) were combined, flushed with nitrogen and stirred for 2 minutes. (Triisopropylsilyl)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 (MgSO₄), filtered, concentrated and chromatographed on silica gel with 10-30% ethyl acetate in hexanes as the eluent to give the product.

30

EXAMPLE 69B

5-ethynyl-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

EXAMPLE 69A (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.

- 5 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 product.

EXAMPLE 69

- 10 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

- The title compound was prepared by substituting EXAMPLE 69B for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.69 (s, 1H), 11.41 (s, 1H), 8.58 (d, 1H), 8.19 (d, 1H), 8.05 (d, 1H), 7.53 (m, 3H), 7.35 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.41 (dd, 1H), 6.18 (d, 1H), 4.56 (s, 1H), 4.24 (d, 2H), 3.87 (dd, 2H), 3.38 (m, 3H), 3.07 (m, 4H), 2.86 (m, 2H), 2.29 (m, 5H), 2.04 (m, 3H), 1.64 (dd, 2H), 1.34 (m, 4H), 0.93 (s, 6H).

- 20

EXAMPLE 70

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(4-oxo-3,4-dihydroquinazolin-6-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 70A

- 25 4-amino-3-cyanobenzenesulfonamide

- 3-Cyano-4-fluorobenzene-1-sulfonyl chloride (1.1 g) was dissolved in dioxane (4 mL). The solution was cooled to 0°C and 7 mL of an ammonia (7N in methanol) solution was added. After the addition was complete, the ice bath was removed and the reaction was stirred at room temperature for 24 hours. After concentration of the reaction mixture, the crude material was purified by flash chromatography eluting with a gradient of 30-100% ethyl acetate/hexanes.
- 30

EXAMPLE 70B

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(4-amino-3-cyanophenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzamide

The title compound was prepared by substituting EXAMPLE 70A for EXAMPLE 1F
5 and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G.

EXAMPLE 70C

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(4-amino-3-carbamoylphenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzamide

10 To a solution of EXAMPLE 70B (90 mg) in ethanol (2 mL) was added tetrahydrofuran (2 mL), hydrogen peroxide (30%, 1 mL) and 1M sodium hydroxide solution (0.48 mL), followed by an additional 2 mL of tetrahydrofuran. The reaction was heated to 45°C for 30 minutes, cooled, and then quenched with 5% HCl solution and extracted twice with dichloromethane. The extracts were combined and concentrated to obtain the product.

15

EXAMPLE 70D

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(4-oxo-3,4-dihydroquinazolin-6-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 70C (80 mg) was combined with trimethyl orthoformate (2.3 mL) and
20 trifluoroacetic acid (0.03 mL) and the resulting solution was stirred at room temperature for 4 hours. The mixture was purified by flash chromatography, eluting with a gradient of 3-10% methanol/dichloromethane. ¹H NMR (300MHz, dimethylsulfoxide-d₆) δ 12.61 (s, 1H), 11.71 (s, 1H), 8.65 (d, 1H), 8.24 (s, 1H), 8.17 (dd, 1H), 8.04 (m, 1H), 7.73 (d, 1H), 7.57 (d, 1H), 7.51 (m, 2H), 7.39 (d, 2H), 7.07 (d, 2H), 6.70 (dd, 1H), 6.40 (m, 1H), 6.24 (br s, 1H), 3.61
25 (m, 6H), 3.03 (m, 2H), 2.75 (m, 2H), 2.17 (m, 2H), 2.01 (m, 2H), 1.44 (m, 2H), 0.94 (s, 6H).

EXAMPLE 71

Trans-4-(4-([8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl)piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

30

EXAMPLE 71A

8-chlorospiro[4.5]dec-7-ene-7-carbaldehyde

To a solution of N,N-dimethylformamide (2.81 mL) in dichloromethane (40 mL) was added dropwise POCl₃ (2.78 mL) at 0°C. The reaction mixture was warmed up to room temperature and spiro[4.5]decan-8-one (3.95 g) in dichloromethane (5 mL) was added dropwise. The mixture was stirred overnight. The reaction was quenched with cold aqueous sodium acetate and the resulting mixture was extracted with ether and the organic layer was dried over Na₂SO₄, filtered, and concentrated to provide the title compound.

EXAMPLE 71B

8-(4-chlorophenyl)spiro[4.5]dec-7-ene-7-carbaldehyde

To a suspension of EXAMPLE 71A (3 g) in water (50 mL) was added 4-chlorophenylboronic acid (2.83 g), tetrabutylammonium (4.87 g), potassium carbonate (6.26 g) and palladium(II) acetate (0.169 g). The reaction mixture was stirred at 45°C for 5 hours and extracted with dichloromethane. The organic layer was concentrated and the residue was loaded onto a silica gel column, and eluted with 5-20% ethyl acetate in hexane to give the title compound.

EXAMPLE 71C

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl)methyl)piperazin-1-yl)benzoate

To a solution of EXAMPLE 71B (274 mg) in dichloroethane (3.5 mL) was added EXAMPLE 15F (387 mg) and sodium triacetoxyborohydride (317 mg). The reaction mixture was stirred overnight. Sodium cyanoborohydride (37.6 mg) was added and the resulting mixture stirred overnight. The reaction was quenched with water and diluted with dichloromethane. The mixture was washed with water extensively and the organic layer was dried over Na₂SO₄, filtered, and concentrated to provide the title compound.

EXAMPLE 71D

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared as described in EXAMPLE 3J using EXAMPLE 71C in place of EXAMPLE 3I.

EXAMPLE 71E

Trans-4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5 The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 71D and EXAMPLE 9C in place of EXAMPLE 3J and EXAMPLE 11B, respectively. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.64 (s, 1H), 8.51 (s, 1H), 8.15 (d, 1H), 8.01 (d, 1H), 7.76 (d, 1H), 7.44 - 7.53 (m, 3H), 7.34 (d, 2H), 7.07 (d, 3H), 6.66 (dd, 1H), 6.37 (dd, 1H), 6.20 (d, 1H), 3.50 - 3.70 (m, 5H), 3.04 (s, 4H), 2.55 - 2.76 (m, 5H), 2.34 - 2.39 (m, 1H),
10 2.20 (d, 6H), 2.03 (s, 4H), 1.91 (s, 2H), 1.61 (q, 4H), 1.51 (t, 2H), 1.36 - 1.46 (m, 8H).

EXAMPLE 72

Cis-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

15 The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 15H and 29A in place of EXAMPLE 3J and EXAMPLE 11B, respectively. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.69 (s, 1H), 11.45 (s, 1H), 8.59 (t, 1H), 8.56 (d, 1H), 8.04 (d, 1H), 7.79 (dd, 1H), 7.54 (d, 1H), 7.47 - 7.52 (m, 2H), 7.37 (d, 2H), 7.13 (d, 2H), 7.08 (d, 1H), 6.68 (dd, 1H), 6.35 - 6.42 (m, 1H), 6.19 (d, 1H), 4.11 (s, 2H), 3.37 (s, 1H), 3.26 (t, 2H),
20 3.20 (s, 3H), 3.07 (s, 4H), 2.83 (s, 2H), 2.17 (d, 6H), 1.81 (dd, 2H), 1.64 - 1.73 (m, 1H), 1.48 (dd, 2H), 1.23 - 1.41 (m, 4H), 1.18 (s, 6H).

EXAMPLE 73

25 4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 71D and EXAMPLE 37D in place of EXAMPLE 3J and EXAMPLE 11B, respectively. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.68 (s, 1H), 8.37 (s, 1H), 7.98 - 8.11 (m, 2H), 4.38 (d, 2H), 3.74 - 3.82 (m, 2H), 3.54 - 3.64 (m, 2H), 3.44 (s, 1H), 3.08 (s, 3H), 2.58 - 2.89 (m, 2H), 2.13 - 2.35 (m, 4H), 2.04 (s, 2H), 1.78 - 1.93 (m, 4H), 1.57 - 1.65 (m, 4H), 1.52 (t, 2H), 1.36 - 1.47 (m, 4H).

EXAMPLE 74

Trans-4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 71D and EXAMPLE 34B in place of EXAMPLE 3J and EXAMPLE 11B, respectively. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.69 (s, 1H), 11.39 (s, 1H), 8.58 (t, 1H), 8.56 (d, 1H), 8.04 (d, 1H), 7.79 (dd, 1H), 7.47 - 7.55 (m, 3H), 7.34 (d, 2H), 7.07 (d, 3H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.25 (t, 2H), 3.22 (s, 3H), 3.06 (s, 5H), 2.71 (s, 2H), 2.21 (s, 6H), 1.94 - 2.06 (m, 4H), 1.79 (d, 2H), 1.57 - 1.65 (m, 5H), 1.51 (t, 2H), 1.39 (t, 4H), 0.95 - 1.11 (m, 4H).

EXAMPLE 75

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

EXAMPLE 75A

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 3A.

EXAMPLE 75B

methyl 2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-enecarboxylate

The title compound was prepared by substituting EXAMPLE 75A for EXAMPLE 3A in EXAMPLE 3B.

EXAMPLE 75C

(2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-enyl)methanol

The title compound was prepared by substituting EXAMPLE 75B for EXAMPLE 3B in EXAMPLE 3C.

EXAMPLE 75D

5 2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-enecarbaldehyde

To a solution of EXAMPLE 75C (2.8 g) in dichloromethane (50 mL) was added Dess-Martin Periodinane (5.68 g). The reaction mixture was stirred at room temperature for 3 hours and diluted with ether and washed with 5% NaOH and brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash
10 chromatography using 20% ethyl acetate in hexanes to provide the title compound.

EXAMPLE 75E

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

15 The title compound was prepared by replacing 4'-chlorobiphenyl-2-carboxaldehyde with EXAMPLE 75D and tert-butyl piperazine-1-carboxylate with EXAMPLE 15F in EXAMPLE 1A.

EXAMPLE 75F

20 2-(1H-pyrrolo[2,3-b]pyridin-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 15H by replacing EXAMPLE 15G with EXAMPLE 75E.

25 EXAMPLE 75G

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

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE
30 75F and EXAMPLE 1F in place of EXAMPLE 3J and EXAMPLE 11B, respectively. ¹H NMR (400 MHz, dimethylsulfoxide-d₆) δ 11.69 (s, 1H), 11.38 (s, 1H), 8.60 (t, 1H), 8.56 (d, 1H), 8.04 (d, 1H), 7.80 (dd, 1H), 7.47 - 7.55 (m, 3H), 7.31 - 7.36 (m, 2H), 7.05 - 7.13 (m, 3H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.18 (d, 1H), 3.85 (dd, 2H), 3.22 - 3.31 (m, 4H), 3.07 (s,

4H), 2.67 - 2.78 (m, 2H), 2.19 (s, 6H), 1.82 - 1.98 (m, 3H), 1.56 - 1.66 (m, 2H), 1.39 (t, 2H), 1.17 - 1.33 (m, 3H), 0.93 (s, 6H).

EXAMPLE 76

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

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 75F and EXAMPLE 36C in place of EXAMPLE 3J and EXAMPLE 11B, respectively. ¹H
10 NMR (400 MHz, dimethylsulfoxide-d₆) δ 11.62 (s, 1H), 8.73 (s, 1H), 8.52 (s, 1H), 7.98 (d, 1H), 7.56 (d, 1H), 7.45 - 7.51 (m, 1H), 7.43 (s, 1H), 7.37 (d, 2H), 7.10 (d, 2H), 6.68 (dd, 1H), 6.35 (dd, 1H), 6.25 (s, 1H), 4.29 (d, 2H), 3.88 (dd, 2H), 3.12 (d, 4H), 2.21 (s, 2H), 2.00 - 2.11 (m, 1H), 1.95 (s, 2H), 1.64 (dd, 2H), 1.27 - 1.46 (m, 4H), 0.95 (s, 6 H)

15 EXAMPLE 77

tert-butyl 3-([4-([4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino)sulfonyl)-2-nitrophenoxy]methyl)morpholine-4-carboxylate

20 EXAMPLE 77A

tert-butyl 3-((2-nitro-4-sulfamoylphenoxy)methyl)morpholine-4-carboxylate

The title compound was prepared as described in EXAMPLE 12A by replacing (1,4-dioxan-2-yl)methanol with tert-butyl 3-(hydroxymethyl)morpholine-4-carboxylate.

25 EXAMPLE 77B

tert-butyl 3-([4-([4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino)sulfonyl)-2-nitrophenoxy]methyl)morpholine-4-carboxylate

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE
30 77A in place of EXAMPLE 11B. ¹H NMR (400 MHz, dimethylsulfoxide-d₆) δ 11.67 (s, 1H), 8.36 (s, 1H), 8.01 - 8.11 (m, 2H), 7.47 - 7.61 (m, 4H), 7.35 (d, 2H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (d, 1H), 6.20 (s, 1H), 4.41 - 4.52 (m, 2H), 4.15 - 4.28 (m, 1H), 3.59 - 3.95 (m,

3H), 3.51 (d, 1H), 3.34 - 3.43 (m, 1H), 3.10 (s, 5H), 2.84 (s, 2H), 2.28 (s, 4H), 2.15 (s, 2H), 1.96 (s, 2H), 1.20 - 1.45 (m, 12H), 0.92 (s, 6H).

EXAMPLE 78

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

EXAMPLE 77B (100 mg) in dichloromethane (10 mL) at 0°C was treated with trifluoroacetic acid (5 mL) for 20 minutes. The reaction mixture was concentrated. The
10 residue was purified by reverse phase HPLC on a C18 column using a gradient of 35-60% acetonitrile in 0.1% trifluoroacetic acid water to give the title compound as a trifluoroacetate salt. The trifluoroacetic acid salt was dissolved in dichloromethane (10 mL) and washed with 50% aqueous NaHCO₃. The organic layer was dried over anhydrous Na₂SO₄ and concentrated to give the title compound. ¹H NMR (400 MHz, dimethylsulfoxide-d₆) δ 11.56
15 (s, 1H), 8.23 (d, 1H), 7.94 (d, 1H), 7.90 (dd, 1H), 7.57 (d, 1H), 7.42 - 7.46 (m, 1H), 7.31 - 7.37 (m, 3H), 7.25 (d, 1H), 7.01 - 7.09 (m, 2H), 6.64 (dd, 1H), 6.29 - 6.37 (m, 1H), 6.24 (d, 1H), 4.17 - 4.31 (m, 2H), 3.90 - 4.05 (m, 1H), 3.77 - 3.85 (m, 1H), 3.45 - 3.59 (m, 4H), 2.94 - 3.13 (m, 6H), 2.76 (s, 2H), 2.18 (d, 6H), 1.96 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

20

EXAMPLE 79

4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE
25 71D and EXAMPLE 1F in place of EXAMPLE 3J and EXAMPLE 11B, respectively. ¹H NMR (400 MHz, dimethylsulfoxide-d₆) δ 11.69 (s, 1H), 11.38 (s, 1H), 8.60 (t, 1H), 8.56 (d, 1H), 8.04 (d, 1H), 7.77 - 7.84 (m, 1H), 7.45 - 7.56 (m, 3H), 7.34 (d, 2H), 7.04 - 7.13 (m, 3H), 6.68 (dd, 1H), 6.39 (d, 1H), 6.19 (d, 1H), 3.85 (dd, 2H), 3.22 - 3.31 (m, 4H), 3.07 (s, 4H), 2.71 (s, 2H), 2.21 (s, 6H), 2.03 (s, 2H), 1.81 - 1.94 (m, 1H), 1.56 - 1.68 (m, 6H), 1.51 (t, 2H),
30 1.34 - 1.45 (m, 4H), 1.20 - 1.33 (m, 2H).

EXAMPLE 80

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

5 The title compound was prepared by substituting 1-(methylsulfonyl)piperidin-4-amine for 1-acetyl piperidin-4-amine in EXAMPLE 53B. ¹H NMR (300MHz, dimethylsulfoxide-d₆) δ 11.67 (br s, 1H), 8.57 (d, 1H), 8.25 (d, 1H), 8.04 (d, 1H), 7.83 (dd, 1H), 7.54-7.46 (m, 3H), 7.35 (d, 2H), 7.17 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (m, 1H), 6.20 (d, 1H), 3.80 (m, 1H), 3.57 (m, 2H), 3.08 (br s, 4H), 2.95 (td, 2H), 2.92 (s, 3H), 2.85-2.72 (m, 2H), 2.30-2.10
10 (m, 6H), 2.07-1.93 (m, 4H), 1.70 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

EXAMPLE 81

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]amino}-3-nitrophenyl)sulfonyl]-2-(1H-
15 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 81A

1,1-Dioxotetrahydro-2H-thiopyran-4-amine

N-Benzyl-1,1-dioxotetrahydro-2H-thiopyran-4-amine (2.00 g) was added to ethanol
20 (40 mL) in a pressure bottle. Palladium hydroxide on carbon (0.587 g,) was added and the solution was stirred under 30 psi of hydrogen at room temperature for 2 hours. The mixture was filtered through a nylon membrane and the solvent was removed under vacuum.

EXAMPLE 81B

25 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]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 81A for 1-acetyl piperidin-4-amine in EXAMPLE 53B. ¹H NMR (300MHz, dimethylsulfoxide-d₆) δ
30 11.65 (br s, 1H), 8.55 (d, 1H), 8.25 (d, 1H), 8.03 (d, 1H), 7.86 (dd, 1H), 7.52-7.47 (m, 3H), 7.35 (d, 2H), 7.17 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (m, 1H), 6.21 (d, 1H), 4.05 (m, 1H), 3.22-3.00 (m, 8H), 2.79 (br s, 2H), 2.31-2.11 (m, 10H), 1.96 (br s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

EXAMPLE 82

N-[(4-chloro-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5 The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and 4-chloro-3-nitrobenzenesulfonamide for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300MHz, dimethylsulfoxide-d₆) δ 11.60 (br s, 1H), 8.38 (br s, 1H), 7.96 (d, 1H), 7.91 (d, 1H), 7.68 (d, 1H), 7.58 (d, 1H), 7.46 (t, 1H), 7.39-7.35 (m, 3H), 7.07 (d, 2H), 6.67 (dd, 1H), 6.34 (m, 1H), 6.28 (d, 1H), 3.31 (br s, 2H), 3.17 (br s, 8H), 2.18 (m, 2H), 1.98 (br s, 2H), 1.42
10 (t, 2H), 0.94 (s, 6H).

EXAMPLE 83

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

EXAMPLE 83A

3-Nitro-4-[1-(2,2,2-trifluoro-ethyl)-piperidin-4-ylamino]-benzenesulfonamide

The title compound was prepared by substituting 1-(2,2,2-trifluoroethyl)piperidin-4-
20 amine hydrochloride for (tetrahydropyran-4-yl)methylamine in EXAMPLE 6A.

EXAMPLE 83B

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

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 82A for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300MHz, dimethylsulfoxide-d₆) δ 11.66 (br s, 1H), 8.56 (d, 1H), 8.24 (d, 1H), 8.04 (d, 1H), 7.81 (dd, 1H), 7.52 (dd, 2H), 7.48 (d, 1H), 7.35 (d, 2H), 7.15 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.38
30 (m, 1H), 6.20 (d, 1H), 3.68 (m, 1H), 3.22 (q, 2H), 3.07 (br s, 4H), 2.90 (m, 2H), 2.75 (br s, 2H), 2.29-2.12 (m, 8H), 1.97-1.86 (m, 4H), 1.63 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 84

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

EXAMPLE 84A

1-(tetrahydro-2H-pyran-4-yl)piperidin-4-ol

10 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°C. Then NaBH₄
(3.8 g) was added in portions over one hour. After 2 hours 1N aqueous NaOH was added,
followed by ethyl acetate addition. After filtration though celite the layers were separated, the
15 aqueous layer extracted with ethyl acetate, and the combined organic layers were dried over
Na₂SO₄. The crude was purified by column chromatography using dichloromethane having 5-
10% 7N NH₃ in methanol.

EXAMPLE 84B

20 5-bromo-6-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yloxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 84A for (tetrahydro-2H-
pyran-4-yl)methanol and EXAMPLE 36A for 4-fluoro-3-nitrobenzenesulfonamide in
EXAMPLE 24A.

25 EXAMPLE 84C

5-cyano-6-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yloxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 84B for EXAMPLE
36B in EXAMPLE 36C.

30 EXAMPLE 84D

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

The title compound was prepared by substituting EXAMPLE 84C for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.50 (s, 1H), 8.60 (d, 1H), 8.37 (d, 1H), 7.90 (d, 1H), 7.60 (d, 1H), 7.42 (dd, 1H), 7.35 (d, 2H), 7.25 (d, 1H), 7.04 (d, 2H), 6.63 (dd, 1H), 6.28 (m, 1H), 6.24 (d, 1H), 5.30 (br s, 1H), 4.50 (d, 2H), 3.95 (dd, 2H), 3.30 (m, 5H), 3.02 (br s, 4H), 2.95 (br s, 2H), 2.24 (br s, 4H), 2.17 (br m, 4H), 1.96 (s, 2H), 1.90 (br m, 4H), 1.60 (br m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

EXAMPLE 85

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([5-isopropyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 85A

5-isopropyl-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

EXAMPLE 36B (0.176 g), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (0.041 g), and palladium(II) acetate (0.011 g) were combined in a 10 mL oven-dried flask. Tetrahydrofuran (1 mL) was added and the mixture was flushed with nitrogen and stirred at ambient temperature for 5 minutes. 2-Propylzinc bromide solution (0.5 M in tetrahydrofuran) (1.5 mL) was added and stirring was continued under nitrogen overnight. Additional 2,2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (0.041 g) and palladium(II) acetate (0.011 g) were added. The mixture was flushed with nitrogen and stirred at ambient temperature for 5 minutes. 2-Propylzinc bromide solution (0.5 M in tetrahydrofuran) (1.5 mL) was added and stirring was continued under nitrogen for 2.5 days. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried (MgSO₄), filtered, concentrated, and chromatographed on silica gel with 0 to 3% methanol in CH₂Cl₂ as the eluent. The obtained material was chromatographed on silica gel a second time with 10-40% ethyl acetate in CH₂Cl₂ as the eluent, triturated with diethyl ether and dried under vacuum at 45 °C to give the product.

EXAMPLE 85B

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([5-isopropyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 85A for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.70 (s, 1H), 8.49 (m, 1H), 8.04 (d, 1H), 7.90 (m, 1H), 7.57 (m, 1H), 7.52 (t, 1H), 7.48 (dd, 1H), 7.34 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.41 (dd, 1H), 6.17 (s, 1H), 4.19 (m, 2H), 3.88 (m, 2H), 3.30 (m, 2H), 3.05 (m, 5H), 2.77 (s, 2H), 2.21 (s, 4H), 2.14 (s, 2H), 2.03 (m, 1H), 1.95 (s, 2H), 1.64 (m, 2H), 1.34 (m, 4H), 1.12 (d, 6H), 0.92 (s, 6H).

EXAMPLE 86

N-({3-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 86A

3-fluoro-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

The title compound was prepared by substituting 3,4-difluorobenzenesulfonamide for 4-chloro-3-nitrobenzenesulfonamide and (tetrahydro-2H-pyran-4-yl)methanamine for 4-methylpiperazin-1-amine dihydrochloride in EXAMPLE 6A.

EXAMPLE 86B

3-chloro-5-fluoro-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 86A for EXAMPLE 52B in EXAMPLE 52C.

EXAMPLE 86C

N-({3-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 86B for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.72 (s, 1H), 11.20 (s, 1H), 8.08 (d, 1H), 7.61 (m, 2H), 7.50 (m, 3H), 7.34 (d, 2H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.42 (dd, 1H), 6.16 (d, 1H), 6.09 (m, 1H), 3.81 (dd, 2H), 3.25 (m, 4H), 3.07 (m, 4H), 2.76 (s, 2H), 2.18 (m, 6H), 1.95 (s, 2H), 1.72 (m, 1H), 1.53 (d, 2H), 1.38 (t, 2H), 1.16 (m, 2H), 0.92 (s, 6H).

EXAMPLE 87

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

5

EXAMPLE 87A

methyl 2-(1H-indol-5-yloxy)-4-fluorobenzoate

The title compound was prepared by substituting 5-hydroxyindole for EXAMPLE 3G in EXAMPLE 3H.

10

EXAMPLE 87B

methyl 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 87A for EXAMPLE 3H in EXAMPLE 3I.

15

EXAMPLE 87C

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 87B for EXAMPLE 3I in EXAMPLE 3J.

20

EXAMPLE 87D

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

25

The title compound was prepared by substituting EXAMPLE 87C for EXAMPLE 1E in EXAMPLE 1G, except here the crude was purified by preparative HPLC using a 250 × 50 mm C18 column and eluting with 20-100% CH₃CN vs. 0.1% trifluoroacetic acid in water, giving the product as a trifluoroacetate salt. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) 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).

30

EXAMPLE 88

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 87C for EXAMPLE 1E and EXAMPLE 2A for EXAMPLE 1F in EXAMPLE 1G, except here the crude was purified by preparative HPLC using a 250 × 50 mm C18 column and eluting with 20-100% CH₃CN vs. 0.1% trifluoroacetic acid in water, giving the product as a trifluoroacetate salt. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) 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 89

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-yl)piperidin-4-yl]amino]phenyl)sulfonyl)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 87C for EXAMPLE 1E and EXAMPLE 3M for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300MHz, dimethylsulfoxide-d₆) δ 11.15 (s, 1H), 8.56 (d, 1H), 8.20 (d, 1H), 7.84 (dd, 1H), 7.52 (d, 1H), 7.39 – 7.31 (m, 4H), 7.12 (d, 2H), 7.04 (d, 2H), 6.84 (dd, 1H), 6.65 (dd, 1H), 6.38 (t, 1H), 6.14 (d, 1H), 3.94 (m, 2H), 3.84 (m, 1H), 3.02 (m, 8H), 2.79 (m, 3H), 2.72 (s, 2H), 2.20-2.02 (m, 8H), 1.85 (m, 6H), 1.60 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 90

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 87C for EXAMPLE 1E and EXAMPLE 4A for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300MHz, dimethylsulfoxide-d₆) 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 91

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

The title compound was prepared by substituting EXAMPLE 6A for EXAMPLE 11B and EXAMPLE 87C for EXAMPLE 3J in EXAMPLE 11D. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.14 (s, 1H), 9.18 (s, 1H), 8.53 (d, 1H), 7.84 (dd, 1H), 7.56 (d, 1H), 7.51 (d, 1H), 7.39 (m, 2H), 7.33 (d, 2H), 7.12 (d, 1H), 7.03 (d, 2H), 6.84 (dd, 1H), 6.62 (dd, 1H), 6.38 (m, 1H), 6.13 (d, 1H), 3.00 (m, 4H), 2.90 (m, 4H), 2.71 (s, 2H), 2.33 (s, 3H), 2.15 (m, 6H), 1.94 (s, 2H), 1.37 (t, 2H), 0.92 (s, 6H).

EXAMPLE 92

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 11D using EXAMPLE 87C and EXAMPLE 12A in place of EXAMPLE 3J and EXAMPLE 11B, respectively. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) 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 93

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 87C for EXAMPLE 3J and EXAMPLE 16A for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (400MHz, dimethylsulfoxide-d₆) 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 (s, 1H), 6.14 (d, 1H), 3.51 (m, 4H), 3.28 (s, 3H), 3.03 (s, 4H), 2.74 (s, 2H), 2.16 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 94

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-
5 [(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 87C for EXAMPLE 3J and EXAMPLE 17A for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (400MHz, dimethylsulfoxide-d₆) δ 11.20 (s, 1H), 8.19 (d, 1H), 7.90 (dd, 1H), 7.53 (d, 1H), 7.40 (m, 4H), 7.33 (t, 1H), 7.17 (d, 1H), 7.07 (m, 3H), 6.86 (dd, 1H), 6.70 (dd, 1H), 6.41 (s, 1H), 6.21
10 (d, 1H), 3.84 (dd, 2H), 3.59 (m, 2H), 3.25 (m, 6H), 3.00 (m, 2H), 2.74 (s, 2H), 2.54 (m, 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 95

15 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-({1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl}amino)-3-nitrophenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 95A

20 1-(1,3-difluoropropan-2-yl)piperidin-4-amine

Tert-butyl piperidin-4-ylcarbamate (0.212 g), 1,3-difluoropropan-2-one (0.149 g) and sodium triacetoxyborohydride (0.337 g) were stirred together in dichloroethane at room temperature. After stirring overnight the reaction was quenched with water (10 mL) and extracted into dichloromethane (2 x 20 mL). The organic layer was dried over magnesium
25 sulfate, filtered, and concentrated. The residue was treated with hydrogen chloride (4.0M in dioxane, 1.323 ml) for 1 hour to give the title compound as the HCl salt after concentration.

EXAMPLE 95B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-
30 ({1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl}amino)-3-nitrophenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 95A (0.057 g) and EXAMPLE 53A (0.162 g) were suspended in dioxane (3 mL) and heated to 105°C overnight. The reaction was concentrated, loaded onto silica gel

(GraceResolv 12 g) and eluted with a gradient of 0.5% to 4% methanol/dichloromethane.

The product containing fractions were concentrated and loaded onto C18 (SF25-75g analogix column) and eluted using a gradient of 30% to 60% acetonitrile/water. The product was partitioned between dichloromethane (20 mL) and saturated aqueous NaHCO₃ solution (20 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated to give the title compound. ¹H NMR (300 MHz, CDCl₃) δ 10.10 (s, 1H), 8.88 (d, 2H), 8.45 (d, 1H), 8.20 (s, 1H), 8.18 - 8.09 (m, 1H), 7.95 (d, 1H), 7.68 (d, 1H), 7.44 (s, 1H), 7.23 - 7.19 (m, 1H), 6.91 (d, 3H), 6.53 (d, 2H), 5.98 (d, 1H), 4.64 (dd, 4H), 3.68 - 3.50 (m, 1H), 3.01 (d, 6H), 2.72 (d, 4H), 2.19 (s, 11H), 1.69 (s, 2H), 1.41 (s, 2H), 0.94 (s, 6H).

EXAMPLE 96

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 96A

5-chloro-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 37C for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

EXAMPLE 96B

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 96A for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.67 (s, 1H), 8.52 (s, 1H), 8.41 (s, 1H), 8.03 (d, 1H), 7.56 (d, 1H), 7.50 (m, 2H), 7.35 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.39 (m, 1H), 6.22 (s, 1H), 4.50 (d, 2H), 3.78 (m, 2H), 3.60 (m, 2H), 3.12 (v br s, 4H), 2.93 (v br s, 2H), 2.38 (v br s, 4H), 2.17 (br m, 2H), 1.96 (s, 2H), 1.86 (m, 4H), 1.40 (t, 2H), 0.93 (s, 6H).

EXAMPLE 97

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

5

EXAMPLE 97A

tert-butyl 4-(2-nitro-4-sulfamoylphenylamino)piperidine-1-carboxylate

The title compound was prepared by substituting tert-butyl 4-aminopiperidine-1-carboxylate for 4-methylpiperazin-1-amine dihydrochloride in EXAMPLE 6A.

10

EXAMPLE 97B

3-nitro-4-(piperidin-4-ylamino)benzenesulfonamide

Tert-butyl 4-(2-nitro-4-sulfamoylphenylamino)piperidine-1-carboxylate was dissolved in dichloromethane (3 mL) and treated with 1N HCl in ether (4 mL). The reaction was stirred overnight then concentrated to give the title compound.

15

EXAMPLE 97C

4-(1-(2,2-difluoroethyl)piperidin-4-ylamino)-3-nitrobenzenesulfonamide

3-nitro-4-(piperidin-4-ylamino)benzenesulfonamide hydrochloride (0.100g), 1,1-difluoro-2-iodoethane (0.063 mL) and diisopropylamine (0.156 mL) were stirred together in N,N-dimethylformamide (3 mL) and heated to 85°C. The reaction was diluted with dichloromethane (50 mL) and washed with water (50 mL), brine (50 mL), dried over magnesium sulfate, filtered, and concentrated. The residue was loaded onto silica gel (GraceResolve 12g) and eluted using a gradient of 0.5% methanol/dichloromethane to 3% methanol/dichloromethane over 30 minutes to give the title compound.

20

25

EXAMPLE 97D

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

30

The title compound was prepared by substituting EXAMPLE 97B for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.67 (s, 1H), 11.54 - 11.27 (m, 1H), 8.55 (d, 1H), 8.24 (d, 1H), 8.03 (d, 1H), 7.81 (d, 1H), 7.50 (dd, 3H), 7.34 (d, 2H), 7.13 (d, 1H), 7.04 (d, 2H), 6.68 (d, 1H),

6.38 (dd, 1H), 6.15 (dt, 2H), 3.64 (s, 1H), 3.07 (s, 4H), 2.79 (ddd, 6H), 2.41 (t, 2H), 2.17 (d, 6H), 1.92 (d, 4H), 1.61 (d, 2H), 1.38 (s, 2H), 0.92 (s, 6H).

EXAMPLE 98

5 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 53B by replacing 1-acetylpiperidin-4-amine with 4-amino-1-cyclopropylpiperidine. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.65 (s, 1H), 8.54 (d, 1H), 8.22 (d, 1H), 8.02 (d, 1H), 7.80 (dd, 1H), 7.49 (m, 3H), 7.34 (d, 2H), 7.11 (d, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.38 (dd, 1H), 6.19 (d, 1H), 3.69 (m, 1H), 3.06 (m, 4H), 2.92 (m, 2H), 2.74 (s, 2H), 2.23 (m, 7H), 1.93 (m, 5H), 1.77 (m, 1H), 1.55 (m, 3H), 1.38 (t, 2H), 0.92 (s, 6H), 0.43 (m, 4H).

15 EXAMPLE 99

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-morpholin-4-yl)cyclohexyl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 53B by replacing 1-acetylpiperidin-4-amine with 1-(4-morpholino)cyclohexanemethylamine. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.70 (s, 1H), 9.06 (s, 1H), 8.59 (d, 1H), 8.06 (d, 1H), 7.83 (dd, 1H), 7.57 (d, 1H), 7.50 (m, 2H), 7.34 (m, 3H), 7.19 (d, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.41 (dd, 1H), 6.17 (d, 1H), 3.56 (m, 6H), 3.44 (m, 2H), 3.07 (m, 5H), 2.57 (m, 5H), 2.24 (m, 6H), 1.95 (s, 3H), 1.45 (m, 6H), 1.23 (m, 3H), 0.92 (s, 6H).

25

EXAMPLE 100

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(dicyclopropylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

30

EXAMPLE 100A

Trans-tert-butyl-4-(dicyclopropylamino)cyclohexylcarbamate

A suspension of trans-tert-butyl-4-aminocyclohexylcarbamate (1 g), molecular sieves 3A (1 g), acetic acid (2.67 ml), (1-ethoxycyclopropoxy)trimethylsilane (3.74 ml) and sodium cyanoborohydride (0.880 g) in dry methanol (10 ml) was heated at reflux for 3 hours. The insolubles were filtered off, the resulting solution was basified with aqueous NaOH (6 M) to
 5 pH 14, and extracted with ether. The combined extracts were washed with brine, dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography (silica gel 80 g, 30 - 100% acetone/hexanes) to provide the title compound.

EXAMPLE 100B

10 (trans)-N¹,N¹-dicyclopropylcyclohexane-1,4-diamine bis(2,2,2-trifluoroacetate)

The title compound was prepared by substituting EXAMPLE 100A for EXAMPLE 39A in EXAMPLE 39B.

EXAMPLE 100C

15 Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(dicyclopropylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

A suspension of EXAMPLE 53A (0.14 g), EXAMPLE 100B (0.112 g) and N,N-diisopropylethylamine (0.310 mL) in dioxane (10 mL) was stirred for 3 days at 100 °C. The
 20 product was concentrated and purified by RP HPLC(C8, 30% - 100% CH₃CN/water/0.1% trifluoroacetic acid). ¹H NMR (500 MHz, pyridine-d₅) δ 13.07 (s, 1H), 9.28 (d, 1H), 8.41 - 8.45 (m, 2H), 8.37 (d, 1H), 8.12 (d, 1H), 7.67 (d, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 7.01 (d, 1H), 6.75 (dd, 1H), 6.53 (d, 1H), 6.48 - 6.51 (m, 1H), 3.43 (ddd, 1H), 3.03 - 3.09 (m, 4H), 2.72 - 2.79 (m, 3H), 2.22 - 2.28 (m, 2H), 2.11 - 2.16 (m, 4H), 2.10 (s, 2H), 2.00 - 2.05 (m, 2H), 1.97 (s, 2H), 1.89
 25 (s, 1H), 1.86 (s, 3H), 1.62 - 1.71 (m, 2H), 1.39 (t, 2H), 1.19 - 1.29 (m, 2H), 0.93 (s, 6H), 0.48 (d, 8H).

EXAMPLE 101

4-(4-{[2-(4-chlorophenyl)-6,6-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-
 30 nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 101A

Ethyl 2-hydroxy-6,6-dimethylcyclohex-1-enecarboxylate

Into a 500 mL flame dried round-bottomed flask was added copper(I) iodide (18 g) in ether (200 mL) to give a suspension. After cooling to -5°C, methyllithium (120 mL, 1.6M in ether) was added dropwise. After stirring at -5°C for 1 hour, 3-methylcyclohex-2-enone (5.15 mL) in 15 ml ether was added dropwise, and the mixture was stirred at -5°C for 1 hour. After cooling to -78°C, hexamethylphosphoramide (60 mL) was added dropwise. Ethyl carbonocyanidate (23.74 mL) was added. After stirring at -78 °C for 20 minutes, the mixture was warmed up to room temperature, and stirred for 1 hour. The mixture was poured into cold water, and the layers were separated. The aqueous layer was extracted with ether (3x 20 mL). The combined organic layers were washed with saturated aqueous NH₄Cl (3x 20 mL), dried over Na₂SO₄, filtered, and dried under vacuum. The crude product was added to a silica gel column and purified by eluting with 0-10% ethyl acetate in hexane.

EXAMPLE 101B

Ethyl 6,6-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

Into a 500 mL round-bottomed flask was added hexane-washed sodium hydride (0.5 g) in dichloromethane (100 mL) to give a suspension. After cooling to -5 °C, EXAMPLE 101A (2.0 g) was added. After stirring at -5 °C for 30 minutes, the mixture was cooled to -78°C. Trifluoromethanesulfonic anhydride (2.2 mL) was added. The mixture was warmed to room temperature and stirred overnight. Water was added slowly to the mixture, the aqueous layer was then extracted by dichloromethane (2x 20 mL). The combined organic layers were washed with saturated NH₄Cl and brine, dried over Na₂SO₄, filtered, and concentrated.

EXAMPLE 101C

ethyl 2-(4-chlorophenyl)-6,6-dimethylcyclohex-1-enecarboxylate

Into a 25 mL microwave tube was added EXAMPLE 101B (2.9 g), 4-chlorophenylboronic acid (2.2 g), and tetrakis(triphenylphosphine)palladium (0.05 g) in 1,2-dimethoxyethane/methanol(2:1, 10 mL) to give a solution. Cesium fluoride (4 g) was then added. The reaction mixture was stirred at 150°C under (100W) in a Biotage Initiator microwave reactor for 30 minutes. After removing the solvents, water was added, and the mixture was extracted with ethyl acetate (2x). The combined organic layers were dried by MgSO₄. After filtering, the crude product was purified by reverse phase chromatography eluting with 50-100% acetonitrile/water with 0.1% trifluoroacetic acid.

EXAMPLE 101D

(2-(4-chlorophenyl)-6,6-dimethylcyclohex-1-enyl)methanol

In a 100 mL round-bottomed flask was placed lithium aluminum hydride (1 g) in ether (20 mL) to give a suspension. EXAMPLE 101C (1 g) dissolved in ether (5 mL) was added slowly by syringe. The mixture was stirred at room temperature overnight. After cooling to 0°C, the reaction was quenched by water. Ether (2x 10 mL) was used to extract the product. The crude product was purified by flash chromatography on silica by eluting with 0-15% ethyl acetate in hexane.

EXAMPLE 101E

Methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-6,6-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

To a 0°C solution of EXAMPLE 101D (0.43 g) in dichloromethane (5 mL) was added triethylamine (1 mL). Methanesulfonyl chloride (0.134 mL) was then added slowly. After 5 minutes, EXAMPLE 15F (0.61 g) was added. The mixture was stirred at room temperature overnight. The crude product was purified by flash chromatography on silica with 0 to 25% ethyl acetate in hexanes to provide the title compound.

EXAMPLE 101F

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-6,6-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

In a 5 mL microwave tube was added lithium hydroxide hydrate (15 mg) and EXAMPLE 101E (45 mg) in dioxane/water(2:1) (2 mL) to give a suspension. The mixture was heated to 130°C in a Biotage Initiator microwave reactor for 20 minutes. After cooling and neutralization by HCl, the crude product was added to a Prep HPLC column and was eluted with 20-80% acetonitrile/water with 0.1% trifluoroacetic acid.

EXAMPLE 101G

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

The title compound was prepared by substituting EXAMPLE 101F for EXAMPLE 3J and EXAMPLE 1F for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.68 (s, 1H), 11.47 (s, 1H), 8.58 (m, 2H), 8.03 (m, 1H), 7.79 (m,

1H), 7.51 (m, 3H), 7.31 (d, 2H), 7.10 (m, 1H), 7.02 (d, 2H), 6.65 (m, 1H), 6.39 (m, 1H), 6.15 (m, 1H), 3.85 (m, 2H), 3.27 (m, 4H), 2.97 (m, 4H), 2.76 (s, 2H), 2.14 (m, 6H), 1.70 (m, 2H), 1.61 (m, 2H), 1.44 (m, 2H), 1.26 (m, 3H), 1.16 (m, 6H)

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EXAMPLE 102

N-({5-bromo-6-[(4-ethylmorpholin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

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EXAMPLE 102A

(4-ethylmorpholin-3-yl)methanol

Morpholin-3-ylmethanol (500 mg) and iodoethane (666 mg) in N,N-dimethylformamide was treated with K₂CO₃ (1.1 g) overnight. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over

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Na₂SO₄, filtered, and concentrated to provide the title compound.

EXAMPLE 102B

5-bromo-6-((4-ethylmorpholin-3-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared as described in EXAMPLE 12A by replacing 4-fluoro-3-nitrobenzenesulfonamide and (1,4-dioxan-2-yl)methanol with 5-bromo-6-fluoropyridine-3-sulfonamide and EXAMPLE 102A, respectively.

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EXAMPLE 102C

N-({5-bromo-6-[(4-ethylmorpholin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

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The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 102B in place of EXAMPLE 11B. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.62 (s, 1H), 8.51 (s, 1H), 8.30 (s, 1H), 8.00 (d, 1H), 7.55 (d, 1H), 7.45 - 7.50 (m, 2H), 7.35 (d, 2H), 7.05 (d, 2H), 6.66 (dd, 1H), 6.37 (s, 1H), 6.21 (d, 1H), 4.58 (dd, 1H), 4.39 - 4.50 (m, 1H), 3.78 - 3.90 (m, 1H), 3.67 - 3.77 (m, 1H), 3.50 - 3.65 (m, 2H), 3.08 (s, 4H), 2.59 - 3.00 (m, 4H), 2.20 - 2.39 (m, 2H), 2.15 (s, 2H), 1.96 (s, 2H), 1.39 (t, 2H), 0.99 - 1.11 (m, 3H), 0.93 (s, 6H)

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EXAMPLE 103

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
[(4-ethylmorpholin-3-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-
yloxy)benzamide

EXAMPLE 103A

4-((4-ethylmorpholin-3-yl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared as described in EXAMPLE 12A by replacing (1,4-
dioxan-2-yl)methanol with EXAMPLE 102A.

EXAMPLE 103B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
[(4-ethylmorpholin-3-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-
yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE
103A in place of EXAMPLE 11B. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.66 (s,
1H), 8.33 (s, 1H), 7.99 - 8.06 (m, 2H), 7.47 - 7.57 (m, 3H), 7.45 (d, 1H), 7.35 (d, 2H), 7.04
(d, 2H), 6.67 (dd, 1H), 6.38 (dd, 1H), 6.20 (d, 1H), 4.42 (dd, 1H), 4.23 (dd, 1H), 3.81 (d, 1H),
3.69 (d, 1H), 3.49 - 3.63 (m, 2H), 3.08 (s, 4H), 2.92 (s, 1H), 2.81 (s, 4H), 2.54 (s, 1H), 2.25
(s, 4H), 2.15 (s, 2H), 1.96 (s, 2H), 1.39 (t, 2H), 1.00 (t, 3H), 0.92 (s, 6H)

EXAMPLE 104

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-
nitro-4-[(4-tetrahydro-2H-pyran-4-yl)morpholin-3-yl]methoxy]phenyl}sulfonyl)-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 78 (20 mg) and dihydro-2H-pyran-4(3H)-one (10 mg) in dichloroethane
(2 mL) was treated with NaCNBH₃ (9.74 mg) overnight. Additional dihydro-2H-pyran-
4(3H)-one (20 mg) and titanium (IV) isopropoxide (0.05 mL) were added. The resulting
mixture was stirred at room temperature overnight and concentrated. The residue was
purified by reverse phase HPLC on a C18 column using a gradient of 35-60% acetonitrile in
0.1% trifluoroacetic acid water to give the title compound as a trifluoroacetate salt. The
trifluoroacetic acid salt was dissolved in dichloromethane (6 mL) and washed with 50%

aqueous NaHCO₃. The organic layer was dried over anhydrous Na₂SO₄ and concentrated to give the title compound. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.68 (s, 1H), 8.35 (s, 1H), 8.04 (s, 2H), 7.44 - 7.58 (m, 4H), 7.35 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.40 (s, 1H), 6.20 (s, 1H), 4.44 (s, 1H), 4.28 (s, 1H), 3.85 (d, 2H), 3.71 (d, 1H), 3.61 (s, 3H), 3.20 - 3.29 (m, 2H), 3.08 (s, 5H), 2.54 - 2.96 (m, 5H), 2.06 - 2.42 (m, 5H), 1.96 (s, 2H), 1.77 (d, 1H), 1.53 - 1.66 (m, 1H), 1.29 - 1.51 (m, 4H), 0.92 (s, 6H)

EXAMPLE 105

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

EXAMPLE 105A

(S)-tert-butyl 1-(tetrahydro-2H-pyran-4-yl)piperidin-3-ylcarbamate

The title compound was prepared by substituting (S)-tert-butyl piperidin-3-ylcarbamate for tert-butyl piperazine-1-carboxylate and dihydro-2H-pyran-4(3H)-one for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

EXAMPLE 105B

(S)-1-(tetrahydro-2H-pyran-4-yl)piperidin-3-amine

The title compound was prepared by substituting EXAMPLE 105A for EXAMPLE 1A in EXAMPLE 1B.

EXAMPLE 105C

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

The title compound was prepared by substituting EXAMPLE 105B for 1-acetylpiperidin-4-amine in EXAMPLE 53B. ¹H NMR (300MHz, dimethylsulfoxide-d₆) δ 8.68 (br s, 1H), 8.54 (br s, 1H), 8.02 (d, 1H), 7.77 (m, 1H), 7.50 (m, 3H), 7.34 (d, 2H), 7.03 (m, 3H), 6.67 (dd, 1H), 6.38 (m, 1H), 6.19 (d, 1H), 3.98 (m, 2H), 3.90 (m, 2H), 3.52 (m, 2H), 3.09 (s, 2H), 3.05 (m, 4H), 2.77 (m, 2H), 2.60 (m, 2H), 2.16 (m, 6H), 1.95 (m, 2H), 1.65 (m, 5H), 1.50 (m, 3H), 1.38 (m, 2H), 0.94 (s, 6H).

EXAMPLE 106

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

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EXAMPLE 106 A

5-Bromo-6-((tetrahydro-2H-pyran-4-yl)methylamino)pyridine-3-sulfonamide

The title compound was prepared by substituting (tetrahydro-2H-pyran-4-yl)methanamine for EXAMPLE 3L in EXAMPLE 61A.

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EXAMPLE 106B

5-cyano-6-((tetrahydro-2H-pyran-4-yl)methylamino)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 106A for EXAMPLE 36B in EXAMPLE 36C.

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EXAMPLE 106C

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

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The title compound was prepared by substituting EXAMPLE 106B for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (400MHz, dimethylsulfoxide-d₆) δ 11.62 (s, 1H), 8.55 (s, 1H), 8.14 (s, 1H), 8.01 (d, 1H), 7.87 (s, 1H), 7.56 (d, 1H), 7.48 (d, 2H), 7.34 (d, 2H), 7.04 (d, 2H), 6.64 (m, 1H), 6.37 (s, 1H), 6.19 (d, 1H), 3.81 (dd, 2H), 3.25 (m, 4H), 3.04 (s, 4H), 2.74 (s, 2H), 2.17 (m, 6H), 1.95 (s, 2H), 1.87 (m, 1H), 1.53 (m, 2H), 1.37 (t, 2H), 1.18 (m, 2H),

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0.91 (s, 6H).

EXAMPLE 107

Trans-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

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EXAMPLE 107A

3-nitro-4-(4-aminothiomorpholine-1,1-dioxide)benzenesulfonamide

The title compound was prepared by substituting 4-aminothiomorpholine-1,1-dioxide for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 107B

5 Trans-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-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 107A for EXAMPLE
11B in EXAMPLE 11D. ¹H NMR (400MHz, dimethylsulfoxide-d₆) δ 11.64 (s, 1H), 9.58 (s,
10 1H), 8.50 (s, 1H), 8.02 (d, 1H), 7.78 (m, 2H), 7.50 (m, 3H), 7.34 (d, 2H), 7.04 (d, 2H), 6.66
(dd, 1H), 6.38 (s, 1H), 6.19 (d, 1H), 3.48 (m, 4H), 3.23 (m, 4H), 3.05 (s, 4H), 2.73 (d, 2H),
2.16 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 108

15 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-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

EXAMPLE 108A

20 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 (tetrahydro-2H-pyran-4-yl)methanamine in EXAMPLE 1F.

EXAMPLE 108B

25 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-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 108A for
EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.55 (s,
30 1H), 8.45 (s, 2H), 7.95 (d, 1H), 7.75-7.77 (m, 1H), 7.57 (d, 2H), 7.44 (s, 1H), 7.34 (d, 2H),
7.09 (d, J = 8.85 Hz, 1H), 7.05 (d, 2H), 6.69 (dd, 1H), 6.33 (d, 1H), 6.22 (d, 1H), 3.59-3.71
(m, 6H), 3.01 (s, 4H), 2.73 (s, 2H), 2.15-2.19 (m, 6H), 1.95 (s, 2H), 1.71-1.74 (m, 2H), 1.59-
1.61 (m, 1H), 1.38 (t, 2H), 0.93 (s, 6H).

EXAMPLE 109

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
({5-cyano-6-[(4-morpholin-4-ylcyclohexyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-
5 b]pyridin-5-yloxy)benzamide

EXAMPLE 109A

Trans-5-bromo-6-(4-morpholinocyclohexyloxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 9B for EXAMPLE 3L
10 in EXAMPLE 61A.

EXAMPLE 109B

Trans-5-cyano-6-(4-morpholinocyclohexylamino)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 109A for EXAMPLE
15 36B in EXAMPLE 36C.

EXAMPLE 109C

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
({5-cyano-6-[(4-morpholin-4-ylcyclohexyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-
20 b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 109B for EXAMPLE
11B in EXAMPLE 11D. ¹H NMR (400MHz, dimethylsulfoxide-d₆) δ 11.59 (s, 1H), 8.56 (d,
1H), 8.13 (s, 1H), 8.00 (d, 1H), 7.55 (d, 1H), 7.47 (m, 2H), 7.34 (d, 2H), 7.04 (d, 2H), 6.64
(dd, 1H), 6.36 (d, 1H), 6.19 (d, 1H), 4.00 (m, 1H), 3.65 (m, 4H), 3.28 (m, 4H), 3.03 (m, 4H),
25 2.73 (m, 4H), 2.16 (m, 6H), 1.90 (m, 6H), 1.40 (m, 6H), 0.93 (s, 6H).

EXAMPLE 110

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-pyrrolo[2,3-
30 b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 52B for EXAMPLE
11B in EXAMPLE 11D. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.71 (s, 1H), 11.23
(s, 1H), 8.08 (d, 1H), 7.91 (d, 1H), 7.74 (dd, 1H), 7.60 (d, 1H), 7.52 (m, 2H), 7.34 (m, 2H),

7.16 (s, 1H), 7.04 (m, 2H), 6.83 (d, 1H), 6.68 (dd, 1H), 6.43 (dd, 1H), 6.16 (d, 1H), 3.83 (dd, 2H), 3.23 (m, 2H), 3.12 (t, 2H), 3.06 (m, 4H), 2.73 (m, 2H), 2.15 (m, 6H), 1.95 (s, 2H), 1.82 (m, 1H), 1.58 (m, 2H), 1.38 (m, 2H), 1.18 (m, 2H), 0.92 (s, 6H).

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EXAMPLE 111

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
{[(1S,3R)-3-morpholin-4-ylcyclopentyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

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EXAMPLE 111A

benzyl (1S,3R)-3-(tert-butoxycarbonylamino)cyclopentylcarbamate

(1S,3R)-3-(tert-butoxycarbonylamino)cyclopentanecarboxylic acid (1.03 g),
diphenylphosphoryl azide (DPPA, 1.00 mL), triethylamine (0.929 mL), and benzyl alcohol
(0.931 mL) were combined in toluene (10 mL) and stirred at 100°C for 24 hours. The solution
was cooled and chromatographed on silica gel using 10% ethyl acetate/ hexanes to give the
pure product.

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EXAMPLE 111B

benzyl (1S,3R)-3-aminocyclopentylcarbamate

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The title compound was prepared by substituting EXAMPLE 111A for
EXAMPLE 1A in EXAMPLE 1B.

EXAMPLE 111C

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benzyl (1S,3R)-3-morpholinocyclopentylcarbamate

A solution of EXAMPLE 111B (400 mg), 1-bromo-2-(2-bromoethoxy)ethane
(0.246 mL), and triethylamine (0.595 mL) in N,N-dimethylformamide (6 mL) was stirred at
70°C for 24 hours. The solution was cooled and poured into ethyl acetate (200 mL). The
solution was extracted with 3x water, washed with brine, concentrated, and chromatographed
on silica gel using 10% methanol/ethyl acetate to give the pure product.

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EXAMPLE 111D

(1S,3R)-3-morpholinocyclopentanamine

EXAMPLE 111C (300 mg) and ethanol (20 ml) were added to wet 20% Pd(OH)₂-C (60.0 mg) in a 50 mL pressure bottle and stirred for 8 hours at 30 psi. The mixture was filtered through a nylon membrane and condensed to give the product.

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EXAMPLE 111E

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(4-[[[(1S,3R)-3-morpholin-4-ylcyclopentyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 111D for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (dimethylsulfoxide-d₆) δ 11.65 (s, 1H), 8.45 (d, 1H), 8.28 (dd, 1H), 7.97 (d, 1H), 7.68 (d, 1H), 7.52 (d, 1H), 7.44 (d, 2H), 7.35 (d, 2H), 7.05 (d, 2H), 6.92 (dd, 1H), 6.85 (dd, 1H), 6.33 (s, 1H), 6.22 (s, 1H), 4.08 (m, 1H), 3.60 (br s, 4H), 3.06 (br s, 4H), 2.73 (br s, 3H), 2.48 (m, 4H), 2.28 (m, 1H), 2.18 (m, 6H), 2.07 (m, 1H), 1.95 (s, 2H), 1.79 (m, 2H), 1.63 (m, 2H), 1.38 (t, 2H), 0.93 (s, 6H).

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EXAMPLE 112

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(4-[[[(1R,3S)-3-morpholin-4-ylcyclopentyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

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EXAMPLE 112A

tert-butyl (1R,3S)-3-aminocyclopentylcarbamate

The title compound was prepared by substituting EXAMPLE 111A for EXAMPLE 111C in EXAMPLE 111D.

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EXAMPLE 112B

tert-butyl (1R,3S)-3-morpholinocyclopentylcarbamate

The title compound was prepared by substituting EXAMPLE 112A for EXAMPLE 111B in EXAMPLE 111C.

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EXAMPLE 112C

(1R,3S)-3-morpholinocyclopentanamine

The title compound was prepared by substituting EXAMPLE 112B for EXAMPLE 1A in EXAMPLE 1B.

EXAMPLE 112D

5 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1R,3S)-3-morpholin-4-ylcyclopentyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 112C for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (dimethylsulfoxide -
10 d₆) δ 11.35 (s, 1H), 8.51 (d, 1H), 8.44 (dd, 1H), 8.00 (d, 1H), 7.77 (d, 1H), 7.50 (d, 1H), 7.48 (s, 2H), 7.34 (d, 2H), 7.04 (d, 2H), 7.02 (dd, 1H), 6.67 (dd, 1H), 6.37 (dd, 1H), 6.21 (d, 1H), 4.11 (m, 1H), 3.61 (br s, 4H), 3.06 (br s, 4H), 2.73 (br s, 3H), 2.50 (m, 4H), 2.28 (m, 1H), 2.18 (m, 6H), 2.06 (m, 1H), 1.95 (s, 2H), 1.77 (m, 2H), 1.66 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

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EXAMPLE 113

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(morpholin-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

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EXAMPLE 113A

tert-butyl 2-((2-nitro-4-sulfamoylphenylamino)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting tert-butyl 2-(aminomethyl)morpholine-4-carboxylate for (tetrahydropyran-4-yl)methylamine in
25 EXAMPLE 1F.

EXAMPLE 113B

tert-butyl 2-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)methyl)morpholine-4-carboxylate

30

The title compound was prepared by substituting EXAMPLE 113A for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G, with the exception that the product was purified on a silica gel column eluted with 4% methanol in dichloromethane.

EXAMPLE 113C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
[(morpholin-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-
yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 113B for EXAMPLE 66B in EXAMPLE 66C. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.60 (s, 1H), 8.55 (br, s, 1H), 8.51 (s, 1H), 8.00 (d, 1H), 7.80 (d, 1H), 7.52 (d, 1H), 7.49-7.46 (m, 2H), 7.34 (d, 2H), 7.07 (d, 1H), 7.04(d, 2H), 6.66 (dd, 1H), 6.36 (s, 1H), 6.20 (d, 1H), 4.00 (dd, 1H), 3.91 (m, 1H), 3.70 (t, 1H), 3.60 (m, 1H), 3.58 (m, 1H), 3.32 (m, 1H), 3.16 (d, 1H), 3.05 (m, 4H), 2.98 (td, 1H), 2.86 (t, 1H), 2.73 (s, 2H), 2.20-2.12 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 114

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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 114A

3-nitro-4-((tetrahydrofuran-3-yl)methylamino)benzenesulfonamide

The title compound was prepared by substituting 3-aminomethyl-tetrahydrofuran for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 114B

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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 114A for EXAMPLE 130C in EXAMPLE 130D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.68 (s, 1H), 11.42 (bs, 1H), 8.63 (t, 1H), 8.56 (d, 1H), 8.04 (d, 1H), 7.80 (dd, 1H), 7.53-7.48 (m, 3H), 7.34 (d, 2H), 7.10 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (m, 1H), 6.19 (d, 1H), 3.82-3.79 (m, 1H), 3.71 (t, 1H), 3.62 (dd, 1H), 3.50 (dd, 1H), 3.38 (m, 1H), 3.32 (m, 1H), 3.07 (m, 4H), 2.76 (s, 2H), 2.58 (m, 1H), 2.25-2.00 (m, 6H), 1.98 (m, 1H), 1.95 (s, 2H), 1.65 (m, 1H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 115

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
({1-[cis-3-fluorotetrahydro-2H-pyran-4-yl]piperidin-4-yl}amino)-3-nitrophenyl]sulfonyl}-2-
5 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 115A

Cis-tert-butyl 1-(3-fluorotetrahydro-2H-pyran-4-yl)piperidin-4-ylcarbamate

The title compound was prepared as a racemate of the cis diastereomer by substituting
10 tert-butyl piperidin-4-ylcarbamate for piperidin-4-ol and 3-fluorodihydro-2H-pyran-4(3H)-
one (prepared by the method described in US2005/0101628A1) for dihydro-2H-pyran-4(3H)-
one) in EXAMPLE 84A.

EXAMPLE 115B

15 Cis-1-(3-fluorotetrahydro-2H-pyran-4-yl)piperidin-4-amine

EXAMPLE 115A (0.29 g) was dissolved in CH₂Cl₂ (9 mL), then 4N HCl in dioxane
(4 mL) was added and the reaction stirred at room temperature for 16 hours. The reaction was
diluted with CH₂Cl₂ (30 mL), then 4N aqueous NaOH (5 mL) was added. After shaking and
separating the layers the aqueous layer was saturated with solid NaCl and extracted with
20 more CH₂Cl₂ (10 mL). The combined organic layers were dried over Na₂SO₄. After filtration
and concentration the amine was used with no further purification.

EXAMPLE 115C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
25 ({1-[cis-3-fluorotetrahydro-2H-pyran-4-yl]piperidin-4-yl}amino)-3-nitrophenyl]sulfonyl}-2-
(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 115B for 1-
acetylpiperidin-4-amine in EXAMPLE 53B. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ
11.64 (s, 1H), 8.54 (d, 1H), 8.43 (br d, 1H), 8.03 (d, 1H), 7.80 (dd, 1H), 7.50 (m, 3H), 7.35
30 (d, 2H), 7.11 (d, 1H), 7.05 (d, 2H), 6.66 (dd, 1H), 6.38 (m, 1H), 6.20 (d, 1H), 4.92 (d, 1H),
3.95 (m, 2H), 3.70 (v br m, 1H), 3.50, 3.40, 3.30 (all m, total 5H), 3.05, 3.00 (both v br m,
total 5H), 2.74 (s, 2H), 2.55 (v br m, 1H), 2.18 (br m, 6H), 1.95 (m, 4H), 1.88 (ddd, 1H), 1.63
(v br m, 3H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 116

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-ylazetidin-3-yl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 116A

1-(tetrahydro-2H-pyran-4-yl)azetidin-3-amine

Tert-butyl azetidin-3-ylcarbamate (0.46 g), dihydro-2H-pyran-4(3H)-one (0.29 g) and sodium triacetoxyborohydride (0.85 g) were stirred together in dichloromethane (5 mL) overnight. The reaction was poured into dichloromethane (50 mL) and saturated aqueous NaHCO₃ solution (25 mL). The organic layer was separated, washed with brine (25 mL), dried over Na₂SO₄, filtered, and concentrated. Silica gel chromatography (GraceResolv 12 g) eluting with a gradient of 0.75% to 7.5% methanol/dichloromethane over 20 minutes gave the Boc-protected intermediate. Treatment with HCl (4.0M in dioxane, 2 mL) and methanol (1 mL) for 1 hour gave the title compound after concentration as the di-HCl salt.

EXAMPLE 116B

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-ylazetidin-3-yl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

A suspension of 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(4-chloro-3-nitrophenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzamide (0.180 g), 1-(tetrahydro-2H-pyran-4-yl)azetidin-3-amine (0.078 g), and triethylamine (0.159 mL) in dioxane (2 mL) was degassed with nitrogen for 30 seconds then sealed. The reaction was heated to 110°C. After stirring for 16 hours, more triethylamine (10 equivalents total) and dimethylsulfoxide (1 mL) were added and the reaction stirred for an additional 18 hours at 110°C. The reaction was cooled, diluted with water (50 mL) and extracted with dichloromethane (2 x 150 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. Silica gel chromatography (GraceResolv 12 g) eluting with a gradient of 0.75% to 7.5% methanol/dichloromethane (Flow = 36 mL/minutes) gave the title compound. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.59 (s, 1H), 8.49 (d, 1H), 8.40 (s, 1H), 7.97 (d, 1H), 7.77 (s, 1H), 7.47 (dd, 3H), 7.34 (d, 2H), 7.04 (d, 2H), 6.90 – 6.78 (m, 1H), 6.65 (d, 1H), 6.35 (s, 1H), 6.21 (s, 1H), 4.47 – 4.23

(m, 1H), 3.83 (s, 3H), 3.05 (s, 6H), 2.73 (s, 2H), 2.18 (s, 8H), 1.95 (s, 2H), 1.68 (s, 2H), 1.38 (s, 2H), 1.24 (s, 4H), 0.92 (s, 6H).

EXAMPLE 117

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

EXAMPLE 117A

10 1-(tetrahydrofuran-3-yl)azetidin-3-amine

Tert-butyl azetidin-3-ylcarbamate (0.550 g), dihydrofuran-3(2H)-one (0.412 g) and sodium triacetoxyborohydride (1.015 g) were stirred together in dichloromethane (5 mL). After stirring overnight, the reaction was poured into saturated aqueous NaHCO₃ solution (25 mL) and extracted with dichloromethane (50 mL). The organic layer was washed with brine
15 (25 mL), dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (GraceResolv 12 g) eluting with a gradient of 0.5% to 7.5% methanol/dichloromethane over 30 minutes gave tert-butyl 1-(tetrahydrofuran-3-yl)azetidin-3-ylcarbamate. The resulting material was treated with HCl/dioxane for 1 hour, and then concentrated to give the title compound.

20

EXAMPLE 117B

3-nitro-4-(1-(tetrahydrofuran-3-yl)azetidin-3-ylamino)benzenesulfonamide

25 4-Fluoro-3-nitrobenzenesulfonamide (0.084 g), 1-(tetrahydrofuran-3-yl)azetidin-3-amine

(0.090 g) and triethylamine (0.266 mL) in tetrahydrofuran (3 mL) was heated to 60°C. After stirring for 4 hours, the reaction was cooled, the tetrahydrofuran was removed and the residue was partitioned between dichloromethane (200 mL) and water (20 mL). The organic layer was separated, washed with brine (25 mL), dried over magnesium sulfate, filtered, and
30 concentrated to give the title compound.

EXAMPLE 117C

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

5 The title compound was prepared by substituting EXAMPLE 117B for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. ¹H NMR (300 MHz, CDCl₃) δ 10.39 - 9.79 (m, 1H), 9.17 (s, 1H), 8.87 (d, 1H), 8.51 (d, 1H), 8.15 (dd, 2H), 7.94 (d, 1H), 7.68 (d, 1H), 7.48 - 7.42 (m, 1H), 7.23 (d, 2H), 6.91 (d, 2H), 6.69 (d, 1H), 6.54 (dd, 2H), 5.99 (d, 1H), 4.29 (d, 1H), 4.01 - 3.73 (m, 4H), 3.66 (d, 2H), 3.08 (s, 6H), 2.76 (s, 2H), 2.21 (s, 10 6H), 2.03 - 1.83 (m, 3H), 1.64 (s, 2H), 1.42 (d, 2H), 0.93 (s, 6H).

EXAMPLE 118

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

15

EXAMPLE 118A

(R)-tert-butyl (1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl)methylcarbamate

The title compound was prepared by substituting (S)-tert-butyl pyrrolidin-3-ylmethylcarbamate for tert-butyl piperazine-1-carboxylate and dihydro-2H-pyran-4(3H)-one for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

20

EXAMPLE 118B

(R)-(1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl)methanamine

25 The title compound was prepared by substituting EXAMPLE 118A for EXAMPLE 1A in EXAMPLE 1B.

EXAMPLE 118C

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

30

The title compound was prepared by substituting EXAMPLE 118B for 1-acetylpiperidin-4-amine in EXAMPLE 53B. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ

11.57 (s, 1H), 8.59 (br s, 1H), 8.45 (br s, 1H), 8.02 (d, 1H), 7.95 (m, 1H), 7.71 (m, 1H), 7.56 (d, 1H), 7.45 (m, 1H), 7.35 (m, 3H), 7.05 (m, 2H), 6.90 (br s, 1H), 6.64 (d, 1H), 6.33 (m, 1H), 6.22 (m, 1H), 3.90 (m, 2H), 3.44 (m, 2H), 3.27 (m, 4H), 3.02 (m, 5H), 2.73 (m, 3H), 2.59 (m, 2H), 2.19 (m, 6H), 1.95 (m, 2H), 1.85 (m, 2H), 1.64 (m, 1H), 1.50 (m, 2H), 1.39 (m, 2H),
 5 1.23 (m, 1H), 0.94 (s, 6H).

EXAMPLE 119

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
 10 [(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 75F and EXAMPLE 37D in place of EXAMPLE 3J and EXAMPLE 11B, respectively. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.69 (s, 1H), 8.39 (s, 1H), 8.08 (d, 1H), 8.04 (d, 1H), 7.41 - 7.59 (m, 4H), 7.35 (d, 2H), 7.08 (d, 2H), 6.68 (dd, 1H), 6.37 - 6.43 (m, 1H), 6.20
 15 (s, 1H), 4.38 (d, 2H), 3.73 - 3.82 (m, 2H), 3.54 - 3.63 (m, 2H), 3.09 (s, 4H), 2.81 (s, 2H), 2.16 - 2.39 (m, 5H), 1.94 (s, 2H), 1.79 - 1.93 (m, 4H), 1.40 (t, 2H), 0.94 (s, 6H).

EXAMPLE 120

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-
 20 enyl)methyl)piperazin-1-yl)-N-(4-((trans-4-hydroxycyclohexyl)methoxy)-3-
 nitrophenylsulfonyl)benzamide

EXAMPLE 120A

Trans-4-(aminomethyl)cyclohexanol

25 Tert-butyl ((1r,4r)-4-hydroxycyclohexyl)methylcarbamate (1 g) in dichloromethane (10 mL) was treated with trifluoroacetic acid (5 mL) at 0°C for 10 minutes and at room temperature for 30 minutes. The reaction mixture was concentrated and dried in vacuo to provide the title compound as a trifluoroacetic acid salt.

30

EXAMPLE 120B

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-
 enyl)methyl)piperazin-1-yl)-N-(4-((trans-4-hydroxycyclohexyl)methoxy)-3-
 nitrophenylsulfonyl)benzamide

A mixture of EXAMPLE 53A (211 mg), EXAMPLE 120A (104 mg) and N-ethyl-N-isopropylpropan-2-amine (0.3 mL) in dimethylsulfoxide (2 mL) was heated at 150°C in a Biotage Initiator microwave synthesizer for 1.5 hours and concentrated. The residue was purified by reverse phase HPLC on a C18 column using a gradient of 40-60% acetonitrile in 0.1% trifluoroacetic acid water to give the title compound as a trifluoroacetate salt. The trifluoroacetic acid salt was dissolved in dichloromethane (30 mL) and washed with 50% aqueous NaHCO₃. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated to give the title compound. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.69 (s, 1H), 11.41 (s, 1H), 8.61 (t, 1H), 8.53 - 8.58 (m, 1H), 8.04 (d, 1H), 7.76 - 7.83 (m, 1H), 7.47 - 7.56 (m, 3H), 7.34 (d, 2H), 7.07 - 7.11 (m, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 4.82 - 4.99 (m, 1H), 4.50 (d, 1H), 3.26 - 3.31 (m, 2H), 3.23 (t, 1H), 3.07 (s, 4H), 2.76 (s, 2H), 2.10 - 2.28 (m, 6H), 2.05 (dd, 1H), 1.95 (s, 2H), 1.84 (t, 2H), 1.52 - 1.76 (m, 2H), 1.41 - 1.51 (m, 1H), 1.38 (t, 2H), 0.95 - 1.25 (m, 4H), 0.92 (s, 6H)

EXAMPLE 121

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(4-((cis-4-methoxycyclohexyl)methoxy)-3-nitrophenylsulfonyl)benzamide

EXAMPLE 121A

(4-methoxycyclohexyl)methanol

4-Methoxycyclohexanecarboxylic acid (7 g) in tetrahydrofuran (20 mL) was treated with 1 M (in tetrahydrofuran) borane-tetrahydrofuran complex (100 mL) overnight. The mixture was concentrated and the residue was dissolved in methanol (100 mL) and concentrated HCl (10 mL). The resulting mixture was stirred for 1 hour and concentrated. The residue was dissolved in dichloromethane and washed with water. The organic layer was dried over Na₂SO₄, filtered, and concentrated to give the title compound.

EXAMPLE 121B

4-((4-methoxycyclohexyl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared as described in EXAMPLE 12A by replacing (1,4-dioxan-2-yl)methanol with EXAMPLE 121A.

EXAMPLE 121C

4-((cis-4-methoxycyclohexyl)methoxy)-3-nitrobenzenesulfonamide

Separation of the cis and trans mixture of EXAMAPLE 121B on a reverse phase HPLC (gradient: 40-55% acetonitrile in 0.1% TFA in water over 25 minutes) provided the
5 title compound.

EXAMPLE 121D

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(4-((cis-4-methoxycyclohexyl)methoxy)-3-
10 nitrophenylsulfonyl)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 121C in place of EXAMPLE 11B. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.69 (s, 1H), 11.39 (s, 1H), 8.34 (s, 1H), 7.96 - 8.07 (m, 2H), 7.48 - 7.56 (m, 3H), 7.31 - 7.42 (m, 3H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 4.02 (d, 2H), 3.39 (s, 1H), 3.20 (s,
15 3H), 3.09 (s, 4H), 2.82 (s, 2H), 2.09 - 2.34 (m, 6H), 1.96 (s, 2H), 1.78 - 1.86 (m, 3H), 1.54 (dd, 2H), 1.28 - 1.46 (m, 6H), 0.92 (s, 6H)

EXAMPLE 122

Cis-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-
20 [(4-{{4-(cyclopropylamino)cyclohexyl}amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 122A

Cis-tert-butyl-4-(cyclopropylamino)cyclohexylcarbamate

The title compound was prepared by substituting tert-butyl 4-oxocyclohexylcarbamate
25 for 4'-chlorobiphenyl-2-carboxaldehyde and cyclopropylamine for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 122B

cis-N¹-cyclopropylcyclohexane-1,4-diamine bis(2,2,2-trifluoroacetate)

30 The title compound was prepared by substituting EXAMPLE 122A for EXAMPLE 39A in EXAMPLE 39B.

EXAMPLE 122C

Cis-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-
[(4-([4-(cyclopropylamino)cyclohexyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
5 b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 122B for EXAMPLE
100B in EXAMPLE 100C. ¹H NMR (500 MHz, pyridine-d₅) δ 13.06 (s, 1H), 9.28 (d, 1H),
8.59 (d, 1H), 8.44 (d, 1H), 8.37 (dd, 1H), 8.12 (d, 1H), 7.67 (t, 2H), 7.43 (t, 2H), 7.07 (d, 2H),
6.90 (d, 1H), 6.75 (dd, 1H), 6.53 (d, 1H), 6.50 (dd, 1H), 3.56 - 3.63 (m, 1H), 3.02 - 3.08 (m,
10 4H), 2.77 (s, 3H), 2.26 (t, 2H), 2.10 - 2.16 (m, 4H), 2.06 (ddd, 1H), 1.97 (s, 2H), 1.74 - 1.82
(m, 2H), 1.61 - 1.71 (m, 5H), 1.39 (t, 2H), 0.93 (s, 6H), 0.39 - 0.44 (m, 4H).

EXAMPLE 123

Trans-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-
15 [(3-nitro-4-([4-(tetrahydro-2H-pyran-4-ylamino)cyclohexyl]amino)phenyl)sulfonyl]-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 123A

Trans-tert-butyl-4-(tetrahydro-2H-pyran-4-ylamino)cyclohexylcarbamate

20 The title compound was prepared by substituting trans-tert-butyl-4-
aminocyclohexylcarbamate for tert-butyl piperazine-1-carboxylate and dihydro-2H-pyran-
4(3H)-one for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

EXAMPLE 123B

25 trans-N1-(tetrahydro-2H-pyran-4-yl)cyclohexane-1,4-diamine bis(2,2,2-trifluoroacetate)

The title compound was prepared by substituting EXAMPLE 123A for EXAMPLE
39A in EXAMPLE 39B.

EXAMPLE 123C

30 Trans-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-
[(3-nitro-4-([4-(tetrahydro-2H-pyran-4-ylamino)cyclohexyl]amino)phenyl)sulfonyl]-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 123B for EXAMPLE 100B in EXAMPLE 100C. ¹H NMR (500 MHz, pyridine-d₅) δ 13.01 (s, 1H), 9.28 (d, 1H), 8.48 (d, 1H), 8.38 (dd, 1H), 8.32 (d, 1H), 8.24 (d, 1H), 7.67 - 7.69 (m, 2H), 7.44 (d, 2H), 7.08 (d, 2H), 6.91 (d, 1H), 6.78 (dd, 1H), 6.59 (d, 1H), 6.48 (dd, 1H), 4.01 (d, 2H), 3.44 - 3.49 (m, 1H), 3.37 - 3.43 (m, 2H), 3.01 - 3.09 (m, 5H), 2.85 (t, 1H), 2.78 (s, 2H), 2.27 (t, 2H), 2.13 - 2.18 (m, 4H), 2.05 (t, 4H), 1.97 (s, 2H), 1.93 (d, 2H), 1.52 - 1.60 (m, 2H), 1.44 - 1.50 (m, 2H), 1.39 (t, 2H), 1.25 - 1.34 (m, 2H), 0.94 (s, 6H).

EXAMPLE 124

Trans-N-({5-bromo-6-[(4-morpholin-4-ylcyclohexyl)oxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 124A

Trans-4-morpholinocyclohexanol

Trans-4-Aminocyclohexanol (0.5 g), 1-bromo-2-(2-bromoethoxy)ethane (1.07 g) and triethylamine (2.42 mL) were dissolved in anhydrous acetonitrile (20 mL). The reaction mixture was heated at 60°C overnight. The organic solvent was removed under vacuum. The residue was purified with flash column chromatography on silica gel eluting with 7%-10% methanol in dichloromethane to give the title compound.

EXAMPLE 124B

Trans-5-bromo-6-(4-morpholinocyclohexyloxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 124A for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 36A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

EXAMPLE 124C

Trans-N-({5-bromo-6-[(4-morpholin-4-ylcyclohexyl)oxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 124B for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (400MHz, dimethylsulfoxide-d₆) δ 11.67 (s, 1H), 8.56 (m,

2H), 8.03 (d, 1H), 7.80 (m, 1H), 7.50 (m, 3H), 7.34 (d, 2H), 7.12 (m, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.99 (m, 1H), 3.67 (m, 1H), 3.37 (m, 2H), 3.24 (m, 2H), 3.07 (m, 4H), 2.89 (m, 1H), 2.71 (m, 2H), 2.16 (m, 6H), 1.96 (s, 3H), 1.80 (m, 4H), 1.38 (t, 2H), 1.27 (m, 2H), 0.92 (s, 6H).

5

EXAMPLE 125

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-((4-[(4-methoxycyclohexyl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

10

EXAMPLE 125A

4-(((trans)-4-methoxycyclohexyl)methoxy)-3-nitrobenzenesulfonamide

Separation of the *cis* and *trans* mixture of EXAMAPLE 121B on a reverse phase HPLC provided the title compound.

15

EXAMPLE 125B

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-((4-[(4-methoxycyclohexyl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

20

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 125A in place of EXAMPLE 11B. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.68 (s, 1H), 8.34 (s, 1H), 7.96 - 8.09 (m, 2H), 7.51 (dd, 3H), 7.32 - 7.39 (m, 3H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.20 (d, 1H), 4.02 (d, 2H), 3.24 (s, 3H), 3.00 - 3.15 (m, 5H), 2.83 (s, 2H), 2.09 - 2.36 (m, 6H), 2.03 (d, 2H), 1.96 (s, 2H), 1.77 - 1.86 (m, 2H), 1.73 (s, 1H), 1.39 (t, 25 2H), 1.02 - 1.17 (m, 4H), 0.92 (s, 6H)

EXAMPLE 126

tert-butyl 4-{[4-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino)sulfonyl]-2-nitrophenoxy)methyl]-4-fluoropiperidine-1-carboxylate

30

EXAMPLE 126A

tert-butyl 4-fluoro-4-(hydroxymethyl)piperidine-1-carboxylate

1-Tert-butyl 4-ethyl 4-fluoropiperidine-1,4-dicarboxylate (1.0 g) in tetrahydrofuran (5 mL) was treated with 1.0 N LiAlH₄ in THF (2.54 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 hours. Water (0.6 mL) was added to the reaction mixture drop-wise, followed by 2 N aqueous NaOH (0.2 mL). The reaction was stirred for another 1
 5 hour. The solid was removed by filtration via a pack of Celite and washed with ethyl acetate. The filtrate was washed with brine, dried over MgSO₄, filtered, and concentrated to give the product.

EXAMPLE 126B

tert-butyl 4-fluoro-4-((2-nitro-4-sulfamoylphenoxy)methyl)piperidine-1-carboxylate

10 The title compound was prepared by substituting EXAMPLE 126A for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

EXAMPLE 126C

tert-butyl 4-{[4-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino)sulfonyl]-2-nitrophenoxy]methyl}-4-fluoropiperidine-1-carboxylate]oxy]benzamide

The title compound was prepared by substituting EXAMPLE 126B for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.67 (s, 1H), 8.36 (s, 2H), 8.02-8.06 (m, 2H), 7.49-7.53 (m, 3H), 7.40 (d, 1H), 7.35 (d, 2H), 7.04 (d, 1H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.21 (d, 1H), 4.36 (d, 2H), 3.83-3.85 (m, 2H), 3.09 (s, 4H),
 20 2.33 (s, 2H), 2.27-2.32 (m, 4H), 2.13-2.16 (m, 2H), 1.96 (s, 2H), 1.83-1.92 (m, 2H), 1.67-1.75 (m, 2H), 1.38-1.41 (m, 11H), 0.92 (s, 6H).

EXAMPLE 127

25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 126C for EXAMPLE 1A in EXAMPLE 1B. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.50 (s, 1H), 8.14 (d, 1H), 7.90 (d, 2H), 7.80 (dd, 1H), 7.60 (d, 1H), 7.40 (t, 1H), 7.35 (d, 2H), 7.25 (t, 1H), 7.13 (d, 1H), 7.05 (d, 2H), 6.61 (dd, 1H), 6.30 (dd, 1H), 6.26 (d, 1H), 4.28 (d, 2H), 3.10-3.13 (m, 2H), 2.91-3.00 (m, 6H), 2.73 (s, 2H), 1.96-2.02 (m, 4H), 1.77-1.89 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

EXAMPLE 128

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
[(3-nitro-4-{[4-(4-tetrahydro-2H-pyran-4-yl)piperazin-1-
yl)cyclohexyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5

EXAMPLE 128A

tert-butyl 4-(tetrahydro-2H-pyran-4-yl)piperazine-1-carboxylate

The title compound was prepared by substituting tert-butyl piperazine-1-carboxylate
for morpholine and dihydro-2H-pyran-4(3H)-one for tert-butyl 4-oxocyclohexylcarbamate in
EXAMPLE 39A.

10

EXAMPLE 128B

1-(tetrahydro-2H-pyran-4-yl)piperazine dihydrochloride

To a solution of EXAMPLE 128A (3.92 g) in ether was added HCl (25 ml, 2M in
ether) and the reaction mixture was stirred for 16 hours at room temperature. The solid
product was filtered off, dried and used in next step without further purification.

15

EXAMPLE 128C

Trans-tert-butyl-4-(4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl)cyclohexylcarbamate

The title compound was prepared by substituting EXAMPLE 128B for morpholine in
EXAMPLE 39A.

20

EXAMPLE 128D

trans-4-(4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl)cyclohexanamine tris(2,2,2-
trifluoroacetate)

The title compound was prepared by substituting EXAMPLE 128C for EXAMPLE
39A in EXAMPLE 39B.

25

EXAMPLE 128E

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
[(3-nitro-4-{[4-(4-tetrahydro-2H-pyran-4-yl)piperazin-1-
yl)cyclohexyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

30

The title compound was prepared by substituting EXAMPLE 128D for EXAMPLE
100B in EXAMPLE 100C. ¹H NMR (500 MHz, pyridine-d₅) δ 13.07 (s, 1H), 9.28 - 9.32 (m,

1H), 8.44 (t, 1H), 8.34 - 8.39 (m, 2H), 8.10 - 8.14 (m, 1H), 7.66 - 7.69 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.92 (t, 1H), 6.73 - 6.77 (m, 1H), 6.52 - 6.55 (m, 1H), 6.49 - 6.52 (m, 1H), 3.99 - 4.06 (m, 2H), 3.29 - 3.36 (m, 2H), 3.03 - 3.09 (m, 4H), 2.77 (s, 2H), 2.62 (s, 8H), 2.24 - 2.29 (m, 3H), 2.10 - 2.16 (m, 5H), 2.05 (s, 2H), 1.97 (s, 2H), 1.92 (s, 2H), 1.70 (d, 2H), 1.57 (td, 2H), 1.34 - 1.43 (m, 4H), 1.20 - 1.30 (m, 2H), 0.93 (s, 6H).

EXAMPLE 129

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-({1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl}methoxy)-3-nitrophenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 129A

(1-(1,3-difluoropropan-2-yl)piperidin-4-yl)methanol

A suspension of piperidin-4-ylmethanol (0.250 g), sodium triacetoxymethylborohydride (0.690 g) and 1,3-difluoropropan-2-one (0.245 g) were stirred together in dichloromethane. After stirring overnight the reaction was poured into saturated aqueous NaHCO₃ solution (10 mL) and stirred for 15 minutes. The reaction was extracted with dichloromethane (3 x 25 mL), dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (GraceResolv 12 g) eluting with a gradient of 0.75% to 3% methanol/dichloromethane gave the title compound.

EXAMPLE 129B

4-((1-(1,3-difluoropropan-2-yl)piperidin-4-yl)methoxy)-3-nitrobenzenesulfonamide

To a solution of (1-(1,3-difluoropropan-2-yl)piperidin-4-yl)methanol (0.068 g) in tetrahydrofuran (1 mL) was added sodium hydride (0.056 g) and the reaction stirred for 30 minutes at room temperature. 4-Fluoro-3-nitrobenzenesulfonamide (0.077 g) was added in one portion and stirring was continued for 1 hour. The reaction was poured into water (20 mL) and extracted with dichloromethane. The pH of the aqueous layer was adjusted to pH~8 and it was extracted with dichloromethane (50 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated to give the title compound.

EXAMPLE 129C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
(1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl)methoxy]-3-nitrophenyl)sulfonyl}-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5 The title compound was prepared by substituting EXAMPLE 129B for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.67 (s, 1H), 11.47 - 10.98 (m, 1H), 8.33 (d, 1H), 8.03 (d, 2H), 7.50 (dd, 3H), 7.36 (t, 3H), 7.04 (d, 2H), 6.67 (d, 1H), 6.39 (dd, 1H), 6.20 (s, 1H), 4.62 (dd, 4H), 4.06 (d, 2H), 3.18 - 2.71 (m, 11H), 2.20 (d, 6H), 1.96 (s, 2H), 1.73 (d, 3H), 1.35 (d, 4H), 0.92
10 (s, 6H).

EXAMPLE 130

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

15

EXAMPLE 130A

(R)-tert-butyl 1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-ylcarbamate

The title compound was prepared by substituting dihydro-2H-pyran-4(3H)-one for 4'-
20 chlorobiphenyl-2-carboxaldehyde and (R)-tert-butyl pyrrolidin-3-ylcarbamate for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 130B

(R)-1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-amine

25 A solution of EXAMPLE 130A (550 mg) in dichloromethane (25 ml) was cooled in an ice bath under nitrogen. 2,2,2-Trifluoroacetic acid (8.333 ml) was added and the reaction was stirred for 2 hours. The product was obtained by concentration and high vacuum drying.

EXAMPLE 130C

30 (R)-3-nitro-4-(1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-ylamino)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 130B for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 130D

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

5 To a solution of EXAMPLE 3J (90 mg), EXAMPLE 130C (64.2 mg), triethylamine (0.077 ml), N,N-dimethylpyridin-4-amine (38.5 mg) in a mixture of dichloromethane (5 ml) and N,N-dimethylformamide (0.5 ml) was added N¹-((ethylimino)methylene)-N³,N³-dimethylpropane-1,3-diamine, hydrochloric acid (60.4 mg) and the mixture was stirred 18 hours. This was concentrated on high vacuum and the crude was purified by reverse phase
10 chromatography with ammonium acetate buffer / acetonitrile. ¹H NMR (500 MHz, pyridine-d₅) δ 13.03 (s, 1H), 9.27 (d, 1H), 8.59 (d, 1H), 8.43 (d, 1H), 8.37 (dd, 1H), 8.11 (d, 1H), 7.65 - 7.67 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.88 (d, 1H), 6.76 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 4.06 (m, 1H), 3.98 (d, 2H), 3.35 (t, 2H), 3.07 (m, 4H), 2.73 - 2.80 (m, 4H), 2.68 - 2.72 (m, 1H), 2.36 (q, 1H), 2.11 - 2.30 (m, 9H), 1.97 (m, 2H), 1.62 - 1.71 (m, 3H), 1.48 - 1.58 (m,
15 2H), 1.39 (t, 2H), 0.94 (s, 6H).

EXAMPLE 131

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

20

EXAMPLE 131A

tert-butyl (3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-ylcarbamate

The title compound was prepared by substituting 2,2-dimethyldihydro-2H-pyran-4(3H)-one for 4'-chlorobiphenyl-2-carboxaldehyde and (R)-tert-butyl pyrrolidin-3-ylcarbamate for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

25

EXAMPLE 131B

(3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-amine

30 The title compound was prepared by substituting EXAMPLE 131A for EXAMPLE 130A in EXAMPLE 130B.

EXAMPLE 131C

4-((3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 131B for
5 (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 131D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
10 {[(3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 131C for EXAMPLE
130C in EXAMPLE 130D. ¹H NMR (500 MHz, pyridine-d₅) δ 13.03 (d, 1H), 9.28 (m, 1H),
8.61 (m, 1H), 8.44 (d, 1H), 8.38 (dd, 1H), 8.11 (d, 1H), 7.64 - 7.68 (m, 2H), 7.44 (d, 2H),
7.07 (d, 2H), 6.89 (m, 1H), 6.76 (dd, 1H), 6.54 (m, 1H), 6.49 (m, 1H), 4.08 (m, 1H), 3.78 (m,
15 1H), 3.61 (m, 1H), 3.07 (m, 4H), 2.71 - 2.82 (m, 5H), 2.37 - 2.44 (m, 2H), 2.19 - 2.29 (m,
3H), 2.14 (m, 5H), 1.97 (s, 2H), 1.76 (m, 1H), 1.66 (m, 2H), 1.32 - 1.49 (m, 4H), 1.28 (d,
3H), 1.20 (s, 3H), 0.94 (s, 6H).

20

EXAMPLE 132

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-
25 {[(3S)-1-tetrahydro-2H-pyran-4-yl]pyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 132A

(S)-tert-butyl 1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-ylcarbamate

The title compound was prepared by substituting dihydro-2H-pyran-4(3H)-one for 4'-
30 chlorobiphenyl-2-carboxaldehyde and (S)-tert-butyl pyrrolidin-3-ylcarbamate for tert-butyl
piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 132B

(S)-1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-amine

The title compound was prepared by substituting EXAMPLE 132A for EXAMPLE
5 130A in EXAMPLE 130B.

EXAMPLE 132C

(S)-3-nitro-4-(1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-ylamino)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 132B for
10 (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 132D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-
nitro-4-{[(3S)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-
15 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 132C for EXAMPLE
130C in EXAMPLE 130D. ¹H NMR (500 MHz, pyridine- d₅) δ 13.04 (m, 1H), 9.27 (d, 1H),
8.58 (d, 1H), 8.43 (d, 1H), 8.37 (dd, 1H), 8.11 (d, 1H), 7.64 - 7.68 (m, 2H), 7.44 (d, 2H), 7.07
(d, 2H), 6.88 (d, 1H), 6.75 (dd, 1H), 6.54 (m, 1H), 6.49 (m, 1H), 4.06 (m, 1H), 3.98 (d, 2H),
20 3.36 (t, 2H), 3.07 (m, 4H), 2.68 - 2.80 (m, 5H), 2.36 (m, 1H), 2.09 - 2.29 (m, 9H), 1.97 (s,
2H), 1.62 - 1.72 (m, 3H), 1.48 - 1.60 (m, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

EXAMPLE 133

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
25 {[(3S)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-
nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 133A

tert-butyl (3S)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-ylcarbamate

The title compound was prepared by substituting 2,2-dimethyldihydro-2H-pyran-
30 4(3H)-one for 4'-chlorobiphenyl-2-carboxaldehyde and (S)-*tert*-butyl pyrrolidin-3-
ylcarbamate for *tert*-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 133B

(3S)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-amine

The title compound was prepared by substituting EXAMPLE 133A for EXAMPLE 130A in EXAMPLE 130B.

5

EXAMPLE 133C

4-(3S)-(1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 133B for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

10

EXAMPLE 133D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

15

The title compound was prepared by substituting EXAMPLE 133C for EXAMPLE 130C in EXAMPLE 130D. ¹H NMR (500 MHz, pyridine- d₅) δ 13.03 (d, 1H), 9.28 (m, 1H), 8.61 (m, 1H), 8.43 (d, 1H), 8.38 (dd, 1H), 8.11 (d, 1H), 7.64 - 7.68 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.89 (m, 1H), 6.76 (dd, 1H), 6.54 (m, 1H), 6.49 (m, 1H), 4.08 (m, 1H), 3.78 (m, 1H), 3.61 (m, 1H), 3.07 (m, 4H), 2.71 - 2.82 (m, 5H), 2.37 - 2.44 (m, 2H), 2.19 - 2.29 (m, 3H), 2.14 (m, 5H), 1.97 (s, 2H), 1.76 (m, 1H), 1.66 (m, 2H), 1.33 - 1.48 (m, 4H), 1.28 (d, 3H), 1.20 (s, 3H), 0.94 (s, 6H).

20

EXAMPLE 134

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

25

EXAMPLE 134A

4-(morpholin-2-ylmethylamino)-3-nitrobenzenesulfonamide

30

A solution of EXAMPLE 113A (0.8 g) in dichloromethane (10 mL) and trifluoroacetic acid (10 mL) was stirred at room temperature for 2 hours. The solvents were evaporated and the residue triturated with diethyl ether. The resulting solid was dissolved in

5% aqueous sodium carbonate solution (20 mL). The solution was concentrated to dryness and the resulting solid was triturated with a solution of 10% methanol in dichloromethane several times. Evaporation of the organic solvents gave the title compound.

5

EXAMPLE 134B

4-((4-methylmorpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

To a solution of EXAMPLE 134A (158 mg) in anhydrous *N,N*-dimethylformamide (4 mL) was added sodium carbonate (64 mg) and methyl iodide (78 mg). After stirring overnight at room temperature, the mixture was evaporated to dryness. The crude product was then absorbed on silica gel (6 g) and purified on a silica gel column eluting with 10% methanol in dichloromethane to give the title compound.

10

EXAMPLE 134C

15 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 134B for EXAMPLE 130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 13.00 (s, 1H), 9.27 (d, 1H), 8.87 (t, 1H), 8.43 (d, 1H), 8.32 (dd, 1H), 8.11 (d, 1H), 7.65 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.91 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.92 (m, 1H), 3.86 (d, 1H), 3.67 (dt, 1H), 3.49-3.39 (m, 2H), 3.07 (m, 4H), 2.77 (s, 2H), 3.71 (m, 1H), 2.49 (d, 1H), 2.26 (m, 2H), 2.16 (s, 3H), 2.14 (m, 4H), 2.03 (dt, 1H), 1.97 (s, 2H), 1.90 (t, 1H), 1.39 (t, 2H), 0.94 (s, 6H).

25

EXAMPLE 135

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

30

EXAMPLE 135A

4-((4-(2-methoxyethyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 2-methoxyethyl bromide for methyl iodide in EXAMPLE 134B.

EXAMPLE 135B

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-
5 ([4-(2-methoxyethyl)morpholin-2-yl]methyl)amino)-3-nitrophenyl]sulfonyl)-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 135A for EXAMPLE
130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 12.98 (s, 1H), 9.26 (d, 1H),
8.88 (t, 1H), 8.43 (d, 1H), 8.32 (dd, 1H), 8.11 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d,
10 2H), 6.91 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.93 (m, 1H), 3.87 (d, 1H), 3.70
(dt, 1H), 3.51 (t, 2H), 3.48-3.38 (m, 2H), 3.27 (s, 3H), 3.07 (m, 4H), 2.95 (d, 1H), 2.77 (s,
2H), 2.70 (m, 1H), 2.57 (t, 2H), 2.27-2.07 (m, 8H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

EXAMPLE 136

15 N-([4-([4-(4-acetylmorpholin-2-yl)methyl]amino)-3-nitrophenyl]sulfonyl)-4-(4-([2-(4-
chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

EXAMPLE 136A

20 4-((4-acetylmorpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting acetic anhydride for methyl iodide in
EXAMPLE 134B.

EXAMPLE 136B

25 N-([4-([4-(4-acetylmorpholin-2-yl)methyl]amino)-3-nitrophenyl]sulfonyl)-4-(4-([2-(4-
chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 136A for EXAMPLE
130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 13.00 (s, 1H), 9.26 (s, 1H),
30 8.85 (s, 1H), 8.43 (d, 1H), 8.32 (dd, 1H), 8.10 (d, 1H), 7.65 (m, 2H), 7.44 (d, 2H), 7.07 (d,
2H), 6.91 (dd, 1H), 6.75 (dd, 1H), 6.54 (s, 1H), 6.48 (s, 1H), 4.73 (dd, 1H), 3.93-3.65 (m,
2H), 3.60-3.40 (m, 4H), 3.12 (m, 1H), 3.07 (m, 4H), 2.77 (s, 2H), 2.70 (m, 1H), 2.57 (t, 2H),
2.14 (s, 3H), 2.27-2.07 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

EXAMPLE 137

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(4-
[[trans-4-(fluoromethyl)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy]-3-nitrophenyl)sulfonyl]-2-
(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5

EXAMPLE 137A

ethyl 4-fluorobut-2-enoate

Ethyl 2-fluoroacetate (21.0 g) in CH₂Cl₂ (200 mL) at -78 °C was treated dropwise
over 45 min with a 1.0 M solution of diisobutylaluminum hydride in CH₂Cl₂ (200 mL)
10 maintaining the internal temperature below -70 °C. Stirring was continued at -78 °C for 30
minutes and then (carbethoxymethylene)triphenylphosphorane (70.0 g) was added in one
portion. The reaction mixture was allowed to slowly reach room temperature while stirring
overnight. It was then quenched with methanol, filtered and concentrated to give the product
as a mixture of isomers (E/Z = 3:1).

15

EXAMPLE 137B

Trans-ethyl 1-benzyl-4-(fluoromethyl)pyrrolidine-3-carboxylate

A mixture of N-benzyl-1-methoxy-N-((trimethylsilyl)methyl)methanamine (4.5 g)
and EXAMPLE 137A (2.5 g) in dichloromethane (50 mL) was cooled to 0 °C, treated
20 dropwise with trifluoroacetic acid (0.15 mL), stirred for 4 hours at 0 °C and neutralized with
saturated aqueous Na₂CO₃ solution. The mixture was poured into a separatory funnel and the
layers separated. The organic layer was washed with water and brine, dried (MgSO₄),
filtered, concentrated and chromatographed on silica gel with 0-20% ethyl acetate in hexanes
as eluent to give both the cis and trans isomers of the product. Only the trans diastereomers
25 were carried on in the following steps.

EXAMPLE 137C

Trans-ethyl 4-(fluoromethyl)pyrrolidine-3-carboxylate

EXAMPLE 137B (0.83 g) in ethanol (9 mL) was treated with 10% Pd/C (0.208 g) and
30 ammonium formate (1.97 g), refluxed for 1.5 hours, concentrated, dissolved in
dichloromethane, filtered through a pad of celite rinsing with dichloromethane, and
concentrated to give the product.

EXAMPLE 137D

Trans-1-benzyl 3-ethyl 4-(fluoromethyl)pyrrolidine-1,3-dicarboxylate

EXAMPLE 137C (0.44 g) in dioxane (4 mL) and water (4 mL) at 0 °C was treated sequentially with Na₂CO₃ (0.89 g) and benzyl chloroformate (0.48 mL). The reaction mixture was stirred at 0 °C for 3 hours and was then allowed to slowly warm to room temperature over 1.5 hours. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried (MgSO₄), filtered, concentrated and chromatographed on silica gel with 10-25% ethyl acetate in hexanes as eluent to give the product.

EXAMPLE 137E

Trans-1-(benzyloxycarbonyl)-4-(fluoromethyl)pyrrolidine-3-carboxylic acid

The title compound was prepared by substituting EXAMPLE 137D for EXAMPLE 15G in EXAMPLE 15H.

EXAMPLE 137F

Trans-benzyl 3-(fluoromethyl)-4-(hydroxymethyl)pyrrolidine-1-carboxylate

EXAMPLE 137E (0.563 g) in tetrahydrofuran (10 mL) at 0 °C was treated dropwise with a 1 M solution of borane in tetrahydrofuran (4 mL), stirred for 3 hours and then slowly quenched with saturated aqueous NH₄Cl solution. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried (MgSO₄), filtered and concentrated to give the product.

EXAMPLE 137G

Trans-benzyl 3-(fluoromethyl)-4-((2-nitro-4-sulfamoylphenoxy)methyl)pyrrolidine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 137F for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

EXAMPLE 137H

Trans-4-((4-(fluoromethyl)pyrrolidin-3-yl)methoxy)-3-nitrobenzenesulfonamide

EXAMPLE 137G (0.232g) in acetic acid (2.5 ml) was treated with hydrobromic acid (33 wt % in acetic acid) (0.875 mL) at ambient temperature, stirred for 1 hour and concentrated. The product was free-based using a MEGA BE-SCX column with 1:1

CH₂Cl₂/methanol as eluent for the hydrobromic acid and acetic acid. The product was released from the column with 10% (7 M ammonia in methanol) in CH₂Cl₂ as eluent.

EXAMPLE 137I

5 Trans-4-((4-(fluoromethyl)-1-(oxetan-3-yl)pyrrolidin-3-yl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 137H for tert-butyl piperazine-1-carboxylate and 3-oxetanone for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

10

EXAMPLE 137J

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(4-
{[trans-4-(fluoromethyl)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-
(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

15 The title compound was prepared by substituting EXAMPLE 137I for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.67 (s, 1H), 8.35 (d, 1H), 8.03 (m, 2H), 7.51 (m, 3H), 7.37 (m, 3H), 7.04 (m, 2H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.21 (d, 1H), 4.45 (m, 6H), 4.21 (d, 2H), 3.62 (m, 1H), 3.08 (m, 4H), 2.72 (m, 5H), 2.31 (m, 9H), 1.96 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

20

EXAMPLE 138

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-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

25

EXAMPLE 138A

(4-fluorotetrahydro-2H-pyran-4-yl)methyl methanesulfonate

A mixture of EXAMPLE 37C (1.4 g), methanesulfonyl chloride (1.054 mL), triethylamine (2.99 mL), and 4-dimethylaminopyridine (0.051 g) in CH₂Cl₂ (20 mL) was
30 stirred at 0 °C for 2 hours, concentrated and chromatographed on silica gel eluting with 30% ethyl acetate in hexanes to give the product.

EXAMPLE 138B

2-((4-fluorotetrahydro-2H-pyran-4-yl)methyl)isoindoline-1,3-dione

A mixture of EXAMPLE 138A (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,
5 washed with water and brine, dried (MgSO₄), filtered, concentrated and chromatographed on silica gel eluting with 30% ethyl acetate in hexanes to give the product.

EXAMPLE 138C

(4-fluorotetrahydro-2H-pyran-4-yl)methanamine

10 A mixture of EXAMPLE 138B (1.4 g) and hydrazine (1.548 mL) in ethanol (40 mL) was heated at 70 °C overnight, cooled to room temperature, slurried with CH₂Cl₂ (200 mL) and the solid removed by filtration. The filtrate was concentrated and chromatographed on silica gel eluting with 100:5:1 ethyl acetate/methanol/NH₄OH to give the product.

15 EXAMPLE 138D

4-((4-fluorotetrahydro-2H-pyran-4-yl)methylamino)-3-nitrobenzenesulfonamide

A mixture of 4-fluoro-3-nitrobenzenesulfonamide (0.44 g), EXAMPLE 138C (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 (MgSO₄), filtered, concentrated
20 and chromatographed on silica gel eluting with 50% ethyl acetate in hexanes to give the product.

EXAMPLE 138E

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
25 {[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 138D for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.68 (s, 1H), 8.62 (t, 1H), 8.56 (d, 1H), 8.04 (d, 1H), 7.82 (dd, 1H), 7.48-7.54 (m, 3H), 7.34 (d, 2H),
30 7.24 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.70-3.77 (m, 4H), 3.50-3.55 (m, 2H), 3.07 (s, 4H), 2.76 (s, 2H), 2.14-2.20 (m, 6H), 1.76-1.84 (m, 4H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 139

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

5

EXAMPLE 139A

tert-butyl 4-(4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)piperidine-1-carboxylate

10 The title compound was prepared as described in EXAMPLE 53B by replacing 1-acetylpiperidin-4-amine with 4-amino-piperidine-1-carboxylic acid tert-butyl ester.

EXAMPLE 139B

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-(piperidin-4-ylamino)phenylsulfonyl)benzamide

15 To a cooled (0°C) solution of EXAMPLE 139A (960 mg) in dichloromethane (10 mL) was added dropwise trifluoroacetic acid (5 mL). The mixture was stirred at the temperature for 3 hours. Then, the mixture was concentrated under vacuum and the residue was dissolved in dichloromethane (200 mL) and washed with aqueous NaHCO₃ and brine.
20 After drying over Na₂SO₄, the mixture was filtered, and evaporation of the solvent from the filtrate gave the title compound.

EXAMPLE 139C

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

To a solution of EXAMPLE 139B (120 mg) in tetrahydrofuran (3 mL) and acetic acid (1 mL) was added oxetan-3-one (50.8 mg) and MP-cyanoborohydride (2.15 mmol/g, 150 mg). The mixture was stirred at room temperature overnight. The mixture was filtered. The
30 filtrate was concentrated and the residue was loaded on a silica gel cartridge and eluted with 5-10% 7N NH₃ in methanol in dichloromethane to give the title compound. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.62 (s, 1H), 8.51 (d, 1H), 8.20 (d, 1H), 7.99 (d, 1H), 7.74 (m, 1H), 7.48 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.66 (dd, 1H), 6.36 (dd, 1H), 6.20 (d, 1H),

4.54 (t, 2H), 4.43 (t, 2H), 3.66 (m, 1H), 3.44 (m, 3H), 3.04 (m, 5H), 2.73 (s, 2H), 2.61 (m, 2H), 2.12 (m, 11H), 1.61 (m, 2H), 1.38 (t, 2H), 0.93 (m, 6H).

EXAMPLE 140

5 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclobutyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 139C by replacing oxetan-3-one with cyclobutanone. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.58 (s, 1H), 8.47 (d, 1H), 8.12 (d, 1H), 7.97 (d, 1H), 7.74 (d, 1H), 7.53 (d, 1H), 7.45 (m, 1H), 7.36 (m, 3H), 7.02 (m, 3H), 6.64 (dd, 1H), 6.33 (m, 1H), 6.22 (d, 1H), 3.74 (m, 1H), 2.97 (m, 6H), 2.73 (s, 3H), 2.15 (m, 15H), 1.67 (m, 4H), 1.38 (t, 2H), 0.93 (s, 6H).

EXAMPLE 141

15 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 139C by replacing oxetan-3-one with 2,2-dimethyltetrahydropyran-4-one. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.60 (s, 1H), 8.50 (d, 1H), 8.15 (m, 1H), 7.99 (d, 1H), 7.78 (m, 1H), 7.62 (m, 1H), 7.47 (m, 3H), 7.34 (m, 3H), 7.05 (m, 3H), 6.65 (m, 2H), 6.35 (dd, 1H), 6.21 (d, 1H), 4.56 (d, 3H), 3.89 (m, 3H), 3.67 (m, 6H), 3.45 (m, 2H), 3.04 (m, 3H), 2.75 (m, 3H), 2.14 (m, 3H), 1.71 (m, 5H), 1.16 (s, 9H).

EXAMPLE 142

25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-cyclopropylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 142A

(S)-tert-butyl 1-cyclopropylpyrrolidin-3-ylcarbamate

(S)-tert-butyl pyrrolidin-3-ylcarbamate (415 mg), (1-ethoxycyclopropoxy)trimethylsilane (1.8 mL) and molecular sieves (500 mg) were combined

in methanol (4.5 mL). Acetic acid (1.3 mL) was added, followed by sodium cyanoborohydride (420 mg). The resulting mixture was heated to reflux for 4 hours. Insoluble material was filtered off and reaction was made basic to pH 14 with addition of 6M aqueous NaOH solution. The solution was extracted three times with diethyl ether, and the combined extracts were dried over MgSO₄, filtered and concentrated to obtain an oil, which was purified by flash chromatography, eluting first with 100% dichloromethane, followed by 5% methanol/dichloromethane and 10% methanol/dichloromethane.

EXAMPLE 142B

(S)-1-cyclopropylpyrrolidin-3-amine

The title compound was prepared by substituting EXAMPLE 142A for EXAMPLE 1A in EXAMPLE 1B.

EXAMPLE 142C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-cyclopropylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 142B for 1-acetylpiperidin-4-amine in EXAMPLE 53B. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.64 (s, 1H), 8.51 (m, 2H), 8.30 (m, 1H), 8.00 (br s, 1H), 7.77 (m, 1H), 7.49 (m, 3H), 7.34 (d, 2H), 7.04 (d, 2H), 6.97 (br s, 1H), 6.67 (dd, 1H), 6.36 (m, 1H), 6.21 (m, 1H), 4.19 (m, 1H), 3.00 (m, 5H), 2.74 (m, 3H), 2.64 (m, 1H), 2.36 (m, 1H), 2.15 (m, 6H), 1.95 (s, 2H), 1.78 (br s, 1H), 1.68 (m, 1H), 1.38 (t, 2H), 1.23 (m, 1H), 0.92 (s, 6H), 0.39 (m, 4H).

EXAMPLE 143

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

The title compound was prepared as described in EXAMPLE 139C by replacing oxetan-3-one with 3-oxotetrahydrofuran. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.65 (s, 1H), 8.53 (d, 1H), 8.21 (m, 1H), 8.02 (m, 1H), 7.80 (dd, 1H), 7.49 (m, 3H), 7.34 (m, 3H), 7.05 (m, 3H), 6.67 (dd, 1H), 6.37 (m, 1H), 6.19 (d, 1H), 4.29 (m, 3H), 3.73 (m, 6H), 3.09 (m, 4H), 2.76 (m, 2H), 2.05 (m, 8H), 1.68 (m, 2H), 1.37 (m, 2H), 0.94 (s, 6H).

EXAMPLE 144

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-[(4-
{{(3R)-1-cyclopropylpyrrolidin-3-yl}amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

5

EXAMPLE 144A

(R)-tert-butyl 1-cyclopropylpyrrolidin-3-ylcarbamate

The title compound was prepared by substituting (R)-tert-butyl pyrrolidin-3-ylcarbamate for (S)-tert-butyl pyrrolidin-3-ylcarbamate in EXAMPLE 142A.

10

EXAMPLE 144B

(R)-1-cyclopropylpyrrolidin-3-amine

The title compound was prepared by substituting EXAMPLE 144A for EXAMPLE 1A in EXAMPLE 1B.

15

EXAMPLE 144C

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-[(4-
{{(3R)-1-cyclopropylpyrrolidin-3-yl}amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

20

The title compound was prepared by substituting EXAMPLE 144B for 1-acetylpiperidin-4-amine in EXAMPLE 53B. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.66 (s, 1H), 8.53 (d, 2H), 8.32 (d, 1H), 8.02 (d, 1H), 7.81 (m, 1H), 7.49 (m, 3H), 7.34 (d, 2H), 7.03 (m, 3H), 6.67 (dd, 1H), 6.37 (m, 1H), 6.20 (d, 1H), 4.21 (m, 1H), 3.00 (m, 5H), 2.74 (m, 3H), 2.64 (m, 1H), 2.36 (m, 1H), 2.15 (m, 6H), 1.95 (s, 2H), 1.74 (br s, 1H), 1.66 (m, 1H), 1.38 (t, 2H), 1.23 (m, 1H), 0.92 (s, 6H), 0.39 (m, 4H).

25

EXAMPLE 145

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

30

EXAMPLE 145A

(S)-tert-butyl (1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl)methylcarbamate

The title compound was prepared by substituting (R)-tert-butyl pyrrolidin-3-ylmethylcarbamate for tert-butyl piperazine-1-carboxylate and dihydro-2H-pyran-4(3H)-one
5 for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

EXAMPLE 145B

(S)-(1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl)methanamine

The title compound was prepared by substituting EXAMPLE 145A for EXAMPLE
10 1A in EXAMPLE 1B.

EXAMPLE 145C

(S)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-((1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl)methylamino)phenylsulfonyl)benzamide
15

The title compound was prepared by substituting EXAMPLE 145B for 1-acetylpiperidin-4-amine in EXAMPLE 53B. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.58 (s, 1H), 8.61 (br s, 1H), 8.46 (s, 1H), 7.96 (d, 1H), 7.72 (m, 1H), 7.54 (d, 1H), 7.45 (t, 1H), 7.37 (br s, 2H), 7.34 (d, 2H), 7.04 (m, 2H), 6.94 (m, 1H), 6.64 (dd, 1H), 6.34 (m, 1H),
20 6.22 (d, 1H), 3.89 (m, 2H), 3.38 (m, 4H), 3.27 (m, 4H), 3.02 (m, 5H), 2.73 (s, 2H), 2.61 (m, 1H), 2.18 (m, 6H), 2.05 (m, 1H), 1.95 (m, 2H), 1.85 (m, 2H), 1.64 (m, 1H), 1.50 (m, 2H), 1.38 (m, 2H), 0.94 (s, 6H).

EXAMPLE 146

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-hydroxy-2,2-dimethylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide
25

The title compound was prepared as described in EXAMPLE 120B using 3-amino-2,2-dimethylpropan-1-ol in place of EXAMPLE 120A. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.68 (s, 1H), 11.35 (s, 1H), 8.96 (t, 1H), 8.56 (d, 1H), 8.05 (d, 1H),
30 7.79 (dd, 1H), 7.46 - 7.56 (m, 3H), 7.34 (d, 2H), 7.10 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 5.10 (t, 1H), 3.29 (d, 1H), 3.24 (d, 1H), 3.07 (s, 4H), 2.75 (s, 2H), 2.17 (d, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.93 (d, 12H).

EXAMPLE 147

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

EXAMPLE 147A

tert-butyl (1-(methylsulfonyl)piperidin-3-yl)methylcarbamate

tert-Butyl piperidin-3-ylmethylcarbamate(500 mg) was dissolved in anhydrous
10 dichloromethane (10 mL), and methanesulfonyl chloride (0.181 mL) was added followed by
the addition of triethylamine (1.3 mL). The reaction mixture was stirred at room temperature
overnight. The organic solvent was removed under vacuum. The residue was purified with
flash column chromatography on silica gel eluting with 0-70% ethyl acetate in hexane to give
the title compound.

15

EXAMPLE 147B

(1-(methylsulfonyl)piperidin-3-yl)methanamine

EXAMPLE 147A (400 mg) was suspended in 4N HCl in dioxane (10 mL) followed
by the addition of anhydrous methanol (1 mL). The clear solution was stirred at room
20 temperature for 2 hours. The organic solvent was removed under vacuum. The solid residue
was used in the next step without further purification.

EXAMPLE 147C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
25 ({[1-(methylsulfonyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 53A (50 mg), EXAMPLE 147B (26 mg) and triethylamine (0.088 mL)
were dissolved in anhydrous dioxane (1mL) and N,N-dimethylformamide (0.2 mL). The
reaction vial was heated in a Biotage Initiator microwave reactor at 130°C for 25 minutes.
30 The solvent was removed under vacuum. 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 (6 mL) and washed with 50% aqueous NaHCO₃. The organic

layer was dried over anhydrous Na₂SO₄ and concentrated to give the title compound. ¹H NMR (400MHz, dimethylsulfoxide-d₆) δ 11.65 (s, 1H), 8.56 (m, 2H), 8.03 (d, 1H), 7.80 (m, 1H), 7.50 (m, 3H), 7.35 (d, 2H), 7.12 (m, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.38 (dd, 1H), 6.19 (d, 1H), 3.52 (m, 1H), 3.40 (m, 2H), 3.06 (m, 4H), 2.84 (s, 3H), 2.75 (m, 2H), 2.75 (m, 4H), 2.58 (m, 1H), 2.16 (m, 6H), 1.95 (s, 3H), 1.76 (m, 2H), 1.52 (m, 1H), 1.37 (m, 2H), 0.92 (s, 6H).

EXAMPLE 148

N-[(4-[(1-acetylpiperidin-3-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-4-(4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 148A

tert-butyl (1-acetylpiperidin-3-yl)methylcarbamate

The title compound was prepared by substituting acetyl chloride for methanesulfonyl chloride in EXAMPLE 147A.

EXAMPLE 148B

1-(3-(aminomethyl)piperidin-1-yl)ethanone

The title compound was prepared by substituting EXAMPLE 148A for EXAMPLE 147A in EXAMPLE 147B.

EXAMPLE 148C

N-[(4-[(1-acetylpiperidin-3-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-4-(4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 148B for EXAMPLE 147B in EXAMPLE 147C. ¹H NMR (400MHz, dimethylsulfoxide-d₆) δ 11.67 (s, 1H), 8.56 (m, 2H), 8.03 (d, 1H), 7.80 (m, 1H), 7.50 (m, 3H), 7.34 (d, 2H), 7.12 (m, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.99 (m, 1H), 3.67 (m, 1H), 3.37 (m, 2H), 3.24 (m, 2H), 3.07 (m, 4H), 2.89 (m, 1H), 2.71 (m, 2H), 2.16 (m, 6H), 1.96 (s, 3H), 1.80 (m, 4H), 1.38 (t, 2H), 1.27 (m, 2H), 0.92 (s, 6H).

EXAMPLE 149

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-[(4-
{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

5

EXAMPLE 149A

(R)-tert-butyl 1-(methylsulfonyl)pyrrolidin-3-ylcarbamate

The title compound was prepared by substituting (R)-tert-butyl pyrrolidin-3-ylcarbamate for tert-butyl piperidin-3-ylmethylcarbamate in EXAMPLE 147A.

10

EXAMPLE 149B

(R)-1-(methylsulfonyl)pyrrolidin-3-amine

The title compound was prepared by substituting EXAMPLE 149A for EXAMPLE 147A in EXAMPLE 147B.

15

EXAMPLE 149C

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-[(4-
{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

20

The title compound was prepared by substituting EXAMPLE 149B for EXAMPLE 147B in EXAMPLE 147C. ¹H NMR (400MHz, dimethylsulfoxide-d₆) δ 11.65 (s, 1H), 8.55 (d, 1H), 8.29 (d, 1H), 8.02 (d, 1H), 7.86 (dd, 1H), 7.49 (m, 3H), 7.33 (d, 2H), 7.17 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.38 (dd, 1H), 6.20 (d, 1H), 4.41 (m, 1H), 3.69 (m, 1H), 3.39 (m, 3H), 3.06 (m, 4H), 2.97 (s, 3H), 2.76 (m, 2H), 2.27 (m, 8H), 1.93 (m, 2H), 1.54 (m, 1H), 1.38 (t, 2H), 0.92 (s, 6H).

25

EXAMPLE 150

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

30

EXAMPLE 150A

Ethyl 2-hydroxy-3,3-dimethylcyclohex-1-enecarboxylate

Into a 500 mL round-bottomed flask was added diisopropylamine (3.5 mL) in ether (200 mL). After cooling to -30°C, butyllithium (16 mL) (1.6M in hexane) was added slowly. After stirring 30 minutes, the temperature was cooled to -5 °C. 2,2-Dimethylcyclohexanone (3 g) was added slowly. The mixture was warmed up to 0°C and stirred for 1 hour. After
5 cooling to -5 °C, hexamethylphosphoramide (8 mL) and ethyl carbonocyanidate (2.5 mL) were added. After stirring at -5 °C for 20 minutes, and warming to room temperature, the reaction was stirred for 1 hour. The mixture was poured into cold water, and the layers were separated. The aqueous layer was extracted with ether (3x 20 mL). The combined the organic layers were washed with saturated aqueous NH₄Cl (3x 20 mL). After drying over Na₂SO₄, the
10 mixture was filtered and the filtrate was concentrated. The crude product was purified by flash chromatography on silica with 0-10% ethyl acetate in hexanes to provide the title compound.

EXAMPLE 150B

Ethyl 3,3-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

15 The title compound was prepared by substituting EXAMPLE 150A for EXAMPLE 101A in EXAMPLE 101B.

EXAMPLE 150C

Ethyl 2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-enecarboxylate

20 The title compound was prepared by substituting EXAMPLE 150B for EXAMPLE 101B in EXAMPLE 101C.

EXAMPLE 150D

(2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-enyl)methanol

25 In a 200 mL round-bottomed flask was added EXAMPLE 150C (0.97 g) and lithium borohydride (0.47 g) in ether (20 mL) to give a suspension. Methanol (2.2 mL) was added slowly. The mixture was refluxed overnight. The reaction was then cooled, and methanol was added to quench the reaction. 1N aqueous HCl was then added until the pH<7, and ether (3x 30 mL) was used to extract the product. The combined organic layers were dried over
30 Na₂SO₄, filtered, and concentrated. The crude material was purified by flash chromatography on silica with 0-25% ethyl acetate in hexanes to provide the title compound.

EXAMPLE 150E

2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-enecarbaldehyde

Into a 100 mL round-bottomed flask was added EXAMPLE 150D (0.3 g) and Dess-Martin Periodinane (0.6 g) in dichloromethane (10 mL) to give a suspension. The mixture
5 was stirred at room temperature overnight. After filtration, the mixture was washed with saturated aqueous NaHCO₃ (2x 20 mL), dried over Na₂SO₄, filtered, and concentrated. The crude product was purified by flash chromatography on silica with 0-25% ethyl acetate in hexanes to provide the title compound.

10

EXAMPLE 150F

Methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 150E for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 15F for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

15

EXAMPLE 150G

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 150F for EXAMPLE 101E in EXAMPLE 101F.

20

EXAMPLE 150H

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

25

The title compound was prepared by substituting EXAMPLE 150G for EXAMPLE 3J and EXAMPLE 1F for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500 MHz, dimethyl sulfoxide-d₆) δ 11.50 (s, 1H), 8.36 (m, 1H), 8.32 (m, 1H), 7.91 (d, 1H), 7.59 (m, 2H), 7.40 (t, 1H), 7.35 (d, 2H), 7.25 (m, 1H), 6.94 (d, 2H), 6.79 (d, 1H), 6.60 (m, 1H), 6.29 (m, 1H), 6.24
30 (d, 1H), 3.83 (m, 2H), 3.25 (m, 4H), 2.98 (m, 4H), 2.42 (s, 2H), 2.14 (m, 6H), 1.60 (m, 6H), 1.25 (m, 3H), 0.86 (s, 6H)

EXAMPLE 151

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
(1-[2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl)amino]-3-nitrophenyl)sulfonyl}-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5

EXAMPLE 151A

1-(1,3-difluoropropan-2-yl)azetidin-3-amine

To a solution of tert-butyl azetidin-3-ylcarbamate (0.256 g) and 1,3-difluoropropan-2-
one (0.154 g) in dichloromethane (2 mL) was added sodium triacetoxyborohydride (0.473 g)
10 and the reaction was allowed to stirred at room temperature. After 16 hours, the reaction was
quenched with saturated NaHCO₃ solution (10 mL) and extracted into dichloromethane (25
mL). The organic layer was dried and concentrated. Silica gel chromatography
(GraceResolv 12 g) eluting with a gradient of 0.5% to 3.5% methanol/dichloromethane
followed by treatment with HCl (4.0M in dioxane, 3 mL) and methanol (0.5 mL) for 2 hours
15 gave the title compound after concentration.

EXAMPLE 151B

4-(1-(1,3-difluoropropan-2-yl)azetidin-3-ylamino)-3-nitrobenzenesulfonamide

To a suspension of 4-chloro-3-nitrobenzenesulfonamide (0.225 g) and 1-(1,3-
20 difluoropropan-2-yl)azetidin-3-amine (0.193 g) in dioxane (5 mL) was added
diisopropylamine (0.832 mL). The reaction was sonicated and then heated to 100°C. After
stirring overnight, the reaction was concentrated and loaded onto silica gel (GraceResolv 12
g) and eluted with a gradient of 0.5% to 3.5% methanol/dichloromethane to give the title
compound.

25

EXAMPLE 151C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
(1-[2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl)amino]-3-nitrophenyl)sulfonyl}-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

30

The title compound was prepared by substituting EXAMPLE 151B for EXAMPLE
1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. ¹H NMR (300 MHz,
dimethylsulfoxide-d₆) δ 11.66 (s, 1H), 11.54 - 11.28 (m, 1H), 8.54 (d, 1H), 8.45 (s, 1H), 8.01
(d, 1H), 7.82 (d, 1H), 7.48 (d, 3H), 7.34 (d, 2H), 7.04 (d, 2H), 6.90 (d, 1H), 6.67 (d, 1H), 6.37

(s, 1H), 6.20 (s, 1H), 4.64 - 4.23 (m, 6H), 3.81 (s, 2H), 3.08 (s, 4H), 2.75 (s, 3H), 2.15 (s, 7H), 1.95 (s, 2H), 1.38 (s, 2H), 0.92 (s, 6H).

EXAMPLE 152

5 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
([1-(methylsulfonyl)pyrrolidin-3-yl]methyl)amino]-3-nitrophenyl]sulfonyl}-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 152A

10 tert-butyl (1-(methylsulfonyl)pyrrolidin-3-yl)methylcarbamate

The title compound was prepared by substituting tert-butyl pyrrolidin-3-ylmethylcarbamate for tert-butyl piperidin-3-ylmethylcarbamate in EXAMPLE 147A.

EXAMPLE 152B

15 (1-(methylsulfonyl)pyrrolidin-3-yl)methanamine

The title compound was prepared by substituting EXAMPLE 152A for EXAMPLE 147A in EXAMPLE 147B.

EXAMPLE 152C

20 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
([1-(methylsulfonyl)pyrrolidin-3-yl]methyl)amino]-3-nitrophenyl]sulfonyl}-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 152B for EXAMPLE
25 147B in EXAMPLE 147C. ¹H NMR (400MHz, dimethylsulfoxide-d₆) δ11.60 (s, 1H), 8.49
(m, 2H), 7.99 (s, 1H), 7.73 (m, 1H), 7.53 (d, 1H), 7.47 (s, 1H), 7.42 (m, 1H), 7.34 (d, 2H),
7.04 (m, 3H), 6.65 (m, 1H), 6.35 (s, 1H), 6.22 (s, 1H), 3.41 (m, 4H), 3.22 (m, 2H), 3.03 (m,
4H), 2.89 (s, 3H), 2.73 (m, 2H), 2.59 (m, 1H), 2.17 (m, 6H), 2.00 (m, 4H), 1.68 (m, 1H), 1.38
(t, 2H), 0.92 (s, 6H).

30

EXAMPLE 153

N-[(4-[(1-acetylpyrrolidin-3-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 153A

tert-butyl (1-acetylpyrrolidin-3-yl)methylcarbamate

The title compound was prepared by substituting tert-butyl pyrrolidin-3-ylmethylcarbamate for tert-butyl piperidin-3-ylmethylcarbamate and acetyl chloride for methanesulfonyl chloride in EXAMPLE 147A.

EXAMPLE 153B

1-(3-(aminomethyl)pyrrolidin-1-yl)ethanone

The title compound was prepared by substituting EXAMPLE 153A for EXAMPLE 147A in EXAMPLE 147B.

EXAMPLE 153C

N-[(4-[(1-acetylpyrrolidin-3-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 153B for EXAMPLE 147B in EXAMPLE 147C. ¹H NMR (400MHz, dimethylsulfoxide-d₆) δ 11.66 (s, 1H), 8.62 (m, 1H), 8.54 (s, 1H), 8.03 (m, 1H), 7.78 (d, 1H), 7.50 (m, 3H), 7.35 (t, 2H), 7.09 (s, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.37 (d, 1H), 6.20 (s, 1H), 3.56 (m, 1H), 3.42 (m, 4H), 3.43 (m, 4H), 3.23 (m, 1H), 3.07 (m, 4H), 2.74 (m, 2H), 2.16 (m, 6H), 1.93 (m, 5H), 1.38 (t, 2H), 0.93 (s, 6H).

EXAMPLE 154

N-[(4-[(3R)-1-acetylpyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 154A

(R)-tert-butyl 1-acetylpyrrolidin-3-ylcarbamate

The title compound was prepared by substituting (R)-tert-butyl pyrrolidin-3-ylcarbamate for tert-butyl piperidin-3-ylmethylcarbamate and acetyl chloride for methanesulfonyl chloride in EXAMPLE 147A.

EXAMPLE 154B

(R)-1-(3-aminopyrrolidin-1-yl)ethanone

The title compound was prepared by substituting EXAMPLE 154A for EXAMPLE 147A in EXAMPLE 147B.

EXAMPLE 154C

N-[(4-{[(3R)-1-acetylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 154B for EXAMPLE 147B in EXAMPLE 147. ¹H NMR (400MHz, dimethylsulfoxide-d₆) δ 11.61 (s, 1H), 8.50 (s, 1H), 8.17 (d, 1H), 7.98 (s, 1H), 7.78 (s, 1H), 7.49 (m, 3H), 7.34 (d, 2H), 7.10 (m, 1H), 7.04 (d, 2H), 6.66 (dd, 1H), 6.35 (s, 1H), 6.22 (s, 1H), 4.34 (m, 1H), 3.81 (m, 1H), 3.58 (m, 1H), 3.43 (m, 1H), 3.05 (m, 4H), 2.74 (s, 2H), 2.19 (m, 9H), 1.96 (m, 5H), 1.38 (t, 2H), 0.94 (s, 6H).

EXAMPLE 155

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-methoxy-2,2-dimethylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 120B using 3-methoxy-2,2-dimethylpropan-1-amine in place of EXAMPLE 120A. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.69 (s, 1H), 11.32 (s, 1H), 8.92 (t, 1H), 8.57 (d, 1H), 8.04 (d, 1H), 7.80 (dd, 1H), 7.46 - 7.55 (m, 3H), 7.34 (d, 2H), 7.08 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.36 - 6.42 (m, 1H), 6.19 (d, 1H), 3.25 - 3.30 (m, 5H), 3.19 (s, 2H), 3.07 (s, 4H), 2.76 (s, 2H), 2.17 (d, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.96 (s, 6H), 0.92 (s, 6H).

EXAMPLE 156

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
({[(1R,3R)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5

EXAMPLE 156A

4-(((1R,3R)-3-hydroxycyclopentyl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting (1R,3R)-3-

10 hydroxycyclopentyl)methylamine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 156B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
({[(1R,3R)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

15

The title compound was prepared by substituting EXAMPLE 156A for EXAMPLE
130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 13.05 (s, 1H), 9.29 (s, 1H),
8.62 (t, 1H), 8.43 (d, 1H), 8.32 (dd, 1H), 8.10 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d,
2H), 6.85 (d, 1H), 6.74 (dd, 1H), 6.54 (s, 1H), 6.49 (m, 1H), 4.60 (m, 1H), 3.19 (dd, 2H), 3.06
20 (m, 4H), 2.77 (s, 2H), 2.70 (m, 1H), 2.26 (t, 2H), 2.20-2.07 (m, 6H), 2.00 (m, 1H), 1.97 (s,
2H), 1.90 (m, 1H), 1.56 (m, 1H), 1.39 (t, 2H), 1.34 (m, 1H), 0.93 (s, 6H).

EXAMPLE 157

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
25 ({[(1S,3S)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

EXAMPLE 157A

4-(((1S,3S)-3-hydroxycyclopentyl)methylamino)-3-nitrobenzenesulfonamide

30 The title compound was prepared by substituting (1S, 3S)-3-
hydroxycyclopentyl)methylamine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 157B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
(((1S,3S)-3-hydroxycyclopentyl)methyl)amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

5 The title compound was prepared by substituting EXAMPLE 157A for EXAMPLE
130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 13.03 (s, 1H), 9.29 (s, 1H),
8.60 (t, 1H), 8.44 (d, 1H), 8.32 (dd, 1H), 8.14 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d,
2H), 6.83 (d, 1H), 6.75 (dd, 1H), 6.55 (s, 1H), 6.49 (m, 1H), 4.60 (m, 1H), 3.19 (dd, 2H), 3.06
(m, 4H), 2.77 (s, 2H), 2.70 (m, 1H), 2.26 (t, 2H), 2.20-2.07 (m, 6H), 2.00 (m, 1H), 1.97 (s,
10 2H), 1.90 (m, 1H), 1.56 (m, 1H), 1.39 (t, 2H), 1.34 (m, 1H), 0.93 (s, 6H).

EXAMPLE 158

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
(((1S,3R)-3-hydroxycyclopentyl)methyl)amino)-3-nitrophenyl]sulfonyl}-2-(1H-
15 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 158A

4-(((1S,3R)-3-hydroxycyclopentyl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting (1S, 3R)-3-
20 hydroxycyclopentyl)methylamine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 158B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
(((1S,3R)-3-hydroxycyclopentyl)methyl)amino)-3-nitrophenyl]sulfonyl}-2-(1H-
25 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 158A for EXAMPLE
130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 12.94 (s, 1H), 9.25 (d, 1H),
8.59 (t, 1H), 8.48 (d, 1H), 8.27 (m, 2H), 7.66 (m, 2H), 7.45 (d, 2H), 7.08 (d, 2H), 6.77 (dd,
1H), 6.72 (d, 1H), 6.60 (d, 1H), 6.47 (m, 1H), 4.53 (m, 1H), 3.30 (m, 2H), 3.06 (m, 4H), 2.78
30 (s, 2H), 2.27 (m, 3H), 2.19-2.10 (m, 5H), 1.98 (m, 3H), 1.85-1.66 (m, 4H), 1.39 (t, 2H), 0.94
(s, 6H).

EXAMPLE 159

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
([[(1R,3S)-3-hydroxycyclopentyl]methyl]amino)-3-nitrophenyl]sulfonyl}-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5

EXAMPLE 159A

4-(((1R,3S)-3-hydroxycyclopentyl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting (1R, 3S)-3-hydroxycyclopentyl)methylamine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

10

EXAMPLE 159B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
([[(1R,3S)-3-hydroxycyclopentyl]methyl]amino)-3-nitrophenyl]sulfonyl}-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

15

The title compound was prepared by substituting EXAMPLE 158A for EXAMPLE 130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 13.02 (s, 1H), 9.28 (d, 1H), 8.59 (t, 1H), 8.44 (d, 1H), 8.29 (d, 1H), 8.13 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.08 (d, 2H), 6.82 (dd, 1H), 6.74 (d, 1H), 6.55 (d, 1H), 6.48 (m, 1H), 4.53 (m, 1H), 3.34 (m, 2H), 3.06 (m, 4H), 2.77 (s, 2H), 2.27 (m, 3H), 2.19-2.10 (m, 5H), 1.97 (m, 3H), 1.85-1.66 (m, 4H), 1.39 (t, 2H), 0.93 (s, 6H).

20

EXAMPLE 160

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

25

The title compound was prepared by substituting (S)-3-aminopiperidin-2-one for 1-acetylpiperidin-4-amine in EXAMPLE 53B. ¹H NMR (300MHz, dimethylsulfoxide-d₆) δ 11.68 (br s, 1H), 8.88 (d, 1H), 8.57 (d, 1H), 8.04 (d, 1H), 7.95 (br s, 1H), 7.83 (dd, 1H), 7.55-7.46 (m, 3H), 7.35 (d, 2H), 7.16 (d, 1H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.38 (m, 1H), 6.21 (d, 1H), 4.41 (m, 1H), 3.22 (m, 2H), 3.09 (br s, 4H), 2.78 (br s, 2H), 2.35-2.09 (m, 8H), 1.96 (br s, 2H), 1.86 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

30

EXAMPLE 161

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
[(1-[2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-
(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5

EXAMPLE 161A

tert-butyl 3-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-
dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-
nitrophenylamino)methyl)azetidine-1-carboxylate

10

EXAMPLE 82 (305 mg), tert-butyl 3-(aminomethyl)azetidine-1-carboxylate (86 mg)
and diisopropyl amine (0.202 mL) in dioxane (3 mL) were heated to 110°C. After stirring
overnight, the reaction was concentrated. Silica gel chromatography (Reveleris, 12 g) eluting
with a gradient of 0.5% to 3% methanol/dichloromethane (Flow = 36 ml/minute) gave the
title compound.

15

EXAMPLE 161B

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(4-(azetidin-3-ylmethylamino)-3-
nitrophenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-
enyl)methyl)piperazin-1-yl)benzamide

20

To a solution of EXAMPLE 161A (0.257 g) in dichloromethane (5 mL) was added
trifluoroacetic acid (0.211 mL). After 30 minutes an additional 0.2 mL of trifluoroacetic acid
was added. After 3 hours, the reaction was concentrated to give the title compound.

EXAMPLE 161C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
[(1-[2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-
(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

A solution of EXAMPLE 161B (0.118 g), sodium triacetoxyborohydride (0.035 g)
and 1,3-difluoropropan-2-one (0.012 g) were stirred together in dichloromethane (1 mL)
overnight. The reaction was quenched with saturated aqueous NaHCO₃ solution (10 mL) and
extracted into dichloromethane (30 mL). The organic layer was dried and concentrated.
Silica gel chromatography (Reveleris 12 g) eluting with a gradient of 0.5% to 3.5%
methanol/dichloromethane over 30 minutes (Flow = 36 ml/min) gave the title compound. ¹H
NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.67 (s, 1H), 11.47 - 11.21 (m, 1H), 8.85 (s, 1H),

30

8.55 (d, 1H), 8.03 (d, 1H), 7.80 (dd, 1H), 7.54 - 7.45 (m, 3H), 7.33 (s, 2H), 7.04 (d, 3H), 6.67 (d, 1H), 6.38 (dd, 1H), 6.20 (d, 1H), 4.43 (dt, 4H), 3.56 (t, 2H), 3.46 (s, 2H), 3.12 (m, 6H), 2.74 (m, 3H), 2.17 (m, 7H), 1.95 (s, 2H), 1.39 (d, 2H), 0.92 (s, 6H).

5

EXAMPLE 162

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

10

The title compound was prepared by substituting oxetan-3-one for 1,3-difluoropropan-2-one in EXAMPLE 161C. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.66 (s, 1H), 11.51 - 11.03 (m, 1H), 8.81 (s, 1H), 8.54 (d, 1H), 8.02 (d, 1H), 7.79 (dd, 1H), 7.50 (dd, 3H), 7.34 (d, 2H), 7.04 (d, 3H), 6.67 (d, 1H), 6.38 (dd, 1H), 6.20 (d, 1H), 4.57 (s, 2H), 4.43 - 4.35 (m, 2H), 3.82 (s, 1H), 3.59 (t, 2H), 3.44 (t, 2H), 3.20 (s, 2H), 3.06 (s, 4H), 2.73 (s, 3H), 2.18 (s, 6H), 1.95 (s, 2H), 1.39 (d, 2H), 0.92 (s, 6H).

15

EXAMPLE 163

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

20

EXAMPLE 163A

tert-butyl 4-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)methyl)piperidine-1-carboxylate

25

The title compound was prepared by substituting tert-butyl 4-(aminomethyl)piperidine-1-carboxylate for 1-acetylpiperidin-4-amine in EXAMPLE 53B.

EXAMPLE 163B

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-(piperidin-4-ylmethylamino)phenylsulfonyl)benzamide

30

The title compound was prepared by substituting EXAMPLE 163A for EXAMPLE 1A in EXAMPLE 1B.

EXAMPLE 163C

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

5 The title compound was prepared by substituting EXAMPLE 163B for EXAMPLE 161B and oxetan-3-one for 1,3-difluoropropan-2-one in EXAMPLE 161C. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.68 (s, 1H), 8.60 (t, 1H), 8.54 (d, 1H), 8.03 (d, 1H), 7.79 (dd, 1H), 7.50 (m, 3H), 7.34 (d, 2H), 7.09 (d, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.39 (m, 1H), 6.19 (d, 1H), 4.55 (t, 2H), 4.46 (t, 2H), 3.52 (br s, 1H), 3.28 (m, 2H), 3.17 (d, 1H), 3.06
10 (m, 4H), 2.82 (m, 2H), 2.74 (m, 2H), 2.17 (m, 6H), 1.95 (m, 3H), 1.72 (m, 3H), 1.38 (t, 2H), 1.28 (m, 2H), 0.92 (s, 6H).

EXAMPLE 164

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-cyclopropylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

 The title compound was prepared by substituting EXMAPLE 163B for (S)-tert-butyl pyrrolidin-3-ylcarbamate in EXAMPLE 142A. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.96 (br s, 1H), 11.62 (br s, 1H), 8.50 (m, 2H), 7.98 (d, 1H), 7.72 (m, 1H), 7.52 (d, 1H), 7.45
20 (m, 2H), 7.34 (d, 2H), 7.04 (m, 2H), 6.94 (m, 1H), 6.64 (dd, 1H), 6.34 (m, 1H), 6.22 (d, 1H), 3.28 (m, 3H), 3.04 (m, 5H), 2.72 (s, 2H), 2.64 (m, 1H), 2.64 (m, 1H), 2.36 (m, 1H), 2.16 (m, 7H), 1.95 (s, 2H), 1.68 (m, 3H), 1.38 (t, 2H), 1.18 (m, 3H), 0.94 (s, 6H), 0.35 (m, 3H).

EXAMPLE 165

25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-(2-fluoroethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 165A

30 4-((4-(2-fluoroethyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

 The title compound was prepared by substituting 2-fluoro-ethyl bromide for methyl iodide in EXAMPLE 134B.

EXAMPLE 165B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
([4-(2-fluoroethyl)morpholin-2-yl]methyl)amino]-3-nitrophenyl]sulfonyl}-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5 The title compound was prepared by substituting EXAMPLE 165A for EXAMPLE 130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 13.00 (s, 1H), 9.26 (d, 1H), 8.87 (t, 1H), 8.43 (d, 1H), 8.32 (dd, 1H), 8.11 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.92 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (dd, 1H), 3.93 (m, 1H), 4.63, 4.51 (dt, 2H), 3.95-3.85 (m, 2H), 3.68 (dt, 1H), 3.43-3.37 (m, 2H), 3.07 (m, 4H), 2.92 (d, 1H), 2.77 (s, 2H), 2.65 (m, 2H), 2.59 (m, 1H), 2.26 (m, 2H), 2.17-2.08 (m, 5H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

EXAMPLE 166

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
15 ([4-(2,2-difluoroethyl)morpholin-2-yl]methyl)amino]-3-nitrophenyl]sulfonyl}-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 166A

4-((4-(2,2-difluoroethyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 2,2-difluoro-ethyl bromide for
20 methyl iodide in EXAMPLE 134B.

EXAMPLE 166B

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}-2-(1H-
25 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 166A for EXAMPLE 130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 13.01 (s, 1H), 9.26 (d, 1H), 8.86 (t, 1H), 8.43 (d, 1H), 8.34 (dd, 1H), 8.11 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.93 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 6.31, 6.20, 6.09 (tt, 1H), 3.90 (m, 1H), 3.85 (d, 1H), 3.67 (dt, 1H), 3.49-3.30 (m, 2H), 3.07 (m, 4H), 2.84 (d, 1H), 2.82-2.75 (m, 4H), 2.69 (d, 1H), 2.33 (dt, 1H), 2.27-2.20 (m, 3H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

EXAMPLE 167

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
[(4-fluoro-1-oxetan-3-yl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

5

EXAMPLE 167A

4-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 173A for tert-butyl
piperazine-1-carboxylate and 3-oxetanone for 4'-chlorobiphenyl-2-carboxaldehyde in

10 EXAMPLE 1A.

EXAMPLE 167B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
[(4-fluoro-1-oxetan-3-yl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

15

The title compound was prepared by substituting EXAMPLE 167A for EXAMPLE
11B in EXAMPLE 11D. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.69 (s, 1H), 8.39 (s,
1H), 8.09 (d, 1H), 8.04 (d, 1H), 7.52 (m, 4H), 7.35 (d, 2H), 7.05 (m, 2H), 6.68 (dd, 1H), 6.40
(dd, 1H), 6.20 (s, 1H), 4.57 (t, 2H), 4.48 (m, 2H), 4.38 (d, 2H), 4.02 (m, 1H), 3.63 (m, 2H),
20 3.08 (m, 4H), 2.74 (m, 4H), 2.17 (m, 6H), 1.88 (m, 6H), 1.40 (t, 2H), 0.93 (s, 6H).

EXAMPLE 168

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
{[(2S)-4,4-difluoro-1-oxetan-3-yl]pyrrolidin-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

25

EXAMPLE 168A

(S)-methyl 4,4-difluoropyrrolidine-2-carboxylate

(S)-1-tert-butyl 2-methyl 4,4-difluoropyrrolidine-1,2-dicarboxylate (0.472 g) in
30 CH₂Cl₂ (1 mL) was treated with trifluoroacetic acid (1.4 mL), stirred at ambient temperature
for 4 hours, and concentrated. The product was free-based using a MEGA BE-SCX column
with 1:1 CH₂Cl₂/methanol as eluent for the trifluoroacetic acid. The product was released
from the column with 5% (7 M ammonia in methanol) in CH₂Cl₂ as eluent.

EXAMPLE 168B

(S)-methyl 4,4-difluoro-1-(oxetan-3-yl)pyrrolidine-2-carboxylate

5 The title compound was prepared by substituting EXAMPLE 168A for tert-butyl piperazine-1-carboxylate and 3-oxetanone for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

EXAMPLE 168C

(S)-(4,4-difluoro-1-(oxetan-3-yl)pyrrolidin-2-yl)methanol

10 EXAMPLE 168B (0.180 g) in tetrahydrofuran (3 mL) was treated sequentially with a solution of calcium chloride (0.245 g) in ethanol (3 mL) and NaBH₄ (0.167 g) and then stirred at ambient temperature for 7 hours. The reaction was quenched with saturated aqueous NH₄Cl solution and extracted with ethyl acetate. The combined extracts were washed with brine, dried (MgSO₄), filtered, concentrated and chromatographed on silica gel
15 with 50% ethyl acetate in hexanes as eluent to give the product.

EXAMPLE 168D

(S)-4-((4,4-difluoro-1-(oxetan-3-yl)pyrrolidin-2-yl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 168C for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

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EXAMPLE 168E

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(4-
{[(2S)-4,4-difluoro-1-oxetan-3-yl]pyrrolidin-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

25 The title compound was prepared by substituting EXAMPLE 168D for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.69 (s, 1H), 8.38 (s, 1H), 8.06 (m, 2H), 7.49 (m, 4H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.40 (m, 1H), 6.21 (s, 1H), 4.54 (m, 3H), 4.43 (t, 1H), 4.23 (m, 1H), 4.12 (m, 2H), 3.44 (m, 2H), 3.12 (m, 7H), 2.58 (m, 1H), 2.29 (m, 7H), 1.97 (s, 2H), 1.40 (t, 2H), 0.93 (s, 6H).

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EXAMPLE 169

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

EXAMPLE 169A

tert-butyl 3-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)methyl)morpholine-4-carboxylate

The title compound was prepared as described in EXAMPLE 53B by replacing 1-acetylpiperidin-4-amine with tert-butyl 3-(aminomethyl)morpholine-4-carboxylate.

EXAMPLE 169B

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(4-(morpholin-3-ylmethylamino)-3-nitrophenylsulfonyl)benzamide

The title compound was prepared as described in EXAMPLE 139B by replacing EXAMPLE 139A with EXAMPLE 169A.

EXAMPLE 169C

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

The title compound was prepared as described in EXAMPLE 139C by replacing EXAMPLE 139B and oxetan-3-one with EXAMPLE 169B and tetrahydropyran-4-one, respectively. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.69 (s, 1H), 8.77 (m, 1H), 8.57 (d, 1H), 8.05 (d, 1H), 7.84 (dd, 1H), 7.52 (m, 3H), 7.34 (m, 2H), 7.03 (m, 3H), 6.68 (dd, 1H), 6.40 (dd, 1H), 6.18 (d, 1H), 3.86 (m, 2H), 3.72 (m, 2H), 3.11 (m, 6H), 2.74 (m, 4H), 2.20 (m, 6H), 1.95 (m, 3H), 1.51 (m, 7H), 0.92 (s, 6H).

EXAMPLE 170

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
5 {[(4-cyclobutylmorpholin-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 139C by replacing
EXAMPLE 139B and oxetan-3-one with EXAMPLE 169B and cyclobutanone. ¹H NMR
(300 MHz, dimethylsulfoxide-d₆) δ 11.68 (s, 1H), 8.72 (s, 1H), 8.57 (d, 1H), 8.04 (d, 1H),
7.84 (dd, 1H), 7.52 (m, 3H), 7.34 (m, 3H), 7.03 (m, 4H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.18
10 (d, 1H), 3.47 (m, 3H), 3.10 (m, 6H), 2.72 (m, 6H), 2.25 (m, 8H), 1.95 (m, 4H), 1.56 (m, 3H),
1.38 (m, 2H), 0.92 (s, 6H).

EXAMPLE 171

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-
15 nitro-4-{[(4-tetrahydrofuran-3-ylmorpholin-3-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 139C by replacing
EXAMPLE 139B and oxetan-3-one with EXAMPLE 169B and 3-oxotetrahydrofuran,
respectively. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.64 (s, 1H), 8.66 (s, 1H), 8.53
20 (d, 1H), 8.01 (d, 1H), 7.80 (d, 1H), 7.50 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.98 (d, 1H),
6.66 (dd, 1H), 6.37 (d, 1H), 6.19 (d, 1H), 3.68 (m, 8H), 3.05 (m, 6H), 2.85 (m, 3H), 2.73 (s,
2H), 2.25 (m, 6H), 1.91 (m, 3H), 1.37 (m, 3H), 0.95 (m, 6H).

EXAMPLE 172

25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
[(1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-
2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 163B for tert-butyl
piperazine-1-carboxylate and 1,3-difluoropropan-2-one for 4'-chlorobiphenyl-2-
30 carboxaldehyde in EXAMPLE 1A. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.67 (s,
1H), 11.40 (br s, 1H), 8.57 (m, 2H), 8.03 (d, 1H), 7.78 (d, 1H), 7.50 (m, 3H), 7.34 (d, 2H),
7.07 (d, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.38 (m 1H), 6.19 (d, 1H), 4.63 (d, 2H), 4.53 (d,

2H), 3.28 (m, 2H), 3.07 (m, 4H), 2.89 (m, 2H), 2.74 (m, 2H), 2.40 (m, 2H), 2.16 (m, 6H), 1.95 (s, 2H), 1.67 (m, 3H), 1.38 (t, 2H), 1.23 (m, 3H), 0.94 (s, 6H).

EXAMPLE 173

5 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropyl-4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 173A

10 4-((4-fluoropiperidin-4-yl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 126B for EXAMPLE 1A in EXAMPLE 1B.

EXAMPLE 173B

15 4-((1-cyclopropyl-4-fluoropiperidin-4-yl)methoxy)-3-nitrobenzenesulfonamide

To EXAMPLE 173A (0.24 g) in methanol (3 mL) was added 3 Å molecular sieves (0.1 g), followed sequentially by acetic acid (0.31 mL), (1-ethoxycyclopropoxy)trimethylsilane (0.64 mL), and sodium cyanoborohydride (0.148 g). The reaction was heated under reflux overnight. After cooling, the reaction mixture was loaded
20 onto a silica gel column. After drying, the column was eluted with 100:2:0.2 ethyl acetate/methanol/NH₄OH to give the title compound.

EXAMPLE 173C

25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropyl-4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 173B for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.65 (s, 1H), 8.33 (s, 1H), 8.01 (m, 2H), 7.53 (d, 1H), 7.48-7.49 (m, 2H), 7.34-7.38 (m, 3H), 7.04 (d, 2H), 6.66 (dd, 1H), 6.38 (dd, 1H), 6.21 (d, 1H), 4.32 (d, 2H), 3.70-3.77 (m, 2H), 3.07 (s, 4H),
30 2.92 (s, 2H), 2.80 (s, 2H), 2.58 (s, 2H), 2.25 (s, 4H), 2.13-2.16 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H), 0.40-0.49 (m, 4H).

EXAMPLE 174

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
[(4-methoxybenzyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-
yloxy)benzamide

5 A suspension of EXAMPLE 53A (120 mg), (4-methoxyphenyl)methanamine (31 mg)
and Hunig'sBase (0.159 mL) in dimethylsulfoxide (2 mL) was heated for 2 hours at 150 °C in
a Biotage Initiator microwave reactor. The reaction mixture was diluted with methanol (2
mL) and purified by reverse phase HPLC (C8, 30% - 100% CH₃CN/water/0.1%
trifluoroacetic acid). ¹H NMR (500 MHz, pyridine-d₅) δ 13.07 (s, 1H), 9.32 (d, 1H), 9.17 (t,
10 1H), 8.43 (d, 1H), 8.28 (dd, 1H), 8.08 (d, 1H), 7.64 - 7.68 (m, 2H), 7.44 (d, 2H), 7.38 (d, 2H),
7.07 (d, 2H), 6.97 - 7.02 (m, 2H), 6.90 (d, 1H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.49 (dd, 1H),
4.55 (d, 2H), 3.68 (s, 3H), 3.03 - 3.09 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.10 - 2.17 (m, 4H),
1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

15 EXAMPLE 175

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

The title compound was prepared by substituting (3-
20 trifluoromethoxyphenyl)methanamine for (4-methoxyphenyl)methanamine in EXAMPLE
174. ¹H NMR (500 MHz, pyridine-d₅) δ 13.06 (s, 1H), 9.38 (t, 1H), 9.31 (d, 1H), 8.42 (d,
1H), 8.28 (dd, 1H), 8.08 (d, 1H), 7.65 (ddd, 2H), 7.41 - 7.46 (m, 3H), 7.36 - 7.40 (m, 2H),
7.07 (d, 2H), 6.88 (d, 1H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.49 (d, 1H), 4.73 (d, 2H), 3.02 - 3.08
(m, 4H), 2.77 (s, 2H), 2.22 - 2.28 (m, 2H), 2.09 - 2.16 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H),
25 0.93 (s, 6H).

EXAMPLE 176

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
[(3-methoxybenzyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-
30 yloxy)benzamide

The title compound was prepared by substituting (3-methoxyphenyl)methanamine for
(4-methoxyphenyl)methanamine in EXAMPLE 174. ¹H NMR (500 MHz, pyridine-d₅) δ
13.06 (s, 1H), 9.27 - 9.32 (m, 2H), 8.42 (d, 1H), 8.26 (dd, 1H), 8.08 (d, 1H), 7.64 - 7.67 (m,

2H), 7.44 (d, 2H), 7.32 (t, 1H), 7.14 (s, 1H), 7.04 - 7.09 (m, 3H), 6.88 - 6.94 (m, 2H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.48 - 6.50 (m, 1H), 4.64 (d, 2H), 3.68 (s, 3H), 3.03 - 3.09 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.10 - 2.18 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

5

EXAMPLE 177

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(difluoromethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting (4-

10 difluoromethoxyphenyl)methanamine for (4-methoxyphenyl)methanamine in EXAMPLE 174. ¹H NMR (500 MHz, pyridine-d₅) δ 13.06 (s, 1H), 9.32 (d, 1H), 9.28 (t, 1H), 8.42 (d, 1H), 8.28 (dd, 1H), 8.07 (d, 1H), 7.66 (t, 1H), 7.64 (d, 1H), 7.58 (s, 1H), 7.44 (s, 2H), 7.26 (s, 1H), 7.25 (d, 1H), 7.07 (d, 2H), 6.87 (d, 1H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.49 (dd, 1H), 4.64 (d, 2H), 3.03 - 3.10 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.11 - 2.17 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

15

EXAMPLE 178

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-(1,4-dioxaspiro[4.5]dec-8-ylamino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

20

The title compound was prepared by substituting 1,4-dioxaspiro[4.5]dec-8-ylamine for 1-acetylpiperidin-4-amine in EXAMPLE 53B. ¹H NMR (300MHz, dimethylsulfoxide-d₆) δ 11.67 (br s, 1H), 8.55 (d, 1H), 8.26 (d, 1H), 8.04 (d, 1H), 7.81 (dd, 1H), 7.54-7.46 (m, 3H), 7.35 (d, 2H), 7.15 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.38 (m, 1H), 6.19 (d, 1H), 3.89 (s, 4H), 3.78 (m, 1H), 3.07 (br s, 4H), 2.78 (br s, 2H), 2.28-2.11 (m, 6H), 2.00-1.88 (m, 4H), 1.75-1.57 (m, 4H), 1.54-1.35 (m, 4H), 0.92 (s, 6H).

25

EXAMPLE 179

Trans-N-[(4-{[4-(acetylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

30

EXAMPLE 179A

tert-butyl trans-4-acetamidocyclohexylcarbamate

Tert-butyl (trans)-4-aminocyclohexylcarbamate (1.500 g) and triethylamine (2.93 mL, 2.125 g) were added to dichloromethane and stirred until the tert-butyl (trans)-4-aminocyclohexylcarbamate had dissolved completely. Acetyl chloride (0.577 g) was added slowly, and the solution was stirred at room temperature for 16 hours. The solvent was removed, and the residue taken up in ethyl acetate, washed with pH 4 buffer, washed with brine, dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under vacuum.

EXAMPLE 179B

N-(trans-4-aminocyclohexyl)acetamide

The title compound was prepared by substituting EXAMPLE 179A for EXAMPLE 1A in EXAMPLE 1B.

EXAMPLE 179C

Trans-N-[(4-{[4-(acetylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 179B for 1-acetyl piperidin-4-amine in EXAMPLE 53B. ¹H NMR (300MHz, dimethylsulfoxide-d₆) δ 11.67 (br s, 1H), 8.55 (d, 1H), 8.20 (d, 1H), 8.04 (d, 1H), 7.82-7.76 (m, 2H), 7.53-7.46 (m, 3H), 7.35 (d, 2H), 7.16 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (m, 1H), 6.19 (d, 1H), 3.57 (m, 2H), 3.07 (br s, 4H), 2.75 (br s, 2H), 2.28-2.10 (m, 6H), 2.03-1.94 (m, 4H), 1.83 (d, 2H), 1.80 (s, 3H), 1.55-1.24 (m, 6H), 0.92 (s, 6H).

EXAMPLE 180

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]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 180A

(R)-tert-butyl 1-(2,2-difluoroethyl)pyrrolidin-3-ylcarbamate

To a solution of (R)-tert-butyl pyrrolidin-3-ylcarbamate (500 mg) and 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 mixture was stirred at 70 °C for 72 hours. The reaction mixture was concentrated and the crude product was purified on silica gel with
 5 methanol / dichloromethane.

EXAMPLE 180B

(R)-1-(2,2-difluoroethyl)pyrrolidin-3-amine

To a solution of EXAMPLE 180A (525 mg) in a mixture of dichloromethane (3 mL)
 10 and methanol (4.0 mL) was added hydrogen chloride, 4M in dioxane (5.24 mL) and the reaction was stirred for 1.5 hours. The reaction was concentrated and the crude material was taken up in dichloromethane and the solvent evaporated, then taken up in ether and the solvent evaporated, and then dried on high vacuum.

15 EXAMPLE 180C

(R)-4-(1-(2,2-difluoroethyl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 180B for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 180D

20 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]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 180C for EXAMPLE 130C in EXAMPLE 130D. ¹H NMR (500 MHz, pyridine- d₅) δ 13.02 (m, 1H), 9.27 (d, 1H),
 25 8.55 (d, 1H), 8.43 (d, 1H), 8.35 (dd, 1H), 8.10 (d, 1H), 7.64 - 7.68 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.83 (d, 1H), 6.75 (dd, 1H), 6.54 (m, 1H), 6.48 (m, 1H), 6.04 - 6.29 (m, 1H), 4.06 (m, 1H), 3.07 (m, 4H), 2.83 - 2.95 (m, 4H), 2.74 - 2.82 (m, 3H), 2.47 (m, 1H), 2.09 - 2.30 (m, 8H), 1.97 (s, 2H), 1.67 (m, 1H), 1.39 (t, 2H), 0.93 (s, 6H).

30 EXAMPLE 181

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 181A

(S)-tert-butyl 1-(2-fluoroethyl)pyrrolidin-3-ylcarbamate

The title compound was prepared by substituting 1-fluoro-2-iodoethane for 1,1-difluoro-2-iodoethane and (S)-tert-butyl pyrrolidin-3-ylcarbamate for (R)-tert-butyl
5 pyrrolidin-3-ylcarbamate in EXAMPLE 180A.

EXAMPLE 181B

(S)-1-(2-fluoroethyl)pyrrolidin-3-amine

The title compound was prepared by substituting EXAMPLE 181A for EXAMPLE
10 180A in EXAMPLE 180B.

EXAMPLE 181C

(S)-4-(1-(2-fluoroethyl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 181B for
15 (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 181D

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(4-
20 {[(3S)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 181C for EXAMPLE
130C in EXAMPLE 130D. ¹H NMR (500 MHz, pyridine- d₅) δ 13.00 (m, 1H), 9.26 (d, 1H),
8.56 (d, 1H), 8.43 (d, 1H), 8.34 (dd, 1H), 8.10 (d, 1H), 7.63 - 7.66 (m, 2H), 7.44 (d, 2H), 7.07
(d, 2H), 6.82 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 4.60 (t, 1H), 4.51 (t, 1H),
25 4.05 (m, 1H), 3.07 (m, 4H), 2.84 (m, 1H), 2.66 - 2.79 (m, 6H), 2.39 (q, 1H), 2.20 - 2.29 (m,
3H), 2.15 (m, 5H), 1.97 (s, 2H), 1.66 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H).

EXAMPLE 182

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(4-
30 {[(3S)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 182A

(S)-tert-butyl 1-(2,2-difluoroethyl)pyrrolidin-3-ylcarbamate

The title compound was prepared by substituting (S)-tert-butyl pyrrolidin-3-ylcarbamate for (R)-tert-butyl pyrrolidin-3-ylcarbamate in EXAMPLE 180A.

5

EXAMPLE 182B

(S)-1-(2,2-difluoroethyl)pyrrolidin-3-amine

The title compound was prepared by substituting EXAMPLE 182A for EXAMPLE 180A in EXAMPLE 180B.

10

EXAMPLE 182C

(S)-4-(1-(2,2-difluoroethyl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 182B for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

15

EXAMPLE 182D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

20

The title compound was prepared by substituting EXAMPLE 182C for EXAMPLE 130C in EXAMPLE 130D. ¹H NMR (500 MHz, pyridine- d₅) δ 13.02 (m, 1H), 9.27 (d, 1H), 8.54 (d, 1H), 8.43 (d, 1H), 8.35 (dd, 1H), 8.11 (d, 1H), 7.64 - 7.68 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.82 (d, 1H), 6.75 (dd, 1H), 6.54 (m, 1H), 6.48 (m, 1H), 6.04 - 6.29 (m, 1H), 4.06 (m, 1H), 3.07 (m, 4H), 2.83 - 2.95 (m, 4H), 2.74 - 2.82 (m, 3H), 2.47 (m, 1H), 2.09 - 2.30 (m, 8H), 1.97 (s, 2H), 1.67 (m, 1H), 1.39 (t, 2H), 0.93 (s, 6H).

25

EXAMPLE 183

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,b]pyridin-5-yloxy)benzamide

30

EXAMPLE 183A

(R)-tert-butyl 1-(2-fluoroethyl)pyrrolidin-3-ylcarbamate

The title compound was prepared by substituting 1-fluoro-2-iodoethane for 1,1-difluoro-2-iodoethane in EXAMPLE 180A.

EXAMPLE 183B

5 (R)-1-(2-fluoroethyl)pyrrolidin-3-amine

The title compound was prepared by substituting EXAMPLE 183A for EXAMPLE 180A in EXAMPLE 180B.

EXAMPLE 183C

10 (R)-4-(1-(2-fluoroethyl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 183B for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 183D

15 4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(4-[(3R)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 183C for EXAMPLE 130C in EXAMPLE 130D. ¹H NMR (500 MHz, pyridine- d₅) δ 13.00 (m, 1H), 9.26 (d, 1H), 8.56 (d, 1H), 8.43 (d, 1H), 8.34 (dd, 1H), 8.10 (d, 1H), 7.63 - 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.83 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 4.60 (t, 1H), 4.50 (t, 1H), 4.04 (m, 1H), 3.07 (m, 4H), 2.84 (m, 1H), 2.66 - 2.79 (m, 6H), 2.39 (q, 1H), 2.19 - 2.28 (m, 3H), 2.14 (m, 5H), 1.97 (s, 2H), 1.66 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H).

25 EXAMPLE 184

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(4-nitro-4-[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

30 EXAMPLE 184A

(S)-tert-butyl 3-((2-nitro-4-sulfamoylphenoxy)methyl)pyrrolidine-1-carboxylate

To a solution of (S)-tert-butyl 3-(hydroxymethyl)pyrrolidine-1-carboxylate (0.300 g) in tetrahydrofuran (5 mL) was added sodium hydride (0.238 g). After stirring for 15 minutes,

4-fluoro-3-nitrobenzenesulfonamide (0.295 g) was added and reaction stirred at room temperature. After 1 hour, the reaction was partitioned between water (25 mL) and dichloromethane (50 mL) and the reaction quenched with 1N aqueous HCl (5.96 mL). The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (Reveleris 12 g) eluting with a gradient of 0.2% to 2% methanol/dichloromethane over 30 minutes (flow = 36 mL/minute) gave the title compound.

EXAMPLE 184B

(S)-3-nitro-4-((1-(oxetan-3-yl)pyrrolidin-3-yl)methoxy)benzenesulfonamide

To (S)-tert-butyl 3-((2-nitro-4-sulfamoylphenoxy)methyl)pyrrolidine-1-carboxylate (0.433 g) was added hydrogen chloride (4.0M in dioxane, 1.0 mL). After stirring for 1 hour, the reaction was concentrated and partitioned between dichloromethane (50 mL) and saturated aqueous NaHCO₃ solution (50 mL). The aqueous layer was separated and concentrated. The residue was triturated with methanol (100 mL), filtered and concentrated and treated with sodium cyanoborohydride (0.068 g) and cyclobutanone (0.078 g) and stirred overnight. The reaction was partitioned between dichloromethane (50 mL) and water (25 mL) and saturated aqueous NaHCO₃ (10 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated to give the title compound.

EXAMPLE 184C

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(3-nitro-4-([(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 184B for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.64 (s, 1H), 11.45 – 11.01 (m, 1H), 8.30 (d, 1H), 7.98 (dd, 2H), 7.60 – 7.43 (m, 3H), 7.33 (t, 3H), 7.04 (d, 2H), 6.74 – 6.59 (m, 1H), 6.37 (dd, 1H), 6.21 (d, 1H), 4.49 (td, 2H), 4.33 (s, 1H), 4.13 (dd, 2H), 3.79 (s, 2H), 3.44 (dd, 2H), 3.07 (s, 4H), 2.74 (d, 6H), 2.19 (d, 6H), 1.98 (d, 2H), 1.74 – 1.52 (m, 1H), 1.39 (t, 2H), 0.92 (s, 6H).

EXAMPLE 185

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-[(4-hydroxybenzyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting (4-hydroxyphenyl)methanamine for (4-methoxyphenyl)methanamine in EXAMPLE 174. ¹H NMR (500 MHz, pyridine-d₅) δ 13.06 (s, 1H), 11.67 (bs, 1H), 9.32 (d, 1H), 9.14 (s, 1H), 8.44 (d, 1H), 8.28 (dd, 1H), 8.09 (d, 1H), 7.65 - 7.68 (m, 2H), 7.44 (d, 2H), 7.37 - 7.41 (m, 2H), 7.19 (s, 2H), 7.07 (d, 2H), 6.93 (d, 1H), 6.75 (dd, 1H), 6.53 (d, 1H), 6.49 (dd, 1H), 4.54 (d, 2H), 3.02 - 3.09 (m, 4H), 2.77 (s, 2H), 2.22 - 2.29 (m, 2H), 2.10 - 2.17 (m, 4H), 1.97 (d, 2H), 1.39 (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-
10 [(3-hydroxybenzyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting (3-hydroxyphenyl)methanamine for (4-methoxyphenyl)methanamine in EXAMPLE 174. ¹H NMR (500 MHz, pyridine-d₅) δ 13.06 (s, 1H), 11.67 (bs, 1H), 9.27 - 9.32 (m, 2H), 8.43 (d, 1H), 8.20 (dd, 1H), 8.08 (d, 1H),
15 7.66 (t, 2H), 7.44 (d, 2H), 7.33 (t, 1H), 7.25 (s, 1H), 7.13 (dd, 1H), 7.07 (d, 2H), 6.98 (d, 1H), 6.88 (d, 1H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.49 (dd, 1H), 4.64 (d, 2H), 3.02 - 3.09 (m, 4H), 2.77 (s, 2H), 2.22 - 2.28 (m, 2H), 2.09 - 2.16 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

EXAMPLE 187

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
20 {[3-(difluoromethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting (3-difluoromethoxyphenyl)methanamine for (4-methoxyphenyl)methanamine in EXAMPLE
25 174. ¹H NMR (500 MHz, pyridine-d₅) δ 13.06 (s, 1H), 9.34 (t, 1H), 9.30 (d, 1H), 8.42 (d, 1H), 8.26 (dd, 1H), 8.08 (d, 1H), 7.66 (ddd, 2H), 7.40 - 7.45 (m, 3H), 7.36 (t, 1H), 7.27 - 7.30 (m, 2H), 7.19 (d, 1H), 7.07 (d, 2H), 6.87 (d, 1H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.49 (dd, 1H), 4.69 (d, 2H), 3.02 - 3.08 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.09 - 2.16 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

30

EXAMPLE 188

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-
([cis-3-morpholin-4-ylcyclopentyl]methyl)amino)-3-nitrophenyl]sulfonyl)-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5

EXAMPLE 188A

Cis-methyl 3-morpholinocyclopentanecarboxylate

The title compound was prepared by substituting methyl 3-oxocyclopentanecarboxylate for 4'-chlorobiphenyl-2-carboxaldehyde and morpholine for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

10

EXAMPLE 188B

Cis-3-morpholinocyclopentyl)methanol

The title compound was prepared by substituting EXAMPLE 188A for EXAMPLE 101C in EXAMPLE 101D.

15

EXAMPLE 188C

4-((Cis-3-morpholinocyclopentyl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 188B for (1,4-dioxan-2-yl)methanol in EXAMPLE 12A.

20

EXAMPLE 188D

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-
([cis-3-morpholin-4-ylcyclopentyl]methyl)amino)-3-nitrophenyl]sulfonyl)-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

25

The title compound was prepared by substituting EXAMPLE 188C for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.57 (s, 1H), 8.17 (m, 1H), 7.94 (m, 1H), 7.82 (m, 1H), 7.56 (d, 1H), 7.44 (t, 1H), 7.34 (m, 3H), 7.16 (m, 1H), 7.05 (d, 2H), 6.64 (dd, 1H), 6.33 (m, 1H), 6.24 (d, 1H), 4.06 (m, 2H), 3.62 (m, 4H), 3.03 (m, 4H), 2.75 (s, 2H), 2.35 (m, 2H), 2.19 (m, 6H), 2.03 (m, 2H), 1.96 (s, 2H), 1.78 (m, 2H), 1.51 (m, 4H), 1.39 (t, 2H), 0.93 (s, 6H)

30

EXAMPLE 189

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
{[4-({4-[(methylsulfonyl)amino]cyclohexyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5

EXAMPLE 189A

Trans-(4-Methanesulfonylamino-cyclohexyl)-carbamic acid tert-butyl ester

The title compound was prepared by substituting methanesulfonyl chloride for acetyl
chloride in EXAMPLE 179A.

10

EXAMPLE 189B

Trans-N-(4-Aminocyclohexyl)-methanesulfonamide

The title compound was prepared by substituting EXAMPLE 189A for EXAMPLE
1A in EXAMPLE 1B.

15

EXAMPLE 189C

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
{[4-({4-[(methylsulfonyl)amino]cyclohexyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

20

The title compound was prepared by substituting EXAMPLE 189B for 1-
acetylpiperidin-4-amine in EXAMPLE 53B. ¹H NMR (300MHz, dimethylsulfoxide-d₆) δ
11.68 (br s, 1H), 8.55 (d, 1H), 8.18 (d, 1H), 8.04 (d, 1H), 7.84 (d, 1H), 7.79 (dd, 1H), 7.56-
7.47 (m, 3H), 7.34 (d, 2H), 7.16 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (m, 1H), 6.19 (d,
1H), 3.56 (m, 1H), 3.17 (m, 1H), 3.07 (br s, 4H), 2.93 (s, 3H), 2.75 (br s, 2H), 2.28-2.10 (m,
25 6H), 2.05-1.90 (m, 6H), 1.55-1.32 (m, 6H), 0.92 (s, 6H).

EXAMPLE 190

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
[(1-cyclopropylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

30

EXAMPLE 190A

4-(1-cyclopropylpiperidin-4-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

The title compound was prepared as described in EXAMPLE 17A by replacing (tetrahydropyran-4-yl)methylamine with 4-amino-1-cyclopropylpiperidine.

EXAMPLE 190B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
5 [(1-cyclopropylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 1G by replacing EXAMPLE 1E and EXAMPLE 1F with EXAMPLE 3J and EXAMPLE 190A, respectively.

¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.66 (s, 1H), 8.13 (d, 1H), 8.02 (d, 1H), 7.91
10 (m, 1H), 7.48 (m, 3H), 7.34 (d, 2H), 7.04 (d, 2H), 6.67 (m, 2H), 6.38 (dd, 1H), 6.19 (d, 1H),
3.64 (m, 1H), 3.13 (m, 5H), 2.73 (m, 5H), 2.22 (m, 6H), 1.92 (m, 5H), 1.70 (m, 1H), 1.41 (m,
5H), 0.94 (s, 6H), 0.41 (m, 4H).

EXAMPLE 191

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-
15 nitro-4-[(1-oxetan-3-yl)piperidin-4-yl]methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

EXAMPLE 191A

20 3-nitro-4-(piperidin-4-ylmethoxy)benzenesulfonamide

To a solution of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (0.300 g) in tetrahydrofuran (5 mL) was added sodium hydride (0.223 g). After stirring for 15 minutes, 4-fluoro-3-nitrobenzenesulfonamide (0.276 g) was added and reaction stirred at room temperature. After 1 hour the reaction was partitioned between water (25 mL) and
25 dichloromethane (50 mL) and the reaction quenched with 1N aqueous HCl (5.57 mL). The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated. Treatment with HCl (4.0M in dioxane, 2 mL) and methanol (2 mL) for 1 hour, followed by concentration, trituration with dichloromethane and filtration gave the title compound.

30 EXAMPLE 191B

3-nitro-4-((1-(oxetan-3-yl)piperidin-4-yl)methoxy)benzenesulfonamide

To a suspension of 3-nitro-4-(piperidin-4-ylmethoxy)benzenesulfonamide (0.100 g) and cyclobutanone (0.030 g) in methanol (1 mL) was added sodium cyanoborohydride (0.027

g). After stirring overnight, the reaction was quenched with saturated NaHCO₃ (5 mL) and extracted into dichloromethane (2 x 10 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated to give the title compound.

5

EXAMPLE 191C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 191B for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.64 (s, 1H), 11.46 - 10.46 (m, 1H), 8.29 (s, 1H), 8.00 (d, 2H), 7.61 - 7.41 (m, 3H), 7.35 (d, 3H), 7.04 (d, 2H), 6.66 (d, 1H), 6.37 (s, 1H), 6.21 (s, 1H), 4.67 - 4.40 (m, 4H), 4.08 (d, 2H), 3.06 (s, 4H), 2.78 (s, 4H), 2.19 (m, 6H), 1.96 (s, 4H), 1.79 (m, 4H), 1.39 (s, 4H), 0.93 (s, 6H).

15

EXAMPLE 192

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

20

EXAMPLE 192A

4-((4-fluoro-1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl)methoxy)-3-nitrobenzenesulfonamide

25

A mixture of EXAMPLE 173A (0.4 g), dihydro-2H-pyran-4(3H)-one (0.179 g), sodium cyanoborohydride (0.112 g), and acetic acid (0.5 mL) in tetrahydrofuran (3 mL) was stirred overnight. The solvents were removed under reduced pressure. The residue was purified with flash column chromatography on silica gel eluting with 100:5:0.5 ethyl acetate/methanol/NH₄OH to give the desired product.

30

EXAMPLE 192B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 192A for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.58 (s, 1H), 8.25 (s, 1H), 7.96 (d, 1H), 7.93 (d, 1H), 7.57 (d, 1H), 7.45 (t, 1H), 7.34-7.37 (m, 3H), 7.26 (d, 1H), 7.05 (d, 2H), 6.64 (dd, 1H), 6.34 (dd, 1H), 6.23 (d, 1H), 4.34 (d, 2H), 3.93 (dd, 2H), 3.03 (s, 6H), 2.76 (s, 4H), 2.09-2.22 (m, 6H), 1.96 (s, 2H), 1.52-1.27 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

EXAMPLE 193

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
 10 [(4-fluoro-1-tetrahydrofuran-3-yl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 193A

4-((4-fluoro-1-(tetrahydrofuran-3-yl)piperidin-4-yl)methoxy)-3-nitrobenzenesulfonamide
 15 The title compound was prepared by substituting dihydrofuran-3(2H)-one for dihydro-2H-pyran-4(3H)-one in EXAMPLE 192A.

EXAMPLE 193B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
 20 [(4-fluoro-1-tetrahydrofuran-3-yl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 193A for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.63 (s, 1H), 8.31 (s, 1H), 7.99-8.00 (m, 2H), 7.54 (d, 1H), 7.46-7.48 (m, 2H), 7.34-7.35 (m, 3H), 7.05 (d2H), 6.66 (dd, 1H), 6.37 (dd, 1H), 6.21 (d, 1H), 4.34 (d, 2H), 3.76-3.83 (m, 3H), 3.62-3.65 (m, 2H), 3.03 (s, 4H), 2.79 (s, 4H), 2.24 (s, 2H), 2.15 (s, 2H), 1.84-1.99 (m, 8H), 1.52-1.27 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

EXAMPLE 194

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
 30 [(4-fluoro-1-(methylsulfonyl)piperidin-4-yl]methoxy)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 194A

4-((4-fluoro-1-(methylsulfonyl)piperidin-4-yl)methoxy)-3-nitrobenzenesulfonamide

A mixture of EXAMPLE 173A (0.4 g), methanesulfonyl chloride (0.113 g), and triethylamine (0.64 mL) in dichloromethane (5 mL) was stirred overnight. The reaction mixture was loaded onto a silica gel column and eluted with 100:1 ethyl acetate:methanol to give the clean product.

EXAMPLE 194B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
10 {4-fluoro-1-(methylsulfonyl)piperidin-4-yl)methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 194A for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.66 (s, 1H), 8.37 (s, 1H), 8.06 (d, 1H), 8.02 (d, 1H), 7.49-7.53 (m, 3H), 7.42 (d, 1H), 7.35 (d, 2H),
15 7.05 (d, 2H), 6.67 (dd, 1H), 6.38-6.39 (m, 1H), 6.21 (d, 1H), 4.40 (d, 2H), 3.51-3.54 (m, 2H), 3.09 (s, 4H), 2.96-3.01 (m, 4H), 2.92 (s, 3H), 2.82 (s, 2H), 2.25-2.34 (m, 4H), 2.13-2.16 (m, 6H), 2.01-2.07 (m, 2H), 1.99 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

EXAMPLE 195

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[3-
20 nitro-4-({[(3R)-1-oxetan-3-ylpyrrolidin-3-yl]methyl}amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 195A

(R)-tert-butyl 3-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-
25 dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)methyl)pyrrolidine-1-carboxylate

The title compound was prepared by substituting (R)-tert-butyl 3-(aminomethyl)pyrrolidine-1-carboxylate for 1-acetylpiperidin-4-amine in EXAMPLE 53B.

30

EXAMPLE 195B

(S)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-(pyrrolidin-3-ylmethylamino)phenylsulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 195A for EXAMPLE 1A in EXAMPLE 1B.

EXAMPLE 195C

- 5 (R)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-((1-(oxetan-3-yl)pyrrolidin-3-yl)methylamino)phenylsulfonyl)benzamide

- The title compound was prepared by substituting EXAMPLE 195B for tert-butyl piperazine-1-carboxylate and oxetan-3-one for 4'-chlorobiphenyl-2-carboxaldehyde in
 10 EXAMPLE 1A. ¹H NMR (500MHz, dimethylsulfoxide-d₆) 11.67 (s, 1H), 8.81 (t, 1H), 8.55 (d, 1H), 8.02 (d, 1H), 7.79 (dd, 1H), 7.50 (m, 3H), 7.35 (m, 2H), 7.04 (m, 3H), 6.67 (dd, 1H), 6.39 (m, 1H), 6.19 (d, 1H), 4.57 (m, 2H), 4.48 (m, 2H), 3.68 (m, 2H), 3.30 (m, 2H), 3.06 (m, 4H), 2.74 (m, 3H), 2.56 (m, 3H), 2.44 (m, 1H), 2.18 (m, 5H), 1.95 (m, 3H), 1.58 (m, 1H), 1.36 (m, 2H), 0.94 (s, 6H).

- 15 EXAMPLE 196

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-hydroxycyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 196A

- 20 Trans-4-(4-(tert-butyldimethylsilyloxy)cyclohexyl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared as described in EXAMPLE 12A by replacing (1,4-dioxan-2-yl)methanol with trans-(4-(tert-butyldimethylsilyloxy)cyclohexyl)methanol (made according to the procedures in WO 2008/124878).

- 25 EXAMPLE 196B

Trans-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(4-(((1r,4r)-4-(tert-butyldimethylsilyloxy)cyclohexyl)methoxy)-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 using EXAMPLE
 30 196A in place of EXAMPLE 1F and EXAMPLE 3J in place of EXAMPLE 1E.

EXAMPLE 196C

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
({4-[(4-hydroxycyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-
5-yloxy)benzamide

EXAMPLE 196B (150 mg) in dichloromethane (5 mL) and methanol (2 mL) was
5 treated with 10% aqueous HCl (3 mL) for 1 hour and concentrated. The residue was purified
by reverse phase HPLC on a C18 column using a gradient of 40-60% acetonitrile in 0.1%
trifluoroacetic acid water to give the title compound as a trifluoroacetate salt. The
trifluoroacetic acid salt was dissolved in dichloromethane (30 mL) and washed with 50%
aqueous NaHCO₃. The organic layer was dried over anhydrous Na₂SO₄, filtered, and
10 concentrated to give the title compound. ¹H NMR (400 MHz, dimethylsulfoxide-d₆) δ 11.69
(s, 1H), 11.27 (s, 1H), 8.34 (d, 1H), 7.95 - 8.08 (m, 2H), 7.47 - 7.55 (m, 3H), 7.32 - 7.40 (m,
3H), 7.01 - 7.07 (m, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.20 (d, 1H), 4.54 (d, 1H), 3.96 - 4.06
(m, 2H), 3.10 (s, 4H), 2.84 (s, 2H), 2.05 - 2.39 (m, 6H), 1.96 (s, 2H), 1.46 - 1.93 (m, 5H),
1.39 (t, 2H), 0.98 - 1.29 (m, 4H), 0.92 (s, 6H)

15

EXAMPLE 197

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
({4-[3-(dimethylamino)propoxy]benzyl}amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

20

EXAMPLE 197A

3-(4-(aminomethyl)phenoxy)-N,N-dimethylpropan-1-amine

4-(3-(Dimethylamino)propoxy)benzonitrile (300 mg) in methanol (20 mL) was
treated with Raney nickel (wet, 1.5 g) under H₂ (30 psi) for 4 hour. The insoluble material
25 was filtered off and the filtrate was concentrated to provide the title compound.

EXAMPLE 197B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
({4-[3-(dimethylamino)propoxy]benzyl}amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

30 The title compound was prepared as described in EXAMPLE 120B using EXAMPLE
197A in place of EXAMPLE 120A. ¹H NMR (400 MHz, dimethylsulfoxide-d₆) δ 11.56 (s,
1H), 8.80 (t, 1H), 8.42 (d, 1H), 7.93 (d, 1H), 7.52 - 7.61 (m, 2H), 7.41 - 7.47 (m, 1H), 7.26 -
7.36 (m, 5H), 7.03 - 7.08 (m, 2H), 6.89 (d, 2H), 6.73 (d, 1H), 6.61 (dd, 1H), 6.31 (dd, 1H),

6.22 (d, 1H), 4.52 (d, 2H), 3.99 (t, 2H), 2.90 - 3.05 (m, 7H), 2.72 (s, 2H), 2.61 (s, 6H), 2.09 - 2.24 (m, 6H), 1.89 - 2.04 (m, 5H), 1.38 (t, 2H), 0.92 (s, 6H)

EXAMPLE 198

5 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(2-morpholin-4-ylethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 198A

10 (4-(2-morpholinoethoxy)phenyl)methanamine

The title compound was prepared as described in EXAMPLE 197A using 4-(2-morpholinoethoxy)benzonitrile in place of 4-(3-(dimethylamino)propoxy)benzonitrile.

EXAMPLE 198B

15 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(2-morpholin-4-ylethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 120B using EXAMPLE 198A in place of EXAMPLE 120A. ¹H NMR (400 MHz, dimethylsulfoxide-d₆) δ 11.69 (s, 1H), 9.00 (t, 1H), 8.56 (d, 1H), 8.02 (d, 1H), 7.72 (dd, 1H), 7.46 - 7.54 (m, 3H), 7.27 - 7.36 (m, 4H), 7.01 - 7.07 (m, 2H), 6.89 - 6.95 (m, 3H), 6.66 (dd, 1H), 6.38 (dd, 1H), 6.18 (d, 1H), 4.56 (d, 2H), 4.07 (t, 2H), 3.54 - 3.61 (m, 4H), 3.06 (s, 4H), 2.71 - 2.78 (m, 4H), 2.07 - 2.24 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

EXAMPLE 199

25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(*E*)-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 199A

4-[(*E*)-4-Hydroxy-adamantan-1-ylmethyl]-amino]-3-nitro-benzenesulfonamide

4-Fluoro-3-nitrobenzenesulfonamide (0.5 g) and 5-(aminomethyl)adamantan-2-ol (0.6 g) in tetrahydrofuran (10 mL) were treated with triethylamine (1 mL) overnight. The reaction

mixture was concentrated and the residue was purified by reverse phase HPLC, eluting 40-60% acetonitrile in 0.1 trifluoroacetic acid water to give two isomers, which were temporarily assigned as EXAMPLE 199A and EXAMPLE 199B, respectively.

5

EXAMPLE 199B

4-[(*(Z)*-4-Hydroxy-adamantan-1-ylmethyl)-amino]-3-nitro-benzenesulfonamide

4-Fluoro-3-nitrobenzenesulfonamide (0.5 g) and 5-(aminomethyl)adamantan-2-ol (0.6 g) in tetrahydrofuran (10 mL) were treated with triethylamine (1 mL) overnight. The reaction mixture was concentrated and the residue was purified by reverse phase HPLC, eluting 40-60% acetonitrile in 0.1 trifluoroacetic acid water to give two isomers, which were temporarily assigned as EXAMPLE 199A and EXAMPLE 199B, respectively.

10

EXAMPLE 199C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
15 {[(*(E)*-4-hydroxy-1-adamantyl]methyl)amino]-3-nitrophenyl}sulfonyl}-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 199A in place of EXAMPLE 11B. ¹H NMR (400 MHz, dimethylsulfoxide-*d*₆) δ 11.68 (s, 1H), 11.40 (s, 1H), 8.55 (d, 1H), 8.50 (t, 1H), 8.03 (d, 1H), 7.77 (dd, 1H), 7.46 - 7.54 (m, 3H), 7.31 - 7.38 (m, 2H), 7.14 (d, 1H), 7.01 - 7.06 (m, 2H), 6.68 (dd, 1H), 6.38 (dd, 1H), 6.19 (d, 1H), 4.61 (d, 1H), 3.63 (d, 1H), 3.02 - 3.16 (m, 6H), 2.75 (s, 2H), 2.17 (d, 6H), 2.04 (d, 2H), 1.95 (s, 2H), 1.76 - 1.88 (m, 3H), 1.49 - 1.61 (m, 6H), 1.38 (t, 2H), 1.29 (d, 2H), 0.92 (s, 6H).

20

EXAMPLE 200

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
25 {[(*(Z)*-4-hydroxy-1-adamantyl]methyl)amino]-3-nitrophenyl}sulfonyl}-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 199B in place of EXAMPLE 11B. ¹H NMR (400 MHz, dimethylsulfoxide-*d*₆) δ 11.68 (s, 1H), 11.39 (s, 1H), 8.55 (d, 1H), 8.51 (t, 1H), 8.04 (d, 1H), 7.77 (dd, 1H), 7.46 - 7.55 (m, 3H), 7.31 - 7.37 (m, 2H), 7.14 (d, 1H), 7.01 - 7.06 (m, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 4.61 (d, 1H), 3.61 (d, 1H), 3.08 (d, 6H), 2.75 (s, 2H), 2.17 (d, 6H), 1.79 - 1.99 (m, 7H), 1.55 - 1.69 (m, 4H), 1.49 (s, 2H), 1.38 (t, 2H), 1.22 (d, 2H), 0.92 (s, 6H).

30

EXAMPLE 201

N-({4-[(1S,4S)-bicyclo[2.2.1]hept-5-en-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 201A

4-((1S,4S)-bicyclo[2.2.1]hept-5-en-2-ylmethoxy)-3-nitrobenzenesulfonamide

The title compound was prepared as described in EXAMPLE 12A by replacing (1,4-dioxan-2-yl)methanol with (1S,4S)-bicyclo[2.2.1]hept-5-en-2-ylmethanol.

EXAMPLE 201B

N-({4-[(1S,4S)-bicyclo[2.2.1]hept-5-en-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 201A in place of EXAMPLE 11B. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.69 (s, 1H), 8.35 (d, 1H), 7.95 - 8.10 (m, 2H), 7.47 - 7.58 (m, 3H), 7.30 - 7.45 (m, 3H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.40 (d, 1H), 5.92 - 6.23 (m, 3H), 3.65 - 4.39 (m, 3H), 3.00 - 3.22 (m, 4H), 2.76 - 2.98 (m, 4H), 2.28 (s, 4H), 2.15 (s, 2H), 1.96 (s, 2H), 1.71 - 1.91 (m, 1H), 1.33 - 1.47 (m, 3H), 1.20 - 1.32 (m, 2H), 0.92 (s, 6H), 0.50 - 0.66 (m, 1H).

EXAMPLE 202

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

EXAMPLE 82 (140 mg) was dissolved in dioxane (3.0 mL), and 4-amino-1-methylpyrrolidin-2-one hydrochloride (30 mg) and triethylamine (0.100 mL) were added. The reaction mixture was heated at 110°C for 40 hours. The reaction 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% CH₃CN 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 NaHCO₃. The organic layer was dried over anhydrous

Na₂SO₄ and concentrated to give the title compound. ¹H NMR (400 MHz, dimethylsulfoxide-d₆) δ 11.65 (s, 1H), 8.74 (d, 1H), 8.37 (br d, 1H), 8.02 (d, 1H), 7.83 (dd, 1H), 7.49 (m, 3H), 7.34 (d, 2H), 7.07 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.38 (m, 1H), 6.21 (d, 1H), 4.46 (m, 1H), 3.81 (dd, 1H), 3.38 (dd, 1H), 3.08 (br m, 4H), 2.82 (dd, 1H), 2.75 (s, 5H), 2.43 (dd, 1H),
5 2.21 (br m, 4H), 2.16 (br t, 2H), 1.95 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

EXAMPLE 203

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
10 {[(1R,4R,5R,6S)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-
(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 203A

4-(((1R,4R,5R,6S)-5,6-dihydroxybicyclo[2.2.1]heptan-2-yl)methoxy)-3-
nitrobenzenesulfonamide

15 To a solution of EXAMPLE 201A (340 mg) in tetrahydrofuran (10 mL) and water (1 mL) was added N-methylmorpholine N-oxide (184 mg) and OsO₄ (2.5% in 2-methyl-2-propanol) (1.05 mL). The reaction mixture was stirred overnight and purified by reverse phase HPLC to provide two isomers, which were temporarily assigned as EXAMPLE 203A and EAMPLE 203B, respectively.

20

EXAMPLE 203B

4-(((1R,4R,5S,6R)-5,6-dihydroxybicyclo[2.2.1]heptan-2-yl)methoxy)-3-
nitrobenzenesulfonamide

To a solution of EXAMPLE 201A (340 mg) in tetrahydrofuran (10 mL) and water (1
25 mL) was added N-methylmorpholine N-oxide (184 mg) and OsO₄ (2.5% in 2-methyl-2-propanol) (1.05 mL). The reaction mixture was stirred overnight and purified by reverse phase HPLC to provide two isomers, which were temporarily assigned as EXAMPLE 203A and EAMPLE 203B, respectively.

30

EXAMPLE 203C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
{[(1R,4R,5R,6S)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-
(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 203A in place of EXAMPLE 11B. ¹H NMR (400 MHz, dimethylsulfoxide-d₆) δ 11.68 (s, 1H), 8.33 (s, 1H), 7.97 - 8.07 (m, 2H), 7.48 - 7.55 (m, 3H), 7.41 (d, 1H), 7.32 - 7.37 (m, 2H), 7.02 - 7.07 (m, 2H), 6.67 (dd, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 4.58 (dd, 2H), 4.07 - 4.19 (m, 2H), 3.82 (t, 1H), 3.51 (t, 1H), 3.09 (s, 4H), 2.81 (s, 2H), 2.09 - 2.34 (m, 8H), 2.04 - 2.09 (m, 2H), 1.93 - 2.01 (m, 3H), 1.62 - 1.77 (m, 2H), 1.39 (t, 2H), 1.11 (d, 1H), 0.92 (s, 6H), 0.67 - 0.76 (m, 1H).

EXAMPLE 204

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([(1R,4R,5S,6R)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 203B in place of EXAMPLE 11B. ¹H NMR (400 MHz, dimethylsulfoxide-d₆) δ 11.68 (s, 1H), 8.33 (s, 1H), 7.98 - 8.07 (m, 2H), 7.49 - 7.54 (m, 3H), 7.41 (d, 1H), 7.32 - 7.36 (m, 2H), 7.02 - 7.07 (m, 2H), 6.67 (dd, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 4.58 (dd, 2H), 4.13 (dd, 2H), 3.82 (t, 1H), 3.51 (t, 1H), 3.09 (s, 4H), 2.81 (s, 2H), 2.09 - 2.35 (m, 8H), 2.07 (s, 2H), 1.93 - 2.02 (m, 3H), 1.61 - 1.80 (m, 2H), 1.39 (t, 2H), 1.11 (d, 1H), 0.92 (s, 6H), 0.66 - 0.78 (m, 1H).

EXAMPLE 205

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-[(3-oxocyclohexyl)methoxy]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 205A

Methyl 1,4-dioxaspiro[4.5]decane-7-carboxylate

To a solution of trimethylsilyltrifluoromethanesulfonate (0.034 mL) in dry dichloromethane (5 mL) was added 1,2-bis(trimethylsiloxy)ethane (4.55 mL) followed by methyl 3-oxocyclohexanecarboxylate (2.9 g). The reaction mixture was stirred for 3 hours at -78 °C. The reaction mixture was quenched with dry pyridine (0.5 mL), poured into saturated aqueous NaHCO₃, and extracted with ether. The ether layer was dried over Na₂CO₃ /

Na₂SO₄. The reaction mixture was concentrated and purified by flash chromatography on silica with 5 to 30% ethyl acetate in hexanes to provide the title compound.

EXAMPLE 205B

5 1,4-dioxaspiro[4.5]decan-7-ylmethanol

The title compound was prepared by substituting EXAMPLE 205A for EXAMPLE 101C in EXAMPLE 101D.

EXAMPLE 205C

10 3-nitro-4-((3-oxocyclohexyl)methoxy)benzenesulfonamide

Into a 250 mL round-bottomed flask was added sodium hydride (0.5 g) in tetrahydrofuran (10 mL) and then 1,4-dioxaspiro[4.5]decan-7-ylmethanol (0.5 g) was added. After the mixture stirred at room temperature for 20 minutes, 4-fluoro-3-nitrobenzenesulfonamide (0.65 g) was added. The mixture was stirred at room temperature for overnight. Water (20 mL) was added slowly. The aqueous layer was extracted by dichloromethane (3x 20 mL). The combined organic layers were dried over Na₂SO₄. After filtration, and concentration of the filtrate, the residue was purified by reverse phase chromatography, eluting with 30-60% acetonitrile in water with 0.1% trifluoroacetic acid.

20 EXAMPLE 205D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3-oxocyclohexyl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 205C for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (400 MHz, dimethylsulfoxide-d₆) δ 11.59 (s, 1H), 8.22 (s, 1H), 7.96 (d, 1H), 7.87 (m, 1H), 7.55 (d, 1H), 7.45 (t, 1H), 7.35 (m, 3H), 7.20 (m, 1H), 7.04 (d, 2H), 6.64 (dd, 1H), 6.34 (m, 1H), 6.23 (d, 1H), 4.07 (d, 2H), 3.04 (m, 4H), 2.76 (s, 2H), 2.35 (m, 2H), 2.20 (m, 8H), 1.96 (m, 4H), 1.58 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

30 EXAMPLE 206

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohexa-1,3-dien-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 206A

2-chloro-5,5-dimethylcyclohexa-1,3-dienecarbaldehyde

In a 250 mL round-bottomed flask was added N,N-dimethylformamide (3.5 mL) in dichloromethane (30 mL), and the mixture was cooled to -10 °C. Phosphoryl trichloride (4 mL) was added dropwise, and the solution was warmed up to room temperature. 4,4-

- 5 Dimethylcyclohex-2-enone (5.5 mL) was then added slowly, and the mixture was heated to reflux overnight. The reaction mixture was cooled and quenched with a 0°C solution of sodium acetate (25 g in 50 mL water). The aqueous layer was extracted with diethyl ether (200 mL x3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated to give the product.

10

EXAMPLE 206B

2-(4-chlorophenyl)-5,5-dimethylcyclohexa-1,3-dienecarbaldehyde

- Into a 1 L round-bottomed flask was added EXAMPLE 206A (6.8 g), 4-chlorophenylboronic acid (6.5 g), and palladium (II) acetate (0.2 g) in water (100 mL) to give
15 a suspension. Potassium carbonate (15 g) and tetrabutylammonium bromide (10 g) were added. After degassing, the mixture was stirred at 45°C for 4 hours. After cooling and filtering through silica gel in a funnel, diethyl ether (4x 200mL) was used to extract the product. The combined organic layers were dried over Na₂SO₄, and filtered. The filtrate was concentrated and purified by flash chromatography on silica with 0-10% ethyl acetate in
20 hexanes to provide the title compound.

EXAMPLE 206C

Methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohexa-1,3-dienyl)methyl)piperazin-1-yl)benzoate

- 25 The title compound was prepared by substituting EXAMPLE 206B for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 15F for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 206D

- 30 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohexa-1,3-dienyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 206C for EXAMPLE 101E in EXAMPLE 101F.

EXAMPLE 206E

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohexa-1,3-dien-1-yl]methyl}piperazin-1-yl)-N-
 ({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 206D for EXAMPLE 3J
 and EXAMPLE 1F for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (400 MHz,
 dimethylsulfoxide-d₆) δ 11.61 (s, 1H), 8.49 (m, 2H), 7.99 (m, 1H), 7.72 (m, 1H), 7.53 (d,
 1H), 7.41 (m, 4H), 7.12 (d, 2H), 6.99 (m, 1H), 6.66 (dd, 1H), 6.35 (m, 1H), 6.23 (d, 1H), 5.74
 (d, 1H), 5.58 (d, 1H), 3.84 (m, 2H), 3.26 (m, 4H), 3.06 (m, 4H), 2.88 (s, 2H), 2.24 (m, 6H),
 1.61 (m, 2H), 1.26 (m, 3H), 1.00 (s, 6H).

EXAMPLE 207

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 207A

(R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-amine

The title compound was prepared by substituting (R)-tert-butyl pyrrolidin-3-
 ylcabamate for tert-butyl azetidin-3-ylcabamate in EXAMPLE 151A.

EXAMPLE 207B

(R)-4-(1-(1,3-difluoropropan-2-yl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 207A for EXAMPLE
 151A in EXAMPLE 151B.

EXAMPLE 207C

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 207B for EXAMPLE
 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. ¹H NMR (300 MHz,
 dimethylsulfoxide-d₆) δ 11.67 (s, 1H), 11.52 - 11.24 (m, 1H), 8.55 (d, 1H), 8.37 (d, 1H), 8.03
 (d, 1H), 7.83 (dd, 1H), 7.57 - 7.45 (m, 3H), 7.34 (d, 2H), 7.06 (t, 3H), 6.67 (d, 1H), 6.38 (dd,

1H), 6.20 (d, 1H), 4.70 (d, 2H), 4.54 (d, 2H), 4.23 (s, 1H), 3.11 - 2.87 (m, 7H), 2.74 (dd, 4H), 2.35 - 2.13 (m, 7H), 1.95 (s, 2H), 1.70 (s, 1H), 1.39 (d, 2H), 0.92 (s, 6H).

EXAMPLE 208

5 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 208A

10 2-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-5-iodo-3-(trifluoromethyl)pyridine

A mixture of EXAMPLE 37C (0.537 g), 5-iodo-3-(trifluoromethyl)pyridin-2-ol (1.156 g), and triphenylphosphine (1.574 g) in tetrahydrofuran (20 mL) was cooled to 0 °C. To this solution was added (E)-di-tert-butyl diazene-1,2-dicarboxylate (0.921 g). The reaction mixture was stirred overnight. The solvent was removed, and the residue was purified with
15 column flash chromatography on silica gel eluting with 4:1 hexanes/ethyl acetate to give the desired product.

EXAMPLE 208B

6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-5-(trifluoromethyl)pyridine-3-sulfonamide
20 EXAMPLE 207A (1.3 g) in tetrahydrofuran (10 mL) was cooled to -42 °C with a cold bath of CH₃CN/dry ice. To this solution was added 2.0 M isopropylmagnesium chloride (1.6 mL) dropwise over 5 minutes. The reaction mixture was stirred for 30 minutes at -42 °C, then allowed to warm to 0 °C over 10 minutes. The reaction mixture was cooled again to -42 °C, and SO₂ was bubbled through it for 10 minutes. The reaction mixture was stirred for another
25 30 minutes. To this solution was sulfuryl dichloride (0.433 g). On warming to room temperature, concentrated NH₄OH (10 mL) was added and the reaction mixture was stirred for another 2 hours. The reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated. The
30 residue was purified by flash column chromatography on silica gel eluting with 3:1 hexanes/ethyl acetate to give the title compound.

EXAMPLE 208C

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-
5 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 208B for
EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.61 (s,
1H), 8.72 (s, 1H), 8.36 (s, 1H), 7.98 (d, 1H), 7.55 (d, 1H), 7.42-7.47 (m, 2H), 7.36 (d, 2H),
7.05 (d, 2H), 6.66 (dd, 1H), 6.35 (s, 1H), 6.23 (s, 1H), 4.56 (d, 2H), 3.75-3.79 (m, 2H), 3.56-
10 3.61 (m, 2H), 3.09 (s, 4H), 2.32-2.37 (m, 2H), 2.16(s, 2H), 1.97-1.99 (m, 2H), 1.79-1.86 (m,
4H), 1.40 (t, 2H), 0.93 (s, 6H).

EXAMPLE 209

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-
15 nitro-4-({[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methyl}amino)phenyl]sulfonyl}-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 209A

(S)-tert-butyl (1-(oxetan-3-yl)pyrrolidin-3-yl)methylcarbamate

20 The title compound was prepared by substituting (R)-tert-butyl pyrrolidin-3-ylmethylcarbamate for tert-butyl piperazine-1-carboxylate and 3-oxetanone for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

EXAMPLE 209B

25 (S)-(1-(oxetan-3-yl)pyrrolidin-3-yl)methanamine

The title compound was prepared by substituting EXAMPLE 209A for (S)-1-tert-butyl 2-methyl 4,4-difluoropyrrolidine-1,2-dicarboxylate in EXAMPLE 168A.

EXAMPLE 209C

30 (S)-3-nitro-4-((1-(oxetan-3-yl)pyrrolidin-3-yl)methylamino)benzenesulfonamide

The title compound was prepared by substituting 4-fluoro-3-nitrobenzenesulfonamide for 4-chloro-3-nitrobenzenesulfonamide and EXAMPLE 209B for 4-methylpiperazin-1-amine dihydrochloride in EXAMPLE 6A.

EXAMPLE 209D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-({[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methyl}amino)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5 The title compound was prepared by substituting EXAMPLE 209C for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500 MHz, pyridine-d₅) δ 13.05 (s, 1H), 9.30 (d, 1H), 9.02 (t, 1H), 8.42 (d, 1H), 8.34 (dd, 1H), 8.10 (d, 1H), 7.67 (dd, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.82 (d, 1H), 6.75 (m, 1H), 6.52 (m, 2H), 4.82 (t, 1H), 4.75 (t, 1H), 4.67 (t, 2H), 3.57 (m, 1H), 3.24 (t, 2H), 3.07 (m, 4H), 2.75 (m, 3H), 2.57 (dd, 1H), 2.45 (s, 1H), 2.36 (t, 1H), 2.26
10 (s, 2H), 2.18 (m, 5H), 1.93 (m, 3H), 1.56 (m, 1H), 1.39 (t, 2H), 0.93 (s, 6H).

EXAMPLE 210

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-pyrrolo[2,3-
15 b]pyridin-5-yloxy)benzamide

EXAMPLE 210A

(4-methoxycyclohexyl)methanol

The title compound was prepared by substituting 4-methoxycyclohexanecarboxylic
20 acid for 1-tert-butyl 4-ethyl 4-fluoropiperidine-1,4-dicarboxylate in EXAMPLE 126A.

EXAMPLE 210B

Trans-5-chloro-6-((4-methoxycyclohexyl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 210A for tetrahydro-
25 2H-pyran-4-yl)methanol and EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

EXAMPLE 210C

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-pyrrolo[2,3-
30 b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 210C for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.67 (s,

1H), 8.50 (s, 1H), 8.17 (s, 1H), 8.02 (d, 1H), 7.49-7.54 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.67 (dd, J 1H), 6.39 (s, 1H), 6.21 (s, 1H), 4.20 (d, 2H), 3.23 (s, 3H), 3.06-3.09 (m, 4H), 2.15-2.37 (m, 4H), 1.96-2.03 (m, 4H), 1.74-1.84 (m, 2H), 1.40 (t, 2H), 1.04-1.13 (m, 4H), 0.93 (s, 6H).

5

EXAMPLE 211

Cis-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

10

EXAMPLE 211A

Cis-5-chloro-6-((4-methoxycyclohexyl)methoxy)pyridine-3-sulfonamide

The title compound was isolated as a by-product in the synthesis of EXAMPLE 210B.

15

EXAMPLE 211B

Cis-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 211A for

20 EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.67 (s, 1H), 8.51 (s, 1H), 8.17 (s, 1H), 8.03 (d, 1H), 7.49-7.54 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.39 (s, 1H), 6.21 (s, 1H), 4.21 (d, 2H), 3.20 (s, 3H), 3.06 (s, 4H), 2.15-2.37 (m, 4H), 1.96 (s, 2H), 1.80-1.84 (m, 2H), 1.50-1.54 (m, 2H), 1.34-1.44 (m, 6H), 0.93 (s, 6H).

25

EXAMPLE 212

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

30

EXAMPLE 212A

(S)-tert-butyl 1-(oxetan-3-yl)pyrrolidin-3-ylcarbamate

The title compound was prepared by substituting (S)-tert-butyl pyrrolidin-3-ylcarbamate for tert-butyl piperazine-1-carboxylate and 3-oxetanone for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

5

EXAMPLE 212B

(S)-1-(oxetan-3-yl)pyrrolidin-3-amine

The title compound was prepared by substituting EXAMPLE 212A for (S)-1-tert-butyl 2-methyl 4,4-difluoropyrrolidine-1,2-dicarboxylate in EXAMPLE 168A.

10

EXAMPLE 212C

(S)-3-nitro-4-(1-(oxetan-3-yl)pyrrolidin-3-ylamino)benzenesulfonamide

The title compound was prepared by substituting 4-fluoro-3-nitrobenzenesulfonamide for 4-chloro-3-nitrobenzenesulfonamide and EXAMPLE 212B for 4-methylpiperazin-1-amine dihydrochloride in EXAMPLE 6A.

15

EXAMPLE 212D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

20

The title compound was prepared by substituting EXAMPLE 212C for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500 MHz, pyridine-d₅) δ 13.03 (s, 1H), 9.27 (d, 1H), 8.58 (d, 1H), 8.42 (d, 1H), 8.37 (dd, 1H), 8.09 (d, 1H), 7.67 (t, 1H), 7.64 (d, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.86 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (dd, 1H), 4.67 (m, 4H), 4.09 (m, 1H), 3.59 (m, 1H), 3.07 (m, 4H), 2.77 (s, 2H), 2.69 (m, 2H), 2.62 (dd, 1H), 2.28 (m, 4H), 2.14 (m, 4H), 1.97 (s, 2H), 1.68 (m, 1H), 1.39 (t, 2H), 0.93 (s, 6H).

25

EXAMPLE 213

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

30

EXAMPLE 213A

4-((4-(2-(2-methoxyethoxy)ethyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 2-(2'-methoxyethoxy)ethyl bromide for methyl iodide in EXAMPLE 134B.

EXAMPLE 213B

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

The title compound was prepared by substituting EXAMPLE 213A for EXAMPLE
130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 12.98 (s, 1H), 9.26 (d, 1H),
10 8.87 (t, 1H), 8.43 (d, 1H), 8.32 (dd, 1H), 8.11 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d,
2H), 6.91 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.96-3.86 (m, 2H), 3.72 (dd, 1H),
3.67-3.61 (m, 4H), 3.51 (t, 2H), 3.48-3.38 (m, 2H), 3.28 (s, 3H), 3.07 (m, 4H), 2.95 (d, 1H),
2.77 (s, 2H), 2.70 (m, 1H), 2.60 (t, 2H), 2.30-2.05 (m, 8H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s,
6H).

15 EXAMPLE 214

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)-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

20 EXAMPLE 214A

4-((4-(cyanomethyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 2-bromoacetonitrile for methyl
iodide in EXAMPLE 134B.

25 EXAMPLE 214B

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)-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 214A for EXAMPLE
30 130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 13.01 (s, 1H), 9.26 (d, 1H),
8.86 (t, 1H), 8.43 (d, 1H), 8.35 (dd, 1H), 8.11 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d,
2H), 6.94 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.93 (m, 1H), 3.87 (d, 1H), 3.77
(s, 2H), 3.65 (dt, 1H), 3.51-3.40 (m, 2H), 3.07 (m, 4H), 2.87 (d, 1H), 2.77 (s, 2H), 2.60 (d,

1H), 2.50 (m, 1H), 2.38 (t, 1H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

EXAMPLE 215

5 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{[4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 215A

10 4-((4-(2-(dimethylamino)acetyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 2-dimethylaminoacetyl chloride hydrochloride for methyl iodide in EXAMPLE 134B.

EXAMPLE 215B

15 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{[4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 215A for EXAMPLE 130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 13.00 (s, 1H), 9.27 (d, 1H), 8.87 (bs, 1H), 8.43 (d, 1H), 8.34 (dd, 1H), 8.10 (dd, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.94 (dd, 1H), 6.75 (d, 1H), 6.54 (s, 1H), 6.48 (s, 1H), 4.55 (dd, 1H), 4.20 (dd, 1H), 3.95-3.76 (m, 2H), 3.60-3.40 (m, 3H), 3.32 (dd, 1H), 3.25-3.12 (m, 2H), 3.07 (m, 4H), 2.80 (m, 1H), 2.77 (s, 2H), 2.26 (s, 6H), 2.23 (s, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

25

EXAMPLE 216

(2-{{[4-{{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]-2-nitrophenyl}amino]methyl}morpholin-4-yl)acetic acid

30

EXAMPLE 216A

tert-butyl 2-(2-((2-nitro-4-sulfamoylphenylamino)methyl)morpholino)acetate

The title compound was prepared by substituting *tert*-butyl 2-bromoacetate for methyl iodide in EXAMPLE 134B.

EXAMPLE 216B

5 *tert*-butyl 2-(2-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)methyl)morpholino)acetate

The title compound was prepared by substituting EXAMPLE 216A for EXAMPLE 130C in EXAMPLE 130D.

10

EXAMPLE 216C

(2-{[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}morpholin-4-yl)acetic acid

15 The title compound was prepared by treating EXAMPLE 216B with 50% trifluoroacetic acid in dichloromethane. ¹H NMR (500MHz, pyridine-d₅) δ 12.97 (s, 1H), 9.26 (d, 1H), 8.87 (t, 1H), 8.43 (d, 1H), 8.30 (dd, 1H), 8.12 (d, 1H), 7.69 (t, 1H), 7.64 (d, 1H), 7.43 (d, 2H), 7.08 (d, 2H), 6.88 (d, 1H), 6.76 (dd, 1H), 6.55 (d, 1H), 6.47 (m, 1H), 4.05-4.00 (m, 1H), 3.91 (d, 1H), 3.79 (dt, 1H), 3.50 (s, 2H), 3.45 (m, 2H), 3.13 (d, 1H), 3.07 (m, 4H),
20 2.88 (d, 1H), 2.78 (s, 2H), 2.57 (dt, 1H), 2.43 (t, 1H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

EXAMPLE 217

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

EXAMPLE 217A

30 The title compound was prepared by substituting EXAMPLE 134A for *tert*-butyl piperazine-1-carboxylate and 3-oxetanone for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

EXAMPLE 217B

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

5 The title compound was prepared by substituting EXAMPLE 217A for EXAMPLE 130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 13.00 (s, 1H), 9.26 (d, 1H), 8.87 (t, 1H), 8.44 (d, 1H), 8.34 (dd, 1H), 8.12 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.94 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 4.64 (m, 4H), 3.93 (m, 1H), 3.89 (d, 1H), 3.68 (dt, 1H), 3.53-3.35 (m, 3H), 3.07 (m, 4H), 2.77 (s, 2H), 2.72 (d, 1H), 2.44 (d, 10 1H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.85 (t, 1H), 1.39 (t, 2H), 0.94 (s, 6H).

EXAMPLE 218

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

15

EXAMPLE 218A

4-((4-cyclopropylmorpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 134A for EXAMPLE 173A in EXAMPLE 173B.

20

EXAMPLE 218B

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

25 The title compound was prepared by substituting EXAMPLE 218A for EXAMPLE 130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 13.00 (s, 1H), 9.26 (d, 1H), 8.88 (t, 1H), 8.44 (d, 1H), 8.34 (dd, 1H), 8.12 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.94 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.88 (d, 1H), 3.84-3.81 (m, 1H), 3.59 (dt, 1H), 3.50-3.40 (m, 2H), 3.07 (m, 4H), 2.93 (d, 1H), 2.77 (s, 2H), 2.69 (d, 1H), 30 2.34 (dt, 1H), 2.26 (m, 2H), 2.21 (t, 1H), 2.14 (m, 4H), 1.97 (s, 2H), 1.58 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H), 0.45-0.39 (m, 4H).

EXAMPLE 219

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([5-(methylsulfonyl)-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5

EXAMPLE 219A

5-(methylthio)-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

A mixture of EXAMPLE 36B (0.1 g) and sodium methanethiolate (0.04 g) in N,N-dimethylformamide (2 mL) was heated at 80°C overnight. After cooling, 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 MgSO₄, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel using 10-50% ethyl acetate in hexanes to provide the title compound.

15

EXAMPLE 219B

5-(methylsulfonyl)-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

A mixture of EXAMPLE 219A (0.15 g) and 75% meta-chloroperoxybenzoic acid (0.217 g) in chloroform (4 mL) was stirred at room temperature. The reaction mixture was stirred overnight. The reaction mixture was then 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 MgSO₄, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel using 10-50% ethyl acetate in hexanes to provide the title compound.

25

EXAMPLE 219C

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([5-(methylsulfonyl)-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

30

The title compound was prepared by substituting EXAMPLE 219B for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.65 (s, 1H), 8.81 (s, 1H), 8.55 (d, 1H), 8.01 (d, 1H), 7.55 (d, 1H), 7.49-7.50 (m, 2H), 7.37 (d, 2H), 7.05 (d, 2H), 6.67 (dd, 1H), 6.38 (dd, 1H), 6.21 (d, 1H), 4.36 (d, 2H), 3.88 (dd, 2H), 3.13 (s,

4H), 2.95 (s, 2H), 2.36-2.38 (m, 2H), 2.03-2.16 (m, 4H), 1.97 (s, 3H), 1.66-1.69 (m, 2H), 1.38-1.402 (m, 4H), 0.93 (s, 6H).

EXAMPLE 220

5 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)sulfonyl]phenyl}sulfonyl)-
2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 220A

10 4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-3-
(trifluoromethylsulfonyl)benzenesulfonamide

To a solution of EXAMPLE 37C (0.500 g) in tetrahydrofuran (5 mL) was added sodium hydride (0.596 g). Additional tetrahydrofuran (25 mL) was added and the mixture stirred for 30 minutes, then 4-fluoro-3-(trifluoromethylsulfonyl)benzenesulfonamide (1.145
15 g) was added as a solution in tetrahydrofuran (5 mL). After stirring for 2 hours, the reaction mixture was partitioned between 1N aqueous HCl (50 mL) and dichloromethane (200 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. The resulting solid was chromatographed over silica gel (Reveleris 80g) eluting with a gradient of 0.5% to 7.5% methanol/dichloromethane over 30 minutes (flow = 40 mL/min) to provide the
20 title compound.

EXAMPLE 220B

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)sulfonyl]phenyl}sulfonyl)-
25 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 220A for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.66 (s, 1H), 8.42 (s, 1H), 8.35 - 8.22 (m, 1H), 8.01 (s, 1H), 7.49 (d, 4H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (s, 1H), 6.38 (s, 1H), 6.21 (s, 1H), 4.42 (d, 2H), 3.76 (s,
30 2H), 3.59 (s, 2H), 3.10 (s, 6H), 2.15 (s, 6H), 2.02 - 1.74 (m, 6H), 1.40 (s, 2H), 0.93 (s, 6H).

EXAMPLE 221

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
[(4-methyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

5

EXAMPLE 221A

4-((4-methyltetrahydro-2H-pyran-4-yl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting (4-methyltetrahydro-2H-pyran-4-yl)methanol for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

10

EXAMPLE 221B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
[(4-methyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

15

The title compound was prepared by substituting EXAMPLE 221A for
EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.69 (s,
1H), 8.36 (s, 1H), 8.04-8.06 (m, 2H), 7.50-7.53 (m, 3H), 7.41 (d, 1H), 7.35 (d, 2H), 7.04 (d,
2H), 6.67 (dd, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 4.00 (s, 2H), 3.63-3.67 (m, 2H), 3.53-3.58
(m, 2H), 3.09 (s, 4H), 2.82 (s, 2H), 2.27 (s, 2H), 2.15 (s, 2H), 1.58-1.63 (m, 2H), 1.39 (t, 2H),
1.30-1.34 (m, 2H), 1.09 (s, 3H), 0.92 (s, 6H).

20

EXAMPLE 222

ethyl 4-(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-
yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)piperazine-1-
carboxylate

25

EXAMPLE 222A

ethyl 4-(2-nitro-4-sulfamoylphenyl)piperazine-1-carboxylate

The title compound was prepared by substituting ethyl piperazine-1-carboxylate for 1-
(tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

30

EXAMPLE 222B

ethyl 4-(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)piperazine-1-carboxylate

5 The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 222A for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.52 (br. s, 1H), 8.08 (d, 1H), 7.89 (d, 1H), 7.59 (m, 2H), 7.43 (t, 1H), 7.35 (d, 2H), 7.23 (d, 1H), 7.05 (d, 2H), 6.94 (d, 1H), 6.63 (dd, 1H), 6.29 (m, 2H), 4.07 (q, 2H), 3.47 (m, 4H), 3.17 (d, 2H), 3.00 (m, 8H), 2.73 (s, 2H), 2.18 (m, 6H), 1.96 (s, 2H),
10 1.39 (t, 2H), 1.20 (t, 3H), 0.93 (s, 6H).

EXAMPLE 223

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

15

EXAMPLE 223A

The title compound was prepared by substituting 4-(piperidin-4-yl)morpholine for 1-(tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

20

EXAMPLE 223B

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

25 The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 223A for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.53 (br. s, 1H), 8.05 (d, 1H), 7.91 (d, 1H), 7.58 (m, 2H), 7.43 (t, 1H), 7.35 (d, 2H), 7.26 (d, 1H), 7.05 (d, 2H), 6.91 (d, 1H), 6.62 (dd, 1H), 6.29 (m, 2H), 5.76 (s, 1H), 3.57 (m, 4H), 3.20 (m, 2H), 3.01 (m, 4H), 2.80 (t, 2H), 2.73 (s, 2H), 2.47 (m, 4H),
30 2.32 (m, 1H), 2.18 (m, 6H), 1.96 (m, 3H), 1.82 (m, 2H), 1.44 (m, 4H), 0.93 (s, 6H).

EXAMPLE 224

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-[(3-nitro-4-[(3R)-1-(oxetan-3-yl)pyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5

EXAMPLE 224A

(R)-tert-butyl 1-(oxetan-3-yl)pyrrolidin-3-ylcarbamate

The title compound was prepared by substituting (R)-tert-butyl pyrrolidin-3-ylcarbamate for tert-butyl piperazine-1-carboxylate and 3-oxetanone for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

10

EXAMPLE 224B

(R)-1-(oxetan-3-yl)pyrrolidin-3-amine

The title compound was prepared by substituting EXAMPLE 224A for (S)-1-tert-butyl 2-methyl 4,4-difluoropyrrolidine-1,2-dicarboxylate in EXAMPLE 168A.

15

EXAMPLE 224C

(R)-3-nitro-4-(1-(oxetan-3-yl)pyrrolidin-3-ylamino)benzenesulfonamide

The title compound was prepared by substituting 4-fluoro-3-nitrobenzenesulfonamide for 4-chloro-3-nitrobenzenesulfonamide and EXAMPLE 224B for 4-methylpiperazin-1-amine dihydrochloride in EXAMPLE 6A.

20

EXAMPLE 224D

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-[(3-nitro-4-[(3R)-1-(oxetan-3-yl)pyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

25

The title compound was prepared by substituting EXAMPLE 224C for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (400 MHz, pyridine-d₅) δ 13.03 (s, 1H), 9.26 (d, 1H), 8.57 (d, 1H), 8.42 (d, 1H), 8.36 (dd, 1H), 8.09 (d, 1H), 7.66 (m, 1H), 7.64 (d, 1H), 7.44 (m, 2H), 7.07 (m, 2H), 6.86 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (dd, 1H), 4.67 (m, 4H), 3.58 (m, 1H), 3.07 (m, 4H), 2.77 (m, 2H), 2.68 (m, 2H), 2.61 (m, 1H), 2.28 (m, 4H), 2.14 (m, 4H), 1.97 (m, 2H), 1.67 (m, 1H), 1.39 (t, 2H), 0.93 (s, 6H).

30

EXAMPLE 225

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
5 [(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino)-3-
[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 225A

(R)-4-(1-(1,3-difluoropropan-2-yl)pyrrolidin-3-ylamino)-3-
(trifluoromethylsulfonyl)benzenesulfonamide

10 To EXAMPLE 207A (0.217 g) and 4-fluoro-3-
(trifluoromethylsulfonyl)benzenesulfonamide (0.281 g) in tetrahydrofuran (5 mL) was added
diisopropylethylamine (0.559 mL) and the reaction was allowed to stir at room temperature
for 1 hour and was then heated to 50°C for 1 hour. The reaction was concentrated, the
residue was loaded onto silica gel (Reveleris 40 g) and eluted with a gradient of 0.75%
15 methanol/dichloromethane to 7.5% methanol/dichloromethane to provide the title compound.

EXAMPLE 225B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
20 [(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino)-3-
[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E
and EXAMPLE 225A for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300 MHz,
dimethylsulfoxide-d₆) δ 11.69 (s, 1H), 11.52 - 11.23 (m, 1H), 8.17 (d, 1H), 8.04 (d, 1H), 7.95
(d, 1H), 7.54 (d, 1H), 7.53 - 7.50 (m, 1H), 7.48 (d, 1H), 7.34 (d, 2H), 7.10 - 6.97 (m, 4H),
25 6.67 (d, 1H), 6.40 (dd, 1H), 6.18 (d, 1H), 4.60 (dd, 4H), 4.20 (s, 1H), 3.11 - 2.63 (m, 12H),
2.19 (d, 6H), 1.95 (s, 2H), 1.58 (s, 1H), 1.40 (d, 2H), 0.92 (s, 6H).

EXAMPLE 226

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
30 [(1-isopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-
yloxy)benzamide

EXAMPLE 226A

tert-butyl 4-(4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)piperidine-1-carboxylate

5 To a solution of EXAMPLE 82 (800 mg) and tert-butyl 4-aminopiperidine-1-carboxylate (203 mg) in dioxane (10 mL) was added Hunig's Base (1 mL). The mixture was stirred at 120°C overnight. The mixture was diluted with ethyl acetate (200 mL) and washed with water, brine and dried over Na₂SO₄. After filtration and evaporation of solvent, the residue was loaded on a silica gel cartridge and eluted with 3% methanol in dichloromethane
10 to give the title compound.

EXAMPLE 226B

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-(piperidin-4-ylamino)phenylsulfonyl)benzamide

15 To a solution of EXAMPLE 226A (902 mg) in dichloromethane (10 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred at room temperature for 3 hours. The mixture was concentrated under vacuum and co-concentrated with dichloromethane twice to afford the crude product which was used in the next step without further purification.

EXAMPLE 226C

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({4-[(1-isopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

20 To a solution of EXAMPLE 226B (79 mg) in tetrahydrofuran (3 mL) and acetic acid (1 mL) was added acetone (54 mg) and MP-cyanoborohydride (150 mg, 2.25mmol/g). The mixture was stirred overnight. The mixture was filtered. The filtrate was concentrated and the residue was loaded on a silica gel cartridge and eluted with 5 to 10% 7N NH₃ in methanol in dichloromethane to provide the title compound. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ
25 12.09 (s, 1 H), 8.34 (m, 1 H), 7.93 (m, 2 H), 7.66 (m, 4 H), 7.35 (d, 2 H), 7.06 (d, 2 H), 6.89 (m, 1 H), 6.74 (dd, 1 H), 6.59 (dd, 1 H), 6.50 (d, 1 H), 3.11 (m, 6 H), 2.73 (m, 4 H), 2.26 (m,
30 9 H), 1.97 (s, 3 H), 1.40 (t, 2 H), 1.23 (s, 8 H), 0.94 (s, 6 H).

EXAMPLE 227

N-({4-[(1-tert-butylpiperidin-4-yl)amino]-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5

EXAMPLE 227A

1-tert-butylpiperidin-4-amine

To a solution of 1-tert-butylpiperidin-4-one (5.0 g) in methanol (100 mL) and water (10 mL) was added ammonium formate (20.3 g) and 0.5 g of Pd/C (10%). The mixture was stirred overnight. The mixture was filtered and the filtrate was concentrated under vacuum and the residue was diluted with ethyl acetate (500 mL) and washed with water and brine. After drying over Na₂SO₄ and filtration, the solvent was evaporated under vacuum to provide the title compound.

10

15

EXAMPLE 227B

4-(1-tert-butylpiperidin-4-ylamino)-3-nitrobenzenesulfonamide

To a mixture of 4-fluoro-3-nitrobenzenesulfonamide (2.2 g) and EXAMPLE 227A (1.56 g) in tetrahydrofuran (20 mL) was added Hunig's Base (6 mL). The mixture was stirred for 3 days. The mixture was diluted with ethyl acetate (300 mL) and water (100 mL) and stirred until the solid disappeared into the solution. The layers were separated and the organic phase was washed with water and brine, dried over Na₂SO₄, and filtered. The combined aqueous layers were extracted again with ethyl acetate and the combined organic phases were dried over Na₂SO₄. After filtration, the solvent was evaporated to provide the title compound.

20

25

EXAMPLE 227C

N-({4-[(1-tert-butylpiperidin-4-yl)amino]-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

30

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 227B for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.51 (s, 1 H), 8.43 (d, 1 H), 8.04 (m, 1 H), 7.93 (d, 1 H), 7.72 (m, 1 H), 7.56 (dd, 1 H), 7.42 (m, 1 H), 7.34 (m, 3 H), 7.05 (d, 2 H), 6.93 (dd, 1 H), 6.62 (dd, 1 H),

6.28 (m, 1 H), 3.04 (m, 6 H), 2.73 (s, 3 H), 2.25 (m, 9 H), 1.95 (s, 2 H), 1.68 (m, 2 H), 1.32 (m, 9 H), 0.93 (s, 6 H).

EXAMPLE 228

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

EXAMPLE 228A

tert-butyl 3-((2-nitro-4-sulfamoylphenylamino)methyl)piperidine-1-carboxylate
10 The title compound was prepared by substituting *tert*-butyl 3-
(aminomethyl)piperidine-1-carboxylate for (tetrahydropyran-4-yl)methylamine in
EXAMPLE 1F.

EXAMPLE 228B

15 3-nitro-4-(piperidin-3-ylmethylamino)benzenesulfonamide
The title compound was prepared by substituting EXAMPLE 228A for EXAMPLE
113A in EXAMPLE 134A.

EXAMPLE 228C

20 4-((1-(2-methoxyethyl)piperidin-3-yl)methylamino)-3-nitrobenzenesulfonamide
The title compound was prepared by substituting EXAMPLE 228B for EXAMPLE
134A and 2-methoxyethyl bromide for methyl iodide in EXAMPLE 134B.

EXAMPLE 228D

25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
(([1-(2-methoxyethyl)piperidin-3-yl]methyl)amino)-3-nitrophenyl]sulfonyl}-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 228C for EXAMPLE
130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅, 90 °C) δ 12.40 (s, 1H), 8.52 (s,
30 1H), 8.43 (s, 1H), 8.20 (m, 2H), 7.95 (bs, 1H), 7.80 (s, 1H), 7.46 (d, 1H), 7.36 (d, 2H), 7.07
(d, 2H), 7.05 (s, 1H), 6.75 (d, 1H), 6.59 (s, 1H), 6.47 (s, 1H), 3.65-3.50 (m, 5H), 3.20 (s, 3H),
3.04 (m, 5H), 2.81 (s, 3H), 2.74 (m, 1H), 2.24 (m, 7H), 2.06 (s, 2H), 2.00 (s, 2H), 1.75 (m,
1H), 1.57 (m, 2H), 1.42 (t, 2H), 1.15 (m, 1H), 0.95 (s, 6H).

EXAMPLE 229

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-
5 ([1-(cyanomethyl)piperidin-3-yl]methyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

EXAMPLE 229A

4-((1-(cyanomethyl)piperidin-3-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 228B for EXAMPLE
10 134A and 2-bromoacetonitrile for methyl iodide in EXAMPLE 134B.

EXAMPLE 229B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-
15 ([1-(cyanomethyl)piperidin-3-yl]methyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 229A for EXAMPLE
130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 13.06 (s, 1H), 9.03 (s, 1H),
8.42 (s, 1H), 8.30 (d, 1H), 8.10 (d, 1H), 7.68 (m, 2H), 7.44 (d, 2H), 7.08 (m, 3H), 6.99 (d,
1H), 6.75 (d, 1H), 6.51 (m, 2H), 3.78 (m, 2H), 3.43 (d, 1H), 3.13 (m, 1H), 3.04 (m, 4H), 2.76
20 (s, 2H), 2.71-2.65 (m, 3H), 2.52 (m, 1H), 2.25 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.84 (m,
1H), 1.68 (m, 1H), 1.50 (m, 2H), 1.39 (t, 2H), 1.07-0.99 (m, 1H), 0.93 (s, 6H).

EXAMPLE 230

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-
25 [(4-fluoro-1-methylpiperidin-4-yl)methoxy]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-
(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 230A

4-((4-fluoro-1-methylpiperidin-4-yl)methoxy)-3-
30 (trifluoromethylsulfonyl)benzenesulfonamide

To a solution of (4-fluoro-1-methylpiperidin-4-yl)methanol (0.315 g) in
tetrahydrofuran (5 mL) was added sodium hydride (0.342 g). After stirring for 15 minutes, 4-
fluoro-3-(trifluoromethylsulfonyl)benzenesulfonamide (0.658 g) was added as a solution in

tetrahydrofuran (2 mL) followed by additional tetrahydrofuran (5 mL). After stirring for 1 hour, the reaction was poured in dichloromethane (50 mL) and water (25 mL) and the pH of the water layer was adjusted to 8. The organic layer was dried over magnesium sulfate, filtered, and concentrated. The resulting oil was chromatographed over silica gel (Reveleris 40 g) eluting with a gradient of 1.0% to 10% 7N NH₃ in methanol/dichloromethane over 20 minutes then maintaining 10% 7N NH₃ in methanol/dichloromethane for 5 minutes (flow = 30 mL/min) to provide the title compound.

EXAMPLE 230B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 230A for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.63 - 11.57 (m, 1H), 8.40 - 8.36 (m, 1H), 8.28 - 8.17 (m, 1H), 7.97 (s, 1H), 7.53 (d, 1H), 7.50 - 7.32 (m, 5H), 7.05 (d, 1H), 7.05 (d, 1H), 6.68 - 6.61 (m, 1H), 6.35 (s, 1H), 6.22 (s, 1H), 4.55 - 4.40 (m, 2H), 3.06 (s, 8H), 2.79 (s, 4H), 2.06 (d, 13H), 1.39 (s, 2H), 0.93 (s, 6H).

EXAMPLE 231

N-[(5-chloro-6-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 231A

(R)-5-chloro-6-(1-(1,3-difluoropropan-2-yl)pyrrolidin-3-ylamino)pyridine-3-sulfonamide

To EXAMPLE 207A (0.051 g) and EXAMPLE 40A (0.049 g) in dioxane (5 mL) was added diisopropylethylamine (0.131 mL) and the reaction was heated to 75°C for 1 hour then 85°C for 2 days. The reaction was concentrated, loaded onto silica gel (Reveleris 12 g) and eluted with a gradient of 0.75% methanol/dichloromethane to 7.5% methanol/dichloromethane to provide the title compound.

EXAMPLE 231B

N-[(5-chloro-6-[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino)pyridin-3-yl)sulfonyl]-4-(4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 231A for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide- d₆) δ 11.71 (s, 1H), 11.44 - 11.11 (m, 1H), 8.44 (d, 1H), 8.07 (d, 1H), 7.90 (d, 1H), 7.61 (d, 1H), 7.52 (dd, 2H), 7.34 (d, 2H), 7.19 (s, 1H), 7.04 (d, 2H), 6.67 (d, 1H), 6.42 (dd, 1H), 6.16 (s, 1H), 4.77 - 4.39 (m, 5H), 3.19 - 2.63 (m, 11H), 2.19 (s, 7H), 1.91 (d, 3H), 1.38 (s, 2H), 0.92 (s, 6H).

EXAMPLE 232

tert-butyl 4-[(4-[4-(4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]-2-nitrophenyl]amino]piperazine-1-carboxylate

EXAMPLE 232A

tert-butyl 4-nitrosopiperazine-1-carboxylate

In a 500 mL round-bottomed flask, 6N aqueous HCl (30 mL) was cooled to -10 °C, and tert-butyl piperazine-1-carboxylate (10 g) was added. Sodium nitrite (4.5 g) dissolved in 35 mL water was added slowly. NaOH (10 g in 20 mL water) was used to neutralize the solution. Dichloromethane (3x 50 mL) was used to extract the product. After drying over Na₂SO₄ and filtration, the solution was concentrated. The crude product was added to a silica gel column (Analogix, SF65-400 g,) and purified by eluting with 0-30% ethyl acetate in hexane.

EXAMPLE 232B

tert-butyl 4-aminopiperazine-1-carboxylate

In a 100 mL round-bottomed flask was added EXAMPLE 232A (0.15 g) and zinc (1 g) in water/methanol (1:1, 10 mL) to give a suspension. The mixture was cooled to 0 °C. 12N Aqueous HCl (2 mL) was added slowly, and the mixture was stirred at 0 °C for 30 minutes. 2N Aqueous NaOH solution was used to adjust the mixture to basic pH. The mixture was filtered, and extracted with ether (3x 30 mL). After drying over Na₂SO₄, filtration, and concentration, the crude product was added to a silica gel column (Analogix, SF15-12g,) and purified by eluting with 0-25% ethyl acetate in hexane.

EXAMPLE 232C

tert-butyl 4-(2-nitro-4-sulfamoylphenylamino)piperazine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 232B for 1-(tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

5

EXAMPLE 232D

tert-butyl 4-[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]piperazine-1-carboxylate

10 The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 232C for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.47 (br. s, 1H), 8.86 (s, 1H), 8.34 (d, 1H), 7.90 (d, 1H), 7.59 (m, 2H), 7.36 (m, 4H), 7.23 (m, 1H), 7.05 (d, 2H), 6.61 (dd, 1H), 6.27 (m, 2H), 2.99 (m, 5H), 2.76 (m, 6H), 2.19 (m, 6H), 1.96 (s, 2H), 1.41 (m, 11H), 1.24 (m, 4H), 0.93 (s, 6H).

15

EXAMPLE 233

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-(pentafluoro-λ⁶-sulfanyl)-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

20

EXAMPLE 233A

2-(5-bromo-2-nitrophenyl)sulfur pentafluoride

To a solution of 3-bromophenylsulfur pentafluoride (2.18 g) in concentrated H₂SO₄ (5 mL) was added KNO₃ (780 mg). The mixture was stirred overnight. The mixture was
25 diluted with diethyl ether (100 mL) and washed with water and brine. After drying over Na₂SO₄ and filtration, the solvent was evaporated under vacuum to provide the title compound.

EXAMPLE 233B

30 2-(5-bromo-2-aminophenyl)sulfur pentafluoride

EXAMPLE 233A (6.4g) and tetrahydrofuran (300 mL) were added to Ra-Ni, (12.80 g) in a 50 mL pressure bottle and the mixture stirred for 2 hours at 30 psi and room

temperature. The mixture was filtered through a nylon membrane and the filtrate was concentrated under vacuum to provide the title compound.

EXAMPLE 233C

5 4-bromo-2-pentafluorosulfanyl-N-(tetrahydro-2H-pyran-4-ylmethyl)aniline

To a solution of EXAMPLE 233B (4.4 g) in methanol (50 mL) was added tetrahydro-2H-pyran-4-carbaldehyde (1.68 g) and decaborane (1.1 g). The mixture was stirred and monitored by thin layer chromatography. More tetrahydro-2H-pyran-4-carbaldehyde (500 mg) was added to the stirring mixture to drive the reaction to completion. The reaction
10 mixture was concentrated under vacuum and ethyl acetate (500 mL) and brine (200 mL) were added. The organic phase was dried over Na₂SO₄. Filtration and evaporation of the solvent and flash chromatography (20% ethyl acetate in hexane) gave the title compound.

EXAMPLE 233D

15 4-thioacetoxy-2-pentafluorosulfanyl-N-(tetrahydro-2H-pyran-4-ylmethyl)aniline

To a solution of EXAMPLE 233C (456 mg) and potassium ethanethioate (197 mg) in dioxane (4 mL) was added tris(dibenzylideneacetone)dipalladium(0) (27 mg) and xantphos (33 mg) followed by N,N-diisopropylethylamine (0.5 mL). The mixture was purged with argon, sealed and stirred under microwave irradiation for 60 minutes at 120°C. The mixture
20 was dissolved in ethyl acetate (300 mL) and water (100 mL). The organic phase was washed with brine and dried over Na₂SO₄. Filtration and evaporation of the solvent followed by flash chromatography (20% ethyl acetate in hexane) provided the title compound.

EXAMPLE 233E

25 3-pentafluorosulfanyl-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenylsulfonamide

N-chlorosuccinimide (527 mg) was added to a mixture of 2N aqueous HCl (1.5 mL) and acetonitrile (12 mL) and then cooled to 0°C. A solution of EXAMPLE 233D (386 mg) in acetonitrile (3 mL) was added to the mixture which was then stirred at 0°C for 2 hours, and then diluted with ethyl acetate (300 mL) and washed with brine and dried over Na₂SO₄. After
30 filtration and evaporation of solvent, the residue was dissolved in isopropyl alcohol (20 mL) and cooled to 0°C with stirring. Then, ammonium hydroxide (conc. 10 mL) was added to mixture. After stirring for 2 hours, the mixture was concentrated under vacuum and the residue was added to ethyl acetate (400 mL) and water (150 mL). The organic layer was

washed with brine and dried over Na₂SO₄. After filtration and evaporation of solvent, the residue was purified by flash column (20% ethyl acetate in dichloromethane) to provide the title compound.

5

EXAMPLE 233F

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({3-(pentafluoro-lambda~6~-sulfanyl)-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 233E for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.71 (s, 1 H), 11.33 (m, 1 H), 8.12 (m, 2 H), 7.72 (d, 1 H), 7.54 (m, 3 H), 7.33 (m, 2 H), 7.02 (m, 3 H), 6.67 (m, 2 H), 6.42 (m, 1 H), 6.16 (d, 1 H), 3.82 (m, 2 H), 3.21 (m, 4 H), 3.05 (m, 4 H), 2.73 (s, 2 H), 2.21 (m, 8 H), 1.97 (m, 3 H), 1.29 (m, 4 H), 0.92 (s, 6 H).

15

EXAMPLE 234

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({4-[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

20

EXAMPLE 234A

4-vinyltetrahydro-2H-pyran-4-ol

Dihydro-2H-pyran-4(3H)-one (8.01 g) in anhydrous ethyl ether (50 mL) was treated with 1.0 M vinylmagnesium bromide (104 mL) over 20 minutes at 0°C. The reaction mixture was stirred at room temperature overnight. The reaction was quenched with saturated NH₄Cl, and the organic layer was separated. The aqueous layer was extracted with additional ethyl ether three times. The combined organic layers were washed with brine, dried, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel using 20% ethyl acetate in hexanes to provide the title compound.

30

EXAMPLE 234B

4-methoxy-4-vinyltetrahydro-2H-pyran

To a solution of EXAMPLE 234A (9.4 g) in tetrahydrofuran (150 mL) was added 60% sodium hydride (5.28 g) at 0°C portionwise. After the addition was complete, the solution

was heated under reflux for three hours. After cooling, to this suspension was added dimethyl sulfate (8.41 mL) slowly. The solution was heated under reflux overnight, cooled to room temperature, and hydrolyzed with cool saturated aqueous NH_4Cl . After extraction with diethyl ether several times, the combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated. The residue was purified by flash column chromatograph
5 on silica gel using 1-10% ethyl acetate in hexanes to provide the title compound.

EXAMPLE 234C

4-methoxytetrahydro-2H-pyran-4-carbaldehyde

10 EXAMPLE 234B (4.3 g) in tetrahydrofuran (200 mL) and water (67 mL) was treated with 4% osmium tetroxide in water (9.24 mL). To this solution was added potassium periodate (13.91 g) portionwise over 2 hours. The solution was stirred overnight at room temperature. Water was added to the mixture followed by repeat extractions with diethyl ether. The combined organic layers were dried over MgSO_4 , filtered, and concentrated. The
15 residue was purified by flash column chromatography on silica gel using 5-20% ethyl acetate in hexanes to provide the title compound.

EXAMPLE 234D

(4-methoxytetrahydro-2H-pyran-4-yl)methanol

20 EXAMPLE 234C (1.8 g) in 2-propanol (28 mL) and water (7 mL) was cooled to 0 °C. To this solution was added sodium borohydride (0.709 g). The solution 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 the mixture was decanted. The
25 combined organic solutions were concentrated. The residue was purified by flash chromatography on silica gel eluting 1:1 ethyl acetate: hexane to provide the title compound.

EXAMPLE 234E

4-((4-methoxytetrahydro-2H-pyran-4-yl)methoxy)-3-nitrobenzenesulfonamide

30 The title compound was prepared by substituting EXAMPLE 234D for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

EXAMPLE 234F

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 234E for

5 EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.68 (s, 1H), 8.36 (s, 1H), 8.04-8.07 (m, 2H), 7.50-7.53 (m, 3H), 7.45 (d, 1H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 4.21 (s, 2H), 3.65-3.67 (m, 2H), 3.53-3.56 (m, 2H), 3.19 (s, 3H), 3.10 (s, 4H), 2.86 (s, 2H), 2.30 (s, 4H), 2.15 (s, 2H), 1.96 (s, 2H), 1.61-1.74 (m, 4H), 1.39 (t, 2H), 0.93 (s, 6H).

10

EXAMPLE 235

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy}-3-nitrophenyl)sulfonyl]-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

15

EXAMPLE 235A

(R)-*tert*-butyl 3-(2-nitro-4-sulfamoylphenoxy)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 24A.

20

EXAMPLE 235B

(R)-*tert*-butyl 3-(4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-
dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-
nitrophenoxy)pyrrolidine-1-carboxylate

25

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 235A for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 235C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
30 {[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy}-3-nitrophenyl)sulfonyl]-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

To a solution of EXAMPLE 235B (0.230 g) in dichloromethane (3 mL) was added trifluoroacetic acid (0.377 mL). After stirring for 4 hours, the reaction was concentrated then

dissolved in dichloromethane (3 mL) and treated with 1,3-difluoropropan-2-one (0.028 g) followed by sodium triacetoxyborohydride (0.078 g). After stirring for 4 hours, the reaction was quenched by the addition of saturated aqueous NaHCO₃ and dichloromethane (5 mL). The reaction was diluted with dichloromethane (250 mL) and saturated aqueous NaHCO₃ (100 mL) was added. The organic layer was separated, washed with brine (100 mL), dried over magnesium sulfate, filtered and concentrated. Trituration with acetonitrile gave the title compound. ¹H NMR (300 MHz, dimethylsulfoxide- d₆) δ 11.67 (s, 1H), 8.34 (s, 1H), 8.03 (s, 2H), 7.52 (d, 3H), 7.35 (d, 3H), 7.04 (d, 2H), 6.75 - 6.60 (m, 1H), 6.40 (s, 1H), 6.20 (s, 1H), 5.17 - 5.06 (m, 1H), 4.60 (d, 4H), 2.98 (d, 12H), 2.37 - 2.02 (m, 6H), 1.96 (s, 3H), 1.39 (s, 2H), 0.93 (s, 6H).

EXAMPLE 236

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(3-nitro-4-([4-(oxetan-3-yl)piperazin-1-yl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 236A

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(3-nitro-4-(piperazin-1-ylamino)phenylsulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 232D for EXAMPLE 1A in EXAMPLE 1B.

EXAMPLE 236B

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(3-nitro-4-([4-(oxetan-3-yl)piperazin-1-yl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 236A for tert-butyl piperazine-1-carboxylate and oxetan-3-one for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A. ¹H NMR (400 MHz, dimethylsulfoxide-d₆) δ 11.67 (br. s, 1H), 9.20 (s, 1H), 8.53 (d, 1H), 8.04 (d, 1H), 7.83 (dd, 1H), 7.53 (m, 4H), 7.34 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.39 (m, 1H), 6.18 (d, 1H), 4.55 (t, 2H), 4.44 (t, 2H), 3.47 (m, 1H), 3.06 (m, 4H), 2.88 (m, 4H), 2.74 (m, 4H), 2.09 (m, 11H), 1.38 (t, 2H), 0.91 (s, 6H).

EXAMPLE 237

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(3-nitro-4-([4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5 The title compound was prepared by substituting EXAMPLE 236A for tert-butyl piperazine-1-carboxylate and dihydro-2H-pyran-4(3H)-one for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A. ¹H NMR (400 MHz, pyridine-d₅) δ 13.05 (br. s, 1H), 9.27 (d, 1H), 9.23 (s, 1H), 8.44 (m, 2H), 8.12 (d, 1H), 7.68 (m, 3H), 7.44 (m, 2H), 7.06 (m, 2H), 6.75 (dd, 1H), 6.51 (m, 2H), 4.02 (m, 2H), 3.31 (m, 2H), 3.06 (m, 4H), 2.91 (m, 5H),
10 2.76 (s, 2H), 2.38 (m, 2H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.65 (m, 2H), 1.39 (m, 7H), 0.93 (s, 6H).

EXAMPLE 238

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-[(3R)-tetrahydrofuran-3-ylamino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 238A

(R)-3-nitro-4-(tetrahydrofuran-3-ylamino)benzenesulfonamide

20 The title compound was prepared by substituting (R)-tetrahydrofuran-3-amine for 4-methylpiperazin-1-amine dihydrochloride in EXAMPLE 6A.

EXAMPLE 238B

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-[(3R)-tetrahydrofuran-3-ylamino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

30 The title compound was prepared by substituting EXAMPLE 238A for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. ¹H NMR (400 MHz, dimethylsulfoxide-d₆) δ 11.59 (s, 1H), 8.47 (d, 1H), 8.19 (m, 2H), 7.97 (d, 1H), 7.74 (m, 1H), 7.52 (d, 1H), 7.46 (t, 1H), 7.34 (m, 2H), 7.05 (m, 2H), 6.96 (d, 1H), 6.89 (d, 1H), 6.65 (dd, 1H), 6.33 (m, 1H), 6.22 (d, 1H), 4.31 (m, 1H), 3.92 (m, 1H), 3.87 (m, 1H), 3.76 (m, 1H), 3.69 (m, 1H), 3.04 (m, 4H), 2.73 (m, 2H), 2.33 (m, 1H), 2.18 (m, 6H), 1.95 (m, 2H), 1.88 (m, 1H), 1.39 (t, 2H), 0.92 (s, 6H).

EXAMPLE 239

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(4-
5 [(4,4-difluorocyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

EXAMPLE 239A

tert-butyl (4,4-difluorocyclohexyl)methylcarbamate

Tert-butyl (4-oxocyclohexyl)methylcarbamate (5 g) and diethylaminosulfur trifluoride
10 (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 by-product in a 3:2 ratio. The crude
material was taken up in tetrahydrofuran (70 mL) and water (30 mL), and N-
15 methylmorpholine-N-oxide (1.75 g), and OsO₄ (2.5 wt % solution in t-butanol) were added,
and the mixture was stirred for 24 hours. Na₂S₂O₃ (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
20 acetate in hexanes to provide the title compound.

EXAMPLE 239B

(4,4-difluorocyclohexyl)methanamine

A solution of EXAMPLE 239A (3 g) in dichloromethane (35 mL), trifluoroacetic acid
25 (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 provide the title compound as its trifluoroacetic acid
salt.

EXAMPLE 239C

30 4-((4,4-difluorocyclohexyl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 239B for
(tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 239D

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-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

5 The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E
and EXAMPLE 239C for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300MHz,
dimethylsulfoxide-d₆) δ 12.40 (s, 1H), 11.61 (br s, 1H), 8.53 (m, 1H), 8.50 (d, 1H), 7.99 (d,
1H), 7.73 (d, 1H), 7.49 (m, 2H), 7.32 (d, 2H), 7.04 (d, 2H), 7.00 (d, 1H), 6.65 (d, 1H), 6.32
(s, 1H), 6.21 (s, 1H), 3.37 (m, 4H), 3.06 (m, 4H), 2.73 (m, 2H), 2.18 (m, 4H), 1.97 (m, 4H),
10 1.81 (m, 4H), 1.38 (m, 2H), 1.20 (m, 4H), 0.92 (s, 6H).

EXAMPLE 240

N-({4-[(1-tert-butylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-4-
(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-
15 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 240A

4-(1-tert-butylpiperidin-4-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

To a mixture of 4-fluoro-3-(trifluoromethylsulfonyl)benzenesulfonamide (307 mg)
20 and EXAMPLE 227A (156 mg) in tetrahydrofuran (4 mL) was added Hunig's Base (1 mL).
The mixture was stirred for 3 days. The mixture was diluted with ethyl acetate (300 mL) and
water (100 mL) and stirred until the solid disappeared into the solution. The layers were
separated and the organic phase was washed with water, brine and dried over Na₂SO₄. After
filtration, the combined aqueous layers were extracted again with ethyl acetate and the
25 combined organic phase was dried over Na₂SO₄. After filtration, the solvent was evaporated
to provide the title compound.

EXAMPLE 240B

N-({4-[(1-tert-butylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-4-
30 (4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E
and EXAMPLE 240A for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300 MHz,

dimethylsulfoxide- d_6) δ 11.53 (s, 1 H), 8.04 (s, 1 H), 7.94 (d, 1 H), 7.86 (m, 1 H), 7.55 (d, 2 H), 7.44 (d, 1 H), 7.33 (m, 3 H), 7.05 (d, 2 H), 6.92 (m, 1 H), 6.62 (dd, 1 H), 6.43 (m, 1 H), 6.29 (d, 2 H), 3.79 (m, 1 H), 3.05 (m, 6 H), 2.73 (s, 3 H), 2.19 (m, 8 H), 1.96 (s, 3 H), 1.27 (m, 12 H), 0.92 (s, 6 H).

5

EXAMPLE 241

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

10

EXAMPLE 241A

tert-butyl 2-((4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino)methyl)morpholine-4-
 carboxylate

The title compound was prepared by substituting tert-butyl 2-
 (aminomethyl)morpholine-4-carboxylate for (tetrahydropyran-4-yl)methylamine and 4-
 fluoro-3-(trifluoromethylsulfonyl)benzenesulfonamide for 4-fluoro-3-
 nitrobenzenesulfonamide in EXAMPLE 1F.

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EXAMPLE 241B

tert-butyl 2-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-
 dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-
 (trifluoromethylsulfonyl)phenylamino)methyl)morpholine-4-carboxylate

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The title compound was prepared by substituting EXAMPLE 241A for EXAMPLE
 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G.

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EXAMPLE 241C

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-
 enyl)methyl)piperazin-1-yl)-N-(4-(morpholin-2-ylmethylamino)-3-
 (trifluoromethylsulfonyl)phenylsulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 241B for EXAMPLE
 1A in EXAMPLE 1B.

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EXAMPLE 241D

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

The title compound was prepared by substituting EXAMPLE 241C for tert-butyl
 5 piperazine-1-carboxylate and oxetan-3-one for 4'-chlorobiphenyl-2-carboxaldehyde in
 EXAMPLE 1A. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.69 (s, 1H), 8.15 (d, 1H),
 8.04 (d, 1H), 7.92 (dd, 1H), 7.54 (d, 1H), 7.51 (t, 1H), 7.48 (d, 1H), 7.34 (d, 2H), 7.25 (m,
 1H), 7.04 (m, 3H), 6.68 (dd, 1H), 6.41 (m, 1H), 6.19 (d, 1H), 4.54 (t, 2H), 4.43 (m, 2H), 3.85
 (m, 1H), 3.69 (m, 1H), 3.52 (m, 1H), 3.48 (m, 1H), 3.39 (m, 2H), 3.07 (m, 4H), 2.77 (br s,
 10 2H), 2.69 (d, 1H), 2.56 (d, 1H), 2.21 (br s, 4H), 2.15 (t, 2H), 1.94 (m, 3H), 1.76 (t, 1H), 1.38
 (t, 2H), 0.92 (s, 6H).

EXAMPLE 242

N-[(5-chloro-6-{{(4-fluorotetrahydro-2H-pyran-4-yl)methyl}amino}pyridin-3-yl)sulfonyl]-4-
 15 (4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 242A

5-chloro-6-((4-fluorotetrahydro-2H-pyran-4-yl)methylamino)pyridine-3-sulfonamide

20 The title compound was prepared by substituting EXAMPLE 40A for 4-fluoro-3-
 nitrobenzenesulfonamide in EXAMPLE 138D.

EXAMPLE 242B

N-[(5-chloro-6-{{(4-fluorotetrahydro-2H-pyran-4-yl)methyl}amino}pyridin-3-yl)sulfonyl]-4-
 25 (4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 242A for
 EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.71 (s,
 1H), 8.41 (d, 1H), 8.07 (d, 1H), 7.93 (d, 1H), 7.60 (d, 1H), 7.51-7.53 (m, 2H), 7.40 (s, 1H),
 30 7.33-7.35 (m, 2H), 7.03-7.05 (m, 2H), 6.68 (dd, 1H), 6.42 (dd, 1H), 6.16 (d, 1H), 3.77 (d,
 1H), 3.69-3.71 (m, 3H), 3.48-3.53 (m, 2H), 3.07 (s, 4H), 2.76 (s, 2H), 2.14-2.20 (m, 6H), 1.96
 (s, 2H), 1.65-1.76 (m, 4H), 1.38 (t, 2H), 0.93 (s, 6H).

EXAMPLE 243

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

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EXAMPLE 243A

5-chloro-6-(1-cyclopropylpiperidin-4-ylamino)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 40A for 4-chloro-3-nitrobenzenesulfonamide, 1-cyclopropylpiperidin-4-amine for 4-methylpiperazin-1-amine dihydrochloride and Hunig's base for N¹,N¹,N²,N²-tetramethylethane-1,2-diamine in EXAMPLE 6A.

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EXAMPLE 243B

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

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The title compound was prepared by substituting EXAMPLE 243A for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (400MHz, dimethylsulfoxide-d₆) δ 11.67 (s, 1H), 8.40 (d, 1H), 8.05 (d, 1H), 7.88 (d, 1H), 7.56 (d, 1H), 7.50 (m, 2H), 7.34 (d, 2H), 7.03 (d, 2H), 6.97 (br d, 1H), 6.66 (dd, 1H), 6.40 (m, 1H), 6.16 (d, 1H), 4.04 (m, 1H), 3.03 (br m, 6H), 2.73 (s, 2H), 2.42 (br m, 2H), 2.18 (br m, 6H), 1.95 (s, 2H), 1.80 (m, 3H), 1.62 (m, 2H), 1.38 (t, 2H), 0.91 (s, 6H), 0.47 (m, 2H), 0.40 (br m, 2H).

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EXAMPLE 244

N-[(5-chloro-6-([(2S)-4-(cyanomethyl)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

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EXAMPLE 244A

(S)-tert-butyl 2-((3-chloro-5-sulfamoylpyridin-2-yloxy)methyl)morpholine-4-carboxylate

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The title compound was prepared by substituting (S)-tert-butyl 2-(hydroxymethyl)-morpholine-4-carboxylate for tetrahydro-2H-pyran-4-yl-methanol and EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

EXAMPLE 244B

(S)-5-chloro-6-(morpholin-2-ylmethoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 244A for EXAMPLE 113A in EXAMPLE 134A.

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EXAMPLE 244C

(S)-5-chloro-6-((4-(cyanomethyl)morpholin-2-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 244B for EXAMPLE 134A and 2-bromoacetonitrile for methyl iodide in EXAMPLE 134B.

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EXAMPLE 244D

N-[(5-chloro-6-{[(2S)-4-(cyanomethyl)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 244C for EXAMPLE 130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 12.99 (s, 1H), 9.09 (d, 1H), 8.70 (d, 1H), 8.42 (d, 1H), 8.12 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.75 (dd, 1H), 6.53 (d, 1H), 6.48 (m, 1H), 4.55 (dd, 1H), 4.43 (dd, 1H), 4.05 (m, 1H), 3.85 (d, 1H), 3.76 (s, 2H), 3.63 (dt, 1H), 3.06 (m, 4H), 2.91 (d, 1H), 2.77 (s, 2H), 2.58 (d, 1H), 2.51-2.44 (m, 2H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

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EXAMPLE 245

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

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EXAMPLE 245A

(S)-5-chloro-6-((4-(2-(dimethylamino)acetyl)morpholin-2-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 244B for EXAMPLE 134A and 2-(dimethylamino)acetyl chloride hydrochloride for methyl iodide in EXAMPLE 134B.

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EXAMPLE 245B

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 245A for EXAMPLE 130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 13.00 (s, 1H), 9.09 (d, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 8.11 (t, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.76 (s, 1H), 6.54 (s, 1H), 6.49 (s, 1H), 4.85-4.46 (m, 3H), 4.45-3.87 (m, 3H), 3.50 (m, 1H), 3.37 (dd, 1H), 3.21 (m, 2H), 3.07 (m, 4H), 2.86 (t, 1H), 2.77 (s, 2H), 2.27 (m, 8H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

EXAMPLE 246

N-[(5-chloro-6-[(2R)-4-(cyanomethyl)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 246A

(R)-tert-butyl 2-((3-chloro-5-sulfamoylpyridin-2-yloxy)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting (R)-tert-butyl 2-(hydroxymethyl)-morpholine-4-carboxylate for tetrahydro-2H-pyran-4-yl-methanol and EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

EXAMPLE 246B

(R)-5-chloro-6-(morpholin-2-ylmethoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 246A for EXAMPLE 113A in EXAMPLE 134A.

EXAMPLE 246C

(R)-5-chloro-6-((4-(cyanomethyl)morpholin-2-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 246B for EXAMPLE 134A and 2-bromoacetonitrile for methyl iodide in EXAMPLE 134B.

EXAMPLE 246D

N-[(5-chloro-6-[(2R)-4-(cyanomethyl)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-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 246C for EXAMPLE
5 130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 12.99 (s, 1H), 9.09 (d, 1H),
8.70 (d, 1H), 8.42 (d, 1H), 8.12 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.75 (dd,
1H), 6.53 (d, 1H), 6.48 (m, 1H), 4.55 (dd, 1H), 4.43 (dd, 1H), 4.05 (m, 1H), 3.85 (d, 1H), 3.76
(s, 2H), 3.63 (dt, 1H), 3.06 (m, 4H), 2.91 (d, 1H), 2.77 (s, 2H), 2.58 (d, 1H), 2.51-2.44 (m,
2H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

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EXAMPLE 247

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

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EXAMPLE 247A

(R)-5-chloro-6-((4-(2-(dimethylamino)acetyl)morpholin-2-yl)methoxy)pyridine-3-
sulfonamide

The title compound was prepared by substituting EXAMPLE 246B for EXAMPLE
20 134A and 2-(dimethylamino)acetyl chloride hydrochloride for methyl iodide in EXAMPLE
134B.

EXAMPLE 247B

N-[(5-chloro-6-[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-
25 yl)sulfonyl]-4-(4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-
yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 247A for EXAMPLE
130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 13.00 (s, 1H), 9.09 (d, 1H),
8.69 (s, 1H), 8.42 (s, 1H), 8.11 (t, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.76 (s, 1H),
30 6.54 (s, 1H), 6.49 (s, 1H), 4.85-4.46 (m, 3H), 4.45-3.87 (m, 3H), 3.50 (m, 1H), 3.37 (dd, 1H),
3.21 (m, 2H), 3.07 (m, 4H), 2.86 (t, 1H), 2.77 (s, 2H), 2.27 (m, 8H), 2.14 (m, 4H), 1.97 (s,
2H), 1.39 (t, 2H), 0.94 (s, 6H).

EXAMPLE 248

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

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EXAMPLE 248A

5-bromo-3-fluoro-2-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine

The title compound was prepared by substituting 5-bromo-2,3-difluoropyridine for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 37C for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

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EXAMPLE 248B

tert-butyl 5-fluoro-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridin-3-ylcarbamate

EXAMPLE 248A (0.308 g), tert-butyl carbamate (0.141 g), palladium(II) acetate (0.011 g), Xantphos (0.043 g) and cesium carbonate (0.489 g) were combined with dioxane (5.0 mL) in a 20-mL vial equipped with a magnetic stir bar. The vial was flushed with nitrogen, capped and stirred at 100°C overnight. Additional palladium(II) acetate (0.011 g), Xantphos (0.043 g) and tert-butyl carbamate (0.141 g) were added and heating was continued at 100°C for 8 hours. The cooled reaction mixture was diluted with ethyl acetate, washed with water and brine, dried (MgSO₄), filtered and concentrated. The concentrate was chromatographed on silica gel with 7-25% ethyl acetate in hexanes as the eluent.

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EXAMPLE 248C

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 SO₂-containing solution. Separately, EXAMPLE 248B (0.295 g) was added to a mixture of 1,4-dioxane (3.2 mL) and concentrated HCl (8 mL) at 0°C. After stirring for 15 minutes, a solution of sodium nitrite (0.065 g) in water (2 mL) was added dropwise and stirring was continued at 0°C for 3 hours. Copper(I) chloride (0.042 g) and then the freshly prepared solution of diazotized material were added sequentially to the previously prepared SO₂-containing solution. The resulting solution was stirred for 30 minutes and then extracted with ethyl acetate (2 x 125 mL). The

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combined extracts were dried (MgSO₄), filtered and concentrated. The concentrate was chromatographed on silica gel with 5% ethyl acetate in hexanes as the eluent.

EXAMPLE 248D

5-fluoro-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

5 EXAMPLE 248C (0.08 g) in isopropanol (2 mL) at 0°C was treated with ammonium hydroxide (1.697 mL), stirred overnight and then concentrated to dryness. The obtained solid was slurried in water, filtered, rinsed with water and dried under high vacuum to provide the title compound.

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EXAMPLE 248E

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 248D for EXAMPLE 15 11B in EXAMPLE 11D. ¹H NMR (500 MHz, pyridine-d₅) δ 13.05 (s, 1H), 9.03 (d, 1H), 8.44 (dd, 1H), 8.41 (d, 1H), 8.10 (d, 1H), 7.67 (m, 1H), 7.65 (d, 1H), 7.44 (m, 2H), 7.07 (m, 2H), 6.77 (dd, 1H), 6.53 (d, 1H), 6.49 (dd, 1H), 4.55 (d, 2H), 3.80 (m, 4H), 3.08 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.88 (m, 4H), 1.39 (t, 2H), 0.94 (s, 6H).

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EXAMPLE 250

N-({5-chloro-6-[3-hydroxy-2-(hydroxymethyl)-2-methylpropoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

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EXAMPLE 250A

5-chloro-6-((3-methyloxetan-3-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting (3-methyloxetan-3-yl)methanol for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

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EXAMPLE 250B

N-({5-chloro-6-[3-hydroxy-2-(hydroxymethyl)-2-methylpropoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 250A for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500 MHz, pyridine-d₅) δ 13.05 (s, 1H), 9.22 (d, 1H), 8.51 (d, 1H), 8.42 (d, 1H), 8.09 (d, 1H), 7.66 (t, 2H), 7.43 - 7.46 (m, 2H), 7.04 - 7.09 (m, 2H), 6.75 (dd, 1H), 6.45 - 6.54 (m, 2H), 4.47 (s, 2H), 3.81 - 3.84 (m, 2H), 3.74 (d, 2H), 3.03 - 3.11 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.10 - 2.17 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 1.16 (s, 3H), 0.94 (s, 6H).

EXAMPLE 251

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]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 251A

5-bromo-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting (4-fluorotetrahydro-2H-pyran-4-yl)methanol for (tetrahydro-2H-pyran-4-yl)methanol and 5-bromo-6-chloropyridine-3-sulfonamide for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

EXAMPLE 251B

6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

To a suspension of 5-bromo-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide (200 mg) and cyclohexene (0.549 mL) in ethyl acetate (10 mL) was added 10% palladium on carbon (57.6 mg). The suspension was stirred for 60 minutes at 120°C. The reaction mixture was filtered and concentrated. The product was purified by reverse-phase flash chromatography (C18, 150g, 10%-100% acetonitrile/H₂O/trifluoroacetic acid 0.1%).

EXAMPLE 251C

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]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 251B for EXAMPLE
5 11B in EXAMPLE 11D. ¹H NMR (500 MHz, pyridine-d₅) δ 13.06 (s, 1H), 9.29 (d, 1H), 8.50
(dd, 1H), 8.41 (d, 1H), 8.07 (d, 1H), 7.66 - 7.70 (m, 1H), 7.64 (d, 1H), 7.44 (d, 2H), 7.07 (d,
2H), 6.84 (d, 1H), 6.75 (dd, 1H), 6.52 (d, 1H), 6.49 (dd, 1H), 4.50 (d, 2H), 3.81 - 3.89 (m,
2H), 3.70 - 3.81 (m, 2H), 3.02 - 3.12 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.10 - 2.18 (m, 4H),
1.97 (s, 2H), 1.77 - 1.94 (m, 4H), 1.39 (t, 2H), 0.94 (s, 6H).

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EXAMPLE 252

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-
([4-(1,3-difluoropropan-2-yl)morpholin-2-yl]methyl)amino)-3-nitrophenyl}sulfonyl)-2-
(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

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EXAMPLE 252A

tert-butyl (4-(1,3-difluoropropan-2-yl)morpholin-2-yl)methylcarbamate

The title compound was prepared by substituting 1,3-difluoropropan-2-one for 4'-
chlorobiphenyl-2-carboxaldehyde and tert-butyl morpholin-2-ylmethylcarbamate for tert-
20 butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 252B

(4-(1,3-difluoropropan-2-yl)morpholin-2-yl)methanamine

A solution of EXAMPLE 252A (538 mg) in dioxane (4 mL) was treated with 4.0M
25 HCl in dioxane solution (1.8 mL). The reaction was stirred at room temperature overnight.
The reaction mixture was concentrated under vacuum and used without further purification.

EXAMPLE 252C

4-((4-(1,3-difluoropropan-2-yl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

30 The title compound was prepared by substituting EXAMPLE 252B for
(tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 252D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
({[4-(1,3-difluoropropan-2-yl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-
(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 252C for EXAMPLE
5 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. ¹H NMR (300 MHz,
dimethylsulfoxide-d₆) δ 11.64 (s, 1H), 8.59 (t, 1H), 8.57 (d, 1H), 8.04 (d, 1H), 7.83 (dd, 1H),
7.51 (m, 3H), 7.33 (d, 2H), 7.07 (d, 1H), 7.03 (d, 2H), 6.66 (dd, 1H), 6.39 (m, 1H), 6.19 (d,
1H), 4.69 (t, 2H), 4.57 (t, 2H), 3.85 (m, 1H), 3.70 (m, 1H), 3.52 (m, 2H), 3.41 (m, 2H), 3.07
(br s, 4H), 2.91 (d, 1H), 2.74 (m, 3H), 2.59 (m, 1H), 2.43 (m, 1H), 2.20 (m, 4H), 2.15 (m,
10 2H), 1.95 (br s, 2H), 1.39 (t, 2H), 0.92 (s, 6H).

EXAMPLE 253

N-[(5-chloro-6-{[1-(cyanomethyl)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-pyrrolo[2,3-
15 b]pyridin-5-yloxy)benzamide

EXAMPLE 253A

tert-butyl 4-((3-chloro-5-sulfamoylpyridin-2-yloxy)methyl)piperidine-1-carboxylate

The title compound was prepared by substituting tert-butyl 4-
20 (hydroxymethyl)piperidine-1-carboxylate for tetrahydro-2H-pyran-4-yl)methanol and
EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

EXAMPLE 253B

5-chloro-6-(piperidin-4-ylmethoxy)pyridine-3-sulfonamide ditrifluoroacetic acid

25 The title compound was prepared by substituting EXAMPLE 253A for EXAMPLE
39A in EXAMPLE 39B.

EXAMPLE 253C

5-chloro-6-((1-(cyanomethyl)piperidin-4-yl)methoxy)pyridine-3-sulfonamide

30 EXAMPLE 253B (0.061 g), 2-chloroacetonitrile (0.017 g), sodium carbonate (0.025
g) and N,N-dimethylformamide (1 mL) were combined in a 4-mL vial and heated at 60°C
overnight. The cooled reaction mixture was diluted with ethyl acetate, washed with water

and brine, dried (MgSO₄), filtered and concentrated. The concentrate was chromatographed on silica gel with 2-10% methanol in CH₂Cl₂ as the eluent.

EXAMPLE 253D

5 N-[(5-chloro-6-[[1-(cyanomethyl)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 253C for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (400 MHz, pyridine-
10 d₅) δ 13.04 (s, 1H), 9.14 (d, 1H), 8.41 (d, 1H), 8.10 (d, 1H), 7.66 (t, 2H), 7.44 (m, 2H), 7.07 (m, 2H), 6.74 (dd, 1H), 6.50 (m, 2H), 4.18 (d, 2H), 3.64 (s, 2H), 3.05 (s, 4H), 2.77 (m, 4H), 2.24 (m, 4H), 2.13 (m, 4H), 1.97 (s, 2H), 1.69 (m, 3H), 1.41 (m, 4H), 0.93 (s, 6H).

EXAMPLE 254

15 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]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 254A

20 (R)-tert-butyl 3-(2-nitro-4-sulfamoylphenylamino)pyrrolidine-1-carboxylate

The title compound was prepared by substituting (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate for 1-(tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 254B

25 (R)-3-nitro-4-(pyrrolidin-3-ylamino)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 254A for EXAMPLE 113A in EXAMPLE 134A.

EXAMPLE 254C

30 (R)-4-(1-(2-(2-methoxyethoxy)ethyl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

To a solution of (R)-3-nitro-4-(pyrrolidin-3-ylamino)benzenesulfonamide (440 mg) in N,N-dimethylformamide (10 mL) was added sodium carbonate (132 mg) and 1-bromo-2-(2-methoxyethoxy)ethane (0.155 mL). The reaction mixture was heated at 60°C for 18 hours

and after an aqueous workup, the crude product was purified on silica gel with a 2.5 - 10% methanol in methylene chloride gradient to provide the title compound.

EXAMPLE 254D

5 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}-2-(1H-
pyrrolo[2,3-b]pyridin-5-yl-oxy)benzamide

The title compound was prepared by substituting EXAMPLE 254C for EXAMPLE
130C in EXAMPLE 130D. ¹H NMR (500 MHz, pyridine-d₅) δ 12.96 (m, 1H), 9.25 (m, 1H),
10 8.57 (d, 1H), 8.43 (d, 1H), 8.34 (dd, 1H), 8.11 (d, 1H), 7.66 (t, 1H) 7.64 (d, 1H), 7.44 (d, 2H),
7.07 (d, 2H), 6.82 (d, 1H), 6.76 (dd, 1H), 6.55 (m, 1H), 6.47 (m, 1H), 5.26 (br s, 1H), 4.02
(m, 1H), 3.63 (m, 4H), 3.53 (m, 2H), 3.28 (s, 3H), 3.07 (m, 4H), 2.89 - 2.81 (m, 2H), 2.78 (s,
2H), 2.75 - 2.66 (m, 3H), 2.37 (m, 1H), 2.26 (m, 2H), 2.24 - 2.18 (m, 1H), 2.15 (m, 4H), 1.97
(s, 2H), 1.65 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H).

15 EXAMPLE 255

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]-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

20 EXAMPLE 255A

(R)-4-(1-(2-(dimethylamino)acetyl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 2-(dimethylamino)acetyl chloride,
hydrochloric acid for 1-bromo-2-(2-methoxyethoxy)ethane in EXAMPLE 254C except the
reaction was stirred at ambient temperature for 18 hours.

25

EXAMPLE 255B

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]-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

30 The title compound was prepared by substituting EXAMPLE 255A for EXAMPLE
130C in EXAMPLE 130D. ¹H NMR (500 MHz, pyridine - d₅) δ 13.01 (d, 1H), 9.26 (m, 1H),
8.46 - 8.33 (m, 3H), 8.14 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 7.01 - 6.89 (m,
1H), 6.76 (dd, 1H), 6.55 (m, 1H), 6.48 (m, 1H), 5.32 (br s, 1H), 4.27 - 4.14 (m, 1H), 4.05-

3.95 (m, 1H), 3.82 - 3.62 (m, 3H), 3.27 - 3.15 (m, 2H), 3.07 (m, 4H), 2.77 (s, 2H), 2.34 (2, 3H), 2.32 (s, 3H), 2.30 - 2.20 (m, 3H), 2.15 (m, 4H), 1.97 (s, 2H), 1.87 - 1.81 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H).

EXAMPLE 256

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

EXAMPLE 256A

10 tert-butyl 3-(2-nitro-4-sulfamoylphenylamino)azetidine-1-carboxylate

The title compound was prepared by substituting tert-butyl 3-aminoazetidine-1-carboxylate for 4-methylpiperazin-1-amine dihydrochloride in EXAMPLE 6A.

EXAMPLE 256B

15 4-(azetidin-3-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 256A for (S)-1-tert-butyl 2-methyl 4,4-difluoropyrrolidine-1,2-dicarboxylate in EXAMPLE 168A.

EXAMPLE 256C

20 3-nitro-4-(1-(oxetan-3-yl)azetidin-3-ylamino)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 256B for tert-butyl piperazine-1-carboxylate and 3-oxetanone for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

EXAMPLE 256D

25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[1-(oxetan-3-yl)azetidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

30 The title compound was prepared by substituting EXAMPLE 256C for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500 MHz, pyridine-d₅) δ 13.04 (s, 1H), 9.27 (d, 1H), 8.62 (d, 1H), 8.42 (d, 1H), 8.35 (dd, 1H), 8.09 (d, 1H), 7.67 (m, 1H), 7.63 (d, 1H), 7.44 (m, 2H), 7.07 (m, 2H), 6.76 (dd, 1H), 6.67 (d, 1H), 6.55 (d, 1H), 6.48 (dd, 1H), 4.66 (t, 2H), 4.58 (m,

2H), 4.23 (m, 1H), 3.71 (m, 3H), 3.12 (dd, 2H), 3.07 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.14 (t, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

EXAMPLE 257

5 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 257A

10 tert-butyl 4-((3-chloro-5-sulfamoylpyridin-2-yloxy)methyl)-4-fluoropiperidine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 126A for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

15 EXAMPLE 257B

5-chloro-6-((4-fluoropiperidin-4-yl)methoxy)pyridine-3-sulfonamide ditrifluoroacetic acid

The title compound was prepared by substituting EXAMPLE 257A for EXAMPLE 39A in EXAMPLE 39B.

20 EXAMPLE 257C

5-chloro-6-((1-(cyanomethyl)-4-fluoropiperidin-4-yl)methoxy)pyridine-3-sulfonamide

EXAMPLE 257B (0.166 g) in acetonitrile (3 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 CH₂Cl₂ as the eluent. The obtained solid was slurried in water, filtered, rinsed with water and diethyl ether, and dried in a vacuum oven at 80°C.

EXAMPLE 257D

30 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 257C for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (400 MHz, pyridine-

d₅) δ 13.05 (s, 1H), 9.12 (d, 1H), 8.72 (d, 1H), 8.41 (d, 1H), 8.10 (d, 1H), 7.66 (m, 2H), 7.44 (m, 2H), 7.07 (m, 2H), 6.75 (dd, 1H), 6.50 (m, 2H), 4.49 (d, 2H), 3.72 (s, 2H), 3.06 (m, 4H), 2.77 (s, 2H), 2.73 (m, 4H), 2.26 (t, 2H), 2.13 (m, 4H), 2.07 (m, 2H), 1.90 (m, 4H), 1.39 (t, 2H), 0.93 (s, 6H).

5

EXAMPLE 258

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]}-2-
(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

10

EXAMPLE 258A

(S)-tert-butyl 2-(tosyloxymethyl)morpholine-4-carboxylate

To a solution of (S)-tert-butyl 2-(hydroxymethyl)morpholine-4-carboxylate (1 g) in dichloromethane (50 mL) was added triethylamine (1.604 mL) and 4-methylbenzene-1-sulfonyl chloride (1.097 g). The mixture was stirred at ambient temperature under nitrogen for 72 hours. The reaction was diluted with methylene chloride (50 mL) and brine (100 mL). The brine layer was extracted with methylene chloride (75 mL). The combined organics were dried over sodium sulfate, filtered and concentrated. The crude material was purified on a silica gel column eluting with a 15-65 % ethyl acetate in hexane gradient to provide the title compound.

20

EXAMPLE 258B

(S)-tert-butyl 2-(azidomethyl)morpholine-4-carboxylate

A solution of EXAMPLE 258A (1.66 g) and sodium azide (0.581 g) in anhydrous N,N-dimethylformamide (10 mL) was stirred at 90 °C for 4 hours. The mixture was cooled and concentrated to dryness. The residue was taken up in 5% aqueous sodium carbonate solution and extracted with methylene chloride. The organic solution was dried (MgSO₄), filtered and concentrated to give a solid.

25

30

EXAMPLE 258C

(R)-tert-butyl 2-(aminomethyl)morpholine-4-carboxylate

This compound was obtained by hydrogenation of EXAMPLE 258B under 60 psi of hydrogen over 10% palladium on carbon in methanol for 24 hours, followed by filtration and evaporation of the solvent.

5

EXAMPLE 258D

(R)-tert-butyl 2-((2-nitro-4-sulfamoylphenylamino)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting EXAMPLE 258C for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

10

EXAMPLE 258E

(S)-4-(morpholin-2-ylmethylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 258D for EXAMPLE 113A in EXAMPLE 134A.

15

EXAMPLE 258F

(R)-4-((4-(2-(dimethylamino)acetyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 258E for EXAMPLE 134A and 2-(dimethylamino)acetyl chloride hydrochloride for methyl iodide in EXAMPLE 134B.

20

EXAMPLE 258G

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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

25

The title compound was prepared by substituting EXAMPLE 258F for EXAMPLE 130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 13.00 (s, 1H), 9.27 (d, 1H), 8.87 (bs, 1H), 8.43 (d, 1H), 8.34 (dd, 1H), 8.10 (dd, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.94 (dd, 1H), 6.75 (d, 1H), 6.54 (s, 1H), 6.48 (s, 1H), 4.55 (dd, 1H), 4.20 (dd, 1H), 3.95-3.76 (m, 2H), 3.60-3.40 (m, 3H), 3.32 (dd, 1H), 3.25-3.12 (m, 2H), 3.07 (m, 4H), 2.80 (m, 1H), 2.77 (s, 2H), 2.26 (s, 6H), 2.23 (s, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

30

EXAMPLE 259

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}-2-
(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5

EXAMPLE 259A

(R)-tert-butyl 2-(tosyloxymethyl)morpholine-4-carboxylate

The title compound was prepared by substituting (R)-tert-butyl 2-
(hydroxymethyl)morpholine-4-carboxylate for (S)-tert-butyl 2-(hydroxymethyl)morpholine-
4-carboxylate in EXAMPLE 258A.

10

EXAMPLE 259B

(R)-tert-butyl 2-(azidomethyl)morpholine-4-carboxylate

The title compound was prepared by substituting EXAMPLE 259A for EXAMPLE
258A in EXAMPLE 258B.

15

EXAMPLE 259C

(S)-tert-butyl 2-(aminomethyl)morpholine-4-carboxylate

The title compound was prepared by substituting EXAMPLE 259B for EXAMPLE
258B in EXAMPLE 258C.

20

EXAMPLE 259D

(S)-tert-butyl 2-((2-nitro-4-sulfamoylphenylamino)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting EXAMPLE 259C for
(tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

25

EXAMPLE 259E

(R)-4-(morpholin-2-ylmethylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 259D for EXAMPLE
113A in EXAMPLE 134A.

30

EXAMPLE 259F

(S)-4-((4-(2-(dimethylamino)acetyl)morpholin-2-yl)methylamino)-3-
nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 259E for EXAMPLE 134A and 2-(dimethylamino)acetyl chloride hydrochloride for methyl iodide in EXAMPLE 134B.

EXAMPLE 259G

5 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}-2-
 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 259F for EXAMPLE 130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 13.00 (s, 1H), 9.27 (d, 1H),
 10 8.87 (bs, 1H), 8.43 (d, 1H), 8.34 (dd, 1H), 8.10 (dd, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d,
 2H), 6.94 (dd, 1H), 6.75 (d, 1H), 6.54 (s, 1H), 6.48 (s, 1H), 4.55 (dd, 1H), 4.20 (dd, 1H),
 3.95-3.76 (m, 2H), 3.60-3.40 (m, 3H), 3.32 (dd, 1H), 3.25-3.12 (m, 2H), 3.07 (m, 4H), 2.80
 (m, 1H), 2.77 (s, 2H), 2.26 (s, 6H), 2.23 (s, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94
 (s, 6H).

15

EXAMPLE 260

N-[(5-chloro-6-{[1-(N,N-dimethylglycyl)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-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

20

EXAMPLE 260A

5-chloro-6-((1-(2-(dimethylamino)acetyl)piperidin-4-yl)methoxy)pyridine-3-sulfonamide

EXAMPLE 253B (0.061 g), 2-(dimethylamino)acetyl chloride, hydrochloric acid
 (0.061 g), and sodium carbonate (0.032 g) were combined in a 4-mL vial with N,N-
 25 dimethylformamide (2 mL). The mixture was stirred at ambient temperature for 3 days.
 Additional 2-(dimethylamino)acetyl chloride, hydrochloric acid (0.037 g), sodium carbonate
 (0.032 g) and N,N-dimethylformamide (1 mL) were added and stirring was continued for 24
 hours. The reaction mixture was diluted with ethyl acetate, washed with water and brine,
 dried (MgSO₄), filtered, concentrated and chromatographed on silica gel with 0 to 20%
 30 methanol in CH₂Cl₂ as the eluent.

EXAMPLE 260B

N-[(5-chloro-6-[[1-(N,N-dimethylglycyl)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-
5 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 260A for EXAMPLE
11B in EXAMPLE 11D. ¹H NMR (400 MHz, pyridine-d₅) δ 12.91 (s, 1H), 9.16 (d, 1H), 8.75
(d, 1H), 8.51 (d, 1H), 8.33 (d, 1H), 7.70 (d, 1H), 7.62 (d, 1H), 7.45 (m, 2H), 7.09 (m, 2H),
6.77 (dd, 1H), 6.60 (d, 1H), 6.45 (d, 1H), 4.81 (d, 1H), 4.15 (m, 3H), 3.24 (m, 2H), 3.04 (m,
10 4H), 2.89 (m, 1H), 2.79 (s, 2H), 2.53 (m, 1H), 2.29 (m, 6H), 2.26 (m, 2H), 2.18 (m, 4H), 1.98
(m, 2H), 1.91 (m, 1H), 1.71 (m, 2H), 1.39 (t, 2H), 1.25 (m, 2H), 0.94 (s, 6H).

EXAMPLE 261

N-[(5-chloro-6-[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]oxy]pyridin-3-yl)sulfonyl]-4-(4-
15 [[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 261A

(R)-tert-Butyl 3-(3-chloro-5-sulfamoylpyridin-2-yloxy)pyrrolidine-1-carboxylate
20 The title compound was prepared by substituting EXAMPLE 40A for 4-fluoro-3-
nitrobenzenesulfonamide and (R)-tert-butyl 3-hydroxypyrrolidine-1-carboxylate for
(tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

EXAMPLE 261B

25 (R)-5-Chloro-6-(pyrrolidin-3-yloxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 261A for tert-butyl (4-
(1,3-difluoropropan-2-yl)morpholin-2-yl)methylcarbamate in EXAMPLE 252B.

EXAMPLE 261C

30 (R)-5-chloro-6-(1-(2,2-difluoroethyl)pyrrolidin-3-yloxy)pyridine-3-sulfonamide

A mixture of EXAMPLE 261B (353 mg), 1, 1-difluoro-2-iodoethane (268 mg),
sodium carbonate (283 mg) in N,N-dimethylformamide (10mL) 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, brine, dried over magnesium sulfate, filtered, and concentrated. The residue was loaded onto silica gel column and eluted using a gradient of 0.5 to 3 % methanol in dichloromethane to provide the title compound.

5

EXAMPLE 261D

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-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 261C for EXAMPLE
10 11B in EXAMPLE 11D. ¹H NMR (400MHz, dimethylsulfoxide-d₆) δ 11.55 (s, 1 H), 8.04 (s, 1 H), 7.95 (d, 1 H), 7.58 (d, 1 H), 7.44 (t, 1 H), 7.35 (m, 3 H), 7.05 (d, 2 H), 6.64 (dd, 1 H), 6.33 (m, 1 H), 6.24 (d, 1 H), 6.25-5.97 (m, 1 H), 5.39 (m, 1 H), 2.98 (m, 6 H), 2.86 (m, 6 H), 2.55 (m, 2 H), 2.24 (m, 7 H), 1.96 (s, 2 H), 1.83 (m, 1 H), 1.39 (t, 2 H), 0.93 (s, 6 H)

15

EXAMPLE 262

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]-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

EXAMPLE 262A

20 (R)-4-(1-(cyanomethyl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 2-bromoacetonitrile for 1-bromo-2-(2-methoxyethoxy)ethane in EXAMPLE 254C.

EXAMPLE 262B

25 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]-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 262A for EXAMPLE
130C in EXAMPLE 130D. ¹H NMR (400 MHz, pyridine - d₅) δ 13.03 (s, 1H), 9.27 (d, 1H),
30 8.53 (d, 1H), 8.43 (d, 1H), 8.35 (dd, 1H), 8.10 (d, 1H), 7.67 - 7.64 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.81 (d, 1H), 6.76 (dd, 1H), 6.54 (m, 1H), 6.48 (m, 1H), 5.15 (br s, 1H), 4.10 (m, 1H), 3.89 (s, 2H), 3.07 (m, 4H), 2.93 - 2.86 (m, 2H), 2.80 - 2.77 (m, 3H), 2.61 - 2.53 (m, 1H),

2.31 - 2.21 (m, 3H), 2.14 (m, 4H), 1.97 (s, 2H), 1.75 - 1.68 (m, 1H), 1.39 (t, 2H), 0.94 (m, 6H).

EXAMPLE 263

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-methoxypiperidin-1-yl}-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 263A

tert-butyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate

10 Sodium hydride (6.63 g, 60% in mineral oil) was added to trimethylsulfoxonium iodide (36.5 g) in dimethyl sulfoxide (150 mL) and tetrahydrofuran (150 mL), was and stirred for 30 minutes. tert-Butyl 4-oxopiperidine-1-carboxylate (25.4 g) was added and the reaction was stirred for 3 hours. The reaction was poured into water (800 mL) and extracted three times with ether. The combined extracts were washed three times with water, and brine, dried
15 over Na₂SO₄, filtered, and concentrated to yield the crude product which was used without further purification.

EXAMPLE 263B

tert-butyl 4-(2-(benzyloxy)benzyl)-4-hydroxypiperidine-1-carboxylate

20 (2-(Benzyloxy)phenyl)magnesium bromide (33.8 mL, 1M) was added to a solution of EXAMPLE 263A (6.0 g) and CuI (1.07 g) in tetrahydrofuran (220 mL) at 0°C over 10 minutes. The reaction was quenched with pH 7 buffer (20 mL), extracted twice with ether, and the combined extracts were washed with brine, dried over Na₂SO₄, filtered, and concentrated. The crude product was chromatographed on silica gel using 2-20% ethyl
25 acetate in hexanes to provide the title compound.

EXAMPLE 263C

tert-butyl 4-hydroxy-4-(2-hydroxybenzyl)piperidine-1-carboxylate

EXAMPLE 263B (11.5 g) and methanol (120 mL) were added to Raney Nickel
30 (1.150 g) in a 250 mL SS pressure bottle and stirred for 1 hour at 30 psi under hydrogen. The mixture was filtered through a nylon membrane and the solution was concentrated to yield the title compound.

EXAMPLE 263D

tert-butyl 4-hydroxy-4-(2-(trifluoromethylsulfonyloxy)benzyl)piperidine-1-carboxylate

A mixture of EXAMPLE 263C (4.6 g), N-phenylbis(trifluoromethanesulfonimide) (5.88 g), and Hunig's base (2.88 mL) in dichloromethane (100 mL) was stirred for 24 hours. The mixture was concentrated and chromatographed on silica gel using 5-50% ethyl acetate in hexanes to provide the title compound.

5

EXAMPLE 263E

tert-butyl 4-((4'-chlorobiphenyl-2-yl)methyl)-4-hydroxypiperidine-1-carboxylate

A mixture of EXAMPLE 263D (4.3 g), 4-chlorophenylboronic acid (1.84 g), K₃PO₄ (2.91 g), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.36 g) in 2-methyltetrahydrofuran (50 mL) was stirred at 70°C for 24 hours. The reaction was cooled and quenched with water (50 mL), extracted twice with ether, and the combined extracts were washed with brine, dried over Na₂SO₄, filtered, and concentrated. The crude product was chromatographed on silica gel using 5-30% ethyl acetate in hexanes to provide the title compound.

15

EXAMPLE 263F

tert-butyl 4-((4'-chlorobiphenyl-2-yl)methyl)-4-methoxypiperidine-1-carboxylate

Sodium hydride (0.36 g, 60% in mineral oil) was added to EXAMPLE 263E (4.3 g), in tetrahydrofuran (40 mL) and the reaction was stirred for 10 minutes. Hexamethylphosphoramide (5 mL) and CH₃I (2.34 mL) were added and the reaction was stirred at 50°C for 18 hours. The reaction was cooled and quenched with water (50 mL), extracted twice with ether, and the combined extracts were washed with brine, dried over Na₂SO₄, filtered, and concentrated. The crude product was chromatographed on silica gel using 5-25% ethyl acetate in hexanes to provide the title compound.

25

EXAMPLE 263G

4-((4'-chlorobiphenyl-2-yl)methyl)-4-methoxypiperidine

The title compound was prepared by substituting EXAMPLE 263F for EXAMPLE 1A in EXAMPLE 1B.

30

EXAMPLE 263H

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((4'-chlorobiphenyl-2-yl)methyl)-4-methoxypiperidin-1-yl)benzoate

A solution of EXAMPLE 263G (1.4 g), EXAMPLE 3H (1.06 g) and Hunig's base (0.75 mL) in dimethylsulfoxide (20 mL) was stirred at 120°C for 18 hours. The reaction was cooled and quenched with water (200 mL), extracted three times with ether, and the combined extracts were washed three times with water, and brine, dried over Na₂SO₄,
5 filtered, and concentrated. The crude product was chromatographed on silica gel using 5-50% ethyl acetate in hexanes to provide the title compound.

EXAMPLE 263I

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((4'-chlorobiphenyl-2-yl)methyl)-4-
10 methoxypiperidin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 263H for EXAMPLE 3I in EXAMPLE 3J.

EXAMPLE 263J

15 4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-methoxypiperidin-1-yl}-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 263I for EXAMPLE 1E and EXAMPLE 96A for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300MHz, dimethylsulfoxide-d₆) δ 11.71 (s, 1H), 11.58 (br s, 1H), 8.58 (d, 1H), 8.28 (d, 1H), 8.05 (d, 1H), 7.56 (d, 1H), 7.52 (m, 1H), 7.46 (d, 1H), 7.44 (d, 2H), 7.28 (m, 5H), 7.11 (dd, 1H), 6.62 (dd, 1H), 6.41 (dd, 1H), 6.11 (d, 1H), 4.54 (d, 2H), 3.75 (m, 2H), 3.59 (m, 2H), 3.20 (m, 2H), 2.97 (s, 3H), 2.81 (m, 2H), 2.74 (m, 2H), 1.89 (m, 2H), 1.83 (m, 2H), 1.36 (m, 2H), 1.09 (m, 2H).
20

25

EXAMPLE 264

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-methoxypiperidin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

30 The title compound was prepared by substituting EXAMPLE 263I for EXAMPLE 1E in EXAMPLE 1G. ¹H NMR (300MHz, dimethylsulfoxide-d₆) δ 11.71 (s, 1H), 11.40 (br s, 1H), 8.62 (t, 1H), 8.58 (d, 1H), 8.03 (d, 1H), 7.81 (dd, 1H), 7.54 (m, 2H), 7.44 (m, 3H), 7.28 (m, 5H), 7.13 (dd, 1H), 6.62 (dd, 1H), 6.41 (dd, 1H), 6.11 (d, 1H), 3.85 (dd, 2H), 3.31 (m,

4H), 3.20 (m, 2H), 2.97 (s, 3H), 2.81 (m, 2H), 2.73 (m, 2H), 1.89 (m, 1H), 1.62 (m, 2H), 1.38 (m, 2H), 1.25 (m, 2H), 1.09 (m, 2H).

EXAMPLE 265

5 4-(4-{[9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 265A

10 benzyl 4-(piperidin-1-ylmethylene)piperidine-1-carboxylate

To a solution of benzyl 4-formylpiperidine-1-carboxylate (12.5g) in toluene (120 mL) was added piperidine (6.46g). The mixture was stirred at reflux under a Dean-Stark trap overnight. The mixture was then concentrated under vacuum and the residue was used directly in the next step.

15

EXAMPLE 265B

benzyl 9-oxo-3-azaspiro[5.5]undec-7-ene-3-carboxylate

To a solution of EXAMPLE 265A (15.88g) in ethanol (300 mL) was added but-3-enone (3.89 g). The mixture was stirred at reflux overnight. Then acetic acid (30 mL) was added to the mixture which was stirred at reflux again overnight. The mixture was then concentrated under vacuum and the residue was diluted with ethyl acetate (400 mL) and washed with water and brine and dried over Na₂SO₄. After filtration and evaporation of the solvent, column purification gave the title compound.

20

25

EXAMPLE 265C

benzyl 9-hydroxy-3-azaspiro[5.5]undecane-3-carboxylate

EXAMPLE 265B (21 g) and tetrahydrofuran (160 mL) were added to 5% Pt-C wet (3.15 g) in a 250 mL pressure bottle and stirred for 1 hour at 30 psi and room temperature. The mixture was filtered through a nylon membrane and the filtrate was concentrated under vacuum to provide the title compound.

30

EXAMPLE 265D

benzyl 9-oxo-3-azaspiro[5.5]undecane-3-carboxylate

To a solution of EXAMPLE 265C (8.0 g) in dichloromethane (200 mL) was added Dess-Martin Periodinane (11.2 g). The mixture was stirred overnight. The mixture was diluted with ethyl acetate (400 mL) and washed with 2N aqueous NaOH, water, and brine. After drying over Na₂SO₄ and filtration, concentration of the solvent gave the crude product which was used directly in the next reaction without further purification.

EXAMPLE 265E

benzyl 9-chloro-8-formyl-3-azaspiro[5.5]undec-8-ene-3-carboxylate

Phosphorus oxychloride (2.33 mL) was added dropwise to a cooled (0°C) solution of EXAMPLE 265D (7.5 g) in N,N-dimethylformamide (10 mL) and dichloromethane (30 mL). The mixture was then stirred overnight before it was diluted with ethyl acetate (300 mL) and washed with aqueous sodium acetate, water (3x), and brine and dried over Na₂SO₄. After filtration and concentration, the crude product was used directly in the next reaction without further purification.

EXAMPLE 265F

benzyl 9-(4-chlorophenyl)-8-formyl-3-azaspiro[5.5]undec-8-ene-3-carboxylate

To a mixture of 4-chlorophenylboronic acid (5.94 g), EXAMPLE 265E (11.01 g), palladium(II) acetate (142 mg), K₂CO₃ (13.2 g) and tetrabutylammonium bromide (10.2 g) was added water (120 mL). The mixture was stirred at 50°C overnight. The mixture was diluted with ethyl acetate (400 mL) and washed with water (3x) and brine and dried over Na₂SO₄. After filtration and concentration, the residue was loaded on a column and eluted with 5 to 20% ethyl acetate in hexane to provide the title compound.

EXAMPLE 265G

benzyl 8-((4-(3-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(methoxycarbonyl)phenyl)piperazin-1-yl)methyl)-9-(4-chlorophenyl)-3-azaspiro[5.5]undec-8-ene-3-carboxylate

To a solution of EXAMPLE 15F (1.37 g) and EXAMPLE 265F (1.65 g) in dichloromethane (20 mL) was added sodium triacetoxymethylborohydride (1.24 g). The mixture was stirred overnight. The mixture was diluted with ethyl acetate (200 mL) and washed with 2N aqueous NaOH, water and brine. After drying over Na₂SO₄, the mixture was filtered and the solvent was evaporated under vacuum to provide the title compound.

EXAMPLE 265H

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((9-(4-chlorophenyl)-3-azaspiro[5.5]undec-8-en-8-yl)methyl)piperazin-1-yl)benzoate

EXAMPLE 265G (2 g) and tetrahydrofuran (10 mL) were added to 20% Pd(OH)₂-C, wet (0.400 g) in a 50 mL pressure bottle and stirred for 16 hours at 30 psi and room temperature. The mixture was filtered through a nylon membrane and evaporation of the solvent gave the title compound.

EXAMPLE 265I

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl)methyl)piperazin-1-yl)benzoate

To a solution of EXAMPLE 265H (320 mg) in dichloromethane (5 mL) was added 1,3-difluoroacetone (139 mg) and sodium triacetoxymethylborohydride (157 mg). The mixture was stirred overnight. The mixture was diluted with ethyl acetate (200 mL) and washed with 2N aqueous NaOH, water and brine. After drying over Na₂SO₄, the mixture was filtered and the solvent was evaporated under vacuum to provide the title compound.

EXAMPLE 265J

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl)methyl)piperazin-1-yl)benzoic acid

To a solution of EXAMPLE 265I (320 mg) in tetrahydrofuran (4 mL) and methanol (2 mL) was added LiOH H₂O (120 mg) and the solution was stirred overnight. The reaction was cooled, carefully neutralized with 1N aqueous HCl and extracted with dichloromethane (3x 50 mL). The combined organic layers were washed with brine (25 mL), dried over sodium sulfate, filtered and concentrated under vacuum to provide the title compound.

EXAMPLE 265K

4-(4-([9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl)methyl)piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 265J for EXAMPLE 1E in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.61 (s, 1 H), 8.49 (d, 2 H), 7.72 (m, 1 H), 7.49 (m, 2 H), 7.32 (d, 2 H), 7.07 (m, 3 H), 6.65 (dd, 1 H), 6.35 (d, 1 H),

6.20 (m, 1 H), 4.66 (m, 2 H), 4.50 (m, 2 H), 3.84 (m, 2 H), 3.04 (m, 5 H), 2.70 (m, 6 H), 2.23 (m, 6 H), 2.00 (m, 4 H), 1.35 (m, 12 H).

EXAMPLE 266

5 4-(4-([9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl)methyl]piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 266A

10 methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl)methyl)piperazin-1-yl)benzoate

To a solution of EXAMPLE 265H (320 mg) in dichloromethane (5 mL) was added acetone (143 mg) and sodium triacetoxyborohydride (157 mg). The mixture was stirred overnight. The mixture was diluted with ethyl acetate (200 mL) and washed with 2N aqueous
15 NaOH, water and brine. After drying over Na₂SO₄, the mixture was filtered and the solvent was evaporated under vacuum to provide the title compound.

EXAMPLE 266B

20 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 266A for EXAMPLE 265I in EXAMPLE 265J.

EXAMPLE 266C

25 4-(4-([9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl)methyl]piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 266B for EXAMPLE 1E in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.54 (s, 1 H), 8.38 (m, 2 H), 7.93 (d, 1 H), 7.60 (m, 3 H), 7.39 (m, 4 H), 7.09 (d, 2 H), 6.85 (d, 1 H), 6.63 (dd, 1 H), 6.27 (dd, 2 H), 3.84 (m, 3 H), 3.08 (m, 8 H), 2.71 (s, 3 H), 2.15 (m, 8 H), 1.71 (m, 9 H), 1.24 (m, 11 H)

EXAMPLE 267

4-(4-{[9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 265J for EXAMPLE 1E and EXAMPLE 40B for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.56 (s, 1 H), 8.38 (s, 1 H), 8.06 (m, 1 H), 7.57 (d, 1 H), 7.38 (m, 5 H), 7.07 (m, 3 H), 6.64 (dd, 1 H), 6.33 (d, 1 H), 6.23 (m, 1 H), 4.68 (d, 2 H), 4.52 (d, 2 H), 4.21 (d, 2 H), 3.86 (dd, 2 H), 3.08 (m, 8 H), 2.71 (m, 6 H), 2.10 (m, 12 H), 1.42 (m, 7 H).

EXAMPLE 268

4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 266B for EXAMPLE 1E and EXAMPLE 40B for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.49 (s, 1 H), 8.28 (d, 1 H), 7.94 (dd, 2 H), 7.60 (d, 1 H), 7.35 (m, 4 H), 7.08 (m, 2 H), 6.61 (dd, 1 H), 6.28 (dd, 2 H), 4.18 (d, 2 H), 3.85 (m, 2 H), 3.05 (m, 7 H), 2.71 (s, 3 H), 2.25 (m, 6 H), 2.02 (m, 2 H), 1.63 (m, 8 H), 1.30 (m, 9 H).

EXAMPLE 269

N-({5-chloro-6-[(4-fluoro-1-methylpiperidin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 269A

5-chloro-6-((4-fluoro-1-methylpiperidin-4-yl)methoxy)pyridine-3-sulfonamide

EXAMPLE 257B (0.131 g) in N,N-dimethylformamide (3.0 mL) was treated with iodomethane (0.043 g) and sodium carbonate (0.079 g) and stirred at ambient temperature for 3 days. The N,N-dimethylformamide was removed on high vacuum and the concentrate was chromatographed on amine functionalized silica gel with 0 to 2% methanol in CH₂Cl₂ as the eluent.

EXAMPLE 269B

N-({5-chloro-6-[(4-fluoro-1-methylpiperidin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5 The title compound was prepared by substituting EXAMPLE 269A for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (400 MHz, pyridine-d₅) δ 13.01 (s, 1H), 9.11 (d, 1H), 8.71 (d, 1H), 8.44 (d, 1H), 8.16 (d, 1H), 7.66 (m, 2H), 7.44 (m, 2H), 7.07 (m, 2H), 6.76 (dd, 1H), 6.54 (d, 1H), 6.49 (dd, 1H), 4.49 (d, 2H), 3.06 (m, 4H), 2.77 (s, 2H), 2.68 (m, 2H), 2.38 (m, 2H), 2.26 (m, 5H), 2.14 (t, 4H), 1.97 (m, 6H), 1.39 (t, 2H), 0.94 (s, 6H).

EXAMPLE 270

N-[(5-chloro-6-{[1-(N,N-dimethylglycyl)-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 270A

5-chloro-6-((1-(2-(dimethylamino)acetyl)-4-fluoropiperidin-4-yl)methoxy)pyridine-3-sulfonamide

EXAMPLE 257B (0.131 g), 2-(dimethylamino)acetyl chloride, hydrochloric acid (0.139 g), and sodium carbonate (0.048 g) were combined in a 5-mL vial with N,N-dimethylformamide (3.0 mL) and stirred overnight at ambient temperature. Additional sodium carbonate (0.048 g) was added followed by 2-(dimethylamino)acetyl chloride, hydrochloric acid (0.139 g) and stirring was continued over a second night. The reaction mixture was concentrated under high vacuum, slurried in CH₂Cl₂, filtered, concentrated and chromatographed on amine functionalized silica gel with 0 to 4% methanol in CH₂Cl₂ as the eluent.

EXAMPLE 270B

N-[(5-chloro-6-{[1-(N,N-dimethylglycyl)-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 270A for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500 MHz, pyridine-d₅) δ 13.04 (s, 1H), 9.12 (d, 1H), 8.73

(d, 1H), 8.42 (d, 1H), 8.11 (d, 1H), 7.66 (m, 2H), 7.44 (m, 2H), 7.07 (m, 2H), 6.76 (dd, 1H), 6.52 (d, 1H), 6.49 (dd, 1H), 4.66 (d, 1H), 4.52 (dd, 2H), 4.07 (d, 1H), 3.46 (m, 1H), 3.40 (m, 1H), 3.30 (m, 1H), 3.11 (m, 1H), 3.06 (m, 4H), 2.77 (s, 2H), 2.35 (s, 6H), 2.26 (t, 2H), 2.14 (m, 4H), 2.05 (m, 2H), 1.97 (s, 2H), 1.81 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

5

EXAMPLE 271

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-fluoropiperidin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

10

EXAMPLE 271A

tert-butyl 4-((4'-chlorobiphenyl-2-yl)methyl)-4-fluoropiperidine-1-carboxylate

A solution of EXAMPLE 263E (2.0 g) and diethylaminosulfur trifluoride (1.39 mL) in dichloromethane (40 mL) was stirred for 24 hours. The reaction was quenched with water (30 mL), extracted twice with ether, and the combined extracts were washed with water, and brine, dried over Na₂SO₄, filtered, and concentrated. The crude product was chromatographed on silica gel using 5% ethyl acetate in hexanes to provide the title compound.

15

EXAMPLE 271B

4-((4'-chlorobiphenyl-2-yl)methyl)-4-fluoropiperidine

20

The title compound was prepared by substituting EXAMPLE 271A for EXAMPLE 1A in EXAMPLE 1B.

EXAMPLE 271C

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((4'-chlorobiphenyl-2-yl)methyl)-4-fluoropiperidin-1-yl)benzoate

25

The title compound was prepared by substituting EXAMPLE 271B for EXAMPLE 263G in EXAMPLE 263H.

EXAMPLE 271D

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((4'-chlorobiphenyl-2-yl)methyl)-4-fluoropiperidin-1-yl)benzoic acid

30

The title compound was prepared by substituting EXAMPLE 271C for EXAMPLE 3I in EXAMPLE 3J.

EXAMPLE 271E

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-fluoropiperidin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5 The title compound was prepared by substituting EXAMPLE 271D for EXAMPLE 1E EXAMPLE 1G. ¹H NMR (300MHz, dimethylsulfoxide-d₆) δ 11.66 (s, 1H), 11.46 (br s, 1H), 8.62 (t, 1H), 8.56 (d, 1H), 8.03 (d, 1H), 7.81 (dd, 1H), 7.52 (m, 3H), 7.44 (d, 2H), 7.28 (m, 5H), 7.14 (m, 1H), 6.68 (dd, 1H), 6.40 (dd, 1H), 6.19 (d, 1H), 3.84 (dd, 2H), 3.31 (m, 9H), 2.95 (d, 2H), 2.81 (m, 2H), 1.91 (m, 1H), 1.62 (m, 2H), 1.45 (m, 2H), 1.29 (m, 2H).

EXAMPLE 272

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-fluoropiperidin-1-yl}-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

15 The title compound was prepared by substituting EXAMPLE 271D for EXAMPLE 1E and EXAMPLE 96A for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300MHz, dimethylsulfoxide-d₆) δ 11.68 (s, 1H), 11.64 (br s, 1H), 8.58 (m, 1H), 8.25 (m, 1H), 8.03 (d, 1H), 7.70 (dd, 1H), 7.50 (m, 4H), 7.43 (m, 3H), 7.28 (m, 4H), 7.15 (m, 1H), 6.68 (dd, 1H), 6.40 (dd, 1H), 6.19 (d, 1H), 4.54 (d, 2H), 4.04 (m, 1H), 3.75 (m, 2H), 3.58 (m, 2H), 2.95 (d, 2H), 2.80 (m, 2H), 1.88 (m, 2H), 1.82 (m, 2H), 1.48 (m, 2H), 1.28 (m, 2H), 0.85 (m, 2H).

EXAMPLE 273

4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl}sulfonyl)benzamide

25 The title compound was prepared by substituting EXAMPLE 266B for EXAMPLE 1E and EXAMPLE 42A for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.57 (s, 1 H), 7.97 (d, 1 H), 7.77 (s, 1 H), 7.55 (m, 2 H), 7.45 (m, 1 H), 7.36 (m, 3 H), 7.08 (d, 2 H), 6.62 (dd, 2 H), 6.35 (dd, 1 H), 6.21 (d, 1 H), 3.82 (m, 3 H), 3.06 (m, 9 H), 2.72 (m, 3 H), 2.25 (m, 8 H), 2.09 (m, 2 H), 1.56 (m, 9 H), 1.20 (m, 10 H).

EXAMPLE 274

N-[(5-chloro-6-{[(3R)-1-(1,3-difluoropropan-2-yl)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5

EXAMPLE 274A

(R)-5-chloro-6-(1-(3-fluoro-2-(fluoromethyl)propyl)pyrrolidin-3-yloxy)pyridine-3-sulfonamide

The title compound was prepared by substituting 1,3-difluoropropan-2-one for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 261B for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

10

EXAMPLE 274B

N-[(5-chloro-6-{[(3R)-1-(1,3-difluoropropan-2-yl)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

15

The title compound was prepared by substituting EXAMPLE 274A for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (400MHz, dimethylsulfoxide-d₆) δ 11.52 (s, 1 H), 8.32 (d, 1 H), 8.01 (d, 1 H), 7.93 (d, 1 H), 7.59 (d, 1 H), 7.42 (m, 1 H), 7.33 (m, 3 H), 7.05 (d, 2 H), 6.63 (dd, 1 H), 6.31 (dd, 1 H), 6.25 (d, 1 H), 5.38 (m, 1 H), 4.65 (t, 2 H), 4.53 (t, 2 H), 3.02 (s, 4 H), 2.94 (m, 5 H), 2.75 (s, 2 H), 2.66 (m, 1 H), 2.23 (m, 7 H), 1.96 (s, 2 H), 1.82 (m, 1 H), 1.39 (t, 2 H), 0.93 (s, 6 H).

20

EXAMPLE 275

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-(3-nitro-4-[2-(tetrahydrofuran-3-yloxy)ethoxy]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

25

EXAMPLE 275A

3-(2-(benzyloxy)ethoxy)tetrahydrofuran

30

Tetrahydrofuran-3-ol (0.881 g) in tetrahydrofuran (15 mL) was treated with 60% sodium hydride (0.8 g). After 10 minutes, ((2-bromoethoxy)methyl)benzene (3.23 g) was added. The solution was stirred for 16 hours. The reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was separated, and was extracted with additional

ethyl acetate twice. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated. The residue was purified by flash chromatography on silica gel eluting with 1:1 ethyl acetate: hexane to provide the title compound.

5

EXAMPLE 275B

2-(tetrahydrofuran-3-yloxy)ethanol

EXAMPLE 275A (0.85 g) and 5% palladium on carbon (0.1 g) in ethanol (10 mL) was treated with a balloon of hydrogen. The reaction was stirred overnight. The solid was filtered off, and the filtrate was concentrated to give the title compound.

10

EXAMPLE 275C

3-nitro-4-(2-(tetrahydrofuran-3-yloxy)ethoxy)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 275B for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

15

EXAMPLE 275D

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-({3-nitro-4-[2-(tetrahydrofuran-3-yloxy)ethoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

20

The title compound was prepared by substituting EXAMPLE 275C for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.65 (s, 1H), 8.32 (s, 1H), 8.00-8.02 (m, 2H), 7.49-7.52 (m, 2H), 7.39-7.41 (m, 1H), 7.38 (d, 2H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.21 (d, 1H), 4.33-4.35 (m, 2H), 4.18-4.21 (m, 1H), 3.62-3.67 (m, 4H), 3.09 (s, 4H), 2.83 (s, 2H), 2.26 (s, 2H), 2.15 (s, 2H), 1.96 (s, 2H), 1.85-1.94 (m, 2H), 1.39 (t, 2H), 0.92 (s, 6H).

25

EXAMPLE 276

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

30

EXAMPLE 276A

trans-4-(aminomethyl)cyclohexanecarbonitrile

To a solution of tert-butyl (trans-4-(cyanomethyl)cyclohexyl)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.

5

EXAMPLE 276B

4-((trans-4-cyanocyclohexyl)methylamino)-3-nitrobenzenesulfonamide

A mixture of 4-fluoro-3-nitrobenzenesulfonamide (347 mg) and EXAMPLE 276A (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.

10

EXAMPLE 276C

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-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide

15

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 276B in place of EXAMPLE 11B. ¹H NMR (400 MHz, dimethylsulfoxide-d₆) δ 11.69 (s, 1 H), 11.36 (s, 1 H), 8.60 (t, 1 H), 8.56 (d, 1 H), 8.04 (d, 1 H), 7.79 (dd, 1 H), 7.47 - 7.54 (m, 3 H), 7.34 (d, 2 H), 7.01 - 7.09 (m, 3 H), 6.68 (dd, 1 H), 6.39 (dd, 1 H), 6.19 (d, 1 H), 3.25 (t, 2 H), 3.07 (s, 4 H), 2.76 (s, 2 H), 2.57 - 2.68 (m, 1 H), 2.17 (d, 6 H), 1.92 - 2.06 (m, 4 H), 1.78 (d, 2 H), 1.66 (s, 1 H), 1.35 - 1.53 (m, 4 H), 0.96 - 1.10 (m, 2 H), 0.92 (s, 6 H).

20

EXAMPLE 277

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-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

25

EXAMPLE 277A

methyl 4,4-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

30

To a suspension of hexane washed NaH (17 g) in dichloromethane (700 mL) was added 5,5-dimethyl-2-methoxycarbonylcyclohexanone (38.5 g) dropwise at 0°C. After stirring for 30 minutes, the mixture was cooled to -78°C and trifluoroacetic 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 277B

5 methyl 2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enecarboxylate

EXAMPLE 277A (62.15g), 4-chlorophenylboronic acid (32.24 g), CsF (64 g) and tetrakis(triphenylphosphine)palladium(0) (2g) in 2:1 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
10 product.

EXAMPLE 277C

(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methanol

To a mixture of LiBH_4 (13g), EXAMPLE 277B (53.8 g) and ether (400 mL), was
15 added methanol (25 mL) 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 with ether (3x 100 mL). The extracts were dried (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 0-30% ethyl acetate/hexanes.

20

EXAMPLE 277D

tert-butyl 4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine-1-carboxylate

Mesyl Chloride (7.5 mL) was added via syringe to EXAMPLE 277C (29.3 g) and
25 triethylamine (30 mL) in CH_2Cl_2 (500 mL) at 0°C , and the mixture was stirred for 1 minute. N-t-butoxycarbonylpiperazine (25 g) was added and the mixture was stirred at room temperature for 24 hours. The suspension was washed with brine, dried, (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 10-20% ethyl acetate/hexanes.

30

EXAMPLE 277E

1-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine

EXAMPLE 277D (1 g) was stirred in dichloromethane (10 mL), trifluoroacetic acid (10 mL), and triethylsilane (1 mL) for 1 hour. The mixture was concentrated, taken up in a

mixture of dichloromethane (100 mL) and saturated aqueous Na_2CO_3 solution (20 mL) and stirred for 10 minutes. The layers were separated, and the organic layer was dried over Na_2SO_4 , filtered, and concentrated to give the product.

5

EXAMPLE 277F

5-bromo-1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridine

To a mixture of 5-bromo-1H-pyrrolo[2,3-b]pyridine (15.4 g) in tetrahydrofuran (250 mL) was added 1M lithium hexamethyldisilazide in tetrahydrofuran (86 mL), and after 10 minutes, TIPS-Cl (triisopropylchlorosilane) (18.2 mL) was added. The mixture was stirred at room temperature for 24 hours. The reaction was diluted with ether, and the resulting solution was washed twice with water. The extracts were dried (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 10% ethyl acetate/hexanes.

10

EXAMPLE 277G

15

1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridin-5-ol

To a mixture of EXAMPLE 277F (24.3 g) in tetrahydrofuran (500 mL) at -78°C was added 2.5M BuLi (30.3 mL). After 2 minutes, trimethylborate (11.5 mL) was added, and the mixture was allowed to warm to room temperature over 1 hour. The reaction was poured into water, extracted three times with ethyl acetate, and the combined extracts were washed with brine and concentrated. The crude product was taken up in tetrahydrofuran (200 mL) at 0°C , and 1M NaOH (69 mL) was added, followed by 30% H_2O_2 (8.43 mL), and the solution was stirred for 1 hour. $\text{Na}_2\text{S}_2\text{O}_3$ (10 g) was added, and the pH was adjusted to 4-5 with concentrated HCl and solid NaH_2PO_4 . The solution was extracted twice with ethyl acetate, and the combined extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 5-25% ethyl acetate/hexanes.

20

25

EXAMPLE 277H

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-fluorobenzoate

30

A mixture of EXAMPLE 277G (8.5 g), methyl 2,4-difluorobenzoate (7.05 g), and K_3PO_4 (9.32 g) in diglyme (40 mL) at 115°C was stirred for 24 hours. The reaction was cooled, diluted with ether (600 mL), and washed twice with water, and brine, and concentrated. The crude product was chromatographed on silica gel with 2-50% ethyl acetate/hexanes.

EXAMPLE 277I

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

5 A mixture of EXAMPLE 277H (1.55 g), EXAMPLE 277E (2.42 g), and HK_2PO_4 (1.42 g) in dimethylsulfoxide (20 mL) at 135°C was stirred for 24 hours. The reaction was cooled, diluted with ether (400 mL), and washed three times with 1M NaOH, and brine, and concentrated. The crude product was chromatographed on silica gel with 10-50% ethyl acetate/hexanes.

10

EXAMPLE 277J

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

15 EXAMPLE 277I (200 mg) in dioxane (10 mL) and 1M NaOH (6 mL) at 50°C was stirred for 24 hours. The reaction was cooled, added to NaH_2PO_4 solution, and extracted three times with ethyl acetate. The combined extracts were washed with brine, and concentrated to give the pure product.

EXAMPLE 277K

20 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 ,
25 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.

30

EXAMPLE 277L

tert-butyl 4-fluoro-4-(hydroxymethyl)piperidine-1-carboxylate

1-Tert-butyl 4-ethyl 4-fluoropiperidine-1,4-dicarboxylate (1.0 g) in tetrahydrofuran (5 mL) was treated with 1.0 N LiAlH_4 in tetrahydrofuran (2.54 mL) at 0°C . The reaction mixture was stirred at room temperature for 2 hours. Water (0.6 mL) was added to the

reaction mixture drop-wise, followed by 2 N aqueous NaOH (0.2 mL). The reaction was stirred for another 1 hour. The solid was removed by filtration via a pack of diatomaceous earth and washed with ethyl acetate. The filtrate was washed with brine, dried over MgSO₄, filtered, and concentrated to give the product.

5

EXAMPLE 277M

tert-butyl 4-((3-chloro-5-sulfamoylpyridin-2-yloxy)methyl)-4-fluoropiperidine-1-carboxylate

To a solution of EXAMPLE 277L (1 g) in tetrahydrofuran (15 mL) was added NaH (60% dispersion in mineral oil, 685 mg), and the solution was stirred for 10 minutes.

EXAMPLE 277K (1 g) was added and the reaction stirred for 24 hours. The mixture was
10 poured into water, neutralized with 10% HCl, and extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel eluting with 30% ethyl acetate in hexanes.

15

EXAMPLE 277N

5-chloro-6-((4-fluoropiperidin-4-yl)methoxy)pyridine-3-sulfonamide ditrifluoroacetic acid

EXAMPLE 277M (13 mL) was treated with trifluoroacetic acid (2.363 mL), stirred at ambient temperature for 2 hours, concentrated and dried to give the title compound.

20

EXAMPLE 277O

5-chloro-6-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)pyridine-3-sulfonamide

EXAMPLE 277N (0.088 g) and oxetan-3-one (0.014 g) were combined in dichloromethane (2.0 mL) and dimethylformamide (1.0 mL) and stirred at ambient temperature for 45 minutes. Sodium triacetoxyborohydride (0.064 g) was added in portions.
25 Stirring was continued overnight at ambient temperature. Additional oxetan-3-one (0.014 g) was added and stirring was continued for 30 minutes at ambient temperature before more sodium triacetoxyborohydride (0.064 g) was added. The reaction mixture was stirred for 72 hours at ambient temperature, concentrated, chromatographed on silica gel with 0 to 5% methanol in dichloromethane as the eluent, and dried in a vacuum oven at 80 °C to give the
30 title compound.

EXAMPLE 277P

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5 EXAMPLE 277J (0.063 g), EXAMPLE 277O (0.042 g), 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (0.032 g), and 4-dimethylaminopyridine (0.027 g) were combined in a 4-mL vial with dichloromethane (1.0 mL) and stirred overnight at ambient temperature. The reaction mixture was chromatographed directly without aqueous workup on silica gel with 0-4% methanol in dichloromethane as the eluent. Fractions
10 containing the desired product were concentrated, slurried in acetonitrile, concentrated and dried overnight in a vacuum oven at 80 °C to give the title compound. ¹H NMR (500 MHz, pyridine-d₅) δ 13.05 (s, 1H), 9.13 (d, 1H), 8.72 (d, 1H), 8.41 (d, 1H), 8.10 (d, 1H), 7.67 (m, 1H), 7.66 (d, 1H), 7.44 (m, 2H), 7.07 (m, 2H), 6.76 (dd, 1H), 6.51 (m, 2H), 4.63 (m, 4H), 4.53 (d, 2H), 3.39 (m, 1H), 3.07 (m, 4H), 2.77 (s, 2H), 2.51 (m, 2H), 2.25 (m, 2H), 2.18 (m,
15 2H), 2.13 (m, 4H), 2.06 (t, 2H), 1.97 (s, 2H), 1.89 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

EXAMPLE 278

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-({5-cyano-6-[2-(tetrahydro-2H-pyran-4-yl)ethoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide
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EXAMPLE 278A

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
25 for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 36B.

EXAMPLE 278B

5-cyano-6-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 278A for EXAMPLE
30 36B in EXAMPLE 36C.

EXAMPLE 278C

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

The title compound was prepared by substituting EXAMPLE 278B for

5 EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.60 (s, 1H), 8.70 (s, 1H), 8.48 (s, 1H), 7.96 (d, 1H), 7.56 (d, 1H), 7.45-7.47 (m, 1H), 7.40 (s, 1H), 7.36 (d, 2H), 7.06 (d, 2H), 6.67 (dd, 1H), 6.34 (dd, 1H), 6.25 (d, 1H), 4.47 (d, 2H), 3.80-3.84 (m, 2H), 3.24-3.28 (m, 2H), 3.12 (s, 2H), 2.16 (s, 2H), 1.97 (s, 2H), 1.61-1.71 (m, 4H), 1.40 (t, 2H), 1.21-1.25 (m, 2H), 0.93 (s, 6H).

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EXAMPLE 279

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-(3-furylmethoxy)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

15

EXAMPLE 279A

4-(furan-3-ylmethoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting furan-3-ylmethanol for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

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EXAMPLE 279B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-(3-furylmethoxy)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 279A for

25

EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.69 (s, 1H), 8.34 (s, 1H), 8.03-8.06 (m, 2H), 7.83 (s, 1H), 7.69 (t, 1H), 7.51-7.53 (m, 4H), 7.34-7.36 (m, 2H), 7.04-7.06 (m, 2H), 6.68 (dd, 1H), 6.57 (s, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 5.23 (s, 2H), 3.10 (s, 4H), 2.83 (s, 2H), 2.15-2.32 (m, 6H), 1.39 (t, 2H), 0.92 (s, 6H).

EXAMPLE 280

30 N-[(5-chloro-6-[(3R)-1-(1,3-difluoropropan-2-yl)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 280A

(R)-tert-butyl 3-((3-chloro-5-sulfamoylpyridin-2-yloxy)methyl)pyrrolidine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide and (R)-tert-butyl 3-(hydroxymethyl)pyrrolidine-1-carboxylate for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

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EXAMPLE 280B

(R)-5-chloro-6-(pyrrolidin-3-ylmethoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 280A for tert-butyl (4-(1,3-difluoropropan-2-yl)morpholin-2-yl)methylcarbamate in EXAMPLE 252B.

10

EXAMPLE 280C

(R)-5-chloro-6-((1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting 1,3-difluoropropan-2-one for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 280B for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

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EXAMPLE 280D

N-[(5-chloro-6-([(3R)-1-(1,3-difluoropropan-2-yl)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

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The title compound was prepared by substituting EXAMPLE 280C for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (400MHz, dimethylsulfoxide-d₆) δ 11.57 (s, 1 H), 8.38 (d, 1 H), 8.07 (d, 1 H), 7.96 (d, 1 H), 7.57 (d, 1 H), 7.44 (m, 1 H), 7.35 (m, 3 H), 7.05 (d, 2 H), 6.64 (dd, 1 H), 6.33 (dd, 1 H), 6.23 (d, 1 H), 4.65 (d, 2 H), 4.53 (dd, 2 H), 2.92 (m, 8 H), 2.75 (m, 4 H), 2.58 (m, 2 H), 2.20 (m, 6 H), 1.96 (m, 4 H), 1.53 (m, 1 H), 1.39 (t, 2 H), 0.89 (s, 6 H).

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EXAMPLE 281

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

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EXAMPLE 281A

(R)-5-chloro-6-((1-(2,2-difluoroethyl)pyrrolidin-3-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 280B for EXAMPLE 261B in EXAMPLE 261C.

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EXAMPLE 281B

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 281A for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (400MHz, dimethylsulfoxide-d₆) δ 11.59 (s, 1 H), 8.41 (d, 1 H), 8.10 (d, 1 H), 7.98 (d, 1 H), 7.56 (d, 1 H), 7.46 (m, 1 H), 7.41 (d, 1 H), 7.34 (d, 2 H), 7.04 (d, 2 H), 6.65 (dd, 1 H), 6.35 (dd, 1 H), 6.23 (m, 1 H), 6.03 (m, 1 H), 3.06 (s, 4 H), 2.84 (m, 6 H), 2.63 (m, 4 H), 2.20 (m, 6 H), 1.94 (m, 3 H), 1.53 (m, 1 H), 1.39 (t, 2 H), 0.91 (s, 6 H).

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EXAMPLE 282

N-[(5-chloro-6-{[1-(1,3-difluoropropan-2-yl)-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

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EXAMPLE 282A

5-chloro-6-((1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl)methoxy)pyridine-3-sulfonamide

EXAMPLE 257B (0.088 g) and 1,3-difluoropropan-2-one (0.028 g) were combined in dichloromethane (2 mL) and N,N-dimethylformamide (0.500 mL) and stirred at ambient temperature for 45 minutes. Sodium triacetoxyborohydride (0.064 g) was added in portions and then the reaction mixture was stirred overnight at ambient temperature. Additional 1,3-difluoropropan-2-one (0.028 g) was added, followed 30 minutes later by the addition of more sodium triacetoxyborohydride (0.064 g). The reaction mixture was stirred at ambient temperature for 72 hours. Additional 1,3-difluoropropan-2-one (0.028 g) was again added, followed 30 minutes later by the addition of more sodium triacetoxyborohydride (0.064 g). The reaction mixture was stirred overnight at ambient temperature. Additional 1,3-difluoropropan-2-one (0.028 g) was again added, followed 30 minutes later by the addition of

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more sodium triacetoxyborohydride (0.064 g). The reaction mixture was stirred overnight at ambient temperature. The reaction mixture was concentrated under high vacuum to remove N,N-dimethylformamide and then chromatographed on silica gel with 0 to 4% methanol in CH₂Cl₂ as the eluent.

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EXAMPLE 282B

N-[(5-chloro-6-{[1-(1,3-difluoropropan-2-yl)-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

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The title compound was prepared by substituting EXAMPLE 282A for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (400 MHz, pyridine-d₅) δ 13.05 (s, 1H), 9.12 (t, 1H), 8.72 (d, 1H), 8.41 (d, 1H), 8.10 (d, 1H), 7.66 (m, 2H), 7.44 (m, 2H), 7.07 (m, 2H), 6.75 (dd, 1H), 6.50 (m, 2H), 4.77 (dd, 1H), 4.65 (dd, 1H), 4.52 (dd, 2H), 3.06 (m, 4H), 2.93 (t, 1H), 2.80 (m, 5H), 2.52 (m, 1H), 2.26 (t, 2H), 2.13 (m, 4H), 2.04 (m, 2H), 1.97 (s, 2H), 1.85 (m, 2H), 1.39 (t, 2H), 1.28 (m, 2H), 0.93 (s, 6H).

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EXAMPLE 283

N-({3-chloro-4-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

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EXAMPLE 283A

3-chloro-4-((4-fluoro-1-methylpiperidin-4-yl)methoxy)benzenesulfonamide

To a solution of (4-fluoro-1-methylpiperidin-4-yl)methanol (0.265 g) in tetrahydrofuran (2 mL) was added sodium hydride (0.288 g). After 15 minutes, 3-chloro-4-fluorobenzenesulfonamide (0.377 g) was added as a solution in tetrahydrofuran (1 mL). The reaction was stirred for 2 hours, quenched with water (5 mL), adjusted to pH~7 with 1N aqueous HCl, and extracted with dichloromethane (2 x 25 mL). The organic layer was washed with brine (25 mL), dried over magnesium sulfate, filtered and concentrated. Silica gel chromatography (Reveleris 40 g) eluting with a gradient of 0.1% to 10% methanol containing 2N NH₃/dichloromethane over 30 minutes gave the title compound.

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EXAMPLE 283B

N-({3-chloro-4-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 283A for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide- d₆) δ 11.60 (s, 1H), 10.68 – 9.84 (m, 1H), 7.99 (d, 1H), 7.79 (d, 1H), 7.63 (t, 1H), 7.54 (d, 1H), 7.50 – 7.38 (m, 2H), 7.34 (d, 2H), 7.04 (d, 3H), 6.64 (dd, 1H), 6.36 (dd, 1H), 6.22 (s, 1H), 4.23 (d, 2H), 3.03 (s, 6H), 2.71 (m, 4H), 2.07 (m, 12H), 1.38 (s, 3H), 1.24 (s, 2H), 0.92 (s, 6H).

EXAMPLE 284

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

EXAMPLE 284A

3-cyano-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

To a solution of (tetrahydro-2H-pyran-4-yl)methanol (0.258 g) in tetrahydrofuran (5 mL) was added sodium hydride (0.355 g) and the reaction stirred at room temperature for 15 minutes. EXAMPLE 52A (0.400 g) was added and the reaction stirred for an additional 1 hour. The reaction was poured into ethyl acetate (50 mL) and 1N aqueous HCl (35 mL). The organic layer was washed with brine (35 mL) dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (Reveleris 40 g) eluting with a gradient of 10% to 100% ethyl acetate/hexanes over 30 minutes gave the title compound.

EXAMPLE 284B

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

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 284A for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide- d₆) δ 11.69 (s, 1H), 11.60 - 11.16 (m, 1H), 8.15 (s, 1H), 8.08 - 8.01 (m, 2H), 7.58 - 7.46 (m, 3H), 7.35 (d, J = 8.4, 2H), 7.29 (d, 1H), 7.04 (d, 2H), 6.68 (d, 1H), 6.40

(dd, 1H), 6.20 (s, 1H), 4.05 (d, 2H), 3.89 (d, 2H), 3.37 (d, 4H), 3.09 (s, 4H), 2.81 (s, 2H), 2.21 (d, 7H), 1.96 (s, 2H), 1.67 (d, 2H), 1.39 (s, 2H), 0.92 (s, 6H).

EXAMPLE 285

5 N-[(5-chloro-6-[[1-(2,2-difluoroethyl)-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 285A

10 5-chloro-6-((1-(2,2-difluoroethyl)-4-fluoropiperidin-4-yl)methoxy)pyridine-3-sulfonamide
EXAMPLE 257B (0.263 g), 1,1-difluoro-2-iodoethane (0.23 g), and sodium carbonate (0.254 g) were combined in a 20-mL vial with N,N-dimethylformamide (6 mL) and stirred at 70 °C overnight. The reaction mixture was concentrated under high vacuum and then chromatographed on silica gel with 0 to 5% methanol in CH₂Cl₂ as the eluent.

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EXAMPLE 285B

N-[(5-chloro-6-[[1-(2,2-difluoroethyl)-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

20 The title compound was prepared by substituting EXAMPLE 285A for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (400 MHz, pyridine-d₅) δ 13.05 (s, 1H), 9.12 (d, 1H), 8.72 (d, 1H), 8.41 (d, 1H), 8.10 (d, 1H), 7.66 (m, 2H), 7.43 (m, 2H), 7.06 (m, 2H), 6.75 (dd, 1H), 6.50 (m, 2H), 6.18 (tt, 2H), 4.51 (d, 2H), 3.07 (m, 4H), 2.80 (m, 6H), 2.60 (td, 2H), 2.25 (t, 2H), 2.13 (m, 4H), 2.03 (t, 2H), 1.97 (s, 2H), 1.93 (m, 1H), 1.85 (m, 1H), 1.39 (t, 2H), 0.93
25 (s, 6H).

EXAMPLE 286

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

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EXAMPLE 286A

3-chloro-4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 37C for (4-fluoro-1-methylpiperidin-4-yl)methanol in EXAMPLE 283A.

EXAMPLE 286B

5 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 286A for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide- d₆) δ 11.71 (s, 1H), 11.56 - 11.16 (m, 1H), 8.06 (d, 1H), 7.90 (d, 1H), 7.81 (d, 1H), 7.64 - 7.45 (m, 3H), 7.34 (d, 2H), 7.26 (d, 1H), 7.04 (d, 2H), 6.68 (d, 1H), 6.42 (dd, 1H), 6.18 (s, 1H), 4.28 (d, 2H), 3.78 (d, 2H), 3.61 (dd, 2H), 3.07 (s, 4H), 2.76 (s, 2H), 2.17 (d, 6H), 1.87 (dd, 6H), 1.38 (t, 2H), 0.92 (s, 6H).

15 EXAMPLE 287

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

20 EXAMPLE 287A

(4,4-difluorocyclohexyl)methanol

Ethyl 4,4-difluorocyclohexanecarboxylate (1.0 g, 5.20 mmol) in diethyl ether (2 mL) was added dropwise to lithium aluminium hydride (0.24 g) in diethyl ether (15 mL), and heated under reflux for 4 hours. The reaction was then cooled to 0°C, and water was added (0.24 mL), followed by 5N aqueous NaOH (0.24 mL) and water (0.72 mL). Then Na₂SO₄ and more diethyl ether (40 mL) were added, and the mixture was stirred for 30 minutes, then filtered through celite. After concentration, the residue was diluted with CH₂Cl₂ and Na₂SO₄ was added, and the mixture was filtered and concentrated to provide the title compound.

30 EXAMPLE 287B

5-chloro-6-((4,4-difluorocyclohexyl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 287A for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

EXAMPLE 287C

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5 The title compound was prepared by substituting EXAMPLE 287B for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (400MHz, dimethylsulfoxide-d₆) δ 11.63 (s, 1H), 8.46 (d, 1H), 8.14 (d, 1H), 8.00 (d, 1H), 7.56 (d, 1H), 7.47 (m, 2H), 7.35 (d, 2H), 7.03 (d, 2H), 6.66 (dd, 1H), 6.37 (m, 1H), 6.21 (d, 1H), 4.25 (d, 2H), 3.07 (br m, 4H), 2.82 (br s, 2H), 2.30 (br m, 4H), 2.16 (br m, 2H), 2.00, 1.95, 1.85 (all m, total 9H), 1.40 (t, 2H), 1.37 (m, 2H), 0.92 (s, 10 6H).

EXAMPLE 288

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{[6-[[1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl]methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

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EXAMPLE 288A

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 fuming nitric acid (6 mL) dropwise over 5 minutes. The reaction mixture was stirred at room temperature for 2 hours, and then heated at 50°C for 3 hours. After cooling, the reaction mixture was poured onto ice (200 g), and the mixture was extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to provide the title compound.

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EXAMPLE 288B

2-Chloro-5-nitro-3-(trifluoromethyl)pyridine

A mixture of EXAMPLE 288A (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 MgSO₄, filtered, and concentrated under reduced pressure. The

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residue was purified by flash column chromatography on silica gel eluting with 10% ethyl acetate in hexanes to provide the title compound.

EXAMPLE 288C

6-Chloro-5-(trifluoromethyl)pyridin-3-amine

5 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 288B in methanol (40 mL). The reaction mixture was stirred at room temperature for 1 hour. More 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
10 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 20% ethyl acetate in hexanes to provide the title compound.

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EXAMPLE 288D

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 288C (1.14 g) in dioxane (5 mL) was added to concentrated
20 HCl (20 mL) at 0°C . The solution was stirred for 5 minutes. To this suspension/solution was added sodium nitrite (0.44 g) in water (6 mL) dropwise at 0°C . The solution was stirred at 0°C for 3 hours. During this time, any solid formed was crushed with a glass rod to make sure that EXAMPLE 288C 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
25 288C 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 5% ethyl acetate in hexanes to provide the title compound.

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EXAMPLE 288E

6-chloro-5-(trifluoromethyl)pyridine-3-sulfonamide

EXAMPLE 288D (2.03 g) in dioxane (20 mL) solution was cooled to 0°C . Ammonium hydroxide solution was added dropwise. The reaction mixture was stirred at 0°C

for 2 hours followed by room temperature over night. The solvent was partially removed, and the residue was partitioned between water and ethyl acetate. The organic phase was washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with 0-3% methanol in dichloromethane to afford the title compound.

EXAMPLE 288F

tert-butyl 4-fluoro-4-((5-sulfamoyl-3-(trifluoromethyl)pyridin-2-yloxy)methyl)piperidine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 288E for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 322A for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

EXAMPLE 288G

6-((4-fluoropiperidin-4-yl)methoxy)-5-(trifluoromethyl)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 288F for tert-butyl (4-(1,3-difluoropropan-2-yl)morpholin-2-yl)methylcarbamate in EXAMPLE 252B.

EXAMPLE 288H

6-((1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl)methoxy)-5-(trifluoromethyl)pyridine-3-sulfonamide

The title compound was prepared by substituting 1,3-difluoropropan-2-one for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 288G for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

EXAMPLE 288I

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([6-([1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl]methoxy)-5-(trifluoromethyl)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 288H for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (400MHz, dimethylsulfoxide-d₆) δ 11.50 (s, 1 H), 8.57 (s, 1 H), 8.27 (d, 1 H), 7.91 (d, 1 H), 7.58 (d, 1 H), 7.40 (m, 1 H), 7.35 (d, 2 H), 7.28 (d, 1 H), 7.05 (d, 2 H), 6.61 (dd, 1 H), 6.29 (dd, 1 H), 6.24 (d, 1 H), 4.67 (d, 2 H), 4.55 (d, 2 H), 4.50

(s, 1 H), 4.44 (s, 1 H), 3.06 (m, 5 H), 2.73 (m, 6 H), 2.19 (d, 6 H), 1.90 (m, 7 H), 1.39 (t, 2 H), 0.93 (s, 6 H).

EXAMPLE 289

5 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-chloro-6-[2-(tetrahydrofuran-2-yl)ethoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 289A

10 5-chloro-6-(2-(tetrahydrofuran-2-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 and EXAMPLE 40A for EXAMPLE 36A in EXAMPLE 36B.

EXAMPLE 289B

15 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-chloro-6-[2-(tetrahydrofuran-2-yl)ethoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 289A for

20 EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.66 (s, 1H), 8.52 (d, 1H), 8.18 (s, 1H), 8.02 (s, 1H), 7.50-7.55 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.38 (dd, 1H), 6.21 (d, 1H), 4.39-4.51 (m, 4H), 3.87-3.94 (m, 1H), 3.73-3.78 (m, 1H), 3.57-3.62 (m, 1H), 3.11 (s, 4H), 2.89 (s, 2H), 2.33 (s, 4H), 2.15 (s, 2H), 1.77-2.01 (m, 7H), 1.45-1.54 (m, 1H), 1.40 (t, 2H), 0.93 (s, 6H).

EXAMPLE 290

30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-methylpiperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 290A

2-chloro-4,4-dimethylcyclohex-1-enecarbaldehyde

Into a 250 ml round-bottomed flask was added N,N-dimethylformamide (3.5 mL) in dichloromethane (30 mL). The mixture was cooled to -10°C, and phosphoryl trichloride (4 mL) was added dropwise. The solution was warmed up to room temperature and 3,3-dimethylcyclohexanone (5.5 mL) was added slowly. The mixture was heated to reflux
5 overnight. The reaction mixture was quenched by 0°C solution of sodium acetate (25 g in 50 mL water). The aqueous layer was extracted with ether (3 x 200 mL). The organic layers were combined, dried over Na₂SO₄, filtered, and dried under vacuum.

EXAMPLE 290B

10 2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enecarbaldehyde

Into a 1 L round-bottomed flask was added EXAMPLE 290A (6.8 g), 4-chlorophenylboronic acid (6.5 g) and palladium(II) acetate (0.2 g) in water (100 mL) to give a suspension. Potassium carbonate (15 g) and tetrabutylammonium bromide (10 g) were added. After degassing after subjecting to vacuum and nitrogen, the mixture was stirred at
15 45°C for 4 hours. After filtering through silica gel, diethyl ether (4x 200 mL) was used to extract the product. The combined organic layers were dried over Na₂SO₄ and filtered. The filtrate was concentrated and purified by flash chromatography on silica with 0-10% ethyl acetate in hexanes to provide the title compound.

20 EXAMPLE 290C

tert-butyl 4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)-3-methylpiperazine-1-carboxylate

To a solution of *tert*-butyl 3-methylpiperazine-1-carboxylate (0.256 g) and EXAMPLE 290B (0.350 g) in dichloromethane (2 mL) was added sodium
25 triacetoxyborohydride (0.406 g) and the reaction was stirred at room temperature overnight. The reaction was quenched with NaHCO₃ solution (50 mL) and extracted with dichloromethane (50 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. Silica gel chromatography (Reveleris 40 g) eluting with a gradient of 0.5% to 2.5% methanol/dichloromethane gave the title compound.

30

EXAMPLE 290D

1-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)-2-methylpiperazine

A solution of EXAMPLE 290C (0.298 g) and HCl (4.0M in dioxane, 2 mL) were stirred for 1 hour. The reaction was concentrated and partitioned between dichloromethane

(100 mL) and NaHCO₃ (100 mL). The organic layer was washed with brine (50 mL), dried over magnesium sulfate, filtered and concentrated to provide the title compound.

EXAMPLE 290E

5 methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)-3-methylpiperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 290D for EXAMPLE 3E in EXAMPLE 3I.

10 EXAMPLE 290F

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)-3-methylpiperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 290E for EXAMPLE 15G in EXAMPLE 15H.

15

EXAMPLE 290G

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)-3-methylpiperazin-1-yl)-N-([3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

20 The title compound was prepared by substituting EXAMPLE 290F for EXAMPLE 1E in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide- d₆) δ 11.66 (s, 1H), 11.54 - 11.30 (m, 1H), 8.62 - 8.53 (m, 2H), 8.03 (d, 1H), 7.78 (d, 1H), 7.48 (d, 3H), 7.34 (d, 2H), 7.06 (t, 3H), 6.68 (d, 1H), 6.38 (dd, 1H), 6.21 (s, 1H), 3.84 (d, 2H), 3.23 (s, 4H), 2.75 (s, 4H), 1.64 (s, 8H), 1.62 (d, 2H), 1.42 - 1.17 (m, 6H), 0.92 (s, 6H), 0.87 (s, 3H).

25

EXAMPLE 291

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(4-{[3-(cyclopropylamino)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

30

EXAMPLE 291A

tert-butyl 2-cyanoethyl(cyclopropyl)carbamate

To a solution of 3-(cyclopropylamino)propanenitrile (5.0g) in tetrahydrofuran (30 mL) was added di-*tert*-butyl dicarbonate (9.91g) and a catalytic amount of 4-dimethylaminopyridine. The mixture was stirred overnight. The mixture was diluted with ethyl acetate (400 mL) and washed with 5% aqueous HCl, water and brine. After drying over Na₂SO₄, the mixture was filtered, and the solvent was evaporated under vacuum to provide the title compound.

EXAMPLE 291B

tert-butyl 3-aminopropyl(cyclopropyl)carbamate

EXAMPLE 291A (9.75 g) and 7M NH₃-methanol (25 mL) were added to a Ra-Ni 2800, water slurry (19.50 g, 332 mmol) in a 250 mL pressure bottle and stirred for 2 hours at 30 psi and room temperature. The mixture was filtered through a nylon membrane and evaporation of the solvent gave the title compound.

EXAMPLE 291C

tert-butyl cyclopropyl(3-(2-nitro-4-sulfamoylphenylamino)propyl)carbamate

To a solution of 4-chloro-3-nitrobenzenesulfonamide (2.5 g), and EXAMPLE 291B (2.26 g) in dioxane (20 mL) was added N,N-diisopropylethylamine (5 mL). The mixture was stirred at reflux overnight. The mixture was diluted with ethyl acetate (400 mL) and washed with water and brine. After drying over Na₂SO₄, the mixture was filtered, and the solvent was evaporated under vacuum to provide the title compound.

EXAMPLE 291D

tert-butyl 3-(4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)propyl(cyclopropyl)carbamate

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 291C for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 291E

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(4-{[3-(cyclopropylamino)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

To a solution of EXAMPLE 291D (2.56 g) in dichloromethane (10 mL) was added trifluoroacetic acid (10 mL). The mixture was stirred for 2 hours. The mixture was concentrated under vacuum and the residue was dissolved in dichloromethane (300 mL) and washed with aqueous NaHCO₃, water, and brine and dried over Na₂SO₄. Filtration and
5 evaporation of the solvent gave the crude product. The title compound was obtained by dissolving 200 mg of the crude material in dimethylsulfoxide/methanol (1:1, 10 mL) and loaded on Gilson, C18(100A) 250x121.2 mm(10micron), eluting with 30% acetonitrile to 65% acetonitrile over 40 minutes. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.54 (s, 1 H), 8.43 (m, 2 H), 7.94 (d, 1 H), 7.71 (dd, 1 H), 7.57 (d, 1 H), 7.43 (m, 1 H), 7.34 (m, 3 H),
10 7.05 (d, 2 H), 6.90 (d, 1 H), 6.63 (dd, 1 H), 6.29 (d, 2 H), 3.43 (m, 2 H), 2.96 (m, 6 H), 2.73 (m, 2 H), 2.22 (m, 7 H), 1.87 (m, 4 H), 1.38 (m, 3 H), 0.94 (m, 6 H), 0.62 (m, 4 H).

EXAMPLE 292

N-{{5-chloro-6-(2-methoxyethoxy)pyridin-3-yl}sulfonyl}-4-(4-{{2-(4-chlorophenyl)-4,4-
15 dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 292A

5-chloro-6-(2-methoxyethoxy)pyridine-3-sulfonamide

20 The title compound was prepared by substituting EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide and 2-methoxyethanol for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

EXAMPLE 292B

25 N-{{5-chloro-6-(2-methoxyethoxy)pyridin-3-yl}sulfonyl}-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 292A for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (400MHz, dimethylsulfoxide-d₆) δ 11.63 (s, 1H), 8.48 (d, 1H), 8.17 (d, 1H), 8.01 (d, 1H), 7.56 (d, 1H), 7.49 (m, 2H), 7.35 (d, 2H), 7.04 (d, 2H), 6.66 (dd, 1H), 6.37 (m, 1H), 6.21 (d, 1H), 4.52 (m, 2H), 3.70 (m, 2H), 3.28 (s, 3H), 3.13 (br m, 4H), 2.88 (br s, 2H), 2.34 (br m, 4H), 2.16 (br m, 2H), 1.97 (s, 2H), 1.40 (t, 2H), 0.92 (s, 6H).
30

EXAMPLE 293

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5

EXAMPLE 293A

The title compound was prepared by substituting 5-bromo-2,3-difluoropyridine for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

10

EXAMPLE 293B

tert-butyl 5-fluoro-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridin-3-ylcarbamate

The title compound was prepared by substituting EXAMPLE 293A for EXAMPLE 248A in EXAMPLE 248B.

15

EXAMPLE 293C

5-fluoro-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonyl chloride

The title compound was prepared by substituting EXAMPLE 293B for EXAMPLE 248B in EXAMPLE 248C.

20

EXAMPLE 293D

5-fluoro-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 293C for EXAMPLE 248C in EXAMPLE 248D.

EXAMPLE 293E

25

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

30

The title compound was prepared by substituting EXAMPLE 293D for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (400 MHz, pyridine-d₅) δ 13.07 (s, 1H), 9.05 (d, 1H), 8.44 (dd, 1H), 8.41 (d, 1H), 8.09 (d, 1H), 7.67 (t, 1H), 7.65 (d, 1H), 7.44 (m, 2H), 7.07 (m, 2H), 6.76 (dd, 1H), 6.53 (d, 1H), 6.49 (dd, 1H), 4.21 (d, 2H), 3.96 (dd, 2H), 3.31 (td, 2H), 3.07 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.14 (m, 4H), 1.97 (m, 3H), 1.58 (dd, 2H), 1.38 (m, 4H), 0.94 (s, 6H).

EXAMPLE 294

N-[(3-chloro-4-{[1-(methoxyacetyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5

EXAMPLE 294A

tert-butyl 4-((2-chloro-4-sulfamoylphenoxy)methyl)piperidine-1-carboxylate

The title compound was prepared by substituting *tert*-butyl-4-(hydroxymethyl)piperidine-1-carboxylate for (4-fluoro-1-methylpiperidin-4-yl)methanol in
10 EXAMPLE 283A.

EXAMPLE 294B

tert-butyl 4-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-
15 chlorophenoxy)methyl)piperidine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 294A for EXAMPLE 1F in EXAMPLE 1G.

EXAMPLE 294C

20 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(3-chloro-4-(piperidin-4-ylmethoxy)phenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzamide

To EXAMPLE 294B (0.286 g) in dichloromethane (3 mL) was added trifluoroacetic acid (1 mL) and the reaction stirred at room temperature. After 3 hours the reaction was
25 concentrated to provide the title compound.

EXAMPLE 294D

N-[(3-chloro-4-{[1-(methoxyacetyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide
30

To EXAMPLE 294C (0.75 g) as a solution in dichloromethane (1 mL) was added N,N-diisopropylethylamine (0.055 mL) followed by 2-methoxyacetyl chloride (6 µl). After stirring for 10 minutes the reaction was loaded onto silica gel (Reveleris 40 g) and eluted using a gradient of 0.5% to 3.5% methanol/dichloromethane over 30 minutes (flow = 40

mL/minutes) to provide the title compound. ¹H NMR (300 MHz, dimethylsulfoxide- d₆) δ 11.71 (s, 1H), 11.55 - 11.24 (m, 1H), 8.06 (d, 1H), 7.88 (d, 1H), 7.78 (d, 1H), 7.57 (s, 1H), 7.51 (s, 1H), 7.48 (d, 1H), 7.34 (d, 2H), 7.21 (d, 1H), 7.04 (d, 2H), 6.67 (d, 1H), 6.42 (dd, 1H), 6.18 (s, 1H), 4.42 - 4.32 (m, 1H), 4.03 (dd, 4H), 3.86 - 3.74 (m, 1H), 3.28 (s, 3H), 3.07 (s, 5H), 2.77 (s, 3H), 2.30 - 1.92 (m, 9H), 1.77 (s, 2H), 1.31 (d, 4H), 0.92 (s, 6H).

EXAMPLE 295

N-[(3-chloro-4-{[1-(N,N-dimethylglycyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting 2-(dimethylamino)acetyl chloride for 2-methoxyacetyl chloride in EXAMPLE 294D. ¹H NMR (300 MHz, dimethylsulfoxide- d₆) δ 11.58 (s, 1H), 10.35 - 9.94 (m, 1H), 7.96 (d, 1H), 7.74 (d, 1H), 7.55 (d, 2H), 7.45 (s, 1H), 7.41 - 7.29 (m, 3H), 7.05 (d, 3H), 6.63 (d, 1H), 6.37 - 6.32 (m, 1H), 6.22 (d, 1H), 4.39 (d, 1H), 3.94 (s, 6H), 3.01 (s, 6H), 2.73 (m, 4H), 2.55 (m, 5H), 2.19 (s, 6H), 1.95 (m, 2H), 1.82 (m, 2H), 1.38 (s, 4H), 0.93 (s, 6H).

EXAMPLE 296

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohexyl]methyl}piperidin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 296A

tert-butyl 4-((4,4-dimethyl-2-oxocyclohexyl)methyl)piperidine-1-carboxylate
3,3-Dimethylcyclohexanone (5.60 mL) was added to sodium bis(trimethylsilyl)amide (45.3 mL, 1M in tetrahydrofuran), and the reaction was stirred for 1 hour. tert-Butyl 4-(bromomethyl)piperidine-1-carboxylate (11.1 g) in dimethylsulfoxide (30 mL) was added, and the reaction was stirred at 50°C for 24 hours. The reaction was cooled, poured into water (300 mL), extracted three times with ether, and the combined extracts were washed three times with water, and brine, dried over Na₂SO₄, filtered, and concentrated. The crude product was chromatographed on silica gel using 5-20% ethyl acetate in hexanes to provide the title compound.

EXAMPLE 296B

tert-butyl 4-((2-(4-chlorophenyl)-2-hydroxy-4,4-dimethylcyclohexyl)methyl)piperidine-1-carboxylate

(4-Chlorophenyl)magnesium bromide (14.1 mL, 1M in ether) was added to
5 EXAMPLE 296A (3.25 g) in tetrahydrofuran (40 mL) at -78°C, and the reaction was stirred for 20 minutes, and then allowed to warm to room temperature overnight. The reaction was quenched with pH 7 buffer (20 mL), extracted with 2x ether, and the combined extracts were washed with brine, dried over Na₂SO₄, filtered, and concentrated. The crude product was chromatographed on silica gel using 1-20% ethyl acetate in hexanes to provide the title
10 compound.

EXAMPLE 296C

trans-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohexyl)methyl)piperidine

The title compound was prepared by substituting EXAMPLE 296B for EXAMPLE
15 1A in EXAMPLE 1B.

EXAMPLE 296D

Trans-methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohexyl)methyl)piperidin-1-yl)benzoate

20 The title compound was prepared by substituting EXAMPLE 296C for EXAMPLE 263G in EXAMPLE 263H.

EXAMPLE 296E

Trans-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohexyl)methyl)piperidin-1-yl)benzoic acid
25

The title compound was prepared by substituting EXAMPLE 296D for EXAMPLE 3I in EXAMPLE 3J.

EXAMPLE 296F

30 Trans-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohexyl)methyl]piperidin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 296E for EXAMPLE 1E in EXAMPLE 1G. ¹H NMR (300MHz, dimethylsulfoxide-d₆) δ 11.69 (s, 1H), 11.36 (br s, 1H), 8.60 (t, 1H), 8.55 (d, 1H), 8.03 (d, 1H), 7.78 (dd, 1H), 7.52 (m, 3H), 7.27 (d, 2H), 7.16 (d, 2H), 7.09 (m, 1H), 6.63 (dd, 1H), 6.38 (dd, 1H), 6.11 (d, 1H), 3.83 (dd, 2H), 3.52 (m, 2H), 3.26 (m, 4H), 2.61 (m, 2H), 2.35 (m, 1H), 1.89 (m, 2H), 1.76 (m, 1H), 1.62 (m, 2H), 1.38 (m, 4H), 1.25 (m, 6H), 1.12 (m, 2H), 0.95 (m, 2H), 0.94 (s, 3H), 0.88 (s, 3H).

EXAMPLE 297

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

EXAMPLE 297A

6-((tetrahydro-2H-pyran-4-yl)methoxy)-5-(trifluoromethyl)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 288E for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

EXAMPLE 297B

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

The title compound was prepared by substituting EXAMPLE 297A for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (400MHz, dimethylsulfoxide-d₆) δ 11.49 (s, 1 H), 8.56 (d, 1 H), 8.23 (d, 1 H), 7.90 (d, 1 H), 7.58 (d, 1 H), 7.40 (m, 1 H), 7.34 (m, 2 H), 7.26 (d, 1 H), 7.05 (d, 2 H), 6.61 (dd, 1 H), 6.28 (dd, 1 H), 6.24 (d, 1 H), 4.24 (d, 2 H), 3.86 (dd, 2 H), 3.30 (m, 4 H), 3.00 (s, 4 H), 2.73 (s, 2 H), 2.16 (m, 6 H), 1.97 (m, 2 H), 1.61 (dd, 2 H), 1.33 (m, 4 H), 0.93 (s, 6 H).

EXAMPLE 298

N-({5-chloro-6-[(trans-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 298A

6-((trans-4-(tert-butyldimethylsilyloxy)cyclohexyl)methoxy)-5-chloropyridine-3-sulfonamide

The title compound was prepared by substituting (trans-4-(tert-butyldimethylsilyloxy)cyclohexyl)methanol for (tetrahydro-2H-pyran-4-yl)methanol and
5 EXAMPLE 40A for EXAMPLE 36A in EXAMPLE 36B.

EXAMPLE 298B

N-({5-chloro-6-[(trans-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-pyrrolo[2,3-
10 b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 298A for
EXAMPLE 11B in EXAMPLE 11D. After the reaction was over, the solvent was removed,
and the residue was treated with 1:1 trifluoroacetic acid/dichloromethane for two hours. The
solvents were removed, and the residue was purified by reverse phase Gilson Prep HPLC
15 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 provide the title
compound. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.65 (s, 1H), 8.47 (s, 1H), 8.15 (s,
1H), 8.01 (d, 1H), 7.54 (d, 1H), 7.48-7.49 (m, 1H), 7.35 (d, 2H), 7.05 (d, 2H), 6.67 (dd, 1H),
6.37 (d, 1H), 6.21 (s, 1H), 4.53 (t, 1H), 4.18 (d, 2H), 3.08 (s, 4H), 2.84 (s, 2H), 2.29 (s, 4H),
20 2.15 (s, 2H), 1.96 (s, 2H), 1.79-1.83 (m, 5H), 1.39 (t, 2H), 1.08-1.13 (m, 5H), 0.93 (s, 6H).

EXAMPLE 299

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-pyrrolo[2,3-
25 b]pyridin-5-yloxy)benzamide

EXAMPLE 299A

3-cyano-4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 37C for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 284A.
30

EXAMPLE 299B

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5 The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 299A for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide- d₆) δ 11.72 (s, 1H), 10.24 - 9.27 (m, 1H), 8.21 (d, 1H), 8.12 (dd, 1H), 8.05 (d, 1H), 7.63 - 7.46 (m, 3H), 7.45 - 7.31 (m, 3H), 7.07 (d, 2H), 6.70 (dd, 1H), 6.42 (s, 1H), 6.23 (s, 1H), 4.38 (d, 2H), 3.91 - 3.73 (m, 2H), 3.68 - 3.51 (m, 2H), 3.22 - 2.96 (m, 10H),
10 2.31 - 2.12 (m, 2H), 1.99 (s, 6H), 1.43 (t, 2H), 0.93 (s, 6H).

EXAMPLE 300

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(trans-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

15

EXAMPLE 300A

6-((trans-4-methoxycyclohexyl)methoxy)-5-(trifluoromethyl)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 288E for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 121A for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

20

EXAMPLE 300B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(trans-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

25

The title compound was prepared by substituting EXAMPLE 300A for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (400MHz, dimethylsulfoxide-d₆) δ 11.50 (s, 1 H), 8.56 (d, 1 H), 8.23 (d, 1 H), 7.90 (d, 1 H), 7.58 (d, 1 H), 7.40 (m, 1 H), 7.35 (d, 2 H), 7.27 (d, 1 H), 7.05 (d, 2 H), 6.61 (dd, 1 H), 6.28 (dd, 1 H), 6.24 (d, 1 H), 4.20 (d, 2 H), 3.23 (s, 3 H), 3.03 (m, 5 H), 2.73 (s, 2 H), 2.18 (m, 6 H), 1.98 (m, 5 H), 1.80 (m, 3 H), 1.39 (t, 2 H), 1.09 (m, 4 H), 0.93 (s, 6 H).

30

EXAMPLE 301

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-
[(cis-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5

EXAMPLE 301A

6-((cis-4-methoxycyclohexyl)methoxy)-5-(trifluoromethyl)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 288E for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 121A for (tetrahydro-2H-pyran-4-yl)methanol in
EXAMPLE 24A.

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EXAMPLE 301B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-
[(cis-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-
pyrrolo[2,3b]pyridin-5-yloxy)benzamide

15

The title compound was prepared by substituting EXAMPLE 301A for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (400MHz, dimethylsulfoxide-d₆) δ 11.49 (m, 1 H), 8.54 (m, 1 H), 8.23 (d, 1 H), 7.91 (d, 1 H), 7.59 (d, 1 H), 7.40 (m, 1 H), 7.34 (m, 2 H), 7.27 (d, 1 H), 7.04 (d, 2 H), 6.61 (dd, 1 H), 6.29 (dd, 1 H), 6.24 (d, 1 H), 4.20 (d, 2 H), 3.37 (m, 2 H),
3.19 (s, 3 H), 3.00 (s, 4 H), 2.73 (s, 2 H), 2.18 (m, 6 H), 1.96 (s, 2 H), 1.80 (m, 3 H), 1.50 (dd, 2 H), 1.37 (m, 6 H), 0.93 (s, 6 H).

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EXAMPLE 302

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}piperidin-1-yl)-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

25

EXAMPLE 302A

4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperidine

EXAMPLE 296B (1.0 g) was stirred in dichloromethane (15 mL) and trifluoroacetic acid (15 mL) at 35°C for 48 hours. The mixture was concentrated, taken up in dichloromethane (100 mL), and stirred, and saturated Na₂CO₃ solution (20 mL) was added

30

slowly. The solution was separated and the organic layer was dried over Na₂SO₄, filtered, and concentrated to provide the title compound.

EXAMPLE 302B

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-
5 dimethylcyclohex-1-enyl)methyl)piperidin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 302A for EXAMPLE 263G in EXAMPLE 263H.

EXAMPLE 302C

10 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperidin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 302B for EXAMPLE 3I in EXAMPLE 3J.

15 EXAMPLE 302D

1,1-difluoro-4-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-Difluorocyclohexanone (3.76 g) in dioxane (150
20 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.

EXAMPLE 302E

4,4-difluoro-1-(hydroxymethyl)cyclohexanol

25 To the solution from EXAMPLE 302D was added water (75 mL), then N-methylmorpholine-N-oxide (6.4 mL, 50% solution in water) and OsO₄ (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 Na₂S₂O₃ solution (100 mL) for 30 minutes, and then acidified with concentrated aqueous HCl. The solution
30 was then extracted three times with ethyl acetate, and the organic layers were combined, washed with 1M 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 302F

5-chloro-6-((4,4-difluoro-1-hydroxycyclohexyl)methoxy)pyridine-3-sulfonamide

This example was prepared by substituting EXAMPLE 302E for tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide in
5 EXAMPLE 24A.

EXAMPLE 302G

N-({5-chloro-6-[(4,4-difluoro-1-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-
10 {2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperidin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 302C for EXAMPLE 1E and EXAMPLE 302F for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300MHz, dimethylsulfoxide-d₆) δ 11.65 (br s, 2H), 8.51 (s, 1H), 8.18 (s, 1H), 8.02 (d, 1H), 7.53 (m, 3H), 7.35 (d, 2H), 7.04 (d, 2H), 6.69 (dd, 1H), 6.39 (dd, 1H), 6.21 (d, 1H), 4.88 (s, 1H), 4.27
15 (s, 2H), 3.10 (m, 4H), 2.88 (m, 1H), 2.33 (m, 2H), 2.15 (m, 4H), 1.97 (s, 2H), 1.91 (m, 2H), 1.73 (m, 4H), 1.52 (m, 1H), 1.40 (m, 2H), 1.31 (m, 1H), 0.93 (s, 3H), 0.91 (m, 2H).

EXAMPLE 303

N-[(3-chloro-4-{[trans-4-(morpholin-4-yl)cyclohexyl]methoxy}phenyl)sulfonyl]-4-(4-{2-(4-
20 chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 303A

trans-4-morpholinocyclohexyl)methanol

To *tert*-butyl trans-4-(hydroxymethyl)cyclohexylcarbamate (0.500 g) was added
25 hydrogen chloride (4.0M in dioxane, 2.2 mL) and the reaction was stirred for 1 hour and concentrated. The resulting solid was dissolved in acetonitrile (4 mL) and treated with N,N-diisopropylethylamine (1.523 mL) followed by 1-bromo-2-(2-bromoethoxy)ethane (0.556 g) and heated to 60°C. After stirring overnight the reaction was concentrated, loaded onto silica gel (Reveleris 40 g) and eluted using a gradient of 1% to 10% methanol/dichloromethane
30 over 30 minutes (flow = 40 mL/min) to provide the title compound.

EXAMPLE 303B

3-chloro-4-(((1r,4r)-4-morpholinocyclohexyl)methoxy)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 303A for (4-fluoro-1-methylpiperidin-4-yl)methanol in EXAMPLE 283A.

EXAMPLE 303C

N-[(3-chloro-4-{[trans-4-(morpholin-4-yl)cyclohexyl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 303B for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide- d₆) δ 11.65 (s, 1H), 10.96 – 10.59 (m, 1H), 8.02 (d, 1H), 7.82 (d, 1H), 7.69 (s, 1H), 7.50 (dd, 3H), 7.38 – 7.30 (m, 2H), 7.15 – 6.99 (m, 3H), 6.65 (dd, 1H), 6.39 (dd, 1H), 6.20 (d, 1H), 3.91 (d, 2H), 3.64 (s, 4H), 3.04 (s, 4H), 2.73 (s, 7H), 2.18 (s, 6H), 1.93 (m, 6H), 1.80 – 1.65 (m, 1H), 1.32 (m, 6H), 0.92 (s, 6H).

EXAMPLE 304

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-({3-[cyclopropyl(1,3-thiazol-5-ylmethyl)amino]propyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

To a solution of EXAMPLE 291E (95 mg) in dichloromethane (2 mL) and acetic acid (0.5 mL) was added thiazole-5-carbaldehyde (13 mg) followed by sodium triacetoxyborohydride (35 mg). The mixture was stirred overnight. The mixture was diluted with dichloromethane (300 mL) and washed with aqueous NaHCO₃, water, and brine and dried over Na₂SO₄. Filtration and evaporation of the solvent gave crude product which was dissolved in dimethylsulfoxide/methanol (6 mL, 1:1) and loaded on Gilson, C18(100A) 250x121.2 mm(10micron), with 30% acetonitrile to 65% acetonitrile over 40 minutes. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.67 (s, 1 H), 8.95 (s, 1 H), 8.57 (m, 2 H), 8.03 (d, 1 H), 7.78 (m, 2 H), 7.49 (m, 3 H), 7.35 (m, 2 H), 7.02 (m, 3 H), 6.67 (dd, 1 H), 6.38 (dd, 1 H), 6.19 (d, 1 H), 4.00 (s, 2 H), 3.05 (d, 4 H), 2.73 (m, 2 H), 2.60 (m, 2 H), 2.18 (m, 7 H), 1.95 (s, 2 H), 1.79 (m, 3 H), 1.37 (m, 3 H), 0.92 (s, 6 H), 0.45 (m, 4 H).

EXAMPLE 305

N-[(3-chloro-4-[(trans-4-hydroxycyclohexyl)methoxy]phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 305A

3-chloro-4-((trans-4-hydroxycyclohexyl)methoxy)benzenesulfonamide
(Trans-4-(tert-butyldimethylsilyloxy)cyclohexyl)methanol (275 mg, prepared according to a procedures in WO 2008/124878) and 3-chloro-4-fluorobenzenesulfonamide (259 mg) in tetrahydrofuran (15 mL) were treated with sodium hydride (180 mg, 60%) overnight. The reaction was quenched with water (1 mL) and trifluoroacetic acid (4 mL) was added. The resulting mixture was stirred for 1 hour and concentrated. The residue was triturated with water and methanol to provide the title compound.

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EXAMPLE 305B

N-({3-chloro-4-[(trans-4-hydroxycyclohexyl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 305A in place of EXAMPLE 11B. ¹H NMR (500 MHz, dimethylsulfoxide-d₆) δ 11.71 (s, 1 H), 11.38 (s, 1 H), 8.06 (d, 1 H), 7.87 (d, 1 H), 7.76 (dd, 1 H), 7.57 (d, 1 H), 7.51 - 7.55 (m, 1 H), 7.49 (d, 1 H), 7.34 (d, 2 H), 7.18 (d, 1 H), 7.04 (d, 2 H), 6.67 (dd, 1 H), 6.42 (dd, 1 H), 6.18 (d, 1 H), 4.54 (d, 1 H), 3.91 (d, 2 H), 3.07 (s, 4 H), 2.75 (s, 2 H), 2.17 (d, 6 H), 1.95 (s, 2 H), 1.78 - 1.90 (m, 4 H), 1.63 - 1.75 (m, 1 H), 1.38 (t, 2 H), 1.00 - 1.25 (m, 4 H), 0.92 (s, 6 H).

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EXAMPLE 306

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

25

EXAMPLE 306A

3-chloro-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

The title compound was prepared by substituting 4-fluoro-3-chlorobenzenesulfonamide for 4-chloro-3-nitrobenzenesulfonamide, (tetrahydro-2H-pyran-4-yl)methanamine for 4-methylpiperazin-1-amine dihydrochloride and Hunig's base for N¹,N¹,N²,N²-tetramethylethane-1,2-diamine in EXAMPLE 6A.

30

EXAMPLE 306B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-chloro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 306A for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (400MHz, dimethylsulfoxide-d₆) δ 11.80 (s, 1H), 11.17 (br s, 1H), 8.09 (d, 1H), 7.71 (d, 1H), 7.63 (d, 1H), 7.58 (dd, 1H), 7.53 (dd, 1H), 7.50 (d, 1H), 7.34 (d, 2H), 7.03 (d, 2H), 6.74 (d, 1H), 6.66 (dd, 1H), 6.42 (m, 1H), 6.40 (t, 1H), 6.16 (d, 1H), 3.83 (m, 2H), 3.24 (m, 2H), 3.10 (m, 2H), 3.06 (br m, 4H), 2.72 (s, 2H), 2.17 (br m, 6H), 1.95 (s, 2H), 1.83 (m, 1H), 1.59 (br m, 2H), 1.38 (t, 2H), 1.20 (ddd, 2H), 0.92 (s, 6H).

EXAMPLE 307

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 307A

4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-3-(trifluoromethyl)benzenesulfonamide

The title compound was prepared by substituting 4-fluoro-3-(trifluoromethyl)benzenesulfonamide for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 37C for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

EXAMPLE 307B

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 307A for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (400 MHz, pyridine-d₅) δ 13.07 (s, 1H), 8.78 (d, 1H), 8.58 (dd, 1H), 8.42 (d, 1H), 8.09 (d, 1H), 7.67 (t, 1H), 7.65 (d, 1H), 7.43 (m, 2H), 7.16 (d, 1H), 7.06 (m, 2H), 6.74 (dd, 1H), 6.51 (m, 2H), 4.21 (d, 2H), 3.87 (m, 2H), 3.78 (td, 2H), 3.06 (m, 4H), 2.76 (s, 2H), 2.25 (t, 2H), 2.13 (m, 4H), 1.95 (m, 6H), 1.39 (t, 2H), 0.93 (s, 6H).

EXAMPLE 308

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
(3-[cyclopropyl(2,2,2-trifluoroethyl)amino]propyl)amino]-3-nitrophenyl]sulfonyl}-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

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EXAMPLE 308A

4-(3-(cyclopropylamino)propylamino)-3-nitrobenzenesulfonamide

To a solution of EXAMPLE 291C (4.14 g) in dichloromethane (10 mL) was added
trifluoroacetic acid (10 mL). The mixture was stirred for 2 hours. The mixture was
10 concentrated under vacuum and the residue was dissolved in dichloromethane (300 mL) and
washed with aqueous NaHCO₃, water, and brine and dried over Na₂SO₄. Filtration and
evaporation of solvent gave the title compound.

EXAMPLE 308B

15 4-(3-(cyclopropyl(2,2,2-trifluoroethyl)amino)propylamino)-3-nitrobenzenesulfonamide

To a solution of EXAMPLE 308A (314 mg) in dichloromethane (6 mL) was added
2,2,2-trifluoroethyl trifluoromethanesulfonate (255 mg) and N,N-diisopropylethylamine (258
mg). The mixture was stirred overnight. The mixture was diluted with dichloromethane (300
mL) and washed with aqueous NaHCO₃, water, brine and dried over Na₂SO₄. Filtration and
20 evaporation of solvent gave the title compound.

EXAMPLE 308C

25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
(3-[cyclopropyl(2,2,2-trifluoroethyl)amino]propyl)amino]-3-nitrophenyl]sulfonyl}-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E
and EXAMPLE 308B for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300 MHz,
dimethylsulfoxide-d₆) δ 11.67 (s, 1 H), 11.38 (m, 1 H), 8.55 (d, 2 H), 8.03 (d, 1 H), 7.81 (dd,
1 H), 7.50 (m, 3 H), 7.34 (d, 2 H), 7.05 (m, 3 H), 6.67 (dd, 1 H), 6.38 (dd, 1 H), 6.19 (d, 1 H),
30 3.07 (m, 4 H), 2.82 (m, 4 H), 2.18 (m, 7 H), 1.38 (m, 2 H), 0.92 (s, 6 H), 0.44 (m, 4 H).

EXAMPLE 309

N-[(3-chloro-4-{[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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5 To a solution of EXAMPLE 294B (0.150 g) in dichloromethane (2 mL) was added trifluoroacetic acid (1 mL). After stirring for 1 hour the reaction was concentrated and dried under high vacuum. The residue was dissolved in dichloromethane (2 mL) and treated with sodium triacetoxyborohydride (0.050 g) and oxetan-3-one (0.017 g) and stirred overnight at room temperature. The reaction was quenched with saturated aqueous NaHCO₃ (20 mL) and
10 extracted into dichloromethane (50 mL). The organic layer was separated, washed with brine (25 mL), dried over Na₂SO₄, filtered, and concentrated. Silica gel chromatography (Reveleris 40 g) eluting with a gradient of 0.5% to 5% methanol/dichloromethane over 30 minutes (flow = 40 mL/min) provided the title compound. ¹H NMR (300 MHz, dimethylsulfoxide- d₆) δ 11.70 (s, 1H), 11.21 (s, 1H), 8.05 (d, 1H), 7.87 (d1H), 7.75 (dd, 1H), 7.61 - 7.42 (m, 3H),
15 7.42 - 7.26 (m, 2H), 7.18 (d, 1H), 7.14 - 6.97 (m, 2H), 6.67 (dd, 1H), 6.41 (dd, 1H), 6.18 (d, 1H), 4.51 (dt, 4H), 3.99 (d, 2H), 3.56 - 3.32 (m, 1H), 3.06 (s, 4H), 2.89 - 2.68 (m, 4H), 2.16 (d, 6H), 2.01 - 1.69 (m, 7H), 1.50 - 1.07 (m, 4H), 0.92 (s, 6H).

EXAMPLE 310

20 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3,5-difluoro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 310A

25 3,5-difluoro-4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

EXAMPLE 37C (0.423 g) in tetrahydrofuran (30 mL) was treated with NaH (60% oil dispersion) (0.480 g), stirred 20 minutes at ambient temperature, treated with 3,4,5-trifluorobenzenesulfonamide (0.633 g) and stirred 30 minutes. N,N-Dimethylacetamide (15 mL) was added to increase solubility of the reactants and stirring was continued overnight at
30 ambient temperature. Additional NaH (60% oil dispersion) (0.480 g) and N,N-dimethylacetamide (15 mL) were added and the mixture was heated overnight at 50°C. The reaction was quenched with saturated aqueous NH₄Cl solution and then partitioned between saturated aqueous NH₄Cl solution and ethyl acetate. The organic layer was washed with water and brine, dried (MgSO₄), filtered and concentrated. The concentrate was

chromatographed on amine functionalized silica gel with 0 to 2% methanol in CH₂Cl₂ as the eluent. The residue was further purified by reverse phase HPLC on a C18 column using a gradient of 10-70% acetonitrile/0.1% trifluoroacetic acid in water to provide the title compound.

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EXAMPLE 310B

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({3,5-difluoro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

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The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 310A for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (500 MHz, pyridine-d₅) δ 13.06 (s, 1H), 8.41 (d, 1H), 8.11 (m, 2H), 8.08 (d, 1H), 7.66 (m, 2H), 7.44 (m, 2H), 7.07 (m, 2H), 6.75 (dd, 1H), 6.52 (d, 1H), 6.50 (dd, 1H), 4.26 (d, 2H), 3.85 (dd, 1H), 3.83 (dd, 1H), 3.74 (m, 2H), 3.07 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.87 (m, 4H), 1.39 (t, 2H), 0.94 (s, 6H).

15

EXAMPLE 311

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-({3-[cyclopropyl(oxetan-3-yl)amino]propyl}amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

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EXAMPLE 311A

4-(3-(cyclopropyl(oxetan-3-yl)amino)propylamino)-3-nitrobenzenesulfonamide

To a solution of EXAMPLE 308A (314 mg) in dichloromethane (5 mL) was added oxetan-3-one (72 mg) followed by sodium triacetoxyborohydride (318 mg). The mixture was stirred overnight. The mixture was diluted with dichloromethane (300 mL) and washed with aqueous NaHCO₃, water and brine and dried over Na₂SO₄. After filtration, evaporation of the solvent gave the crude title compound.

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EXAMPLE 311B

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-({3-[cyclopropyl(oxetan-3-yl)amino]propyl}amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 311A for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.65 (s, 1 H), 11.37 (s, 1 H), 8.68 (s, 1 H), 8.54 (d, 1 H), 8.02 (d, 1 H), 7.79 (d, 1 H), 7.49 (m, 3 H), 7.34 (d, 2 H), 7.03 (m, 3 H), 6.67 (dd, 1 H), 6.38 (dd, 1 H), 6.19 (d, 1 H), 4.62 (m, 2 H), 4.48 (t, 2 H), 3.98 (m, 1 H), 3.37 (m, 2 H), 3.06 (m, 4 H), 2.73 (d, 2 H), 2.59 (m, 2 H), 2.23 (m, 6 H), 1.95 (s, 2 H), 1.74 (m, 3 H), 1.38 (t, 2 H), 0.92 (s, 6 H), 0.41 (m, 4 H).

EXAMPLE 312

10 N-[(3-chloro-4-{[1-(1-methyl-L-prolyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

To EXAMPLE 294B (0.065 g) was added hydrogen chloride (4.0M in dioxane, 0.339 mL) and a few drops of methanol. After 30 minutes, the reaction was concentrated, and (S)-
 15 1-methylpyrrolidine-2-carboxylic acid (0.013 g), N¹-((ethylimino)methylene)-N³,N³-dimethylpropane-1,3-diamine hydrochloride (0.026 g), suspended in dichloromethane (0.5 mL) were added followed by diisopropylethylamine (0.036 mL). The mixture stirred at room temperature. After stirring overnight, the reaction mixture was loaded onto silica gel (Reveleris 40g) and eluted using a gradient of 1% to 10% methanol (containing 1N
 20 NH₃)/dichloromethane over 30 minutes (flow = 40 mL/minutes) to provide the title compound. ¹H NMR (300 MHz, dimethylsulfoxide- d₆) δ 11.51 (s, 1H), 10.00 – 9.22 (m, 1H), 7.92 (d, 1H), 7.68 (d, 1H), 7.57 (d, 1H), 7.47 (dd, 1H), 7.44 – 7.38 (m, 1H), 7.38 – 7.31 (m, 2H), 7.29 (d, 1H), 7.12 – 7.01 (m, 2H), 6.90 (d, 1H), 6.61 (dd, 1H), 6.31 (dd, 1H), 6.25 (d, 1H), 5.85 (d, 1H), 4.40 (s, 1H), 3.92 (s, 4H), 3.17 – 2.89 (m, 8H), 2.73 (s, 4H), 2.38 (s, 3H), 2.18 (m, 6H), 1.96 (s, 2H), 1.80 (m, 2H), 1.57 (s, 2H), 1.39 (s, 2H), 1.22 (m, 2H), 0.96
 25 (m, 6H).

EXAMPLE 313

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3,4-difluoro-5-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 313A

3,4-difluoro-5-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

The title compound was obtained as a side product in EXAMPLE 310A.

5

EXAMPLE 313B

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-((3,4-difluoro-5-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E
10 and EXAMPLE 313A for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (400 MHz, pyridine-
d₅) δ 13.05 (s, 1H), 8.41 (d, 1H), 8.10 (d, 1H), 7.98 (m, 2H), 7.66 (m, 1H), 7.63 (d, 1H), 7.44
(m, 2H), 7.07 (m, 2H), 6.77 (dd, 1H), 6.54 (d, 1H), 6.48 (dd, 1H), 4.12 (d, 2H), 3.83 (m, 2H),
3.75 (m, 2H), 3.08 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.15 (m, 4H), 1.97 (s, 2H), 1.82 (m,
4H), 1.39 (t, 2H), 0.94 (s, 6H).

15

EXAMPLE 314

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-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

20

EXAMPLE 314A

(S)-5-chloro-6-((4-cyclopropylmorpholin-2-yl)methoxy)pyridine-3-sulfonamide

A solution of EXAMPLE 244B (250 mg), anhydrous methanol (6 mL), (1-ethoxycyclopropoxy)trimethylsilane (0.474 mL), and acetic acid (0.509 mL) was heated at 70
25 °C for 30 minutes. After cooling to ambient temperature, sodium cyanoborohydride (112 mg)
was added and the mixture was stirred for 18 hours. Additional sodium cyanoborohydride
(75 mg) was added and stirring was continued 18 hours. The reaction was concentrated and
the residue was partitioned between methylene chloride and saturated sodium bicarbonate
solution. The crude product was isolated from the dried methylene chloride layer and was
30 purified on silica gel and was eluted with a 1, 2.5, 5, 10% methanol in methylene chloride
step gradient to provide the title compound.

EXAMPLE 314B

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5 The title compound was prepared by substituting EXAMPLE 314A for EXAMPLE 130C in EXAMPLE 130D. ¹H NMR (400 MHz, pyridine- d₅) δ 12.98 (s, 1H), 9.09 (d, 1H), 8.69 (d, 1H), 8.41 (d, 1H), 8.11 (d, 1H), 7.66 - 7.64 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.75 (dd, 1H), 6.53 (m, 1H), 6.48 (m, 1H), 5.72 (br s, 1H), 4.62 - 4.57 (m, 1H), 4.51 - 4.47 (m, 1H), 3.99 (m, 1H), 3.85 (m, 1H), 3.57 (m, 1H), 3.08 - 3.01 (m, 5H), 2.77 (s, 2H), 2.69 (m, 10 1H), 2.39 - 2.24 (m, 4H), 2.14 (m, 4H), 1.97 (s, 2H), 1.57 (m, 1H), 1.39 (t, 2H), 0.94 (m, 6H), 0.48 - 0.3 (m, 4H).

EXAMPLE 315

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

The title compound was prepared by substituting EXAMPLE 302C for EXAMPLE 1E and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. ¹H NMR (300MHz, dimethylsulfoxide-d₆) δ 11.70 (s, 1H), 11.35 (br s, 1H), 8.61 (m, 1H), 8.57 (d, 1H), 8.04 (d, 20 1H), 7.82 (dd, 1H), 7.45-7.57 (m, 3H), 7.33 (d, 2H), 7.15 (d, 1H), 7.01 (d, 2H), 6.65 (dd, 1H), 6.40 (dd, 1H), 6.11 (d, 1H), 3.85 (dd, 2H), 3.53 (m, 2H), 3.27 (m, 4H), 2.63 (m, 2H), 2.04 (m, 2H), 1.91 (s, 2H), 1.77 (m, 2H), 1.62 (m, 4H), 1.45 (m, 2H), 1.38 (m, 2H), 1.27 (m, 1H), 1.23 (m, 4H), 0.92 (s, 6H).

25 EXAMPLE 316

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-N-({3-chloro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

30 EXAMPLE 316A

3-chloro-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

The title compound was prepared by substituting (tetrahydro-2H-pyran-4-yl)methanol for (4-fluoro-1-methylpiperidin-4-yl)methanol in EXAMPLE 283A.

EXAMPLE 316B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-N-{[3-chloro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 302C for EXAMPLE 1E and EXAMPLE 316A for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300MHz, dimethylsulfoxide-d₆) δ 11.77 (s, 1H), 11.35 (br s, 1H), 8.06 (m, 1H), 7.88 (d, 1H), 7.79 (dd, 1H), 7.58 (s, 1H), 7.53 (t, 1H), 7.46 (d, 1H), 7.34 (d, 2H), 7.22 (d, 1H), 7.01 (d, 2H), 6.66 (dd, 1H), 6.42 (dd, 1H), 6.11 (d, 1H), 3.99 (d, 2H), 3.88 (dd, 2H), 3.52 (m, 2H), 3.34 (m, 4H), 2.62 (m, 2H), 2.04 (m, 4H), 1.76 (m, 2H), 1.68 (m, 2H), 1.46 (m, 2H), 1.38 (m, 4H), 0.92 (s, 6H), 0.75 (m, 2H).

EXAMPLE 317

methyl 2-[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl]morpholine-4-carboxylate

EXAMPLE 317A

methyl 2-((2-nitro-4-sulfamoylphenylamino)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting methyl chloroformate for methyl iodide in EXAMPLE 134B.

EXAMPLE 317B

methyl 2-[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl]morpholine-4-carboxylate

The title compound was prepared by substituting EXAMPLE 317A for EXAMPLE 130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 13.00 (s, 1H), 9.26 (d, 1H), 8.84 (t, 1H), 8.43 (d, 1H), 8.35 (d, 1H), 8.12 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.91 (bs, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 4.29-4.03 (m, 1H), 3.89-3.70 (m, 3H), 3.71 (s, 3H), 3.55-3.38 (m, 3H), 3.07 (m, 4H), 2.96 (dt, 1H), 2.86 (dd, 1H), 2.77 (s, 2H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

EXAMPLE 318

2-{{[4-{{[4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-
2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}-N-
ethyl-N-methylmorpholine-4-carboxamide

EXAMPLE 318A

N-ethyl-N-methyl-2-((2-nitro-4-sulfamoylphenylamino)methyl)morpholine-4-carboxamide

The title compound was prepared by substituting *N*-methyl-*N*-ethyl carbamyl chloride
for methyl iodide in EXAMPLE 134B.

EXAMPLE 318B

2-{{[4-{{[4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-
2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}-N-
ethyl-N-methylmorpholine-4-carboxamide

The title compound was prepared by substituting EXAMPLE 318A for EXAMPLE
130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 13.00 (s, 1H), 9.26 (d, 1H),
8.86 (t, 1H), 8.44 (d, 1H), 8.33 (dd, 1H), 8.12 (d, 1H), 7.67 (t, 1H), 7.64 (d, 1H), 7.44 (d, 2H),
7.07 (d, 2H), 6.91 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.92-3.85 (m, 2H), 3.75
(d, 1H), 3.62 (dt, 1H), 3.55-3.48 (m, 1H), 3.45-3.39 (m, 2H), 3.21 (q, 2H), 3.07 (m, 4H), 2.99
(dt, 1H), 2.90 (dd, 1H), 2.77 (s, 2H), 2.76 (s, 3H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H),
1.39 (t, 2H), 1.06 (t, 3H), 0.93 (s, 6H).

EXAMPLE 319

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}-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 319A

4-((4-(methylsulfonyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting methanesulfonyl chloride for methyl
iodide in EXAMPLE 134B.

EXAMPLE 319B

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}-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5 The title compound was prepared by substituting EXAMPLE 319A for EXAMPLE 130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 13.00 (s, 1H), 9.25 (d, 1H), 8.84 (t, 1H), 8.43 (d, 1H), 8.32 (dd, 1H), 8.13 (d, 1H), 7.67 (t, 1H), 7.65 (d, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.92 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.99 (m, 1H), 3.92-3.88 (m, 2H), 3.64 (m, 2H), 3.56 (m, 1H), 3.50 (m, 1H), 3.07 (m, 4H), 3.04 (s, 3H), 2.95-2.88 (m,
10 2H), 2.77 (s, 2H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

EXAMPLE 320

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
((3-[cyclobutyl(cyclopropyl)amino]propyl)amino)-3-nitrophenyl]sulfonyl}-2-(1H-
15 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 320A

4-(3-(cyclobutyl(cyclopropyl)amino)propylamino)-3-nitrobenzenesulfonamide

To a solution of EXAMPLE 308A (314 mg) in dichloromethane (5 mL) was added
20 cyclobutanone (70 mg) followed by sodium triacetoxyborohydride (318 mg). The mixture
was stirred overnight. The mixture was diluted with dichloromethane (300 mL) and washed
with aqueous NaHCO₃, water and brine and dried over Na₂SO₄. After filtration, evaporation
of solvent gave the title compound.

25 EXAMPLE 320B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
((3-[cyclobutyl(cyclopropyl)amino]propyl)amino)-3-nitrophenyl]sulfonyl}-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E
30 and EXAMPLE 320A for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.65 (s, 1 H), 8.70 (m, 1 H), 8.54 (d, 1 H), 8.02 (d, 1 H), 7.79 (dd, 1 H), 7.49 (m, 3 H), 7.34 (d, 2 H), 7.03 (m, 3 H), 6.66 (dd, 1 H), 6.38 (dd, 1 H), 6.19 (d, 1 H),

3.37 (q, 2 H), 3.06 (m, 4 H), 2.73 (s, 2 H), 2.63 (m, 2 H), 2.21 (m, 8 H), 1.82 (m, 3 H), 1.53 (m, 2 H), 1.38 (t, 2 H), 0.94 (m, 6 H), 0.41 (m, 4 H).

EXAMPLE 321

5 4-(4-([2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 321A

10 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
15 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 321B

ethyl 5,5-difluoro-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

20 To a solution of EXAMPLE 321A (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), and the combined organics
25 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 321C

ethyl 2-(4-chlorophenyl)-5,5-difluorocyclohex-1-enecarboxylate

30 A solution of EXAMPLE 321B (3.47 g), 4-chlorophenylboronic acid (1.925 g) and cesium fluoride (3.43 g) in 30 ml of 1,2-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) and 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 321D

5 (2-(4-chlorophenyl)-5,5-difluorocyclohex-1-enyl)methanol

To a solution of EXAMPLE 321C (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 diluted with diethyl ether (100 mL). The organic layer was separated, washed with brine (50 mL) dried
10 over magnesium sulfate, filtered and concentrated to provide the title compound.

EXAMPLE 321E

2-(4-chlorophenyl)-5,5-difluorocyclohex-1-enecarbaldehyde

To a solution of EXAMPLE 321D (1.38 g) in dichloromethane (25 mL) was added
15 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 was 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
20 over 40 minutes gave the title compound.

EXAMPLE 321F

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-
difluorocyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

25 The title compound was prepared by substituting EXAMPLE 321E for EXAMPLE 15E in EXAMPLE 15G.

EXAMPLE 321G

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-difluorocyclohex-1-
30 enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 321F for EXAMPLE 15G in EXAMPLE 15H.

EXAMPLE 321H

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

5 The title compound was prepared by substituting EXAMPLE 321G for EXAMPLE 1E and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G.. ¹H NMR (300 MHz, dimethylsulfoxide- d₆) δ 11.74 - 11.63 (m, 1H), 11.53 - 11.29 (m, 1H), 8.57 (d, 2H), 8.05 (d, 1H), 7.85 - 7.77 (m, 1H), 7.49 (d, 3H), 7.38 (d, 2H), 7.16 - 7.06 (m, 3H), 6.73 - 6.64 (m, 1H), 6.43 - 6.36 (m, 1H), 6.21 - 6.14 (m, 1H), 3.93 - 3.77 (m, 2H), 3.29 (d, 4H), 3.07 (s, 4H), 2.79
10 - 2.57 (m, 4H), 2.45 (dd, 2H), 2.19 (s, 6H), 1.99 - 1.80 (m, 1H), 1.70 - 1.54 (m, 2H), 1.38 - 1.13 (m, 2H).

EXAMPLE 322

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 322A

tert-butyl 4-fluoro-4-(hydroxymethyl)piperidine-1-carboxylate

20 1-Tert-butyl 4-ethyl 4-fluoropiperidine-1,4-dicarboxylate (2 g) was taken up in tetrahydrofuran (20 ml) and cooled in an ice bath. Lithium aluminum hydride (1.0M in dioxane, 5.09 mL) was added dropwise. The reaction was stirred at room temperature for 2 hours. The reaction was quenched with water and with 1M aqueous NaOH solution and then stirred another 1 hour at room temperature. The mixture was extracted with ethyl acetate,
25 and the extracts were combined and washed with water and with brine, dried over MgSO₄, filtered and concentrated under vacuum. The crude product was used without further purification.

EXAMPLE 322B

30 tert-butyl 4-((2-chloro-4-sulfamoylphenoxy)methyl)-4-fluoropiperidine-1-carboxylate

 The title compound was prepared by substituting EXAMPLE 322A for (tetrahydro-2H-pyran-4-yl)methanol and 3-chloro-4-fluorobenzenesulfonamide for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

EXAMPLE 322C

3-chloro-4-((4-fluoropiperidin-4-yl)methoxy)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 322B for EXAMPLE 1A in EXAMPLE 1B.

5

EXAMPLE 322D

3-chloro-4-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)benzenesulfonamide

To a solution of EXAMPLE 322C (830 mg) in tetrahydrofuran (15 mL) and acetic acid (5 mL) was added oxetan-3-one (163 mg) and MP-cyanoborohydride (2.38 mmol/g, 1.9 g). The mixture was stirred at room temperature overnight. The reaction was then filtered and the filtrate was concentrated under vacuum. The residue was slurried in ether and the solid product was collected by filtration.

10

EXAMPLE 322E

15 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 322D for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. ¹H NMR (400 MHz, dimethylsulfoxide-d₆) δ 11.71 (s, 1H), 8.06 (d, 1H), 7.89 (d, 1H), 7.79 (m, 1H), 7.58 (d, 1H), 7.52 (t, 1H), 7.49 (d, 1H), 7.34 (d, 2H), 7.25 (d, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.42 (m, 1H), 6.18 (d, 1H), 4.55 (t, 2H), 4.44 (t, 2H), 4.24 (d, 2H), 3.44 (m, 2H), 3.07 (br s, 4H), 2.74 (m, 2H), 2.59 (m, 2H), 2.14 (m, 7H), 1.95 (m, 4H), 1.78 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

20

25

EXAMPLE 323

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-chloro-4-(tetrahydrofuran-3-ylmethoxy)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

30

EXAMPLE 323A

3-chloro-4-((tetrahydrofuran-3-yl)methoxy)benzenesulfonamide

The title compound was prepared by substituting 4-fluoro-3-chlorobenzenesulfonamide for 4-fluoro-3-nitrobenzenesulfonamide and (tetrahydrofuran-3-

yl)methanol for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A, except here, dimethylformamide was used in place of tetrahydrofuran and the reaction was heated at 70° C for two days.

5

EXAMPLE 323B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[3-chloro-4-(tetrahydrofuran-3-ylmethoxy)phenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 323A for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.73 (s, 1H), 8.07 (d, 1H), 7.89 (d, 1H), 7.80 (dd, 1H), 7.59 (d, 1H), 7.51 (dd, 1H), 7.49 (d, 1H), 7.34 (d, 2H), 7.23 (d, 1H), 7.03 (d, 2H), 6.66 (dd, 1H), 6.42 (m, 1H), 6.19 (d, 1H), 4.07 (m, 2H), 3.80 (m, 2H), 3.68 (m, 1H) 3.56 (m, 1H), 3.10 (br m, 4H), 2.85 (br s, 2H), 2.69 (m, 1H), 2.32 (br m, 4H), 2.17 (br m, 2H), 2.02 (m, 1H), 1.96 (s, 2H), 1.69 (m, 1H), 1.40 (t, 2H), 0.92 (s, 6H).

15

EXAMPLE 324 4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 324A

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4-((trans-4-hydroxycyclohexyl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 120A for EXAMPLE 39B in EXAMPLE 39C.

EXAMPLE 324B

25

4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 321G for EXAMPLE 1E and EXAMPLE 324A for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide- d₆) δ 11.69 (s, 1H), 11.41 (s, 1H), 8.65 - 8.50 (m, 2H), 8.05 (d, 1H), 7.80 (dd, 1H), 7.60 - 7.44 (m, 3H), 7.41 - 7.34 (m, 2H), 7.14 - 7.02 (m, 3H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.17 (d, 1H), 4.50 (d, 1H), 3.23 (t, 2H), 3.06 (s, 4H), 2.70 (d4H), 2.44 (s, 2H), 2.33 - 1.94 (m, 6H), 1.78 (dd, 4H), 1.51 (d, 2H), 1.23 (s, 2H), 1.16 - 0.92 (m, 2H).

30

EXAMPLE 325

N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl)sulfonyl)-4-(4-{[9-(4-chlorophenyl)-3-(oxetan-3-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5

EXAMPLE 325A

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((9-(4-chlorophenyl)-3-(oxetan-3-yl)-3-azaspiro[5.5]undec-8-en-8-yl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting oxetan-3-one for 1,3-difluoropropan-2-one in EXAMPLE 265G.

10

EXAMPLE 325B

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((9-(4-chlorophenyl)-3-(oxetan-3-yl)-3-azaspiro[5.5]undec-8-en-8-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 325A for EXAMPLE 15G in EXAMPLE 15H.

15

EXAMPLE 325C

N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl)sulfonyl)-4-(4-{[9-(4-chlorophenyl)-3-(oxetan-3-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

20

The title compound was prepared by substituting EXAMPLE 325B for EXAMPLE 1E and EXAMPLE 286A for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide- d₆) δ 11.67 (s, 1H), 11.13 (s, 1H), 8.05 (d, 1H), 7.87 (d, 1H), 7.80 - 7.70 (m, 1H), 7.59 - 7.46 (m, 3H), 7.34 (d, 2H), 7.21 (d, 1H), 7.11 - 7.03 (m, 2H), 6.66 (d, 1H), 6.41 (dd, 1H), 6.18 (d, 1H), 4.50 (dd, 4H), 4.26 (d, 2H), 3.85 - 3.69 (m, 2H), 3.61 (d, 3H), 3.05 (s, 4H), 2.69 (s, 2H), 2.37 (s, 4H), 2.17 (s, 6H), 2.04 (s, 2H), 1.87 (d, 4H), 1.49 (d, 6H).

25

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EXAMPLE 326

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-(((2R)-4-cyclopropylmorpholin-2-yl)methyl)amino]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 326A

(R)-4-((4-cyclopropylmorpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 258E for EXAMPLE 173A in EXAMPLE 173B.

5

EXAMPLE 326B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
(((2R)-4-cyclopropylmorpholin-2-yl)methyl)amino)-3-nitrophenyl]sulfonyl}-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

10 The title compound was prepared by substituting EXAMPLE 326A for EXAMPLE 130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 13.00 (s, 1H), 9.26 (d, 1H), 8.88 (t, 1H), 8.44 (d, 1H), 8.34 (dd, 1H), 8.12 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.94 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.88 (d, 1H), 3.84-3.81 (m, 1H), 3.59 (dt, 1H), 3.50-3.40 (m, 2H), 3.07 (m, 4H), 2.93 (d, 1H), 2.77 (s, 2H), 2.69 (d, 1H),
15 2.34 (dt, 1H), 2.26 (m, 2H), 2.21 (t, 1H), 2.14 (m, 4H), 1.97 (s, 2H), 1.58 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H), 0.45-0.39 (m, 4H).

EXAMPLE 327

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
20 (((2S)-4-cyclopropylmorpholin-2-yl)methyl)amino)-3-nitrophenyl]sulfonyl}-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 327A

(S)-4-((4-cyclopropylmorpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

25 The title compound was prepared by substituting EXAMPLE 259E for EXAMPLE 173A in EXAMPLE 173B.

EXAMPLE 327B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-
30 (((2S)-4-cyclopropylmorpholin-2-yl)methyl)amino)-3-nitrophenyl]sulfonyl}-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 327A for EXAMPLE 130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 13.00 (s, 1H), 9.26 (d, 1H),

8.88 (t, 1H), 8.44 (d, 1H), 8.34 (dd, 1H), 8.12 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.94 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.88 (d, 1H), 3.84-3.81 (m, 1H), 3.59 (dt, 1H), 3.50-3.40 (m, 2H), 3.07 (m, 4H), 2.93 (d, 1H), 2.77 (s, 2H), 2.69 (d, 1H), 2.34 (dt, 1H), 2.26 (m, 2H), 2.21 (t, 1H), 2.14 (m, 4H), 1.97 (s, 2H), 1.58 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H), 0.45-0.39 (m, 4H).

EXAMPLE 328

4-(4-([5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 328A

spiro[2.5]octan-5-one

To a solution of 3-ethoxycyclohex-2-enone (48.1 mL) in ether (1000 mL) was added titanium(IV) isopropoxide (110 mL) followed by addition of ethylmagnesium bromide (357 mL) at ambient temperature. The reaction mixture was stirred for 2 hours at ambient temperature and was then quenched with water (500 mL). The organic layer was separated (decanted) and the water layer was extracted with ether (3 x 300 mL). The combined extracts were partially concentrated to approximately 300 mL. p-Toluenesulfonic acid monohydrate (3.0 g) was added and the reaction mixture was stirred overnight at ambient temperature. The reaction mixture was then washed with saturated aqueous NaHCO₃ solution., dried (MgSO₄), filtered and concentrated. The concentrate was purified by fractional distillation (1st fraction b.p. 27°C at 23 torr (not product), 2nd fraction (product) b.p. 75°C at 8 torr).

EXAMPLE 328B

5-chlorospiro[2.5]oct-5-ene-6-carbaldehyde

N,N-dimethylformamide (2.1 mL) in dichloromethane (3.2 mL) at -5 °C was treated slowly with POCl₃ (2.33 mL) keeping the bath temperature less than 0°C. The cooling bath was removed and the mixture was stirred at ambient temperature for 30 minutes. The reaction mixture was returned to the cooling bath and EXAMPLE 328A (2.484 g) in dichloromethane (4 mL) was added slowly to the reaction mixture. The reaction mixture was heated at 45°C for 15 hours, cooled to room temperature and then poured into a mixture of ice and saturated aqueous sodium acetate solution. After the ice melted, the mixture was extracted with diethyl ether. The combined extracts were washed with saturated aqueous

NaHCO₃ solution and brine, dried (MgSO₄), filtered and concentrated. The concentrate was chromatographed with 0 to 10% CH₂Cl₂ in hexanes, then 25% CH₂Cl₂ in hexanes and then 100% CH₂Cl₂ as the eluents.

EXAMPLE 328C

5 5-(4-chlorophenyl)spiro[2.5]oct-5-ene-6-carbaldehyde

EXAMPLE 328B (2.9 g), 4-chlorophenylboronic acid (2.87 g), palladium(II) acetate (0.103 g), K₂CO₃ (5.28 g) and tetrabutylammonium bromide (4.93 g) were combined in a 100-mL round bottomed flask with water (17.0 mL). The flask was flushed with nitrogen and stirred at 45°C for 14 hours. The reaction mixture was partitioned between brine and
10 diethyl ether. The organic layer was washed with brine, dried (MgSO₄), filtered through a plug of celite, concentrated and chromatographed on silica gel with 0 to 2% ethyl acetate in hexanes as the eluent.

EXAMPLE 328D

15 methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 15F for tert-butyl piperazine carboxylate and EXAMPLE 328C for 4-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

EXAMPLE 328E

20 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl)methyl)piperazin-1-yl)benzoic acid hydrochloride

EXAMPLE 328D (0.85 g) in a mixture of tetrahydrofuran (4.8 mL), methanol (2.4 mL) and water (2.4 mL) was treated with LiOH•H₂O (0.184 g) and heated overnight at 50°C. The reaction mixture was cooled to room temperature, concentrated to remove
25 tetrahydrofuran and methanol and acidified with 1 N aqueous HCl causing precipitation of the product. The solid was collected by filtration, rinsed with water and dried overnight in a vacuum oven at 80°C to provide the title compound.

EXAMPLE 328F

30 4-(4-([5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl)piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 328E for EXAMPLE 1E in EXAMPLE 1G. ¹H NMR (500 MHz, pyridine-d₅) δ 13.07 (s, 1H), 9.32 (d, 1H), 8.68 (t, 1H), 8.44 (d, 1H), 8.38 (dd, 1H), 8.10 (d, 1H), 7.68 (m, 1H), 7.66 (d, 1H), 7.43 (m, 2H), 7.10 (m, 2H), 6.91 (d, 1H), 6.75 (dd, 1H), 6.51 (m, 2H), 3.97 (dd, 2H), 3.30 (td, 2H), 3.16 (t, 2H), 3.06 (m, 4H), 2.81 (s, 2H), 2.37 (t, 2H), 2.16 (m, 4H), 2.11 (s, 2H), 1.81 (m, 1H), 1.58 (dd, 2H), 1.45 (t, 2H), 1.32 (qd, 2H), 0.38 (s, 4H).

EXAMPLE 329

N-{{[5-chloro-6-({4-[cyclopropyl(oxetan-3-yl)amino]cyclohexyl}methoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 329A

ethyl 4-(cyclopropylamino)cyclohexanecarboxylate

To a solution of ethyl 4-oxocyclohexanecarboxylate (3.4 g) in dichloromethane (30 mL) was added cyclopropanamine (1.14 g) followed by sodium triacetoxyborohydride (4.24 g). The mixture was stirred overnight. The mixture was diluted with dichloromethane (300 mL) and washed with 2N NaOH, water, brine and dried over Na₂SO₄. Filtration and evaporation of the solvent gave the title compound.

EXAMPLE 329B

ethyl 4-(cyclopropyl(oxetan-3-yl)amino)cyclohexanecarboxylate

To a solution of EXAMPLE 329A (1.05g) in dichloromethane (10 mL) was added oxetan-3-one (0.358 g) followed by sodium triacetoxyborohydride (1.05 g). The mixture was stirred overnight. The mixture was diluted with dichloromethane (300 mL) and washed with 2N aqueous NaOH, water, brine and dried over Na₂SO₄. Filtration and evaporation of the solvent gave the title compound.

EXAMPLE 329C

(4-(cyclopropyl(oxetan-3-yl)amino)cyclohexyl)methanol

To a solution of EXAMPLE 329B (1.2 g) in tetrahydrofuran (20 mL) was added lithium aluminum hydride (0.681 g). The mixture was stirred overnight. 2N aqueous NaOH solution was added dropwise to the reaction mixture. The mixture was then diluted with ethyl

acetate (300 mL) and washed with water, brine and dried over Na₂SO₄. Filtration and evaporation of the solvent gave the title compound.

EXAMPLE 329D

5 5-chloro-6-((4-(cyclopropyl(oxetan-3-yl)amino)cyclohexyl)methoxy)pyridine-3-sulfonamide

To a solution of EXAMPLE 329C (706 mg) in N,N-dimethylformamide (6 mL) was added NaH (60% in mineral oil, 300 mg). The mixture was stirred for 30 minutes, and then 5,6-dichloropyridine-3-sulfonamide (706 mg) was added. The mixture was stirred overnight. The mixture was poured over aqueous NH₄Cl and extracted with ethyl acetate (3x 200 mL).
 10 The combined organic layers were washed with water, brine and dried over Na₂SO₄. After filtration and evaporation of the solvent the residue was loaded on a silica gel cartridge and eluted with 5 to 10% 7N NH₃ in methanol in dichloromethane to provide the title compound.

EXAMPLE 329E

15 N-([5-chloro-6-({4-[cyclopropyl(oxetan-3-yl)amino]cyclohexyl)methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 329D for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.64 (s, 1 H), 8.50 (m, 1 H), 8.16 (s, 1 H), 8.02 (d, 1 H), 7.51 (m, 3 H), 7.35 (d, 2 H), 7.04 (d, 2 H), 6.67 (dd, 1 H), 6.38 (m, 1 H), 6.21 (s, 1 H), 4.70 (m, 2 H), 4.43 (t, 3 H), 4.19 (m, 2 H), 3.12 (m, 4 H), 2.84 (m, 2 H), 2.19 (m, 6 H), 1.96 (s, 3 H), 1.77 (m, 3 H), 1.38 (m, 7 H), 0.93 (s, 6 H), 0.44 (m, 4 H).

25 EXAMPLE 330

4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-N-([4-{[(4-cyclopropylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 328E for EXAMPLE 3J and EXAMPLE 218A for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (400 MHz, pyridine-d₅) δ 13.01 (s, 1H), 9.26 (d, 1H), 8.88 (t, 1H), 8.43 (d, 1H), 8.34 (dd, 1H), 8.11 (d, 1H), 7.66 (m, 2H), 7.42 (m, 2H), 7.09 (m, 2H), 6.95 (d, 1H), 6.75 (dd, 1H), 6.53 (d, 1H), 6.49 (dd, 1H), 3.84 (m, 2H), 3.58 (td, 1H), 3.45 (m, 2H), 3.06 (m, 4H), 2.93 (d, 1H), 2.81 (s, 2H),

2.69 (d, 1H), 2.35 (m, 3H), 2.19 (m, 5H), 2.11 (s, 2H), 1.58 (m, 1H), 1.45 (t, 2H), 0.42 (m, 8H).

EXAMPLE 331

5 N-({3-chloro-4-[(4-cyclopropylmorpholin-2-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 331A

10 *tert*-butyl 2-((2-chloro-4-sulfamoylphenoxy)methyl)morpholine-4-carboxylate

To a solution of *tert*-butyl 2-(hydroxymethyl)morpholine-4-carboxylate (0.478 g) in anhydrous N,N-dimethylformamide (5 mL) was added sodium hydride (0.280 g). The mixture was stirred at room temperature for 30 minutes, followed by addition of 3-chloro-4-fluorobenzenesulfonamide (0.419 g). The mixture was stirred at 40°C overnight. The
15 reaction was quenched with water (10 mL), and the mixture was adjusted to ~pH 7 and extracted with ethyl acetate. The crude product was purified on a silica gel column eluting with 60% ethyl acetate in hexane to provide the title compound.

EXAMPLE 331B

20 3-chloro-4-(morpholin-2-ylmethoxy)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 331A for EXAMPLE 113A in EXAMPLE 134A.

EXAMPLE 331C

25 3-chloro-4-((4-cyclopropylmorpholin-2-yl)methoxy)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 331B for EXAMPLE 173A in EXAMPLE 173B.

EXAMPLE 331D

30 N-({3-chloro-4-[(4-cyclopropylmorpholin-2-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 331C for EXAMPLE 130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 13.04 (s, 1H), 8.54 (d, 1H), 8.43 (d, 1H), 8.27 (dd, 1H), 8.09 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 7.05 (d, 1H), 6.75 (dd, 1H), 6.52 (d, 1H), 6.50 (m, 1H), 4.20 (dd, 1H), 4.10 (dd, 1H), 3.94 (m, 1H),
5 3.86 (d, 1H), 3.58 (dt, 1H), 3.06 (m, 5H), 2.77 (s, 2H), 2.69 (d, 1H), 2.40-2.20 (m, 4H), 2.14 (m, 4H), 1.97 (s, 2H), 1.60 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H), 0.41 (m, 4H).

EXAMPLE 332

N-[(3-chloro-4-[(4-cyclopropylmorpholin-2-yl)methyl]amino)phenyl)sulfonyl]-4-(4-{[2-(4-
10 chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

EXAMPLE 332A

tert-butyl 2-((2-chloro-4-sulfamoylphenylamino)methyl)morpholine-4-carboxylate
15 A solution of 3-chloro-4-fluorobenzenesulfonamide (1.0 g), tert-butyl 2-(aminomethyl)morpholine-4-carboxylate (1.135 g) and N-ethyl-N-isopropylpropan-2-amine (1.246 mL) in dimethylsulfoxide (15 mL) was stirred at 115°C for 72 hours. The mixture was concentrated, and the residue was purified on a silica gel column eluting with 60% ethyl acetate to provide the title compound.

20

EXAMPLE 332B

3-chloro-4-(morpholin-2-ylmethylamino)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 332A for EXAMPLE 113A in EXAMPLE 134A.

25

EXAMPLE 332C

The title compound was prepared by substituting EXAMPLE 332B for EXAMPLE 173A in EXAMPLE 173B.

30

EXAMPLE 332D

N-[(3-chloro-4-[(4-cyclopropylmorpholin-2-yl)methyl]amino)phenyl)sulfonyl]-4-(4-{[2-(4-
chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 332C for EXAMPLE 130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 13.05 (s, 1H), 8.45 (m, 2H), 8.21 (dd, 1H), 8.12 (d, 1H), 7.69 (d, 1H), 7.67 (t, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.78 (d, 1H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.50 (m, 1H), 6.37 (m, 1H), 3.84 (d, 1H), 3.77 (m, 1H), 3.54 (dt, 1H), 3.35 (m, 2H), 3.05 (m, 4H), 2.94 (d, 1H), 2.77 (s, 2H), 2.68 (d, 1H), 2.32 (dt, 1H), 2.26 (m, 2H), 2.18-2.12 (m, 5H), 1.97 (s, 2H), 1.55 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H), 0.41 (m, 4H).

EXAMPLE 333

2-([(2-chloro-4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}phenyl)amino)methyl]-N-ethyl-N-methylmorpholine-4-carboxamide

EXAMPLE 333A

2-((2-chloro-4-sulfamoylphenylamino)methyl)-N-ethyl-N-methylmorpholine-4-carboxamide

The title compound was prepared by substituting EXAMPLE 332B for EXAMPLE 134A and *N*-methyl-*N*-ethyl carbamyl chloride for methyl iodide in EXAMPLE 134B.

EXAMPLE 333B

2-([(2-chloro-4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}phenyl)amino)methyl]-N-ethyl-N-methylmorpholine-4-carboxamide

The title compound was prepared by substituting EXAMPLE 333A for EXAMPLE 130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 13.05 (s, 1H), 8.46 (s, 1H), 8.45 (s, 1H), 8.20 (dd, 1H), 8.10 (d, 1H), 7.69 (d, 1H), 7.67 (t, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.79 (d, 1H), 6.73 (dd, 1H), 6.52 (dd, 1H), 6.49 (d, 1H), 6.43 (m, 1H), 3.83 (d, 2H), 3.73 (d, 1H), 3.59 (dt, 1H), 3.41-3.35 (m, 3H), 3.20 (q, 2H), 3.05 (m, 4H), 2.95 (t, 1H), 2.84 (dd, 1H), 2.76 (s, 2H), 2.73 (s, 3H), 2.25 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 1.04 (t, 3H), 0.94 (s, 6H).

EXAMPLE 334

(2S)-2-[[[3-chloro-5-[[4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]pyridin-2-yl)oxy]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide

5

EXAMPLE 334A

(S)-2-((3-chloro-5-sulfamoylpyridin-2-yloxy)methyl)-N-ethyl-N-methylmorpholine-4-carboxamide

The title compound was prepared by substituting EXAMPLE 244B for EXAMPLE 134A and *N*-methyl-*N*-ethyl carbamyl chloride for methyl iodide in EXAMPLE 134B.

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EXAMPLE 334B

(2S)-2-[[[3-chloro-5-[[4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]pyridin-2-yl)oxy]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide

15

The title compound was prepared by substituting EXAMPLE 334A for EXAMPLE 130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 12.98 (s, 1H), 9.08 (d, 1H), 8.70 (d, 1H), 8.42 (d, 1H), 8.11 (d, 1H), 7.67 (t, 1H), 7.64 (d, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.75 (dd, 1H), 6.53 (d, 1H), 6.48 (m, 1H), 4.58 (dd, 1H), 4.47 (dd, 1H), 4.03 (m, 1H), 3.84 (m, 2H), 3.63 (dt, 1H), 3.45 (d, 1H), 3.22 (q, 2H), 3.07 (m, 4H), 3.05-2.95 (m, 2H), 2.78 (s, 3H), 2.77 (s, 2H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 1.07 (t, 3H), 0.94 (s, 6H).

20

EXAMPLE 335

N-[(5-chloro-6-[[4-(cyclopropylmorpholin-2-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

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EXAMPLE 335A

tert-butyl 2-((3-chloro-5-sulfamoylpyridin-2-ylamino)methyl)morpholine-4-carboxylate

30

The title compound was prepared by substituting EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide and tert-butyl 2-(aminomethyl)morpholine-4-carboxylate for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

EXAMPLE 335B

5-chloro-6-(morpholin-2-ylmethylamino)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 335A for EXAMPLE 113A in EXAMPLE 134A.

EXAMPLE 335C

5-chloro-6-((4-cyclopropylmorpholin-2-yl)methylamino)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 335B for EXAMPLE 173A in EXAMPLE 173B.

EXAMPLE 335D

N-[(5-chloro-6-{[(4-cyclopropylmorpholin-2-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-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

15 The title compound was prepared by substituting EXAMPLE 335C for EXAMPLE 130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 13.02 (s, 1H), 9.15 (d, 1H), 8.49 (d, 1H), 8.43 (d, 1H), 8.11 (d, 1H), 7.80 (t, 1H), 7.69 (d, 1H), 7.65 (t, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.73 (dd, 1H), 6.52 (m, 1H), 6.49 (d, 1H), 3.92 (m, 1H), 3.84 (m, 2H), 3.70 (m, 1H), 3.54 (dt, 1H), 3.05 (m, 4H), 2.99 (d, 1H), 2.76 (s, 2H), 2.68 (d, 1H), 2.32 (dt, 1H), 2.25
20 (m, 2H), 2.12 (m, 5H), 1.97 (s, 2H), 1.53 (m, 1H), 1.39 (t, 2H), 0.93 (s, 6H), 0.40 (m, 4H).

EXAMPLE 336

25 2-{[(3-chloro-5-{[4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}pyridin-2-yl)amino]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide

EXAMPLE 336A

30 2-((3-chloro-5-sulfamoylpyridin-2-ylamino)methyl)-N-ethyl-N-methylmorpholine-4-carboxamide

The title compound was prepared by substituting EXAMPLE 335B for EXAMPLE 134A and *N*-methyl-*N*-ethyl carbamyl chloride for methyl iodide in EXAMPLE 134B.

EXAMPLE 336B

2-[[[3-chloro-5-[[4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]pyridin-2-yl)amino]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide

5 The title compound was prepared by substituting EXAMPLE 336A for EXAMPLE 130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 13.03 (s, 1H), 9.14 (d, 1H), 8.51 (d, 1H), 8.43 (d, 1H), 8.11 (d, 1H), 7.89 (m, 1H), 7.69 (d, 1H), 7.66 (t, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.74 (dd, 1H), 6.51 (m, 1H), 6.48 (d, 1H), 3.96 (m, 1H), 3.90-3.70 (m, 4H), 3.59 (dt, 1H), 3.43 (d, 1H), 3.17 (q, 2H), 3.05 (m, 4H), 2.95 (dt, 1H), 2.81 (dd, 1H), 2.76 (s, 2H),
10 2.72 (s, 3H), 2.25 (m, 2H), 2.13 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 1.03 (t, 3H), 0.93 (s, 6H).

EXAMPLE 337

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[[4-
15 [[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 337A

methyl 4,4-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

To a suspension of hexane washed NaH (17 g) in dichloromethane (700 mL) was
20 added 5,5-dimethyl-2-methoxycarbonylcyclohexanone (38.5 g) dropwise at 0°C. After stirring for 30 minutes, the mixture was cooled to -78°C and trifluoroacetic 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 (Na₂SO₄), filtered, and concentrated to give the product.

25

EXAMPLE 337B

methyl 2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enecarboxylate

EXAMPLE 337A (62.15g), 4-chlorophenylboronic acid (32.24 g), CsF (64 g) and tetrakis(triphenylphosphine)palladium(0) (2g) in 2:1 dimethoxyethane /methanol (600 mL)
30 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 337C

(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methanol

To a mixture of LiBH_4 (13g), EXAMPLE 337B (53.8 g) and ether (400 mL), was added methanol (25 mL) 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 with ether (3x 100 mL). The extracts were dried (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 0-30% ethyl acetate/hexanes.

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EXAMPLE 337D

tert-butyl 4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine-1-carboxylate

Mesyl Chloride (7.5 mL) was added via syringe to EXAMPLE 337C (29.3 g) and triethylamine (30 mL) in CH_2Cl_2 (500 mL) at 0°C , and the mixture was stirred for 1 minute. N-t-butoxycarbonylpiperazine (25 g) was added and the mixture was stirred at room temperature for 24 hours. The suspension was washed with brine, dried, (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 10-20% ethyl acetate/hexanes.

20

EXAMPLE 337E

1-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine

EXAMPLE 337D (1 g) was stirred in dichloromethane (10 mL), trifluoroacetic acid (10 mL), and triethylsilane (1 mL) for 1 hour. The mixture was concentrated, taken up in a mixture of dichloromethane (100 mL) and saturated aqueous Na_2CO_3 solution (20 mL) and stirred for 10 minutes. The layers were separated, and the organic layer was dried over Na_2SO_4 , and concentrated to give the product.

25

EXAMPLE 337F

5-bromo-1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridine

To a mixture of 5-bromo-1H-pyrrolo[2,3-b]pyridine (15.4 g) in tetrahydrofuran (250 mL) was added 1M lithium hexamethyldisilazide in tetrahydrofuran (86 mL), and after 10 minutes, TIPS-Cl (triisopropylchlorosilane) (18.2 mL) was added. The mixture was stirred at room temperature for 24 hours. The reaction was diluted with ether, and the resulting solution

30

was washed twice with water. The extracts were dried (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 10% ethyl acetate/hexanes.

EXAMPLE 337G

5 1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridin-5-ol

To a mixture of EXAMPLE 337F (24.3 g) in tetrahydrofuran (500 mL) at -78°C was added 2.5M BuLi (30.3 mL). After 2 minutes, trimethylborate (11.5 mL) was added, and the mixture was allowed to warm to room temperature over 1 hour. The reaction was poured into water, extracted three times with ethyl acetate, and the combined extracts were washed with
10 brine and concentrated. The crude product was taken up in tetrahydrofuran (200 mL) at 0°C , and 1M aqueous NaOH (69 mL) was added, followed by 30% aqueous H_2O_2 (8.43 mL), and the solution was stirred for 1 hour. $\text{Na}_2\text{S}_2\text{O}_3$ (10 g) was added, and the pH was adjusted to 4-5 with concentrated HCl and solid NaH_2PO_4 . The solution was extracted twice with ethyl acetate, and the combined extracts were washed with brine, dried (Na_2SO_4), filtered, and
15 concentrated. The crude product was chromatographed on silica gel with 5-25% ethyl acetate/hexanes.

EXAMPLE 337H

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-fluorobenzoate

20 A mixture of EXAMPLE 337G (8.5 g), methyl 2,4-difluorobenzoate (7.05 g), and K_3PO_4 (9.32 g) in diglyme (40 mL) at 115°C was stirred for 24 hours. The reaction was cooled, diluted with ether (600 mL), and washed twice with water, and brine, and concentrated. The crude product was chromatographed on silica gel with 2-50% ethyl acetate/hexanes.

25 EXAMPLE 337I

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

A mixture of EXAMPLE 337H (1.55 g), EXAMPLE 337E (2.42 g), and HK_2PO_4 (1.42 g) in dimethylsulfoxide (20 mL) at 135°C was stirred for 24 hours. The reaction was
30 cooled, diluted with ether (400 mL), and washed three times with 1M aqueous NaOH, and brine, and concentrated. The crude product was chromatographed on silica gel with 10-50% ethyl acetate/hexanes.

EXAMPLE 337J

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

EXAMPLE 337I (200 mg) in dioxane (10 mL) and 1M aqueous NaOH (6 mL) at 50°C was stirred for 24 hours. The reaction was cooled, added to NaH₂PO₄ solution, and extracted three times with ethyl acetate. The combined extracts were washed with brine, and concentrated to give the pure product.

EXAMPLE 337K

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 NH₄Cl aqueous solution. The resulting mixture was extracted with dichloromethane (100 mL, three times) and the organic layer was dried over Na₂SO₄, filtered, and concentrated. The residue was dissolved in dichloromethane and loaded onto an Analogix purification system, and it was eluted with 0 - 50% ethyl acetate in dichloromethane to provide the title compound.

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EXAMPLE 337L

4-(aminomethyl)-1-methylcyclohexanol

EXAMPLE 337K (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 hour. The reaction mixture was concentrated and the residue was directly used for next step.

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EXAMPLE 337M

4-((trans-4-hydroxy-4-methylcyclohexyl)methylamino)-3-nitrobenzenesulfonamide

EXAMPLE 337L (732 mg) and 4-fluoro-3-nitrobenzenesulfonamide (1.1 g) in tetrahydrofuran (15 mL) was 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 isolate the title compound.

EXAMPLE 337N

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-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5 A mixture of EXAMPLE 337J (3.0 g), EXAMPLE 337M (1.98 g), N, N-
dimethylpyridin-4-amine (1.93 g) and N¹-((ethylimino)methylene)-N³,N³-dimethylpropane-
1,3-diamine hydrochloride (1.31 g) in dichloromethane (50 ml) was stirred overnight and
concentrated. The residue was purified by reverse chromatography, eluted with 40%-70%
acetonitrile in 0.1% TFA water. The desired fractions were concentrated to remove
10 acetonitrile, neutralized with NaHCO₃ and extracted with dichloromethane. The organic
layer was dried over Na₂SO₄, concentrated and dried to provide the title compound. ¹H NMR
(400 MHz, dimethylsulfoxide-d₆) δ 11.68 (s, 1 H), 8.52 - 8.58 (m, 2 H), 8.04 (d, 1 H), 7.79
(dd, 1 H), 7.53 (d, 1 H), 7.47 - 7.52 (m, 2 H), 7.30 - 7.37 (m, 2 H), 7.07 (d, 1 H), 7.01 - 7.06
(m, 2 H), 6.68 (dd, 1 H), 6.39 (dd, 1 H), 6.19 (d, 1 H), 4.25 (s, 1 H), 3.25 - 3.32 (m, 4 H), 3.07
15 (s, 4 H), 2.75 (s, 2 H), 2.09 - 2.24 (m, 6 H), 1.95 (s, 2 H), 1.50 - 1.73 (m, 5 H), 1.28 - 1.43 (m,
4 H), 1.06 - 1.18 (m, 5 H), 0.92 (s, 6 H).

EXAMPLE 338

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-[(4-
20 {{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 338A

methyl 4,4-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

25 To a suspension of hexane washed NaH (17 g) in dichloromethane (700 mL) was
added 5,5-dimethyl-2-methoxycarbonylcyclohexanone (38.5 g) dropwise at 0°C. After
stirring for 30 minutes, the mixture was cooled to -78°C and trifluoroacetic 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 (Na₂SO₄), filtered, and concentrated to
30 give the product.

EXAMPLE 338B

methyl 2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enecarboxylate

EXAMPLE 338A (62.15g), 4-chlorophenylboronic acid (32.24 g), CsF (64 g) and tetrakis(triphenylphosphine)palladium(0) (2g) in 2:1 dimethoxyethane /methanol (600 mL) were heated to 70⁰C 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 338C

(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methanol

To a mixture of LiBH₄ (13g), EXAMPLE 338B (53.8 g) and ether (400 mL), was added methanol (25 mL) 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 100 mL). The extracts were dried (Na₂SO₄), filtered, and concentrated. The crude product was chromatographed on silica gel with 0-30% ethyl acetate/hexanes.

EXAMPLE 338D

tert-butyl 4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine-1-carboxylate

Mesyl Chloride (7.5 mL) was added via syringe to EXAMPLE 338C (29.3 g) and triethylamine (30 mL) in CH₂Cl₂ (500 mL) at 0⁰C, and the mixture was stirred for 1 minute. N-t-butoxycarbonylpiperazine (25 g) was added and the mixture was stirred at room temperature for 24 hours. The suspension was washed with brine, dried, (Na₂SO₄), filtered, and concentrated. The crude product was chromatographed on silica gel with 10-20% ethyl acetate/hexanes.

EXAMPLE 338E

1-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine

EXAMPLE 338D (1 g) was stirred in dichloromethane (10 mL), trifluoroacetic acid (10 mL), and triethylsilane (1 mL) for 1 hour. The mixture was concentrated, taken up in a mixture of dichloromethane (100 mL) and saturated aqueous Na₂CO₃ solution (20 mL) and stirred for 10 minutes. The layers were separated, and the organic layer was dried over Na₂SO₄, filtered, and concentrated to give the product.

EXAMPLE 338F

5-bromo-1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridine

To a mixture of 5-bromo-1H-pyrrolo[2,3-b]pyridine (15.4 g) in tetrahydrofuran (250 mL) was added 1M lithium hexamethyldisilazide in tetrahydrofuran (86 mL), and after 10 minutes, TIPS-Cl (triisopropylchlorosilane) (18.2 mL) was added. The mixture was stirred at room temperature for 24 hours. The reaction was diluted with ether, and the resulting solution was washed twice with water. The extracts were dried (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 10% ethyl acetate/hexanes.

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EXAMPLE 338G

1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridin-5-ol

To a mixture of EXAMPLE 338F (24.3 g) in tetrahydrofuran (500 mL) at -78°C was added 2.5M BuLi (30.3 mL). After 2 minutes, trimethylborate (11.5 mL) was added, and the mixture was allowed to warm to room temperature over 1 hour. The reaction was poured into water, extracted three times with ethyl acetate, and the combined extracts were washed with brine and concentrated. The crude product was taken up in tetrahydrofuran (200 mL) at 0°C , and 1M aqueous NaOH (69 mL) was added, followed by 30% aqueous H_2O_2 (8.43 mL), and the solution was stirred for 1 hour. $\text{Na}_2\text{S}_2\text{O}_3$ (10 g) was added, and the pH was adjusted to 4-5 with concentrated HCl and solid NaH_2PO_4 . The solution was extracted twice with ethyl acetate, and the combined extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on silica gel with 5-25% ethyl acetate/hexanes.

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EXAMPLE 338H

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-fluorobenzoate

A mixture of EXAMPLE 338G (8.5 g), methyl 2,4-difluorobenzoate (7.05 g), and K_3PO_4 (9.32 g) in diglyme (40 mL) at 115°C was stirred for 24 hours. The reaction was cooled, diluted with ether (600 mL), and washed twice with water, and brine, and concentrated. The crude product was chromatographed on silica gel with 2-50% ethyl acetate/hexanes.

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EXAMPLE 338I

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

A mixture of EXAMPLE 338H (1.55 g), EXAMPLE 338E (2.42 g), and HK_2PO_4 (1.42 g) in dimethylsulfoxide (20 mL) at 135°C was stirred for 24 hours. The reaction was cooled, diluted with ether (400 mL), and washed three times with 1M aqueous NaOH, and brine, and concentrated. The crude product was chromatographed on silica gel with 10-50% ethyl acetate/hexanes.

EXAMPLE 338J

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

EXAMPLE 338I (200 mg) in dioxane (10 mL) and 1M NaOH (6 mL) at 50°C was stirred for 24 hours. The reaction was cooled, added to NaH_2PO_4 solution, and extracted three times with ethyl acetate. The combined extracts were washed with brine, and concentrated to give the pure product.

15

EXAMPLE 338K

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 NH_4Cl aqueous solution. The resulting mixture was extracted with dichloromethane (100 ml, three times) 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 it was eluted with 0 - 50% ethyl acetate in dichloromethane to provide the title compound.

EXAMPLE 338L

4-(aminomethyl)-1-methylcyclohexanol

EXAMPLE 338K (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 hour. The reaction mixture was concentrated and the residue was directly used for next step.

EXAMPLE 338M

4-((cis-4-hydroxy-4-methylcyclohexyl)methylamino)-3-nitrobenzenesulfonamide

EXAMPLE 338L (732 mg) and 4-fluoro-3-nitrobenzenesulfonamide (1.1 g) in tetrahydrofuran (15 mL) was 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 isolate the title compound.

EXAMPLE 338N

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-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

A mixture of EXAMPLE 338J (144 mg), EXAMPLE 338M (95 mg), N, N-dimethylpyridin-4-amine (123 mg) and N¹-((ethylimino)methylene)-N³,N³-dimethylpropane-1,3-diamine hydrochloride (62.7 mg) in dichloromethane (7 ml) was stirred overnight and concentrated. The residue was purified by reverse chromatography, eluted with 40%-70% acetonitrile in 0.1% TFA water. The desired fractions were concentrated, neutralized with NaHCO₃ and extracted with dichloromethane. The organic layer was dried over Na₂SO₄, filtered, concentrated and dried to provide the title compound. ¹H NMR (400 MHz, dimethylsulfoxide-d₆) δ 11.69 (s, 1 H), 11.38 (s, 1 H), 8.59 (t, 1 H), 8.55 (d, 1 H), 8.04 (d, 1 H), 7.79 (dd, 1 H), 7.54 (d, 1 H), 7.46 - 7.52 (m, 2 H), 7.30 - 7.38 (m, 2 H), 7.00 - 7.10 (m, 3 H), 6.68 (dd, 1 H), 6.39 (dd, 1 H), 6.19 (d, 1 H), 3.95 (s, 1 H), 3.25 (t, 4 H), 3.07 (s, 4 H), 2.75 (s, 2 H), 2.10 - 2.26 (m, 6 H), 1.95 (s, 2 H), 1.29 - 1.62 (m, 8 H), 1.16 - 1.30 (m, 2 H), 1.08 (s, 3 H), 0.92 (s, 6 H).

EXAMPLE 339

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 339A

(1R,4S)-methyl spiro[bicyclo[2.2.1]heptane-2,2'-[1,3]dioxolane]-5-carboxylate

A reaction mixture of 1,4-dioxaspiro[4.4]non-6-ene (5 g), methyl acrylate (10.24 g), and hydroquinone (0.13 g) was heated 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 provide the title compound as a mixture of two isomers.

EXAMPLE 339B

5 (1R,4S)-spiro[bicyclo[2.2.1]heptane-2,2'-[1,3]dioxolane]-5-ylmethanol

EXAMPLE 339A (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
10 distilled to remove any trace amount of water. The title compound was used for the next reaction without further purification.

EXAMPLE 339C

5-chloro-6-(((1S,2R,4R)-5-oxobicyclo[2.2.1]heptan-2-yl)methoxy)pyridine-3-sulfonamide
15 The title compound was prepared by substituting EXAMPLE 339B for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 40A for EXAMPLE 36A in EXAMPLE 36B. The two stereoisomers at the 5 position 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. The desired fractions were collected,
20 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 MgSO₄, filtered and concentrated to give the title compound.

25 EXAMPLE 339D

5-chloro-6-(((1S,2R,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]heptan-2-yl)methoxy)pyridine-3-sulfonamide

EXAMPLE 339C (0.44 g) in tetrahydrofuran (15 mL) was treated with 3.0 M methylmagnesium bromide (5.3 mL) at 0 °C. The solution was stirred for 16 hours. The
30 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 MgSO₄, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel using 10-50% ethyl acetate in hexanes to provide the title compound.

EXAMPLE 339E

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 339D for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.66 (s, 1H), 8.50 (s, 1H), 8.16 (s, 1H), 8.02 (d, 1H), 7.49-7.55 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.67 (dd, 1H), 6.38 (dd, 1H), 6.20 (s, 1H), 4.40-4.48 (m, 2H), 4.31 (s, 1H), 3.09 (s, 4H), 2.83 (s, 2H), 2.15-2.33 (m, 7H), 1.96 (s, 2H), 1.87 (d, 1H), 1.65-1.69 (m, 1H), 1.54-1.56 (m, 2H), 1.36-1.47 (m, 6H), 1.26-1.30 (m, 1H), 1.19 (s, 3H), 0.93 (s, 6H).

EXAMPLE 340

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-cyanoethyl)(cyclopropyl)amino]cyclohexyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 340A

4-(1,4-dioxaspiro[4.5]decan-8-ylamino)-3-nitrobenzenesulfonamide

To a solution of 4-fluoro-3-nitrobenzenesulfonamide (1.4 g) in tetrahydrofuran (30 mL) was added 1,4-dioxaspiro[4.5]decan-8-amine (1.0 g) and diisopropylethylamine (5 mL). The mixture was stirred overnight. The mixture was diluted with ethyl acetate (300 mL) and washed with water, brine and dried over Na₂SO₄. Filtration and evaporation of the solvent gave the title compound.

EXAMPLE 340B

N-(4-(1,4-dioxaspiro[4.5]decan-8-ylamino)-3-nitrophenylsulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzamide

To a solution of EXAMPLE 3J (617 mg) and EXAMPLE 340A (386 mg) in dichloromethane (10 mL) was added 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (288 mg) and 4-(dimethylamino)pyridine (183 mg). The mixture was stirred overnight. The mixture was diluted with dichloromethane (300 mL) and washed with

aqueous NaHCO₃, water, brine and dried over Na₂SO₄. Filtration and evaporation of the solvent gave the title compound.

EXAMPLE 340C

5 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-(4-oxocyclohexylamino)phenylsulfonyl)benzamide

To a solution of EXAMPLE 340B (386 mg) in acetone (10 mL) and water (5 mL) was added para-toluenesulfonic acid monohydrate (50 mg). The mixture was stirred at 120°C in a Biotage Initiator microwave reactor for 30 minutes. The mixture was diluted with
10 dichloromethane (300 mL) and washed with aqueous NaHCO₃, water, brine and dried over Na₂SO₄. Filtration and evaporation of the solvent gave the title compound.

EXAMPLE 340D

15 4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-((4-((2-cyanoethyl)(cyclopropyl)amino)cyclohexyl)amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

To a solution of EXAMPLE 340C (240 mg) and 3-(cyclopropylamino)propanenitrile (62 mg) in tetrahydrofuran (10 mL) was added acetic acid (2 mL) and MP-cyanoborohydride
20 (300 mg, 2.15mmol/g). The mixture was stirred overnight. The mixture was filtered and concentrated under vacuum and the residue was dissolved in dimethylsulfoxide/methanol (1:1, 10 mL) and loaded on Gilson, C18(100A) 250x121.2 mm(10 micron), with 30% acetonitrile to 65% acetonitrile over 40 minutes. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ
11.66 (s, 1 H), 8.55 (dd, 1 H), 8.17 (d, 1 H), 8.03 (d, 1 H), 7.79 (d, 1 H), 7.49 (m, 3 H), 7.34
25 (d, 2 H), 7.11 (m, 1 H), 7.04 (d, 2 H), 6.67 (dd, 1 H), 6.38 (d, 1 H), 6.19 (d, 1 H), 4.01 (m, 1 H), 3.56 (m, 1 H), 3.06 (m, 4 H), 2.88 (t, 2 H), 2.65 (m, 6 H), 2.19 (m, 6 H), 2.00 (m, 7 H), 1.51 (m, 6 H), 0.92 (s, 6 H), 0.42 (m, 4 H).

EXAMPLE 341

30 N-([5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl]sulfonyl)-4-(4-([5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 341A

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 under high vacuum.

EXAMPLE 341B

1,4-dioxaspiro[4.5]decan-8-ylmethanol

To a suspension of lithium aluminum hydride (8.19 g) in tetrahydrofuran (400 mL) was added dropwise a solution of EXAMPLE 341A (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 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 was filtered. The title compound was isolated by concentration of the filtrate.

EXAMPLE 341C

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 341B (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 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 provide the title compound.

EXAMPLE 341D

4-(benzyloxymethyl)cyclohexanone

To a solution of EXAMPLE 341C (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- 50% ethyl acetate in hexanes step gradient to provide the title compound.

5

EXAMPLE 341E

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) trimethylaluminum (95 mL) somewhat carefully to control methane evolution and a small exotherm. The reaction mixture was stirred at ambient temperature under N₂ for 75 minutes and was then cooled to -77° C. A solution of EXAMPLE 341D (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 N₂ 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 (Na₂SO₄), 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 provide the title compound.

15

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EXAMPLE 341F

Trans-4-(hydroxymethyl)-1-methylcyclohexanol

EXAMPLE 341E (12.6 g) and ethanol (120 ml) were added to 20% Pd(OH)₂/C, wet (1.260 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 provide the title compound.

25

30

EXAMPLE 341G

5-chloro-6-((trans-4-hydroxy-4-methylcyclohexyl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 341F for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

5

EXAMPLE 341H

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 328E for EXAMPLE 3J and EXAMPLE 341G for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500 MHz, pyridine-d₅) δ 13.09 (s, 1H), 9.18 (d, 1H), 8.74 (d, 1H), 8.41 (d, 1H), 8.09 (d, 1H), 7.67 (m, 2H), 7.42 (m, 2H), 7.09 (m, 2H), 6.74 (dd, 1H), 6.52 (dd, 1H), 6.49 (d, 1H), 4.29 (d, 2H), 3.05 (m, 4H), 2.80 (s, 2H), 2.37 (t, 2H), 2.15 (m, 4H), 2.11 (s, 2H), 1.89 (m, 6H), 1.75 (m, 2H), 1.45 (t, 2H), 1.41 (s, 3H), 1.32 (m, 2H), 0.37 (m, 4H).

15

EXAMPLE 342

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

20

EXAMPLE 342A

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 taken up in ethyl acetate. It was then washed with saturated sodium bicarbonate, brine, dried over MgSO₄, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel using 10-100% ethyl acetate in hexanes to provide the title compound.

30

EXAMPLE 342B

(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-yl)methanol

The title compound was prepared by substituting EXAMPLE 342A for EXAMPLE 339A in EXAMPLE 339B.

EXAMPLE 342C

5 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 342B for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 40A for EXAMPLE 36A in EXAMPLE 36B.

EXAMPLE 342D

10 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-yl)methoxy]pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 342C for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.54 (s, 1H), 8.36 (s, 1H), 8.06 (s, 1H), 7.93 (s, 1H), 7.58 (d, 1H), 7.41-7.44 (m, 2H), 7.2-7.36 (m, 4H), 7.05 (d, 2H), 6.63 (dd, 1H), 6.32 (dd, 1H), 6.24 (d, 1H), 4.42-4.51 (m, 1H), 4.37-4.40 (m, 1H), 4.29 (dd, 1H), 3.91 (dd, 1H), 3.03 (s, 4H), 2.90-2.95 (m, 2H), 2.77 (s, 2H), 2.51-2.52 (m, 1H), 2.07-2.23 (m, 7H), 1.96 (s, 2H), 1.76-1.82 (m, 1H), 1.65-1.69 (m, 2H), 1.54-1.56 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

20

EXAMPLE 343

N-([5-chloro-6-([(1R,2S,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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

25

EXAMPLE 343A

5-chloro-6-(((1S,2S,4R)-5-oxobicyclo[2.2.1]heptan-2-yl)methoxy)pyridine-3-sulfonamide

The title compound was isolated as another isomer in EXAMPLE 339C.

30

EXAMPLE 343B

5-chloro-6-(((1S,2S,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]heptan-2-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 343A for EXAMPLE 339B in EXAMPLE 339C.

EXAMPLE 343C

5 N-[(5-chloro-6-[(1R,2S,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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 343B for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.67 (s, 1H), 8.51 (s, 1H), 8.17 (s, 1H), 8.03 (s, 1H), 7.49-7.55 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.20 (d, 1H), 4.27 (s, 1H), 4.11-4.19 (m, 2H), 3.11 (s, 4H), 2.87 (s, 2H), 1.96-2.23 (m, 10H), 1.88 (d, 1H), 1.50 (dd, 1H), 1.33-1.44 (m, 2H), 1.13-1.19 (m, 4H), 0.88-0.93 (m, 8H).

15 EXAMPLE 344

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

20 EXAMPLE 344A

4-((cis-4-hydroxy-4-methylcyclohexyl)methoxy)-3-nitrobenzenesulfonamide

EXAMPLE 347A (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 Na₂SO₄, filtered, and concentrated. The residue was purified by a reverse phase chromatography, eluting with 30-50% CH₃CN in 0.1% trifluoroacetic acid water to provide the title compound as a single enantiomer.

30

EXAMPLE 344B

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-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

5 The title compound was prepared by substituting EXAMPLE 344A for EXAMPLE
1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. ¹H NMR (400 MHz,
dimethylsulfoxide-d₆) δ 11.69 (s, 1H), 8.34 (d, 1H), 8.04 (m, 2H), 7.52 (m, 3H), 7.40 (d,
1H), 7.35 (d, 2H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.40 (m, 1H), 6.20 (d, 1H), 4.02 (d, 2H), 3.96
(s, 1H), 3.10 (br s, 4H), 2.85 (m, 2H), 2.29 (m, 3H), 2.15 (t, 2H), 1.96 (br s, 2H), 1.68 (m,
10 1H), 1.55(m, 4H), 1.42 (m, 4H), 1.27 (m, 2H), 1.10 (s, 3H), 0.92 (s, 6H).

EXAMPLE 345

N-[(5-chloro-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-
(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-
15 b]pyridin-5-yloxy)benzamide

 The title compound was prepared by substituting EXAMPLE 328E for EXAMPLE 3J
and EXAMPLE 277O for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500 MHz,
pyridine-d₅) δ 13.07 (s, 1H), 9.13 (d, 1H), 8.41 (d, 1H), 8.09 (d, 1H), 7.68 (t, 1H), 7.66 (d,
1H), 7.42 (m, 2H), 7.09 (m, 2H), 6.75 (dd, 1H), 6.51 (m, 2H), 4.64 (d, 4H), 4.53 (d, 2H), 3.39
20 (m, 1H), 3.06 (m, 4H), 2.81 (s, 2H), 2.51 (m, 2H), 2.37 (m, 2H), 2.12 (m, 10H), 1.90 (m, 2H),
1.45 (t, 2H), 0.38 (s, 4H).

EXAMPLE 346

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
25 {[4-(3,3-difluoropyrrolidin-1-yl)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

 The title compound was prepared by substituting 3,3-difluoropyrrolidine
hydrochloride for 3-(cyclopropylamino)propanenitrile in EXAMPLE 340D. ¹H NMR (300
MHz, dimethylsulfoxide-d₆) δ 11.68 (s, 1 H), 11.38 (m, 1 H), 8.55 (m, 1 H), 8.36 (d, 1 H),
30 8.03 (d, 1 H), 7.80 (m, 1 H), 7.50 (m, 3 H), 7.34 (d, 2 H), 7.13 (d, 1 H), 7.04 (d, 2 H), 6.83
(m, 1 H), 6.68 (m, 1 H), 6.38 (d, 1 H), 6.19 (s, 1 H), 4.02 (s, 1 H), 3.83 (m, 1 H), 3.06 (m, 4
H), 2.96 (m, 2 H), 2.73 (m, 4 H), 2.26 (m, 8 H), 1.97 (m, 4 H), 1.68 (m, 4 H), 1.37 (m, 2 H),
0.92 (s, 6 H).

EXAMPLE 347

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-
5 { [2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl }piperazin-1-yl)-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 347A

4-(hydroxymethyl)-1-methylcyclohexanol

4-(Hydroxymethyl)cyclohexanone (800 mg) in tetrahydrofuran (15 mL) was treated
10 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.

15

EXAMPLE 347B

5-chloro-6-((trans-4-hydroxy-4-methylcyclohexyl)methoxy)pyridine-3-sulfonamide

EXAMPLE 347A (970 mg) and EXAMPLE 40A (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
20 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 Na₂SO₄,
filtered, and concentrated. The residue was purified by a reverse phase chromatography,
eluting with 30-45% acetonitrile in 0.1% trifluoroacetic acid water to isolate the title
compound.

25

EXAMPLE 347C

5-chloro-6-((cis-4-hydroxy-4-methylcyclohexyl)methoxy)pyridine-3-sulfonamide

The title compound was prepared and isolated as described in Example 347B.

30

EXAMPLE 347D

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-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE
 5 347B in place of EXAMPLE 11B. ¹H NMR (400 MHz, dimethylsulfoxide-d₆) δ 11.67 (s, 1
 H), 8.51 (d, 1 H), 8.18 (d, 1 H), 8.03 (d, 1 H), 7.48 - 7.56 (m, 3 H), 7.35 (d, 2 H), 7.05 (d, 2
 H), 6.68 (dd, 1 H), 6.39 (dd, 1 H), 6.21 (d, 1 H), 4.17 - 4.34 (m, 3 H), 3.11 (s, 4 H), 2.89 (s, 2
 H), 2.24 - 2.42 (m, 4 H), 2.15 (s, 2 H), 1.96 (s, 2 H), 1.66 - 1.82 (m, 3 H), 1.55 (d, 2 H), 1.31 -
 1.44 (m, 4 H), 1.12 - 1.27 (m, 2 H), 1.10 (s, 3 H), 0.93 (s, 6 H).

10

EXAMPLE 348

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-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

15 The title compound was prepared as described in EXAMPLE 11D using EXAMPLE
 347C in place of EXAMPLE 11B. ¹H NMR (400 MHz, dimethylsulfoxide-d₆) δ 11.67 (s, 1
 H), 8.51 (d, 1 H), 8.18 (d, 1 H), 8.03 (d, 1 H), 7.47 - 7.58 (m, 3 H), 7.35 (d, 2 H), 7.05 (d, 2
 H), 6.68 (dd, 1 H), 6.39 (dd, 1 H), 6.21 (d, 1 H), 4.21 (d, 2 H), 3.95 (s, 1 H), 3.11 (s, 4 H),
 2.89 (s, 2 H), 2.33 (d, 4 H), 2.15 (s, 2 H), 1.96 (s, 2 H), 1.63 - 1.77 (m, 1 H), 1.48 - 1.60 (m, 4
 20 H), 1.35 - 1.48 (m, 4 H), 1.20 - 1.33 (m, 2 H), 1.09 (s, 3 H), 0.93 (s, 6 H).

EXAMPLE 349

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-
 ({4-[(2,2-difluorocyclopropyl)amino]cyclohexyl)amino}-3-nitrophenyl}sulfonyl)-2-(1H-
 25 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting 2,2-difluorocyclopropanamine
 hydrochloride for 3-(cyclopropylamino)propanenitrile in EXAMPLE 340D. ¹H NMR (300
 MHz, dimethylsulfoxide-d₆) δ 11.60 (s, 1 H), 8.47 (m, 2 H), 8.12 (m, 1 H), 7.98 (m, 1 H),
 7.72 (m, 2 H), 7.47 (m, 3 H), 7.34 (m, 3 H), 7.05 (m, 3 H), 6.65 (dd, 1 H), 6.35 (m, 1 H), 6.22
 30 (d, 1 H), 3.54 (m, 2 H), 3.08 (m, 4 H), 2.74 (m, 4 H), 2.25 (m, 4 H), 2.01 (m, 4 H), 1.38 (m, 4
 H), 0.92 (s, 6 H).

EXAMPLE 350

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-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5

EXAMPLE 350A

ethyl spiro[benzo[d][1,3]dioxole-2,1'-cyclohexane]-4'-carboxylate

To a solution of ethyl 4-oxocyclohexanecarboxylate (22.75 g) and pyrocatechol
(14.75 g) in toluene (200 mL) was added catalytic amount of para-toluenesulfonic acid
monohydrate and the mixture was stirred under reflux and a Dean-Stark trap overnight. The
10 mixture was diluted with diethyl ether (600 mL) and washed with aqueous NaHCO₃, water
and brine. After drying over Na₂SO₄, the mixture was filtered and the solvent was evaporated
under vacuum to provide the title compound.

EXAMPLE 350B

15 ethyl 4'-fluorospiro[benzo[d][1,3]dioxole-2,1'-cyclohexane]-4'-carboxylate

A solution of EXAMPLE 350A (5.25g) in tetrahydrofuran (40 mL) was added
dropwise to a solution of lithium diisopropylamide (12 mL, 2.0M in
tetrahydrofuran/heptane/ethylbenzene) at 0°C. The solution was stirred at 0°C for 30 minutes,
and then was transferred by cannula to a pre-cooled (0°C) stirring solution of N-
20 fluorobenzenesulfonylimide (7.89g) in dry tetrahydrofuran (20 mL). The reaction mixture was
stirred at 0°C for 30 minutes, and then at 20°C for 18 hours. The reaction mixture was poured
over aqueous NH₄Cl and extracted with diethyl ether (3x200 mL). The combined organic
layers were washed with water, brine and dried over Na₂SO₄. Filtration and evaporation of
the solvent gave the crude product.

25

EXAMPLE 350C

(4'-fluorospiro[benzo[d][1,3]dioxole-2,1'-cyclohexane]-4'-yl)methanol

To a solution of EXAMPLE 350B (23 g) in tetrahydrofuran (150 mL) was added
lithium aluminum hydride (3.11 g). The mixture was stirred overnight. Aqueous 2N NaOH
30 solution was added dropwise to the reaction mixture. The mixture was then diluted with ethyl
acetate (600 mL) and washed with water, brine and dried over Na₂SO₄. Filtration and
evaporation of the solvent gave the crude product which was loaded on a 600 g analogics
column and eluted with 10% to 20% ethyl acetate in hexane to provide the title compound.

EXAMPLE 350D

5-chloro-6-((4'-fluorospiro[benzo[d][1,3]dioxole-2,1'-cyclohexane]-4'-yl)methoxy)pyridine-3-sulfonamide

To a solution of EXAMPLE 350C (89 mg) in N,N-dimethylformamide (3 mL) was added NaH (65% in mineral oil, 36 mg). The mixture was stirred for 30 minutes, and then 5, 6-dichloropyridine-3-sulfonamide (85 mg) was added. The mixture was stirred overnight. The mixture was poured over aqueous NH₄Cl and extracted with ethyl acetate (100 mL). The combined organic layers were washed with water, brine and dried over Na₂SO₄. 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 provide the title compound.

EXAMPLE 350E

5-chloro-6-((1-fluoro-4-oxocyclohexyl)methoxy)pyridine-3-sulfonamide

To a solution of EXAMPLE 350D (1.6g) and pyridinium p-toluenesulfonate (1.2 g) in acetone (10 mL) was added water (2 mL) and the mixture was stirred under microwave irradiation at 100°C for 10 minutes. The mixture was diluted with dichloromethane (300 mL) and washed with aqueous NaHCO₃, water, brine and dried over Na₂SO₄. Filtration and evaporation of the solvent gave the title compound.

EXAMPLE 350F

5-chloro-6-((cis-1-fluoro-4-hydroxycyclohexyl)methoxy)pyridine-3-sulfonamide

To a solution of EXAMPLE 350E (336 mg) in tetrahydrofuran (10 mL) was added NaBH₄ (75 mg). The mixture was stirred for 45 minutes. The mixture was diluted with ethyl acetate (300 mL) and washed with 2N aqueous NaOH, water, and brine. After drying over Na₂SO₄, the mixture was filtered and the solvent was evaporated to give the crude product.

EXAMPLE 350G

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 350F for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.63 (s, 1 H), 8.48 (s, 1 H), 8.18 (s, 1 H), 8.01 (d, 1 H), 7.50 (m, 3 H), 7.35 (d, 2 H), 7.05 (d, 2 H), 6.67 (dd, 1 H), 6.37 (dd, 1 H), 6.21 (d, 1 H), 4.62 (d, 1 H), 4.47 (s, 1 H), 4.40 (s, 1 H), 3.46 (m, 1 H), 3.06 (m, 4 H), 2.88 (m, 1 H), 2.25 (m, 6 H), 1.99 (m, 4 H), 1.58 (m, 8 H), 0.93 (s, 6 H).

EXAMPLE 351

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-(2-oxaspiro[3.5]non-7-ylmethoxy)phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 351A

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 N₂ 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 NH₄Cl and was diluted with diethyl ether. The layers were separated, the aqueous layer was extracted with diethyl ether and the combined organics were dried (Na₂SO₄), filtered and concentrated by rotary evaporation. The residue was purified by regular phase flash column chromatography (Analogix, 0-65% hexanes / ethyl acetate).

EXAMPLE 351B

1,4-dioxaspiro[4.5]decane-8,8-diyl dimethanol

To a 1 L round-bottomed flask was added EXAMPLE 351A (26.6 g) and tetrahydrofuran (310 mL) to give a colorless solution. 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 and quenched slowly with 4.7 mL water, 4.7 mL 10% aqueous NaOH and 14 mL water. The mixture was allowed to stir until salts were formed and was then 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 351C

2,8,11-trioxa-dispiro[3.2.4]tridecane

1. To a 1 L round-bottomed flask was added EXAMPLE 351B (13 g) in tetrahydrofuran (321 mL). The solution was cooled to -78 °C under N₂ and n-BuLi (25.7 mL) was added dropwise via syringe. After addition was complete, the mixture stirred for 30 minutes and a tetrahydrofuran solution of 4-toluenesulfonyl chloride (12.25 g) was added via addition
5 funnel. The reaction was allowed to stir overnight, and gradually warm to room temperature. The reaction mixture was cooled to -78 °C and n-BuLi (25.7mL) was added. The mixture was warmed to room temperature and stirred for 3 hours. The reaction was quenched with sat aqueous NH₄Cl and diluted with diethyl ether. The layers were separated, the aqueous layers extracted with diethyl ether and the combined organics were dried (Na₂SO₄), filtered
10 and concentrated by rotary evaporation. The residue was purified by regular phase flash column chromatography (Analogix, 0-20% acetone / hexanes).

EXAMPLE 351D

2-oxaspiro[3.5]nonan-7-one

- 15 To a 500 mL round-bottomed flask was added EXAMPLE 351C (11 g) in 80 % aqueous 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).

- 20 EXAMPLE 351E

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) to give a suspension. The suspension was cooled to -15 °C. n-BuLi (2.5 M in hexanes, 4.28 mL) was added dropwise and the mixture was stirred at -
25 15 °C for 40 minutes and EXAMPLE 351D (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 NH₄Cl 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,
30 dried (Na₂SO₄), filtered and concentrated by rotary evaporation. The residue was purified by regular phase chromatography (Analogix, 80 g Grace silica gel column, 0-50% hexanes/ethyl acetate).

EXAMPLE 351F

2-oxaspiro[3.5]nonan-7-ylmethanol

To a 25 mL round-bottomed flask was added EXAMPLE 351E (568 mg) and
EXAMPLE 351F tetrahydrofuran (4.11 mL) to give a colorless solution. 9-
Borabicyclo[3.3.1]nonane (0.5 M in tetrahydrofuran, 24.7 mL) was added and the reaction
5 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 hydrogen peroxide (2.1 mL) was added. The
reaction was heated at 50 °C for 2 hours. The mixture was concentrated by rotary
evaporation, and diluted with water and ethyl acetate. The aqueous layer was extracted with
ethyl acetate (3x) and the combined organics were dried (Na₂SO₄), filtered and concentrated
10 by rotary evaporation. The residue was purified by regular phase flash column
chromatography (Analogix, 80 g Grace, 0-70 % hexanes / ethyl acetate).

EXAMPLE 351G

4-(2-oxaspiro[3.5]nonan-7-ylmethoxy)-3-nitrobenzenesulfonamide

15 EXAMPLE 351G was prepared substituting EXAMPLE 351F for (tetrahydro-2H-
pyran-4-yl)methanol in EXAMPLE 24A.

EXAMPLE 351H

20 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(4-(2-oxaspiro[3.5]nonan-7-ylmethoxy)-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 3J for EXAMPLE 1E
and EXAMPLE 351G for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300 MHz,
dimethylsulfoxide-d₆) δ 11.67 (s, 1 H) 8.34 (s, 1 H) 8.03 (d, 2 H) 7.45 - 7.57 (m, 3 H) 7.30 -
25 7.40 (m, 3 H) 7.04 (d, 2 H) 6.67 (dd, 1 H) 6.39 (dd, 1 H) 6.17 - 6.23 (m, 1 H) 4.29 (s, 2 H)
4.20 (s, 2 H) 4.00 (d, 2 H) 3.08 (s, 4 H) 2.73 - 2.90 (m, 2 H) 2.72 (s, 1 H) 2.01 - 2.32 (m, 6 H)
1.96 (s, 2 H) 1.64 - 1.78 (m, 4 H) 1.33 - 1.50 (m, 6 H) 0.96 - 1.15 (m, 2 H) 0.92 (s, 6 H).

30

EXAMPLE 352

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-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide

5

EXAMPLE 352A

4-((trans-4-hydroxy-4-methylcyclohexyl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 341F for (tetrahydro-
 2H-pyran-4-yl)methanol in EXAMPLE 24A.

10

EXAMPLE 352B

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-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 352A for EXAMPLE
 15 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. ¹H NMR (400 MHz,
 dimethylsulfoxide-d₆) δ 11.66 (s, 1H), 8.31 (br s, 1H), 8.01 (m, 2H), 7.49 (m, 3H), 7.33 (m,
 3H), 7.03 (m, 2H), 6.66 (dd, 1H), 6.37 (m, 1H), 6.19 (d, 1H), 4.27 (s, 1H), 4.05 (d, 2H), 3.40
 (m, 2H), 3.17 (s, 1H), 3.07 (m, 3H), 2.79 (m, 1H), 2.24 (m, 3H), 2.14 (m, 2H), 1.94 (m, 2H),
 1.71 (m, 3H), 1.52 (m, 2H), 1.38 (m, 4H), 1.22 (m, 2H), 1.09 (s, 3H), 0.91 (s, 6H).

20

EXAMPLE 353

4-(4-{[2-(4-chlorophenyl)-5,5-bis(fluoromethyl)cyclohex-1-en-1-yl]methyl}piperazin-1-yl)-
 N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide

25

EXAMPLE 353A

1,4-dioxaspiro[4.5]decane-8,8-diylbis(methylene) bis(4-methylbenzenesulfonate)

To a 500 mL round-bottomed flask was added EXAMPLE 351B (10 g) and
 dichloromethane (165 mL) to give a colorless solution. Triethylamine (24.1 mL) and
 toluene-2-sulfonyl chloride (19.8 g) were added followed by 4-dimethylaminopyridine (0.604
 30 g). The reaction was refluxed overnight. Saturated aqueous NH₄Cl was added followed by
 dilution with water and additional dichloromethane. The aqueous layer was extracted with
 dichloromethane (2x) and the combined organics were dried (MgSO₄), filtered and

concentrated by rotary evaporation. The residue was purified by regular phase flash column chromatography (Analogix, 0-55% hexanes / ethyl acetate).

EXAMPLE 353B

5 8,8-bis(fluoromethyl)-1,4-dioxaspiro[4.5]decane

To a 500 mL round-bottomed flask was added EXAMPLE 353A (20 g). tetra-*n*-Butylammonium fluoride (1M in tetrahydrofuran, 200 mL) was added and the resulting solution was refluxed for 6 days. The reaction was cooled, diluted with diethyl ether and washed with water (3x). The organics were dried (Na₂SO₄), filtered and concentrated by
10 rotary evaporation. The residue was purified by regular phase flash column chromatography (Analogix, 0-30% hexanes / ethyl acetate).

EXAMPLE 353C

4,4-bis(fluoromethyl)cyclohexanone

15 To a 250 mL round bottom flask was added EXAMPLE 353B (1.1 g) and 80% aqueous acetic acid (50 mL). The reaction was heated at 65 °C for 3 hours, cooled and concentrated by rotary evaporation to remove most of the acetic acid and water. The residue was purified by regular phase flash column chromatography (Analogix, 0-50% hexanes / ethyl acetate).

20

EXAMPLE 353D

2-chloro-5,5-bis(fluoromethyl)cyclohex-1-enecarbaldehyde

To a 100 mL pear flask was added N,N-dimethylformamide (498 µl) and dichloromethane (8.9 mL) to give a colorless solution. The solution was cooled to 0 °C and
25 POCl₃ (550 µl) was added dropwise and then the mixture was warmed to room temperature for 30 minutes. In the meantime, to a 100 mL pear shaped flask was added EXAMPLE 353C (870 mg, 5.36 mmol) in dichloromethane (8941 µl) to give a colorless solution. The Vilsmeier reagent was then taken up in a syringe and added dropwise to the 4,4-bis(fluoromethyl)cyclohexanone (870 mg) solution at room temperature. The resulting
30 solution was stirred overnight. The reaction was poured into saturated aqueous NaHCO₃ and ice, warmed to room temperature and extracted with dichloromethane (3 x 30 mL). The organics were combined, dried over MgSO₄, filtered and concentrated by rotary evaporation. The residue was purified by regular phase flash column chromatography (Analogix (0-60% hexanes / ethyl acetate).

EXAMPLE 353E

2-(4-chlorophenyl)-5,5-bis(fluoromethyl)cyclohex-1-enecarbaldehyde

To a 20 mL vial was added EXAMPLE 353D (460 mg), 4-chlorophenylboronic acid
5 (414 mg), potassium carbonate (762 mg), tetrabutylammonium bromide (711 mg), palladium
(II) acetate (14.85 mg) and water (2450 μ L) to give a suspension which was degassed with N₂
for 2 minutes. The reaction was stirred at 45 °C overnight, cooled, and poured over a Supelco
silica gel Buchner funnel, washing with ethyl acetate several times. The filtrate was
concentrated by rotary evaporation and the residue was purified by regular phase flash
10 column chromatography (Analogix, 0-60% hexanes / ethyl acetate).

EXAMPLE 353F

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-
bis(fluoromethyl)cyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

15 To a 20 mL vial was added EXAMPLE 353E (240 mg), EXAMPLE 15F (297 mg)
and dichloromethane (4.2 mL). Sodium triacetoxyborohydride (268 mg) was added and the
reaction was stirred overnight at room temperature. The reaction was loaded directly onto
silica gel and purified by regular phase flash column chromatography (Analogix, 0-80%
hexanes / ethyl acetate).

20

EXAMPLE 353G

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-
bis(fluoromethyl)cyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 353F for EXAMPLE
25 15G in EXAMPLE 15 H.

EXAMPLE 353H

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-
bis(fluoromethyl)cyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-((tetrahydro-2H-
30 pyran-4-yl)methylamino)phenylsulfonyl)benzamide

EXAMPLE 353H was prepared by replacing EXAMPLE 3J with EXAMPLE 353G
and EXAMPLE 11B with EXAMPLE 1F in EXAMPLE 11D. ¹H NMR (300 MHz,
dimethylsulfoxide-d₆) δ 11.69 (s, 1 H) 11.44 (s, 1 H) 8.48 - 8.70 (m, 1 H) 8.05 (d, 2 H) 7.81

(dd, 1 H) 7.46 - 7.59 (m, 3 H) 7.35 (d, 2 H) 7.12 (d, 2 H) 6.68 (dd, 1 H) 6.40 (dd, 1 H) 6.16 (d, 1 H) 4.39 - 4.49 (m, 2 H) 4.23 - 4.35 (m, 2 H) 3.85 (dd, $J=11.87, 2.71$ Hz, 2 H) 3.20 - 3.30 (m, 4 H) 2.98 - 3.10 (m, 4 H) 2.66 - 2.77 (m, 2 H) 2.11 - 2.30 (m, 6 H) 2.02 - 2.12 (m, 3 H) 1.99 (s, 1 H) 1.82 - 1.97 (m, 1 H) 1.54 - 1.67 (m, 4 H) 1.20 - 1.34 (m, 2 H).

5

EXAMPLE 354

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-cyclopropylmorpholin-2-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

10

EXAMPLE 354A

tert-butyl 2-((2-nitro-4-sulfamoylphenoxy)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting tert-butyl 2-(hydroxymethyl)-morpholine-4-carboxylate for tetrahydro-2H-pyran-4-yl-methanol EXAMPLE 24A.

15

EXAMPLE 354B

4-(morpholin-2-ylmethoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 354A for EXAMPLE 113A in EXAMPLE 134A.

20

EXAMPLE 354C

4-((4-cyclopropylmorpholin-2-yl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 354B for EXAMPLE 173A in EXAMPLE 173B.

25

EXAMPLE 354D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-cyclopropylmorpholin-2-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

30

The title compound was prepared by substituting EXAMPLE 354C for EXAMPLE 130C in EXAMPLE 130D. ^1H NMR (500MHz, pyridine- d_5) δ 12.98 (s, 1H), 9.06 (d, 1H), 8.50 (dd, 1H), 8.41 (d, 1H), 8.09 (d, 1H), 7.66 (t, 1H), 7.62 (d, 1H), 7.44 (d, 2H), 7.26 (d, 1H), 7.07 (d, 2H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 4.31 (dd, 1H), 4.22 (dd, 1H),

3.92 (m, 1H), 3.83 (d, 1H), 3.56 (dt, 1H), 3.07 (m, 5H), 2.77 (s, 2H), 2.68 (d, 1H), 2.35 (m, 2H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.59 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H), 0.40 (m, 4H).

5

EXAMPLE 355

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

10

EXAMPLE 355A

5-chloro-6-((trans-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy)pyridine-3-sulfonamide

To a cooled (0°C) solution of EXAMPLE 350E (1.2 g) in tetrahydrofuran (30 mL) was added dropwise a solution of methylmagnesium bromide (5 mL, 3.0M in ether). Upon 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 NH₄Cl and extracted with ethyl acetate (3x 150 mL). The combined organic layers were washed with water, brine and dried over Na₂SO₄. The mixture was filtered and concentrated. The residue was dissolved in dimethylsulfoxide/methanol (20 mL, 1:1) and loaded on Gilson, C18(100A) 250x121.2 mm (10 micron), with 30% acetonitrile to 65% acetonitrile over 40 minutes to separate the two isomers and isolate the title compound.

20

EXAMPLE 355B

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

25

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 355A for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.63 (s, 1 H), 8.47 (s, 1 H), 8.17 (s, 1 H), 7.54 (d, 1 H), 7.48 (m, 2 H), 7.35 (d, 2 H), 7.05 (d, 2 H), 6.67 (dd, 1 H), 6.37 (d, 1 H), 6.22 (d, 1 H), 4.49 (s, 1 H), 4.42 (s, 1 H), 4.15 (s, 1 H), 3.06 (m, 4 H), 2.84 (m, 1 H), 2.25 (m, 6 H), 1.96 (s, 3 H), 1.83 (m, 4 H), 1.44 (m, 6 H), 1.14 (s, 3 H), 0.93 (s, 6 H).

30

EXAMPLE 356

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5

EXAMPLE 356A

5-chloro-6-((cis-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy)pyridine-3-sulfonamide

The title compound was prepared as described in EXAMPLE 355A.

EXAMPLE 356B

10

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 356A for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300 MHz,

15

dimethylsulfoxide-d₆) δ 11.65 (s, 1 H), 8.52 (s, 1 H), 8.20 (s, 1 H), 8.03 (d, 1 H), 7.51 (m, 3 H), 7.35 (d, 2 H), 7.05 (d, 2 H), 6.67 (dd, 1 H), 6.39 (dd, 1 H), 6.21 (d, 1 H), 4.55 (s, 1 H), 4.48 (s, 1 H), 4.34 (s, 1 H), 3.08 (m, 4 H), 2.89 (d, 2 H), 2.27 (m, 5 H), 1.93 (m, 4 H), 1.66 (m, 4 H), 1.43 (m, 4 H), 1.11 (s, 3 H), 0.93 (s, 6 H).

EXAMPLE 357

20

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 357A

25

ethyl 4-fluoro-1-(oxetan-3-yl)piperidine-4-carboxylate

To 1-*tert*-butyl 4-ethyl 4-fluoropiperidine-1,4-dicarboxylate (1.000 g) was added HCl (4.0M in dioxane, 4.54 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 (1.155 g) and oxetan-3-one (0.262 g) and stirred overnight.

30

The reaction was quenched with saturated NaHCO₃ 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 = 30mL/min) gave the title compound.

EXAMPLE 357B

5 (4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methanol

To a solution of EXAMPLE 357A (0.59 g) in tetrahydrofuran (5 mL) was added lithium aluminum hydride (1.80 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
10 filtered through celite and rinsed with ethyl acetate (50 mL). The mixture and the residue was loaded onto silica gel (Reveleris 40 g) and eluted using a gradient of 0.75% to 7.5% methanol/dichloromethane over 30 minutes (flow = 40 mL/minutes) to provide the title compound.

15 EXAMPLE 357C

3-cyano-4-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 357B for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 284A.

20

EXAMPLE 357D

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

25 The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 357C for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide- d₆) δ 11.67 (s, 1H), 11.49 - 11.14 (m, 1H), 8.17 (d, 1H), 8.03 (d, 2H), 7.51 (dd, 3H), 7.43 - 7.26 (m, 3H), 7.12 - 6.96 (m, 2H), 6.67 (dd, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 4.55 (t, 2H), 4.45 (t, 2H), 4.34 (d, 2H), 3.49 (s, 1H), 3.09 (s, 8H), 2.39 - 1.66 (m, 14H), 1.39
30 (s, 2H), 0.92 (s, 6H).

EXAMPLE 358

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
{[(trans-4-ethyl-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5

EXAMPLE 358A

benzyl (4-ethyl-4-hydroxycyclohexyl)methylcarbamate

To a vigorous stirring solution of benzyl (4-oxocyclohexyl)methylcarbamate (1 g) in
10 tetrahydrofuran (20 mL) at -78°C was slowly added 1 M ethylmagnesium bromide (11.48 mL,
11.48 mmol) in ether. After completion of the addition, the mixture was stirred at -78°C for 2
hours and was warmed to 0°C, and stirred in an ice bath for 30 minutes. The reaction was
quenched with a cold NH₄Cl aqueous solution. The precipitates were filtered off and washed
with ethyl acetate. The filtrate was concentrated. The residue was dissolved in
15 dichloromethane and loaded onto Analogix purification system, and was eluted with 0 - 50%
ethyl acetate in dichloromethane to provide the title compound.

EXAMPLE 358B

4-(aminomethyl)-1-ethylcyclohexanol

20 A mixture of EXAMPLE 358A (500 mg) and 10% Pd/C (100 mg) in tetrahydrofuran
(15 mL) was stirred under H₂ for 3 hours. The insoluble material was removed by filtration,
and the filtrate was concentrated to provide the title compound.

EXAMPLE 358C

25 4-((trans-4-ethyl-4-hydroxycyclohexyl)methylamino)-3-nitrobenzenesulfonamide

EXAMPLE 358B (270 mg) and 4-fluoro-3-nitrobenzenesulfonamide (417 mg) in
tetrahydrofuran were treated with triethylamine (0.8 mL) overnight. 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 Na₂SO₄, filtered and
30 concentrated. The residue was purified by a reverse phase chromatography, eluting with 40-
55% acetonitrile in 0.1% trifluoroacetic acid water to isolate the title compound.

EXAMPLE 358D

4-((cis-4-ethyl-4-hydroxycyclohexyl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared and isolated as described in Example 358C.

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EXAMPLE 358E

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
{[(trans-4-ethyl-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE
10 358C in place of EXAMPLE 11B. ¹H NMR (400 MHz, dimethylsulfoxide-d₆) δ 11.69 (s, 1
H), 11.35 (s, 1 H), 8.56 (d, 2 H), 8.05 (d, 1 H), 7.80 (dd, 1 H), 7.45 - 7.57 (m, 3 H), 7.34 (d, 2
H), 7.00 - 7.10 (m, 3 H), 6.68 (dd, 1 H), 6.39 (dd, 1 H), 6.19 (d, 1 H), 3.98 (s, 1 H), 3.24 -
3.31 (m, 4 H), 3.07 (s, 4 H), 2.75 (s, 2 H), 2.17 (d, 6 H), 1.95 (s, 2 H), 1.54 - 1.73 (m, 5 H),
1.35 - 1.47 (m, 4 H), 1.20 - 1.32 (m, 2 H), 1.03 - 1.18 (m, 2 H), 0.92 (s, 6 H), 0.81 (t, 3 H).

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EXAMPLE 359

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-
{[(cis-4-ethyl-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE
20 358D in place of EXAMPLE 11B. ¹H NMR (400 MHz, dimethylsulfoxide-d₆) δ 11.69 (s, 1
H), 11.34 (s, 1 H), 8.60 (t, 1 H), 8.56 (d, 1 H), 8.05 (d, 1 H), 7.80 (dd, 1 H), 7.54 (d, 1 H),
7.47 - 7.52 (m, 2 H), 7.34 (d, 2 H), 7.01 - 7.10 (m, 3 H), 6.68 (dd, 1 H), 6.39 (dd, 1 H), 6.19
(d, 1 H), 3.77 (s, 1 H), 3.26 (t, 2 H), 3.07 (s, 4 H), 2.76 (s, 2 H), 2.10 - 2.26 (m, 6 H), 1.95 (s,
25 2 H), 1.46 - 1.61 (m, 5 H), 1.28 - 1.46 (m, 6 H), 1.12 - 1.24 (m, 2 H), 0.92 (s, 6 H), 0.82 (t, 3
H).

EXAMPLE 360

4-(4-{[2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-en-1-
30 yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-
ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 360A

ethyl 8-methyl-1,4-dioxaspiro[4.5]decane-8-carboxylate

Into a 500 mL round-bottomed flask was added diisopropylamine (7.98 mL) in tetrahydrofuran (233 mL) to give a colorless solution. The mixture was cooled to -78 °C under N₂ and n-BuLi (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 CH₃I (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 (Na₂SO₄), filtered and concentrated by rotary evaporation. The residue was purified by normal phase flash column chromatography (Analogix, 0-50% hexanes / ethyl acetate).

EXAMPLE 360B

(8-methyl-1,4-dioxaspiro[4.5]decan-8-yl)methanol

In a 500 mL round-bottomed flask was lithium aluminum hydride (1.772 g) in tetrahydrofuran (234 mL) to give a suspension. This suspension was cooled to 0 °C and ethyl 8-methyl-1,4-dioxaspiro[4.5]decane-8-carboxylate (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 was 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).

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EXAMPLE 360C

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) to give a suspension. EXAMPLE 360B was added as a tetrahydrofuran solution at room temperature. The suspension was stirred for 30 minutes and then CH₃I (0.611 mL) was added. The reaction was stirred under N₂ 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 (Na₂SO₄), filtered and concentrated by rotary evaporation. The residue was purified by flash column chromatography (Analogix, 0-60% hexanes / ethyl acetate).

EXAMPLE 360D

4-(methoxymethyl)-4-methylcyclohexanone

The title compound was prepared by substituting EXAMPLE 360C for EXAMPLE 353B in EXAMPLE 353C.

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EXAMPLE 360E

2-chloro-5-(methoxymethyl)-5-methylcyclohex-1-enecarbaldehyde

The title compound was prepared by substituting EXAMPLE 360D for EXAMPLE 353C in EXAMPLE 353D.

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EXAMPLE 360F

2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-enecarbaldehyde

The title compound was prepared by substituting EXAMPLE 360E for EXAMPLE 353D in EXAMPLE 353E.

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EXAMPLE 360G

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 360F for EXAMPLE 353E in EXAMPLE 353F.

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EXAMPLE 360H

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 360G for EXAMPLE 15G in EXAMPLE 15H.

25

EXAMPLE 360I

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)phenylsulfonyl)benzamide

30

The title compound was prepared by replacing EXAMPLE 3J with EXAMPLE 360H and EXAMPLE 11B with EXAMPLE 1F in EXAMPLE 11D. ¹H NMR (300 MHz,

dimethylsulfoxide-d₆) δ 11.68 (s, 1 H) 11.43 (s, 1 H) 8.45 - 8.72 (m, 2 H) 8.04 (d, 1 H) 7.80 (dd, 1 H) 7.44 - 7.61 (m, 3 H) 7.34 (d, 2 H) 6.99 - 7.20 (m, 3 H) 6.68 (dd, 1 H) 6.39 (dd, 1 H) 6.18 (d, 1 H) 3.85 (dd, 2 H) 3.25 - 3.30 (m, 4 H) 3.24 (s, 3 H) 3.02 - 3.17 (m, 6 H) 2.72 (dd, 2 H) 2.18 (s, 5 H) 2.03 - 2.13 (m, 2 H) 1.81 - 1.93 (m, 2 H) 1.57 - 1.67 (m, 2 H) 1.47 - 1.56 (m, 1 H) 1.17 - 1.41 (m, 3 H) 0.91 (s, 3 H).

EXAMPLE 361

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}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

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EXAMPLE 361A

(S)-3-nitro-4-((4-(oxetan-3-yl)morpholin-2-yl)methylamino)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 259E for tert-butyl piperazine-1-carboxylate and 3-oxetanone for 4'-chlorobiphenyl-2-carboxaldehyde in

15 EXAMPLE 1A.

EXAMPLE 361B

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}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

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The title compound was prepared by substituting EXAMPLE 361A for EXAMPLE 130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 13.00 (s, 1H), 9.26 (d, 1H), 8.87 (t, 1H), 8.43 (d, 1H), 8.35 (dd, 1H), 8.11 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.96 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 4.64 (m, 4H), 3.93 (m, 1H), 3.89 (d, 1H), 3.68 (dt, 1H), 3.53-3.35 (m, 3H), 3.07 (m, 4H), 2.77 (s, 2H), 2.72 (d, 1H), 2.44 (d, 1H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.85 (t, 1H), 1.39 (t, 2H), 0.94 (s, 6H).

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EXAMPLE 362

N-({3-chloro-4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

30

EXAMPLE 362A

3-chloro-4-(((1*r*, 4*r*)-4-hydroxy-4-methylcyclohexyl)methoxy)benzenesulfonamide

To a solution of EXAMPLE 34IF (300 mg) in N,N-dimethylformamide (10 mL) was added sodium hydride (416 mg) portionwise. The resulting suspension was stirred for 15 minutes. 3-Chloro-4-fluorobenzenesulfonamide (425 mg) was added and stirring was continued for 72 hours. The reaction was quenched with water and the pH was adjusted to ca. 7. The mixture was diluted with brine (75 mL) and extracted with methylene chloride. The crude product was isolated from the dried methylene chloride layer by concentration and was purified on silica gel eluted with a 10, 25, 50 % ethyl acetate in methylene chloride step gradient to provide the title compound.

10

EXAMPLE 362B

N-({3-chloro-4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

15

The title compound was prepared by substituting EXAMPLE 362A for EXAMPLE 130C in EXAMPLE 130D. ¹H NMR (400 MHz, pyridine- d₅) δ 13.07 (m, 1H), 8.58 (d, 1H), 8.45 (d, 1H), 8.31 (dd, 1H), 8.11 (d, 1H), 7.69 - 7.67 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.97 (d, 1H), 6.74 (dd, 1H), 6.52 (m, 2H), 5.34 (br s, 2H), 3.82 (d, 2H), 3.06 (m, 4H), 2.77 (s, 2H), 2.25 (m, 2H), 2.13 (m, 4H), 1.97 - 1.85 (m, 7H), 1.82 - 1.73 (m, 2H), 1.44 - 1.32 (m, 7H), 0.94 (m, 6H).

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EXAMPLE 363

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({4-[(2-cyanoethyl)(cyclopropyl)amino]-1-fluorocyclohexyl)methoxy}-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

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EXAMPLE 363A

4-((4'-fluorospiro[benzo[d][1,3]dioxole-2,1'-cyclohexane]-4'-yl)methoxy)-3-nitrobenzenesulfonamide

30

To a solution of EXAMPLE 350C (495 mg) in N,N-dimethylformamide (6 mL) was added NaH (65% in mineral oil, 320 mg). The mixture was stirred for 30 minutes, and then 4-fluoro-3-nitrobenzenesulfonamide (457 mg) was added. The mixture was stirred overnight. The mixture was poured over aqueous NH₄Cl and extracted with ethyl acetate (300 mL). The

combined organic layers were washed with water, brine and dried over Na₂SO₄. After filtration and evaporation of the solvent, the residue was loaded on a silica gel cartridge and was eluted with 30% ethyl acetate in hexane to provide the title compound.

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EXAMPLE 363B

4-((1-fluoro-4-oxocyclohexyl)methoxy)-3-nitrobenzenesulfonamide

To a solution of EXAMPLE 363A (860 mg) in ethanol (30 mL) was added concentrated HCl (10 mL) and the mixture was stirred at 100°C for 3 hours. The mixture was neutralized with solid Na₂CO₃ and extracted with dichloromethane (300 mL) and washed
10 with aqueous NaHCO₃, water, brine and dried over Na₂SO₄. Filtration and evaporation of the solvent gave the title compound.

EXAMPLE 363C

4-((4-((2-cyanoethyl)(cyclopropyl)amino)-1-fluorocyclohexyl)methoxy)-3-
15 nitrobenzenesulfonamide

To a solution of EXAMPLE 363B (200 mg) in dichloromethane (6 mL) was added 3-(cyclopropylamino)propanenitrile (64 mg) followed by sodium triacetoxyborohydride (184 mg). The mixture was stirred overnight. The reaction mixture was diluted with dichloromethane (400 mL) and washed with 2N aqueous NaOH, water, and brine. After
20 drying over Na₂SO₄, the mixture was filtered and evaporation of the solvent gave the title compound.

EXAMPLE 363D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-
25 ({4-[(2-cyanoethyl)(cyclopropyl)amino]-1-fluorocyclohexyl)methoxy)-3-nitrophenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 363C for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.66 (s, 1 H), 8.35 (s, 1 H), 8.02 (d, 2 H), 7.51 (m, 3 H), 7.40 (m, 1
30 H), 7.35 (d, 2 H), 7.04 (d, 2 H), 6.67 (dd, 1 H), 6.39 (d, 1 H), 6.20 (s, 1 H), 4.27 (d, 2 H), 3.13 (m, 4 H), 2.88 (m, 3 H), 2.67 (m, 4 H), 2.09 (m, 10 H), 1.49 (m, 9 H), 0.93 (s, 6 H), 0.45 (m, 4 H).

EXAMPLE 364

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

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EXAMPLE 364A

6-amino-5-nitropyridine-3-sulfonic acid

6-Aminopyridine-3-sulfonic acid (20 g) in concentrated H₂SO₄ (80 mL) was heated at 50°C until it was completely dissolved. To this solution was added fuming HNO₃ slowly over 20 minutes, so the internal temperature did not exceed 55 °C. After the addition was complete, the reaction mixture was heated at 50°C for 1 hour. After it was cooled to room temperature, it was poured into 150 g of ice. The mixture was stirred for another hour. The flask was cooled to 0°C, and was kept at 0°C for another 2 hours. The solid was collected by filtration, and 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 provide the title compound.

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EXAMPLE 364B

6-hydroxy-5-nitropyridine-3-sulfonic acid

EXAMPLE 364A (4.0 g) in aqueous 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 heated at reflux for 2 hours. Water was distilled off to give a dry residue. After the residue was cooled to room temperature, a solution of 1:1 ethano/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 provide the title compound.

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EXAMPLE 364C

6-chloro-5-nitropyridine-3-sulfonyl chloride

A mixture of EXAMPLE 364B (2.6 g), PCl₅ (5.91 g), and POCl₃ (10 mL) was heated at 120 °C for 4 hours. The initial suspension became a clear solution. The excess of POCl₃ 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

30

MgSO₄, filtered, and concentrated to give crude product that was used in the next step without further purification.

EXAMPLE 364D

5 6-chloro-5-nitropyridine-3-sulfonamide

EXAMPLE 364C 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
10 with additional ethyl acetate. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel using 5-50% ethyl acetate in hexanes to provide the title compound.

15 EXAMPLE 364E

5-nitro-6-((tetrahydro-2H-pyran-4-yl)methylamino)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 364D for 4-fluoro-3-nitrobenzenesulfonamide and (tetrahydro-2H-pyran-4-yl)methanamine for (4-fluorotetrahydro-2H-pyran-4-yl)methanamine in EXAMPLE 138D.

20

EXAMPLE 364F

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

25 The title compound was prepared by substituting EXAMPLE 364E for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.63 (s, 1H), 8.93 (s, 1H), 8.73 (d, 1H), 8.69 (d, 1H), 8.00 (d, 1H), 7.54 (d, 1H), 7.47-7.48 (m, 2H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.35 (dd, 1H), 6.22 (d, 1H), 3.83 (dd, 2H), 3.51 (t, 2H), 3.21-3.27 (m, 2H), 3.10 (s, 4H), 2.83 (s, 2H), 1.90-2.27 (m, 12H), 1.58 (dd, 2H), 1.39 (t, 30 2H), 1.18-1.28 (m, 2H), 0.88-0.93 (m, 8H).

EXAMPLE 365

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(2-oxaspiro[3.5]non-7-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

5

EXAMPLE 365A

7-(azidomethyl)-2-oxaspiro[3.5]nonane

To a 250 mL round-bottomed flask was EXAMPLE 351F (350 mg) in tetrahydrofuran (75.0 mL) to give a colorless solution. The solution was cooled to 0 °C, triphenylphosphine (2.94 g), diisopropyl azodicarboxylate (2.18 mL) and diphenyl phosphorazidate (2.32 mL) were added and the reaction was stirred for 30 minutes at room temperature. The mixture was concentrated and purified the residue by regular phase flash column chromatography (Analogix, 0-20% hexanes / ethyl acetate).

15

EXAMPLE 365B

2-oxaspiro[3.5]nonan-7-ylmethanamine

To a 50 mL round-bottomed flask was added 10% palladium on carbon (58.7 mg). The flask was flushed with N₂ and EXAMPLE 365A (400 mg) was added as a methanol solution (10.5 mL). The flask was then flushed several times with H₂ (via balloon) and heated to 45 °C for 2 hours. The reaction was cooled to room temperature, filtered through celite and the filtrate was concentrated by rotary evaporation. The residue was used in the next step without further purification.

20

EXAMPLE 365C

4-(2-oxaspiro[3.5]nonan-7-ylmethylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 365B for 1-(tetrahydropyran-4-yl)methanamine in EXAMPLE 1F.

25

EXAMPLE 365D

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(4-(2-oxaspiro[3.5]nonan-7-ylmethylamino)-3-nitrophenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzamide

30

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 365C for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300 MHz,

dimethylsulfoxide- d_6) δ 11.67 (s, 1 H) 11.25 - 11.49 (m, 1 H) 8.48 - 8.66 (m, 2 H) 8.03 (d, 1 H) 7.79 (dd, 1 H) 7.41 - 7.61 (m, 3 H) 7.27 - 7.40 (m, 2 H) 7.05 (t, 3 H) 6.67 (dd, 1 H) 6.39 (dd, 1 H) 6.18 (d, 1 H) 4.29 (s, 2 H) 4.19 (s, 2 H) 3.17 - 3.27 (m, 2 H) 2.99 - 3.14 (m, 4 H) 2.69 - 2.79 (m, 2 H) 2.09 - 2.28 (m, 6 H) 2.04 (d, 2 H) 1.95 (s, 2 H) 1.66 (d, 2 H) 1.49 - 1.61 (m, 1 H) 1.29 - 1.45 (m, 4 H) 0.93 - 1.05 (m, 2 H) 0.92 (s, 6 H).

EXAMPLE 366

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(4-
10 {[(4-cyano-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

EXAMPLE 366A

tert-butyl (4-cyano-4-methylcyclohexyl)methylcarbamate

To a cooled (-78°C) solution of tert-butyl (4-cyanocyclohexyl)methylcarbamate (500
15 mg) in tetrahydrofuran (10 mL) was added lithium diisopropylamide (2.0 mL, 2M in
heptane). The mixture was stirred at -78°C for 30 minutes before the addition of CH_3I (1 mL).
The mixture was then stirred and the temperature was allowed to warm to room temperature.
The reaction was quenched with aqueous NH_4Cl and the mixture was extracted with ethyl
acetate (300 mL) and washed with water, brine and dried over Na_2SO_4 . Filtration and
20 evaporation of the solvent and silica gel chromatography (40% ethyl acetate in hexane) of the
crude material gave the title compound.

EXAMPLE 366B

4-(aminomethyl)-1-methylcyclohexanecarbonitrile

To a solution of EXAMPLE 366A (480 mg) in dichloromethane (10 mL) was added
25 trifluoroacetic acid (10 mL). The mixture was stirred for 3 hours. The mixture was then
concentrated under vacuum and was used directly in the next reaction without further
purification.

30

EXAMPLE 366C

4-((4-cyano-4-methylcyclohexyl)methylamino)-3-nitrobenzenesulfonamide

To a solution of 4-fluoro-3-nitrobenzenesulfonamide (362 mg) in tetrahydrofuran (10
mL) was added EXAMPLE 366B (250 mg) and N,N-diisopropylethylamine (2 mL). The

mixture was stirred overnight. The mixture was diluted with ethyl acetate (300 mL) and washed with water, brine and dried over Na₂SO₄. Filtration and evaporation of the solvent gave the title compound.

5

EXAMPLE 366D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyano-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 366C for EXAMPLE 1F in EXAMPLE 1G. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.67 (s, 1 H), 11.37 (m, 1 H), 8.59 (m, 2 H), 8.04 (d, 1 H), 7.80 (d, 1 H), 7.51 (m, 3 H), 7.34 (d, 2 H), 7.10 (d, 1 H), 7.04 (d, 2 H), 6.68 (dd, 1 H), 6.39 (m, 1 H), 6.19 (s, 1 H), 3.07 (m, 4 H), 2.75 (m, 2 H), 2.17 (m, 7 H), 1.76 (m, 9 H), 1.32 (m, 9 H), 0.92 (s, 6 H).

15

EXAMPLE 367

{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)amino)methyl pivalate

This example was prepared by substituting chloromethyl pivalate for chloromethyl butyrate in EXAMPLE 368. ¹H NMR (400 MHz, dimethylsulfoxide-d₆) δ 11.72 (s, 1H), 8.43 (d, 1H), 8.22 (dd, 1H), 8.01 (d, 1H), 7.55 (m, 3H), 7.36 (m, 3H), 7.03 (d, 2H), 6.68 (dd, 1H), 6.41 (m, 1H), 6.17 (d, 1H), 5.83 (s, 2H), 4.40 (d, 2H), 3.78 (m, 2H), 3.59 (m, 2H), 3.08 (br m, 4H), 2.73 (br s, 2H), 2.18 (br m, 6H), 1.96 (s, 2H), 1.84 (m, 4H), 1.39 (m, 2H), 1.00 (s, 9H), 0.92 (s, 6H).

25

EXAMPLE 368

{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)amino)methyl butyrate

30

EXAMPLE 37E (500 mg) was dissolved in acetonitrile (3.7 mL) and chloromethyl butyrate (77 mg) and Hunig's base (73 mg) were added. The reaction was heated under reflux for one day. After cooling and dilution with dimethylsulfoxide (4 mL) the reaction was

purified by preparative HPLC using a 250 × 50 mm C18 column and eluting with 20-100% CH₃CN vs. 0.1% trifluoroacetic acid in water, giving the product as a trifluoroacetate salt. The trifluoroacetic acid salt was dissolved in dichloromethane (6 ml) and washed with 50% aqueous NaHCO₃. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated to provide the title compound. ¹H NMR (400 MHz, dimethylsulfoxide-*d*₆) δ 11.72 (s, 1H), 8.43 (d, 1H), 8.22 (dd, 1H), 8.01 (d, 1H), 7.55 (m, 3H), 7.36 (m, 3H), 7.03 (d, 2H), 6.68 (dd, 1H), 6.41 (m, 1H), 6.17 (d, 1H), 5.83 (s, 2H), 4.40 (d, 2H), 3.78 (m, 2H), 3.59 (m, 2H), 3.08 (br m, 4H), 2.73 (br s, 2H), 2.18 (m, 8H), 1.96 (s, 2H), 1.84 (m, 4H), 1.39 (m, 4H), 0.92 (s, 6H), 0.75 (t, 3H).

EXAMPLE 369

4-[4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl](²H₈)piperazin-1-yl]-*N*-([3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)benzamide

EXAMPLE 369A

methyl 4-[(2,2,3,3,5,5,6,6-²H₈)piperazin-1-yl]-2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)benzoate

Into a 40 mL vial were added EXAMPLE 3H (1.55 g) and piperazine-*d*₈ (2.040 g) in dimethylsulfoxide (13 mL). The solution was heated to 85°C for 2.5 hours, and was then allowed to cool to room temperature overnight. The mixture was transferred to a 120 mL flask and was cooled to 5-10 °C. Dichloromethane (30 mL) was added, then water (10 mL) was added via syringe over 5 minutes maintaining temp at no more than 15°C. The layers were separated and the organic layer was washed with water (4x 10-15 mL) until pH of aqueous layer was 8-9. The organic layer was filtered through Na₂SO₄ and rinsed with dichloromethane (5 mL), and concentrated to provide the title compound.

EXAMPLE 369B

methyl 4-[4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl](²H₈)piperazin-1-yl]-2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)benzoate

In a 100 mL round-bottomed flask, EXAMPLE 369A (3.4 g), EXAMPLE 290B (1.321 g) and dichloromethane (3 mL) were added to a 100 mL round bottom flask at room temperature. To a separate 50 mL 3 neck round bottom flask, sodium triacetoxyborohydride (1.330 g) and dichloromethane (12 mL) were added to give a slurry. After cooling the 50 mL

round bottom flask to 18-20 °C, the piperazine adduct/aldehyde solution was added via syringe over 5 minutes. The triacetoxyborohydride gradually dissolved to give a clear solution after ~5 minutes. After an additional 10 minutes, the solution became hazy. After 16 hours, the reaction was cooled to 5-10 °C. Saturated aqueous NaHCO₃ (12 mL) was added
5 over 5 minutes maintaining the temperature at no more than 10 °C. The layers were separated and the organic layer was washed with saturated aqueous NaHCO₃, and 10% NaCl (12 mL), and then filtered through Na₂SO₄ and rinsed with dichloromethane (4 mL). The solution was concentrated on a rotovap, and chase concentrated with methanol (40 mL). The resulting solution was cooled to 5-10 °C, and the product precipitated. The solution was
10 mixed at room temperature for 30 minutes, then filtered and rinsed with methanol (5 mL), and the product was air dried.

EXAMPLE 369C

4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}(²H₈)piperazin-1-yl]-2-
15 (1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)benzoic acid

The title compound was prepared by substituting EXAMPLE 369B for EXAMPLE 15G in EXAMPLE 15H.

EXAMPLE 369D

20 4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}(²H₈)piperazin-1-yl]-*N*-({3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)benzamide

To a mixture of EXAMPLE 369C (2.0g), EXAMPLE 1F (1.1g) and *N,N*-dimethylpyridin-4-amine (0.7 g) in dichloromethane (20 mL) was added 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (0.8 g). The reaction mixture was
25 stirred at room temperature overnight. The reaction was quenched with *N,N*-dimethylethane-1,2-diamine (0.6g) and stirred at room temperature for 3 hours. The mixture was extracted with 20% aqueous acetic acid and washed with 5% aqueous NaCl. Methanol (2 mL) and ethyl acetate (18 mL) were added and the precipitate was collected by filtration to provide the
30 title compound. ¹H NMR (400 MHz, dimethylsulfoxide -*d*₆) δ 11.71 (s, 1H), 11.37 (s, br, 1H), 8.60 (t, 1H), 8.55 (d, 1H), 8.04 (d, 1H), 7.80 (dd, 1H), 7.47 - 7.54 (m, 3H), 7.31 - 7.34 (m, 2H), 7.09 (d, 1H), 7.01 - 7.03 (m, 2H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.83

(dd, 2H), 3.21 - 3.30 (m, 4H), 3.00 - 3.10 (s, 4H), 2.75 (s, 2H), 2.05 - 2.24 (m, 6H), 1.95 (s, 2H), 1.80 - 1.93 (m, 1H), 1.55 - 1.64 (m, 2H), 1.37 (t, 2H), 1.18 - 1.31 (m, 2H), 0.90 (s, 6H).

EXAMPLE 370

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

EXAMPLE 370A

10 5-amino-6-((tetrahydro-2H-pyran-4-yl)methylamino)pyridine-3-sulfonamide

A mixture of EXAMPLE 364E (0.16 g) and 5% palladium on carbon (0.025 g) in ethanol (5 mL) was treated with a balloon of hydrogen. The reaction mixture was stirred overnight. The solid was filtered off. The filtrate was concentrated. The residue was purified by flash chromatography on silica gel to give the title compound.

15

EXAMPLE 370B

3-((tetrahydro-2H-pyran-4-yl)methyl)-3H-[1,2,3]triazolo[4,5-b]pyridine-6-sulfonamide

EXAMPLE 370A (0.085 g) in water (10 mL) was treated with concentrated H₂SO₄ (0.5 mL). The solution was cooled to 0 °C. To this solution was added NaNO₂ (0.023 g) in
20 water (1 mL) dropwise. The solution was stirred for 1 hour at 0 °C. The reaction mixture was poured into saturated NaHCO₃ solution, and extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated to give the title compound.

25

EXAMPLE 370C

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(3-((tetrahydro-2H-pyran-4-yl)methyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-6-ylsulfonyl)benzamide

This example was prepared by substituting EXAMPLE 370B for EXAMPLE
30 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.60 (s, 1H), 9.11 (s, 1H), 8.92 (d, 1H), 7.96 (d, 1H), 7.55 (d, 1H), 7.45-7.46 (m, 1H), 7.42 (s, 1H), 7.36 (d, 2H), 7.05 (d, 2H), 6.66 (dd, 1H), 6.32 (s, 1H), 6.22 (s, 1H), 4.63 (d, 2H), 3.80 (dd, 2H), 3.21-3.30

(m, 2H), 3.16 (s, 4H), 2.83 (s, 2H), 2.19-2.29 (m, 6H), 1.97 (s, 2H), 1.33-1.41 (m, 6H), 0.93 (s, 2H).

EXAMPLE 371

5 4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(6-
{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-5-nitropyridin-3-yl)sulfonyl]-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 371A

10 6-((trans-4-hydroxy-4-methylcyclohexyl)methylamino)-5-nitropyridine-3-sulfonamide

This example was prepared by substituting EXAMPLE 364D for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 376B for EXAMPLE 138C in EXAMPLE 138D. The title compound was 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%
15 acetonitrile in water with 0.1% TFA.

EXAMPLE 371B

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(6-
{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-5-nitropyridin-3-yl)sulfonyl]-2-(1H-
20 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 371A for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.63 (s, 1H), 11.53 - 10.99 (m, 1H), 8.91 (s, 1H), 8.71 (dd, 2H), 8.01 (d, 1H), 7.61 - 7.44 (m, 3H), 7.44 - 7.28 (m, 2H), 7.12 - 6.97 (m, 2H), 6.76 - 6.61 (m, 1H), 6.36 (dd, 1H), 6.21 (d, 1H), 3.92 (s, 1H), 3.48
25 (t, 2H), 3.10 (s, 4H), 2.83 (s, 2H), 2.24 (dd, 6H), 1.96 (s, 2H), 1.37 (ddd, 11H), 1.07 (s, 3H), 0.93 (s, 6H).

EXAMPLE 372

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(5-
30 cyano-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 372A

ethyl 4-fluoro-1-(oxetan-3-yl)piperidine-4-carboxylate

To 1-*tert*-butyl 4-ethyl 4-fluoropiperidine-1,4-dicarboxylate (1.00 g) was added HCl (4.0M in dioxane, 4.54 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 (1.155 g) and oxetan-3-one (0.262 g) and stirred overnight.

5 The reaction was quenched with saturated NaHCO₃ 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/minute) gave the title compound.

10 EXAMPLE 372B

(4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methanol

To a solution of EXAMPLE 372A (0.59 g) in tetrahydrofuran (5 mL) was added lithium aluminum hydride (1.80 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
15 addition of 0.6 mL of water followed by 0.2 ml of 2N aqueous NaOH. The reaction was filtered through diatomaceous earth and rinsed with ethyl acetate (50 mL). The organics were concentrated and loaded onto silica gel (Reveleris 40 g) and eluted using a gradient of 0.75% to 7.5% methanol/dichloromethane over 30 minute (flow = 40 mL/minutes) to give the title compound.

20 EXAMPLE 372C

5-bromo-6-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)pyridine-3-sulfonamide

This example was prepared by substituting EXAMPLE 372B for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 36A for 4-fluoro-3-nitrobenzenesulfonamide in
EXAMPLE 24A.

25 EXAMPLE 372D

5-cyano-6-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)pyridine-3-sulfonamide

This example was prepared by substituting EXAMPLE 372C for EXAMPLE 36B in
EXAMPLE 36C.

30 EXAMPLE 372E

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-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)benzamide

The title compound was prepared by substituting EXAMPLE 372D for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (300 MHz, dimethylsulfoxide-d₆) δ 11.58 (s, 1H), 8.71 (s, 1H), 8.52 (s, 1H), 7.96 (d, 1H), 7.57 (d, 1H), 7.48 - 7.30 (m, 4H), 7.06 (d, 2H), 6.68 (d, 1H), 6.37 - 6.22 (m, 2H), 4.65 - 4.40 (m, 6H), 3.58 (s, 1H), 3.12 (s, 6H), 2.84 - 2.59 (m, 4H), 2.17 (s, 6H), 1.96 (d, 6H), 1.41 (s, 2H), 0.93 (s, 6H).

EXAMPLE 373

N-(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)morpholine-4-carboxamide

EXAMPLE 373A

morpholine-4-carboxamide

A solution of morpholine-4-carbonyl chloride (2.0 g) in methanol (10 mL) and 7 N NH₃ in methanol (5 mL) was stirred at 45 °C overnight. The mixture was concentrated to give a solid, which was dried under vacuum.

EXAMPLE 373B

N-(2-nitro-4-sulfamoylphenyl)morpholine-4-carboxamide

This example was prepared by substituting EXAMPLE 373A for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

EXAMPLE 373C

N-(4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenyl)morpholine-4-carboxamide

This example was prepared by substituting EXAMPLE 373B for EXAMPLE 130C in EXAMPLE 130D. ¹H NMR (500MHz, pyridine-d₅) δ 13.02 (s, 1H), 10.41 (s, 1H), 9.27 (d, 1H), 8.81 (d, 1H), 8.50 (dd, 1H), 8.40 (d, 1H), 8.09 (d, 1H), 7.65 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.76 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.67 (m, 4H), 3.58 (m, 4H), 3.07 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

EXAMPLE 374

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-
({[4-(methoxymethyl)cyclohexyl]methyl}amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

5

EXAMPLE 374A

(4,4-diethoxycyclohexyl)methanol

Ethyl 4, 4-diethoxycyclohexanecarboxylate (6.67 g) synthesized according to a
literature procedure (*European Journal of Organic Chemistry*, 2008, 5, 895) in
10 tetrahydrofuran (60 mL) was treated with 2 M lithium aluminum hydride in tetrahydrofuran
(14.5 mL) at 0°C for 1 hour. Water (3 mL) was slowly added to quench the reaction. The
precipitates were filtered off and washed with ethyl acetate. The filtrate was dried over
Na₂SO₄, filtered, and concentrated to provide the title compound.

15

EXAMPLE 374B

1,1-diethoxy-4-(methoxymethyl)cyclohexane

EXAMPLE 374A (665 mg) in tetrahydrofuran (20 mL) was treated with NaH (394
mg) for 30 minutes and then CH₃I (0.267 mL) was slowly added. The resulting mixture was
stirred overnight and the reaction was quenched with a few drops of water. The mixture was
20 concentrated and the residue was suspended in water and extracted with dichloromethane.
The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was
purified by flash chromatography, and was eluted with 0-15% ethyl acetate in
dichloromethane to provide the title compound.

25

EXAMPLE 374C

4-(methoxymethyl)cyclohexanone

EXAMPLE 374B (2.2 g) in a mixture of water (3 mL) and acetic acid (12 mL) was
heated at 65°C for 2 hours. The reaction mixture was concentrated. The residue was mixed
with water and saturated aqueous NaHCO₃ and extracted with dichloromethane. The
30 dichloromethane layer was dried over Na₂SO₄, filtered, and concentrated to provide the title
compound.

EXAMPLE 374D

4-(methoxymethyl)cyclohexanecarbonitrile

To a cold (-10°C) solution of EXAMPLE 374C (1.18 g) and toluenesulfonylmethyl isocyanide (2.268 g) in dimethoxyethane (3 mL) and absolute ethanol (0.1 mL) was added (in
5 small portions) potassium tert-butoxide (2.235 g). The reaction mixture was continued to stir at <5°C for 30 minutes, warmed to room temperature, heated at 35°C for 30 minutes and then at room temperature for 2 hours. The reaction mixture was concentrated and the residue was dissolved in water-brine, and extracted with dichloromethane. The dichloromethane layer was purified by flash chromatography, and was eluted with 5% ethyl acetate in
10 dichloromethane to provide the title compound.

EXAMPLE 374E

(4-(methoxymethyl)cyclohexyl)methanamine

To a solution of EXAMPLE 374D (460 mg) in tetrahydrofuran (15 mL) was added
15 2M lithium aluminum hydride in tetrahydrofuran (2.252 mL) slowly. The reaction mixture was stirred at room temperature for 1 hour, refluxed for 1 hour and cooled. 2 ml of 2M aqueous NaOH and water (5 mL) was added. The solid was filtered off and washed with ether. The filtrate was concentrated. The residue was mixed with dichloromethane (50 mL) and the resulting mixture was dried over Na₂SO₄ and concentrated to provide the title
20 compound.

EXAMPLE 374F

4-((4-(methoxymethyl)cyclohexyl)methylamino)-3-nitrobenzenesulfonamide

EXAMPLE 374E (450 mg) and 4-fluoro-3-nitrobenzenesulfonamide (693 mg) in
25 tetrahydrofuran (10 mL) were stirred overnight. The reaction mixture was concentrated and the residue was suspended in a mixture of CH₃CN, methanol and water. The precipitates were collected, washed with water and dried to give the title compound.

EXAMPLE 374G

30 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(4-((4-(methoxymethyl)cyclohexyl)methylamino)-3-nitrophenylsulfonyl)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 374F in place of EXAMPLE 11B. ¹H NMR (400 MHz, dimethylsulfoxide-d₆) δ 11.69 (s,

1H), 11.40 (s, 1H), 8.53 - 8.61 (m, 2H), 8.04 (d, 1H), 7.77 - 7.82 (m, 1H), 7.47 - 7.55 (m, 3H), 7.34 (d, 2H), 7.02 - 7.09 (m, 3H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.18 - 3.27 (m, 5H), 3.04 - 3.14 (m, 5H), 2.75 (s, 2H), 2.11 - 2.24 (m, 6H), 1.95 (s, 2H), 1.69 - 1.84 (m, 3H), 1.33 - 1.63 (m, 7H), 0.84 - 1.05 (m, 9H).

5

EXAMPLE 375

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

10

EXAMPLE 375A

methyl 1-(thiazol-2-yl)piperidine-4-carboxylate

A mixture of methyl piperidine-4-carboxylate (2.045 g), 2-bromothiazole (1.64 g), and Cs₂CO₃ (5.86 g) in dimethylformamide (15 mL) was heated at 100 °C overnight. After it 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 MgSO₄, filtered, and concentrated. The residue was purified by flash chromatography on silica gel to give the title compound.

20

EXAMPLE 375B

(1-(thiazol-2-yl)piperidin-4-yl)methanol

This example was prepared by substituting EXAMPLE 375A for EXAMPLE 339A in EXAMPLE 339B.

25

EXAMPLE 375C

5-chloro-6-((1-(thiazol-2-yl)piperidin-4-yl)methoxy)pyridine-3-sulfonamide

This example was prepared by substituting EXAMPLE 375B for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 40A for EXAMPLE 36A in EXAMPLE 36B.

30

EXAMPLE 375D

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(5-chloro-6-((1-(thiazol-2-yl)piperidin-4-yl)methoxy)pyridin-3-ylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzamide

This example was prepared by substituting EXAMPLE 375C for EXAMPLE 11B in EXAMPLE 11D. ¹H NMR (500MHz, dimethylsulfoxide-d₆) δ 11.65 (s, 1H), 8.49 (s, 1H), 8.17 (s, 1H), 8.01 (d, 1H), 7.54 (d, 1H), 7.48-7.49 (m, 2H), 7.35 (d, 2H), 7.14 (d, 1H), 7.05 (d, 2H), 6.80 (d, 1H), 6.67 (dd, 1H), 6.38 (dd, 1H), 6.21 (d, 1H), 4.28 (d, 2H), 3.92 (d, 2H), 2.98-3.10 (m, 6H), 2.86 (s, 2H), 2.30 (m, 4H), 2.03-2.15 (m, 3H), 1.96 (s, 2H), 1.96 (s, 2H), 1.82-1.86 (m, 2H), 1.33-1.44 (m, 4H), 0.93 (s, 6H).

EXAMPLE 376

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 376A

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), washed with ammonium chloride (25 mL), washed with 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 376B

4-(aminomethyl)-1-methylcyclohexanol

To a solution of EXAMPLE 376A (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 2h added additional trifluoroacetic acid (0.5 mL). After an additional 4 h the reaction 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 trifluoroacetic acid salt and a mixture of cis and trans isomers.

EXAMPLE 376C

6-((cis-4-hydroxy-4-methylcyclohexyl)methylamino)-5-nitropyridine-3-sulfonamide

This example was prepared by substituting EXAMPLE 364D for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 376B for (4-fluorotetrahydro-2H-pyran-4-yl)methanamine in EXAMPLE 138D. The title compound was isolated by reverse phase Gilson Prep HPLC system with a Phenomenex prep column (Luna, 5 μ , C18(2), 250X21.20 mm, 5 $\text{\AA}$) eluting with 20-80% acetonitrile in water with 0.1% TFA.

EXAMPLE 376D

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

This example was prepared by substituting EXAMPLE 376C for EXAMPLE 11B in EXAMPLE 11D. ^1H NMR (500MHz, dimethylsulfoxide- d_6) δ 11.64 (s, 1H), 8.91 (s, 1H), 8.72 (d, 1H), 8.70 (d, 1H), 8.01 (d, 1H), 7.47-7.54 (m, 3H), 7.35 (d, 2H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.36 (dd, 1H), 6.21 (d, 1H), 3.93 (s, 1H), 3.48 (t, 2H), 3.10 (s, 4H), 2.83 (s, 2H), 2.15-2.33 (m, 6H), 1.96 (s, 1H), 1.34-1.59 (m, 9H), 1.17-1.24 (m, 2H), 1.07 (s, 2H), 0.92 (s, 6H).

EXAMPLE 377

4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 378D for EXAMPLE 1E and EXAMPLE 337M for EXAMPLE 1F in EXAMPLE 1G. ^1H NMR (500 MHz, pyridine- d_5) δ 13.07 (s, 1H), 9.31 (d, 1H), 8.68 (t, 1H), 8.44 (d, 1H), 8.37 (dd, 1H), 8.10 (d, 1H), 7.68 (m, 1H), 7.66 (d, 1H), 7.41 (m, 2H), 7.09 (m, 2H), 6.92 (d, 1H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.50 (dd, 1H), 3.20 (m, 5H), 3.06 (t, 4H), 2.77 (m, 2H), 2.57 (d, 1H), 2.49 (m, 1H), 2.17 (m, 6H), 1.86 (m, 5H), 1.69 (m, 4H), 1.40 (s, 3H), 1.23 (m, 5H).

EXAMPLE 378

4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-
N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide

5

EXAMPLE 378A

2-chloro-5-methoxy-5-methylcyclohex-1-enecarbaldehyde

Dimethylformamide (1.298 mL) in dichloromethane (2.0 mL) at -10 °C was treated dropwise with POCl₃ (1.426 mL) to give a colorless solution. The mixture was stirred 5 minutes and then warmed to room temperature and stirred 30 minutes. The solution was
10 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% aqueous sodium acetate solution. After the ice 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 NaHCO₃
15 solution and brine, dried (MgSO₄), filtered and concentrated. The concentrate was chromatographed on silica gel with 0 to 5% ethyl acetate in hexanes as the eluent.

EXAMPLE 378B

2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-enecarbaldehyde

20 EXAMPLE 378A (1.55 g), 4-chlorophenylboronic acid (1.542 g), PdOAc₂ (0.055 g), K₂CO₃ (2.84 g) and tetrabutylammonium 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
25 layer was washed with brine, dried (MgSO₄), filtered through a plug of celite, concentrated and chromatographed on silica gel with 5 to 20% ethyl acetate in hexanes as the eluent.

EXAMPLE 378C

30 methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-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 378B for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 15F for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A except that a small amount of DMSO was added to the reaction mixture.

EXAMPLE 378D

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

5 The title compound was prepared by substituting EXAMPLE 378C for EXAMPLE 15G in EXAMPLE 15H.

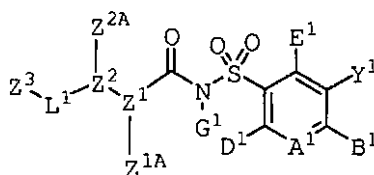
EXAMPLE 378E

10 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-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 378D for EXAMPLE 1E in EXAMPLE 1G. ¹H NMR (500 MHz, pyridine-d₅) δ 13.07 (s, 1H), 9.31 (d, 1H), 8.68 (t, 1H), 8.43 (d, 1H), 8.37 (dd, 1H), 8.09 (d, 1H), 7.68 (m, 1H), 7.66 (d, 1H), 7.41 (m, 2H), 7.09 (m, 2H), 6.90 (d, 1H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.50 (dd, 1H), 3.97 (dd, 2H), 3.30 (td, 2H), 3.21 (s, 3H), 3.15 (m, 2H), 3.06 (t, 4H), 2.77 (m, 2H), 2.57 (d, 1H), 2.50 (m, 1H), 2.16 (m, 6H), 1.81 (m, 2H), 1.63 (m, 1H), 1.57 (dd, 2H), 1.32 (m, 2H), 1.21 (s, 3H).

WHAT IS CLAIMED IS:

1. A compound having Formula (I)



5

(I),

or a therapeutically acceptable salt thereof, wherein

A¹ is N or C(A²);

- A² is H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹,
 N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹,
 10 NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹,
 NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹,
 NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH,
 C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂,
 NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃,
 15 OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR^{1A};

- B¹ is H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹,
 N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹,
 NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹,
 NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹,
 20 NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH,
 C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂,
 NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃,
 OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR^{1A};

- D¹ is H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹,
 25 N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹,
 NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹,
 NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹,
 NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH,
 C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂,
 30 NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃,
 OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR^{1A};

- E^1 is H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$, $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, 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} , SO_2R^{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
- E^1 and Y^1 , together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and
- A^2 , B^1 , and D^1 are independently selected H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$, $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 , $C(O)OH$, $C(O)NH_2$ or $C(O)OR^{1A}$; or
- Y^1 and B^1 , together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and
- A^2 , D^1 , and E^1 are independently selected H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$, $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I,

CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR^{1A}; or

A² and B¹, together with the atoms to which they are attached, are benzene, naphthylene, heteroarene cycloalkane, cycloalkene, heterocycloalkane or

5 heterocycloalkene; and

D¹, E¹, and Y¹ are independently selected H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NH₂SO₂R¹, NR¹SO₂R¹, NH₂SO₂NHR¹, NH₂SO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NH₂SO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NH₂SO₂NHR¹, NH₂SO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR^{1A}; or

15 A² and D¹, together with the atoms to which they are attached, are benzene, naphthalene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

B¹, E¹, and Y¹ are independently selected H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NH₂SO₂R¹, NR¹SO₂R¹, NH₂SO₂NHR¹, NH₂SO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NH₂SO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NH₂SO₂NHR¹, NH₂SO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR^{1A};

G¹ is H, or C(O)OR;

R is alkyl;

R¹ is R², R³, R⁴ or R⁵;

30 R^{1A} is cycloalkyl, cycloalkenyl or cycloalkynyl;

R² is phenyl, which is unfused or fused with R^{2A}; R^{2A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R³ is heteroaryl, which is unfused or fused with R^{3A}; R^{3A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

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

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

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} ;

15 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 R^{8A} ; R^{8A} is benzene, heteroarene,
 20 cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

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

R^{10} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{10A} ; R^{10A} is benzene, heteroarene, cycloalkane,
 25 cycloalkene, heterocycloalkane or heterocycloalkene;

R^{11} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{12} , OR^{12} , SR^{12} , $S(O)R^{12}$, SO_2R^{12} , $C(O)R^{12}$, $CO(O)R^{12}$, $OC(O)R^{12}$, $OC(O)OR^{12}$, NH_2 , NHR^{12} , $N(R^{12})_2$, $NHC(O)R^{12}$, $NR^{12}C(O)R^{12}$, $NHS(O)_2R^{12}$, $NR^{12}S(O)_2R^{12}$, $NHC(O)OR^{12}$, $NR^{12}C(O)OR^{12}$,
 30 $NHC(O)NH_2$, $NHC(O)NHR^{12}$, $NHC(O)N(R^{12})_2$, $NR^{12}C(O)NHR^{12}$, $NR^{12}C(O)N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, $C(O)NHOH$, $C(O)NHOR^{12}$, $C(O)NHSO_2R^{12}$, $C(O)NR^{12}SO_2R^{12}$, SO_2NH_2 , SO_2NHR^{12} , $SO_2N(R^{12})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{12}$, $C(N)N(R^{12})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br or I ;

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

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

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

R^{15} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene, each of which is unfused or fused with R^{15A} ; R^{15A} is benzene, heteroarene, 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 R^{18A} ; R^{18A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

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

R^{20} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl each of which is unfused or fused with R^{20A} ; R^{20A} is benzene, heteroarene, 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 of independently selected R^{22} , OR^{22} , SR^{22} , $S(O)R^{22}$, SO_2R^{22} , $C(O)R^{22}$, $CO(O)R^{22}$, $OC(O)R^{22}$, $OC(O)OR^{22}$, NH_2 , NHR^{22} , $N(R^{22})_2$, $NHC(O)R^{22}$, $NR^{22}C(O)R^{22}$, $NHS(O)_2R^{22}$, $NR^{22}S(O)_2R^{22}$, $NHC(O)OR^{22}$, $NR^{22}C(O)OR^{22}$, $NHC(O)NH_2$, $NHC(O)NHR^{22}$, $NHC(O)N(R^{22})_2$, $NR^{22}C(O)NHR^{22}$, $NR^{22}C(O)N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, $C(O)NHOH$, $C(O)NHOR^{22}$, $C(O)NHSO_2R^{22}$, $C(O)NR^{22}SO_2R^{22}$, SO_2NH_2 , SO_2NHR^{22} , $SO_2N(R^{22})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{22}$, $C(N)N(R^{22})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br or I ;

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

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

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

R^{25} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{25A} ; R^{25A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

- Z^1 is R^{26} or R^{27} ;
 Z^2 is R^{28} , R^{29} or R^{30} ;
 Z^{1A} and Z^{2A} are both absent or are taken together to form CH_2 , CH_2CH_2 or Z^{12A} ;
5 Z^{12A} is C_2 - C_6 -alkylene having one or two CH_2 moieties replaced by NH , $N(CH_3)$, S , $S(O)$ or SO_2 ;
 L^1 is a R^{37} , OR^{37} , SR^{37} , $S(O)R^{37}$, SO_2R^{37} , $C(O)R^{37}$, $CO(O)R^{37}$, $OC(O)R^{37}$, $OC(O)OR^{37}$, NHR^{37} , $C(O)NH$, $C(O)NR^{37}$, $C(O)NHOR^{37}$, $C(O)NHSO_2R^{37}$, SO_2NH , SO_2NHR^{37} , $C(N)NH$, $C(N)NHR^{37}$;
10 R^{26} is phenylene, which is unfused or fused with R^{26A} ; R^{26A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
 R^{27} is heteroarylene, which is unfused or fused with R^{27A} ; R^{27A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
 R^{28} is phenylene, which is unfused or fused with R^{28A} ; R^{28A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
15 R^{29} is heteroarylene, which is unfused or fused with R^{29A} ; R^{29A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
 R^{30} is cycloalkylene, cycloalkenylene, heterocycloalkylene or heterocycloalkenylene, each of which is unfused or fused with R^{30A} ; R^{30A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
20 R^{37} is a bond or R^{37A} ;
 R^{37A} is alkylene, alkenylene, or alkynylene, each of which is unsubstituted or substituted with one or two or three independently selected R^{37B} , OR^{37B} , SR^{37B} , $S(O)R^{37B}$, SO_2R^{37B} , $C(O)R^{37B}$, $CO(O)R^{37B}$, $OC(O)R^{37B}$, $OC(O)OR^{37B}$, NH_2 , NHR^{37B} ,
25 $N(R^{37B})_2$, $NHC(O)R^{37B}$, $NR^{37B}C(O)R^{37B}$, $NHS(O)_2R^{37B}$, $NR^{37B}S(O)_2R^{37B}$, $NHC(O)OR^{37B}$, $NR^{37B}C(O)OR^{37B}$, $NHC(O)NH_2$, $NHC(O)NHR^{37B}$, $NHC(O)N(R^{37B})_2$, $NR^{37B}C(O)NHR^{37B}$, $NR^{37B}C(O)N(R^{37B})_2$, $C(O)NH_2$, $C(O)NHR^{37B}$, $C(O)N(R^{37B})_2$, $C(O)NHOH$, $C(O)NHOR^{37B}$, $C(O)NHSO_2R^{37B}$, $C(O)NR^{37B}SO_2R^{37B}$, SO_2NH_2 , SO_2NHR^{37B} , $SO_2N(R^{37B})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{37B}$, $C(N)N(R^{37B})_2$,
30 $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br and I substituents;
 R^{37B} is alkyl, alkenyl, alkynyl, or R^{37C} ;
 R^{37C} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

Z^3 is R^{38} , R^{39} or R^{40} ;

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

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

R^{40} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{40A} ; R^{40A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein the moieties represented by R^{26} and R^{27} are substituted (i.e., if Z^{1A} and Z^{2A} are absent) or further substituted (i.e., if Z^{1A} and Z^{2A} are present) with R^{41} , OR^{41} , SR^{41} , $S(O)R^{41}$, SO_2R^{41} , $C(O)R^{41}$, $CO(O)R^{41}$, $OC(O)R^{41}$, $OC(O)OR^{41}$, NHR^{41} , $N(R^{41})_2$, $NHC(O)R^{41}$, $NR^{41}C(O)R^{41}$, $NHS(O)_2R^{41}$, $NR^{41}S(O)_2R^{41}$, $NHC(O)OR^{41}$, $NR^{41}C(O)OR^{41}$, $NHC(O)NHR^{41}$, $NHC(O)N(R^{41})_2$, $NR^{41}C(O)NHR^{41}$, $NR^{41}C(O)N(R^{41})_2$, $C(O)NHR^{41}$, $C(O)N(R^{41})_2$, $C(O)NHOR^{41}$, $C(O)NHSO_2R^{41}$, $C(O)NR^{41}SO_2R^{41}$, SO_2NHR^{41} , $SO_2N(R^{41})_2$, $C(N)NHR^{41}$, or $C(N)N(R^{41})_2$;

R^{41} is heteroaryl, which is fused with R^{43A} ; R^{43A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; which is unfused or fused with benzene, heteroarene or R^{43B} ; R^{43B} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein the cyclic moieties represented by E^1 and Y^1 together, Y^1 and B^1 together, A^2 and B^1 together, A^2 and D^1 together, R^{1A} , R^2 , R^{2A} , R^3 , R^{3A} , R^4 , R^{4A} , R^6 , R^{6C} , R^8 , R^{8A} , R^9 , R^{9A} , 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^{26A} , R^{27} , R^{27A} , R^{28} , R^{28A} , R^{29} , R^{29A} , R^{30} , R^{30A} , R^{37B} , R^{38} , R^{38A} , R^{39} , R^{39A} , R^{40} , and R^{40A} are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five of independently selected R^{57A} , R^{57} , OR^{57} , SR^{57} , $S(O)R^{57}$, SO_2R^{57} , $C(O)R^{57}$, $CO(O)R^{57}$, $OC(O)R^{57}$, $OC(O)OR^{57}$, NH_2 , NHR^{57} , $N(R^{57})_2$, $NHC(O)R^{57}$, $NR^{57}C(O)R^{57}$, $NHS(O)_2R^{57}$, $NR^{57}S(O)_2R^{57}$, $NHC(O)OR^{57}$, $NR^{57}C(O)OR^{57}$, $NHC(O)NH_2$, $NHC(O)NHR^{57}$, $NHC(O)N(R^{57})_2$, $NR^{57}C(O)NHR^{57}$, $NR^{57}C(O)N(R^{57})_2$, $C(O)NH_2$, $C(O)NHR^{57}$, $C(O)N(R^{57})_2$, $C(O)NHOH$, $C(O)NHOR^{57}$, $C(O)NHSO_2R^{57}$, $C(O)NR^{57}SO_2R^{57}$, SO_2NH_2 , SO_2NHR^{57} , $SO_2N(R^{57})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{57}$, $C(N)N(R^{57})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br or I ;

R^{57A} is spiroalkyl, or spiroheteroalkyl;

R^{57} is R^{58} , R^{59} , R^{60} or R^{61} ;

R^{58} is phenyl, which is unfused or fused with R^{58A} ; R^{58A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{59} is heteroaryl, which is unfused or fused with R^{59A} ; R^{59A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{60} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{60A} ; R^{60A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{61} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{62} , OR^{62} , SR^{62} , $S(O)R^{62}$, SO_2R^{62} , $C(O)R^{62}$, $CO(O)R^{62}$, $OC(O)R^{62}$, $OC(O)OR^{62}$, NH_2 , NHR^{62} , $N(R^{62})_2$, $NHC(O)R^{62}$, $NR^{62}C(O)R^{62}$, $NHS(O)_2R^{62}$, $NR^{62}S(O)_2R^{62}$, $NHC(O)OR^{62}$, $NR^{62}C(O)OR^{62}$, $NHC(O)NH_2$, $NHC(O)NHR^{62}$, $NHC(O)N(R^{62})_2$, $NR^{62}C(O)NHR^{62}$, $NR^{62}C(O)N(R^{62})_2$, $C(O)NH_2$, $C(O)NHR^{62}$, $C(O)N(R^{62})_2$, $C(O)NHOH$, $C(O)NHOR^{62}$, $C(O)NHSO_2R^{62}$, $C(O)NR^{62}SO_2R^{62}$, SO_2NH_2 , SO_2NHR^{62} , $SO_2N(R^{62})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{62}$, $C(N)N(R^{62})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br or I ;

R^{62} is R^{63} , R^{64} , R^{65} or R^{66} ;

R^{63} is phenyl, which is unfused or fused with R^{63A} ; R^{63A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{64} is heteroaryl, which is unfused or fused with R^{64A} ; R^{64A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{65} is cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, each of which is unfused or fused with R^{65A} ; R^{65A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{66} is alkyl, alkenyl or alkenyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{67} , OR^{67} , SR^{67} , $S(O)R^{67}$, SO_2R^{67} , $C(O)R^{67}$, $CO(O)R^{67}$, $OC(O)R^{67}$, $OC(O)OR^{67}$, NH_2 , NHR^{67} , $N(R^{67})_2$, $NHC(O)R^{67}$, $NR^{67}C(O)R^{67}$, $NHS(O)_2R^{67}$, $NR^{67}S(O)_2R^{67}$, $NHC(O)OR^{67}$, $NR^{67}C(O)OR^{67}$, $NHC(O)NH_2$, $NHC(O)NHR^{67}$, $NHC(O)N(R^{67})_2$, $NR^{67}C(O)NHR^{67}$, $NR^{67}C(O)N(R^{67})_2$, $C(O)NH_2$, $C(O)NHR^{67}$, $C(O)N(R^{67})_2$, $C(O)NHOH$, $C(O)NHOR^{67}$, $C(O)NHSO_2R^{67}$, $C(O)NR^{67}SO_2R^{67}$, SO_2NH_2 , SO_2NHR^{67} , $SO_2N(R^{67})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{67}$, $C(N)N(R^{67})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br or I substituents;

R^{67} is alkyl, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl;

wherein the cyclic moieties represented by R^{57A} , R^{58} , R^{59} , R^{60} , R^{63} , R^{64} , R^{65} , and R^{67} are unsubstituted or substituted with one or two or three or four of independently selected R^{68} , OR^{68} , SR^{68} , $S(O)R^{68}$, SO_2R^{68} , $C(O)R^{68}$, $CO(O)R^{68}$, $OC(O)R^{68}$, $OC(O)OR^{68}$, NH_2 , NHR^{68} , $N(R^{68})_2$, $NHC(O)R^{68}$, $NR^{68}C(O)R^{68}$, $NHS(O)_2R^{68}$, $NR^{68}S(O)_2R^{68}$, $NHC(O)OR^{68}$, $NR^{68}C(O)OR^{68}$, $NHC(O)NH_2$, $NHC(O)NHR^{68}$, $NHC(O)N(R^{68})_2$, $NR^{68}C(O)NHR^{68}$, $NR^{68}C(O)N(R^{68})_2$, $C(O)NH_2$, $C(O)NHR^{68}$, $C(O)N(R^{68})_2$, $C(O)NHOH$, $C(O)NHOR^{68}$, $C(O)NHSO_2R^{68}$, $C(O)NR^{68}SO_2R^{68}$, SO_2NH_2 , SO_2NHR^{68} , $SO_2N(R^{68})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{68}$, $C(N)N(R^{68})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br or I ;

R^{68} is R^{69} , R^{70} , R^{71} or R^{72} ;

R^{69} is phenyl, which is unfused or fused with R^{69A} ; R^{69A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{70} is heteroaryl, which is unfused or fused with R^{70A} ; R^{70A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{71} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{71A} ; R^{71A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

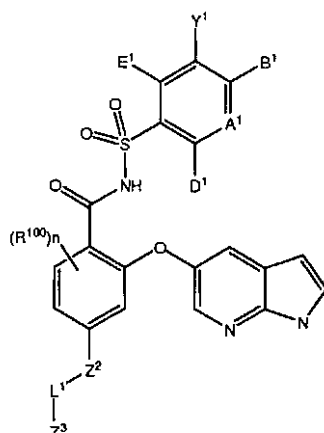
R^{72} is alkyl, alkenyl or alkenyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{73} , OR^{73} , SR^{73} , $S(O)R^{73}$, SO_2R^{73} , $C(O)R^{73}$, $CO(O)R^{73}$, $OC(O)R^{73}$, $OC(O)OR^{73}$, NH_2 , NHR^{73} , $N(R^{73})_2$, $NHC(O)R^{73}$, $NR^{73}C(O)R^{73}$, $NHS(O)_2R^{73}$, $NR^{73}S(O)_2R^{73}$, $NHC(O)OR^{73}$, $NR^{73}C(O)OR^{73}$, $NHC(O)NH_2$, $NHC(O)NHR^{73}$, $NHC(O)N(R^{73})_2$, $NR^{73}C(O)NHR^{73}$, $NR^{73}C(O)N(R^{73})_2$, $C(O)NH_2$, $C(O)NHR^{73}$, $C(O)N(R^{73})_2$, $C(O)NHOH$, $C(O)NHOR^{73}$, $C(O)NHSO_2R^{73}$, $C(O)NR^{73}SO_2R^{73}$, SO_2NH_2 , SO_2NHR^{73} , $SO_2N(R^{73})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{73}$, $C(N)N(R^{73})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br or I ;

R^{73} is alkyl, alkenyl, alkenyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; and

wherein the moieties represented by R^{69} , R^{70} , and R^{71} are unsubstituted or substituted with one or two or three or four of independently selected NH_2 , $C(O)NH_2$,

C(O)NHOH, SO₂NH₂, CF₃, CF₂CF₃, C(O)H, C(O)OH, C(N)NH₂, OH, (O), CN, N₃, NO₂, CF₃, CF₂CF₃, OCF₃, OCF₂CF₃, F, Cl, Br or I.

- 5 2. A compound having Formula (II)



(II),

or a therapeutically acceptable salt thereof, wherein

R¹⁰⁰ is as described for substituents on R²⁶;

10 n is 0, 1, 2, or 3;

A¹ is N or C(A²);

A² is H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NH₂SO₂R¹, NR¹SO₂R¹, NH₂SO₂NHR¹, NH₂SO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNHOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NH₂SO₂NHR¹, NH₂SO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR^{1A};

20 B¹ is H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NH₂SO₂R¹, NR¹SO₂R¹, NH₂SO₂NHR¹, NH₂SO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNHOH, 25 C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂

- NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR^{1A};
- D¹ is H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹,
- 5 NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂
- 10 NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR^{1A};
- E¹ is H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹,
- 15 NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂
- NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR^{1A}; and
- Y¹ is H, CN, NO₂, C(O)OH, F, Cl, Br, I, CF₃, OCF₃, CF₂CF₃, OCF₂CF₃, R¹⁷,
- 20 OR¹⁷, C(O)R¹⁷, C(O)OR¹⁷, SR¹⁷, SO₂R¹⁷, NH₂, NHR¹⁷, N(R¹⁷)₂, NHC(O)R¹⁷, C(O)NH₂, C(O)NHR¹⁷, C(O)N(R¹⁷)₂, NHS(O)R¹⁷ or NHSO₂R¹⁷; or
- E¹ and Y¹, together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and
- 25 A², B¹, and D¹ are independently selected H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂,
- 30 C(O)NHNOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR^{1A}; or

Y^1 and B^1 , together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

A^2 , D^1 , and E^1 are independently selected H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$, $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 , $C(O)OH$, $C(O)NH_2$ or $C(O)OR^{1A}$; or

A^2 and B^1 , together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

D^1 , E^1 , and Y^1 are independently selected H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$, $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 , $C(O)OH$, $C(O)NH_2$ or $C(O)OR^{1A}$; or

A^2 and D^1 , together with the atoms to which they are attached, are benzene, naphthalene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

B^1 , E^1 , and Y^1 are independently selected H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$, $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I,

CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR^{1A};

R¹ is R², R³, R⁴ or R⁵;

R^{1A} is cycloalkyl, cycloalkenyl or cycloalkynyl;

5 R² is phenyl, which is unfused or fused with R^{2A}; R^{2A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R³ is heteroaryl, which is unfused or fused with R^{3A}; R^{3A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

10 R⁴ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{4A}; R^{4A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R⁵ is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R⁶, NC(R^{6A})(R^{6B}), R⁷, OR⁷, SR⁷, S(O)R⁷, SO₂R⁷, NHR⁷, N(R⁷)₂, C(O)R⁷, C(O)NH₂, C(O)NHR⁷, C(O)N(R⁷)₂,

15 NHC(O)R⁷, NR⁷C(O)R⁷, NHSO₂R⁷, NHC(O)OR⁷, SO₂NH₂, SO₂NHR⁷, SO₂N(R⁷)₂, NHC(O)NH₂, NHC(O)NHR⁷, NHC(O)CH(CH₃)NHC(O)CH(CH₃)NH₂,

NHC(O)CH(CH₃)NHC(O)CH(CH₃)NHR⁷, OH, (O), C(O)OH, N₃, CN, NH₂, CF₃, CF₂CF₃, F, Cl, Br or I;

20 R⁶ is C₂-C₅-spiroalkyl, each of which is unsubstituted or substituted with OH, (O), N₃, CN, CF₃, CF₂CF₃, F, Cl, Br, I, NH₂, NH(CH₃) or N(CH₃)₂;

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

25 R^{6C} is aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, each having one CH₂ moiety unreplaced or replaced with O, C(O), CNOH, CNOCH₃, S, S(O), SO₂ or NH;

R⁷ is R⁸, R⁹, R¹⁰ or R¹¹;

R⁸ is phenyl, which is unfused or fused with R^{8A}; R^{8A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

30 R⁹ is heteroaryl, which is unfused or fused with R^{9A}; R^{9A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R¹⁰ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{10A}; R^{10A} is benzene, heteroarene, 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 of independently selected R^{12} , OR^{12} , SR^{12} , $S(O)R^{12}$, SO_2R^{12} , $C(O)R^{12}$, $CO(O)R^{12}$, $OC(O)R^{12}$, $OC(O)OR^{12}$, NH_2 , NHR^{12} , $N(R^{12})_2$, $NHC(O)R^{12}$, $NR^{12}C(O)R^{12}$, $NHS(O)_2R^{12}$, $NR^{12}S(O)_2R^{12}$, $NHC(O)OR^{12}$, $NR^{12}C(O)OR^{12}$,
5 $NHC(O)NH_2$, $NHC(O)NHR^{12}$, $NHC(O)N(R^{12})_2$, $NR^{12}C(O)NHR^{12}$, $NR^{12}C(O)N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, $C(O)NHOH$, $C(O)NHOR^{12}$, $C(O)NHSO_2R^{12}$, $C(O)NR^{12}SO_2R^{12}$, SO_2NH_2 , SO_2NHR^{12} , $SO_2N(R^{12})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{12}$, $C(N)N(R^{12})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br or I ;
- 10 R^{12} is R^{13} , R^{14} , R^{15} or R^{16} ;
- R^{13} is phenyl, which is unfused or fused with R^{13A} ; R^{13A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
- R^{14} is heteroaryl, which is unfused or fused with R^{14A} ; R^{14A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
- 15 R^{15} is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene, each of which is unfused or fused with R^{15A} ; R^{15A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
- R^{16} is alkyl, alkenyl or alkynyl;
- R^{17} is R^{18} , R^{19} , R^{20} or R^{21} ;
- 20 R^{18} is phenyl, which is unfused or fused with R^{18A} ; R^{18A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
- R^{19} is heteroaryl, which is unfused or fused with R^{19A} ; R^{19A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
- R^{20} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl each of
25 which is unfused or fused with R^{20A} ; R^{20A} is benzene, heteroarene, 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 of independently selected R^{22} , OR^{22} , SR^{22} , $S(O)R^{22}$, SO_2R^{22} , $C(O)R^{22}$, $CO(O)R^{22}$, $OC(O)R^{22}$, $OC(O)OR^{22}$, NH_2 , NHR^{22} , $N(R^{22})_2$, $NHC(O)R^{22}$,
30 $NR^{22}C(O)R^{22}$, $NHS(O)_2R^{22}$, $NR^{22}S(O)_2R^{22}$, $NHC(O)OR^{22}$, $NR^{22}C(O)OR^{22}$, $NHC(O)NH_2$, $NHC(O)NHR^{22}$, $NHC(O)N(R^{22})_2$, $NR^{22}C(O)NHR^{22}$, $NR^{22}C(O)N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, $C(O)NHOH$, $C(O)NHOR^{22}$, $C(O)NHSO_2R^{22}$, $C(O)NR^{22}SO_2R^{22}$, SO_2NH_2 , SO_2NHR^{22} , $SO_2N(R^{22})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$,

- C(N)NHR²², C(N)N(R²²)₂, CNOH, CNOCH₃, OH, (O), CN, N₃, NO₂, CF₃, CF₂CF₃, OCF₃, OCF₂CF₃, F, Cl, Br or I;
 R²² is R²³, R²⁴ or R²⁵;
 R²³ is phenyl, which is unfused or fused with R^{23A}; R^{23A} is benzene,
 5 heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
 R²⁴ is heteroarene, which is unfused or fused with R^{24A}; R^{24A} is benzene,
 heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
 R²⁵ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each
 of which is unfused or fused with R^{25A}; R^{25A} is benzene, heteroarene, cycloalkane,
 10 cycloalkene, heterocycloalkane or heterocycloalkene;
 Z² is R²⁸, R²⁹ or R³⁰;
 L¹ is a R³⁷, OR³⁷, SR³⁷, S(O)R³⁷, SO₂R³⁷, C(O)R³⁷, CO(O)R³⁷, OC(O)R³⁷,
 OC(O)OR³⁷, NHR³⁷, C(O)NH, C(O)NR³⁷, C(O)NHOR³⁷, C(O)NHSO₂R³⁷, SO₂NH,
 SO₂NHR³⁷, C(N)NH, C(N)NHR³⁷;
 15 R²⁸ is phenylene, which is unfused or fused with R^{28A}; R^{28A} is benzene,
 heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
 R²⁹ is heteroarylene, which is unfused or fused with R^{29A}; R^{29A} is benzene,
 heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
 R³⁰ is cycloalkylene, cycloalkenylene, heterocycloalkylene or
 20 heterocycloalkenylene, each of which is unfused or fused with R^{30A}; R^{30A} is benzene,
 heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
 R³⁷ is a bond or R^{37A};
 R^{37A} is alkylene, alkenylene, or alkynylene, each of which is unsubstituted or
 substituted with one or two or three independently selected R^{37B}, OR^{37B}, SR^{37B},
 25 S(O)R^{37B}, SO₂R^{37B}, C(O)R^{37B}, CO(O)R^{37B}, OC(O)R^{37B}, OC(O)OR^{37B}, NH₂, NHR^{37B},
 N(R^{37B})₂, NHC(O)R^{37B}, NR^{37B}C(O)R^{37B}, NHS(O)₂R^{37B}, NR^{37B}S(O)₂R^{37B},
 NHC(O)OR^{37B}, NR^{37B}C(O)OR^{37B}, NHC(O)NH₂, NHC(O)NHR^{37B}, NHC(O)N(R^{37B})₂,
 NR^{37B}C(O)NHR^{37B}, NR^{37B}C(O)N(R^{37B})₂, C(O)NH₂, C(O)NHR^{37B}, C(O)N(R^{37B})₂,
 C(O)NHOH, C(O)NHOR^{37B}, C(O)NHSO₂R^{37B}, C(O)NR^{37B}SO₂R^{37B}, SO₂NH₂,
 30 SO₂NHR^{37B}, SO₂N(R^{37B})₂, C(O)H, C(O)OH, C(N)NH₂, C(N)NHR^{37B}, C(N)N(R^{37B})₂,
 CNOH, CNOCH₃, OH, (O), CN, N₃, NO₂, CF₃, CF₂CF₃, OCF₃, OCF₂CF₃, F, Cl, Br
 and I substituents;
 R^{37B} is alkyl, alkenyl, alkynyl, or R^{37C};

R^{37C} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

Z^3 is R^{38} , R^{39} or R^{40} ;

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

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

R^{40} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{40A} ; R^{40A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein the cyclic moieties represented by E^1 and Y^1 together, Y^1 and B^1 together, A^2 and B^1 together, A^2 and D^1 together, R^{1A} , R^2 , R^{2A} , R^3 , R^{3A} , R^4 , R^{4A} , R^6 , R^{6C} , R^8 , R^{8A} , R^9 , R^{9A} , 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^{26A} , R^{27} , R^{27A} , R^{28} , R^{28A} , R^{29} , R^{29A} , R^{30} , R^{30A} , R^{37B} , R^{38} , R^{38A} , R^{39} , R^{39A} , R^{40} , and R^{40A} are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five of independently selected R^{57A} , R^{57} , OR^{57} , SR^{57} , $S(O)R^{57}$, SO_2R^{57} , $C(O)R^{57}$, $CO(O)R^{57}$, $OC(O)R^{57}$, $OC(O)OR^{57}$, NH_2 , NHR^{57} , $N(R^{57})_2$, $NHC(O)R^{57}$, $NR^{57}C(O)R^{57}$, $NHS(O)_2R^{57}$, $NR^{57}S(O)_2R^{57}$, $NHC(O)OR^{57}$, $NR^{57}C(O)OR^{57}$, $NHC(O)NH_2$, $NHC(O)NHR^{57}$, $NHC(O)N(R^{57})_2$, $NR^{57}C(O)NHR^{57}$, $NR^{57}C(O)N(R^{57})_2$, $C(O)NH_2$, $C(O)NHR^{57}$, $C(O)N(R^{57})_2$, $C(O)NHOH$, $C(O)NHOR^{57}$, $C(O)NHOSO_2R^{57}$, $C(O)NR^{57}SO_2R^{57}$, SO_2NH_2 , SO_2NHR^{57} , $SO_2N(R^{57})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{57}$, $C(N)N(R^{57})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br or I ;

R^{57A} is spiroalkyl or heterospiroalkyl;

R^{57} is R^{58} , R^{59} , R^{60} or R^{61} ;

R^{58} is phenyl, which is unfused or fused with R^{58A} ; R^{58A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{59} is heteroaryl, which is unfused or fused with R^{59A} ; R^{59A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{60} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{60A} ; R^{60A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

- R^{61} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{62} , OR^{62} , SR^{62} , $S(O)R^{62}$, SO_2R^{62} , $C(O)R^{62}$, $CO(O)R^{62}$, $OC(O)R^{62}$, $OC(O)OR^{62}$, NH_2 , NHR^{62} , $N(R^{62})_2$, $NHC(O)R^{62}$, $NR^{62}C(O)R^{62}$, $NHS(O)_2R^{62}$, $NR^{62}S(O)_2R^{62}$, $NHC(O)OR^{62}$, $NR^{62}C(O)OR^{62}$,
 5 $NHC(O)NH_2$, $NHC(O)NHR^{62}$, $NHC(O)N(R^{62})_2$, $NR^{62}C(O)NHR^{62}$, $NR^{62}C(O)N(R^{62})_2$, $C(O)NH_2$, $C(O)NHR^{62}$, $C(O)N(R^{62})_2$, $C(O)NHOH$, $C(O)NHOR^{62}$, $C(O)NHSO_2R^{62}$, $C(O)NR^{62}SO_2R^{62}$, SO_2NH_2 , SO_2NHR^{62} , $SO_2N(R^{62})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{62}$, $C(N)N(R^{62})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br or I ;
- 10 R^{62} is R^{63} , R^{64} , R^{65} or R^{66} ;
- R^{63} is phenyl, which is unfused or fused with R^{63A} ; R^{63A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
- R^{64} is heteroaryl, which is unfused or fused with R^{64A} ; R^{64A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
- 15 R^{65} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R^{65A} ; R^{65A} is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
- R^{66} is alkyl, alkenyl or alkenyl, each of which is unsubstituted or substituted with one or two or three of independently selected R^{67} , OR^{67} , SR^{67} , $S(O)R^{67}$, SO_2R^{67} ,
 20 $C(O)R^{67}$, $CO(O)R^{67}$, $OC(O)R^{67}$, $OC(O)OR^{67}$, NH_2 , NHR^{67} , $N(R^{67})_2$, $NHC(O)R^{67}$, $NR^{67}C(O)R^{67}$, $NHS(O)_2R^{67}$, $NR^{67}S(O)_2R^{67}$, $NHC(O)OR^{67}$, $NR^{67}C(O)OR^{67}$, $NHC(O)NH_2$, $NHC(O)NHR^{67}$, $NHC(O)N(R^{67})_2$, $NR^{67}C(O)NHR^{67}$, $NR^{67}C(O)N(R^{67})_2$, $C(O)NH_2$, $C(O)NHR^{67}$, $C(O)N(R^{67})_2$, $C(O)NHOH$, $C(O)NHOR^{67}$, $C(O)NHSO_2R^{67}$, $C(O)NR^{67}SO_2R^{67}$, SO_2NH_2 , SO_2NHR^{67} , $SO_2N(R^{67})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$,
 25 $C(N)NHR^{67}$, $C(N)N(R^{67})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br or I substituents;

R^{67} is alkyl, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl;

- wherein the cyclic moieties represented by R^{57A} , R^{58} , R^{59} , R^{60} , R^{63} , R^{64} , R^{65} ,
 30 and R^{67} are unsubstituted or substituted with one or two or three or four of independently selected R^{68} , OR^{68} , SR^{68} , $S(O)R^{68}$, SO_2R^{68} , $C(O)R^{68}$, $CO(O)R^{68}$, $OC(O)R^{68}$, $OC(O)OR^{68}$, NH_2 , NHR^{68} , $N(R^{68})_2$, $NHC(O)R^{68}$, $NR^{68}C(O)R^{68}$, $NHS(O)_2R^{68}$, $NR^{68}S(O)_2R^{68}$, $NHC(O)OR^{68}$, $NR^{68}C(O)OR^{68}$, $NHC(O)NH_2$, $NHC(O)NHR^{68}$, $NHC(O)N(R^{68})_2$, $NR^{68}C(O)NHR^{68}$, $NR^{68}C(O)N(R^{68})_2$, $C(O)NH_2$,

C(O)NHR⁶⁸, C(O)N(R⁶⁸)₂, C(O)NHOH, C(O)NHOR⁶⁸, C(O)NHSO₂R⁶⁸,
 C(O)NR⁶⁸SO₂R⁶⁸, SO₂NH₂, SO₂NHR⁶⁸, SO₂N(R⁶⁸)₂, C(O)H, C(O)OH, C(N)NH₂,
 C(N)NHR⁶⁸, C(N)N(R⁶⁸)₂, CNOH, CNOCH₃, OH, (O), CN, N₃, NO₂, CF₃, CF₂CF₃,
 OCF₃, OCF₂CF₃, F, Cl, Br or I;

5 R⁶⁸ is R⁶⁹, R⁷⁰, R⁷¹ or R⁷²;

R⁶⁹ is phenyl, which is unfused or fused with R^{69A}; R^{69A} is benzene,
 heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R⁷⁰ is heteroaryl, which is unfused or fused with R^{70A}; R^{70A} is benzene,
 heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

10 R⁷¹ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each
 of which is unfused or fused with R^{71A}; R^{71A} is benzene, heteroarene, cycloalkane,
 cycloalkene, heterocycloalkane or heterocycloalkene;

R⁷² is alkyl, alkenyl or alkenyl, each of which is unsubstituted or substituted
 with one or two or three of independently selected R⁷³, OR⁷³, SR⁷³, S(O)R⁷³, SO₂R⁷³,

15 C(O)R⁷³, CO(O)R⁷³, OC(O)R⁷³, OC(O)OR⁷³, NH₂, NHR⁷³, N(R⁷³)₂, NHC(O)R⁷³,
 NR⁷³C(O)R⁷³, NHS(O)₂R⁷³, NR⁷³S(O)₂R⁷³, NHC(O)OR⁷³, NR⁷³C(O)OR⁷³,
 NHC(O)NH₂, NHC(O)NHR⁷³, NHC(O)N(R⁷³)₂, NR⁷³C(O)NHR⁷³, NR⁷³C(O)N(R⁷³)₂,
 C(O)NH₂, C(O)NHR⁷³, C(O)N(R⁷³)₂, C(O)NHOH, C(O)NHOR⁷³, C(O)NHSO₂R⁷³,
 C(O)NR⁷³SO₂R⁷³, SO₂NH₂, SO₂NHR⁷³, SO₂N(R⁷³)₂, C(O)H, C(O)OH, C(N)NH₂,
 20 C(N)NHR⁷³, C(N)N(R⁷³)₂, CNOH, CNOCH₃, OH, (O), CN, N₃, NO₂, CF₃, CF₂CF₃,
 OCF₃, OCF₂CF₃, F, Cl, Br or I;

R⁷³ is alkyl, alkenyl, alkenyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl,
 heterocycloalkyl or heterocycloalkenyl; and

25 wherein the moieties represented by R⁶⁹, R⁷⁰, and R⁷¹ are unsubstituted or
 substituted with one or two or three or four of independently selected NH₂, C(O)NH₂,
 C(O)NHOH, SO₂NH₂, CF₃, CF₂CF₃, C(O)H, C(O)OH, C(N)NH₂, OH, (O), CN, N₃,
 NO₂, CF₃, CF₂CF₃, OCF₃, OCF₂CF₃, F, Cl, Br or I.

30 3. The compound of claim 1, wherein
 G¹ is H;
 A¹ is N or C(A²); and
 A² is H.

4. The compound of claim 1, wherein

G¹ is H;
 A¹ is N or C(A²);
 A² is H; and
 B¹ is NHR¹.

5

5. The compound of claim 1, wherein

G¹ is H;
 A¹ is N or C(A²);
 A² is H;
 B¹ is NHR¹; and
 D¹ is H.

10

6. The compound of claim 1, wherein

G¹ is H;
 A¹ is N or C(A²);
 A² is H;
 B¹ is NHR¹;
 D¹ is H; and
 E¹ is H.

15

7. The compound of claim 1, wherein

G¹ is H;
 A¹ is N or C(A²);
 A² is H;
 B¹ is NHR¹;
 D¹ is H;
 E¹ is H; and
 Y¹ is NO₂.

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8. A compound of claim 1 or claim 2, 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-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

30

- 4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 5 ({3-nitro-4-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 ({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 Trans-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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 20 ({4-[(2-methoxyethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 [(3-nitro-4-{[(3S)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 [(3-nitro-4-{[(3R)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 (2-naphthylsulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 5 ({4-[(2-methoxyethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)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-pyrrolo[2,3-
 15 b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 20 ({3-nitro-4-[(3,3,3-trifluoropropyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 Cis-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]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)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-pyrrolo[2,3-
 30 b]pyridin-5-yloxy)benzamide;
- 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{{4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl}piperazin-1-yl)-N-{{4-(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-4-(4-{{4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-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]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{{4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl}piperazin-1-yl)-N-{{5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 Cis-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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{{4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl}piperazin-1-yl)-N-{{5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 4-(4-{{4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-{{4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl}sulfonyl}benzamide;

- 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;
- 5 Trans-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 5-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino}sulfonyl)-2-(tetrahydro-2H-pyran-4-ylmethoxy)nicotinamide;
- 15 N-({5-bromo-6-[(1-methylpiperidin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 N-({5-bromo-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-pyrrolo[2,3-b]pyridin-5-yloxy)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 N-({3-chloro-5-cyano-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- N-({4-[(1-acetyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-morpholin-4-yl)propyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 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-pyrrolo[2,3-b]pyridin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 b]pyridin-5-yloxy)benzamide;
- N-[(3-chloro-4-{[2-(2-methoxyethoxy)ethyl]sulfonyl}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[2-(2-methoxyethoxy)ethyl]sulfonyl}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 b]pyridin-5-yloxy)benzamide;
- Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-yl)cyclohexyl]oxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 N-({5-bromo-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-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-pyrrolo[2,3-b]pyridin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 yloxy)benzamide;
- Cis-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-yl)cyclohexyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- Trans-N-({4-({4-[bis(cyclopropylmethyl)amino]cyclohexyl)amino}-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 5 [(4-{[(1-methylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(morpholin-3-ylmethyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 10 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylbut-2-ynyl)oxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 15 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 20 [(4-oxo-3,4-dihydroquinazolin-6-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 Trans-4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 25 Cis-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 30 Trans-4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
5 {5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- tert-butyl 3-{[4-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-
yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-
yloxy)benzoyl]amino}sulfonyl)-2-nitrophenoxy]methyl}morpholine-4-carboxylate;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
{[4-(morpholin-3-ylmethoxy)-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-
yloxy)benzamide;
- 4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({3-
nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-
15 b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
[4-({[1-(methylsulfonyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
20 ({4-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-
(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(4-chloro-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-
dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-
yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
[(3-nitro-4-({[1-(2,2,2-trifluoroethyl)piperidin-4-yl]amino}phenyl)sulfonyl]-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
({5-cyano-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]oxy]pyridin-3-yl}sulfonyl)-
30 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
{[5-isopropyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl]-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({3-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

and therapeutically acceptable salts, and metabolites thereof.

5 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-({1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl}amino)-3-nitrophenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yl oxy)benzamide;

10 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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

15 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropyl)piperidin-4-yl]amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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

20

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

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

25

N-({5-bromo-6-[(4-ethylmorpholin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-[(4-ethylmorpholin-3-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 ({3-nitro-4-[(4-tetrahydro-2H-pyran-4-ylmorpholin-3-yl)methoxy]phenyl}sulfonyl)-
 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 5 [(3-nitro-4-{[(3S)-1-tetrahydro-2H-pyran-4-yl]piperidin-3-yl}amino}phenyl)sulfonyl]-
 2-(1H-pyrrolo[2,3-b]pyridin-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-ylmethyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 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-
 pyrrolo[2,3-b]pyridin-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-
 15 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-
 1-yl)-N-({5-cyano-6-[(4-morpholin-4-ylcyclohexyl)amino]pyridin-3-yl}sulfonyl)-2-
 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 20 ({3-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 [(4-{[(1S,3R)-3-morpholin-4-ylcyclopentyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 [(4-{[(1R,3S)-3-morpholin-4-ylcyclopentyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 ({4-[(morpholin-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-
 30 b]pyridin-5-yloxy)benzamide;
- 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)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({1-[cis-3-fluorotetrahydro-2H-pyran-4-yl]piperidin-4-yl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 5 ({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylazetidin-3-yl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydrofuran-3-ylazetidin-3-yl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-({[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl}amino)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(4-((trans-4-hydroxycyclohexyl)methoxy)-3-nitrophenylsulfonyl)benzamide;
- 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(4-((cis-4-methoxycyclohexyl)methoxy)-3-nitrophenylsulfonyl)benzamide;
- 20 Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(cyclopropylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(tetrahydro-2H-pyran-4-ylamino)cyclohexyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-N-({5-bromo-6-[(4-morpholin-4-ylcyclohexyl)oxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- tert-butyl 4-([4-([4-(4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino)sulfonyl]-2-nitrophenoxy)methyl]-4-fluoropiperidine-1-carboxylate;
- 5 4-(4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-4-(4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(3-nitro-4-[4-(4-tetrahydro-2H-pyran-4-yl)piperazin-1-yl)cyclohexyl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-{[4-([1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide};
- 15 4-(4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(3-nitro-4-[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(4-[(3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 4-(4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(3-nitro-4-[(3S)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(4-[(3S)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(4-[(4-methylmorpholin-2-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 4-(4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-{[4-([4-(2-methoxyethyl)morpholin-2-yl]methyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide};

- N-[(4-{[(4-acetylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 5 [(4-{[trans-4-(fluoromethyl)-1-oxetan-3-yl]pyrrolidin-3-yl}methoxy)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-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)methyl]amino}-3-nitrophenyl)sulfonyl]-2-
 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 ({3-nitro-4-[(1-oxetan-3-yl)piperidin-4-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 ({4-[(1-cyclobutyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-
 15 b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 [(4-{[1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}-3-
 nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 20 [(4-{[(3S)-1-cyclopropylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 ({3-nitro-4-[(1-tetrahydrofuran-3-yl)piperidin-4-yl]amino}phenyl)sulfonyl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 [(4-{[(3R)-1-cyclopropylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 {[3-nitro-4-({[(3S)-1-tetrahydro-2H-pyran-4-yl]pyrrolidin-3-
 30 yl)methyl}amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 ({4-[(3-hydroxy-2,2-dimethylpropyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[1-(methylsulfonyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(4-{[(1-acetylpiperidin-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[1-[2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl]amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[1-(methylsulfonyl)pyrrolidin-3-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(4-{[(1-acetylpyrrolidin-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(4-{[(3R)-1-acetylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-methoxy-2,2-dimethylpropyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(1R,3R)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(1S,3S)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(1S,3R)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 5 { [4-({[(1R,3S)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-2-oxopiperidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[4-({[1-[2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(1-oxetan-3-ylazetidin-3-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-
 15 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(1-oxetan-3-ylpiperidin-4-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 20 [(4-{[(1-cyclopropyl)piperidin-4-yl]methyl}amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(2-fluoroethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 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}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[4-({[4-fluoro-1-oxetan-3-ylpiperidin-4-yl]methoxy)-3-nitrophenyl]sulfonyl}-2-(1H-
 30 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(2S)-4,4-difluoro-1-oxetan-3-ylpyrrolidin-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
[(3-nitro-4-{[(4-tetrahydro-2H-pyran-4-yl)morpholin-3-
yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
5 [(4-{[(4-cyclobutyl)morpholin-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
[(3-nitro-4-{[(4-tetrahydrofuran-3-yl)morpholin-3-yl)methyl]amino}phenyl)sulfonyl]-
2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
({4-[(1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl)methyl]amino}-3-
nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
({4-[(1-cyclopropyl-4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-
15 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
({4-[(4-methoxybenzyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-
5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
20 [(3-nitro-4-{[3-(trifluoromethoxy)benzyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
({4-[(3-methoxybenzyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-
5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
[(4-{[4-(difluoromethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
{[4-(1,4-dioxaspiro[4.5]dec-8-ylamino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
30 b]pyridin-5-yloxy)benzamide;
- Trans-N-[(4-{[4-(acetylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-
(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 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]-2-
 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 5 [(4-{[(3S)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 [(4-{[(3S)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-
 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 [(4-{[(3R)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 [(3-nitro-4-{[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy}phenyl)sulfonyl]-2-(1H-
 15 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 ({4-[(4-hydroxybenzyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-
 5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 20 ({4-[(3-hydroxybenzyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-
 5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 [(4-{[3-(difluoromethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 {[4-({[cis-3-morpholin-4-ylcyclopentyl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-
 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-
 1-yl)-N-{[4-({4-[(methylsulfonyl)amino]cyclohexyl}amino)-3-nitrophenyl)sulfonyl]-
 30 2-(1H-pyrrolo[2,3-b]pyridin-5-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-
 [(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-
 yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 ((3-nitro-4-[(1-oxetan-3-yl)piperidin-4-yl]methoxy]phenyl)sulfonyl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 5 ((4-[(4-fluoro-1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]methoxy]-3-
 nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 ((4-[(4-fluoro-1-tetrahydrofuran-3-yl)piperidin-4-yl]methoxy]-3-
 nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 [(4-{[4-fluoro-1-(methylsulfonyl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-
 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 {[3-nitro-4-({(3R)-1-oxetan-3-ylpyrrolidin-3-yl]methyl}amino)phenyl)sulfonyl]-2-
 15 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-
 1-yl)-N-({4-[(4-hydroxycyclohexyl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 20 {[4-({4-[3-(dimethylamino)propoxy]benzyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 [(4-{[4-(2-morpholin-4-ylethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 {[4-({(E)-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 {[4-({(Z)-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-
 30 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-({4-[(1S,4S)-bicyclo[2.2.1]hept-5-en-2-ylmethoxy]-3-nitrophenyl)sulfonyl)-4-(4-
 {[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
({4-[(1-methyl-5-oxopyrrolidin-3-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
5 [(4-{[(1R,4R,5R,6S)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy}-3-
nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
[(4-{[(1R,4R,5S,6R)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy}-3-
nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
({3-nitro-4-[(3-oxocyclohexyl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohexa-1,3-dien-1-yl]methyl}piperazin-1-
yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-
15 pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
20 {[6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-5-(trifluoromethyl)pyridin-3-
yl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
{[3-nitro-4-({[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methyl}amino)phenyl}sulfonyl]-2-
(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 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-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Cis-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-
30 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
[(3-nitro-4-({[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]amino}phenyl)sulfonyl)-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 ({4-[(4-[2-(2-methoxyethoxy)ethyl]morpholin-2-yl)methyl]amino}-3-
 nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 5 {4-[(4-(cyanomethyl)morpholin-2-yl)methyl]amino)-3-nitrophenyl)sulfonyl}-2-
 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 {[4-[(4-(N,N-dimethylglycyl)morpholin-2-yl)methyl]amino]-3-
 nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 (2-{[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-
 yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-
 2-nitrophenyl)amino]methyl}morpholin-4-yl)acetic acid;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 {[3-nitro-4-[(4-(oxetan-3-yl)morpholin-2-yl)methyl]amino]phenyl)sulfonyl}-2-(1H-
 15 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 [(4-{[(4-cyclopropyl)morpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 20 {[5-(methylsulfonyl)-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl)sulfonyl]-2-
 (1H-pyrrolo[2,3-b]pyridin-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-
 [(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-
 25 yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 ({4-[(4-methyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- ethyl 4-(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-
 30 yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-
 2-nitrophenyl)piperazine-1-carboxylate;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 ({4-[4-(morpholin-4-yl)piperidin-1-yl]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
[(3-nitro-4-{[(3R)-1-(oxetan-3-yl)pyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
5 [(4-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino}-3-
[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-
yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
({4-[(1-isopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-
10 b]pyridin-5-yloxy)benzamide;
- N-({4-[(1-tert-butylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-
chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
15 {[4-({[1-(2-methoxyethyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl}sulfonyl]-2-
(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
{[4-({[1-(cyanomethyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl}sulfonyl]-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
({4-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]-3-
[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-
yloxy)benzamide;
- N-[(5-chloro-6-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino}pyridin-3-
25 yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-
yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- tert-butyl 4-[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-
yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]-
2-nitrophenyl)amino]piperazine-1-carboxylate;
- 30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
({3-(pentafluoro- λ^6 -sulfanyl)-4-[(tetrahydro-2H-pyran-4-
ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 ({4-[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 5 [(4-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy}-3-nitrophenyl)sulfonyl]-
 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 [(3-nitro-4-{[4-(oxetan-3-yl)piperazin-1-yl]amino}phenyl)sulfonyl]-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 [(3-nitro-4-{[4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl]amino}phenyl)sulfonyl]-2-
 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 ({3-nitro-4-[(3R)-tetrahydrofuran-3-ylamino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-
 15 b]pyridin-5-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-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-({4-[(1-tert-butylpiperidin-4-yl)amino]-3-
 20 [(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-
 dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-
 yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 ({4-({[4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)-3-
 25 [(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-
 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 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-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- N-[(5-chloro-6-{[(2S)-4-(cyanomethyl)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(5-chloro-6-{[(2R)-4-(cyanomethyl)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 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-pyrrolo[2,3-b]pyridin-5-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-
- 15 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-({5-chloro-6-[3-hydroxy-2-(hydroxymethyl)-2-methylpropoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
- 20 ({6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(1,3-difluoropropan-2-yl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 N-[(5-chloro-6-{[1-(cyanomethyl)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 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-
- 30 nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 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]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
[(3-nitro-4-{[1-(oxetan-3-yl)azetidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide;
- 5 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 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]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 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]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(5-chloro-6-{[1-(N,N-dimethylglycyl)piperidin-4-yl]methoxy}pyridin-3-
yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-
15 yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
20 [(4-{[(3R)-1-(cyanomethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-methoxypiperidin-1-yl}-N-({5-chloro-6-[(4-
fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide;
- 25 4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-methoxypiperidin-1-yl}-N-({3-nitro-4-
[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide;
- 4-(4-{[9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-
yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-
30 ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-
yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-
ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 5 N-({5-chloro-6-[(4-fluoro-1-methylpiperidin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 N-[(5-chloro-6-{[1-(N,N-dimethylglycyl)-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-fluoropiperidin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-
- 15 b]pyridin-5-yloxy)benzamide;
- 4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-fluoropiperidin-1-yl}-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({4-[(tetrahydro-
- 20 2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl}sulfonyl)benzamide;
- N-[(5-chloro-6-{[(3R)-1-(1,3-difluoropropan-2-yl)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[2-(tetrahydrofuran-3-yloxy)ethoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-
- 30 pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
({5-cyano-6-[2-(tetrahydro-2H-pyran-4-yl)ethoxy]pyridin-3-yl}sulfonyl)-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
5 { [4-(3-furylmethoxy)-3-nitrophenyl]sulfonyl }-2-(1H-pyrrolo[2,3-b]pyridin-5-
yloxy)benzamide;
- N-[(5-chloro-6-[(3R)-1-(1,3-difluoropropan-2-yl)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(5-chloro-6-[[1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-
yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-
15 1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-({3-chloro-4-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]phenyl}sulfonyl)-4-(4-
{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
20 {[3-cyano-4-(tetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl}-2-(1H-pyrrolo[2,3-
b]pyridin-5-yloxy)benzamide;
- N-[(5-chloro-6-[[1-(2,2-difluoroethyl)-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 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-
pyrrolo[2,3-b]pyridin-5-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-
30 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
{[6-[[1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl]methoxy]-5-
(trifluoromethyl)pyridin-3-yl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-
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-yl)ethoxy]pyridin-3-yl}sulfonyl)-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-
5 methylpiperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-
ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
[(4-{[3-(cyclopropylamino)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 N-([5-chloro-6-(2-methoxyethoxy)pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-
4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-
5-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-
15 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(3-chloro-4-{[1-(methoxyacetyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-
{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(3-chloro-4-{[1-(N,N-dimethylglycyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-
20 (4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-
(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohexyl]methyl}piperidin-1-yl)-N-
({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-
(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-{[6-(tetrahydro-2H-pyran-4-ylmethoxy)-5-
(trifluoromethyl)pyridin-3-yl}sulfonyl}benzamide;
- N-([5-chloro-6-[(trans-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-
30 pyrrolo[2,3-b]pyridin-5-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-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
({6-[(trans-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-
yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
5 ({6-[(cis-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-
2-(1H-pyrrolo[2,3-b]pyridin-5-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}piperidin-1-yl)-2-
(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 N-[(3-chloro-4-{[trans-4-(morpholin-4-yl)cyclohexyl]methoxy}phenyl)sulfonyl]-4-
(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-
(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
{[4-(3-[cyclopropyl(1,3-thiazol-5-ylmethyl)amino]propyl)amino]-3-
15 nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-({3-chloro-4-[(trans-4-hydroxycyclohexyl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-
chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
20 ({3-chloro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-
pyrrolo[2,3-b]pyridin-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-
(trifluoromethyl)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
{[4-(3-[cyclopropyl(2,2,2-trifluoroethyl)amino]propyl)amino]-3-
nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(3-chloro-4-{[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-
30 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
({3,5-difluoro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-
(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({3-[cyclopropyl(oxetan-3-yl)amino]propyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(3-chloro-4-{[1-(1-methyl-L-prolyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-
- 5 (4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3,4-difluoro-5-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-
- 15 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-N-({3-chloro-4-(tetrahydro-2H-pyran-4-yl)methoxy}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- methyl 2-{[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-
- 20 yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide;
- 25 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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({3-[cyclobutyl(cyclopropyl)amino]propyl}amino)-3-nitrophenyl}sulfonyl)-2-
- 30 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-chloro-4-(tetrahydrofuran-3-ylmethoxy)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl)sulfonyl)-4-(4-{[9-(4-chlorophenyl)-3-(oxetan-3-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2R)-4-cyclopropylmorpholin-2-yl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 15 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 20 N-([5-chloro-6-({4-[cyclopropyl(oxetan-3-yl)amino]cyclohexyl)methoxy}pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-N-[(4-({[(4-cyclopropylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-({3-chloro-4-[(4-cyclopropylmorpholin-2-yl)methoxy]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 30 N-[(3-chloro-4-({[(4-cyclopropylmorpholin-2-yl)methyl]amino}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 2-[[2-chloro-4-[[4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]phenyl]amino]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide;
- 5 (2S)-2-[[3-chloro-5-[[4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]pyridin-2-yl)oxy]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide;
- 10 N-[(5-chloro-6-[[4-(cyclopropylmorpholin-2-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 2-[[3-chloro-5-[[4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]pyridin-2-yl)amino]methyl]-N-ethyl-N-methylmorpholine-
- 15 4-carboxamide;
- 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-
- 20 [(4-[[cis-4-hydroxy-4-methylcyclohexyl)methyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 25 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[[4-((4-[(2-cyanoethyl)(cyclopropyl)amino]cyclohexyl)amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-[[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl]piperazin-1-
- 30 yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- N-[(5-chloro-6-[(1R,2S,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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 5 ((4-[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 N-[(5-chloro-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-
 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 [(4-{[4-(3,3-difluoropyrrolidin-1-yl)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-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-
 15 yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 20 {[4-([4-(2,2-difluorocyclopropyl)amino]cyclohexyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 {[3-nitro-4-(2-oxaspiro[3.5]non-7-ylmethoxy)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 30 4-(4-{[2-(4-chlorophenyl)-5,5-bis(fluoromethyl)cyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 ({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 ({4-[(4-cyclopropylmorpholin-2-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 N-({5-chloro-6-[(trans-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-
 5 yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-
 yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 10 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 [(4-{[(trans-4-ethyl-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-
 15 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 [(4-{[(cis-4-ethyl-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-
 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 4-(4-{[2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-en-1-
 20 yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-
 ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 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]-2-
 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 25 N-({3-chloro-4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]phenyl}sulfonyl)-4-
 (4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-
 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 {[4-({4-[(2-cyanoethyl)(cyclopropyl)amino]-1-fluorocyclohexyl}methoxy)-3-
 30 nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 ({5-nitro-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 ({3-nitro-4-[(2-oxaspiro[3.5]non-7-ylmethyl)amino]phenyl)sulfonyl}-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 5 [(4-{[(4-cyano-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- {[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-
 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]({4-[(4-fluorotetrahydro-2H-pyran-4-
 yl)methoxy]-3-nitrophenyl)sulfonyl)amino}methyl pivalate;
- 10 {[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-
 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]({4-[(4-fluorotetrahydro-2H-pyran-4-
 yl)methoxy]-3-nitrophenyl)sulfonyl)amino}methyl butyrate;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-
 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-{[3-(tetrahydro-2H-pyran-4-ylmethyl)-3H-
 15 [1,2,3]triazolo[4,5-b]pyridin-6-yl)sulfonyl}benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 [(6-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-5-nitropyridin-3-
 yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 20 [(5-cyano-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-
 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-
 1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-
 nitrophenyl)morpholine-4-carboxamide;
- 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 {[4-({[4-(methoxymethyl)cyclohexyl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-
 pyrrolo[2,3-b]pyridin-5-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-
 30 (1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 and therapeutically acceptable salts, and metabolites thereof.

9. The compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

10. The compound Trans-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)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

11. The compound Cis-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]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

12. The compound Trans-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]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

13. The compound 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

14. The compound 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

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15. The compound 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

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16. The compound 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

15

17. The compound N-({5-bromo-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

20

18. The compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

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19. The compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-{cyclopropyl(oxetan-3-yl)amino}propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

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20. The compound 4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

21. A compound of claim 1 or claim 2, wherein the compound is chosen from:

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 5 [(4-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-
 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-
 dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-
 (methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-
 10 1-yl]methyl}piperazin-1-yl)-N-{[4-(3-[cyclopropyl(oxetan-3-
 yl)amino]propyl)amino]-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-
 yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

22. A compound of claim 1 or claim 2, wherein the compound is chosen from:

15 N-[(5-chloro-6-[[1-(cyanomethyl)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 20 {[4-(3-[cyclopropyl(oxetan-3-yl)amino]propyl)amino]-3-nitrophenyl)sulfonyl}-2-
 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt
 thereof.

23. A compound of claim 1 or claim 2, wherein the compound is chosen from:

25 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-
 dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(cis-4-hydroxy-4-
 30 methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-
 b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

24. The compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(3-[cyclopropyl(oxetan-3-

yl)amino]propyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
or a pharmaceutically acceptable salt thereof.

5 25. A compound of claim 1 or claim 2, wherein the compound is chosen from:

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-({[(3R)-1-tetrahydro-2H-pyran-4-yl]pyrrolidin-3-yl)methyl}amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

15 26. A compound of claim 1 or claim 2, wherein the compound is chosen from:

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-({[(3S)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
20 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
N-({5-bromo-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
25 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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
30 {[3-nitro-4-({[(3R)-1-tetrahydro-2H-pyran-4-yl]pyrrolidin-3-yl)methyl}amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 [(4-{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 5 ({4-[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-
 pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(5-chloro-6-{[1-(cyanomethyl)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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-
 {[4-({3-[cyclopropyl(oxetan-3-yl)amino]propyl}amino)-3-nitrophenyl}sulfonyl]-2-
 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- N-[(5-chloro-6-{[(1R,2S,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-
 15 1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- 4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-
 20 1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-
 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
- or a pharmaceutically acceptable salt thereof.

27. The compound N-[(5-chloro-6-{[1-(cyanomethyl)piperidin-4-
 25 yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-
 1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;
 or a pharmaceutically acceptable salt thereof.

28. A compound of claim 1 or claim 2, wherein the compound is chosen
 30 from:

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-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-
 dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxytetrahydro-

2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

29. The compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

30. 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 a compound of claim 1 or claim 2.

31. 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 or claim 2.

32. 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 or claim 2 and a

therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.



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Delegatura de Propiedad Industrial
División de Nuevas Creaciones

SOLICITUD DE

**PATENTE DE INVENCION
PCT ENTRADA EN FASE NACIONAL
(PARTE II)**

21. EXPEDIENTE No. _____

54. TITULO: AGENTES INDUCTORES DE APOPTOSIS PARA EL
TRATAMIENTO DE CANCER Y ENFERMEDADES
INMUNES Y AUTOINMUNES

52. CLASIFICACION INTERNACIONAL: C07D 471/04

71. SOLICITANTE: ABBOTT LABORATORIES

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60064, ESTADOS UNIDOS DE AMERICA

74. APODERADO: Dra. MARGARITA CASTELLANOS A.

22. BOGOTA, D.C., _____

AGENTES INDUCTORES DE APOPTOSIS PARA EL TRATAMIENTO DE CÁNCER Y ENFERMEDADES INMUNES Y AUTOINMUNES

Esta solicitud invoca el beneficio de prioridad de la Solicitud Provisional de Patente de EE.UU. N° Acta: 61/181.203, presentada el 26 de mayo, 2009, que se incorpora como referencia en su totalidad.

CAMPO DE LA INVENCION

La presente invención se refiere a compuestos que inhiben la actividad de las proteínas Bcl-2 anti-apoptóticas, composiciones que contienen dichos compuestos, y métodos para tratar enfermedades durante las cuales se expresan las proteínas anti-apoptóticas Bcl-2.

ANTECEDENTES DE LA INVENCION

Las proteínas anti-apoptóticas Bcl-2 están asociadas con numerosas enfermedades. Por ello persiste la necesidad en el arte terapéutico de compuestos que inhiben la actividad de las proteínas anti-apoptóticas Bcl-2.

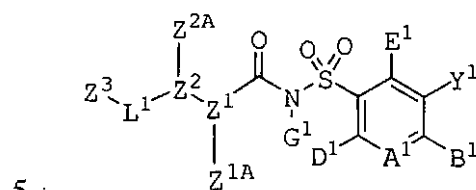
Existe una correlación entre la sobreexpresión de la proteína Bcl-2 y la resistencia a la quimioterapia, los resultados clínicos, el progreso de la enfermedad, pronosis general o una combinación de los mismos en diversos tipos de cáncer y trastornos del sistema inmune.

La relación de las proteínas 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 ovario, cáncer de pulmón de células no pequeñas, cáncer de próstata, cáncer de pulmón de células pequeñas, 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 en enfermedades inmunes y autoinmunes se describe en *Current Allergy and 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 las proteínas Bcl-2 en la artritis se divulga en la Solicitud Provisional de Patente de los EE.UU. N° Acta: 60/988.479 de propiedad común. La relación de las proteínas Bcl-2 en el rechazo de trasplante de médula ósea se divulga en la Solicitud de Patente de los EE.UU. N° Acta: 11/941.196 de propiedad común.

SÍNTESIS DE LA INVENCION

Una forma de realización de esta invención, por lo tanto, se refiere a compuestos o sus sales terapéuticamente aceptables, que son útiles como inhibidores de proteínas anti-apoptóticas Bcl-2, los compuestos de fórmula (I)



(I),

donde

A¹ es N o C(A²);

A² es H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂,
 10 C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂,
 NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹,
 SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹,
 NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹,
 C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃,
 15 OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ o C(O)OR^{1A};

B¹ es H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂,
 C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂,
 NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹,
 SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹,
 20 NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹,
 C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃,
 OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ o C(O)OR^{1A};

D¹ es H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂,
 C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂,
 25 NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹,
 SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹,
 NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹,
 C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃,
 OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ o C(O)OR^{1A};

E¹ es H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂,
 C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂,
 NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹,
 30 SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹,

A² y D¹, junto con los átomos a los cuales están unidos, son benceno, naftaleno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; y

B¹, E¹, y Y¹ se seleccionan en forma independiente entre H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹,
 5 NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHOSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃,
 10 C(O)OH, C(O)NH₂ o C(O)OR^{1A};

G¹ es H, o C(O)O;

R es alquilo;

R¹ es R², R³, R⁴ o R⁵;

R^{1A} es cicloalquilo, cicloalquenilo o cicloalquinilo;

15 R² es fenilo, que no está fusionado o está fusionado con R^{2A}; R^{2A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R³ es heteroarilo, que no está fusionado o está fusionado con R^{3A}; R^{3A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R⁴ es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{4A}; R^{4A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R⁵ 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 R⁶, NC(R^{6A})(R^{6B}), R⁷, OR⁷, SR⁷, S(O)R⁷, SO₂R⁷, NHR⁷, N(R⁷)₂, C(O)R⁷, C(O)NH₂, C(O)NHR⁷,
 25 C(O)N(R⁷)₂, NHC(O)R⁷, NR⁷C(O)R⁷, NHSO₂R⁷, NHC(O)OR⁷, SO₂NH₂, SO₂NHR⁷, SO₂N(R⁷)₂, NHC(O)NH₂, NHC(O)NHR⁷, NHC(O)CH(CH₃)NHC(O)CH(CH₃)NH₂, NHC(O)CH(CH₃)NHC(O)CH(CH₃)NHR⁷, OH, (O), C(O)OH, N₃, CN, NH₂, CF₃, CF₂CF₃, F, Cl, Br o I;

R⁶ es C₂-C₅-espiroalquilo, cada uno de los cuales no está sustituido o está sustituido con OH, (O), N₃, CN, CF₃, CF₂CF₃, F, Cl, Br, I, NH₂, NH(CH₃) o N(CH₃)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 sin reemplazar o reemplazada con O, C(O), CNOH, CNOCH₃, S, S(O),
 35 SO₂ o NH;

R⁷ es R⁸, R⁹, R¹⁰ o R¹¹;

R^8 es fenilo, que no está fusionado o está fusionado con R^{8A} ; R^{8A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^9 es heteroarilo, que no está fusionado o está fusionado con R^{9A} ; R^{9A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

5 R^{10} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{10A} ; R^{10A} es benceno, heteroareno, 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 en forma independiente entre
 10 R^{12} , OR^{12} , SR^{12} , $S(O)R^{12}$, SO_2R^{12} , $C(O)R^{12}$, $CO(O)R^{12}$, $OC(O)R^{12}$, $OC(O)OR^{12}$, NH_2 , NHR^{12} , $N(R^{12})_2$, $NHC(O)R^{12}$, $NR^{12}C(O)R^{12}$, $NHS(O)_2R^{12}$, $NR^{12}S(O)_2R^{12}$, $NHC(O)OR^{12}$, $NR^{12}C(O)OR^{12}$, $NHC(O)NH_2$, $NHC(O)NHR^{12}$, $NHC(O)N(R^{12})_2$, $NR^{12}C(O)NHR^{12}$, $NR^{12}C(O)N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, $C(O)NHOH$, $C(O)NHOR^{12}$, $C(O)NHSO_2R^{12}$, $C(O)NR^{12}SO_2R^{12}$, SO_2NH_2 , SO_2NHR^{12} , $SO_2N(R^{12})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{12}$, $C(N)N(R^{12})_2$,
 15 $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_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 R^{13A} ; R^{13A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{14} es heteroarilo, que no está fusionado o está fusionado con R^{14A} ; R^{14A} es benceno, heteroareno, 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 R^{15A} ; R^{15A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{16} es alquilo, alquenilo o alquinilo;

25 R^{17} es R^{18} , R^{19} , R^{20} o R^{21} ;

R^{18} es fenilo, que no está fusionado o está fusionado con R^{18A} ; R^{18A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{19} es heteroarilo, que no está fusionado o está fusionado con R^{19A} ; R^{19A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

30 R^{20} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo cada uno de los cuales no está fusionado o está fusionado con R^{20A} ; R^{20A} es benceno, heteroareno, 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 en forma independiente entre
 35 R^{22} , OR^{22} , SR^{22} , $S(O)R^{22}$, SO_2R^{22} , $C(O)R^{22}$, $CO(O)R^{22}$, $OC(O)R^{22}$, $OC(O)OR^{22}$, NH_2 , NHR^{22} , $N(R^{22})_2$, $NHC(O)R^{22}$, $NR^{22}C(O)R^{22}$, $NHS(O)_2R^{22}$, $NR^{22}S(O)_2R^{22}$, $NHC(O)OR^{22}$, $NR^{22}C(O)OR^{22}$,

NHC(O)NH₂, NHC(O)NHR²², NHC(O)N(R²²)₂, NR²²C(O)NHR²², NR²²C(O)N(R²²)₂, C(O)NH₂, C(O)NHR²², C(O)N(R²²)₂, C(O)NHOH, C(O)NHOR²², C(O)NH₂SO₂R²², C(O)NR²²SO₂R²², SO₂NH₂, SO₂NHR²², SO₂N(R²²)₂, C(O)H, C(O)OH, C(N)NH₂, C(N)NHR²², C(N)N(R²²)₂, CNOH, CNOCH₃, OH, (O), CN, N₃, NO₂, CF₃, CF₂CF₃, OCF₃, OCF₂CF₃, F, Cl, Br o I;

5 R²² es R²³, R²⁴ o R²⁵;

R²³ es fenilo, que no está fusionado o está fusionado con R^{23A}; R^{23A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R²⁴ es heteroareno, que no está fusionado o está fusionado con R^{24A}; R^{24A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

10 R²⁵ es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{25A}; R^{25A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

Z¹ es R²⁶ o R²⁷;

Z² es R²⁸, R²⁹ o R³⁰;

15 Z^{1A} y Z^{2A} están ambos ausentes o se toman juntos para formar CH₂, CH₂CH₂ o Z^{12A};

Z^{12A} es C₂-C₆-alquileo con uno de las unidades CH₂ se reemplaza con NH, N(CH₃), S, S(O) o SO₂;

20 L¹ es un R³⁷, OR³⁷, SR³⁷, S(O)R³⁷, SO₂R³⁷, C(O)R³⁷, CO(O)R³⁷, OC(O)R³⁷, OC(O)OR³⁷, NHR³⁷, C(O)NH, C(O)NR³⁷, C(O)NHOR³⁷, C(O)NH₂SO₂R³⁷, SO₂NH, SO₂NHR³⁷, C(N)NH, C(N)NHR³⁷;

R²⁶ es fenileno, que no está fusionado o está fusionado con R^{26A}; R^{26A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R²⁷ es heteroarileno, que no está fusionado o está fusionado con R^{27A}; R^{27A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

25 R²⁸ es fenileno, que no está fusionado o está fusionado con R^{28A}; R^{28A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R²⁹ es heteroarileno, que no está fusionado o está fusionado con R^{29A}; R^{29A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

30 R³⁰ es cicloalquileo, cicloalquenileo, heterocicloalquileo o heterocicloalquenileo, cada uno de los cuales no está fusionado o está fusionado con R^{30A}; R^{30A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R³⁷ es una unión o R^{37A};

35 R^{37A} es alquileo, alquenileo, o alquinileo, cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre R^{37B}, OR^{37B}, SR^{37B}, S(O)R^{37B}, SO₂R^{37B}, C(O)R^{37B}, CO(O)R^{37B}, OC(O)R^{37B}, OC(O)OR^{37B}, NH₂, NHR^{37B}, N(R^{37B})₂, NHC(O)R^{37B}, NR^{37B}C(O)R^{37B}, NHS(O)₂R^{37B}, NR^{37B}S(O)₂R^{37B},

- $\text{NHC(O)OR}^{37\text{B}}$, $\text{NR}^{37\text{B}}\text{C(O)OR}^{37\text{B}}$, NHC(O)NH_2 , $\text{NHC(O)NHR}^{37\text{B}}$, $\text{NHC(O)N(R}^{37\text{B}})_2$,
 $\text{NR}^{37\text{B}}\text{C(O)NHR}^{37\text{B}}$, $\text{NR}^{37\text{B}}\text{C(O)N(R}^{37\text{B}})_2$, C(O)NH_2 , $\text{C(O)NHR}^{37\text{B}}$, $\text{C(O)N(R}^{37\text{B}})_2$, C(O)NHOH ,
 $\text{C(O)NHOR}^{37\text{B}}$, $\text{C(O)NHSO}_2\text{R}^{37\text{B}}$, $\text{C(O)NR}^{37\text{B}}\text{SO}_2\text{R}^{37\text{B}}$, SO_2NH_2 , $\text{SO}_2\text{NHR}^{37\text{B}}$, $\text{SO}_2\text{N(R}^{37\text{B}})_2$,
 C(O)H , C(O)OH , C(N)NH_2 , $\text{C(N)NHR}^{37\text{B}}$, $\text{C(N)N(R}^{37\text{B}})_2$, CNOH , CNOCH_3 , OH , (O) , CN , N_3 ,
5 NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br e I ;
 $\text{R}^{37\text{B}}$ es alquilo, alquenilo, alquinilo, o $\text{R}^{37\text{C}}$;
 $\text{R}^{37\text{C}}$ es fenilo, heteroarilo, cicloalquilo, cicloalquenilo, heterocicloalquilo, o
heterocicloalquenilo;
 Z^3 es R^{38} , R^{39} o R^{40} ;
10 R^{38} es fenilo, que no está fusionado o está fusionado con $\text{R}^{38\text{A}}$; $\text{R}^{38\text{A}}$ es benceno,
heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;
 R^{39} es heteroarilo, que no está fusionado o está fusionado con $\text{R}^{39\text{A}}$; $\text{R}^{39\text{A}}$ es benceno,
heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;
 R^{40} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno
15 de los cuales no está fusionado o está fusionado con $\text{R}^{40\text{A}}$; $\text{R}^{40\text{A}}$ es benceno, heteroareno,
cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;
donde las unidades representadas por R^{26} y R^{27} están sustituidas (por ejemplo, si $\text{Z}^{1\text{A}}$
y $\text{Z}^{2\text{A}}$ están ausentes) o adicionalmente sustituidas (por ejemplo, si $\text{Z}^{1\text{A}}$ y $\text{Z}^{2\text{A}}$ están presentes)
con R^{41} , OR^{41} , SR^{41} , S(O)R^{41} , SO_2R^{41} , C(O)R^{41} , CO(O)R^{41} , OC(O)R^{41} , OC(O)OR^{41} , NHR^{41} ,
20 $\text{N(R}^{41})_2$, NHC(O)R^{41} , $\text{NR}^{41}\text{C(O)R}^{41}$, $\text{NHS(O)}_2\text{R}^{41}$, $\text{NR}^{41}\text{S(O)}_2\text{R}^{41}$, NHC(O)OR^{41} , $\text{NR}^{41}\text{C(O)OR}^{41}$,
 NHC(O)NHR^{41} , $\text{NHC(O)N(R}^{41})_2$, $\text{NR}^{41}\text{C(O)NHR}^{41}$, $\text{NR}^{41}\text{C(O)N(R}^{41})_2$, C(O)NHR^{41} , $\text{C(O)N(R}^{41})_2$,
 C(O)NHOR^{41} , $\text{C(O)NHSO}_2\text{R}^{41}$, $\text{C(O)NR}^{41}\text{SO}_2\text{R}^{41}$, $\text{SO}_2\text{NHR}^{41}$, $\text{SO}_2\text{N(R}^{41})_2$, C(N)NHR^{41} , o
 $\text{C(N)N(R}^{41})_2$;
 R^{41} es heteroarilo, que está fusionado con $\text{R}^{43\text{A}}$; $\text{R}^{43\text{A}}$ es benceno, heteroareno,
25 cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; que no está fusionado o
está fusionado con benceno, heteroareno o $\text{R}^{43\text{B}}$; $\text{R}^{43\text{B}}$ es cicloalcano, cicloalqueno,
heterocicloalcano o heterocicloalqueno;
donde las unidades cíclicas representadas por E^1 y Y^1 juntos, Y^1 y B^1 juntos, A^2 y B^1
juntos, A^2 y D^1 juntos, $\text{R}^{1\text{A}}$, R^2 , $\text{R}^{2\text{A}}$, R^3 , $\text{R}^{3\text{A}}$, R^4 , $\text{R}^{4\text{A}}$, R^6 , $\text{R}^{6\text{C}}$, R^8 , $\text{R}^{8\text{A}}$, R^9 , $\text{R}^{9\text{A}}$, R^{10} , $\text{R}^{10\text{A}}$, R^{13} ,
30 $\text{R}^{13\text{A}}$, R^{14} , $\text{R}^{14\text{A}}$, R^{15} , $\text{R}^{15\text{A}}$, R^{18} , $\text{R}^{18\text{A}}$, R^{19} , $\text{R}^{19\text{A}}$, R^{20} , $\text{R}^{20\text{A}}$, R^{23} , $\text{R}^{23\text{A}}$, R^{24} , $\text{R}^{24\text{A}}$, R^{25} , $\text{R}^{25\text{A}}$, R^{26} ,
 $\text{R}^{26\text{A}}$, R^{27} , $\text{R}^{27\text{A}}$, R^{28} , $\text{R}^{28\text{A}}$, R^{29} , $\text{R}^{29\text{A}}$, R^{30} , $\text{R}^{30\text{A}}$, $\text{R}^{37\text{B}}$, R^{38} , $\text{R}^{38\text{A}}$, R^{39} , $\text{R}^{39\text{A}}$, R^{40} , y $\text{R}^{40\text{A}}$ no están
sustituidas, no están adicionalmente sustituidas, están sustituidas o adicionalmente
sustituidas en forma independiente con uno o dos o tres o cuatro o cinco sustituyentes
seleccionados en forma independiente entre $\text{R}^{57\text{A}}$, R^{57} , OR^{57} , SR^{57} , S(O)R^{57} , SO_2R^{57} ,
35 C(O)R^{57} , CO(O)R^{57} , OC(O)R^{57} , OC(O)OR^{57} , NH_2 , NHR^{57} , $\text{N(R}^{57})_2$, NHC(O)R^{57} , $\text{NR}^{57}\text{C(O)R}^{57}$,
 $\text{NHS(O)}_2\text{R}^{57}$, $\text{NR}^{57}\text{S(O)}_2\text{R}^{57}$, NHC(O)OR^{57} , $\text{NR}^{57}\text{C(O)OR}^{57}$, NHC(O)NH_2 , NHC(O)NHR^{57} ,

$\text{NHC(O)N(R}^{57})_2$, $\text{NR}^{57}\text{C(O)NHR}^{57}$, $\text{NR}^{57}\text{C(O)N(R}^{57})_2$, C(O)NH_2 , C(O)NHR^{57} , $\text{C(O)N(R}^{57})_2$, C(O)NHOH , C(O)NHOR^{57} , $\text{C(O)NHSO}_2\text{R}^{57}$, $\text{C(O)NR}^{57}\text{SO}_2\text{R}^{57}$, SO_2NH_2 , $\text{SO}_2\text{NHR}^{57}$, $\text{SO}_2\text{N(R}^{57})_2$, C(O)H , C(O)OH , C(N)NH_2 , C(N)NHR^{57} , $\text{C(N)N(R}^{57})_2$, CNOH , CNOCH_3 , OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I ;

5 $\text{R}^{57\text{A}}$ es espiroalquilo, o espiroheteroalquilo;

R^{57} es R^{58} , R^{59} , R^{60} o R^{61} ;

R^{58} es fenilo, que no está fusionado o está fusionado con $\text{R}^{58\text{A}}$; $\text{R}^{58\text{A}}$ es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{59} es heteroarilo, que no está fusionado o está fusionado con $\text{R}^{59\text{A}}$; $\text{R}^{59\text{A}}$ es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

10 R^{60} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con $\text{R}^{60\text{A}}$; $\text{R}^{60\text{A}}$ es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{61} 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^{62} , OR^{62} , SR^{62} , S(O)R^{62} , SO_2R^{62} , C(O)R^{62} , CO(O)R^{62} , OC(O)R^{62} , OC(O)OR^{62} , NH_2 , NHR^{62} , $\text{N(R}^{62})_2$, NHC(O)R^{62} , $\text{NR}^{62}\text{C(O)R}^{62}$, $\text{NHS(O)}_2\text{R}^{62}$, $\text{NR}^{62}\text{S(O)}_2\text{R}^{62}$, NHC(O)OR^{62} , $\text{NR}^{62}\text{C(O)OR}^{62}$, NHC(O)NH_2 , NHC(O)NHR^{62} , $\text{NHC(O)N(R}^{62})_2$, $\text{NR}^{62}\text{C(O)NHR}^{62}$, $\text{NR}^{62}\text{C(O)N(R}^{62})_2$, C(O)NH_2 , C(O)NHR^{62} , $\text{C(O)N(R}^{62})_2$, C(O)NHOH , C(O)NHOR^{62} , $\text{C(O)NHSO}_2\text{R}^{62}$, $\text{C(O)NR}^{62}\text{SO}_2\text{R}^{62}$, SO_2NH_2 , $\text{SO}_2\text{NHR}^{62}$, $\text{SO}_2\text{N(R}^{62})_2$, C(O)H , C(O)OH , C(N)NH_2 , C(N)NHR^{62} , $\text{C(N)N(R}^{62})_2$, CNOH , CNOCH_3 , OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I ;

20 R^{62} es R^{63} , R^{64} , R^{65} o R^{66} ;

R^{63} es fenilo, que no está fusionado o está fusionado con $\text{R}^{63\text{A}}$; $\text{R}^{63\text{A}}$ es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

25 R^{64} es heteroarilo, que no está fusionado o está fusionado con $\text{R}^{64\text{A}}$; $\text{R}^{64\text{A}}$ es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{65} es cicloalquilo, cicloalquenilo, heterocicloalquilo, o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con $\text{R}^{65\text{A}}$; $\text{R}^{65\text{A}}$ es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

30 R^{66} 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^{67} , OR^{67} , SR^{67} , S(O)R^{67} , SO_2R^{67} , C(O)R^{67} , CO(O)R^{67} , OC(O)R^{67} , OC(O)OR^{67} , NH_2 , NHR^{67} , $\text{N(R}^{67})_2$, NHC(O)R^{67} , $\text{NR}^{67}\text{C(O)R}^{67}$, $\text{NHS(O)}_2\text{R}^{67}$, $\text{NR}^{67}\text{S(O)}_2\text{R}^{67}$, NHC(O)OR^{67} , $\text{NR}^{67}\text{C(O)OR}^{67}$, NHC(O)NH_2 , NHC(O)NHR^{67} , $\text{NHC(O)N(R}^{67})_2$, $\text{NR}^{67}\text{C(O)NHR}^{67}$, $\text{NR}^{67}\text{C(O)N(R}^{67})_2$, C(O)NH_2 , C(O)NHR^{67} , $\text{C(O)N(R}^{67})_2$, C(O)NHOH , C(O)NHOR^{67} , $\text{C(O)NHSO}_2\text{R}^{67}$, $\text{C(O)NR}^{67}\text{SO}_2\text{R}^{67}$,

35

SO_2NH_2 , $\text{SO}_2\text{NHR}^{67}$, $\text{SO}_2\text{N(R}^{67})_2$, C(O)H , C(O)OH , C(N)NH_2 , C(N)NHR^{67} , $\text{C(N)N(R}^{67})_2$, CNOH , CNOCH_3 , OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I ;

R^{67} es alquilo, alquenilo, alquinilo, fenilo, heteroarilo, cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo;

- 5 donde las unidades cíclicas representadas por $\text{R}^{57\text{A}}$, R^{68} , R^{69} , R^{60} , R^{63} , R^{64} , R^{65} , y R^{67} no están sustituidas o están sustituidas con uno o dos o tres o cuatro sustituyentes seleccionados en forma independiente entre R^{68} , OR^{68} , SR^{68} , S(O)R^{68} , SO_2R^{68} , C(O)R^{68} , CO(O)R^{68} , OC(O)R^{68} , OC(O)OR^{68} , NH_2 , NHR^{68} , $\text{N(R}^{68})_2$, NHC(O)R^{68} , $\text{NR}^{68}\text{C(O)R}^{68}$, $\text{NHS(O)}_2\text{R}^{68}$, $\text{NR}^{68}\text{S(O)}_2\text{R}^{68}$, NHC(O)OR^{68} , $\text{NR}^{68}\text{C(O)OR}^{68}$, NHC(O)NH_2 , NHC(O)NHR^{68} , $\text{NHC(O)N(R}^{68})_2$, $\text{NR}^{68}\text{C(O)NHR}^{68}$, $\text{NR}^{68}\text{C(O)N(R}^{68})_2$, C(O)NH_2 , C(O)NHR^{68} , $\text{C(O)N(R}^{68})_2$, C(O)NHOH , C(O)NHOR^{68} , $\text{C(O)NHSO}_2\text{R}^{68}$, $\text{C(O)NR}^{68}\text{SO}_2\text{R}^{68}$, SO_2NH_2 , $\text{SO}_2\text{NHR}^{68}$, $\text{SO}_2\text{N(R}^{68})_2$, C(O)H , C(O)OH , C(N)NH_2 , C(N)NHR^{68} , $\text{C(N)N(R}^{68})_2$, CNOH , CNOCH_3 , OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I ;

R^{68} es R^{69} , R^{70} , R^{71} o R^{72} ;

- 15 R^{69} es fenilo, que no está fusionado o está fusionado con $\text{R}^{69\text{A}}$; $\text{R}^{69\text{A}}$ es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{70} es heteroarilo, que no está fusionado o está fusionado con $\text{R}^{70\text{A}}$; $\text{R}^{70\text{A}}$ es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

- 20 R^{71} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con $\text{R}^{71\text{A}}$; $\text{R}^{71\text{A}}$ es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

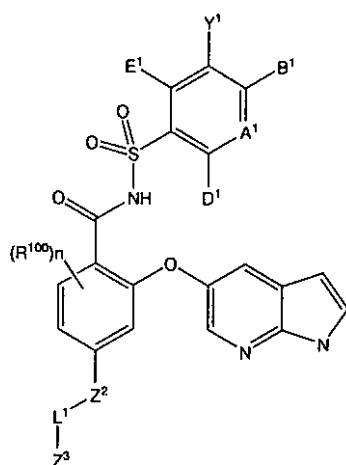
R^{72} es alquilo, alquenilo o alquinilo, cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre R^{73} , OR^{73} , SR^{73} , S(O)R^{73} , SO_2R^{73} , C(O)R^{73} , CO(O)R^{73} , OC(O)R^{73} , OC(O)OR^{73} , NH_2 , NHR^{73} , $\text{N(R}^{73})_2$, NHC(O)R^{73} , $\text{NR}^{73}\text{C(O)R}^{73}$, $\text{NHS(O)}_2\text{R}^{73}$, $\text{NR}^{73}\text{S(O)}_2\text{R}^{73}$, NHC(O)OR^{73} , $\text{NR}^{73}\text{C(O)OR}^{73}$, NHC(O)NH_2 , NHC(O)NHR^{73} , $\text{NHC(O)N(R}^{73})_2$, $\text{NR}^{73}\text{C(O)NHR}^{73}$, $\text{NR}^{73}\text{C(O)N(R}^{73})_2$, C(O)NH_2 , C(O)NHR^{73} , $\text{C(O)N(R}^{73})_2$, C(O)NHOH , C(O)NHOR^{73} , $\text{C(O)NHSO}_2\text{R}^{73}$, $\text{C(O)NR}^{73}\text{SO}_2\text{R}^{73}$, SO_2NH_2 , $\text{SO}_2\text{NHR}^{73}$, $\text{SO}_2\text{N(R}^{73})_2$, C(O)H , C(O)OH , C(N)NH_2 , C(N)NHR^{73} , $\text{C(N)N(R}^{73})_2$, CNOH , CNOCH_3 , OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I ;

- 30 R^{73} es alquilo, alquenilo, alquinilo, fenilo, heteroarilo, cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo; y

donde las unidades representadas por R^{69} , R^{70} , y R^{71} no están sustituidas o están sustituidas con uno o dos o tres o cuatro sustituyentes seleccionados en forma independiente entre NH_2 , C(O)NH_2 , C(O)NHOH , SO_2NH_2 , CF_3 , CF_2CF_3 , C(O)H , C(O)OH ,

- 35 C(N)NH_2 , OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I .

Otra forma de realización de esta invención se refiere a compuestos o sus sales terapéuticamente aceptables, que son útiles como inhibidores de proteínas anti-apoptóticas Bcl-2, los compuestos de fórmula (II)



5 (II),

o una sal terapéuticamente aceptable del mismo, donde

R¹⁰⁰ tiene los valores que se describen para los sustituyentes de R²⁶;

n es 0, 1, 2, o 3;

A¹ es N o C(A²);

10 A² es H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹,
 15 C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ o C(O)OR^{1A};

B¹ es H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹,
 20 SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ o C(O)OR^{1A};

D¹ es H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂,
 25 C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹,

D¹, E¹, y Y¹ se seleccionan en forma independiente entre H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ o C(O)OR^{1A}; o

A² y D¹, junto con los átomos a los cuales están unidos, son benceno, naftaleno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; y

B¹, E¹, y Y¹ se seleccionan en forma independiente entre H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ o C(O)OR^{1A};

R¹ es R², R³, R⁴ o R⁵;

R^{1A} es cicloalquilo, cicloalquenilo o cicloalquinilo;

R² es fenilo, que no está fusionado o está fusionado con R^{2A}; R^{2A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R³ es heteroarilo, que no está fusionado o está fusionado con R^{3A}; R^{3A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R⁴ es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{4A}; R^{4A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R⁵ 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 R⁶, NC(R^{6A})(R^{6B}), R⁷, OR⁷, SR⁷, S(O)R⁷, SO₂R⁷, NHR⁷, N(R⁷)₂, C(O)R⁷, C(O)NH₂, C(O)NHR⁷, C(O)N(R⁷)₂, NHC(O)R⁷, NR⁷C(O)R⁷, NHSO₂R⁷, NHC(O)OR⁷, SO₂NH₂, SO₂NHR⁷, SO₂N(R⁷)₂, NHC(O)NH₂, NHC(O)NHR⁷, NHC(O)CH(CH₃)NHC(O)CH(CH₃)NH₂, NHC(O)CH(CH₃)NHC(O)CH(CH₃)NHR⁷, OH, (O), C(O)OH, N₃, CN, NH₂, CF₃, CF₂CF₃, F, Cl, Br o I;

R⁶ es C₂-C₅-espiroalquilo, cada uno de los cuales no está sustituido o está sustituido con OH, (O), N₃, CN, CF₃, CF₂CF₃, F, Cl, Br, I, NH₂, NH(CH₃) o N(CH₃)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 sin reemplazar o reemplazada con O, C(O), CNOH, CNOCH₃, S, S(O),
5 SO₂ 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 R^{8A} ; R^{8A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^9 es heteroarilo, que no está fusionado o está fusionado con R^{9A} ; R^{9A} es benceno,
10 heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{10} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{10A} ; R^{10A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{11} es alquilo, alquenilo o alquinilo, cada uno de los cuales no está sustituido o está
15 sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre R^{12} , OR¹², SR¹², S(O)R¹², SO₂R¹², C(O)R¹², CO(O)R¹², OC(O)R¹², OC(O)OR¹², NH₂, NHR¹², N(R¹²)₂, NHC(O)R¹², NR¹²C(O)R¹², NHS(O)₂R¹², NR¹²S(O)₂R¹², NHC(O)OR¹², NR¹²C(O)OR¹², NHC(O)NH₂, NHC(O)NHR¹², NHC(O)N(R¹²)₂, NR¹²C(O)NHR¹², NR¹²C(O)N(R¹²)₂, C(O)NH₂, C(O)NHR¹², C(O)N(R¹²)₂, C(O)NHOH, C(O)NHOR¹², C(O)NHSO₂R¹², C(O)NR¹²SO₂R¹²,
20 SO₂NH₂, SO₂NHR¹², SO₂N(R¹²)₂, C(O)H, C(O)OH, C(N)NH₂, C(N)NHR¹², C(N)N(R¹²)₂, CNOH, CNOCH₃, OH, (O), CN, N₃, NO₂, CF₃, CF₂CF₃, OCF₃, OCF₂CF₃, 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 R^{13A} ; R^{13A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{14} es heteroarilo, que no está fusionado o está fusionado con R^{14A} ; R^{14A} es benceno,
25 heteroareno, 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 R^{15A} ; R^{15A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

30 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 R^{18A} ; R^{18A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{19} es heteroarilo, que no está fusionado o está fusionado con R^{19A} ; R^{19A} es benceno,
35 heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{20} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo cada uno de los cuales no está fusionado o está fusionado con R^{20A} ; R^{20A} es benceno, heteroareno, 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 en forma independiente entre R^{22} , OR^{22} , SR^{22} , $S(O)R^{22}$, SO_2R^{22} , $C(O)R^{22}$, $CO(O)R^{22}$, $OC(O)R^{22}$, $OC(O)OR^{22}$, NH_2 , NHR^{22} , $N(R^{22})_2$, $NHC(O)R^{22}$, $NR^{22}C(O)R^{22}$, $NHS(O)_2R^{22}$, $NR^{22}S(O)_2R^{22}$, $NHC(O)OR^{22}$, $NR^{22}C(O)OR^{22}$, $NHC(O)NH_2$, $NHC(O)NHR^{22}$, $NHC(O)N(R^{22})_2$, $NR^{22}C(O)NHR^{22}$, $NR^{22}C(O)N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, $C(O)NHOH$, $C(O)NHOR^{22}$, $C(O)NHSO_2R^{22}$, $C(O)NR^{22}SO_2R^{22}$, SO_2NH_2 , SO_2NHR^{22} , $SO_2N(R^{22})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{22}$, $C(N)N(R^{22})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_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 R^{23A} ; R^{23A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{24} es heteroareno, que no está fusionado o está fusionado con R^{24A} ; R^{24A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{25} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{25A} ; R^{25A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

Z^2 es R^{28} , R^{29} o R^{30} ;

L^1 es un R^{37} , OR^{37} , SR^{37} , $S(O)R^{37}$, SO_2R^{37} , $C(O)R^{37}$, $CO(O)R^{37}$, $OC(O)R^{37}$, $OC(O)OR^{37}$, NHR^{37} , $C(O)NH$, $C(O)NR^{37}$, $C(O)NHOR^{37}$, $C(O)NHSO_2R^{37}$, SO_2NH , SO_2NHR^{37} , $C(N)NH$, $C(N)NHR^{37}$;

R^{28} es fenileno, que no está fusionado o está fusionado con R^{28A} ; R^{28A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{29} es heteroarileno, que no está fusionado o está fusionado con R^{29A} ; R^{29A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{30} es cicloalquileno, cicloalquenileno, heterocicloalquileno o heterocicloalquenileno, cada uno de los cuales no está fusionado o está fusionado con R^{30A} ; R^{30A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{37} es una unión o R^{37A} ;

R^{37A} es alquilenilo, alquenileno, o alquinileno, cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre R^{37B} , OR^{37B} , SR^{37B} , $S(O)R^{37B}$, SO_2R^{37B} , $C(O)R^{37B}$, $CO(O)R^{37B}$, $OC(O)R^{37B}$, $OC(O)OR^{37B}$, NH_2 , NHR^{37B} , $N(R^{37B})_2$, $NHC(O)R^{37B}$, $NR^{37B}C(O)R^{37B}$, $NHS(O)_2R^{37B}$, $NR^{37B}S(O)_2R^{37B}$, $NHC(O)OR^{37B}$, $NR^{37B}C(O)OR^{37B}$, $NHC(O)NH_2$, $NHC(O)NHR^{37B}$, $NHC(O)N(R^{37B})_2$,

$\text{NR}^{37\text{B}}\text{C}(\text{O})\text{NHR}^{37\text{B}}$, $\text{NR}^{37\text{B}}\text{C}(\text{O})\text{N}(\text{R}^{37\text{B}})_2$, $\text{C}(\text{O})\text{NH}_2$, $\text{C}(\text{O})\text{NHR}^{37\text{B}}$, $\text{C}(\text{O})\text{N}(\text{R}^{37\text{B}})_2$, $\text{C}(\text{O})\text{NHOH}$, $\text{C}(\text{O})\text{NHOR}^{37\text{B}}$, $\text{C}(\text{O})\text{NH}\text{SO}_2\text{R}^{37\text{B}}$, $\text{C}(\text{O})\text{NR}^{37\text{B}}\text{SO}_2\text{R}^{37\text{B}}$, SO_2NH_2 , $\text{SO}_2\text{NHR}^{37\text{B}}$, $\text{SO}_2\text{N}(\text{R}^{37\text{B}})_2$, $\text{C}(\text{O})\text{H}$, $\text{C}(\text{O})\text{OH}$, $\text{C}(\text{N})\text{NH}_2$, $\text{C}(\text{N})\text{NHR}^{37\text{B}}$, $\text{C}(\text{N})\text{N}(\text{R}^{37\text{B}})_2$, CNOH , CNOCH_3 , OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br e I ;

5 $\text{R}^{37\text{B}}$ es alquilo, alquenilo, alquinilo, o $\text{R}^{37\text{C}}$;

$\text{R}^{37\text{C}}$ es fenilo, heteroarilo, cicloalquilo, cicloalquenilo, heterocicloalquilo, o heterocicloalquenilo;

Z^3 es R^{38} , R^{39} o R^{40} ;

10 R^{38} es fenilo, que no está fusionado o está fusionado con $\text{R}^{38\text{A}}$; $\text{R}^{38\text{A}}$ es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{39} es heteroarilo, que no está fusionado o está fusionado con $\text{R}^{39\text{A}}$; $\text{R}^{39\text{A}}$ es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

15 R^{40} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con $\text{R}^{40\text{A}}$; $\text{R}^{40\text{A}}$ es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

20 donde las unidades cíclicas representadas por E^1 y Y^1 juntos, Y^1 y B^1 juntos, A^2 y B^1 juntos, A^2 y D^1 juntos, $\text{R}^{1\text{A}}$, R^2 , $\text{R}^{2\text{A}}$, R^3 , $\text{R}^{3\text{A}}$, R^4 , $\text{R}^{4\text{A}}$, R^6 , $\text{R}^{6\text{C}}$, R^8 , $\text{R}^{8\text{A}}$, R^9 , $\text{R}^{9\text{A}}$, R^{10} , $\text{R}^{10\text{A}}$, R^{13} , $\text{R}^{13\text{A}}$, R^{14} , $\text{R}^{14\text{A}}$, R^{15} , $\text{R}^{15\text{A}}$, R^{18} , $\text{R}^{18\text{A}}$, R^{19} , $\text{R}^{19\text{A}}$, R^{20} , $\text{R}^{20\text{A}}$, R^{23} , $\text{R}^{23\text{A}}$, R^{24} , $\text{R}^{24\text{A}}$, R^{25} , $\text{R}^{25\text{A}}$, R^{26} , $\text{R}^{26\text{A}}$, R^{27} , $\text{R}^{27\text{A}}$, R^{28} , $\text{R}^{28\text{A}}$, R^{29} , $\text{R}^{29\text{A}}$, R^{30} , $\text{R}^{30\text{A}}$, $\text{R}^{37\text{B}}$, R^{38} , $\text{R}^{38\text{A}}$, R^{39} , $\text{R}^{39\text{A}}$, R^{40} , y $\text{R}^{40\text{A}}$ no están
25 substituidas, no están adicionalmente substituidas, están sustituidas o adicionalmente substituidas en forma independiente con uno o dos o tres o cuatro o cinco sustituyentes seleccionados en forma independiente entre $\text{R}^{57\text{A}}$, R^{57} , OR^{57} , SR^{57} , $\text{S}(\text{O})\text{R}^{57}$, SO_2R^{57} , $\text{C}(\text{O})\text{R}^{57}$, $\text{CO}(\text{O})\text{R}^{57}$, $\text{OC}(\text{O})\text{R}^{57}$, $\text{OC}(\text{O})\text{OR}^{57}$, NH_2 , NHR^{57} , $\text{N}(\text{R}^{57})_2$, $\text{NHC}(\text{O})\text{R}^{57}$, $\text{NR}^{57}\text{C}(\text{O})\text{R}^{57}$, $\text{NHS}(\text{O})_2\text{R}^{57}$, $\text{NR}^{57}\text{S}(\text{O})_2\text{R}^{57}$, $\text{NHC}(\text{O})\text{OR}^{57}$, $\text{NR}^{57}\text{C}(\text{O})\text{OR}^{57}$, $\text{NHC}(\text{O})\text{NH}_2$, $\text{NHC}(\text{O})\text{NHR}^{57}$,
30 $\text{NHC}(\text{O})\text{N}(\text{R}^{57})_2$, $\text{NR}^{57}\text{C}(\text{O})\text{NHR}^{57}$, $\text{NR}^{57}\text{C}(\text{O})\text{N}(\text{R}^{57})_2$, $\text{C}(\text{O})\text{NH}_2$, $\text{C}(\text{O})\text{NHR}^{57}$, $\text{C}(\text{O})\text{N}(\text{R}^{57})_2$, $\text{C}(\text{O})\text{NHOH}$, $\text{C}(\text{O})\text{NHOR}^{57}$, $\text{C}(\text{O})\text{NH}\text{SO}_2\text{R}^{57}$, $\text{C}(\text{O})\text{NR}^{57}\text{SO}_2\text{R}^{57}$, SO_2NH_2 , $\text{SO}_2\text{NHR}^{57}$, $\text{SO}_2\text{N}(\text{R}^{57})_2$, $\text{C}(\text{O})\text{H}$, $\text{C}(\text{O})\text{OH}$, $\text{C}(\text{N})\text{NH}_2$, $\text{C}(\text{N})\text{NHR}^{57}$, $\text{C}(\text{N})\text{N}(\text{R}^{57})_2$, CNOH , CNOCH_3 , OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I ;

$\text{R}^{57\text{A}}$ es espiroalquilo o heteroespiroalquilo;

30 R^{57} es R^{58} , R^{59} , R^{60} o R^{61} ;

R^{58} es fenilo, que no está fusionado o está fusionado con $\text{R}^{58\text{A}}$; $\text{R}^{58\text{A}}$ es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{59} es heteroarilo, que no está fusionado o está fusionado con $\text{R}^{59\text{A}}$; $\text{R}^{59\text{A}}$ es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{60} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{60A} ; R^{60A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{61} 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^{62} , OR^{62} , SR^{62} , $S(O)R^{62}$, SO_2R^{62} , $C(O)R^{62}$, $CO(O)R^{62}$, $OC(O)R^{62}$, $OC(O)OR^{62}$, NH_2 , NHR^{62} , $N(R^{62})_2$, $NHC(O)R^{62}$, $NR^{62}C(O)R^{62}$, $NHS(O)_2R^{62}$, $NR^{62}S(O)_2R^{62}$, $NHC(O)OR^{62}$, $NR^{62}C(O)OR^{62}$, $NHC(O)NH_2$, $NHC(O)NHR^{62}$, $NHC(O)N(R^{62})_2$, $NR^{62}C(O)NHR^{62}$, $NR^{62}C(O)N(R^{62})_2$, $C(O)NH_2$, $C(O)NHR^{62}$, $C(O)N(R^{62})_2$, $C(O)NHOH$, $C(O)NHOR^{62}$, $C(O)NHSO_2R^{62}$, $C(O)NR^{62}SO_2R^{62}$, SO_2NH_2 , SO_2NHR^{62} , $SO_2N(R^{62})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{62}$, $C(N)N(R^{62})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I ;

R^{62} es R^{63} , R^{64} , R^{65} o R^{66} ;

R^{63} es fenilo, que no está fusionado o está fusionado con R^{63A} ; R^{63A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{64} es heteroarilo, que no está fusionado o está fusionado con R^{64A} ; R^{64A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{65} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{65A} ; R^{65A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{66} 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^{67} , OR^{67} , SR^{67} , $S(O)R^{67}$, SO_2R^{67} , $C(O)R^{67}$, $CO(O)R^{67}$, $OC(O)R^{67}$, $OC(O)OR^{67}$, NH_2 , NHR^{67} , $N(R^{67})_2$, $NHC(O)R^{67}$, $NR^{67}C(O)R^{67}$, $NHS(O)_2R^{67}$, $NR^{67}S(O)_2R^{67}$, $NHC(O)OR^{67}$, $NR^{67}C(O)OR^{67}$, $NHC(O)NH_2$, $NHC(O)NHR^{67}$, $NHC(O)N(R^{67})_2$, $NR^{67}C(O)NHR^{67}$, $NR^{67}C(O)N(R^{67})_2$, $C(O)NH_2$, $C(O)NHR^{67}$, $C(O)N(R^{67})_2$, $C(O)NHOH$, $C(O)NHOR^{67}$, $C(O)NHSO_2R^{67}$, $C(O)NR^{67}SO_2R^{67}$, SO_2NH_2 , SO_2NHR^{67} , $SO_2N(R^{67})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{67}$, $C(N)N(R^{67})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I sustituyentes;

R^{67} es alquilo, alquenilo, alquinilo, fenilo, heteroarilo, cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo;

donde las unidades cíclicas representadas por R^{57A} , R^{58} , R^{59} , R^{60} , R^{63} , R^{64} , R^{65} , y R^{67} no están sustituidas o están sustituidas con uno o dos o tres o cuatro sustituyentes seleccionados en forma independiente entre R^{68} , OR^{68} , SR^{68} , $S(O)R^{68}$, SO_2R^{68} , $C(O)R^{68}$, $CO(O)R^{68}$, $OC(O)R^{68}$, $OC(O)OR^{68}$, NH_2 , NHR^{68} , $N(R^{68})_2$, $NHC(O)R^{68}$, $NR^{68}C(O)R^{68}$, $NHS(O)_2R^{68}$, $NR^{68}S(O)_2R^{68}$, $NHC(O)OR^{68}$, $NR^{68}C(O)OR^{68}$, $NHC(O)NH_2$, $NHC(O)NHR^{68}$, $NHC(O)N(R^{68})_2$, $NR^{68}C(O)NHR^{68}$, $NR^{68}C(O)N(R^{68})_2$, $C(O)NH_2$, $C(O)NHR^{68}$, $C(O)N(R^{68})_2$,

$C(O)NHOH$, $C(O)NHR^{68}$, $C(O)NHSO_2R^{68}$, $C(O)NR^{68}SO_2R^{68}$, SO_2NH_2 , SO_2NHR^{68} , $SO_2N(R^{68})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{68}$, $C(N)N(R^{68})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I ;

R^{68} es R^{69} , R^{70} , R^{71} o R^{72} ;

5 R^{69} es fenilo, que no está fusionado o está fusionado con R^{69A} ; R^{69A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{70} es heteroarilo, que no está fusionado o está fusionado con R^{70A} ; R^{70A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

10 R^{71} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{71A} ; R^{71A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{72} es alquilo, alquenilo o alqueniilo, cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre R^{73} , OR^{73} , SR^{73} , $S(O)R^{73}$, SO_2R^{73} , $C(O)R^{73}$, $CO(O)R^{73}$, $OC(O)R^{73}$, $OC(O)OR^{73}$, NH_2 , NHR^{73} , $N(R^{73})_2$, $NHC(O)R^{73}$, $NR^{73}C(O)R^{73}$, $NHS(O)_2R^{73}$, $NR^{73}S(O)_2R^{73}$, $NHC(O)OR^{73}$, $NR^{73}C(O)OR^{73}$, $NHC(O)NH_2$, $NHC(O)NHR^{73}$, $NHC(O)N(R^{73})_2$, $NR^{73}C(O)NHR^{73}$, $NR^{73}C(O)N(R^{73})_2$, $C(O)NH_2$, $C(O)NHR^{73}$, $C(O)N(R^{73})_2$, $C(O)NHOH$, $C(O)NHOR^{73}$, $C(O)NHSO_2R^{73}$, $C(O)NR^{73}SO_2R^{73}$, SO_2NH_2 , SO_2NHR^{73} , $SO_2N(R^{73})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{73}$, $C(N)N(R^{73})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I ;

20 R^{73} es alquilo, alquenilo, alqueniilo, fenilo, heteroarilo, cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo; y

donde las unidades representadas por R^{69} , R^{70} , y R^{71} no están sustituidas o están sustituidas con uno o dos o tres o cuatro sustituyentes seleccionados en forma independiente entre NH_2 , $C(O)NH_2$, $C(O)NHOH$, SO_2NH_2 , CF_3 , CF_2CF_3 , $C(O)H$, $C(O)OH$, $C(N)NH_2$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I .

Otra forma de realización se refiere a compuestos de fórmula (I) donde A^1 es N o $C(A^2)$; A^2 es H , y G^1 es H .

Otra forma de realización se refiere a compuestos de fórmula (I) donde A^1 es N o $C(A^2)$; A^2 es H ; G^1 es H , y B^1 es NHR^1 .

30 Otra forma de realización se refiere a compuestos de fórmula (I) donde A^1 es N o $C(A^2)$; A^2 es H ; G^1 es H , B^1 es NHR^1 ; y D^1 es H .

Otra forma de realización se refiere a compuestos de fórmula (I) donde A^1 es N o $C(A^2)$; A^2 es H ; G^1 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) donde A^1 es N o $C(A^2)$; A^2 es H ; G^1 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 de fórmula (I) o Fórmula (II), 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-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 5 4-{4-[(4'-cloro-1,1'-bifenil-2-il)metil]piperazin-1-il}-N-({4-[(3-morfolin-4-ilpropil)amino]-3-nitrofenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)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-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 10 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-(1H-pirrol[2,3-b]piridin-5-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-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 15 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)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- Trans-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)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(2-metoxietil)amino]-3-nitrofenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 20 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(3S)-tetrahidro-2H-piran-3-ilmetil]amino]fenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 25 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(3R)-tetrahidro-2H-piran-3-ilmetil]amino]fenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-(2-naftilsulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(2-metoxietil)amino]-3-[(trifluorometil)sulfonil]fenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-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-({3-nitro-4-(tetrahidro-2H-piran-4-ilmetoxi)fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({3-nitro-4-[(2,2,2-trifluoroetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({3-nitro-4-[(3,3,3-trifluoropropil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- Cis-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)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil]piperazin-1-il)-N-({4-[(1,4-dioxan-2-ilmetil)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil]piperazin-1-il)-N-({4-(1,4-dioxan-2-ilmetoxi)-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- Trans-4-(4-[[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil]piperazin-1-il)-N-({4-[(4-morfolin-4-ilciclohexil)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- Trans-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)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil]piperazin-1-il)-N-({5-ciano-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il}sulfonil)-2-(1H-pirrol[2,3-b]piridin-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-pirrol[2,3-b]piridin-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 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-pirrol[2,3-b]piridin-5-iloxi)benzamida;

- Cis-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)-2-(1H-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 5 4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-N-({5-cloro-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)-N-({4-[(tetrahidro-2H-piran-4-ilmetil)amino]-3-(trifluorometil)fenil}sulfonil})benzamida;
 10 4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)-N-({4-[(tetrahidro-2H-piran-4-ilmetil)amino]-3-(trifluorometil)sulfonil}fenil)sulfonil)benzamida;
 15 Trans-4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-N-({4-[(4-morfolin-4-ilciclohexil)amino]-3-[(trifluorometil)sulfonil}fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-N-({4-[(1-metilpiperidin-4-il)amino]-3-[(trifluorometil)sulfonil}fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 20 5-({[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzoil]amino}sulfonil)-2-(tetrahidro-2H-piran-4-ilmetoxi)nicotinamida;
 N-({5-bromo-6-[(1-metilpiperidin-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 25 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(1-metilpiperidin-4-il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({5-ciano-6-(1,4-dioxan-2-ilmetoxi)piridin-3-il}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 N-({5-bromo-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 30 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 N-({3-cloro-5-ciano-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 35

- 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-({2-cloro-5-fluoro-4-[(tetraidro-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5 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-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({5-ciano-6-[(4-fluorotetraidro-2H-piran-4-il)metoksi]piridin-3-il}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-[(3-cloro-4-{[2-(2-metoxietoksi)etil}sulfonil}fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[2-(2-metoxietoksi)etil}sulfonil]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-morfolin-4-ilciclohexil)oxi]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-({5-bromo-6-[(1-tetraidro-2H-piran-4-ilpiperidin-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- Cis-4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-N-({4-[(4-morfolin-4-ilciclohexil)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 Trans-N-({4-[(4-[bis(ciclopropilmetil)amino]ciclohexil)amino]-3-nitrofenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 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)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(morfolin-3-ilmetil)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-N-({4-[(4-metilpiperazin-1-il)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-morfolin-4-ilbut-2-inil)oxi]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 35

- 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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-oxo-3,4-dihidroquinazolin-6-il)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 5 Trans-4-(4-{[8-(4-clorofenil)espiro[4,5]dec-7-en-7-il]metil}piperazin-1-il)-N-({4-[(4-morfolin-4-ilciclohexil)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- Cis-4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-N-[(4-{[(4-metoxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 10 4-(4-{[8-(4-clorofenil)espiro[4,5]dec-7-en-7-il]metil}piperazin-1-il)-N-({4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- Trans-4-(4-{[8-(4-clorofenil)espiro[4,5]dec-7-en-7-il]metil}piperazin-1-il)-N-[(4-{[(4-metoxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 15 [(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({5-ciano-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 20 3-{[4-({[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]amino}sulfonil)-2-nitrofenoxi]metil}morfolina-4-carboxilato de tert-butilo ;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-(morfolin-3-ilmetoxi)-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 25 4-(4-{[8-(4-clorofenil)espiro[4,5]dec-7-en-7-il]metil}piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[1-(metilsulfonil)piperidin-4-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 30 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)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-[(4-cloro-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 35 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{[1-(2,2,2-trifluoroetil)piperidin-4-il]amino}fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([5-ciano-6-([1-tetrahidro-2H-piran-4-ilpiperidin-4-il]oxi)piridin-3-il]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([5-isopropil-6-
5 (tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-([3-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- y sus sales terapéuticamente aceptables, y sus metabolitos.
- 10 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-(2-fluoro-1-(fluorometil)etil]piperidin-4-il]amino)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-
15 iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-(2,2-difluoroetil)piperidin-4-il]amino)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-
20 iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-(1-morfolin-4-ilciclohexil)metil]amino)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- Trans-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-(diciclopropilamino)ciclohexil]amino)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-
25 iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-6,6-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([tetrahidro-2H-piran-4-ilmetil]amino)fenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 30 N-([5-bromo-6-([4-etilmorfolin-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-etilmorfolin-3-il]metoxi)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([4-tetrahidro-2H-piran-4-il]morfolin-3-il]metoxi)fenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-
35 iloxi)benzamida;

- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{[(3S)-1-tetrahidro-2H-piran-4-il]piperidin-3-il}amino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({5-ciano-6-
5 [(tetrahidro-2H-piran-4-ilmetil)amino]piridin-3-il}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
N-[(4-{[(4-aminotetrahidro-2H-piran-4-il)metil]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-
10 clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({5-ciano-6-[(4-morfolin-4-ilciclohexil)amino]piridin-3-il}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-ciano-4-
15 [(tetrahidro-2H-piran-4-ilmetil)amino]fenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(1S,3R)-3-morfolin-4-ilciclopentil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(1R,3S)-3-morfolin-4-ilciclopentil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(morfolin-2-ilmetil)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-
25 [(tetrahidrofurano-3-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(1-[cis-3-fluorotetrahidro-2H-piran-4-il]piperidin-4-il)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)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-ilazetidid-3-il)amino]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(1-tetrahidrofurano-3-ilazetidid-3-il)amino]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 35 iloxi)benzamida;

- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([(3R)-1-tetrahidro-2H-piran-4-ilpirrolidin-3-il]metil)amino)fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-fluorotetrahidro-2H-piran-4-il]metoxi)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-enil]metil)piperazin-1-il)-N-(4-([trans-4-hidroxiciclohexil]metoxi)-3-nitrofenil)sulfonil]benzamida;
- 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-enil]metil)piperazin-1-il)-N-(4-([cis-4-metoxiciclohexil]metoxi)-3-nitrofenil)sulfonil]benzamida;
- Cis-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-(ciclopropilamino)ciclohexil]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- Trans-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([4-(tetrahidro-2H-piran-4-ilamino)ciclohexil]amino)fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- Trans-N-([5-bromo-6-([4-morfolin-4-ilciclohexil]oxi)piridin-3-il)sulfonil]-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- Trans-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-metoxiciclohexil]metoxi)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-([4-([4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]amino)sulfonil]-2-nitrofenoxi]metil)-4-fluoropiperidin-1-carboxilato de tert-butilo ;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-fluoropiperidin-4-il]metoxi)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- Trans-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([4-(4-tetrahidro-2H-piran-4-ilpiperazin-1-il)ciclohexil]amino)fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-[2-fluoro-1-(fluorometil)etil]piperidin-4-il]metoxi)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([(3R)-1-tetrahidro-2H-piran-4-ilpirrolidin-3-il]amino)fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3R)-1-(2,2-dimetiltetrahidro-2H-piran-4-il)pirrolidin-3-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{[(3S)-1-tetrahidro-2H-piran-4-il]pirrolidin-3-il]amino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3S)-1-(2,2-dimetiltetrahidro-2H-piran-4-il)pirrolidin-3-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4-metilmorfolin-2-il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[4-(2-metoxietil)morfolin-2-il]metil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-[(4-{[(4-acetilmorfolin-2-il)metil]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[trans-4-(fluorometil)-1-oxetan-3-il]pirrolidin-3-il]metoxi}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-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)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{[1-oxetan-3-il]piperidin-4-il]amino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[1-ciclobutilpiperidin-4-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[1-(2,2-dimetiltetrahidro-2H-piran-4-il)piperidin-4-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3S)-1-ciclopropilpirrolidin-3-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{[1-tetrahidrofurano-3-il]piperidin-4-il]amino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3R)-1-ciclopropilpirrolidin-3-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-nitro-4-{[(3S)-1-tetrahidro-2H-piran-4-ilpirrolidin-3-il]metil}amino]fenil}sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[3-hidroxi-2,2-dimetilpropil]amino}-3-nitrofenil}sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[1-(metilsulfonil)piperidin-3-il]metil}amino]-3-nitrofenil}sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-[(4-{[(1-acetilpiperidin-3-il)metil]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3R)-1-(metilsulfonil)pirrolidin-3-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-3,3-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-nitro-4-{[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[1-[2-fluoro-1-(fluorometil)etil]azetidin-3-il]amino}-3-nitrofenil}sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[1-(metilsulfonil)pirrolidin-3-il]metil}amino]-3-nitrofenil}sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-[(4-{[(1-acetilpirrolidin-3-il)metil]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-[(4-{[(3R)-1-acetilpirrolidin-3-il]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[3-metoksi-2,2-dimetilpropil]amino}-3-nitrofenil}sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[(1R,3R)-3-hidroxiciclopentil]metil}amino]-3-nitrofenil}sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(1S,3S)-3-hidroxiciclopentil}metil}amino)-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(1S,3R)-3-hidroxiciclopentil}metil}amino)-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(1R,3S)-3-hidroxiciclopentil}metil}amino)-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(3-nitro-4-{{(3S)-2-oxopiperidin-3-il}amino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{1-[2-fluoro-1-(fluorometil)etil]azetidín-3-il}metil}amino)-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(3-nitro-4-{{(1-oxetan-3-ilazetidín-3-il)metil}amino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(3-nitro-4-{{(1-oxetan-3-ilpiperidin-4-il)metil}amino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(1-ciclopropilpiperidin-4-il)metil}amino)-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(4-(2-fluoroetil)morfolin-2-il}metil}amino)-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 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]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 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]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(4-fluoro-1-oxetan-3-ilpiperidin-4-il)metoxi)-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(2S)-4,4-difluoro-1-oxetan-3-ilpirrolidin-2-il}metoxi)-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(3-nitro-4-{{(4-tetrahidro-2H-piran-4-il morfolin-3-il)metil}amino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
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- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(4-ciclobutilmorfolin-3-il)metil}amino}-3-nitrofenil)sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-{{(4-tetrahidrofurano-3-ilmorfolin-3-il)metil}amino}fenil)sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{1-[2-fluoro-1-(fluorometil)etil]piperidin-4-il}metil}amino}-3-nitrofenil)sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{1-ciclopropil-4-fluoropiperidin-4-il}metoxi}-3-nitrofenil)sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{4-metoxibencil}amino}-3-nitrofenil)sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-{{3-(trifluorometoxi)bencil}amino}fenil)sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{3-metoxibencil}amino}-3-nitrofenil)sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{4-(difluorometoxi)bencil}amino}-3-nitrofenil)sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-(1,4-dioxaespiro[4,5]dec-8-ilamino)-3-nitrofenil)sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- Trans-N-{{4-{{4-(acetilamino)ciclohexil}amino}-3-nitrofenil)sulfonil}-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 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}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(3S)-1-(2-fluoroetil)pirrolidin-3-il}amino}-3-nitrofenil)sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(3S)-1-(2,2-difluoroetil)pirrolidin-3-il}amino}-3-nitrofenil)sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(3R)-1-(2-fluoroetil)pirrolidin-3-il}amino}-3-nitrofenil)sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(3-nitro-4-[(3S)-1-oxetan-3-ilpirrolidin-3-il]metoxi]fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({4-[(4-hidroxibencil)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({4-[(3-hidroxibencil)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(4-{3-(difluorometoxi)bencil}amino)-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({4-[(cis-3-morfolin-4-ilciclopentil]metil)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 Trans-4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(4-{4-[(metilsulfonil)amino]ciclohexil}amino)-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-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-[(trifluorometil)sulfonil]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({3-nitro-4-[(1-oxetan-3-ilpiperidin-4-il)metoxi]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({4-[(4-fluoro-1-tetrahidro-2H-piran-4-ilpiperidin-4-il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({4-[(4-fluoro-1-tetrahidrofurano-3-ilpiperidin-4-il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(4-{4-fluoro-1-(metilsulfonil)piperidin-4-il}metoxi)-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({3-nitro-4-[(3R)-1-oxetan-3-ilpirrolidin-3-il]metil}amino)fenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 Trans-4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({4-[(4-hidroxiciclohexil)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({4-[(4-{3-(dimetilamino)propoxi}bencil)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 35 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(4-{4-(2-morfolin-4-iletoxi)bencil}amino)-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({[(E)-4-hidroxi-1-adamantil]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({[(Z)-4-hidroxi-1-adamantil]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 5 N-({4-[(1S,4S)-biciclo[2,2,1]hept-5-en-2-ilmetoxi]-3-nitrofenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(1-metil-5-oxopirrolidin-3-il)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-([4-({[(1R,4R,5R,6S)-
- 10 5,6-dihidroxibiciclo[2,2,1]hept-2-il]metoxi)-3-nitrofenil}sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-([4-({[(1R,4R,5S,6R)-5,6-dihidroxibiciclo[2,2,1]hept-2-il]metoxi)-3-nitrofenil}sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 15 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(3-oxociclohexil)metoxi]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-5,5-dimetilciclohexa-1,3-dien-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 20 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-pirrol[2,3-b]piridin-5-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-pirrol[2,3-
- 25 b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-({[(3S)-1-oxetan-3-ilpirrolidin-3-il]metil}amino)fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 30 Cis-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-([3-nitro-4-({[(3S)-1-oxetan-3-ilpirrolidin-3-il]amino)fenil}sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-([4-2-(2-
- 35 metoxietoxi)etil]morfolin-2-il]metil}amino)-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

- 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]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-(N,N-dimetilglicil)morfolin-2-il]metil)amino]-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- ácido (2-([4-([4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]sulfamoil]-2-nitrofenil)amino]metil)morfolin-4-il)acético;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([4-(oxetan-3-il)morfolin-2-il]metil)amino]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([5-(metilsulfonil)-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil]-2-(1H-pirrol[2,3-b]piridin-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-[(trifluorometil)sulfonil]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-metiltetrahidro-2H-piran-4-il)metoxi]-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]sulfamoil]-2-nitrofenil)piperazin-1-carboxilato de etilo ;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-(morfolin-4-il)piperidin-1-il]-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([(3R)-1-(oxetan-3-il)pirrolidin-3-il]amino]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([(3R)-1-(1,3-difluoropropan-2-il)pirrolidin-3-il]amino)-3-[(trifluorometil)sulfonil]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-isopropilpiperidin-4-il]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-([4-([1-tert-butilpiperidin-4-il]amino)-3-nitrofenil)sulfonil]-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[1-(2-metoxietil)piperidin-3-il]metil}amino]-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[1-(cianometil)piperidin-3-il]metil}amino]-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[4-fluoro-1-metilpiperidin-4-il]metoxi]-3-[(trifluorometil)sulfonil]fenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 N-[(5-cloro-6-{[(3R)-1-(1,3-difluoropropan-2-il)pirrolidin-3-il]amino}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-{[4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzoil}sulfamoi]-2-nitrofenil}amino]piperazin-1-carboxilato de tert-butilo;
- 15 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-(pentafluoro- $\square^6$ -sulfanil)-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[4-metoxitetrahidro-2H-piran-4-il]metoxi]-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[(3R)-1-(1,3-difluoropropan-2-il)pirrolidin-3-il]oxi]-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-nitro-4-{[4-(oxetan-3-il)piperazin-1-il]amino}fenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-nitro-4-{[4-(tetrahidro-2H-piran-4-il)piperazin-1-il]amino}fenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-nitro-4-{(3R)-tetrahidrofurano-3-ilamino}fenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-{[4-{[1-tert-butilpiperidin-4-il]amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 35

- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-({[4-(oxetan-3-il)morfolin-2-il]metil}amino)-3-[(trifluorometil)sulfonil]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5 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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 N-[(5-cloro-6-{{(2S)-4-(cianometil)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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 N-[(5-cloro-6-{{(2R)-4-(cianometil)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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-({5-cloro-6-[3-hidroxi-2-(hidroximetil)-2-metilpropoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 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}piridin-3-il}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{{4-{{[4-(1,3-difluoropropan-2-il)morfolin-2-il]metil}amino)-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-[(5-cloro-6-{{1-(cianometil)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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

- 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}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 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}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-{{1-(oxetan-3-il)azetidid-3-il}amino}fenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 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}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 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}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-{{5-cloro-6-{{1-(N,N-dimetilglicil)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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 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}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-{4-{{4'-clorobifenil-2-il}metil}-4-metoxipiperidin-1-il}-N-{{5-cloro-6-{{4-fluorotetrahidro-2H-piran-4-il}metoxi}piridin-3-il}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-{4-{{4'-clorobifenil-2-il}metil}-4-metoxipiperidin-1-il}-N-{{3-nitro-4-{{tetrahidro-2H-piran-4-ilmetil}amino}fenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{9-(4-clorofenil)-3-(1,3-difluoropropan-2-il)-3-azaespiro[5,5]undec-8-en-8-il}metil}piperazin-1-il)-N-{{3-nitro-4-{{tetrahidro-2H-piran-4-ilmetil}amino}fenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{9-(4-clorofenil)-3-isopropil-3-azaespiro[5,5]undec-8-en-8-il}metil}piperazin-1-il)-N-{{3-nitro-4-{{tetrahidro-2H-piran-4-ilmetil}amino}fenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-{{9-(4-clorofenil)-3-(1,3-difluoropropan-2-il)-3-azaespiro[5,5]undec-8-en-8-il}metil}piperazin-1-il)-N-{{5-cloro-6-(tetrahydro-2H-piran-4-ilmetoxi)piridin-3-il}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{9-(4-clorofenil)-3-isopropil-3-azaespiro[5,5]undec-8-en-8-il}metil}piperazin-1-il)-N-{{5-cloro-6-(tetrahydro-2H-piran-4-ilmetoxi)piridin-3-il}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5 N-{{5-cloro-6-{{4-fluoro-1-metilpiperidin-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 N-{{5-cloro-6-{{1-(N,N-dimetilglicil)-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-{{4-{{4'-clorobifenil-2-il}metil}-4-fluoropiperidin-1-il)-N-{{3-nitro-4-{{tetrahydro-2H-piran-4-ilmetil}amino}fenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-{{4-{{4'-clorobifenil-2-il}metil}-4-fluoropiperidin-1-il)-N-{{5-cloro-6-{{4-fluorotetrahydro-2H-piran-4-il}metoxi}piridin-3-il}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 4-(4-{{9-(4-clorofenil)-3-isopropil-3-azaespiro[5,5]undec-8-en-8-il}metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)-N-{{4-{{tetrahydro-2H-piran-4-ilmetil}amino}-3-(trifluorometil)fenil}sulfonil}benzamida;
- N-{{5-cloro-6-{{(3R)-1-(1,3-difluoropropan-2-il)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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-{{2-(tetrahydrofurano-3-iloxi)etoxi}fenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{5-ciano-6-{{2-(tetrahydro-2H-piran-4-il)etoxi}piridin-3-il}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{3-furilmetoxi}-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-{{5-cloro-6-{{(3R)-1-(1,3-difluoropropan-2-il)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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
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- 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5 N-[(5-cloro-6-[[1-(1,3-difluoropropan-2-il)-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-({3-cloro-4-[(4-fluoro-1-metilpiperidin-4-il)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-ciano-4-(tetraidro-2H-piran-4-ilmetoxi)fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-[(5-cloro-6-[[1-(2,2-difluoroetil)-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-({3-cloro-4-[(4-fluorotetraidro-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({6-[[1-(1,3-difluoropropan-2-il)-4-fluoropiperidin-4-il]metoxi]-5-(trifluorometil)piridin-3-il}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({5-cloro-6-[2-(tetraidrofurano-2-il)etoxi]piridin-3-il}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}-3-metilpiperazin-1-il)-N-({3-nitro-4-[(tetraidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[[3-(ciclopropilamino)propil]amino]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-({5-cloro-6-(2-metoxietoxi)piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({5-fluoro-6-(tetraidro-2H-piran-4-ilmetoxi)piridin-3-il}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-[(3-cloro-4-[[1-(metoxiacetil)piperidin-4-il]metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
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- N-[(3-cloro-4-[[1-(N,N-dimetilglicil)piperidin-4-il]metoxi]fenil)sulfonil]-4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 Trans-4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohexil]metil]piperidin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 5 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)-N-[[6-(tetrahidro-2H-piran-4-ilmetoxi)-5-(trifluorometil)piridin-3-il]sulfonil]benzamida;
- N-({5-cloro-6-[(trans-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 10 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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({6-[(trans-4-metoxiciclohexil)metoxi]-5-(trifluorometil)piridin-3-il}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 15 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({6-[(cis-4-metoxiciclohexil)metoxi]-5-(trifluorometil)piridin-3-il}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-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]piperidin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 20 N-[(3-cloro-4-[[trans-4-(morfolin-4-il)ciclohexil]metoxi]fenil)sulfonil]-4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[4-({3-[ciclopropil(1,3-tiazol-5-ilmetil)amino]propil]amino)-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 25 N-({3-cloro-4-[(trans-4-hidroxiciclohexil)metoxi]fenil}sulfonil)-4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-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-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 30 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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[4-({3-[ciclopropil(2,2,2-trifluoroetil)amino]propil]amino)-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
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- N-[(3-cloro-4-[[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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3,5-difluoro-4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]fenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 5 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({3-[ciclopropil(oxetan-3-il)amino]propil}amino)-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 N-[(3-cloro-4-[[1-(1-metil-L-prolil)piperidin-4-il]metoxi]fenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 10 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3,4-difluoro-5-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]fenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 15 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperidin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperidin-1-il)-N-[[3-cloro-4-(tetrahidro-2H-piran-4-ilmetoxi)fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 20 2-[[4-[[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzoil]sulfamoil]-2-nitrofenil)amino]metil]morfolina-4-carboxilato de metilo;
 2-[[4-[[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzoil]sulfamoil]-2-nitrofenil)amino]metil]-N-etil-N-metilmorfolina-4-carboxamida;
 25 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]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({3-[ciclobutil(ciclopropil)amino]propil}amino)-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 30 4-(4-{[2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
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- 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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-cloro-4-(tetrahidrofurano-3-ilmetoxi)fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 5 4-(4-{[2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[(trans-4-hidroxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 N-{[3-cloro-4-{[4-fluorotetrahidro-2H-piran-4-il]metoxi}fenil)sulfonil]-4-(4-{[9-(4-clorofenil)-3-(oxetan-3-il)-3-azaespiro[5,5]undec-8-en-8-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 10 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[(2R)-4-ciclopropilmorfolin-2-il]metil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 15 4-(4-{[5-(4-clorofenil)espiro[2,5]oct-5-en-6-il]metil}piperazin-1-il)-N-{[3-nitro-4-{(tetrahidro-2H-piran-4-ilmetil)amino}fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 N-{[5-cloro-6-{[4-{ciclopropil(oxetan-3-il)amino}ciclohexil]metoxi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 20 4-(4-{[5-(4-clorofenil)espiro[2,5]oct-5-en-6-il]metil}piperazin-1-il)-N-{[4-{[(4-ciclopropilmorfolin-2-il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 N-{[3-cloro-4-{[4-ciclopropilmorfolin-2-il]metoxi}fenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 25 N-[(3-cloro-4-{[(4-ciclopropilmorfolin-2-il)metil]amino}fenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 2-{[(2-cloro-4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]sulfamoil}fenil)amino]metil}-N-etil-N-metilmorfolina-4-carboxamida;
 30 (2S)-2-{[(3-cloro-5-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]sulfamoil}piridin-2-il)oxi]metil}-N-etil-N-metilmorfolina-4-carboxamida;
 N-{[5-cloro-6-{[(4-ciclopropilmorfolin-2-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;

- 2-[[[3-cloro-5-[[4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzoil]sulfamoil]piridin-2-il)amino]metil]-N-etil-N-metilmorfolina-4-carboxamida;
- 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5 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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[4-[(2-cianoetil)(ciclopropil)amino]ciclohexil]amino]-3-nitrofenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-[(5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il)sulfonil]-4-(4-[[5-(4-clorofenil)espiro[2,5]oct-5-en-6-il]metil]piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 N-[(5-cloro-6-[(1R,2S,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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 N-[(5-cloro-6-[[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi]piridin-3-il)sulfonil]-4-(4-[[5-(4-clorofenil)espiro[2,5]oct-5-en-6-il]metil]piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[4-[(4-(3,3-difluoropirrolidin-1-il)ciclohexil]amino)-3-nitrofenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 35 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[4-((2,2-difluorociclopropil)amino)ciclohexil]amino]-3-nitrofenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[3-nitro-4-(2-oxaesp[iro][3,5]non-7-ilmetoxi)fenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 4-(4-[[2-(4-clorofenil)-5,5-bis(fluorometil)ciclohex-1-en-1-il]metil]piperazin-1-il)-N-((3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-((4-[(4-ciclopropilmorfolin-2-il)metoxi]-3-nitrofenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(4-[(trans-4-etil-4-hidroxiciclohexil)metil]amino)-3-nitrofenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(4-[(cis-4-etil-4-hidroxiciclohexil)metil]amino)-3-nitrofenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-5-(metoximetil)-5-metilciclohex-1-en-1-il]metil]piperazin-1-il)-N-((3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 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]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-((3-cloro-4-[(trans-4-hidroxi-4-metilciclohexil)metoxi]fenil)sulfonil)-4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
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- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(2-cianoetil)(ciclopropil)amino}-1-fluorociclohexil}metoxi)-3-nitrofenil}sulfonil]-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{5-nitro-6-
5 {{(tetrahidro-2H-piran-4-ilmetil)amino}piridin-3-il}sulfonil]-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-{{2-oxaespino[3,5]non-7-ilmetil)amino}fenil}sulfonil]-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(4-ciano-4-
10 metilciclohexil)metil}amino}-3-nitrofenil}sulfonil]-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- pivalato de {{4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzoil}}{4-{{(4-fluorotetrahidro-2H-piran-4-il)metoxi}-3-nitrofenil}sulfonil}amino}metilo;
- butirato de {{4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-
15 pirrololo[2,3-b]piridin-5-iloxi)benzoil}}{4-{{(4-fluorotetrahidro-2H-piran-4-il)metoxi}-3-nitrofenil}sulfonil}amino}metilo;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)-N-{{3-(tetrahidro-2H-piran-4-ilmetil)-3H-[1,2,3]triazolo[4,5-b]piridin-6-il}sulfonil}benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{6-{{(trans-4-hidroxi-4-metilciclohexil)metil}amino)-5-nitropiridin-3-il}sulfonil]-2-(1H-pirrololo[2,3-b]piridin-5-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-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 25 N-(4-{{4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzoil}sulfamoil}-2-nitrofenil)morfolina-4-carboxamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{4-(metoximetil)ciclohexil}metil}amino)-3-nitrofenil}sulfonil]-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 30 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-pirrololo[2,3-b]piridin-5-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-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
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4-(4-{{2-(4-clorofenil)-5-metoxi-5-metilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(trans-4-hidroxi-4-metilciclohexil)metil}amino}-3-nitrofenil)sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

4-(4-{{2-(4-clorofenil)-5-metoxi-5-metilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-
5 [(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida; y sus sales terapéuticamente aceptables, y sus metabolitos.

Otra forma de realización se refiere al compuesto 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-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida o una sal aceptable
10 farmacéuticamente del mismo.

Otra forma de realización se refiere al compuesto Trans-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}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida o una sal aceptable
farmacéuticamente del mismo.

Otra forma de realización se refiere al compuesto Cis-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}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida o una sal aceptable
15 farmacéuticamente del mismo.

Otra forma de realización se refiere al compuesto Trans-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}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida o una sal aceptable
20 farmacéuticamente del mismo.

Otra forma de realización se refiere al compuesto 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-pirrol[2,3-b]piridin-5-iloxi)benzamida o una sal aceptable
25 farmacéuticamente del mismo.

Otra forma de realización se refiere al compuesto 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-pirrol[2,3-b]piridin-5-iloxi)benzamida o
30 una sal aceptable farmacéuticamente del mismo.

Otra forma de realización se refiere al compuesto 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-pirrol[2,3-b]piridin-5-iloxi)benzamida o
una sal aceptable farmacéuticamente del mismo.

Otra forma de realización se refiere al compuesto 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-
35

il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida o una sal aceptable farmacéuticamente del mismo.

Otra forma de realización se refiere al compuesto N-({5-bromo-6-[(1-tetrahydro-2H-piran-4-il)piperidin-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida; o una sal aceptable farmacéuticamente del mismo.

Otra forma de realización se refiere al compuesto 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3R)-1-(metilsulfonil)pirrolidin-3-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida; o una sal aceptable farmacéuticamente del mismo.

Otra forma de realización se refiere al compuesto 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[3-(ciclopropil(oxetan-3-il)amino]propil}amino)-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida; o una sal aceptable farmacéuticamente del mismo.

Otra forma de realización se refiere al compuesto 4-(4-{[2-(4-clorofenil)-5-metoxi-5-metilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-[(tetrahydro-2H-piran-4-ilmetil)amino]fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida; o una sal aceptable farmacéuticamente del mismo.

Aún otra forma de realización se refiere a compuestos de fórmula (I) o Fórmula (II), que son 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida; 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3R)-1-(metilsulfonil)pirrolidin-3-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida; 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[3-(ciclopropil(oxetan-3-il)amino]propil}amino)-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida; o una sal aceptable farmacéuticamente del mismo.

Aún otra forma de realización se refiere a compuestos de fórmula (I) o Fórmula (II), que son N-[(5-cloro-6-{[1-(cianometil)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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[3-(ciclopropil(oxetan-3-il)amino]propil}amino)-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida; o una sal aceptable farmacéuticamente del mismo.

Aún otra forma de realización se refiere a compuestos de fórmula (I) o Fórmula (II), que son 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-pirrolo[2,3-b]piridin-5-

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-pirrolo[2,3-b]piridin-5-iloxi)benzamida o una sal aceptable farmacéuticamente del mismo.

Otra forma de realización se refiere al compuesto 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[3-(ciclopropil(oxetan-3-il)amino]propil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida; o una sal aceptable farmacéuticamente del mismo.

Aún otra forma de realización se refiere a compuestos de fórmula (I) o Fórmula (II), que son 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-
10 {[(3R)-1-tetrahidro-2H-piran-4-ilpirrolidin-3-il]metil]amino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida; 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4-metilmorfolin-2-il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida; o una sal aceptable farmacéuticamente del mismo.

Aún otra forma de realización se refiere a compuestos de fórmula (I) o Fórmula (II), que son 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-
15 {[(3S)-tetrahidro-2H-piran-3-ilmetil]amino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
20 N-[(5-bromo-6-[(1-tetrahidro-2H-piran-4-il)piperidin-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-pirrolo[2,3-b]piridin-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
25

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-[(3R)-1-tetrahidro-2H-piran-4-ilpirrolidin-3-il]metil]amino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4-metilmorfolin-2-il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
30

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3R)-1-(metilsulfonil)pirrolidin-3-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4-metoxitetrahidro-2H-piran-4-il)metoxi]-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
35

N-[(5-cloro-6-[[1-(cianometil)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-pirrol[2,3-b]piridin-5-iloxi)benzamida;

4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[4-([3-ciclopropil(oxetan-3-il)amino]propil)amino]-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

N-[(5-cloro-6-[[[(1R,2S,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-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;

4-(4-[[2-(4-clorofenil)-5-metoxi-5-metilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(3-nitro-4-[(tetrahidro-2H-piran-4-il)metil]amino]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida; o una sal aceptable farmacéuticamente del mismo.

Otra forma de realización se refiere al compuesto N-[(5-cloro-6-[[1-(cianometil)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-pirrol[2,3-b]piridin-5-iloxi)benzamida; o una sal aceptable farmacéuticamente del mismo.

Aún otra forma de realización se refiere a compuestos de fórmula (I) o Fórmula (II), que son 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-pirrol[2,3-b]piridin-5-iloxi)benzamida; 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[4-[(4-metoxitetrahidro-2H-piran-4-il)metoxi]-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida; o una sal aceptable farmacéuticamente del mismo.

Otra forma de realización se refiere al compuesto 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[4-[(4-metoxitetrahidro-2H-piran-4-il)metoxi]-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida o una sal aceptable farmacéuticamente del mismo.

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 de un compuesto de la fórmula (I) o de la fórmula (II)..

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) o de la fórmula (II).

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 la fórmula (I) o de la fórmula (II) y una cantidad terapéuticamente efectiva de un agente terapéutico adicional o más de un agente terapéutico adicional.

DESCRIPCIÓN DETALLADA DE LA INVENCION

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 "alqueno" 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 alquénilo" significa un grupo alquénilo que contiene 3-6 átomos de carbono. Los ejemplos representativos de alquénilos 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.

5 El término "alquénileno" 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 alquénileno" 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
10 ejemplos representativos de alquénileno incluyen, en un sentido no limitativo, $-CH=CH-$ y $-CH_2CH=CH-$.

El término "alquilo" según se usa en la presente, se refiere a 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,
15 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.
20

El término "alquileneno" 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 alquileneno" significa un grupo divalente derivado de un hidrocarburo saturado de cadena lineal o ramificada, que contiene entre x e y
25 átomos de carbono. Por ejemplo " C_2-C_6 alquileneno" significa un hidrocarburo saturado de cadena lineal o ramificada, que contiene entre 2 y 6 átomos de carbono. Los ejemplos representativos de alquilenenos 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 "alquínilo" según se usa en la presente, hace referencia a un grupo de cadena hidrocarbonada lineal o ramificada que contiene entre 2 y 10 átomos de carbono y que
30 contiene al menos un enlace triple carbono-carbono. El término " C_x-C_y alquínilo" significa un grupo hidrocarburo de cadena lineal o ramificada que contiene entre x e y átomos de carbono. Por ejemplo " C_3-C_6 alquínilo" 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
35 unión triple carbono-carbono. Los ejemplos representativos de alquínilo 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.

5 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.

10 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 monocíclico puede contener 1 ó 2 puentes alquileno, donde cada uno consiste en 1, 2 ó 3
15 átomos de carbono, cada uno de los cuales une 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[3.2.2]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
20 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
25 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 enlaces dobles. Los ejemplos representativos de grupos
30 cicloalquenilo monocíclicos incluyen, pero en un sentido no limitativo, ciclobutenilo, ciclopentenilo, ciclohexenilo, cicloheptenilo y ciclooctenilo. El anillo cicloalquenilo monocíclico puede contener 1 ó 2 puentes alquileno, donde cada uno consiste en 1, 2 ó 3 átomos de carbono, cada uno de los cuales une dos átomos de carbono no adyacentes del sistema de anillos. Los ejemplos representativos de los grupos cicloalquenilo con puente
35 incluyen, pero de manera no taxativa, 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 enlaces triples. El anillo cicloalquinilo monocíclico puede contener 1 o 2 puentes alquileo, 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 de manera independiente 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 de manera independiente entre el grupo que consiste en O, N y S y cero enlaces 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, 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, tritiano y tritiano.

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 de manera independiente entre el grupo que consiste en O, N y S y una o más enlaces 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 "fenilo", según se usa en la presente, significa un radical monovalente formado por eliminación de un átomo de hidrógeno del benceno.

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 alquileo, del cual ambos extremos están unidas al mismo átomo de carbono y pueden ser ejemplificados por C₂-espiroalquilo, C₃-espiroalquilo, C₄-espiroalquilo, C₅-espiroalquilo, C₆-espiroalquilo, C₇-espiroalquilo, C₈-espiroalquilo, C₉-espiroalquilo y semejantes.

El término "espiroheteroalquilo", según se usa aquí, significa espiroalquilo donde una o dos unidades CH₂ han sido reemplazadas por una unidad que se selecciona de manera independiente entre: O, C(O), CNOH, CNOCH₃, S, S(O), SO₂ 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 CH₂ han sido reemplazadas por una unidad que se selecciona de manera independiente entre: O, C(O), CNOH, CNOCH₃, S, S(O), SO₂ 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 CH₂ que no han sido reemplazadas o han sido reemplazadas por una unidad que se selecciona de manera independiente entre: O, C(O), CNOH, CNOCH₃, S, S(O), SO₂ o NH y una o dos unidades CH han sido reemplazadas por N.

El término "C₂-C₅-espiroalquilo", según se usa aquí, significa C₂-espiroalquilo, C₃-espiroalquilo, C₄-espiroalquilo y C₅-espiroalquilo.

El término "C₂-espiroalquilo", según se usa aquí, significa et-1,2-ileno, del cual ambos extremos remplazan átomos de hidrógeno de la misma unidad CH₂.

El término "C₃-espiroalquilo", según se usa aquí, significa prop-1,3-ileno, del cual ambos extremos remplazan átomos de hidrógeno de la misma unidad CH₂.

5 El término "C₄-espiroalquilo", según se usa aquí, significa but-1,4-ileno, del cual ambos extremos remplazan átomos de hidrógeno de la misma unidad CH₂.

El término "C₅-espiroalquilo", según se usa aquí, significa pent-1,5-ileno, del cual ambos extremos remplazan átomos de hidrógeno de la misma unidad CH₂.

10 El término "C₆-espiroalquilo", según se usa aquí, significa hex-1,6-ileno, del cual ambos extremos remplazan átomos de hidrógeno de la misma unidad CH₂.

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-hidroxí-5-clorobencilideno, 2-hidroxí-1-naftil-metileno, 3-hidroxí-4-piridilmetileno, ciclohexilideno, 2-etoxicarbonilciclohexilideno, 2-etoxicarbonilciclopentilideno, 2-acetilciclohexilideno, 3,3-dimetil-5-oxíciclo-hexilideno, difenilfosforilo, dibencilfosforilo, 5-metil-2-oxo-2H-1,3-dioxol-4-il-metilo, trimetilsililo, trietilsililo y trifenilsililo.

25 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, 30 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.

35 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, metiltiommetilo, 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.

15 *Compuestos*

Los compuestos de la presente pueden presentarse como isómeros geométricos. Los compuestos de esta invención también pueden contener dobles enlaces carbono-carbono o dobles enlaces carbono-nitrógeno en la configuración E o Z, en donde el término "E" representa sustituyentes de orden superior a ambos lados del enlace doble carbono-carbono o carbono-nitrógeno y el término "Z" representa sustituyentes de orden superior por el mismo lado del enlace doble carbono-carbono o carbono-nitrógeno, determinado según 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 consultar ejemplos, véase C. D. Jones, M. Kaselj, R. N. Salvatore, W. J. le Noble *J. Org. Chem.* **1998**, 63, 2758-2760.

Los compuestos de la presente invención pueden contener 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 Recommendations 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,

preferentemente en más de aproximadamente 85%-90%, más preferentemente en más de aproximadamente 95%-99%, y aún más preferentemente 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.

Compuestos marcados o enriquecidos en un isótopo

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 yodo incluyen, pero en un sentido no limitativo, ^2H , ^3H , ^{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/o de otros átomos se encuentran dentro del alcance de esta invención.

En otra forma de realización, los compuestos marcados con isótopos contienen deuterio (^2H), tritio (^3H) 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 $\text{D}_2\text{SO}_4/\text{D}_2\text{O}$. 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 de drogas 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, las drogas que contienen isótopos no radioactivos, tales como las drogas deuteradas denominadas "drogas pesadas", 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; Thomson J F, *Ann. New York Acad. Sci.*, 1960 84: 736; Czajka 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)).

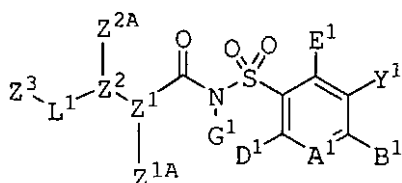
Una marcación estable con isótopos de una droga alterar sus propiedades fisicoquímicas tales como pKa y solubilidad de lípidos. Estos efectos y alteraciones pueden afectar la respuesta farmacodinámica de la molécula de droga si la sustitución isotópica afecta una región comprometida en una interacción 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.

Los grupos adecuados para A^1 , B^1 , D^1 , E^1 , G^1 , Y^1 , L^1 , Z^{1A} , Z^{2A} , Z^1 , Z^2 y Z^3 en los compuestos de la fórmula (I) se seleccionan de manera independiente. Las formas de realización descritas de la presente invención se pueden combinar. Dicha combinación está contemplada y se encuentra dentro del alcance de la presente invención. Por ejemplo, se

5 contempla que las formas de realización para cualquiera de A^1 , B^1 , D^1 , E^1 , G^1 , Y^1 , L^1 , Z^{1A} , Z^{2A} , Z^1 , Z^2 y Z^3 se pueden combinar con las formas de realización definidas para cualquiera de los demás A^1 , B^1 , D^1 , E^1 , G^1 , Y^1 , L^1 , Z^{1A} , Z^{2A} , Z^1 , Z^2 y Z^3 .

Una forma de realización de esta invención, por lo tanto, se refiere a compuestos o sus sales terapéuticamente aceptables, que son útiles como inhibidores de proteínas anti-

10 apoptóticas Bcl-2, los compuestos de fórmula (I)



(I),

donde

A^1 es N o $C(A^2)$;

15 A^2 es H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$, $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 , $C(O)OH$, $C(O)NH_2$ o $C(O)OR^{1A}$;

20

B^1 es H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$, $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 , $C(O)OH$, $C(O)NH_2$ o $C(O)OR^{1A}$;

25

D^1 es H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$, $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 , $C(O)OH$, $C(O)NH_2$ o $C(O)OR^{1A}$;

30

$C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 , $C(O)OH$, $C(O)NH_2$ o $C(O)OR^{1A}$;

E^1 es H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$,
 5 $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$, $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 , $C(O)OH$, $C(O)NH_2$ o $C(O)OR^{1A}$; y

10 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} , SO_2R^{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

E^1 y Y^1 , junto con los átomos a los cuales están unidos, son benceno, naftileno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; y

15 A^2 , B^1 , y D^1 se seleccionan en forma independiente entre H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$,
 20 $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 , $C(O)OH$, $C(O)NH_2$ o $C(O)OR^{1A}$; o

Y^1 y B^1 , junto con los átomos a los cuales están unidos, son benceno, naftileno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; y

25 A^2 , D^1 , y E^1 se seleccionan en forma independiente entre H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$,
 30 $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 , $C(O)OH$, $C(O)NH_2$ o $C(O)OR^{1A}$; o

A^2 y B^1 , junto con los átomos a los cuales están unidos, son benceno, naftileno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; y

35 D^1 , E^1 , y Y^1 se seleccionan en forma independiente entre H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$,

$\text{NR}^1\text{C}(\text{O})\text{R}^1$, $\text{NHC}(\text{O})\text{OR}^1$, $\text{NR}^1\text{C}(\text{O})\text{OR}^1$, $\text{NHC}(\text{O})\text{NH}_2$, $\text{NHC}(\text{O})\text{NHR}^1$, $\text{NHC}(\text{O})\text{N}(\text{R}^1)_2$,
 $\text{NR}^1\text{C}(\text{O})\text{NHR}^1$, $\text{NR}^1\text{C}(\text{O})\text{N}(\text{R}^1)_2$, SO_2NH_2 , SO_2NHR^1 , $\text{SO}_2\text{N}(\text{R}^1)_2$, NHSO_2R^1 , $\text{NR}^1\text{SO}_2\text{R}^1$,
 $\text{NHSO}_2\text{NHR}^1$, $\text{NHSO}_2\text{N}(\text{R}^1)_2$, $\text{NR}^1\text{SO}_2\text{NHR}^1$, $\text{NR}^1\text{SO}_2\text{N}(\text{R}^1)_2$, $\text{C}(\text{O})\text{NHNOH}$, $\text{C}(\text{O})\text{NHNOR}^1$,
 $\text{C}(\text{O})\text{NHSO}_2\text{R}^1$, $\text{C}(\text{NH})\text{NH}_2$, $\text{C}(\text{NH})\text{NHR}^1$, $\text{C}(\text{NH})\text{N}(\text{R}^1)_2$, $\text{NHSO}_2\text{NHR}^1$, $\text{NHSO}_2\text{N}(\text{CH}_3)\text{R}^1$,
 5 $\text{N}(\text{CH}_3)\text{SO}_2\text{N}(\text{CH}_3)\text{R}^1$, F , Cl , Br , I , CN , NO_2 , N_3 , OH , $\text{C}(\text{O})\text{H}$, CHNOH , $\text{CH}(\text{NOCH}_3)$, CF_3 ,
 $\text{C}(\text{O})\text{OH}$, $\text{C}(\text{O})\text{NH}_2$ o $\text{C}(\text{O})\text{OR}^{1A}$; o

A^2 y D^1 , junto con los átomos a los cuales están unidos, son benceno, naftaleno,
 heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; y

B^1 , E^1 , y Y^1 se seleccionan en forma independiente entre H , R^1 , OR^1 , SR^1 , $\text{S}(\text{O})\text{R}^1$,
 10 SO_2R^1 , $\text{C}(\text{O})\text{R}^1$, $\text{C}(\text{O})\text{OR}^1$, $\text{OC}(\text{O})\text{R}^1$, NHR^1 , $\text{N}(\text{R}^1)_2$, $\text{C}(\text{O})\text{NHR}^1$, $\text{C}(\text{O})\text{N}(\text{R}^1)_2$, $\text{NHC}(\text{O})\text{R}^1$,
 $\text{NR}^1\text{C}(\text{O})\text{R}^1$, $\text{NHC}(\text{O})\text{OR}^1$, $\text{NR}^1\text{C}(\text{O})\text{OR}^1$, $\text{NHC}(\text{O})\text{NH}_2$, $\text{NHC}(\text{O})\text{NHR}^1$, $\text{NHC}(\text{O})\text{N}(\text{R}^1)_2$,
 $\text{NR}^1\text{C}(\text{O})\text{NHR}^1$, $\text{NR}^1\text{C}(\text{O})\text{N}(\text{R}^1)_2$, SO_2NH_2 , SO_2NHR^1 , $\text{SO}_2\text{N}(\text{R}^1)_2$, NHSO_2R^1 , $\text{NR}^1\text{SO}_2\text{R}^1$,
 $\text{NHSO}_2\text{NHR}^1$, $\text{NHSO}_2\text{N}(\text{R}^1)_2$, $\text{NR}^1\text{SO}_2\text{NHR}^1$, $\text{NR}^1\text{SO}_2\text{N}(\text{R}^1)_2$, $\text{C}(\text{O})\text{NHNOH}$, $\text{C}(\text{O})\text{NHNOR}^1$,
 $\text{C}(\text{O})\text{NHSO}_2\text{R}^1$, $\text{C}(\text{NH})\text{NH}_2$, $\text{C}(\text{NH})\text{NHR}^1$, $\text{C}(\text{NH})\text{N}(\text{R}^1)_2$, $\text{NHSO}_2\text{NHR}^1$, $\text{NHSO}_2\text{N}(\text{CH}_3)\text{R}^1$,
 15 $\text{N}(\text{CH}_3)\text{SO}_2\text{N}(\text{CH}_3)\text{R}^1$, F , Cl , Br , I , CN , NO_2 , N_3 , OH , $\text{C}(\text{O})\text{H}$, CHNOH , $\text{CH}(\text{NOCH}_3)$, CF_3 ,
 $\text{C}(\text{O})\text{OH}$, $\text{C}(\text{O})\text{NH}_2$ o $\text{C}(\text{O})\text{OR}^{1A}$;

G^1 es H , o $\text{C}(\text{O})\text{O}$;

R es alquilo;

R^1 es R^2 , R^3 , R^4 o R^5 ;

20 R^{1A} es cicloalquilo, cicloalquenilo o cicloalquinilo;

R^2 es fenilo, que no está fusionado o está fusionado con R^{2A} ; R^{2A} es benceno,
 heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^3 es heteroarilo, que no está fusionado o está fusionado con R^{3A} ; R^{3A} es benceno,
 heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

25 R^4 es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno
 de los cuales no está fusionado o está fusionado con R^{4A} ; R^{4A} es benceno, heteroareno,
 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 en forma independiente entre
 30 R^6 , $\text{NC}(\text{R}^{6A})(\text{R}^{6B})$, R^7 , OR^7 , SR^7 , $\text{S}(\text{O})\text{R}^7$, SO_2R^7 , NHR^7 , $\text{N}(\text{R}^7)_2$, $\text{C}(\text{O})\text{R}^7$, $\text{C}(\text{O})\text{NH}_2$, $\text{C}(\text{O})\text{NHR}^7$,
 $\text{C}(\text{O})\text{N}(\text{R}^7)_2$, $\text{NHC}(\text{O})\text{R}^7$, $\text{NR}^7\text{C}(\text{O})\text{R}^7$, NHSO_2R^7 , $\text{NHC}(\text{O})\text{OR}^7$, SO_2NH_2 , SO_2NHR^7 , $\text{SO}_2\text{N}(\text{R}^7)_2$,
 $\text{NHC}(\text{O})\text{NH}_2$, $\text{NHC}(\text{O})\text{NHR}^7$, $\text{NHC}(\text{O})\text{CH}(\text{CH}_3)\text{NHC}(\text{O})\text{CH}(\text{CH}_3)\text{NH}_2$,
 $\text{NHC}(\text{O})\text{CH}(\text{CH}_3)\text{NHC}(\text{O})\text{CH}(\text{CH}_3)\text{NHR}^7$, OH , (O) , $\text{C}(\text{O})\text{OH}$, N_3 , CN , NH_2 , CF_3 , CF_2CF_3 , F , Cl ,
 Br o I ;

35 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 , $\text{NH}(\text{CH}_3)$ o $\text{N}(\text{CH}_3)_2$;

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 sin reemplazar o reemplazada con O, C(O), CNOH, CNOCH₃, S, S(O),
5 SO₂ 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 R^{8A} ; R^{8A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^9 es heteroarilo, que no está fusionado o está fusionado con R^{9A} ; R^{9A} es benceno,
10 heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{10} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{10A} ; R^{10A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{11} es alquilo, alquenilo o alquinilo, cada uno de los cuales no está sustituido o está
15 sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre R^{12} , OR^{12} , SR^{12} , $S(O)R^{12}$, SO_2R^{12} , $C(O)R^{12}$, $CO(O)R^{12}$, $OC(O)R^{12}$, $OC(O)OR^{12}$, NH_2 , NHR^{12} , $N(R^{12})_2$, $NHC(O)R^{12}$, $NR^{12}C(O)R^{12}$, $NHS(O)_2R^{12}$, $NR^{12}S(O)_2R^{12}$, $NHC(O)OR^{12}$, $NR^{12}C(O)OR^{12}$, $NHC(O)NH_2$, $NHC(O)NHR^{12}$, $NHC(O)N(R^{12})_2$, $NR^{12}C(O)NHR^{12}$, $NR^{12}C(O)N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, $C(O)NHOH$, $C(O)NHOR^{12}$, $C(O)NHSO_2R^{12}$, $C(O)NR^{12}SO_2R^{12}$,
20 SO_2NH_2 , SO_2NHR^{12} , $SO_2N(R^{12})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{12}$, $C(N)N(R^{12})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_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 R^{13A} ; R^{13A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{14} es heteroarilo, que no está fusionado o está fusionado con R^{14A} ; R^{14A} es benceno,
25 heteroareno, 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 R^{15A} ; R^{15A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

30 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 R^{18A} ; R^{18A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{19} es heteroarilo, que no está fusionado o está fusionado con R^{19A} ; R^{19A} es benceno,
35 heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{20} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo cada uno de los cuales no está fusionado o está fusionado con R^{20A} ; R^{20A} es benceno, heteroareno, 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 en forma independiente entre R^{22} , OR^{22} , SR^{22} , $S(O)R^{22}$, SO_2R^{22} , $C(O)R^{22}$, $CO(O)R^{22}$, $OC(O)R^{22}$, $OC(O)OR^{22}$, NH_2 , NHR^{22} , $N(R^{22})_2$, $NHC(O)R^{22}$, $NR^{22}C(O)R^{22}$, $NHS(O)_2R^{22}$, $NR^{22}S(O)_2R^{22}$, $NHC(O)OR^{22}$, $NR^{22}C(O)OR^{22}$, $NHC(O)NH_2$, $NHC(O)NHR^{22}$, $NHC(O)N(R^{22})_2$, $NR^{22}C(O)NHR^{22}$, $NR^{22}C(O)N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, $C(O)NHOH$, $C(O)NHOR^{22}$, $C(O)NHSO_2R^{22}$, $C(O)NR^{22}SO_2R^{22}$, SO_2NH_2 , SO_2NHR^{22} , $SO_2N(R^{22})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{22}$, $C(N)N(R^{22})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_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 R^{23A} ; R^{23A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{24} es heteroareno, que no está fusionado o está fusionado con R^{24A} ; R^{24A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{25} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{25A} ; R^{25A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

Z^1 es R^{26} o R^{27} ;

Z^2 es R^{28} , R^{29} o R^{30} ;

Z^{1A} y Z^{2A} están ambos ausentes o se toman juntos para formar CH_2 , CH_2CH_2 o Z^{12A} ;

Z^{12A} es C_2 - C_6 -alquileno con uno dos unidades $CH\#2$ se reemplaza con NH , $N(CH_3)$, S , $S(O)$ o SO_2 ;

L^1 es un R^{37} , OR^{37} , SR^{37} , $S(O)R^{37}$, SO_2R^{37} , $C(O)R^{37}$, $CO(O)R^{37}$, $OC(O)R^{37}$, $OC(O)OR^{37}$, NHR^{37} , $C(O)NH$, $C(O)NR^{37}$, $C(O)NHOR^{37}$, $C(O)NHSO_2R^{37}$, SO_2NH , SO_2NHR^{37} , $C(N)NH$, $C(N)NHR^{37}$;

R^{26} es fenileno, que no está fusionado o está fusionado con R^{26A} ; R^{26A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{27} es heteroarileno, que no está fusionado o está fusionado con R^{27A} ; R^{27A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{28} es fenileno, que no está fusionado o está fusionado con R^{28A} ; R^{28A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{29} es heteroarileno, que no está fusionado o está fusionado con R^{29A} ; R^{29A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{30} es cicloalquileno, cicloalquenileno, heterocicloalquileno o heterocicloalquenileno, cada uno de los cuales no está fusionado o está fusionado con R^{30A} ; R^{30A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{37} es una unión o R^{37A} ;

5 R^{37A} es alquileno, alquenileno, o alquinileno, cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre R^{37B} , OR^{37B} , SR^{37B} , $S(O)R^{37B}$, SO_2R^{37B} , $C(O)R^{37B}$, $CO(O)R^{37B}$, $OC(O)R^{37B}$, $OC(O)OR^{37B}$, NH_2 , NHR^{37B} , $N(R^{37B})_2$, $NHC(O)R^{37B}$, $NR^{37B}C(O)R^{37B}$, $NHS(O)_2R^{37B}$, $NR^{37B}S(O)_2R^{37B}$, $NHC(O)OR^{37B}$, $NR^{37B}C(O)OR^{37B}$, $NHC(O)NH_2$, $NHC(O)NHR^{37B}$, $NHC(O)N(R^{37B})_2$,
10 $NR^{37B}C(O)NHR^{37B}$, $NR^{37B}C(O)N(R^{37B})_2$, $C(O)NH_2$, $C(O)NHR^{37B}$, $C(O)N(R^{37B})_2$, $C(O)NHOH$, $C(O)NHOR^{37B}$, $C(O)NHSO_2R^{37B}$, $C(O)NR^{37B}SO_2R^{37B}$, SO_2NH_2 , SO_2NHR^{37B} , $SO_2N(R^{37B})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{37B}$, $C(N)N(R^{37B})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br e I ;

R^{37B} es alquilo, alquenilo, alquinilo, o R^{37C} ;

15 R^{37C} es fenilo, heteroarilo, cicloalquilo, cicloalquenilo, heterocicloalquilo, o heterocicloalquenilo;

Z^3 es R^{38} , R^{39} o R^{40} ;

R^{38} es fenilo, que no está fusionado o está fusionado con R^{38A} ; R^{38A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

20 R^{39} es heteroarilo, que no está fusionado o está fusionado con R^{39A} ; R^{39A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{40} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{40A} ; R^{40A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

25 donde las unidades representadas por R^{26} y R^{27} están sustituidas (por ejemplo, si Z^{1A} y Z^{2A} están ausentes) o adicionalmente sustituidas (por ejemplo, si Z^{1A} y Z^{2A} están presentes) con R^{41} , OR^{41} , SR^{41} , $S(O)R^{41}$, SO_2R^{41} , $C(O)R^{41}$, $CO(O)R^{41}$, $OC(O)R^{41}$, $OC(O)OR^{41}$, NHR^{41} , $N(R^{41})_2$, $NHC(O)R^{41}$, $NR^{41}C(O)R^{41}$, $NHS(O)_2R^{41}$, $NR^{41}S(O)_2R^{41}$, $NHC(O)OR^{41}$, $NR^{41}C(O)OR^{41}$, $NHC(O)NHR^{41}$, $NHC(O)N(R^{41})_2$, $NR^{41}C(O)NHR^{41}$, $NR^{41}C(O)N(R^{41})_2$, $C(O)NHR^{41}$, $C(O)N(R^{41})_2$,
30 $C(O)NHOR^{41}$, $C(O)NHSO_2R^{41}$, $C(O)NR^{41}SO_2R^{41}$, SO_2NHR^{41} , $SO_2N(R^{41})_2$, $C(N)NHR^{41}$, o $C(N)N(R^{41})_2$;

R^{41} es heteroarilo, que está fusionado con R^{43A} ; R^{43A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; que no está fusionado o está fusionado con benceno, heteroareno o R^{43B} ; R^{43B} es cicloalcano, cicloalqueno,
35 heterocicloalcano o heterocicloalqueno;

- donde las unidades cíclicas representadas por E¹ y Y¹ juntos, Y¹ y B¹ juntos, A² y B¹ juntos, A² y D¹ juntos, R^{1A}, R², R^{2A}, R³, R^{3A}, R⁴, R^{4A}, R⁶, R^{6C}, R⁸, R^{8A}, R⁹, R^{9A}, R¹⁰, R^{10A}, R¹³, R^{13A}, R¹⁴, R^{14A}, R¹⁵, R^{15A}, R¹⁸, R^{18A}, R¹⁹, R^{19A}, R²⁰, R^{20A}, R²³, R^{23A}, R²⁴, R^{24A}, R²⁵, R^{25A}, R²⁶, R^{26A}, R²⁷, R^{27A}, R²⁸, R^{28A}, R²⁹, R^{29A}, R³⁰, R^{30A}, R^{37B}, R³⁸, R^{38A}, R³⁹, R^{39A}, R⁴⁰, y R^{40A} no están
- 5 sustituidas, no están adicionalmente sustituidas, están sustituidas o adicionalmente sustituidas en forma independiente con uno o dos o tres o cuatro o cinco sustituyentes seleccionados en forma independiente entre R^{57A}, R⁵⁷, OR⁵⁷, SR⁵⁷, S(O)R⁵⁷, SO₂R⁵⁷, C(O)R⁵⁷, CO(O)R⁵⁷, OC(O)R⁵⁷, OC(O)OR⁵⁷, NH₂, NHR⁵⁷, N(R⁵⁷)₂, NHC(O)R⁵⁷, NR⁵⁷C(O)R⁵⁷, NHS(O)₂R⁵⁷, NR⁵⁷S(O)₂R⁵⁷, NHC(O)OR⁵⁷, NR⁵⁷C(O)OR⁵⁷, NHC(O)NH₂, NHC(O)NHR⁵⁷, NHC(O)N(R⁵⁷)₂, NR⁵⁷C(O)NHR⁵⁷, NR⁵⁷C(O)N(R⁵⁷)₂, C(O)NH₂, C(O)NHR⁵⁷, C(O)N(R⁵⁷)₂, C(O)NHOH, C(O)NHOR⁵⁷, C(O)NHSO₂R⁵⁷, C(O)NR⁵⁷SO₂R⁵⁷, SO₂NH₂, SO₂NHR⁵⁷, SO₂N(R⁵⁷)₂, C(O)H, C(O)OH, C(N)NH₂, C(N)NHR⁵⁷, C(N)N(R⁵⁷)₂, CNOH, CNOCH₃, OH, (O), CN, N₃, NO₂, CF₃, CF₂CF₃, OCF₃, OCF₂CF₃, F, Cl, Br o I;
- R^{57A} es espiroalquilo, o espiroheteroalquilo;
- 15 R⁵⁷ es R⁵⁸, R⁵⁹, R⁶⁰ o R⁶¹;
- R⁵⁸ es fenilo, que no está fusionado o está fusionado con R^{58A}; R^{58A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;
- R⁵⁹ es heteroarilo, que no está fusionado o está fusionado con R^{59A}; R^{59A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;
- 20 R⁶⁰ es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{60A}; R^{60A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;
- R⁶¹ 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
- 25 R⁶², OR⁶², SR⁶², S(O)R⁶², SO₂R⁶², C(O)R⁶², CO(O)R⁶², OC(O)R⁶², OC(O)OR⁶², NH₂, NHR⁶², N(R⁶²)₂, NHC(O)R⁶², NR⁶²C(O)R⁶², NHS(O)₂R⁶², NR⁶²S(O)₂R⁶², NHC(O)OR⁶², NR⁶²C(O)OR⁶², NHC(O)NH₂, NHC(O)NHR⁶², NHC(O)N(R⁶²)₂, NR⁶²C(O)NHR⁶², NR⁶²C(O)N(R⁶²)₂, C(O)NH₂, C(O)NHR⁶², C(O)N(R⁶²)₂, C(O)NHOH, C(O)NHOR⁶², C(O)NHSO₂R⁶², C(O)NR⁶²SO₂R⁶², SO₂NH₂, SO₂NHR⁶², SO₂N(R⁶²)₂, C(O)H, C(O)OH, C(N)NH₂, C(N)NHR⁶², C(N)N(R⁶²)₂, CNOH, CNOCH₃, OH, (O), CN, N₃, NO₂, CF₃, CF₂CF₃, OCF₃, OCF₂CF₃, F, Cl, Br o I;
- 30 R⁶² es R⁶³, R⁶⁴, R⁶⁵ o R⁶⁶;
- R⁶³ es fenilo, que no está fusionado o está fusionado con R^{63A}; R^{63A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;
- R⁶⁴ es heteroarilo, que no está fusionado o está fusionado con R^{64A}; R^{64A} es benceno,
- 35 heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{65} es cicloalquilo, cicloalquenilo, heterocicloalquilo, o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{65A} ; R^{65A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{66} es alquilo, alquenilo o alquienilo, cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre R^{67} , OR^{67} , SR^{67} , $S(O)R^{67}$, SO_2R^{67} , $C(O)R^{67}$, $CO(O)R^{67}$, $OC(O)R^{67}$, $OC(O)OR^{67}$, NH_2 , NHR^{67} , $N(R^{67})_2$, $NHC(O)R^{67}$, $NR^{67}C(O)R^{67}$, $NHS(O)_2R^{67}$, $NR^{67}S(O)_2R^{67}$, $NHC(O)OR^{67}$, $NR^{67}C(O)OR^{67}$, $NHC(O)NH_2$, $NHC(O)NHR^{67}$, $NHC(O)N(R^{67})_2$, $NR^{67}C(O)NHR^{67}$, $NR^{67}C(O)N(R^{67})_2$, $C(O)NH_2$, $C(O)NHR^{67}$, $C(O)N(R^{67})_2$, $C(O)NHOH$, $C(O)NHOR^{67}$, $C(O)NHSO_2R^{67}$, $C(O)NR^{67}SO_2R^{67}$, SO_2NH_2 , SO_2NHR^{67} , $SO_2N(R^{67})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{67}$, $C(N)N(R^{67})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I sustituyentes;

R^{67} es alquilo, alquenilo, alquinilo, fenilo, heteroarilo, cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo;

donde las unidades cíclicas representadas por R^{57A} , R^{58} , R^{59} , R^{60} , R^{63} , R^{64} , R^{65} , y R^{67} no están sustituidas o están sustituidas con uno o dos o tres o cuatro sustituyentes seleccionados en forma independiente entre R^{68} , OR^{68} , SR^{68} , $S(O)R^{68}$, SO_2R^{68} , $C(O)R^{68}$, $CO(O)R^{68}$, $OC(O)R^{68}$, $OC(O)OR^{68}$, NH_2 , NHR^{68} , $N(R^{68})_2$, $NHC(O)R^{68}$, $NR^{68}C(O)R^{68}$, $NHS(O)_2R^{68}$, $NR^{68}S(O)_2R^{68}$, $NHC(O)OR^{68}$, $NR^{68}C(O)OR^{68}$, $NHC(O)NH_2$, $NHC(O)NHR^{68}$, $NHC(O)N(R^{68})_2$, $NR^{68}C(O)NHR^{68}$, $NR^{68}C(O)N(R^{68})_2$, $C(O)NH_2$, $C(O)NHR^{68}$, $C(O)N(R^{68})_2$, $C(O)NHOH$, $C(O)NHOR^{68}$, $C(O)NHSO_2R^{68}$, $C(O)NR^{68}SO_2R^{68}$, SO_2NH_2 , SO_2NHR^{68} , $SO_2N(R^{68})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{68}$, $C(N)N(R^{68})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I ;

R^{68} es R^{69} , R^{70} , R^{71} o R^{72} ;

R^{69} es fenilo, que no está fusionado o está fusionado con R^{69A} ; R^{69A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{70} es heteroarilo, que no está fusionado o está fusionado con R^{70A} ; R^{70A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{71} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{71A} ; R^{71A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{72} es alquilo, alquenilo o alquienilo, cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre R^{73} , OR^{73} , SR^{73} , $S(O)R^{73}$, SO_2R^{73} , $C(O)R^{73}$, $CO(O)R^{73}$, $OC(O)R^{73}$, $OC(O)OR^{73}$, NH_2 , NHR^{73} , $N(R^{73})_2$, $NHC(O)R^{73}$, $NR^{73}C(O)R^{73}$, $NHS(O)_2R^{73}$, $NR^{73}S(O)_2R^{73}$, $NHC(O)OR^{73}$, $NR^{73}C(O)OR^{73}$, $NHC(O)NH_2$, $NHC(O)NHR^{73}$, $NHC(O)N(R^{73})_2$, $NR^{73}C(O)NHR^{73}$, $NR^{73}C(O)N(R^{73})_2$, $C(O)NH_2$,

$C(O)NHR^{73}$, $C(O)N(R^{73})_2$, $C(O)NHOH$, $C(O)NHOR^{73}$, $C(O)NHSO_2R^{73}$, $C(O)NR^{73}SO_2R^{73}$, SO_2NH_2 , SO_2NHR^{73} , $SO_2N(R^{73})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{73}$, $C(N)N(R^{73})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I ;

R^{73} es alquilo, alquenilo, alquenilo, fenilo, heteroarilo, cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo; y

donde las unidades representadas por R^{69} , R^{70} , y R^{71} no están sustituidas o están sustituidas con uno o dos o tres o cuatro sustituyentes seleccionados en forma independiente entre NH_2 , $C(O)NH_2$, $C(O)NHOH$, SO_2NH_2 , CF_3 , CF_2CF_3 , $C(O)H$, $C(O)OH$, $C(N)NH_2$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I .

Otra forma de realización de esta invención se refiere a compuestos de fórmula (I), donde

A^1 es N o $C(A^2)$;

A^2 es H , 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNHOH$, $C(O)NHNOR^1$, $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F , Cl , Br , I , CN , NO_2 , N_3 , OH , $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 , $C(O)OH$, $C(O)NH_2$ o $C(O)OR^{1A}$;

B^1 es H , 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNHOH$, $C(O)NHNOR^1$, $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F , Cl , Br , I , CN , NO_2 , N_3 , OH , $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 , $C(O)OH$, $C(O)NH_2$ o $C(O)OR^{1A}$;

D^1 es H , 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNHOH$, $C(O)NHNOR^1$, $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F , Cl , Br , I , CN , NO_2 , N_3 , OH , $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 , $C(O)OH$, $C(O)NH_2$ o $C(O)OR^{1A}$;

E^1 es H , 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 ,

$\text{SO}_2\text{N(R}^1)_2$, NHSO_2R^1 , $\text{NR}^1\text{SO}_2\text{R}^1$, $\text{NHSO}_2\text{NHR}^1$, $\text{NHSO}_2\text{N(R}^1)_2$, $\text{NR}^1\text{SO}_2\text{NHR}^1$, $\text{NR}^1\text{SO}_2\text{N(R}^1)_2$, C(O)NHNOH , C(O)NHNOR^1 , $\text{C(O)NHSO}_2\text{R}^1$, C(NH)NH_2 , C(NH)NHR^1 , $\text{C(NH)N(R}^1)_2$, $\text{NHSO}_2\text{NHR}^1$, $\text{NHSO}_2\text{N(CH}_3)_2$, $\text{N(CH}_3)_2\text{SO}_2\text{N(CH}_3)_2$, F , Cl , Br , I , CN , NO_2 , N_3 , OH , C(O)H , CHNOH , $\text{CH(NOCH}_3)_2$, CF_3 , C(O)OH , C(O)NH_2 o C(O)OR^{1A} ; y

- 5 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} , SO_2R^{17} , NH_2 , NHR^{17} , $\text{N(R}^{17})_2$, NHC(O)R^{17} , C(O)NH_2 , C(O)NHR^{17} , $\text{C(O)N(R}^{17})_2$, NHS(O)R^{17} o $\text{NHSO}_2\text{R}^{17}$; o

E^1 y Y^1 , junto con los átomos a los cuales están unidos, son benceno, naftileno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; y

- 10 A^2 , B^1 , y D^1 se seleccionan en forma independiente entre H , 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 , $\text{N(R}^1)_2$, C(O)NHR^1 , $\text{C(O)N(R}^1)_2$, NHC(O)R^1 , $\text{NR}^1\text{C(O)R}^1$, NHC(O)OR^1 , $\text{NR}^1\text{C(O)OR}^1$, NHC(O)NH_2 , NHC(O)NHR^1 , $\text{NHC(O)N(R}^1)_2$, $\text{NR}^1\text{C(O)NHR}^1$, $\text{NR}^1\text{C(O)N(R}^1)_2$, SO_2NH_2 , SO_2NHR^1 , $\text{SO}_2\text{N(R}^1)_2$, NHSO_2R^1 , $\text{NR}^1\text{SO}_2\text{R}^1$, $\text{NHSO}_2\text{NHR}^1$, $\text{NHSO}_2\text{N(R}^1)_2$, $\text{NR}^1\text{SO}_2\text{NHR}^1$, $\text{NR}^1\text{SO}_2\text{N(R}^1)_2$, C(O)NHNOH , C(O)NHNOR^1 ,
15 $\text{C(O)NHSO}_2\text{R}^1$, C(NH)NH_2 , C(NH)NHR^1 , $\text{C(NH)N(R}^1)_2$, $\text{NHSO}_2\text{NHR}^1$, $\text{NHSO}_2\text{N(CH}_3)_2$, $\text{N(CH}_3)_2\text{SO}_2\text{N(CH}_3)_2$, F , Cl , Br , I , CN , NO_2 , N_3 , OH , C(O)H , CHNOH , $\text{CH(NOCH}_3)_2$, CF_3 , C(O)OH , C(O)NH_2 o C(O)OR^{1A} ; o

Y^1 y B^1 , junto con los átomos a los cuales están unidos, son benceno, naftileno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; y

- 20 A^2 , D^1 , y E^1 se seleccionan en forma independiente entre H , 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 , $\text{N(R}^1)_2$, C(O)NHR^1 , $\text{C(O)N(R}^1)_2$, NHC(O)R^1 , $\text{NR}^1\text{C(O)R}^1$, NHC(O)OR^1 , $\text{NR}^1\text{C(O)OR}^1$, NHC(O)NH_2 , NHC(O)NHR^1 , $\text{NHC(O)N(R}^1)_2$, $\text{NR}^1\text{C(O)NHR}^1$, $\text{NR}^1\text{C(O)N(R}^1)_2$, SO_2NH_2 , SO_2NHR^1 , $\text{SO}_2\text{N(R}^1)_2$, NHSO_2R^1 , $\text{NR}^1\text{SO}_2\text{R}^1$, $\text{NHSO}_2\text{NHR}^1$, $\text{NHSO}_2\text{N(R}^1)_2$, $\text{NR}^1\text{SO}_2\text{NHR}^1$, $\text{NR}^1\text{SO}_2\text{N(R}^1)_2$, C(O)NHNOH , C(O)NHNOR^1 ,
25 $\text{C(O)NHSO}_2\text{R}^1$, C(NH)NH_2 , C(NH)NHR^1 , $\text{C(NH)N(R}^1)_2$, $\text{NHSO}_2\text{NHR}^1$, $\text{NHSO}_2\text{N(CH}_3)_2$, $\text{N(CH}_3)_2\text{SO}_2\text{N(CH}_3)_2$, F , Cl , Br , I , CN , NO_2 , N_3 , OH , C(O)H , CHNOH , $\text{CH(NOCH}_3)_2$, CF_3 , C(O)OH , C(O)NH_2 o C(O)OR^{1A} ; o

A^2 y B^1 , junto con los átomos a los cuales están unidos, son benceno, naftileno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; y

- 30 D^1 , E^1 , y Y^1 se seleccionan en forma independiente entre H , 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 , $\text{N(R}^1)_2$, C(O)NHR^1 , $\text{C(O)N(R}^1)_2$, NHC(O)R^1 , $\text{NR}^1\text{C(O)R}^1$, NHC(O)OR^1 , $\text{NR}^1\text{C(O)OR}^1$, NHC(O)NH_2 , NHC(O)NHR^1 , $\text{NHC(O)N(R}^1)_2$, $\text{NR}^1\text{C(O)NHR}^1$, $\text{NR}^1\text{C(O)N(R}^1)_2$, SO_2NH_2 , SO_2NHR^1 , $\text{SO}_2\text{N(R}^1)_2$, NHSO_2R^1 , $\text{NR}^1\text{SO}_2\text{R}^1$, $\text{NHSO}_2\text{NHR}^1$, $\text{NHSO}_2\text{N(R}^1)_2$, $\text{NR}^1\text{SO}_2\text{NHR}^1$, $\text{NR}^1\text{SO}_2\text{N(R}^1)_2$, C(O)NHNOH , C(O)NHNOR^1 ,
35 $\text{C(O)NHSO}_2\text{R}^1$, C(NH)NH_2 , C(NH)NHR^1 , $\text{C(NH)N(R}^1)_2$, $\text{NHSO}_2\text{NHR}^1$, $\text{NHSO}_2\text{N(CH}_3)_2$, $\text{N(CH}_3)_2\text{SO}_2\text{N(CH}_3)_2$, F , Cl , Br , I , CN , NO_2 , N_3 , OH , C(O)H , CHNOH , $\text{CH(NOCH}_3)_2$, CF_3 , C(O)OH , C(O)NH_2 o C(O)OR^{1A} ; o

$N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 , $C(O)OH$, $C(O)NH_2$ o $C(O)OR^{1A}$; o

A^2 y D^1 , junto con los átomos a los cuales están unidos, son benceno, naftaleno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; y

- 5 B^1 , E^1 , y Y^1 se seleccionan en forma independiente entre H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$,
10 $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 , $C(O)OH$, $C(O)NH_2$ o $C(O)OR^{1A}$;

G^1 es H, o $C(O)O$;

R es alquilo;

- 15 R^1 es R^2 , R^3 , R^4 o R^5 ;

R^{1A} es cicloalquilo, cicloalquenilo o cicloalquinilo;

R^2 es fenilo, que no está fusionado o está fusionado con R^{2A} ; R^{2A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

- 20 R^3 es heteroarilo, que no está fusionado o está fusionado con R^{3A} ; R^{3A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^4 es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{4A} ; R^{4A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

- 25 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 en forma independiente entre R^6 , $NC(R^{6A})(R^{6B})$, R^7 , OR^7 , SR^7 , $S(O)R^7$, SO_2R^7 , NHR^7 , $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $C(O)N(R^7)_2$, $NHC(O)R^7$, $NR^7C(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2 , SO_2NHR^7 , $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^7$, OH, (O), $C(O)OH$, N_3 , CN, NH_2 , CF_3 , CF_2CF_3 , F, Cl,
30 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-ilo o piperidin-1-ilo, teniendo cada uno una unidad CH_2 sin reemplazar o reemplazada con O, C(O), CNOH, CNOCH₃, S, S(O), SO₂ o NH;

R^7 es R^8 , R^9 , R^{10} o R^{11} ;

5 R^8 es fenilo, que no está fusionado o está fusionado con R^{8A} ; R^{8A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^9 es heteroarilo, que no está fusionado o está fusionado con R^{9A} ; R^{9A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

10 R^{10} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{10A} ; R^{10A} es benceno, heteroareno, 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 en forma independiente entre R^{12} , OR^{12} , SR^{12} , $S(O)R^{12}$, SO_2R^{12} , $C(O)R^{12}$, $CO(O)R^{12}$, $OC(O)R^{12}$, $OC(O)OR^{12}$, NH_2 , NHR^{12} , $N(R^{12})_2$, $NHC(O)R^{12}$, $NR^{12}C(O)R^{12}$, $NHS(O)_2R^{12}$, $NR^{12}S(O)_2R^{12}$, $NHC(O)OR^{12}$, $NR^{12}C(O)OR^{12}$, $NHC(O)NH_2$, $NHC(O)NHR^{12}$, $NHC(O)N(R^{12})_2$, $NR^{12}C(O)NHR^{12}$, $NR^{12}C(O)N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, $C(O)NHOH$, $C(O)NHOR^{12}$, $C(O)NHSO_2R^{12}$, $C(O)NR^{12}SO_2R^{12}$, SO_2NH_2 , SO_2NHR^{12} , $SO_2N(R^{12})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{12}$, $C(N)N(R^{12})_2$, CNOH, CNOCH₃, OH, (O), CN, N₃, NO₂, CF₃, CF₂CF₃, OCF₃, OCF₂CF₃, F, Cl, Br o I;

20 R^{12} es R^{13} , R^{14} , R^{15} o R^{16} ;

R^{13} es fenilo, que no está fusionado o está fusionado con R^{13A} ; R^{13A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{14} es heteroarilo, que no está fusionado o está fusionado con R^{14A} ; R^{14A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

25 R^{15} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno, cada uno de los cuales no está fusionado o está fusionado con R^{15A} ; R^{15A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{16} es alquilo, alquenilo o alquinilo;

R^{17} es R^{18} , R^{19} , R^{20} o R^{21} ;

30 R^{18} es fenilo, que no está fusionado o está fusionado con R^{18A} ; R^{18A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{19} es heteroarilo, que no está fusionado o está fusionado con R^{19A} ; R^{19A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

35 R^{20} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo cada uno de los cuales no está fusionado o está fusionado con R^{20A} ; R^{20A} es benceno, heteroareno, 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 en forma independiente entre R^{22} , OR^{22} , SR^{22} , $S(O)R^{22}$, SO_2R^{22} , $C(O)R^{22}$, $CO(O)R^{22}$, $OC(O)R^{22}$, $OC(O)OR^{22}$, NH_2 , NHR^{22} , $N(R^{22})_2$, $NHC(O)R^{22}$, $NR^{22}C(O)R^{22}$, $NHS(O)_2R^{22}$, $NR^{22}S(O)_2R^{22}$, $NHC(O)OR^{22}$, $NR^{22}C(O)OR^{22}$, $NHC(O)NH_2$, $NHC(O)NHR^{22}$, $NHC(O)N(R^{22})_2$, $NR^{22}C(O)NHR^{22}$, $NR^{22}C(O)N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, $C(O)NHOH$, $C(O)NHOR^{22}$, $C(O)NHSO_2R^{22}$, $C(O)NR^{22}SO_2R^{22}$, SO_2NH_2 , SO_2NHR^{22} , $SO_2N(R^{22})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{22}$, $C(N)N(R^{22})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I ;

R^{22} es R^{23} , R^{24} o R^{25} ;

10 R^{23} es fenilo, que no está fusionado o está fusionado con R^{23A} ; R^{23A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{24} es heteroareno, que no está fusionado o está fusionado con R^{24A} ; R^{24A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

15 R^{25} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{25A} ; R^{25A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

Z^1 es R^{26} o R^{27} ;

Z^2 es R^{28} , R^{29} o R^{30} ;

Z^{1A} y Z^{2A} están ambos ausentes o se toman juntos para formar CH_2 , CH_2CH_2 o Z^{12A} ;

20 Z^{12A} es C_2 - C_6 -alquileno con uno dos unidades $CH\#2$ se reemplaza con NH , $N(CH_3)$, S , $S(O)$ o SO_2 ;

L^1 es un R^{37} , OR^{37} , SR^{37} , $S(O)R^{37}$, SO_2R^{37} , $C(O)R^{37}$, $CO(O)R^{37}$, $OC(O)R^{37}$, $OC(O)OR^{37}$, NHR^{37} , $C(O)NH$, $C(O)NR^{37}$, $C(O)NHOR^{37}$, $C(O)NHSO_2R^{37}$, SO_2NH , SO_2NHR^{37} , $C(N)NH$, $C(N)NHR^{37}$;

25 R^{26} es fenileno, que no está fusionado o está fusionado con R^{26A} ; R^{26A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{27} es heteroarileno, que no está fusionado o está fusionado con R^{27A} ; R^{27A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

30 R^{28} es fenileno, que no está fusionado o está fusionado con R^{28A} ; R^{28A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{29} es heteroarileno, que no está fusionado o está fusionado con R^{29A} ; R^{29A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

35 R^{30} es cicloalquileno, cicloalquenileno, heterocicloalquileno o heterocicloalquenileno, cada uno de los cuales no está fusionado o está fusionado con R^{30A} ; R^{30A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{37} es una unión o R^{37A} ;

- R^{37A} es alquileo, alquenileno, o alquinileno, cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre R^{37B} , OR^{37B} , SR^{37B} , $S(O)R^{37B}$, SO_2R^{37B} , $C(O)R^{37B}$, $CO(O)R^{37B}$, $OC(O)R^{37B}$, $OC(O)OR^{37B}$, NH_2 , NHR^{37B} , $N(R^{37B})_2$, $NHC(O)R^{37B}$, $NR^{37B}C(O)R^{37B}$, $NHS(O)_2R^{37B}$, $NR^{37B}S(O)_2R^{37B}$, $NHC(O)OR^{37B}$, $NR^{37B}C(O)OR^{37B}$, $NHC(O)NH_2$, $NHC(O)NHR^{37B}$, $NHC(O)N(R^{37B})_2$, $NR^{37B}C(O)NHR^{37B}$, $NR^{37B}C(O)N(R^{37B})_2$, $C(O)NH_2$, $C(O)NHR^{37B}$, $C(O)N(R^{37B})_2$, $C(O)NHOH$, $C(O)NHOR^{37B}$, $C(O)NH SO_2R^{37B}$, $C(O)NR^{37B}SO_2R^{37B}$, SO_2NH_2 , SO_2NHR^{37B} , $SO_2N(R^{37B})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{37B}$, $C(N)N(R^{37B})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br e I ;
- 10 R^{37B} es alquilo, alquenilo, alquinilo, o R^{37C} ;
- R^{37C} es fenilo, heteroarilo, cicloalquilo, cicloalquenilo, heterocicloalquilo, o heterocicloalquenilo;
- Z^3 es R^{38} , R^{39} o R^{40} ;
- R^{38} es fenilo, que no está fusionado o está fusionado con R^{38A} ; R^{38A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;
- 15 R^{39} es heteroarilo, que no está fusionado o está fusionado con R^{39A} ; R^{39A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;
- R^{40} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{40A} ; R^{40A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;
- 20 donde las unidades representadas por R^{26} y R^{27} están sustituidas (por ejemplo, si Z^{1A} y Z^{2A} están ausentes) o adicionalmente sustituidas (por ejemplo, si Z^{1A} y Z^{2A} están presentes) con R^{41} , OR^{41} , SR^{41} , $S(O)R^{41}$, SO_2R^{41} , $C(O)R^{41}$, $CO(O)R^{41}$, $OC(O)R^{41}$, $OC(O)OR^{41}$, NHR^{41} , $N(R^{41})_2$, $NHC(O)R^{41}$, $NR^{41}C(O)R^{41}$, $NHS(O)_2R^{41}$, $NR^{41}S(O)_2R^{41}$, $NHC(O)OR^{41}$, $NR^{41}C(O)OR^{41}$, $NHC(O)NHR^{41}$, $NHC(O)N(R^{41})_2$, $NR^{41}C(O)NHR^{41}$, $NR^{41}C(O)N(R^{41})_2$, $C(O)NHR^{41}$, $C(O)N(R^{41})_2$, $C(O)NHOR^{41}$, $C(O)NH SO_2R^{41}$, $C(O)NR^{41}SO_2R^{41}$, SO_2NHR^{41} , $SO_2N(R^{41})_2$, $C(N)NHR^{41}$, o $C(N)N(R^{41})_2$;
- R^{41} es heteroarilo, que está fusionado con R^{43A} ; R^{43A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; which es unfused;
- 30 donde las unidades cíclicas representadas por E^1 y Y^1 juntos, Y^1 y B^1 juntos, A^2 y B^1 juntos, A^2 y D^1 juntos, R^{1A} , R^2 , R^{2A} , R^3 , R^{3A} , R^4 , R^{4A} , R^6 , R^{6C} , R^8 , R^{8A} , R^9 , R^{9A} , 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^{26A} , R^{27} , R^{27A} , R^{28} , R^{28A} , R^{29} , R^{29A} , R^{30} , R^{30A} , R^{37B} , R^{38} , R^{38A} , R^{39} , R^{39A} , R^{40} , y R^{40A} no están sustituidas, no están adicionalmente sustituidas, están sustituidas o adicionalmente sustituidas en forma independiente con uno o dos o tres o cuatro o cinco sustituyentes seleccionados en forma independiente entre R^{57A} , R^{57} , OR^{57} , SR^{57} , $S(O)R^{57}$, SO_2R^{57} ,
- 35

$C(O)R^{57}$, $CO(O)R^{57}$, $OC(O)R^{57}$, $OC(O)OR^{57}$, NH_2 , NHR^{57} , $N(R^{57})_2$, $NHC(O)R^{57}$, $NR^{57}C(O)R^{57}$,
 $NHS(O)_2R^{57}$, $NR^{57}S(O)_2R^{57}$, $NHC(O)OR^{57}$, $NR^{57}C(O)OR^{57}$, $NHC(O)NH_2$, $NHC(O)NHR^{57}$,
 $NHC(O)N(R^{57})_2$, $NR^{57}C(O)NHR^{57}$, $NR^{57}C(O)N(R^{57})_2$, $C(O)NH_2$, $C(O)NHR^{57}$, $C(O)N(R^{57})_2$,
 $C(O)NHOH$, $C(O)NHOR^{57}$, $C(O)NHSO_2R^{57}$, $C(O)NR^{57}SO_2R^{57}$, SO_2NH_2 , SO_2NHR^{57} ,
 5 $SO_2N(R^{57})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{57}$, $C(N)N(R^{57})_2$, $CNOH$, $CNOCH_3$, OH , (O) ,
 CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I ;

R^{57A} es espiroalquilo, o espiroheteroalquilo;

R^{57} es R^{58} , R^{59} , R^{60} o R^{61} ;

R^{58} es fenilo, que no está fusionado o está fusionado con R^{58A} ; R^{58A} es benceno,
 10 heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{59} es heteroarilo, que no está fusionado o está fusionado con R^{59A} ; R^{59A} es benceno,
 heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{60} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno
 de los cuales no está fusionado o está fusionado con R^{60A} ; R^{60A} es benceno, heteroareno,
 15 cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{61} 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^{62} , OR^{62} , SR^{62} , $S(O)R^{62}$, SO_2R^{62} , $C(O)R^{62}$, $CO(O)R^{62}$, $OC(O)R^{62}$, $OC(O)OR^{62}$, NH_2 , NHR^{62} ,
 $N(R^{62})_2$, $NHC(O)R^{62}$, $NR^{62}C(O)R^{62}$, $NHS(O)_2R^{62}$, $NR^{62}S(O)_2R^{62}$, $NHC(O)OR^{62}$, $NR^{62}C(O)OR^{62}$,
 20 $NHC(O)NH_2$, $NHC(O)NHR^{62}$, $NHC(O)N(R^{62})_2$, $NR^{62}C(O)NHR^{62}$, $NR^{62}C(O)N(R^{62})_2$, $C(O)NH_2$,
 $C(O)NHR^{62}$, $C(O)N(R^{62})_2$, $C(O)NHOH$, $C(O)NHOR^{62}$, $C(O)NHSO_2R^{62}$, $C(O)NR^{62}SO_2R^{62}$,
 SO_2NH_2 , SO_2NHR^{62} , $SO_2N(R^{62})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{62}$, $C(N)N(R^{62})_2$,
 $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I ;

R^{62} es R^{63} , R^{64} , R^{65} o R^{66} ;

R^{63} es fenilo, que no está fusionado o está fusionado con R^{63A} ; R^{63A} es benceno,
 25 heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{64} es heteroarilo, que no está fusionado o está fusionado con R^{64A} ; R^{64A} es benceno,
 heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{65} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno
 de los cuales no está fusionado o está fusionado con R^{65A} ; R^{65A} es benceno, heteroareno,
 30 cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{66} 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^{67} , OR^{67} , SR^{67} , $S(O)R^{67}$, SO_2R^{67} , $C(O)R^{67}$, $CO(O)R^{67}$, $OC(O)R^{67}$, $OC(O)OR^{67}$, NH_2 , NHR^{67} ,
 35 $N(R^{67})_2$, $NHC(O)R^{67}$, $NR^{67}C(O)R^{67}$, $NHS(O)_2R^{67}$, $NR^{67}S(O)_2R^{67}$, $NHC(O)OR^{67}$, $NR^{67}C(O)OR^{67}$,
 $NHC(O)NH_2$, $NHC(O)NHR^{67}$, $NHC(O)N(R^{67})_2$, $NR^{67}C(O)NHR^{67}$, $NR^{67}C(O)N(R^{67})_2$, $C(O)NH_2$,

$C(O)NHR^{67}$, $C(O)N(R^{67})_2$, $C(O)NHOH$, $C(O)NHOR^{67}$, $C(O)NHSO_2R^{67}$, $C(O)NR^{67}SO_2R^{67}$, SO_2NH_2 , SO_2NHR^{67} , $SO_2N(R^{67})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{67}$, $C(N)N(R^{67})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I sustituyentes;

- 5 R^{67} es alquilo, alquenilo, alquinilo, fenilo, heteroarilo, cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo;

donde las unidades cíclicas representadas por R^{57A} , R^{58} , R^{59} , R^{60} , R^{63} , R^{64} , R^{65} , y R^{67} no están sustituidas o están sustituidas con uno o dos o tres o cuatro sustituyentes seleccionados en forma independiente entre R^{68} , OR^{68} , SR^{68} , $S(O)R^{68}$, SO_2R^{68} , $C(O)R^{68}$,
 10 $CO(O)R^{68}$, $OC(O)R^{68}$, $OC(O)OR^{68}$, NH_2 , NHR^{68} , $N(R^{68})_2$, $NHC(O)R^{68}$, $NR^{68}C(O)R^{68}$, $NHS(O)_2R^{68}$, $NR^{68}S(O)_2R^{68}$, $NHC(O)OR^{68}$, $NR^{68}C(O)OR^{68}$, $NHC(O)NH_2$, $NHC(O)NHR^{68}$, $NHC(O)N(R^{68})_2$, $NR^{68}C(O)NHR^{68}$, $NR^{68}C(O)N(R^{68})_2$, $C(O)NH_2$, $C(O)NHR^{68}$, $C(O)N(R^{68})_2$, $C(O)NHOH$, $C(O)NHOR^{68}$, $C(O)NHSO_2R^{68}$, $C(O)NR^{68}SO_2R^{68}$, SO_2NH_2 , SO_2NHR^{68} , $SO_2N(R^{68})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{68}$, $C(N)N(R^{68})_2$, $CNOH$, $CNOCH_3$, OH , (O) ,
 15 CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I ;

R^{68} es R^{69} , R^{70} , R^{71} o R^{72} ;

R^{69} es fenilo, que no está fusionado o está fusionado con R^{69A} ; R^{69A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{70} es heteroarilo, que no está fusionado o está fusionado con R^{70A} ; R^{70A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

20 R^{71} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{71A} ; R^{71A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{72} 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^{73} , OR^{73} , SR^{73} , $S(O)R^{73}$, SO_2R^{73} , $C(O)R^{73}$, $CO(O)R^{73}$, $OC(O)R^{73}$, $OC(O)OR^{73}$, NH_2 , NHR^{73} , $N(R^{73})_2$, $NHC(O)R^{73}$, $NR^{73}C(O)R^{73}$, $NHS(O)_2R^{73}$, $NR^{73}S(O)_2R^{73}$, $NHC(O)OR^{73}$, $NR^{73}C(O)OR^{73}$, $NHC(O)NH_2$, $NHC(O)NHR^{73}$, $NHC(O)N(R^{73})_2$, $NR^{73}C(O)NHR^{73}$, $NR^{73}C(O)N(R^{73})_2$, $C(O)NH_2$, $C(O)NHR^{73}$, $C(O)N(R^{73})_2$, $C(O)NHOH$, $C(O)NHOR^{73}$, $C(O)NHSO_2R^{73}$, $C(O)NR^{73}SO_2R^{73}$,
 25 SO_2NH_2 , SO_2NHR^{73} , $SO_2N(R^{73})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{73}$, $C(N)N(R^{73})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I ;

30 R^{73} es alquilo, alquenilo, alquinilo, fenilo, heteroarilo, cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo; y

donde las unidades representadas por R^{69} , R^{70} , y R^{71} no están sustituidas o están sustituidas con uno o dos o tres o cuatro sustituyentes seleccionados en forma

E^1 y Y^1 , junto con los átomos a los cuales están unidos, son benceno, naftileno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; y

A^2 , B^1 , y D^1 se seleccionan en forma independiente entre H , 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$,
 5 $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$,
 $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$,
 $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$,
 $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$,
 $N(CH_3)SO_2N(CH_3)R^1$, F , Cl , Br , I , CN , NO_2 , N_3 , OH , $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 ,
 10 $C(O)OH$, $C(O)NH_2$ o $C(O)OR^{1A}$; o

Y^1 y B^1 , junto con los átomos a los cuales están unidos, son benceno, naftileno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; y

A^2 , D^1 , y E^1 se seleccionan en forma independiente entre H , 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$,
 15 $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$,
 $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$,
 $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$,
 $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$,
 $N(CH_3)SO_2N(CH_3)R^1$, F , Cl , Br , I , CN , NO_2 , N_3 , OH , $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 ,
 20 $C(O)OH$, $C(O)NH_2$ o $C(O)OR^{1A}$; o

A^2 y B^1 , junto con los átomos a los cuales están unidos, son benceno, naftileno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; y

D^1 , E^1 , y Y^1 se seleccionan en forma independiente entre H , 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$,
 25 $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$,
 $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$,
 $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$,
 $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$,
 $N(CH_3)SO_2N(CH_3)R^1$, F , Cl , Br , I , CN , NO_2 , N_3 , OH , $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 ,
 30 $C(O)OH$, $C(O)NH_2$ o $C(O)OR^{1A}$; o

A^2 y D^1 , junto con los átomos a los cuales están unidos, son benceno, naftileno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; y

B^1 , E^1 , y Y^1 se seleccionan en forma independiente entre H , 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$,
 35 $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$,
 $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$,

NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ o C(O)OR^{1A};

5 G¹ es H, o C(O)O;

R es alquilo;

R¹ es R², R³, R⁴ o R⁵;

R^{1A} es cicloalquilo, cicloalquenilo o cicloalquinilo;

10 R² es fenilo, que no está fusionado o está fusionado con R^{2A}; R^{2A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R³ es heteroarilo, que no está fusionado o está fusionado con R^{3A}; R^{3A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

15 R⁴ es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{4A}; R^{4A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

20 R⁵ 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 R⁶, NC(R^{6A})(R^{6B}), R⁷, OR⁷, SR⁷, S(O)R⁷, SO₂R⁷, NHR⁷, N(R⁷)₂, C(O)R⁷, C(O)NH₂, C(O)NHR⁷, C(O)N(R⁷)₂, NHC(O)R⁷, NR⁷C(O)R⁷, NHSO₂R⁷, NHC(O)OR⁷, SO₂NH₂, SO₂NHR⁷, SO₂N(R⁷)₂, NHC(O)NH₂, NHC(O)NHR⁷, NHC(O)CH(CH₃)NHC(O)CH(CH₃)NH₂, NHC(O)CH(CH₃)NHC(O)CH(CH₃)NHR⁷, OH, (O), C(O)OH, N₃, CN, NH₂, CF₃, CF₂CF₃, F, Cl, Br o I;

R⁶ es C₂-C₅-espiroalquilo, cada uno de los cuales no está sustituido o está sustituido con OH, (O), N₃, CN, CF₃, CF₂CF₃, F, Cl, Br, I, NH₂, NH(CH₃) o N(CH₃)₂;

25 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 sin reemplazar o reemplazada con O, C(O), CNOH, CNOCH₃, S, S(O), SO₂ o NH;

30 R⁷ es R⁸, R⁹, R¹⁰ o R¹¹;

R⁸ es fenilo, que no está fusionado o está fusionado con R^{8A}; R^{8A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R⁹ es heteroarilo, que no está fusionado o está fusionado con R^{9A}; R^{9A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{10} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{10A} ; R^{10A} es benceno, heteroareno, 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 en forma independiente entre R^{12} , OR^{12} , SR^{12} , $S(O)R^{12}$, SO_2R^{12} , $C(O)R^{12}$, $CO(O)R^{12}$, $OC(O)R^{12}$, $OC(O)OR^{12}$, NH_2 , NHR^{12} , $N(R^{12})_2$, $NHC(O)R^{12}$, $NR^{12}C(O)R^{12}$, $NHS(O)_2R^{12}$, $NR^{12}S(O)_2R^{12}$, $NHC(O)OR^{12}$, $NR^{12}C(O)OR^{12}$, $NHC(O)NH_2$, $NHC(O)NHR^{12}$, $NHC(O)N(R^{12})_2$, $NR^{12}C(O)NHR^{12}$, $NR^{12}C(O)N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, $C(O)NHOH$, $C(O)NHOR^{12}$, $C(O)NHSO_2R^{12}$, $C(O)NR^{12}SO_2R^{12}$, SO_2NH_2 , SO_2NHR^{12} , $SO_2N(R^{12})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{12}$, $C(N)N(R^{12})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_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 R^{13A} ; R^{13A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{14} es heteroarilo, que no está fusionado o está fusionado con R^{14A} ; R^{14A} es benceno, heteroareno, 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 R^{15A} ; R^{15A} es benceno, heteroareno, 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 R^{18A} ; R^{18A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{19} es heteroarilo, que no está fusionado o está fusionado con R^{19A} ; R^{19A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{20} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo cada uno de los cuales no está fusionado o está fusionado con R^{20A} ; R^{20A} es benceno, heteroareno, 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 en forma independiente entre R^{22} , OR^{22} , SR^{22} , $S(O)R^{22}$, SO_2R^{22} , $C(O)R^{22}$, $CO(O)R^{22}$, $OC(O)R^{22}$, $OC(O)OR^{22}$, NH_2 , NHR^{22} , $N(R^{22})_2$, $NHC(O)R^{22}$, $NR^{22}C(O)R^{22}$, $NHS(O)_2R^{22}$, $NR^{22}S(O)_2R^{22}$, $NHC(O)OR^{22}$, $NR^{22}C(O)OR^{22}$, $NHC(O)NH_2$, $NHC(O)NHR^{22}$, $NHC(O)N(R^{22})_2$, $NR^{22}C(O)NHR^{22}$, $NR^{22}C(O)N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, $C(O)NHOH$, $C(O)NHOR^{22}$, $C(O)NHSO_2R^{22}$, $C(O)NR^{22}SO_2R^{22}$, SO_2NH_2 , SO_2NHR^{22} , $SO_2N(R^{22})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{22}$, $C(N)N(R^{22})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_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 R^{23A} ; R^{23A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

5 R^{24} es heteroareno, que no está fusionado o está fusionado con R^{24A} ; R^{24A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{25} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{25A} ; R^{25A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

Z^1 es R^{26} o R^{27} ;

10 Z^2 es R^{28} , R^{29} o R^{30} ;

Z^{1A} y Z^{2A} están ambos ausentes o se toman juntos para formar CH_2 , CH_2CH_2 o Z^{12A} ;

Z^{12A} es C_2 - C_6 -alquileo con uno de las unidades CH_2 se reemplaza con NH , $N(CH_3)$, S , $S(O)$ o SO_2 ;

15 L^1 es un R^{37} , OR^{37} , SR^{37} , $S(O)R^{37}$, SO_2R^{37} , $C(O)R^{37}$, $CO(O)R^{37}$, $OC(O)R^{37}$, $OC(O)OR^{37}$, NHR^{37} , $C(O)NH$, $C(O)NR^{37}$, $C(O)NHR^{37}$, $C(O)NHSO_2R^{37}$, SO_2NH , SO_2NHR^{37} , $C(N)NH$, $C(N)NHR^{37}$;

R^{26} es fenileno, que no está fusionado o está fusionado con R^{26A} ; R^{26A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

20 R^{27} es heteroarileno, que no está fusionado o está fusionado con R^{27A} ; R^{27A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{28} es fenileno, que no está fusionado o está fusionado con R^{28A} ; R^{28A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{29} es heteroarileno, que no está fusionado o está fusionado con R^{29A} ; R^{29A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

25 R^{30} es cicloalquileo, cicloalquenileo, heterocicloalquileo o heterocicloalquenileo, cada uno de los cuales no está fusionado o está fusionado con R^{30A} ; R^{30A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{37} es una unión o R^{37A} ;

30 R^{37A} es alquileo, alquenileo, o alquinileo, cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre R^{37B} , OR^{37B} , SR^{37B} , $S(O)R^{37B}$, SO_2R^{37B} , $C(O)R^{37B}$, $CO(O)R^{37B}$, $OC(O)R^{37B}$, $OC(O)OR^{37B}$, NH_2 , NHR^{37B} , $N(R^{37B})_2$, $NHC(O)R^{37B}$, $NR^{37B}C(O)R^{37B}$, $NHS(O)_2R^{37B}$, $NR^{37B}S(O)_2R^{37B}$, $NHC(O)OR^{37B}$, $NR^{37B}C(O)OR^{37B}$, $NHC(O)NH_2$, $NHC(O)NHR^{37B}$, $NHC(O)N(R^{37B})_2$, $NR^{37B}C(O)NHR^{37B}$, $NR^{37B}C(O)N(R^{37B})_2$, $C(O)NH_2$, $C(O)NHR^{37B}$, $C(O)N(R^{37B})_2$, $C(O)NHOH$,
35 $C(O)NHR^{37B}$, $C(O)NHSO_2R^{37B}$, $C(O)NR^{37B}SO_2R^{37B}$, SO_2NH_2 , SO_2NHR^{37B} , $SO_2N(R^{37B})_2$,

C(O)H, C(O)OH, C(N)NH₂, C(N)NHR^{37B}, C(N)N(R^{37B})₂, CNOH, CNOCH₃, OH, (O), CN, N₃, NO₂, CF₃, CF₂CF₃, OCF₃, OCF₂CF₃, F, Cl, Br e I;

R^{37B} es alquilo, alquenilo, alquinilo, o R^{37C};

R^{37C} es fenilo, heteroarilo, cicloalquilo, cicloalquenilo, heterocicloalquilo, o
5 heterocicloalquenilo;

Z³ es R³⁸, R³⁹ o R⁴⁰;

R³⁸ es fenilo, que no está fusionado o está fusionado con R^{38A}; R^{38A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R³⁹ es heteroarilo, que no está fusionado o está fusionado con R^{39A}; R^{39A} es benceno,
10 heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R⁴⁰ es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{40A}; R^{40A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

donde las unidades representadas por R²⁶ y R²⁷ están sustituidas (por ejemplo, si Z^{1A}
15 y Z^{2A} están ausentes) o adicionalmente sustituidas (por ejemplo, si Z^{1A} y Z^{2A} están presentes) con R⁴¹, OR⁴¹, SR⁴¹, S(O)R⁴¹, SO₂R⁴¹, C(O)R⁴¹, CO(O)R⁴¹, OC(O)R⁴¹, OC(O)OR⁴¹, NHR⁴¹, N(R⁴¹)₂, NHC(O)R⁴¹, NR⁴¹C(O)R⁴¹, NHS(O)₂R⁴¹, NR⁴¹S(O)₂R⁴¹, NHC(O)OR⁴¹, NR⁴¹C(O)OR⁴¹, NHC(O)NHR⁴¹, NHC(O)N(R⁴¹)₂, NR⁴¹C(O)NHR⁴¹, NR⁴¹C(O)N(R⁴¹)₂, C(O)NHR⁴¹, C(O)N(R⁴¹)₂, C(O)NHOR⁴¹, C(O)NHSO₂R⁴¹, C(O)NR⁴¹SO₂R⁴¹, SO₂NHR⁴¹, SO₂N(R⁴¹)₂, C(N)NHR⁴¹, o
20 C(N)N(R⁴¹)₂;

R⁴¹ es heteroarilo, que está fusionado con R^{43A}; R^{43A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; que está fusionado con benceno, heteroareno o R^{43B}; R^{43B} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

donde las unidades cíclicas representadas por E¹ y Y¹ juntos, Y¹ y B¹ juntos, A² y B¹ juntos, A² y D¹ juntos, R^{1A}, R², R^{2A}, R³, R^{3A}, R⁴, R^{4A}, R⁶, R^{6C}, R⁸, R^{8A}, R⁹, R^{9A}, R¹⁰, R^{10A}, R¹³, R^{13A}, R¹⁴, R^{14A}, R¹⁵, R^{15A}, R¹⁸, R^{18A}, R¹⁹, R^{19A}, R²⁰, R^{20A}, R²³, R^{23A}, R²⁴, R^{24A}, R²⁵, R^{25A}, R²⁶, R^{26A}, R²⁷, R^{27A}, R²⁸, R^{28A}, R²⁹, R^{29A}, R³⁰, R^{30A}, R^{37B}, R³⁸, R^{38A}, R³⁹, R^{39A}, R⁴⁰, y R^{40A} no están
25 sustituidas, no están adicionalmente sustituidas, están sustituidas o adicionalmente sustituidas en forma independiente con uno o dos o tres o cuatro o cinco sustituyentes seleccionados en forma independiente entre R^{57A}, R⁵⁷, OR⁵⁷, SR⁵⁷, S(O)R⁵⁷, SO₂R⁵⁷, C(O)R⁵⁷, CO(O)R⁵⁷, OC(O)R⁵⁷, OC(O)OR⁵⁷, NH₂, NHR⁵⁷, N(R⁵⁷)₂, NHC(O)R⁵⁷, NR⁵⁷C(O)R⁵⁷, NHS(O)₂R⁵⁷, NR⁵⁷S(O)₂R⁵⁷, NHC(O)OR⁵⁷, NR⁵⁷C(O)OR⁵⁷, NHC(O)NH₂, NHC(O)NHR⁵⁷, NHC(O)N(R⁵⁷)₂, NR⁵⁷C(O)NHR⁵⁷, NR⁵⁷C(O)N(R⁵⁷)₂, C(O)NH₂, C(O)NHR⁵⁷, C(O)N(R⁵⁷)₂,
30 C(O)NHOH, C(O)NHOR⁵⁷, C(O)NHSO₂R⁵⁷, C(O)NR⁵⁷SO₂R⁵⁷, SO₂NH₂, SO₂NHR⁵⁷,

$\text{SO}_2\text{N}(\text{R}^{57})_2$, $\text{C}(\text{O})\text{H}$, $\text{C}(\text{O})\text{OH}$, $\text{C}(\text{N})\text{NH}_2$, $\text{C}(\text{N})\text{NHR}^{57}$, $\text{C}(\text{N})\text{N}(\text{R}^{57})_2$, CNOH , CNOCH_3 , OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I ;

$\text{R}^{57\text{A}}$ es espiroalquilo, o espiroheteroalquilo;

R^{57} es R^{58} , R^{59} , R^{60} o R^{61} ;

5 R^{58} es fenilo, que no está fusionado o está fusionado con $\text{R}^{58\text{A}}$; $\text{R}^{58\text{A}}$ es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{59} es heteroarilo, que no está fusionado o está fusionado con $\text{R}^{59\text{A}}$; $\text{R}^{59\text{A}}$ es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

10 R^{60} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con $\text{R}^{60\text{A}}$; $\text{R}^{60\text{A}}$ es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{61} 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^{62} , OR^{62} , SR^{62} , $\text{S}(\text{O})\text{R}^{62}$, SO_2R^{62} , $\text{C}(\text{O})\text{R}^{62}$, $\text{CO}(\text{O})\text{R}^{62}$, $\text{OC}(\text{O})\text{R}^{62}$, $\text{OC}(\text{O})\text{OR}^{62}$, NH_2 , NHR^{62} , $\text{N}(\text{R}^{62})_2$, $\text{NHC}(\text{O})\text{R}^{62}$, $\text{NR}^{62}\text{C}(\text{O})\text{R}^{62}$, $\text{NHS}(\text{O})_2\text{R}^{62}$, $\text{NR}^{62}\text{S}(\text{O})_2\text{R}^{62}$, $\text{NHC}(\text{O})\text{OR}^{62}$, $\text{NR}^{62}\text{C}(\text{O})\text{OR}^{62}$, $\text{NHC}(\text{O})\text{NH}_2$, $\text{NHC}(\text{O})\text{NHR}^{62}$, $\text{NHC}(\text{O})\text{N}(\text{R}^{62})_2$, $\text{NR}^{62}\text{C}(\text{O})\text{NHR}^{62}$, $\text{NR}^{62}\text{C}(\text{O})\text{N}(\text{R}^{62})_2$, $\text{C}(\text{O})\text{NH}_2$, $\text{C}(\text{O})\text{NHR}^{62}$, $\text{C}(\text{O})\text{N}(\text{R}^{62})_2$, $\text{C}(\text{O})\text{NHOH}$, $\text{C}(\text{O})\text{NHOR}^{62}$, $\text{C}(\text{O})\text{NHSO}_2\text{R}^{62}$, $\text{C}(\text{O})\text{NR}^{62}\text{SO}_2\text{R}^{62}$, SO_2NH_2 , $\text{SO}_2\text{NHR}^{62}$, $\text{SO}_2\text{N}(\text{R}^{62})_2$, $\text{C}(\text{O})\text{H}$, $\text{C}(\text{O})\text{OH}$, $\text{C}(\text{N})\text{NH}_2$, $\text{C}(\text{N})\text{NHR}^{62}$, $\text{C}(\text{N})\text{N}(\text{R}^{62})_2$, CNOH , CNOCH_3 , OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I ;

20 R^{62} es R^{63} , R^{64} , R^{65} o R^{66} ;

R^{63} es fenilo, que no está fusionado o está fusionado con $\text{R}^{63\text{A}}$; $\text{R}^{63\text{A}}$ es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{64} es heteroarilo, que no está fusionado o está fusionado con $\text{R}^{64\text{A}}$; $\text{R}^{64\text{A}}$ es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

25 R^{65} es cicloalquilo, cicloalquenilo, heterocicloalquilo, o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con $\text{R}^{65\text{A}}$; $\text{R}^{65\text{A}}$ es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{66} 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^{67} , OR^{67} , SR^{67} , $\text{S}(\text{O})\text{R}^{67}$, SO_2R^{67} , $\text{C}(\text{O})\text{R}^{67}$, $\text{CO}(\text{O})\text{R}^{67}$, $\text{OC}(\text{O})\text{R}^{67}$, $\text{OC}(\text{O})\text{OR}^{67}$, NH_2 , NHR^{67} , $\text{N}(\text{R}^{67})_2$, $\text{NHC}(\text{O})\text{R}^{67}$, $\text{NR}^{67}\text{C}(\text{O})\text{R}^{67}$, $\text{NHS}(\text{O})_2\text{R}^{67}$, $\text{NR}^{67}\text{S}(\text{O})_2\text{R}^{67}$, $\text{NHC}(\text{O})\text{OR}^{67}$, $\text{NR}^{67}\text{C}(\text{O})\text{OR}^{67}$, $\text{NHC}(\text{O})\text{NH}_2$, $\text{NHC}(\text{O})\text{NHR}^{67}$, $\text{NHC}(\text{O})\text{N}(\text{R}^{67})_2$, $\text{NR}^{67}\text{C}(\text{O})\text{NHR}^{67}$, $\text{NR}^{67}\text{C}(\text{O})\text{N}(\text{R}^{67})_2$, $\text{C}(\text{O})\text{NH}_2$, $\text{C}(\text{O})\text{NHR}^{67}$, $\text{C}(\text{O})\text{N}(\text{R}^{67})_2$, $\text{C}(\text{O})\text{NHOH}$, $\text{C}(\text{O})\text{NHOR}^{67}$, $\text{C}(\text{O})\text{NHSO}_2\text{R}^{67}$, $\text{C}(\text{O})\text{NR}^{67}\text{SO}_2\text{R}^{67}$, SO_2NH_2 , $\text{SO}_2\text{NHR}^{67}$, $\text{SO}_2\text{N}(\text{R}^{67})_2$, $\text{C}(\text{O})\text{H}$, $\text{C}(\text{O})\text{OH}$, $\text{C}(\text{N})\text{NH}_2$, $\text{C}(\text{N})\text{NHR}^{67}$, $\text{C}(\text{N})\text{N}(\text{R}^{67})_2$, CNOH , CNOCH_3 , OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I sustituyentes;

R^{67} es alquilo, alquenilo, alquinilo, fenilo, heteroarilo, cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo;

donde las unidades cíclicas representadas por R^{57A} , R^{58} , R^{59} , R^{60} , R^{63} , R^{64} , R^{65} , y R^{67} no están sustituidas o están sustituidas con uno o dos o tres o cuatro sustituyentes seleccionados en forma independiente entre R^{68} , OR^{68} , SR^{68} , $S(O)R^{68}$, SO_2R^{68} , $C(O)R^{68}$, $CO(O)R^{68}$, $OC(O)R^{68}$, $OC(O)OR^{68}$, NH_2 , NHR^{68} , $N(R^{68})_2$, $NHC(O)R^{68}$, $NR^{68}C(O)R^{68}$, $NHS(O)_2R^{68}$, $NR^{68}S(O)_2R^{68}$, $NHC(O)OR^{68}$, $NR^{68}C(O)OR^{68}$, $NHC(O)NH_2$, $NHC(O)NHR^{68}$, $NHC(O)N(R^{68})_2$, $NR^{68}C(O)NHR^{68}$, $NR^{68}C(O)N(R^{68})_2$, $C(O)NH_2$, $C(O)NHR^{68}$, $C(O)N(R^{68})_2$, $C(O)NHOH$, $C(O)NHOR^{68}$, $C(O)NHSO_2R^{68}$, $C(O)NR^{68}SO_2R^{68}$, SO_2NH_2 , SO_2NHR^{68} , $SO_2N(R^{68})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{68}$, $C(N)N(R^{68})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I ;

R^{68} es R^{69} , R^{70} , R^{71} o R^{72} ;

R^{69} es fenilo, que no está fusionado o está fusionado con R^{69A} ; R^{69A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{70} es heteroarilo, que no está fusionado o está fusionado con R^{70A} ; R^{70A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{71} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{71A} ; R^{71A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{72} 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^{73} , OR^{73} , SR^{73} , $S(O)R^{73}$, SO_2R^{73} , $C(O)R^{73}$, $CO(O)R^{73}$, $OC(O)R^{73}$, $OC(O)OR^{73}$, NH_2 , NHR^{73} , $N(R^{73})_2$, $NHC(O)R^{73}$, $NR^{73}C(O)R^{73}$, $NHS(O)_2R^{73}$, $NR^{73}S(O)_2R^{73}$, $NHC(O)OR^{73}$, $NR^{73}C(O)OR^{73}$, $NHC(O)NH_2$, $NHC(O)NHR^{73}$, $NHC(O)N(R^{73})_2$, $NR^{73}C(O)NHR^{73}$, $NR^{73}C(O)N(R^{73})_2$, $C(O)NH_2$, $C(O)NHR^{73}$, $C(O)N(R^{73})_2$, $C(O)NHOH$, $C(O)NHOR^{73}$, $C(O)NHSO_2R^{73}$, $C(O)NR^{73}SO_2R^{73}$, SO_2NH_2 , SO_2NHR^{73} , $SO_2N(R^{73})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{73}$, $C(N)N(R^{73})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I ;

R^{73} es alquilo, alquenilo, alquinilo, fenilo, heteroarilo, cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo; y

donde las unidades representadas por R^{69} , R^{70} , y R^{71} no están sustituidas o están sustituidas con uno o dos o tres o cuatro sustituyentes seleccionados en forma independiente entre NH_2 , $C(O)NH_2$, $C(O)NHOH$, SO_2NH_2 , CF_3 , CF_2CF_3 , $C(O)H$, $C(O)OH$, $C(N)NH_2$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I .

En una forma de realización de Fórmula (I), A^1 es N , y G^1 es H . En otra forma de realización de Fórmula (I), A^1 es $C(A^2)$ y G^1 es H . En otra forma de realización de Fórmula (I),

A^1 es $C(A^2)$; A^2 es H, F, Cl, Br, o I; y G^1 es H. En otra forma de realización de Fórmula (I), A^1 es $C(A^2)$; A^2 es H; y G^1 es H.

En una forma de realización de Fórmula (I), B^1 es R^1 , OR^1 , NHR^1 , $NHC(O)R^1$, F, Cl, Br, o I. En otra forma de realización de Fórmula (I), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 , y G^1 es H. En otra forma de realización de Fórmula (I), A^1 es $C(A^2)$; A^2 es H; B^1 es OR^1 , y G^1 es H. En otra forma de realización de Fórmula (I), A^1 es $C(A^2)$; A^2 es H; B^1 es Cl; y G^1 es H. En otra forma de realización de Fórmula (I), A^1 es $C(A^2)$; A^2 es H; B^1 es R^1 ; y G^1 es H. En otra forma de realización de Fórmula (I), A^1 es N; B^1 es NHR^1 ; y G^1 es H. En otra forma de realización de Fórmula (I), A^1 es N; B^1 es OR^1 ; y G^1 es H. En otra forma de realización de Fórmula (I), A^1 es N; B^1 es Cl; y G^1 es H. En otra forma de realización de Fórmula (I), A^1 es N; B^1 es R^1 ; y G^1 es H.

En una forma de realización de Fórmula (I), D^1 es H o Cl. En otra forma de realización de Fórmula (I), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 ; D^1 es H; y G^1 es H. En otra forma de realización de Fórmula (I), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 ; D^1 es Cl; y G^1 es H. En otra forma de realización de Fórmula (I), A^1 es $C(A^2)$; A^2 es H; B^1 es OR^1 ; D^1 es H; y G^1 es H. En otra forma de realización de Fórmula (I), A^1 es $C(A^2)$; A^2 es H; B^1 es Cl; D^1 es H; y G^1 es H. En otra forma de realización de Fórmula (I), A^1 es $C(A^2)$; A^2 es H; B^1 es R^1 ; D^1 es H; y G^1 es H. En otra forma de realización de Fórmula (I), A^1 es N; B^1 es NHR^1 ; D^1 es H; y G^1 es H. En otra forma de realización de Fórmula (I), A^1 es N; B^1 es NHR^1 ; D^1 es Cl; y G^1 es H. En otra forma de realización de Fórmula (I), A^1 es N; B^1 es OR^1 ; D^1 es H; y G^1 es H. En otra forma de realización de Fórmula (I), A^1 es N; B^1 es Cl; D^1 es H; y G^1 es H. En otra forma de realización de Fórmula (I), A^1 es N; B^1 es R^1 ; D^1 es H; y G^1 es H.

En una forma de realización de Fórmula (I), E^1 es H. En otra forma de realización de Fórmula (I), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 ; D^1 es H; E^1 es H; y G^1 es H. En otra forma de realización de Fórmula (I), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 ; E^1 es H; D^1 es Cl; y G^1 es H. En otra forma de realización de Fórmula (I), A^1 es $C(A^2)$; A^2 es H; B^1 es OR^1 ; D^1 es H; E^1 es H; y G^1 es H. En otra forma de realización de Fórmula (I), A^1 es $C(A^2)$; A^2 es H; B^1 es Cl; D^1 es H; E^1 es H; y G^1 es H. En otra forma de realización de Fórmula (I), A^1 es $C(A^2)$; A^2 es H; B^1 es R^1 ; D^1 es H; E^1 es H; y G^1 es H. En otra forma de realización de Fórmula (I), A^1 es N; B^1 es NHR^1 ; D^1 es H; E^1 es H; y G^1 es H. En otra forma de realización de Fórmula (I), A^1 es N; B^1 es NHR^1 ; E^1 es H; D^1 es Cl, y G^1 es H. En otra forma de realización de Fórmula (I), A^1 es N; B^1 es OR^1 ; D^1 es H; E^1 es H; y G^1 es H. En otra forma de realización de Fórmula (I), A^1 es N; B^1 es Cl; D^1 es H; E^1 es H; y G^1 es H. En otra forma de realización de Fórmula (I), A^1 es N; B^1 es R^1 ; D^1 es H; E^1 es H; y G^1 es H.

En una forma de realización de Fórmula (I), Y^1 es H, CN, NO_2 , F, Cl, Br, I, CF_3 , R^{17} , OR^{17} , SR^{17} , SO_2R^{17} , o $C(O)NH_2$. En otra forma de realización de Fórmula (I), Y^1 es H. En otra

forma de realización de Fórmula (I), Y^1 es CN. En otra forma de realización de Fórmula (I), Y^1 es F, Cl, Br, o I. En otra forma de realización de Fórmula (I), Y^1 es CF_3 . En otra forma de realización de Fórmula (I), Y^1 es SR^{17} . En otra forma de realización de Fórmula (I), Y^1 es OR^{17} . En otra forma de realización de Fórmula (I), Y^1 es NO_2 . En otra forma de realización de Fórmula (I), Y^1 es SO_2R^{17} ; donde R^{17} es como se ha definido. En otra forma de realización de Fórmula (I), Y^1 es SO_2R^{17} ; donde R^{17} es alquilo. En otra forma de realización de Fórmula (I), Y^1 es R^{17} ; donde R^{17} es alquinilo. En otra forma de realización de Fórmula (I), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 ; D^1 es H; E^1 es H; G^1 es H; y Y^1 es NO_2 o SO_2R^{17} ; donde R^{17} es alquilo o alquinilo. En otra forma de realización de Fórmula (I), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 ; D^1 es H; E^1 es H; G^1 es H; y Y^1 es NO_2 . En otra forma de realización de Fórmula (I), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 ; D^1 es H; E^1 es H; G^1 es H; y Y^1 es SO_2R^{17} ; donde R^{17} es alquilo sustituido con tres F. En otra forma de realización de Fórmula (I), A^1 es N; B^1 es NHR^1 ; D^1 es H; E^1 es H; G^1 es H; y Y^1 es NO_2 o SO_2R^{17} ; donde R^{17} es alquilo o alquinilo. En otra forma de realización de Fórmula (I), A^1 es N; B^1 es NHR^1 ; D^1 es H; E^1 es H; G^1 es H; y Y^1 es NO_2 . En otra forma de realización de Fórmula (I), A^1 es N; B^1 es NHR^1 ; D^1 es H; E^1 es H; G^1 es H; y Y^1 es SO_2R^{17} ; donde R^{17} es alquilo sustituido con tres F.

En una forma de realización de Fórmula (I), G^1 es H; A^1 es N o $C(A^2)$; y A^2 es H. En otra forma de realización de Fórmula (I), G^1 es H; A^1 es N o $C(A^2)$; A^2 es H; y B^1 es NHR^1 . En otra forma de realización de Fórmula (I), G^1 es H; A^1 es N o $C(A^2)$; A^2 es H; B^1 es NHR^1 ; y D^1 es H. En otra forma de realización de Fórmula (I), G^1 es H; A^1 es N o $C(A^2)$; A^2 es H; B^1 es NHR^1 ; D^1 es H; y E^1 es H. En otra forma de realización de Fórmula (I), G^1 es H; A^1 es N o $C(A^2)$; A^2 es H; B^1 es NHR^1 ; D^1 es H; E^1 es H; y Y^1 es NO_2 .

En una forma de realización de Fórmula (I), Y^1 y B^1 , junto con los átomos a los cuales están unidos, son benceno. En otra forma de realización de Fórmula (I), Y^1 y B^1 , junto con los átomos a los cuales están unidos, son heteroareno. En otra forma de realización de Fórmula (I), A^1 es $C(A^2)$; A^2 , G^1 , E^1 , y D^1 se seleccionan en forma independiente entre H; y Y^1 y B^1 , junto con los átomos a los cuales están unidos, son benceno. En otra forma de realización de Fórmula (I), A^1 es $C(A^2)$; A^2 , G^1 , E^1 , y D^1 se seleccionan en forma independiente entre H; y Y^1 y B^1 , junto con los átomos a los cuales están unidos, son heteroareno.

En una forma de realización de Fórmula (I), R^1 es R^4 o R^5 . En una forma de realización de Fórmula (I), R^1 es R^4 . En una forma de realización de Fórmula (I), R^1 es R^5 . En una forma de realización de Fórmula (I), R^1 es R^4 ; y R^4 es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo. En una forma de realización de Fórmula (I), R^1 es R^4 ; y R^4 es cicloalquilo o heterocicloalquilo. En una forma de realización de Fórmula (I), R^1 es R^4 ; y R^4 es cicloalquilo. En una forma de realización de Fórmula (I), R^1 es R^4 ; y R^4 es heterocicloalquilo.

En una forma de realización de Fórmula (I), R^1 es R^4 ; y R^4 es cicloalquilo; donde R^4 no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (I), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo está sustituido como se ha definido. En otra forma de realización de Fórmula (I), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo está sustituido con R^{57} o $N(R^{57})_2$. En otra forma de realización de Fórmula (I), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con R^{57} ; y R^{57} es R^{60} . En otra forma de realización de Fórmula (I), R^1 es R^4 ; R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con R^{57} ; R^{57} es R^{60} ; y R^{60} es heterocicloalquilo. En otra forma de realización de Fórmula (I), R^1 es R^4 ; R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con R^{57} ; R^{57} es R^{60} ; R^{60} es heterocicloalquilo; donde el anillo heterocicloalquilo es morfolinilo. En otra forma de realización de Fórmula (I), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo está sustituido con $N(R^{57})_2$. En otra forma de realización de Fórmula (I), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con $N(R^{57})_2$. En otra forma de realización de Fórmula (I), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con $N(R^{57})_2$; R^{57} es R^{61} ; y R^{61} es alquilo que no está sustituido o está sustituido con R^{62} . En otra forma de realización de Fórmula (I), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con R^{57} ; R^{57} es R^{61} ; y R^{61} es alquilo que no está sustituido o está sustituido con R^{62} ; R^{62} es R^{65} ; y R^{65} es cicloalquilo. En otra forma de realización de Fórmula (I), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con R^{57} ; R^{57} es R^{61} ; y R^{61} es alquilo el cual está sustituido con R^{62} ; R^{62} es R^{65} ; y R^{65} es ciclopropilo.

En una forma de realización de Fórmula (I), R^1 es R^4 ; y R^4 es heterocicloalquilo; donde R^4 no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (I), R^1 es R^4 ; y R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo está sustituido como se ha definido. En otra forma de realización de Fórmula (I), R^1 es R^4 ; y R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo está sustituido con R^{57} . En otra forma de realización de Fórmula (I), R^1 es R^4 ; y R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo es piperidinilo o piperizinilo; y donde el anillo heterocicloalquilo está sustituido con R^{57} ; y R^{57} es R^{60} o R^{61} . En otra forma de realización de Fórmula (I), R^1 es R^4 ; R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo es piperidinilo o piperizinilo; y donde el anillo piperidinilo o piperizinilo está sustituido con R^{57} ; R^{57} es R^{60} o R^{61} ; R^{60} es heterocicloalquilo; y R^{61} es alquilo. En otra forma de realización de Fórmula (I), R^1 es R^4 ; R^4 es heterocicloalquilo; donde el anillo

heterocicloalquilo es piperidinilo o piperizinilo; y donde el anillo piperidinilo o piperizinilo está sustituido con R^{57} ; R^{57} es R^{60} ; R^{60} es heterocicloalquilo; donde el heterocicloalquilo es tetrahidropiranilo. En otra forma de realización de Fórmula (I), R^1 es R^4 ; R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo es piperidinilo o piperizinilo; y donde el anillo piperidinilo o piperizinilo está sustituido con R^{57} ; R^{57} es R^{61} ; R^{61} es alquilo; y el alquilo es metilo. En otra forma de realización de Fórmula (I), R^1 es R^4 ; R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo es piperidinilo o piperizinilo; y donde el anillo piperidinilo o piperizinilo está sustituido con $C(O)OR^{57}$; R^{57} es R^{61} ; R^{61} es alquilo; y el alquilo es metilo.

En una forma de realización de Fórmula (I), R^1 es R^5 ; y R^5 es alquilo que no está sustituido o está sustituido. En una forma de realización de Fórmula (I), R^1 es R^5 ; y R^5 es alquilo que no está sustituido o está sustituido con R^7 , OR^7 , OH , CN , o F . En otra forma de realización de Fórmula (I), R^1 es R^5 ; y R^5 es alquilo el cual está sustituido con R^7 , OR^7 , NHR^7 , o $N(R^7)_2$.

En una forma de realización de Fórmula (I), R^7 es R^8 , R^9 , R^{10} o R^{11} que no están sustituidos o están sustituidos como se ha definido. En otra forma de realización de Fórmula (I), R^7 es R^8 que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (I), R^7 es R^9 que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (I), R^7 es R^{10} que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (I), R^7 es R^{11} que no está sustituido o está sustituido como se ha definido.

En una forma de realización de Fórmula (I), R^8 es fenilo que no está sustituido o está sustituido como se ha definido.

En una forma de realización de Fórmula (I), R^9 es heteroarilo que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (I), R^9 es furanilo; que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (I), R^9 es furanilo; que no está sustituido.

En una forma de realización de Fórmula (I), R^{10} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, heterocicloalquilo que no están sustituidos o están sustituidos como se ha definido. En otra forma de realización de Fórmula (I), R^{10} es heterocicloalquilo que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (I), R^{10} es tetrahidrofuranilo, tetrahidropiranilo, morfolinilo, dioxanilo, oxetanilo, piperidinilo, o pirrolidinilo, que no están sustituidos o están sustituidos como se ha definido. En otra forma de realización de Fórmula (I), R^{10} es tetrahidropiranilo; que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (I), R^{10} es morfolinilo; que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (I), R^{10} es cicloalquilo que no está sustituido o está

sustituido como se ha definido. En otra forma de realización de Fórmula (I), R^{10} es cicloalquilo que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (I), R^{10} es ciclohexilo, ciclopropilo, ciclobutilo, o biciclo[2,2,1]heptanilo, que no está sustituido o está sustituido como se ha definido. En otra forma de realización de

5 Fórmula (I), R^{10} es heterocicloalquilo que está fusionado con R^{10A} ; y R^{10A} es heteroareno. En otra forma de realización de Fórmula (I), R^{10} es 5,6,7,8-tetrahidroimidazo[1,2-a]piridinilo.

En una forma de realización de Fórmula (I), R^{11} es alquilo, alqueno o alquínilo que no están sustituidos o están sustituidos como se ha definido. En otra forma de realización de Fórmula (I), R^{11} es alquilo. En otra forma de realización de Fórmula (I), R^{11} es metilo; que no

10 está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (I), R^{11} es alquilo; que está sustituido como se ha definido. En otra forma de realización de Fórmula (I), R^{11} es alquilo; que está sustituido con R^{12} , OR^{12} , o CF_3 . En otra forma de realización de Fórmula (I), R^{11} es alquilo; que está sustituido con OR^{12} , R^{12} es R^{16} ; y R^{16} es alquilo. En otra forma de realización de Fórmula (I), R^{11} es alquilo; que está sustituido

15 con CF_3 . En otra forma de realización de Fórmula (I), R^{11} es alquilo; que está sustituido con R^{12} ; R^{12} es R^{14} ; y R^{14} es heteroarilo.

En una forma de realización de Fórmula (I), A^1 es N o $C(A^2)$;

A^2 es H, F, Br, I, o Cl;

B^1 es R^1 , OR^1 , NHR^1 , $NHC(O)R^1$, F, Br, I o Cl;

20 D^1 es H, F, Br, I, o Cl;

E^1 es H; y

Y^1 es H, CN, NO_2 , F, Cl, Br, I, CF_3 , R^{17} , OR^{17} , SR^{17} , SO_2R^{17} , o $C(O)NH_2$; o

Y^1 y B^1 , junto con los átomos a los cuales están unidos, son benceno, heteroareno, o heterocicloalqueno; y

25 A^2 , D^1 , y E^1 se seleccionan en forma independiente entre H;

G^1 es H, o $C(O)O$;

R es alquilo;

R^1 es R^4 o R^5 ;

R^4 es cicloalquilo, o heterocicloalquilo;

30 R^5 es alquilo, o alquínilo, cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre R^7 , OR^7 , NHR^7 , $N(R^7)_2$, CN, OH, F, Cl, Br o I;

R^7 es R^8 , R^9 , R^{10} , o R^{11} ;

R^8 es fenilo;

35 R^9 es heteroarilo;

R^{10} es cicloalquilo, cicloalquenilo, o heterocicloalquilo; cada uno de los cuales no está fusionado o está fusionado con R^{10A} , R^{10A} es heteroareno;

R^{11} es alquilo cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre R^{12} , OR^{12} or CF_3 ;

5 R^{12} es R^{14} o R^{16} ;

R^{14} es heteroarilo;

R^{16} es alquilo;

R^{17} es R^{21} ;

10 R^{21} es alquilo, o alquínilo, cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre R^{22} , F, Cl, Br o I;

R^{22} es R^{25} ;

R^{25} es heterocicloalquilo;

Z^1 es R^{26} ;

15 Z^2 es R^{30} ;

Z^{1A} y Z^{2A} están ambos ausentes;

L^1 es un R^{37} ;

R^{26} es fenileno;

R^{30} es heterocicloalquileno;

20 R^{37} es R^{37A} ;

R^{37A} es alquileno;

Z^3 es R^{38} , o R^{40} ;

R^{38} es fenilo;

R^{40} es cicloalquilo, cicloalquenilo, o heterocicloalquenilo;

25 donde la unidad representada por R^{26} está sustituida con OR^{41} ;

R^{41} es heteroarilo, que está fusionado con R^{43A} ; R^{43A} es heteroareno; que no está fusionado o está fusionado con benceno;

30 donde las unidades cíclicas representadas por Y^1 y B^1 juntos, R^4 , R^8 , R^{10} , R^{25} , R^{30} , R^{38} , y R^{40} no están sustituidas, no están adicionalmente sustituidas, están sustituidas o adicionalmente sustituidas en forma independiente con uno o dos o tres o cuatro o cinco sustituyentes seleccionados en forma independiente entre R^{57A} , R^{57} , OR^{57} , SO_2R^{57} , $C(O)R^{57}$, $CO(O)R^{57}$, $C(O)N(R^{57})_2$, NH_2 , NHR^{57} , $N(R^{57})_2$, $NHC(O)R^{57}$, $NHS(O)_2R^{57}$, OH , CN , (O) , F, Cl, Br o I;

R^{57A} es espiroalquilo, o espiroheteroalquilo;

35 R^{57} es R^{58} , R^{59} , R^{60} o R^{61} ;

R^{58} es fenilo;

R^{59} es heteroarilo;

R^{60} es cicloalquilo, o heterocicloalquilo;

R^{61} es alquilo que no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre R^{62} , OR^{62} , $N(R^{62})_2$, $C(O)OH$, CN ,
5 F, Cl, Br o I;

R^{62} es R^{65} , o R^{66} ;

R^{65} es cicloalquilo, o heterocicloalquilo;

R^{66} es alquilo que no está sustituido o está sustituido con OR^{67} ;

R^{67} es alquilo;

10 donde las unidades cíclicas representadas por R^{57A} , R^{58} , y R^{60} no están sustituidas o están sustituidas con uno o dos o tres o cuatro sustituyentes seleccionados en forma independiente entre R^{68} , F, Cl, Br o I;

R^{68} es R^{71} o R^{72} ;

R^{71} es heterocicloalquilo; y

15 R^{72} es alquilo, que no está sustituido o está sustituido con uno o dos F.

Aún otra forma de realización se refiere a compuestos de fórmula (I), que son

4-{4-[(4'-cloro-1,1'-bifenil-2-il)metil]piperazin-1-il}-N-({3-nitro-4-[(tetrahydro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol-2,3-b)piridin-5-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-(1H-pirrol-2,3-b)piridin-5-iloxi)benzamida;

20 4-{4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il}-N-({3-nitro-4-[(1-tetrahydro-2H-piran-4-ilpiperidin-4-il)amino]fenil}sulfonil)-2-(1H-pirrol-2,3-b)piridin-5-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-(1H-pirrol-2,3-b)piridin-5-iloxi)benzamida;

25 4-{4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il}-N-({3-nitro-4-[(tetrahydro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol-2,3-b)piridin-5-iloxi)benzamida;

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)-2-(1H-pirrol-2,3-b)piridin-5-iloxi)benzamida;

2-(9H-carbazol-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-(9H-carbazol-4-iloxi)-4-{4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il}-N-({3-nitro-4-[(3-pirrolidin-1-ilpropil)amino]fenil}sulfonil)benzamida;

35 Trans-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)-2-(1H-pirrol-2,3-b)piridin-5-iloxi)benzamida;

- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({4-[(2-metoxietil)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(3-nitro-4-[(3S)-tetrahidro-2H-piran-3-ilmetil]amino)fenil}sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 5 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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(3-nitro-4-[(3R)-tetrahidro-2H-piran-3-ilmetil]amino)fenil}sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-(2-naftilsulfonil)-2-
- 10 (1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil]piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({4-[(2-metoxietil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 15 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)-N-({4-[(tetrahidro-2H-piran-4-ilmetil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida;
- 20 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({3-nitro-4-(tetrahidro-2H-piran-4-ilmetoxi)fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({3-nitro-4-[(2,2,2-trifluoroetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 25 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({3-nitro-4-[(3,3,3-trifluoropropil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 30 Cis-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]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil]piperazin-1-il)-N-({4-[(1,4-
- 35 dioxan-2-ilmetil)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-N-{[4-(1,4-dioxan-2-ilmetoxi)-3-nitrofenil]sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 Trans-4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-N-{[4-[(4-morfolin-4-ilciclohexil)amino]-3-nitrofenil]sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 5 Trans-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}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-N-{[5-ciano-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 10 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-pirrolo[2,3-b]piridin-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 15 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 Cis-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}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 20 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-N-{[5-cloro-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 25 4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)-N-{[4-[(tetrahidro-2H-piran-4-ilmetil)amino]-3-(trifluorometil)fenil]sulfonil}benzamida;
 4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)-N-{[4-[(tetrahidro-2H-piran-4-ilmetil)amino]-3-(trifluorometil)sulfonil]fenil}sulfonil}benzamida;
 30 Trans-4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-N-{[4-[(4-morfolin-4-ilciclohexil)amino]-3-[(trifluorometil)sulfonil]fenil]sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-([4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil)piperazin-1-il)-N-([4-([1-metilpiperidin-4-il]amino)-3-([trifluorometil]sulfonil)fenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 5-([4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]amino)sulfonil)-2-(tetrahidro-2H-piran-4-ilmetoxi)nicotinamida;
- 5 N-([5-bromo-6-([1-metilpiperidin-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-metilpiperidin-4-il]metoxi)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 10 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([5-ciano-6-(1,4-dioxan-2-ilmetoxi)piridin-3-il]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-([5-bromo-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([2,2-
- 15 dimetiltetrahidro-2H-piran-4-il]metoxi)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-([3-cloro-5-ciano-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-([4-([1-acetilpiperidin-4-il]amino)-3-nitrofenil]sulfonil)-4-(4-([2-(4-clorofenil)-4,4-
- 20 dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)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-pirrol[2,3-b]piridin-5-iloxi)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-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 25 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-pirrol[2,3-b]piridin-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 30 N-([3-cloro-4-([2-(2-metoxietoxi)etil]sulfonil)fenil]sulfonil)-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([2-(2-metoxietoxi)etil]sulfonil)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- Trans-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-
- 35 morfolin-4-ilciclohexil]oxi)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

- N-({5-bromo-6-[(1-tetraidro-2H-piran-4-il)piperidin-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-pirrolo[2,3-b]piridin-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5 Cis-4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-N-({4-[(4-morfolin-4-ilciclohexil)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- Trans-N-({4-({4-[bis(ciclopropilmetil)amino]ciclohexil)amino}-3-nitrofenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 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)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(morfolin-3-ilmetil)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-N-({4-[(4-metilpiperazin-1-il)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-morfolin-4-ilbut-2-inil)oxi]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({5-etinil-6-(tetraidro-2H-piran-4-ilmetoxi)piridin-3-il}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-oxo-3,4-dihidroquinazolin-6-il}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- Trans-4-(4-{[8-(4-clorofenil)espiro[4,5]dec-7-en-7-il]metil}piperazin-1-il)-N-({4-[(4-morfolin-4-ilciclohexil)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 Cis-4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-N-({4-[(4-metoxiciclohexil)metil]amino}-3-nitrofenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[8-(4-clorofenil)espiro[4,5]dec-7-en-7-il]metil}piperazin-1-il)-N-({4-[(4-fluorotetraidro-2H-piran-4-il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 Trans-4-(4-{[8-(4-clorofenil)espiro[4,5]dec-7-en-7-il]metil}piperazin-1-il)-N-({4-[(4-metoxiciclohexil)metil]amino}-3-nitrofenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(tetraidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-{{2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{5-ciano-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il}sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 3-{{4-{{4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil}amino}sulfonil}-2-nitrofenoxi}metil}morfolina-4-carboxilato de tert-butilo;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-(morfolin-3-ilmetoxi)-3-nitrofenil}sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{8-(4-clorofenil)espiro[4,5]dec-7-en-7-il}metil}piperazin-1-il)-N-{{3-nitro-4-((tetrahidro-2H-piran-4-ilmetil)amino)fenil}sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{1-(metilsulfonil)piperidin-4-il}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-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}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-{{4-cloro-3-nitrofenil}sulfonil}-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-{{1-(2,2,2-trifluoroetil)piperidin-4-il}amino}fenil}sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{5-ciano-6-{{1-(tetrahidro-2H-piran-4-il)piperidin-4-il}oxi}piridin-3-il}sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{5-isopropil-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il}sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-{{3-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-pirrol[2,3-b]piridin-5-iloxi)benzamida; y sus sales terapéuticamente aceptables, y sus metabolitos.
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{1-{{2-fluoro-1-(fluorometil)etil}piperidin-4-il}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(4-([1-(2,2-difluoroetil)piperidin-4-il]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-morfolin-4-ilciclohexil]metil]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- Trans-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-(diciclopropilamino)ciclohexil]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-6,6-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil]amino]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-([5-bromo-6-([4-etilmorfolin-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-etilmorfolin-3-il]metoxi]-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-[(4-tetrahidro-2H-piran-4-ilmorfolin-3-il]metoxi]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-[(3S)-1-tetrahidro-2H-piran-4-ilpiperidin-3-il]amino]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-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-ilmetil]amino]piridin-3-il)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1,1-dioxidotiormorfolin-4-il]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- Trans-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([5-ciano-6-[(4-morfolin-4-ilciclohexil]amino]piridin-3-il)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-
iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-([4-({(1S,3R)-3-
5 morfolin-4-ilciclopentil]amino)-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-
iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-([4-({(1R,3S)-3-
morfolin-4-ilciclopentil]amino)-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-
iloxi)benzamida;
- 10 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(morfolin-2-
ilmetil)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-
[(tetrahidrofurano-3-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-([4-({1-[cis-3-
15 fluorotetrahidro-2H-piran-4-il]piperidin-4-il}amino)-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-
b]piridin-5-iloxi)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-ilazetidil-3-il)amino]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-
iloxi)benzamida;
- 20 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(1-
tetrahidrofurano-3-ilazetidil-3-il)amino]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-
iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-([3-nitro-4-({(3R)-1-
tetrahidro-2H-piran-4-ilpirrolidin-3-il]metil}amino)fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-
25 iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-
fluorotetrahidro-2H-piran-4-il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-
iloxi)benzamida;
- 2-(1H-pirrolo[2,3-b]piridin-5-iloxi)-4-(4-[(2-(4-clorofenil)-4,4-dimetilciclohex-1-
30 enil]metil}piperazin-1-il)-N-4-[(trans-4-hidroxiciclohexil)metoxi]-3-nitrofenil)sulfonil)benzamida;
- 2-(1H-pirrolo[2,3-b]piridin-5-iloxi)-4-(4-[(2-(4-clorofenil)-4,4-dimetilciclohex-1-
enil]metil}piperazin-1-il)-N-4-[(cis-4-metoxiciclohexil)metoxi]-3-nitrofenil)sulfonil)benzamida;
- Cis-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-([4-([4-
(ciclopropilamino)ciclohexil]amino)-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-
35 iloxi)benzamida;

- Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{[4-(tetrahidro-2H-piran-4-ilamino)ciclohexil]amino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- Trans-N-({5-bromo-6-[(4-morfolin-4-ilciclohexil)oxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-metoxiciclohexil)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-{[4-({[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzoil]amino}sulfonil)-2-nitrofenoxi]metil}-4-fluoropiperidin-1-carboxilato de tert-butilo;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-fluoropiperidin-4-il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{[4-(4-tetrahidro-2H-piran-4-ilpiperazin-1-il)ciclohexil]amino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(1-[2-fluoro-1-(fluorometil)etil]piperidin-4-il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{[(3R)-1-tetrahidro-2H-piran-4-ilpirrolidin-3-il]amino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3R)-1-(2,2-dimetiltetrahidro-2H-piran-4-il)pirrolidin-3-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{[(3S)-1-tetrahidro-2H-piran-4-ilpirrolidin-3-il]amino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3S)-1-(2,2-dimetiltetrahidro-2H-piran-4-il)pirrolidin-3-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4-metilmorfolin-2-il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-(2-metoxietil)morfolin-2-il]metil}amino)-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

- N-[(4-{[(4-acetilmorfolin-2-il)metil]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[trans-4-(fluorometil)-1-oxetan-3-ilpirrolidin-3-il]metoxi}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 5 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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{[1-oxetan-3-ilpiperidin-4-il]amino}fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 10 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[1-ciclobutilpiperidin-4-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[1-(2,2-dimetiltetrahidro-2H-piran-4-il)piperidin-4-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 15 b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3S)-1-ciclopropilpirrolidin-3-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{[1-tetrahidrofurano-3-ilpiperidin-4-il]amino}fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 20 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3R)-1-ciclopropilpirrolidin-3-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 25 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{[(3S)-1-tetrahidro-2H-piran-4-ilpirrolidin-3-il]metil]amino}fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[3-hidroxi-2,2-dimetilpropil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 30 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[1-(metilsulfonil)piperidin-3-il]metil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 N-[(4-{[1-acetilpiperidin-3-il]metil]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3R)-1-(metilsulfonil)pirrolidin-3-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-3,3-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-
5 [(tetrahidro-2H-piran-4-ilmetil)amino]fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[1-[2-fluoro-1-(fluorometil)etil]azetidin-3-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxy)benzamida;
- 10 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[1-(metilsulfonil)pirrolidin-3-il]metil}amino)-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-[(4-{[(1-acetilpirrolidin-3-il)metil]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 N-[(4-{[(3R)-1-acetilpirrolidin-3-il]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3-metoxi-2,2-dimetilpropil)amino]-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(1R,3R)-3-
20 hidroxiciclopentil]metil}amino)-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(1S,3S)-3-hidroxiciclopentil]metil}amino)-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(1S,3R)-3-hidroxiciclopentil]metil}amino)-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(1R,3S)-3-hidroxiciclopentil]metil}amino)-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-
30 iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{[(3S)-2-oxopiperidin-3-il]amino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[1-[2-fluoro-1-(fluorometil)etil]azetidin-3-il]metil}amino)-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-
35 iloxi)benzamida;

- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(3-nitro-4-{{(1-oxetan-3-ilazetidín-3-il)metil}amino}fenil)sulfonil]-2-(1H-pirrólo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(3-nitro-4-{{(1-oxetan-3-ilpiperidin-4-il)metil}amino}fenil)sulfonil]-2-(1H-pirrólo[2,3-b]piridin-5-iloxi)benzamida;
- 5 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{(1-ciclopropilpiperidin-4-il)metil}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrólo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(4-(2-fluoroetil)morfolín-2-il)metil}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrólo[2,3-b]piridin-5-iloxi)benzamida;
- 10 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(4-(2,2-difluoroetil)morfolín-2-il)metil}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrólo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(4-(2,2-difluoroetil)morfolín-2-il)metil}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrólo[2,3-b]piridin-5-iloxi)benzamida;
- 15 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(4-(2,2-difluoroetil)morfolín-2-il)metil}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrólo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(4-fluoro-1-oxetan-3-ilpiperidin-4-il)metoxi}-3-nitrofenil)sulfonil]-2-(1H-pirrólo[2,3-b]piridin-5-iloxi)benzamida;
- 15 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(4-fluoro-1-oxetan-3-ilpiperidin-4-il)metoxi}-3-nitrofenil)sulfonil]-2-(1H-pirrólo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(2S)-4,4-difluoro-1-oxetan-3-ilpirrolidin-2-il}metoxi}-3-nitrofenil)sulfonil]-2-(1H-pirrólo[2,3-b]piridin-5-iloxi)benzamida;
- 20 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(3-nitro-4-{{(4-tetrahidro-2H-piran-4-ilmorfolín-3-il)metil}amino}fenil)sulfonil]-2-(1H-pirrólo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{(4-ciclobutilmorfolín-3-il)metil}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrólo[2,3-b]piridin-5-iloxi)benzamida;
- 25 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(3-nitro-4-{{(4-tetrahidrofurano-3-ilmorfolín-3-il)metil}amino}fenil)sulfonil]-2-(1H-pirrólo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(1-[2-fluoro-1-(fluorometil)etil]piperidin-4-il)metil}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrólo[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(1-ciclopropil-4-fluoropiperidin-4-il)metoxi}-3-nitrofenil)sulfonil]-2-(1H-pirrólo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(4-metoxibencil)amino}-3-nitrofenil)sulfonil]-2-(1H-pirrólo[2,3-b]piridin-5-iloxi)benzamida;
- 35 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(4-metoxibencil)amino}-3-nitrofenil)sulfonil]-2-(1H-pirrólo[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(3-nitro-4-{{3-(trifluorometoxi)bencil}amino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({4-{{3-metoxibencil}amino}-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 5 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{4-(difluorometoxi)bencil}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-(1,4-dioxaespiro[4,5]dec-8-ilamino)-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 10 Trans-N-{{4-{{4-(acetilamino)ciclohexil}amino}-3-nitrofenil}sulfonil}-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 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}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 15 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(3S)-1-(2-fluoroetil)pirrolidin-3-il}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(3S)-1-(2,2-difluoroetil)pirrolidin-3-il}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 20 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(3R)-1-(2-fluoroetil)pirrolidin-3-il}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-{{(3S)-1-oxetan-3-ilpirrolidin-3-il}metoxi}fenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 25 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({4-{{4-hidroxi-bencil}amino}-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({4-{{3-hidroxi-bencil}amino}-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 30 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{3-(difluorometoxi)bencil}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(cis-3-morfolin-4-ilciclopentil}metil}amino)-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 Trans-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{4-[(metilsulfonil)amino]ciclohexil}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
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- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({4-[(1-ciclopropilpiperidin-4-il)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({3-nitro-4-[(1-oxetan-3-ilpiperidin-4-il)metoxi]fenil}sulfonil)-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({4-[(4-fluoro-1-tetrahidro-2H-piran-4-ilpiperidin-4-il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({4-[(4-fluoro-1-tetrahidrofurano-3-ilpiperidin-4-il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({4-[(4-fluoro-1-(metilsulfonil)piperidin-4-il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({3-nitro-4-[(3R)-1-oxetan-3-ilpirrolidin-3-il]metil}amino)fenil}sulfonil)-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- Trans-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({4-[(4-hidroxiciclohexil)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({4-[(4-[3-(dimetilamino)propoxi]bencil}amino)-3-nitrofenil}sulfonil)-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({4-[(4-(2-morfolin-4-iletoxi)bencil}amino)-3-nitrofenil}sulfonil)-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({4-[(E)-4-hidroxi-1-adamantil]metil}amino)-3-nitrofenil}sulfonil)-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({4-[(Z)-4-hidroxi-1-adamantil]metil}amino)-3-nitrofenil}sulfonil)-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- N-({4-[(1S,4S)-biciclo[2,2,1]hept-5-en-2-ilmetoxi]-3-nitrofenil}sulfonil)-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({4-[(1-metil-5-oxopirrolidin-3-il)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({4-[(1R,4R,5R,6S)-5,6-dihidroxibiciclo[2,2,1]hept-2-il]metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(4-((1R,4R,5S,6R)-5,6-dihidroxiciclo[2,2,1]hept-2-il]metoxi)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([3-oxociclohexil]metoxi)fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-5,5-dimetilciclohexa-1,3-dien-1-il]metil)piperazin-1-il)-N-([3-nitro-4-[(tetrahidro-2H-piran-4-il]metil)amino]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([(3S)-1-oxetan-3-il]pirrolidin-3-il]metil)amino)fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- Cis-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([(3S)-1-oxetan-3-il]pirrolidin-3-il]amino)fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-[2-(2-metoxietoxi)etil]morfolin-2-il]metil)amino]-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 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]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-(N,N-dimetilglicil)morfolin-2-il]metil)amino]-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- ácido (2-([4-([4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]sulfamoil)-2-nitrofenil)amino]metil]morfolin-4-il)acético;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([4-(oxetan-3-il)morfolin-2-il]metil)amino]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-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-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{5-(metilsulfonil)-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il}sulfonil}-2-(1H-pirrololo[2,3-b]piridin-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-[(trifluorometil)sulfonil]fenil}sulfonil}-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{4-metiltetrahidro-2H-piran-4-il}metoxi}-3-nitrofenil}sulfonil}-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzoil}sulfamoil}-2-nitrofenil)piperazin-1-carboxilato de etilo;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{4-(morfolin-4-il)piperidin-1-il}-3-nitrofenil}sulfonil}-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(3-nitro-4-{{(3R)-1-(oxetan-3-il)pirrolidin-3-il}amino}fenil)sulfonil]-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{(3R)-1-(1,3-difluoropropan-2-il)pirrolidin-3-il}amino}-3-[(trifluorometil)sulfonil]fenil)sulfonil]-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{1-isopropilpiperidin-4-il}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- N-{{4-{{1-tert-butilpiperidin-4-il}amino}-3-nitrofenil}sulfonil}-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{1-(2-metoxietil)piperidin-3-il}metil}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{1-(cianometil)piperidin-3-il}metil}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{4-fluoro-1-metilpiperidin-4-il}metoxi}-3-[(trifluorometil)sulfonil]fenil}sulfonil}-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;

- N-[(5-cloro-6-[(3R)-1-(1,3-difluoropropan-2-il)pirrolidin-3-il]amino}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-[(4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil}sulfamoil]-2-nitrofenil)amino]piperazin-1-carboxilato de tert-butilo;
- 5 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-(pentafluoro- $\square^6$ -sulfanil)-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[4-metoxitetrahidro-2H-piran-4-il]metoxi]-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 10 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3R)-1-(1,3-difluoropropan-2-il)pirrolidin-3-il]oxi]-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 15 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{[4-(oxetan-3-il)piperazin-1-il]amino}fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{[4-(tetrahidro-2H-piran-4-il)piperazin-1-il]amino}fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 20 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-[(3R)-tetrahidrofurano-3-ilamino]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 25 N-[(4-{[1-tert-butilpiperidin-4-il]amino}-3-[(trifluorometil)sulfonil]fenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[4-(oxetan-3-il)morfolin-2-il]metil]amino}-3-[(trifluorometil)sulfonil]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 30 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-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 35

- N-[(5-cloro-6-[[[(2S)-4-(cianometil)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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-[(5-cloro-6-[[[(2R)-4-(cianometil)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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 N-[(5-cloro-6-[3-idroxi-2-(hidroximetil)-2-metilpropoxi]piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-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]piridin-3-il)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-[(4-(1,3-difluoropropan-2-il)morfolin-2-il]metil)amino)-3-nitrofenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 N-[(5-cloro-6-[[1-(cianometil)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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 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]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 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]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-[[1-(oxetan-3-il)azetidin-3-il]amino]fenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 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]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 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]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 N-[(5-cloro-6-[[1-(N,N-dimetilglicil)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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 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]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-{4-[[4'-(clorobifenil-2-il)metil]-4-metoxipiperidin-1-il]-N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 4-{4-[[4'-(clorobifenil-2-il)metil]-4-metoxipiperidin-1-il]-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[9-(4-clorofenil)-3-(1,3-difluoropropan-2-il)-3-azaespiro[5,5]undec-8-en-8-il]metil}piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 4-(4-{[9-(4-clorofenil)-3-isopropil-3-azaespiro[5,5]undec-8-en-8-il]metil}piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[9-(4-clorofenil)-3-(1,3-difluoropropan-2-il)-3-azaespiro[5,5]undec-8-en-8-il]metil}piperazin-1-il)-N-({5-cloro-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-{[9-(4-clorofenil)-3-isopropil-3-azaespiro[5,5]undec-8-en-8-il]metil}piperazin-1-il)-N-({5-cloro-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 35 N-({5-cloro-6-[(4-fluoro-1-metilpiperidin-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

- N-[(5-cloro-6-[[1-(N,N-dimetilglicil)-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-{4-[(4'-clorobifenil-2-il)metil]-4-fluoropiperidin-1-il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-{4-[(4'-clorobifenil-2-il)metil]-4-fluoropiperidin-1-il}-N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[9-(4-clorofenil)-3-isopropil-3-azaespiro[5,5]undec-8-en-8-il]metil]piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)-N-({4-[(tetrahidro-2H-piran-4-ilmetil)amino]-3-(trifluorometil)fenil}sulfonil)benzamida;
- N-[(5-cloro-6-[[[(3R)-1-(1,3-difluoropropan-2-il)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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({3-nitro-4-[2-(tetrahidrofurano-3-iloxi)etoxi]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({5-ciano-6-[2-(tetrahidro-2H-piran-4-il)etoxi]piridin-3-il}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({4-(3-furilmetoxi)-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-[(5-cloro-6-[[[(3R)-1-(1,3-difluoropropan-2-il)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-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-[(5-cloro-6-[[1-(1,3-difluoropropan-2-il)-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-({3-cloro-4-[(4-fluoro-1-metilpiperidin-4-il)metoxi]fenil}sulfonil)-4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-ciano-4-(tetrahydro-2H-piran-4-ilmetoxi)fenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
N-[(5-cloro-6-{{1-(2,2-difluoroetil)-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5 N-{{3-cloro-4-[(4-fluorotetrahydro-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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{6-{{1-(1,3-difluoropropan-2-il)-4-fluoropiperidin-4-il}metoxi}-5-(trifluorometil)piridin-3-il}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{5-cloro-6-[2-(tetrahydrofurano-2-il)etoxi]piridin-3-il}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}-3-metilpiperazin-1-il)-N-{{3-nitro-4-[(tetrahydro-2H-piran-4-ilmetil)amino]fenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{3-(ciclopropilamino)propil}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 N-{{5-cloro-6-(2-metoxietoxi)piridin-3-il}sulfonil}-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{5-fluoro-6-(tetrahydro-2H-piran-4-ilmetoxi)piridin-3-il}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 N-{{3-cloro-4-{{1-(metoxiacetil)piperidin-4-il}metoxi}fenil}sulfonil}-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-{{3-cloro-4-{{1-(N,N-dimetilglicil)piperidin-4-il}metoxi}fenil}sulfonil}-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 Trans-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohexil}metil}piperidin-1-il)-N-{{3-nitro-4-[(tetrahydro-2H-piran-4-ilmetil)amino]fenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)-N-{{6-(tetrahydro-2H-piran-4-ilmetoxi)-5-(trifluorometil)piridin-3-il}sulfonil}benzamida;
- 35 N-{{5-cloro-6-[(trans-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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([6-([trans-4-metoxiciclohexil)metoxi]-5-(trifluorometil)piridin-3-il)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([6-([cis-4-metoxiciclohexil)metoxi]-5-(trifluorometil)piridin-3-il)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 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)piperidin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-([3-cloro-4-([trans-4-(morfolin-4-il)ciclohexil)metoxi]fenil)sulfonil]-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([3-
- 15 [ciclopropil(1,3-tiazol-5-ilmetil)amino]propil)amino)-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-([3-cloro-4-([trans-4-hidroxiciclohexil)metoxi]fenil)sulfonil]-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-cloro-4-
- 20 [(tetrahidro-2H-piran-4-ilmetil)amino]fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-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-(trifluorometil)fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([3-
- 25 [ciclopropil(2,2,2-trifluoroetil)amino]propil)amino)-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-([3-cloro-4-([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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3,5-difluoro-4-((4-fluorotetrahidro-2H-piran-4-il)metoxi)fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([3-
- 35 [ciclopropil(oxetan-3-il)amino]propil)amino)-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

- N-[(3-cloro-4-[[1-(1-metil-L-prolil)piperidin-4-il]metoxi]fenil)sulfonil]-4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({3,4-difluoro-5-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]fenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 5 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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperidin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 10 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperidin-1-il)-N-[[3-cloro-4-(tetrahidro-2H-piran-4-ilmetoxi)fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 2-[[{4-[[4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]sulfamoil]-2-nitrofenil)amino]metil]morfolina-4-carboxilato de metilo;
- 15 2-[[{4-[[4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]sulfamoil]-2-nitrofenil)amino]metil]-N-etil-N-metilmorfolina-4-carboxamida;
 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]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 20 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[4-[[4-(ciclobutil(ciclopropil)amino)propil]amino]-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-[[2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil]piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 25 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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[3-cloro-4-(tetrahidrofurano-3-ilmetoxi)fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-[[2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil]piperazin-1-il)-N-[[4-[[trans-4-hidroxiciclohexil]metil]amino]-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 N-({3-cloro-4-[[4-fluorotetrahidro-2H-piran-4-il]metoxi]fenil)sulfonil)-4-(4-[[9-(4-clorofenil)-3-(oxetan-3-il)-3-azaespiro[5,5]undec-8-en-8-il]metil]piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 35

- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-(((2R)-4-ciclopropilmorfolin-2-il}metil)amino)-3-nitrofenil}sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{5-(4-clorofenil)espiro[2,5]oct-5-en-6-il}metil}piperazin-1-il)-N-{{3-nitro-4-{{tetrahidro-2H-piran-4-ilmetil}amino}fenil}sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-{{5-cloro-6-{{4-{{ciclopropil(oxetan-3-il)amino}ciclohexil}metoxi}piridin-3-il}sulfonil}-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{5-(4-clorofenil)espiro[2,5]oct-5-en-6-il}metil}piperazin-1-il)-N-{{4-{{(4-ciclopropilmorfolin-2-il)metil}amino)-3-nitrofenil}sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-{{3-cloro-4-{{4-ciclopropilmorfolin-2-il}metoxi}fenil}sulfonil}-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-{{3-cloro-4-{{4-ciclopropilmorfolin-2-il}metil}amino}fenil}sulfonil}-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 2-{{(2-cloro-4-{{4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil}sulfamoil}fenil)amino}metil}-N-etil-N-metilmorfolina-4-carboxamida;
- (2S)-2-{{(3-cloro-5-{{4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil}sulfamoil}piridin-2-il)oxi}metil}-N-etil-N-metilmorfolina-4-carboxamida;
- N-{{5-cloro-6-{{4-ciclopropilmorfolin-2-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 2-{{(3-cloro-5-{{4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil}sulfamoil}piridin-2-il)amino}metil}-N-etil-N-metilmorfolina-4-carboxamida;
- 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-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-{{5-cloro-6-{{(1R,2R,4R,5R)-5-hidroxi-5-metilbicio[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-pirrol[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[4-[[2-cianoetil](ciclopropil)amino]ciclohexil]amino)-3-nitrofenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5 N-([5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il]sulfonil)-4-(4-[[5-(4-clorofenil)espiro[2,5]oct-5-en-6-il]metil]piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 N-[(5-cloro-6-[(1R,2S,4R,5R)-5-hidroxi-5-metilbicio[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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 N-[(5-cloro-6-[[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi]piridin-3-il)sulfonil]-4-(4-[[5-(4-clorofenil)espiro[2,5]oct-5-en-6-il]metil]piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[4-[[4-(3,3-difluoropirrolidin-1-il)ciclohexil]amino]-3-nitrofenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[4-[[4-[(2,2-difluorociclopropil)amino]ciclohexil]amino]-3-nitrofenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[3-nitro-4-(2-oxaespiro[3,5]non-7-ilmetoxi)fenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-{[2-(4-clorofenil)-5,5-bis(fluorometil)ciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-
[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-
iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-{[4-
5 ciclopropilmorfolin-2-il]metoxi}-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-
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-pirrolo[2,3-b]piridin-5-
iloxi)benzamida;
- 10 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-pirrolo[2,3-b]piridin-5-
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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(trans-4-etil-4-
hidroxiciclohexil)metil]amino}-3-nitrofenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(cis-4-etil-4-
hidroxiciclohexil)metil]amino}-3-nitrofenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-5-(metoximetil)-5-metilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-
20 4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-
iloxi)benzamida;
- 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)-2-(1H-pirrolo[2,3-b]piridin-5-
iloxi)benzamida;
- 25 N-({3-cloro-4-[(trans-4-hidroxi-4-metilciclohexil)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-
dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(2-
cianoetil)(ciclopropil)amino]-1-fluorociclohexil}metoxi)-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-
b]piridin-5-iloxi)benzamida;
- 30 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({5-nitro-6-
[(tetrahidro-2H-piran-4-ilmetil)amino]piridin-3-il}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-
iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(2-
oxaespiro[3,5]non-7-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 35 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4-ciano-4-
metilciclohexil)metil]amino}-3-nitrofenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

- pivalato de {[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzoil]}(4-{(4-fluorotetrahidro-2H-piran-4-il)metoxi}-3-nitrofenil)sulfonil)amino}metilo;
- butirato de {[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzoil]}(4-{(4-fluorotetrahidro-2H-piran-4-il)metoxi}-3-nitrofenil)sulfonil)amino}metilo;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)-N-{[3-(tetrahidro-2H-piran-4-ilmetil)-3H-[1,2,3]triazolo[4,5-b]piridin-6-il]sulfonil}benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(6-{[(trans-4-hidroxi-4-metilciclohexil)metil]amino}-5-nitropiridin-3-il)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-(4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzoil]sulfamoi]-2-nitrofenil)morfolina-4-carboxamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[4-(metoximetil)ciclohexil]metil]amino}-3-nitrofenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-5-metoxi-5-metilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(trans-4-hidroxi-4-metilciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-5-metoxi-5-metilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida; y sus sales terapéuticamente aceptables, y sus metabolitos.

Aún otra forma de realización se refiere a 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-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida; y sus sales terapéuticamente aceptables, y sus metabolitos.

Aún otra forma de realización se refiere a Trans-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)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida; y sus sales terapéuticamente aceptables, y sus metabolitos.

- 5 Aún otra forma de realización se refiere a Cis-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]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida; y sus sales terapéuticamente aceptables, y sus metabolitos.

- 10 Aún otra forma de realización se refiere a Trans-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]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida; y sus sales terapéuticamente aceptables, y sus metabolitos.

- 15 Aún otra forma de realización se refiere a 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-pirrol[2,3-b]piridin-5-iloxi)benzamida; y sus sales terapéuticamente aceptables, y sus metabolitos.

- 20 Otra forma de realización se refiere al compuesto 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-pirrol[2,3-b]piridin-5-iloxi)benzamida o una sal aceptable farmacéuticamente del mismo.

- Otra forma de realización se refiere al compuesto 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-pirrol[2,3-b]piridin-5-iloxi)benzamida; o una sal aceptable farmacéuticamente del mismo.

- 25 Otra forma de realización se refiere al compuesto 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-pirrol[2,3-b]piridin-5-iloxi)benzamida; o una sal aceptable farmacéuticamente del mismo.

- 30 Otra forma de realización se refiere al compuesto 4-[4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}(²H₈)piperazin-1-il]-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida; o una sal aceptable farmacéuticamente del mismo.

- 35 Otra forma de realización se refiere al compuesto N-({5-bromo-6-[(1-tetrahidro-2H-piran-4-ilpiperidin-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-pirrol[2,3-b]piridin-5-iloxi)benzamida; o una sal aceptable farmacéuticamente del mismo.

Otra forma de realización se refiere al compuesto 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3R)-1-(metilsulfonil)pirrolidin-3-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-ilo)benzamida; o una sal aceptable farmacéuticamente del mismo.

5 Otra forma de realización se refiere al compuesto 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[3-(ciclopropil(oxetan-3-il)amino]propil)amino]-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-ilo)benzamida; o una sal aceptable farmacéuticamente del mismo.

10 Otra forma de realización se refiere al compuesto 4-(4-{[2-(4-clorofenil)-5-metoxi-5-metilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-[(tetrahydro-2H-piran-4-ilmetil)amino]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-ilo)benzamida; o una sal aceptable farmacéuticamente del mismo.

Aún otra forma de realización se refiere a compuestos de fórmula (I) o Fórmula (II), que son 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-pirrol[2,3-b]piridin-5-ilo)benzamida; 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3R)-1-(metilsulfonil)pirrolidin-3-il]amino]-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-ilo)benzamida; 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[3-(ciclopropil(oxetan-3-il)amino]propil)amino]-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-ilo)benzamida; o una sal aceptable farmacéuticamente del mismo.

Aún otra forma de realización se refiere a compuestos de fórmula (I) o Fórmula (II), que son N-[(5-cloro-6-{[1-(cianometil)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-pirrol[2,3-b]piridin-5-ilo)benzamida; 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[3-(ciclopropil(oxetan-3-il)amino]propil)amino]-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-ilo)benzamida; o una sal aceptable farmacéuticamente del mismo.

Aún otra forma de realización se refiere a compuestos de fórmula (I) o Fórmula (II), que son 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-pirrol[2,3-b]piridin-5-ilo)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-pirrol[2,3-b]piridin-5-ilo)benzamida o una sal aceptable farmacéuticamente del mismo.

Otra forma de realización se refiere al compuesto 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[3-(ciclopropil(oxetan-3-

il)amino]propil}amino)-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-ilo)benzamida; o una sal aceptable farmacéuticamente del mismo.

Aún otra forma de realización se refiere a compuestos de fórmula (I) o Fórmula (II), que son 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-nitro-4-
5 {[(3R)-1-tetrahidro-2H-piran-4-ilpirrolidin-3-il]metil}amino]fenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-ilo)benzamida; 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[(4-metilmorfolin-2-il)metil]amino}-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-ilo)benzamida; o una sal aceptable farmacéuticamente del mismo.

Aún otra forma de realización se refiere a compuestos de fórmula (I) o Fórmula (II), que son 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-nitro-4-
10 {[(3S)-tetrahidro-2H-piran-3-ilmetil]amino]fenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-ilo)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-pirrol[2,3-b]piridin-5-ilo)benzamida;

15 N-{[5-bromo-6-{[1-tetrahidro-2H-piran-4-ilpiperidin-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-pirrol[2,3-b]piridin-5-ilo)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-pirrol[2,3-b]piridin-5-ilo)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-nitro-4-{[(3R)-1-tetrahidro-2H-piran-4-ilpirrolidin-3-il]metil}amino]fenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-ilo)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[(4-metilmorfolin-2-il)metil]amino}-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-ilo)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[(3R)-1-(metilsulfonil)pirrolidin-3-il]amino}-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-ilo)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[4-metoxitetrahidro-2H-piran-4-il]metoxi]-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-ilo)benzamida;

N-{[5-cloro-6-{[1-(cianometil)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-pirrol[2,3-b]piridin-5-ilo)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[3-(ciclopropil(oxetan-3-il)amino)propil]amino}-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-ilo)benzamida;

N-[(5-cloro-6-[(1R,2S,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-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;

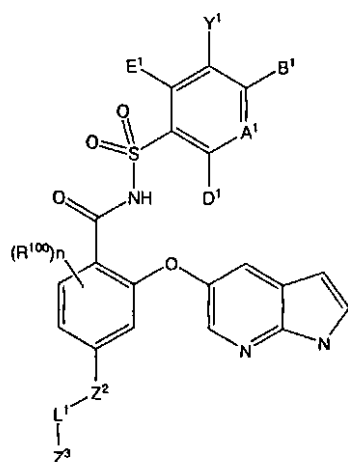
4-(4-{[2-(4-clorofenil)-5-metoxi-5-metilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida; o una sal aceptable farmacéuticamente del mismo.

Otra forma de realización se refiere al compuesto N-[(5-cloro-6-[(1-cianometil)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-pirrol[2,3-b]piridin-5-iloxi)benzamida; o una sal aceptable farmacéuticamente del mismo.

Aún otra forma de realización se refiere a compuestos de fórmula (I) o Fórmula (II), que son 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-pirrol[2,3-b]piridin-5-iloxi)benzamida; 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-[(4-metoxitetrahidro-2H-piran-4-il)metoxi]-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida; o una sal aceptable farmacéuticamente del mismo.

Otra forma de realización se refiere al compuesto 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-[(4-metoxitetrahidro-2H-piran-4-il)metoxi]-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida o una sal aceptable farmacéuticamente del mismo.

En otro aspecto, la presente invención provee compuestos de fórmula (II)



(II)

y sus sales terapéuticamente aceptables, y sus metabolitos,

donde A^1 , B^1 , D^1 , E^1 , Y^1 , Z^2 , L^1 , y Z^3 tienen los valores definidos para la Fórmula (II); n es 0, 1, 2, o 3; que describen la cantidad de sustituyentes on Z^1 ; y R^{100} tiene los valores que se describen para los sustituyentes de R^{26} .

En una forma de realización de Fórmula (II), n es 0 o 1. En otra forma de realización de Fórmula (II), n es 0.

En una forma de 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, F, Cl, Br, o I. En otra forma de realización de Fórmula (II), A^1 es $C(A^2)$; y A^2 es H.

En una forma de realización de Fórmula (II), B^1 es R^1 , OR^1 , NHR^1 , $NHC(O)R^1$, F, Cl, Br, o I. En otra forma de realización de Fórmula (II), A^1 es $C(A^2)$; A^2 es H; y B^1 es NHR^1 . En otra forma de realización de Fórmula (II), A^1 es $C(A^2)$; A^2 es H; y B^1 es OR^1 . En otra forma de realización de Fórmula (II), A^1 es $C(A^2)$; A^2 es H; y B^1 es Cl. En otra forma de realización de Fórmula (II), A^1 es $C(A^2)$; A^2 es H; y B^1 es R^1 . En otra forma de realización de Fórmula (II), A^1 es N; y B^1 es NHR^1 . En otra forma de realización de Fórmula (II), A^1 es N; y B^1 es OR^1 . En otra forma de realización de Fórmula (II), A^1 es N; y B^1 es Cl. En otra forma de realización de Fórmula (II), A^1 es N; y B^1 es R^1 .

En una forma de realización de Fórmula (II), D^1 es H o Cl. En otra forma de realización de Fórmula (II), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 ; y D^1 es H. En otra forma de realización de Fórmula (II), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 ; y D^1 es Cl. En otra forma de realización de Fórmula (II), A^1 es $C(A^2)$; A^2 es H; B^1 es OR^1 ; y D^1 es H. En otra forma de realización de Fórmula (II), A^1 es $C(A^2)$; A^2 es H; B^1 es Cl; y D^1 es H. En otra forma de realización de Fórmula (II), A^1 es $C(A^2)$; A^2 es H; B^1 es R^1 ; y D^1 es H. En otra forma de realización de Fórmula (II), A^1 es N; B^1 es NHR^1 ; y D^1 es H. En otra forma de realización de Fórmula (II), A^1 es N; B^1 es NHR^1 ; y D^1 es Cl. En otra forma de realización de Fórmula (II), A^1 es N; B^1 es OR^1 ; y D^1 es H. En otra forma de realización de Fórmula (II), A^1 es N; B^1 es Cl; y D^1 es H. En otra forma de realización de Fórmula (II), A^1 es N; B^1 es R^1 ; y D^1 es H.

En una forma de realización de Fórmula (II), E^1 es H. En otra forma de realización de Fórmula (II), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 ; D^1 es H; y E^1 es H. En otra forma de realización de Fórmula (II), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 ; E^1 es H; y D^1 es Cl. En otra forma de realización de Fórmula (II), A^1 es $C(A^2)$; A^2 es H; B^1 es OR^1 ; D^1 es H; y E^1 es H. En otra forma de realización de Fórmula (II), A^1 es $C(A^2)$; A^2 es H; B^1 es Cl; D^1 es H; y E^1 es H. En otra forma de realización de Fórmula (II), A^1 es $C(A^2)$; A^2 es H; B^1 es R^1 ; D^1 es H; y E^1 es H. En otra forma de realización de Fórmula (II), A^1 es N; B^1 es NHR^1 ; D^1 es H; y E^1 es H. En otra forma de realización de Fórmula (II), A^1 es N; B^1 es NHR^1 ; E^1 es H; y D^1 es Cl. En otra forma de realización de Fórmula (II), A^1 es N; B^1 es OR^1 ; D^1 es H; y E^1 es H. En otra forma de

realización de Fórmula (II), A¹ es N; B¹ es Cl; D¹ es H; y E¹ es H. En otra forma de realización de Fórmula (II), A¹ es N; B¹ es R¹; D¹ es H; y E¹ es H.

En una forma de realización de Fórmula (II), Y¹ es H, CN, NO₂, F, Cl, Br, I, CF₃, R¹⁷, OR¹⁷, SR¹⁷, SO₂R¹⁷, o C(O)NH₂. En otra forma de realización de Fórmula (II), Y¹ es H. En
 5 otra forma de realización de Fórmula (II), Y¹ es CN. En otra forma de realización de Fórmula (II), Y¹ es F, Cl, Br, o I. En otra forma de realización de Fórmula (II), Y¹ es CF₃. En otra forma de realización de Fórmula (II), Y¹ es SR¹⁷. En otra forma de realización de Fórmula (II), Y¹ es OR¹⁷. En otra forma de realización de Fórmula (II), Y¹ es NO₂. En otra forma de realización de Fórmula (II), Y¹ es SO₂R¹⁷; donde R¹⁷ es como se ha definido. En otra forma de
 10 realización de Fórmula (II), Y¹ es SO₂R¹⁷; donde R¹⁷ es alquilo. En otra forma de realización de Fórmula (II), Y¹ es R¹⁷; donde R¹⁷ es alquínilo. En otra forma de realización de Fórmula (II), A¹ es C(A²); A² es H; B¹ es NHR¹; D¹ es H; E¹ es H; y Y¹ es NO₂ o SO₂R¹⁷; donde R¹⁷ es alquilo o alquínilo. En otra forma de realización de Fórmula (II), A¹ es C(A²); A² es H; B¹ es NHR¹; D¹ es H; E¹ es H; y Y¹ es NO₂. En otra forma de realización de Fórmula (II), A¹ es
 15 C(A²); A² es H; B¹ es NHR¹; D¹ es H; E¹ es H; y Y¹ es SO₂R¹⁷; donde R¹⁷ es alquilo sustituido con tres F. En otra forma de realización de Fórmula (II), A¹ es N; B¹ es NHR¹; D¹ es H; E¹ es H; y Y¹ es NO₂ o SO₂R¹⁷; donde R¹⁷ es alquilo o alquínilo. En otra forma de realización de Fórmula (II), A¹ es N; B¹ es NHR¹; D¹ es H; E¹ es H; y Y¹ es NO₂. En otra forma de realización de Fórmula (II), A¹ es N; B¹ es NHR¹; D¹ es H; E¹ es H; y Y¹ es SO₂R¹⁷; donde R¹⁷ es alquilo
 20 sustituido con tres F.

En una forma de realización de Fórmula (II), G¹ es H; A¹ es N o C(A²); y A² es H. En otra forma de realización de Fórmula (II), G¹ es H; A¹ es N o C(A²); A² es H; y B¹ es NHR¹. En otra forma de realización de Fórmula (II), G¹ es H; A¹ es N o C(A²); A² es H; B¹ es NHR¹; y D¹ es H. En otra forma de realización de Fórmula (II), G¹ es H; A¹ es N o C(A²); A² es H; B¹
 25 es NHR¹; D¹ es H; y E¹ es H. En otra forma de realización de Fórmula (II), G¹ es H; A¹ es N o C(A²); A² es H; B¹ es NHR¹; D¹ es H; E¹ es H; y Y¹ es NO₂.

En una forma de realización de Fórmula (II), Y¹ y B¹, junto con los átomos a los cuales están unidos, son benceno. En otra forma de realización de Fórmula (II), Y¹ y B¹, junto con los átomos a los cuales están unidos, son heteroareno. En otra forma de realización de
 30 Fórmula (II), A¹ es C(A²); A², G¹, E¹, y D¹ se seleccionan en forma independiente entre H; y Y¹ y B¹, junto con los átomos a los cuales están unidos, son benceno. En otra forma de realización de Fórmula (II), A¹ es C(A²); A², G¹, E¹, y D¹ se seleccionan en forma independiente entre H; y Y¹ y B¹, junto con los átomos a los cuales están unidos, son heteroareno.

35 En una forma de realización de Fórmula (II), R¹ es R⁴ o R⁵. En una forma de realización de Fórmula (II), R¹ es R⁴. En una forma de realización de Fórmula (II), R¹ es R⁵.

En una forma de realización de Fórmula (II), R^1 es R^4 ; y R^4 es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo. En una forma de realización de Fórmula (II), R^1 es R^4 ; y R^4 es cicloalquilo o heterocicloalquilo. En una forma de realización de Fórmula (II), R^1 es R^4 ; y R^4 es cicloalquilo. En una forma de realización de Fórmula (II), R^1 es R^4 ; y R^4 es heterocicloalquilo.

En una forma de realización de Fórmula (II), R^1 es R^4 ; y R^4 es cicloalquilo; donde R^4 no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (II), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo está sustituido como se ha definido. En otra forma de realización de Fórmula (II), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo está sustituido con R^{57} o $N(R^{57})_2$. En otra forma de realización de Fórmula (II), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con R^{57} ; y R^{57} es R^{60} . En otra forma de realización de Fórmula (II), R^1 es R^4 ; R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con R^{57} ; R^{57} es R^{60} ; y R^{60} es heterocicloalquilo. En otra forma de realización de Fórmula (II), R^1 es R^4 ; R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con R^{57} ; R^{57} es R^{60} ; R^{60} es heterocicloalquilo; donde el anillo heterocicloalquilo es morfolinilo. En otra forma de realización de Fórmula (II), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo está sustituido con $N(R^{57})_2$. En otra forma de realización de Fórmula (II), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con $N(R^{57})_2$. En otra forma de realización de Fórmula (II), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con $N(R^{57})_2$; R^{57} es R^{61} ; y R^{61} es alquilo que no está sustituido o está sustituido con R^{62} . En otra forma de realización de Fórmula (II), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con R^{57} ; R^{57} es R^{61} ; y R^{61} es alquilo que no está sustituido o está sustituido con R^{62} ; R^{62} es R^{65} ; y R^{65} es cicloalquilo. En otra forma de realización de Fórmula (II), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con R^{57} ; R^{57} es R^{61} ; y R^{61} es alquilo el cual está sustituido con R^{62} ; R^{62} es R^{65} ; y R^{65} es ciclopropilo.

En una forma de realización de Fórmula (II), R^1 es R^4 ; y R^4 es heterocicloalquilo; donde R^4 no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (II), R^1 es R^4 ; y R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo está sustituido como se ha definido. En otra forma de realización de Fórmula (II), R^1 es R^4 ; y R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo está sustituido con R^{57} . En otra forma de realización de Fórmula (II), R^1 es R^4 ; y R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo es piperidinilo o piperizinilo; y donde el

anillo heterocicloalquilo está sustituido con R^{57} ; y R^{57} es R^{60} o R^{61} . En otra forma de realización de Fórmula (II), R^1 es R^4 ; R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo es piperidinilo o piperizinilo; y donde el anillo piperidinilo o piperizinilo está sustituido con R^{57} ; R^{57} es R^{60} o R^{61} ; R^{60} es heterocicloalquilo; y R^{61} es alquilo. En otra forma de realización de Fórmula (II), R^1 es R^4 ; R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo es piperidinilo o piperizinilo; y donde el anillo piperidinilo o piperizinilo está sustituido con R^{57} ; R^{57} es R^{60} ; R^{60} es heterocicloalquilo; donde el heterocicloalquilo es tetrahidropiranilo. En otra forma de realización de Fórmula (II), R^1 es R^4 ; R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo es piperidinilo o piperizinilo; y donde el anillo piperidinilo o piperizinilo está sustituido con R^{57} ; R^{57} es R^{61} ; R^{61} es alquilo; y el alquilo es metilo. En otra forma de realización de Fórmula (II), R^1 es R^4 ; R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo es piperidinilo o piperizinilo; y donde el anillo piperidinilo o piperizinilo está sustituido con $C(O)OR^{57}$; R^{57} es R^{61} ; R^{61} es alquilo; y el alquilo es metilo.

En una forma de realización de Fórmula (II), R^1 es R^5 ; y R^5 es alquilo que no está sustituido o está sustituido. En una forma de realización de Fórmula (II), R^1 es R^5 ; y R^5 es alquilo que no está sustituido o está sustituido con R^7 , OR^7 , OH , CN , o F . En otra forma de realización de Fórmula (II), R^1 es R^5 ; y R^5 es alquilo el cual está sustituido con R^7 , OR^7 , NHR^7 , o $N(R^7)_2$.

En una forma de realización de Fórmula (II), R^7 es R^8 , R^9 , R^{10} o R^{11} que no están sustituidos o están sustituidos como se ha definido. En otra forma de realización de Fórmula (II), R^7 es R^8 que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (II), R^7 es R^9 que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (II), R^7 es R^{10} que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (II), R^7 es R^{11} que no está sustituido o está sustituido como se ha definido.

En una forma de realización de Fórmula (II), R^8 es fenilo que no está sustituido o está sustituido como se ha definido.

En una forma de realización de Fórmula (II), R^9 es heteroarilo que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (II), R^9 es furanilo; que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (II), R^9 es furanilo; que no está sustituido.

En una forma de realización de Fórmula (II), R^{10} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, heterocicloalquilo que no están sustituidos o están sustituidos como se ha definido. En otra forma de realización de Fórmula (II), R^{10} es heterocicloalquilo que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (II), R^{10} es tetrahidrofuranilo, tetrahidropiranilo, morfolinilo,

dioxanilo, oxetanilo, piperdinilo, o pirrolidinilo, que no están sustituidos o están sustituidos como se ha definido. En otra forma de realización de Fórmula (II), R^{10} es tetrahidropiranilo, que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (II), R^{10} es morfolinilo; que no está sustituido o está sustituido como se ha definido.

5 En otra forma de realización de Fórmula (II), R^{10} es cicloalquilo que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (II), R^{10} es cicloalquilo que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (II), R^{10} es ciclohexilo, ciclopropilo, ciclobutilo, o biciclo[2,2,1]heptanilo, que no está sustituido o está sustituido como se ha definido. En otra
10 forma de realización de Fórmula (II), R^{10} es heterocicloalquilo que está fusionado con R^{10A} ; y R^{10A} es heteroareno. En otra forma de realización de Fórmula (II), R^{10} es 5,6,7,8-tetrahidroimidazo[1,2-a]piridinilo.

En una forma de realización de Fórmula (II), R^{11} es alquilo, alquienilo o alquinilo que no están sustituidos o están sustituidos como se ha definido. En otra forma de realización de
15 Fórmula (II), R^{11} es alquilo. En otra forma de realización de Fórmula (II), R^{11} es metilo; que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (II), R^{11} es alquilo; que está sustituido como se ha definido. En otra forma de realización de Fórmula (II), R^{11} es alquilo; que está sustituido con R^{12} , OR^{12} , o CF_3 . En otra forma de realización de Fórmula (II), R^{11} es alquilo; que está sustituido con OR^{12} ; R^{12} es R^{16} ,
20 y R^{16} es alquilo. En otra forma de realización de Fórmula (II), R^{11} es alquilo; que está sustituido con CF_3 . En otra forma de realización de Fórmula (II), R^{11} es alquilo; que está sustituido con R^{12} , R^{12} es R^{14} , y R^{14} es heteroarilo.

En una forma de realización de Fórmula (II),

n es 0;

25 A^1 es N o C(A^2);

A^2 es H, F, Br, I, o Cl;

B^1 es R^1 , OR^1 , NHR^1 , $NHC(O)R^1$, F, Br, I o Cl;

D^1 es H, F, Br, I, o Cl;

E^1 es H; y

30 Y^1 es H, CN, NO_2 , F, Cl, Br, I, CF_3 , R^{17} , OR^{17} , SR^{17} , SO_2R^{17} , o $C(O)NH_2$; o

Y^1 y B^1 , junto con los átomos a los cuales están unidos, son benceno, heteroareno, o heterocicloalqueno; y

A^2 , D^1 , y E^1 se seleccionan en forma independiente entre H;

R^1 es R^4 o R^5 ;

35 R^4 es cicloalquilo, o heterocicloalquilo;

- R^5 es alquilo, 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^7 , OR^7 , NHR^7 , $N(R^7)_2$, CN , OH , F , Cl , Br o I ;
- R^7 es R^8 , R^9 , R^{10} , o R^{11} ;
- 5 R^8 es fenilo;
- R^9 es heteroarilo;
- R^{10} es cicloalquilo, cicloalquenilo, o heterocicloalquilo; cada uno de los cuales no está fusionado o está fusionado con R^{10A} , R^{10A} es heteroareno;
- R^{11} es alquilo cada uno de los cuales no está sustituido o está sustituido con uno o
- 10 dos o tres sustituyentes seleccionados en forma independiente entre R^{12} , OR^{12} or CF_3 ;
- R^{12} es R^{14} o R^{16} ;
- R^{14} es heteroarilo;
- R^{16} es alquilo;
- R^{17} es R^{21} ;
- 15 R^{21} es alquilo, 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^{22} , F , Cl , Br o I ;
- R^{22} es R^{25} ;
- R^{25} es heterocicloalquilo;
- 20 Z^2 es R^{30} ;
- Z^{1A} y Z^{2A} están ambos ausentes;
- L^1 es un R^{37} ;
- R^{30} es heterocicloalquilenilo;
- R^{37} es R^{37A} ;
- 25 R^{37A} es alquilenilo;
- Z^3 es R^{38} , o R^{40} ;
- R^{38} es fenilo;
- R^{40} es cicloalquilo, cicloalquenilo, o heterocicloalquenilo;
- donde las unidades cíclicas representadas por Y^1 y B^1 juntos, R^4 , R^8 , R^{10} , R^{25} , R^{30} ,
- 30 R^{38} , y R^{40} no están sustituidas, no están adicionalmente sustituidas, están sustituidas o adicionalmente sustituidas en forma independiente con uno o dos o tres o cuatro o cinco sustituyentes seleccionados en forma independiente entre R^{57A} , R^{57} , OR^{57} , SO_2R^{57} , $C(O)R^{57}$, $CO(O)R^{57}$, $C(O)N(R^{57})_2$, NH_2 , NHR^{57} , $N(R^{57})_2$, $NHC(O)R^{57}$, $NHS(O)_2R^{57}$, OH , CN , (O) , F , Cl , Br o I ;
- 35 R^{57A} es espiroalquilo, o espiroheteroalquilo;
- R^{57} es R^{58} , R^{60} o R^{61} ;

R^{58} es fenilo;

R^{60} es cicloalquilo, o heterocicloalquilo;

R^{61} es alquilo que no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre R^{62} , OR^{62} , $N(R^{62})_2$, $C(O)OH$, CN ,

5 F, Cl, Br o I;

R^{62} es R^{65} , o R^{66} ;

R^{65} es cicloalquilo, o heterocicloalquilo;

R^{66} es alquilo que no está sustituido o está sustituido con OR^{67} ;

R^{67} es alquilo;

10 donde las unidades cíclicas representadas por R^{57A} , R^{58} , y R^{60} no están sustituidas o están sustituidas con uno o dos o tres o cuatro sustituyentes seleccionados en forma independiente entre R^{68} , F, Cl, Br o I;

R^{68} es R^{71} o R^{72} ;

R^{71} es heterocicloalquilo; y

15 R^{72} es alquilo, que no está sustituido o está sustituido con uno o dos F.

Aún otra forma de realización se refiere a compuestos de fórmula (II), que son

4-{4-[(4'-cloro-1,1'-bifenil-2-il)metil]piperazin-1-il}-N-({3-nitro-4-[(tetrahydro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-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-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(1-tetrahydro-2H-piran-4-ilpiperidin-4-il)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-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-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(tetrahydro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

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)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

Trans-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)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(2-metoxietil)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

35 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(3S)-tetrahydro-2H-piran-3-ilmetil]amino}fenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(3-nitro-4-[(3R)-tetrahidro-2H-piran-3-ilmetil]amino)fenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-(2-naftilsulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil]piperazin-1-il)-N-[(3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil]amino)fenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-([4-[(2-metoxietil)amino]-3-[(trifluorometil)sulfonil]fenil]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)-N-([4-[(tetrahidro-2H-piran-4-ilmetil]amino)-3-[(trifluorometil)sulfonil]fenil]sulfonil)benzamida;
- 15 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(3-nitro-4-(tetrahidro-2H-piran-4-ilmetoxi)fenil]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(3-nitro-4-[(2,2,2-trifluoroetil)amino]fenil]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(3-nitro-4-[(3,3,3-trifluoropropil)amino]fenil]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 Cis-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)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-[[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil]piperazin-1-il)-N-([4-[(1,4-dioxan-2-ilmetil)amino]-3-nitrofenil]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil]piperazin-1-il)-N-([4-(1,4-dioxan-2-ilmetoxi)-3-nitrofenil]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- Trans-4-(4-[[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil]piperazin-1-il)-N-([4-[(4-morfolin-4-ilciclohexil)amino]-3-nitrofenil]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 35

- Trans-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]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil)piperazin-1-il)-N-([5-ciano-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5 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-pirrolo[2,3-b]piridin-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- Cis-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]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil)piperazin-1-il)-N-([5-cloro-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 4-(4-([4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil)piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)-N-([4-([tetrahidro-2H-piran-4-ilmetil]amino)-3-(trifluorometil)fenil]sulfonil]benzamida;
- 25 4-(4-([4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil)piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)-N-([4-([tetrahidro-2H-piran-4-ilmetil]amino)-3-(trifluorometil)sulfonil]fenil]sulfonil]benzamida;
- Trans-4-(4-([4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil)piperazin-1-il)-N-([4-([4-morfolin-4-ilciclohexil]amino)-3-(trifluorometil)sulfonil]fenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-([4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil)piperazin-1-il)-N-([4-([1-metilpiperidin-4-il]amino)-3-(trifluorometil)sulfonil]fenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5-([4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzoil]amino)sulfonil]-2-(tetrahidro-2H-piran-4-ilmetoxi)nicotinamida;
- 35

- N-({5-bromo-6-[(1-metilpiperidin-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(1-metilpiperidin-4-il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 5 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({5-ciano-6-(1,4-dioxan-2-ilmetoxi)piridin-3-il}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 N-({5-bromo-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(2,2-
- 10 dimetiltetrahidro-2H-piran-4-il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 N-({3-cloro-5-ciano-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 N-({4-[(1-acetilpiperidin-4-il)amino]-3-nitrofenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-
- 15 dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)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-pirrol[2,3-b]piridin-5-iloxi)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-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 20 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-pirrol[2,3-b]piridin-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 25 N-[(3-cloro-4-{[2-(2-metoxietoxi)etil]sulfonil}fenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[2-(2-metoxietoxi)etil]sulfonil}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-
- 30 morfolin-4-ilciclohexil)oxi]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 N-({5-bromo-6-[(1-tetrahidro-2H-piran-4-ilpiperidin-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(2-
- 35 cianoetil)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

- Cis-4-(4-([4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil)piperazin-1-il)-N-([4-([4-morfolin-4-ilciclohexil)amino]-3-nitrofenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 Trans-N-([4-([4-[bis(ciclopropilmetil)amino]ciclohexil)amino]-3-nitrofenil)sulfonil)-4-(4-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 5 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)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([morfolin-3-ilmetil)amino]-3-nitrofenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 10 4-(4-([4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil)piperazin-1-il)-N-([4-([4-metilpiperazin-1-il)amino]-3-nitrofenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-morfolin-4-ilbut-2-il]oxi)-3-nitrofenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([5-etinil-6-
 15 (tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-oxo-3,4-dihidroquinazolin-6-il)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 Trans-4-(4-([8-(4-clorofenil)espiro[4,5]dec-7-en-7-il]metil)piperazin-1-il)-N-([4-([4-morfolin-4-ilciclohexil)amino]-3-nitrofenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 20 Cis-4-(4-([4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil)piperazin-1-il)-N-([4-([4-metoxiciclohexil)metil]amino]-3-nitrofenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-([8-(4-clorofenil)espiro[4,5]dec-7-en-7-il]metil)piperazin-1-il)-N-([4-([4-fluorotetrahidro-2H-piran-4-il)metoxi]-3-nitrofenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 25 Trans-4-(4-([8-(4-clorofenil)espiro[4,5]dec-7-en-7-il]metil)piperazin-1-il)-N-([4-([4-metoxiciclohexil)metil]amino]-3-nitrofenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-[2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-
 [(tetrahidro-2H-piran-4-ilmetil)amino]fenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 30 4-(4-[2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([5-ciano-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 3-([4-([4-(4-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzoil]amino)sulfonil)-2-nitrofenoxi]metil)morfolina-4-carboxilato
 35 de tert-butilo;

- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-(morfolin-3-ilmetoxi)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([8-(4-clorofenil)espiro[4,5]dec-7-en-7-il]metil)piperazin-1-il)-N-([3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 5 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-(metilsulfonil)piperidin-4-il]amino)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-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]amino)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 10 N-([4-cloro-3-nitrofenil]sulfonil)-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([1-(2,2,2-trifluoroetil)piperidin-4-il]amino)fenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 15 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([5-ciano-6-([1-tetrahidro-2H-piran-4-il]piperidin-4-il)oxi]piridin-3-il]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([5-isopropil-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 20 N-([3-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- y sus sales terapéuticamente aceptables, y sus metabolitos.
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-[2-fluoro-1-(fluorometil)etil]piperidin-4-il]amino)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 25 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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-(2,2-difluoroetil)piperidin-4-il]amino)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 35

- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{(1-morfolin-4-ilciclohexil)metil}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 Trans-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{4-(dicropropilamino)ciclohexil}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 5 4-(4-{{2-(4-clorofenil)-6,6-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 N-({5-bromo-6-[(4-etilmorfolin-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 10 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({4-[(4-etilmorfolin-3-il)metoxi]-3-nitrofenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({3-nitro-4-[(4-tetrahidro-2H-piran-4-ilmorfolin-3-il)metoxi]fenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 15 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(3-nitro-4-{{{3S}-1-tetrahidro-2H-piran-4-ilpiperidin-3-il}amino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-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-ilmetil)amino]piridin-3-il)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 20 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({4-[(1,1-dioxidotiormorfolin-4-il)amino]-3-nitrofenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 25 Trans-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({5-ciano-6-[(4-morfolin-4-ilciclohexil)amino]piridin-3-il)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 30 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{{1S,3R}-3-morfolin-4-ilciclopentil}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([[(1R,3S)-3-morfolin-4-ilciclopentil]amino]-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([morfolin-2-ilmetil]amino]-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 5 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([tetrahidrofurano-3-ilmetil]amino)fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-[cis-3-fluorotetrahidro-2H-piran-4-il]piperidin-4-il]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 10 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-ilazetid-3-il]amino)fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([1-tetrahidrofurano-3-ilazetid-3-il]amino)fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 15 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([1-tetrahidrofurano-3-ilazetid-3-il]amino)fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([[(3R)-1-tetrahidro-2H-piran-4-ilpirrolidin-3-il]metil]amino)fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 20 4-(4-([2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-fluorotetrahidro-2H-piran-4-il]metoxi)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-enil]metil)piperazin-1-il)-N-([4-([trans-4-hidroxiciclohexil]metoxi)-3-nitrofenil)sulfonil]benzamida;
- 25 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-enil]metil)piperazin-1-il)-N-([4-([cis-4-metoxiciclohexil]metoxi)-3-nitrofenil)sulfonil]benzamida;
- Cis-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-(ciclopropilamino)ciclohexil]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 30 Trans-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([4-(tetrahidro-2H-piran-4-ilamino)ciclohexil]amino)fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- Trans-N-([5-bromo-6-([4-morfolin-4-ilciclohexil]oxi)piridin-3-il)sulfonil]-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 35 Trans-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-metoxiciclohexil]metoxi)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

- 4-([4-([4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzoil]amino)sulfonil]-2-nitrofenoxi]metil]-4-fluoropiperidin-1-carboxilato de tert-butilo;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-fluoropiperidin-4-il]metoxi]-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5 Trans-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([4-(4-tetrahidro-2H-piran-4-il)piperazin-1-il)ciclohexil]amino)fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-[2-fluoro-1-(fluorometil)etil]piperidin-4-il]metoxi]-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([(3R)-1-tetrahidro-2H-piran-4-il]pirrolidin-3-il]amino)fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([(3R)-1-(2,2-dimetiltetrahidro-2H-piran-4-il]pirrolidin-3-il]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([(3S)-1-tetrahidro-2H-piran-4-il]pirrolidin-3-il]amino)fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([(3S)-1-(2,2-dimetiltetrahidro-2H-piran-4-il]pirrolidin-3-il]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([(4-metilmorfolin-2-il]metil]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-(2-metoxietil)morfolin-2-il]metil]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-([4-([(4-acetilmorfolin-2-il]metil]amino)-3-nitrofenil)sulfonil]-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([trans-4-(fluorometil)-1-oxetan-3-il]pirrolidin-3-il]metoxi)-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-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]metil]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
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- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({3-nitro-4-{{1-oxetan-3-ilpiperidin-4-il}amino}fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({4-{{1-ciclobutilpiperidin-4-il}amino}-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{1-(2,2-dimetiltetrahidro-2H-piran-4-il)piperidin-4-il}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{(3S)-1-ciclopropilpirrolidin-3-il}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-
- 10 iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({3-nitro-4-{{1-tetrahidrofurano-3-ilpiperidin-4-il}amino}fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{(3R)-1-ciclopropilpirrolidin-3-il}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-
- 15 iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({3-nitro-4-{{(3S)-1-tetrahidro-2H-piran-4-ilpirrolidin-3-il}metil}amino}fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({4-{{3-hidroxi-2,2-dimetilpropil}amino}-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({4-{{1-(metilsulfonil)piperidin-3-il}metil}amino}-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 N-[(4-{{1-acetilpiperidin-3-il}metil}amino)-3-nitrofenil}sulfonil]-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{(3R)-1-(metilsulfonil)pirrolidin-3-il}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-{{2-(4-clorofenil)-3,3-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{1-[2-fluoro-1-(fluorometil)etil]azetidin-3-il}amino}-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-ilo
- 35 xy)benzamida;

- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[4-[[1-(metilsulfonil)pirrolidin-3-il]metil]amino]-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 5 N-[[4-[[1-acetilpirrolidin-3-il]metil]amino]-3-nitrofenil]sulfonil]-4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-[[4-[[3R)-1-acetilpirrolidin-3-il]amino]-3-nitrofenil]sulfonil]-4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[4-[[3-metoxi-2,2-dimetilpropil]amino]-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 10 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[4-[[1R,3R)-3-hidroxiciclopentil]metil]amino]-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[4-[[1S,3S)-3-hidroxiciclopentil]metil]amino]-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 15 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[4-[[1S,3R)-3-hidroxiciclopentil]metil]amino]-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[4-[[1R,3S)-3-hidroxiciclopentil]metil]amino]-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 20 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[3-nitro-4-[[3S)-2-oxopiperidin-3-il]amino]fenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[4-[[1-[2-fluoro-1-(fluorometil)etil]azetidin-3-il]metil]amino]-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 25 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[3-nitro-4-[[1-oxetan-3-ilazetidin-3-il]metil]amino]fenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[3-nitro-4-[[1-oxetan-3-ilpiperidin-4-il]metil]amino]fenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[4-[[1-ciclopropilpiperidin-4-il]metil]amino]-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[4-[[4-(2-fluoroetil)morfolin-2-il]metil]amino]-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 35

- 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]-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-fluoro-1-oxetan-3-ilpiperidin-4-il]metoxi)-3-nitrofenil)sulfonil]-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-(2S)-4,4-difluoro-1-oxetan-3-ilpirrolidin-2-il]metoxi)-3-nitrofenil)sulfonil]-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([4-tetrahidro-2H-piran-4-ilmorfolin-3-il]metil)amino]fenil)sulfonil]-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-ciclobutilmorfolin-3-il]metil)amino]-3-nitrofenil)sulfonil]-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([4-tetrahidrofurano-3-ilmorfolin-3-il]metil)amino]fenil)sulfonil]-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-2-fluoro-1-(fluorometil)etil]piperidin-4-il]metil)amino]-3-nitrofenil)sulfonil]-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-ciclopropil-4-fluoropiperidin-4-il]metoxi)-3-nitrofenil)sulfonil]-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-metoxibencil]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([3-(trifluorometoxi)bencil]amino]fenil)sulfonil]-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([3-metoxibencil]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-(difluorometoxi)bencil]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-(1,4-dioxaespiro[4,5]dec-8-ilamino)-3-nitrofenil)sulfonil]-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;
- Trans-N-([4-([4-(acetilamino)ciclohexil]amino)-3-nitrofenil)sulfonil]-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida;

- 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]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(4-([(3S)-1-(2-fluoroetil)pirrolidin-3-il]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(4-([(3S)-1-(2,2-difluoroetil)pirrolidin-3-il]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(4-([(3R)-1-(2-fluoroetil)pirrolidin-3-il]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(3-nitro-4-([(3S)-1-oxetan-3-ilpirrolidin-3-il]metoxi)fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(4-[(3-hidroxibencil)amino]-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(4-[(3-hidroxibencil)amino]-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(4-[(3-(difluorometoxi)bencil]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(4-([(cis-3-morfolin-4-ilciclopentil]metil]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- Trans-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(4-[(4-[(metilsulfonil]amino)ciclohexil]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-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-[(trifluorometil)sulfonil]fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(3-nitro-4-[(1-oxetan-3-ilpiperidin-4-il]metoxi]fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(4-[(4-fluoro-1-tetrahidro-2H-piran-4-il]piperidin-4-il]metoxi]-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(4-[(4-fluoro-1-tetrahidrofurano-3-il]piperidin-4-il]metoxi]-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{4-fluoro-1-(metilsulfonil)piperidin-4-il}metoxi}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-(((3R)-1-oxetan-3-ilpirrolidin-3-il}metil)amino)fenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5 Trans-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{4-hidroxiciclohexil}metoxi}-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{4-3-(dimetilamino)propoxi}bencil}amino)-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{4-(2-morfolin-4-iletoxi)bencil}amino)-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(E)-4-hidroxi-1-adamantil}metil}amino)-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(Z)-4-hidroxi-1-adamantil}metil}amino)-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-{{4-[(1S,4S)-biciclo[2,2,1]hept-5-en-2-ilmetoxi]-3-nitrofenil}sulfonil]-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{1-metil-5-oxopirrolidin-3-il}amino)-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{(1R,4R,5R,6S)-5,6-dihidroxibiciclo[2,2,1]hept-2-il}metoxi}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{(1R,4R,5S,6R)-5,6-dihidroxibiciclo[2,2,1]hept-2-il}metoxi}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-{{3-oxociclohexil}metoxi}fenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-5,5-dimetilciclohexa-1,3-dien-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 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-pirrolo[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([(3S)-1-oxetan-3-ilpirrolidin-3-il]metil)amino)fenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 5 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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- Cis-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 10 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([(3S)-1-oxetan-3-ilpirrolidin-3-il]amino)fenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-2-(2-metoxietoxi)etil]morfolin-2-il]metil)amino]-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 15 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)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-(N,N-dimetilglicil]morfolin-2-il]metil)amino]-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 20 ácido 2-([4-([4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]sulfamoi]-2-nitrofenil]amino]metil]morfolin-4-il]acético;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([4-(oxetan-3-il]morfolin-2-il]metil)amino)fenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 25 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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([5-(metilsulfonil)-6-(tetrahidro-2H-piran-4-il]metoxi)piridin-3-il]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 30 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]sulfonil]fenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-metiltetrahidro-2H-piran-4-il]metoxi)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]sulfamoil]-2-nitrofenil)piperazin-1-carboxilato de etilo;
- 5 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-(4-(morfolin-4-il)piperidin-1-il]-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(3-nitro-4-[(3R)-1-(oxetan-3-il)pirrolidin-3-il]amino]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 10 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-[(3R)-1-(1,3-difluoropropan-2-il)pirrolidin-3-il]amino]-3-[(trifluorometil)sulfonil]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-[(1-isopropilpiperidin-4-il)amino]-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 15 N-([4-[(1-tert-butilpiperidin-4-il)amino]-3-nitrofenil]sulfonil)-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-[(1-(2-metoxietil)piperidin-3-il]metil]amino)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 20 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-[(1-(cianometil)piperidin-3-il]metil]amino)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-[(4-fluoro-1-metilpiperidin-4-il)metoxi]-3-[(trifluorometil)sulfonil]fenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 25 N-[(5-cloro-6-[(3R)-1-(1,3-difluoropropan-2-il)pirrolidin-3-il]amino]piridin-3-il)sulfonil]-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-[(4-([4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]sulfamoil]-2-nitrofenil)amino]piperazin-1-carboxilato de tert-butilo;
- 30 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-(pentafluoro- $\square^6$ -sulfanil)-4-[(tetrahidro-2H-piran-4-il]metil]amino]fenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-[(4-metoxitetrahidro-2H-piran-4-il]metoxi)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 35

- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3R)-1-(1,3-difluoropropan-2-il)pirrolidin-3-il]oxi}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{[4-(oxetan-3-il)piperazin-1-il]amino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{[4-(tetrahidro-2H-piran-4-il)piperazin-1-il]amino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{(3R)-tetrahidrofurano-3-ilamino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-[(4-{[1-tert-butilpiperidin-4-il]amino}-3-[(trifluorometil)sulfonil]fenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[4-(oxetan-3-il)morfolin-2-il]metil}amino)-3-[(trifluorometil)sulfonil]fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 N-[(5-cloro-6-{[(2S)-4-(cianometil)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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(5-cloro-6-{[(2R)-4-(cianometil)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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 35 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-pirrolo[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-([5-cloro-6-[3-hidroxi-2-(hidroximetil)-2-metilpropoxi]piridin-3-il)sulfonil)-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-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]piridin-3-il)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-(1,3-difluoropropan-2-il)morfolin-2-il]metil)amino]-3-nitrofenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-([5-cloro-6-([1-(cianometil)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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-(3R)-1-[2-(2-metoxietoxi)etil]pirrolidin-3-il]amino)-3-nitrofenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-(3R)-1-(N,N-dimetilglicil)pirrolidin-3-il]amino)-3-nitrofenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([1-(oxetan-3-il)azetidina-3-il]amino)fenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-(2R)-4-(N,N-dimetilglicil)morfolin-2-il]metil)amino]-3-nitrofenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-(2S)-4-(N,N-dimetilglicil)morfolin-2-il]metil)amino]-3-nitrofenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-([5-cloro-6-([1-(N,N-dimetilglicil)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-pirrol[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 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]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-{4-[(4'-clorobifenil-2-il)metil]-4-metoxipiperidin-1-il}-N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-{4-[(4'-clorobifenil-2-il)metil]-4-metoxipiperidin-1-il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[9-(4-clorofenil)-3-(1,3-difluoropropan-2-il)-3-azaespiro[5,5]undec-8-en-8-il]metil}piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[9-(4-clorofenil)-3-isopropil-3-azaespiro[5,5]undec-8-en-8-il]metil}piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[9-(4-clorofenil)-3-(1,3-difluoropropan-2-il)-3-azaespiro[5,5]undec-8-en-8-il]metil}piperazin-1-il)-N-({5-cloro-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[9-(4-clorofenil)-3-isopropil-3-azaespiro[5,5]undec-8-en-8-il]metil}piperazin-1-il)-N-({5-cloro-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-({5-cloro-6-[(4-fluoro-1-metilpiperidin-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-[(5-cloro-6-[[1-(N,N-dimetilglicil)-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-{4-[(4'-clorobifenil-2-il)metil]-4-fluoropiperidin-1-il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-{4-[(4'-clorobifenil-2-il)metil]-4-fluoropiperidin-1-il}-N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[9-(4-clorofenil)-3-isopropil-3-azaespiro[5,5]undec-8-en-8-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)-N-({4-[(tetrahidro-2H-piran-4-ilmetil)amino]-3-(trifluorometil)fenil}sulfonil)benzamida;

- N-[(5-cloro-6-[(3R)-1-(1,3-difluoropropan-2-il)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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(3-nitro-4-[2-(tetrahydrofurano-3-iloxi)etoxi]fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5 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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(5-ciano-6-[2-(tetrahydro-2H-piran-4-il)etoxi]piridin-3-il)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(4-(3-furilmetoxi)-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 N-[(5-cloro-6-[(3R)-1-(1,3-difluoropropan-2-il)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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-[(5-cloro-6-[1-(1,3-difluoropropan-2-il)-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-[(3-cloro-4-[(4-fluoro-1-metilpiperidin-4-il)metoxi]fenil)sulfonil]-4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(3-ciano-4-(tetrahydro-2H-piran-4-ilmetoxi)fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-[(5-cloro-6-[1-(2,2-difluoroetil)-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-[(3-cloro-4-[(4-fluorotetrahydro-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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[6-{[1-(1,3-difluoropropan-2-il)-4-fluoropiperidin-4-il]metoxi}-5-(trifluorometil)piridin-3-il]sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-([5-cloro-6-[2-(tetrahidrofurano-2-il)etoxi]piridin-3-il]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}-3-metilpiperazin-1-il)-N-([3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-([4-{[3-(ciclopropilamino)propil]amino}-3-nitrofenil]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-([5-cloro-6-(2-metoxietoxi)piridin-3-il]sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-([3-cloro-4-{[1-(metoxiacetil)piperidin-4-il]metoxi}fenil]sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-([3-cloro-4-{[1-(N,N-dimetilglicil)piperidin-4-il]metoxi}fenil]sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohexil]metil}piperidin-1-il)-N-([3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)-N-([6-(tetrahidro-2H-piran-4-ilmetoxi)-5-(trifluorometil)piridin-3-il]sulfonil)benzamida;
- N-([5-cloro-6-[(trans-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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-([6-[(trans-4-metoxiciclohexil)metoxi]-5-(trifluorometil)piridin-3-il]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-([6-[(cis-4-metoxiciclohexil)metoxi]-5-(trifluorometil)piridin-3-il]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

- N-({5-cloro-6-[(4,4-difluoro-1-idroxiciclohexil)metoxi]piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperidin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 N-[(3-cloro-4-{[trans-4-(morfolin-4-il)ciclohexil]metoxi}fenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 5 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-{[3-(ciclopropil(1,3-tiazol-5-ilmetil)amino]propil}amino)-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 N-({3-cloro-4-{[trans-4-idroxiciclohexil]metoxi}fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 10 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-cloro-4-[(tetraidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-{[4-fluorotetraidro-2H-piran-4-il]metoxi}-3-(trifluorometil)fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 15 5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-{[3-(ciclopropil(2,2,2-trifluoroetil)amino]propil}amino)-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 N-[(3-cloro-4-{[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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 20 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3,5-difluoro-4-{[4-fluorotetraidro-2H-piran-4-il]metoxi}fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-{[3-(ciclopropil(oxetan-3-il)amino]propil}amino)-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 25 [ciclopropil(oxetan-3-il)amino]propil}amino)-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 N-[(3-cloro-4-{[1-(1-metil-L-prolil)piperidin-4-il]metoxi}fenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3,4-difluoro-5-{[4-fluorotetraidro-2H-piran-4-il]metoxi}fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 30 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperidin-1-il)-N-({3-nitro-4-[(tetraidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 35 [(tetraidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperidin-1-il)-N-{[3-cloro-4-(tetrahidro-2H-piran-4-ilmetoxi)fenil]sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 2-{{[4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]sulfamoil}-2-nitrofenil]amino]metil}morfolina-4-carboxilato
- 5 de metilo;
- 2-{{[4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]sulfamoil}-2-nitrofenil]amino]metil}-N-etil-N-metilmorfolina-4-carboxamida;
- 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}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 10 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[3-[ciclobutil(ciclopropil)amino]propil]amino)-3-nitrofenil]sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil]sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 15 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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-cloro-4-(tetrahidrofurano-3-ilmetoxi)fenil]sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[(trans-4-hidroxiciclohexil)metil]amino)-3-nitrofenil]sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-{[3-cloro-4-{[4-fluorotetrahidro-2H-piran-4-il]metoxi}fenil]sulfonil}-4-(4-{[9-(4-clorofenil)-3-(oxetan-3-il)-3-azaespiro[5,5]undec-8-en-8-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 25 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[(2R)-4-ciclopropilmorfolin-2-il]metil]amino)-3-nitrofenil]sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-{[5-(4-clorofenil)espiro[2,5]oct-5-en-6-il]metil}piperazin-1-il)-N-{[3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil]sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

- N-[[5-cloro-6-({4-[ciclopropil(oxetan-3-il)amino]ciclohexil}metoxi)piridin-3-il]sulfonil]-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{5-(4-clorofenil)espiro[2,5]oct-5-en-6-il]metil}piperazin-1-il)-N-[(4-{{(4-ciclopropilmorfolin-2-il)metil}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5 N-{{3-cloro-4-{{(4-ciclopropilmorfolin-2-il)metoxi}fenil}sulfonil]-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-[(3-cloro-4-{{(4-ciclopropilmorfolin-2-il)metil}amino}fenil)sulfonil]-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 2-{{(2-cloro-4-{{4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzoil}sulfamoil}fenil)amino}metil]-N-etil-N-metilmorfolina-4-carboxamida;
- (2S)-2-{{(3-cloro-5-{{4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzoil}sulfamoil}piridin-2-il)oxi]metil]-N-etil-N-metilmorfolina-4-
- 15 carboxamida;
- N-[(5-cloro-6-{{(4-ciclopropilmorfolin-2-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 2-{{(3-cloro-5-{{4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzoil}sulfamoil}piridin-2-il)amino}metil]-N-etil-N-metilmorfolina-4-
- 20 carboxamida;
- 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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{{(2-cianoetil)(ciclopropil)amino]ciclohexil}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-
- 30 iloxi)benzamida;
- N-{{5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil]-4-(4-{{5-(4-clorofenil)espiro[2,5]oct-5-en-6-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)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-
- 35 tetrahidroimidazo[1,2-a]piridin-6-ilmetoxi]piridin-3-il]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

- N-[(5-cloro-6-[(1R,2S,4R,5R)-5-hidroxi-5-metilbicio[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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5 N-[(5-cloro-6-[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi]piridin-3-il)sulfonil]-4-(4-[[5-(4-clorofenil)espiro[2,5]oct-5-en-6-il]metil]piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({4-[(3,3-difluoropirrolidin-1-il)ciclohexil]amino}-3-nitrofenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({4-[(2,2-difluorociclopropil)amino]ciclohexil}amino)-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({3-nitro-4-(2-oxaespiro[3,5]non-7-ilmetoxi)fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-5,5-bis(fluorometil)ciclohex-1-en-1-il]metil]piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({4-[(4-ciclopropilmorfolin-2-il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(trans-4-etil-4-hidroxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(cis-4-etil-4-hidroxiciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-5-(metoximetil)-5-metilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{(tetrahydro-2H-piran-4-ilmetil)amino}fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 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]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-({3-cloro-4-[(trans-4-hidroxi-4-metilciclohexil)metoxi]fenil)sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(2-cianoetil)(ciclopropil)amino]-1-fluorociclohexil)metoxi}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(5-nitro-6-[(tetrahydro-2H-piran-4-ilmetil)amino]piridin-3-il)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-[(2-oxaespiro[3,5]non-7-ilmetil)amino]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4-ciano-4-metilciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)-N-[(3-(tetrahydro-2H-piran-4-ilmetil)-3H-[1,2,3]triazolo[4,5-b]piridin-6-il)sulfonil]benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(6-{[(trans-4-hidroxi-4-metilciclohexil)metil]amino}-5-nitropiridin-3-il)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;

N-(4-([4-(4-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil)sulfamoil)-2-nitrofenil)morfolina-4-carboxamida;

4-(4-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-(metoximetil)ciclohexil]metil)amino]-3-nitrofenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

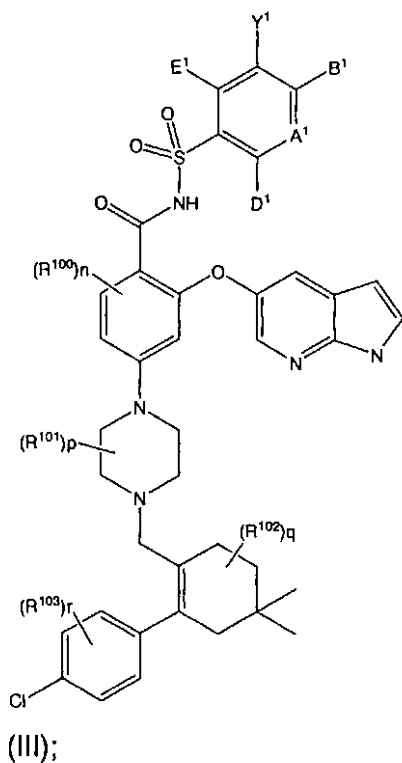
4-(4-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([5-cloro-6-([1-(1,3-tiazol-2-il)piperidin-4-il]metoxi)piridin-3-il)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

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-pirrol[2,3-b]piridin-5-iloxi)benzamida;

4-(4-[2-(4-clorofenil)-5-metoxi-5-metilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([trans-4-hidroxi-4-metilciclohexil]metil)amino]-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

4-(4-[2-(4-clorofenil)-5-metoxi-5-metilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida; y sus sales terapéuticamente aceptables, y sus metabolitos.

En otro aspecto, la presente invención provee compuestos de fórmula (III)



y sus sales terapéuticamente aceptables, y sus metabolitos,

donde A^1 , B^1 , D^1 , E^1 , y Y^1 tienen los valores definidos para la Fórmula (I); R^{100} tiene los valores que se describen para los sustituyentes de R^{26} ; n es 0, 1, 2, o 3; R^{101} tiene los valores que se describen para los sustituyentes de R^{30} ; p es 0, 1, 2, 3, 4, 5, o 6; R^{102} tiene los valores

que se describen para los sustituyentes de R^{40} ; q es 0, 1, 2, 3, 4, 5, o 6; R^{103} tiene los valores que se describen para los sustituyentes de R^{58} ; y r es 0, 1, 2, 3, o 4.

En una forma de realización de Fórmula (III), n, p, r, y q son cada uno 0.

En una forma de 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, F, Cl, Br, o I. En otra forma de realización de Fórmula (III), A^1 es $C(A^2)$; y A^2 es H.

En una forma de realización de Fórmula (III), B^1 es R^1 , OR^1 , NHR^1 , $NHC(O)R^1$, F, Cl, Br, o I. En otra forma de realización de Fórmula (III), A^1 es $C(A^2)$; A^2 es H; y B^1 es NHR^1 . En otra forma de realización de Fórmula (III), A^1 es $C(A^2)$; A^2 es H; y B^1 es OR^1 . En otra forma de realización de Fórmula (III), A^1 es $C(A^2)$; A^2 es H; y B^1 es Cl. En otra forma de realización de Fórmula (III), A^1 es $C(A^2)$; A^2 es H; y B^1 es R^1 . En otra forma de realización de Fórmula (III), A^1 es N; y B^1 es NHR^1 . En otra forma de realización de Fórmula (III), A^1 es N; y B^1 es OR^1 . En otra forma de realización de Fórmula (III), A^1 es N; y B^1 es Cl. En otra forma de realización de Fórmula (III), A^1 es N; y B^1 es R^1 .

En una forma de realización de Fórmula (III), D^1 es H o Cl. En otra forma de realización de Fórmula (III), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 ; y D^1 es H. En otra forma de realización de Fórmula (III), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 ; y D^1 es Cl. En otra forma de realización de Fórmula (III), A^1 es $C(A^2)$; A^2 es H; B^1 es OR^1 ; y D^1 es H. En otra forma de realización de Fórmula (III), A^1 es $C(A^2)$; A^2 es H; B^1 es Cl; y D^1 es H. En otra forma de realización de Fórmula (III), A^1 es $C(A^2)$; A^2 es H; B^1 es R^1 ; y D^1 es H. En otra forma de realización de Fórmula (III), A^1 es N; B^1 es NHR^1 ; y D^1 es H. En otra forma de realización de Fórmula (III), A^1 es N; B^1 es NHR^1 ; y D^1 es Cl. En otra forma de realización de Fórmula (III), A^1 es N; B^1 es OR^1 ; y D^1 es H. En otra forma de realización de Fórmula (III), A^1 es N; B^1 es Cl; y D^1 es H. En otra forma de realización de Fórmula (III), A^1 es N; B^1 es R^1 ; y D^1 es H.

En una forma de realización de Fórmula (III), E^1 es H. En otra forma de realización de Fórmula (III), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 ; D^1 es H; y E^1 es H. En otra forma de realización de Fórmula (III), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 ; E^1 es H; y D^1 es Cl. En otra forma de realización de Fórmula (III), A^1 es $C(A^2)$; A^2 es H; B^1 es OR^1 ; D^1 es H; y E^1 es H. En otra forma de realización de Fórmula (III), A^1 es $C(A^2)$; A^2 es H; B^1 es Cl; D^1 es H; y E^1 es H. En otra forma de realización de Fórmula (III), A^1 es $C(A^2)$; A^2 es H; B^1 es R^1 ; D^1 es H; y E^1 es H. En otra forma de realización de Fórmula (III), A^1 es N; B^1 es NHR^1 ; D^1 es H; y E^1 es H. En otra forma de realización de Fórmula (III), A^1 es N; B^1 es NHR^1 ; E^1 es H; y D^1 es Cl. En otra forma de realización de Fórmula (III), A^1 es N; B^1 es OR^1 ; D^1 es H; y E^1 es H. En otra forma de realización de Fórmula (III), A^1 es N; B^1 es Cl; D^1 es H; y E^1 es H. En otra forma de realización de Fórmula (III), A^1 es N; B^1 es R^1 ; D^1 es H; y E^1 es H.

En una forma de realización de Fórmula (III), Y^1 es H, CN, NO_2 , F, Cl, Br, I, CF_3 , R^{17} , OR^{17} , SR^{17} , SO_2R^{17} , o $C(O)NH_2$. En otra forma de realización de Fórmula (III), Y^1 es H. En otra forma de realización de Fórmula (III), Y^1 es CN. En otra forma de realización de Fórmula (III), Y^1 es F, Cl, Br, o I. En otra forma de realización de Fórmula (III), Y^1 es CF_3 . En otra forma de realización de Fórmula (III), Y^1 es SR^{17} . En otra forma de realización de Fórmula (III), Y^1 es OR^{17} . En otra forma de realización de Fórmula (III), Y^1 es NO_2 . En otra forma de realización de Fórmula (III), Y^1 es SO_2R^{17} ; donde R^{17} es como se ha definido. En otra forma de realización de Fórmula (III), Y^1 es SO_2R^{17} ; donde R^{17} es alquilo. En otra forma de realización de Fórmula (III), Y^1 es R^{17} ; donde R^{17} es alquinilo. En otra forma de realización de Fórmula (III), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 ; D^1 es H; E^1 es H; y Y^1 es NO_2 o SO_2R^{17} ; donde R^{17} es alquilo o alquinilo. En otra forma de realización de Fórmula (III), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 ; D^1 es H; E^1 es H; y Y^1 es NO_2 . En otra forma de realización de Fórmula (III), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 ; D^1 es H; E^1 es H; y Y^1 es SO_2R^{17} ; donde R^{17} es alquilo sustituido con tres F. En otra forma de realización de Fórmula (III), A^1 es N; B^1 es NHR^1 ; D^1 es H; E^1 es H; y Y^1 es NO_2 o SO_2R^{17} ; donde R^{17} es alquilo o alquinilo. En otra forma de realización de Fórmula (III), A^1 es N; B^1 es NHR^1 ; D^1 es H; E^1 es H; y Y^1 es NO_2 . En otra forma de realización de Fórmula (III), A^1 es N; B^1 es NHR^1 ; D^1 es H; E^1 es H; y Y^1 es SO_2R^{17} ; donde R^{17} es alquilo sustituido con tres F.

En una forma de realización de Fórmula (III), Y^1 y B^1 , junto con los átomos a los cuales están unidos, son benceno. En otra forma de realización de Fórmula (III), Y^1 y B^1 , junto con los átomos a los cuales están unidos, son heteroareno. En otra forma de realización de Fórmula (III), A^1 es $C(A^2)$; A^2 , G^1 , E^1 , y D^1 se seleccionan en forma independiente entre H; y Y^1 y B^1 , junto con los átomos a los cuales están unidos, son benceno. En otra forma de realización de Fórmula (III), A^1 es $C(A^2)$; A^2 , G^1 , E^1 , y D^1 se seleccionan en forma independiente entre H; y Y^1 y B^1 , junto con los átomos a los cuales están unidos, son heteroareno.

En una forma de realización de Fórmula (III), R^1 es R^4 o R^5 . En una forma de realización de Fórmula (III), R^1 es R^4 . En una forma de realización de Fórmula (III), R^1 es R^5 . En una forma de realización de Fórmula (III), R^1 es R^4 ; y R^4 es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo. En una forma de realización de Fórmula (III), R^1 es R^4 ; y R^4 es cicloalquilo o heterocicloalquilo. En una forma de realización de Fórmula (III), R^1 es R^4 ; y R^4 es cicloalquilo. En una forma de realización de Fórmula (III), R^1 es R^4 ; y R^4 es heterocicloalquilo.

En una forma de realización de Fórmula (III), R^1 es R^4 ; y R^4 es cicloalquilo; donde R^4 no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (III), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo está sustituido como

se ha definido. En otra forma de realización de Fórmula (III), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo está sustituido con R^{57} o $N(R^{57})_2$. En otra forma de realización de Fórmula (III), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con R^{57} ; y R^{57} es R^{60} . En otra forma de realización de

5 Fórmula (III), R^1 es R^4 ; R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con R^{57} ; R^{57} es R^{60} ; y R^{60} es heterocicloalquilo. En otra forma de realización de Fórmula (III), R^1 es R^4 ; R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con R^{57} ; R^{57} es R^{60} ; R^{60} es heterocicloalquilo; donde el anillo heterocicloalquilo es morfolinilo. En otra forma de

10 realización de Fórmula (III), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo está sustituido con $N(R^{57})_2$. En otra forma de realización de Fórmula (III), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con $N(R^{57})_2$. En otra forma de realización de Fórmula (III), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está

15 sustituido con $N(R^{57})_2$; R^{57} es R^{61} ; y R^{61} es alquilo que no está sustituido o está sustituido con R^{62} . En otra forma de realización de Fórmula (III), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con R^{57} ; R^{57} es R^{61} ; y R^{61} es alquilo que no está sustituido o está sustituido con R^{62} ; R^{62} es R^{65} ; y R^{65} es cicloalquilo. En otra forma de realización de Fórmula (III), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con R^{57} ; R^{57} es R^{61} ; y R^{61} es alquilo el cual está sustituido con R^{62} ; R^{62} es R^{65} ; y R^{65} es ciclopropilo.

En una forma de realización de Fórmula (III), R^1 es R^4 ; y R^4 es heterocicloalquilo; donde R^4 no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (III), R^1 es R^4 ; y R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo está sustituido como se ha definido. En otra forma de realización de

25 Fórmula (III), R^1 es R^4 ; y R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo está sustituido con R^{57} . En otra forma de realización de Fórmula (III), R^1 es R^4 ; y R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo es piperidinilo o piperizinilo; y donde el anillo heterocicloalquilo está sustituido con R^{57} ; y R^{57} es R^{60} o R^{61} . En otra forma de realización de Fórmula (III), R^1 es R^4 ; R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo es piperidinilo o piperizinilo; y donde el anillo piperidinilo o piperizinilo está sustituido con R^{57} ; R^{57} es R^{60} o R^{61} ; R^{60} es heterocicloalquilo; y R^{61} es alquilo. En otra forma de realización de Fórmula (III), R^1 es R^4 ; R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo es piperidinilo o piperizinilo; y donde el anillo piperidinilo o piperizinilo está

30 sustituido con R^{57} ; R^{57} es R^{60} ; R^{60} es heterocicloalquilo; donde el heterocicloalquilo es tetrahidropiranilo. En otra forma de realización de Fórmula (III), R^1 es R^4 ; R^4 es

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heterocicloalquilo; donde el anillo heterocicloalquilo es piperdinilo o piperizinilo; y donde el anillo piperidinilo o piperizinilo está sustituido con R^{57} ; R^{57} es R^{61} ; R^{61} es alquilo; y el alquilo es metilo. En otra forma de realización de Fórmula (III), R^1 es R^4 ; R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo es piperdinilo o piperizinilo; y donde el anillo piperidinilo o piperizinilo está sustituido con $C(O)OR^{57}$; R^{57} es R^{61} ; R^{61} es alquilo; y el alquilo es metilo.

En una forma de realización de Fórmula (III), R^1 es R^5 ; y R^5 es alquilo que no está sustituido o está sustituido. En una forma de realización de Fórmula (III), R^1 es R^5 ; y R^5 es alquilo que no está sustituido o está sustituido con R^7 , OR^7 , OH , CN , o F . En otra forma de realización de Fórmula (III), R^1 es R^5 ; y R^5 es alquilo el cual está sustituido con R^7 , OR^7 , NHR^7 , o $N(R^7)_2$.

En una forma de realización de Fórmula (III), R^7 es R^8 , R^9 , R^{10} o R^{11} que no están sustituidos o están sustituidos como se ha definido. En otra forma de realización de Fórmula (III), R^7 es R^8 que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (III), R^7 es R^9 que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (III), R^7 es R^{10} que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (III), R^7 es R^{11} que no está sustituido o está sustituido como se ha definido.

En una forma de realización de Fórmula (III), R^8 es fenilo que no está sustituido o está sustituido como se ha definido.

En una forma de realización de Fórmula (III), R^9 es heteroarilo que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (III), R^9 es furanilo; que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (III), R^9 es furanilo; que no está sustituido.

En una forma de realización de Fórmula (III), R^{10} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, heterocicloalquilo que no están sustituidos o están sustituidos como se ha definido. En otra forma de realización de Fórmula (III), R^{10} es heterocicloalquilo que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (III), R^{10} es tetrahidrofuranilo, tetrahidropiranilo, morfolinilo, dioxanilo, oxetanilo, piperdinilo, o pirrolidinilo, que no están sustituidos o están sustituidos como se ha definido. En otra forma de realización de Fórmula (III), R^{10} es tetrahidropiranilo; que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (III), R^{10} es morfolinilo; que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (III), R^{10} es cicloalquilo que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (III), R^{10} es cicloalquilo que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (III), R^{10} es ciclohexilo, ciclopropilo, ciclobutilo, o

biciclo[2,2,1]heptanilo; que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (III), R^{10} es heterocicloalquilo que está fusionado con R^{10A} ; y R^{10A} es heteroareno. En otra forma de realización de Fórmula (III), R^{10} es 5,6,7,8-tetrahidroimidazo[1,2-a]piridinilo.

- 5 En una forma de realización de Fórmula (III), R^{11} es alquilo, alquenilo o alquinilo que no están sustituidos o están sustituidos como se ha definido. En otra forma de realización de Fórmula (III), R^{11} es alquilo. En otra forma de realización de Fórmula (III), R^{11} es metilo; que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (III), R^{11} es alquilo; que está sustituido como se ha definido. En otra forma de
- 10 realización de Fórmula (III), R^{11} es alquilo; que está sustituido con R^{12} , OR^{12} , o CF_3 . En otra forma de realización de Fórmula (III), R^{11} es alquilo; que está sustituido con OR^{12} ; R^{12} es R^{16} ; y R^{16} es alquilo. En otra forma de realización de Fórmula (III), R^{11} es alquilo; que está sustituido con CF_3 . En otra forma de realización de Fórmula (III), R^{11} es alquilo; que está sustituido con R^{12} ; R^{12} es R^{14} ; y R^{14} es heteroarilo.
- 15 En una forma de realización de Fórmula (III),
 n , p , r , y q son cada uno 0;
 A^1 es N o C(A^2);
 A^2 es H, F, Br, I, o Cl;
 B^1 es R^1 , OR^1 , NHR^1 , $NHC(O)R^1$, F, Br, I o Cl;
- 20 D^1 es H, F, Br, I, o Cl;
 E^1 es H; y
 Y^1 es H, CN, NO_2 , F, Cl, Br, I, CF_3 , R^{17} , OR^{17} , SR^{17} , SO_2R^{17} , o $C(O)NH_2$; o
 Y^1 y B^1 , junto con los átomos a los cuales están unidos, son benceno, heteroareno, o heterocicloalqueno; y
- 25 A^2 , D^1 , y E^1 se seleccionan en forma independiente entre H;
 R^1 es R^4 o R^5 ;
 R^4 es cicloalquilo, o heterocicloalquilo;
 R^5 es alquilo, 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^7 , OR^7 ,
30 NHR^7 , $N(R^7)_2$, CN, OH, F, Cl, Br o I;
 R^7 es R^8 , R^9 , R^{10} , o R^{11} ;
 R^8 es fenilo;
 R^9 es heteroarilo;
 R^{10} es cicloalquilo, cicloalquenilo, o heterocicloalquilo; cada uno de los cuales no está
35 fusionado o está fusionado con R^{10A} , R^{10A} es heteroareno;

R^{11} es alquilo cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre R^{12} , OR^{12} or CF_3 ;

R^{12} es R^{14} o R^{16} ;

R^{14} es heteroarilo;

5 R^{16} es alquilo;

R^{17} es R^{21} ;

R^{21} es alquilo, 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^{22} , F, Cl, Br o I;

10 R^{22} es R^{25} ;

R^{25} es heterocicloalquilo;

15 donde las unidades cíclicas representadas por Y^1 y B^1 juntos, R^4 , R^8 , R^{10} , y R^{25} , no están sustituidas, no están adicionalmente sustituidas, están sustituidas o adicionalmente sustituidas en forma independiente con uno o dos o tres o cuatro o cinco sustituyentes seleccionados en forma independiente entre R^{57A} , R^{57} , OR^{57} , SO_2R^{57} , $C(O)R^{57}$, $CO(O)R^{57}$, $C(O)N(R^{57})_2$, NH_2 , NHR^{57} , $N(R^{57})_2$, $NHC(O)R^{57}$, $NHS(O)_2R^{57}$, OH, CN, (O), F, Cl, Br o I;

R^{57A} es espiroalquilo, o espiroheteroalquilo;

R^{57} es R^{58} , R^{60} o R^{61} ;

20 R^{58} es fenilo;

R^{60} es cicloalquilo, o heterocicloalquilo;

R^{61} es alquilo que no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre R^{62} , OR^{62} , $N(R^{62})_2$, $C(O)OH$, CN, F, Cl, Br o I;

25 R^{62} es R^{65} , o R^{66} ;

R^{65} es cicloalquilo, o heterocicloalquilo;

R^{66} es alquilo que no está sustituido o está sustituido con OR^{67} ;

R^{67} es alquilo;

30 donde las unidades cíclicas representadas por R^{57A} , R^{58} , y R^{60} no están sustituidas o están sustituidas con uno o dos o tres o cuatro sustituyentes seleccionados en forma independiente entre R^{68} , F, Cl, Br o I;

R^{68} es R^{71} o R^{72} ;

R^{71} es heterocicloalquilo; y

R^{72} es alquilo, que no está sustituido o está sustituido con uno o dos F.

35 Aún otra forma de realización se refiere a compuestos de fórmula (III), que son

- 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-(1H-pirrol[2,3-b]piridin-5-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-(1H-pirrol[2,3-b]piridin-5-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-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 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)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- Trans-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)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({4-{{2-metoxietil}amino}-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({3-nitro-4-{{(3S)-tetrahidro-2H-piran-3-ilmetil}amino}fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({3-nitro-4-{{(3R)-tetrahidro-2H-piran-3-ilmetil}amino}fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-(2-naftilsulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({4-{{2-metoxietil}amino}-3-{{trifluorometil}sulfonil}fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-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-({3-nitro-4-{{tetrahidro-2H-piran-4-ilmetoxi}fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({3-nitro-4-{{2,2,2-trifluoroetil}amino}fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({3-nitro-4-{{3,3,3-trifluoropropil}amino}fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 Cis-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)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 5 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 Trans-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)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({5-ciano-6-
 10 (tetraidro-2H-piran-4-ilmetoxi)piridin-3-il}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({4-([4-fluorotetraidro-2H-piran-4-il]metoxi)-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 15 N-({3-(aminocarbonil)-4-(tetraidro-2H-piran-4-ilmetoxi)fenil}sulfonil)-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 Cis-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)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({5-cloro-6-
 20 (tetraidro-2H-piran-4-ilmetoxi)piridin-3-il}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 5-({4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzoil}amino)sulfonil)-2-(tetraidro-2H-piran-4-ilmetoxi)nicotinamida;
 N-({5-bromo-6-[(1-metilpiperidin-4-il)metoxi]piridin-3-il}sulfonil)-4-(4-([2-(4-clorofenil)-4,4-
 25 dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({4-[(1-metilpiperidin-4-il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({5-ciano-6-(1,4-
 dioxan-2-ilmetoxi)piridin-3-il}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 30 N-({5-bromo-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({4-([2,2-dimetiltetraidro-2H-piran-4-il]metoxi)-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 35 N-({3-cloro-5-ciano-4-[(tetraidro-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-pirrolo[2,3-b]piridin-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-pirrolo[2,3-b]piridin-5-iloxi)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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 5 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-(1H-pirrolo[2,3-b]piridin-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 10 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 N-[(3-cloro-4-{[2-(2-metoxietoxi)etil}sulfonil}]fenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[2-(2-
 15 metoxietoxi)etil}sulfonil]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-morfolin-4-ilciclohexil)oxi]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 N-({5-bromo-6-[(1-tetrahidro-2H-piran-4-ilpiperidin-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-pirrolo[2,3-b]piridin-5-
 20 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 N-({4-[(4-[bis(ciclopropilmetil)amino]ciclohexil)amino]-3-nitrofenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-
 25 iloxi)benzamida;
 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]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(morfolin-3-ilmetil)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 30 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-morfolin-4-ilbut-2-inil)oxi]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 35 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-oxo-3,4-dihidroquinazolin-6-il)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

- 3-{{4-{{4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzoil}amino}sulfonil)-2-nitrofenoxi]metil}morfolina-4-carboxilato de tert-butilo;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-(morfolin-3-ilmetoxi)-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{1-(metilsulfonil)piperidin-4-il}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-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}amino}-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 N-{{4-cloro-3-nitrofenil}sulfonil}-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-{{1-(2,2,2-trifluoroetil)piperidin-4-il}amino}fenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{5-ciano-6-{{1-tetrahidro-2H-piran-4-il}piperidin-4-il}oxi}piridin-3-il}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{5-isopropil-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 N-{{3-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{1-{{2-fluoro-1-(fluorometil)etil}piperidin-4-il}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{1-(2,2-difluoroetil)piperidin-4-il}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
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- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{(1-morfolin-4-ilciclohexil)metil}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 Trans-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{4-(diciclopropilamino)ciclohexil}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 5 N-{{5-bromo-6-[(4-etilmorfolin-3-il)metoxil]piridin-3-il}sulfonil}-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{4-etilmorfolin-3-il)metoxil}-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 10 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(3-nitro-4-{{4-tetraidro-2H-piran-4-ilmorfolin-3-il)metoxil}fenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(3-nitro-4-{{(3S)-1-tetraidro-2H-piran-4-ilpiperidin-3-il}amino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 15 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(5-ciano-6-{{tetraidro-2H-piran-4-ilmetil}amino}piridin-3-il)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{(1,1-dioxidotiormorfolin-4-il)amino}-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 20 N-[(4-{{(4-aminotetraidro-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 Trans-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(5-ciano-6-{{4-morfolin-4-ilciclohexil}amino}piridin-3-il)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 25 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(3-ciano-4-{{tetraidro-2H-piran-4-ilmetil}amino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{(1S,3R)-3-morfolin-4-ilciclopentil}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 30 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{(1R,3S)-3-morfolin-4-ilciclopentil}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{(morfolin-2-ilmetil}amino)-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
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- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-
[(tetrahidrofurano-3-ilmetil)amino]fenil}sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{1-[cis-3-
fluorotetrahidro-2H-piran-4-il]piperidin-4-il}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrol[2,3-
5 b]piridin-5-iloxi)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-ilazetid-3-il}amino}fenil}sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-
iloxi)benzamida;
4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-{{1-
10 tetrahidrofurano-3-ilazetid-3-il}amino}fenil}sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-
iloxi)benzamida;
4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-{{(3R)-1-
tetrahidro-2H-piran-4-ilpirrolidin-3-il}metil}amino}fenil}sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-
iloxi)benzamida;
15 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-
enil}metil}piperazin-1-il)-N-(4-{{trans-4-hidroxiciclohexil}metoxi}-3-nitrofenilsulfonil)benzamida;
2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-
enil}metil}piperazin-1-il)-N-(4-{{cis-4-metoxiciclohexil}metoxi}-3-nitrofenilsulfonil)benzamida;
Cis-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{4-
20 (ciclopropilamino)ciclohexil}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-
iloxi)benzamida;
Trans-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-{{4-
(tetrahidro-2H-piran-4-ilamino)ciclohexil}amino}fenil}sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-
iloxi)benzamida;
25 Trans-N-{{5-bromo-6-{{4-morfolin-4-ilciclohexil}oxi}piridin-3-il}sulfonil}-4-(4-{{2-(4-clorofenil)-
4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
Trans-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{4-
metoxiciclohexil}metoxi}-3-nitrofenil}sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
4-{{4-{{4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-
30 pirrol[2,3-b]piridin-5-iloxi)benzoil}amino}sulfonil}-2-nitrofenoxi}metil}-4-fluoropiperidin-1-
carboxilato de tert-butilo;
4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{4-
fluoropiperidin-4-il}metoxi}-3-nitrofenil}sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
Trans-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-{{4-
35 (4-tetrahidro-2H-piran-4-ilpiperazin-1-il)ciclohexil}amino}fenil}sulfonil}-2-(1H-pirrol[2,3-
b]piridin-5-iloxi)benzamida;

- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{1-{2-fluoro-1-(fluorometil)etil}piperidin-4-il}metoxi}-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-{{(3R)-1-tetraidro-2H-piran-4-ilpirrolidin-3-il}amino}fenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(3R)-1-(2,2-dimetiltetraidro-2H-piran-4-il)pirrolidin-3-il}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-{{(3S)-1-tetraidro-2H-piran-4-ilpirrolidin-3-il}amino}fenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(3S)-1-(2,2-dimetiltetraidro-2H-piran-4-il)pirrolidin-3-il}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(4-metilmorfolin-2-il)metil}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{4-(2-metoxietil)morfolin-2-il}metil}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-{{4-{{(4-acetilmorfolin-2-il)metil}amino}-3-nitrofenil}sulfonil}-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{trans-4-(fluorometil)-1-oxetan-3-ilpirrolidin-3-il}metoxi}-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{4-fluorotetraidro-2H-piran-4-il}metil}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-{{1-oxetan-3-ilpiperidin-4-il}amino}fenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{1-ciclobutilpiperidin-4-il}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{1-(2,2-dimetiltetraidro-2H-piran-4-il)piperidin-4-il}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{(3S)-1-ciclopropilpirrolidin-3-il}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-{{(1-tetrahidrofurano-3-ilpiperidin-4-il}amino)fenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{(3R)-1-ciclopropilpirrolidin-3-il}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-{{(3S)-1-tetrahidro-2H-piran-4-ilpirrolidin-3-il}metil}amino)fenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(3-hidroxi-2,2-dimetilpropil)amino}-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{1-(metilsulfonil)piperidin-3-il}metil}amino)-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-[(4-{{1-acetilpiperidin-3-il}metil}amino)-3-nitrofenil)sulfonil]-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{(3R)-1-(metilsulfonil)pirrolidin-3-il}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{1-[2-fluoro-1-(fluorometil)etil]azetidin-3-il}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxy)benzamida;
- 25 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{1-(metilsulfonil)pirrolidin-3-il}metil}amino)-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-[(4-{{1-acetilpirrolidin-3-il}metil}amino)-3-nitrofenil)sulfonil]-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 N-[(4-{{(3R)-1-acetilpirrolidin-3-il}amino)-3-nitrofenil)sulfonil]-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{3-metoksi-2,2-dimetilpropil)amino}-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{{{(1R,3R)-3-hidroxiciclopentil]metil}amino)-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{{{(1S,3S)-3-hidroxiciclopentil]metil}amino)-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{{{(1S,3R)-3-hidroxiciclopentil]metil}amino)-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{{{(1R,3S)-3-hidroxiciclopentil]metil}amino)-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{[(3S)-2-oxopiperidin-3-il]amino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-([4-[[[1-[2-fluoro-1-(fluorometil)etil]azetid-3-il]metil]amino]-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{[(1-oxetan-3-ilazetid-3-il)metil]amino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{[(1-oxetan-3-ilpiperidin-4-il)metil]amino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-([4-[[[1-ciclopropilpiperidin-4-il]metil]amino]-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-[[[4-(2-fluoroetil)morfolin-2-il]metil]amino)-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 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]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-([4-[[[4-fluoro-1-oxetan-3-ilpiperidin-4-il]metoxi]-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-([4-[[[4-(2S)-4,4-difluoro-1-oxetan-3-ilpirrolidin-2-il]metoxi]-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(3-nitro-4-{{(4-tetrahidro-2H-piran-4-ilmorfolin-3-il)metil}amino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{(4-ciclobutilmorfolin-3-il)metil}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(3-nitro-4-{{(4-tetrahidrofurano-3-ilmorfolin-3-il)metil}amino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{(1-[2-fluoro-1-(fluorometil)etil]piperidin-4-il)metil}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{(1-ciclopropil-4-fluoropiperidin-4-il)metoxi}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{(4-metoxibencil)amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(3-nitro-4-{{(3-(trifluorometoxi)bencil)amino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{(3-metoxibencil)amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{(4-(difluorometoxi)bencil)amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-(1,4-dioxaespiro[4,5]dec-8-ilamino)-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 Trans-N-[(4-{{(4-(acetilamino)ciclohexil}amino)-3-nitrofenil)sulfonil]-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 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]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{(3S)-1-(2-fluoroetil)pirrolidin-3-il}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{(3S)-1-(2,2-difluoroetil)pirrolidin-3-il}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
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- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(4-[(3R)-1-(2-fluoroetil)pirrolidin-3-il]amino)-3-nitrofenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(3-nitro-4-[(3S)-1-oxetan-3-ilpirrolidin-3-il]metoxi]fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(4-[(4-hidroxibencil)amino]-3-nitrofenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(4-[(4-hidroxibencil)amino]-3-nitrofenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(4-[(3-(difluorometoxi)bencil]amino)-3-nitrofenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(4-[(4-[(cis-3-morfolin-4-ilciclopentil]metil]amino)-3-nitrofenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- Trans-4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(4-[(4-[(metilsulfonil)amino]ciclohexil)amino]-3-nitrofenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-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-[(trifluorometil)sulfonil]fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(3-nitro-4-[(1-oxetan-3-ilpiperidin-4-il)metoxi]fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(4-[(4-fluoro-1-tetrahidro-2H-piran-4-ilpiperidin-4-il)metoxi]-3-nitrofenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(4-[(4-fluoro-1-tetrahidrofurano-3-ilpiperidin-4-il)metoxi]-3-nitrofenil]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(4-[(4-fluoro-1-(metilsulfonil)piperidin-4-il)metoxi]-3-nitrofenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(3-nitro-4-[(3R)-1-oxetan-3-ilpirrolidin-3-il]metil]amino)fenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- Trans-4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(4-[(4-hidroxiciclohexil)metoxi]-3-nitrofenil]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[3-(dimetilamino)propoxi]bencil}amino)-3-nitrofenil]sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[4-(2-morfolin-4-iletoxi)bencil]amino)-3-nitrofenil]sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[(E)-4-hidroxi-1-adamantil]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[(Z)-4-hidroxi-1-adamantil]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 N-{[4-{[(1S,4S)-biciclo[2,2,1]hept-5-en-2-ilmetoxi]-3-nitrofenil]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[(1-metil-5-oxopirrolidin-3-il)amino]-3-nitrofenil]sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[(1R,4R,5R,6S)-5,6-dihidroxibiciclo[2,2,1]hept-2-il]metoxi]-3-nitrofenil]sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[(1R,4R,5S,6R)-5,6-dihidroxibiciclo[2,2,1]hept-2-il]metoxi]-3-nitrofenil]sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[(1R,4R,5S,6R)-5,6-dihidroxibiciclo[2,2,1]hept-2-il]metoxi]-3-nitrofenil]sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-nitro-4-{[3-oxociclohexil]metoxi]fenil]sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-nitro-4-{[(3S)-1-oxetan-3-ilpirrolidin-3-il]metil}amino]fenil]sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- Cis-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-nitro-4-{[(3S)-1-oxetan-3-ilpirrolidin-3-il]amino]fenil]sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
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- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-{[4-{2-(2-metoxietoxi)etil]morfolin-2-il}metil}amino]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 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)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-{[4-(N,N-dimetilglicil)morfolin-2-il]metil}amino]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 10 ácido (2-{[4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil}sulfamoil]-2-nitrofenil}amino]metil}morfolin-4-il)acético;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-{[4-(oxetan-3-il)morfolin-2-il]metil}amino}fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 15 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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({5-(metilsulfonil)-6-(tetrahydro-2H-piran-4-ilmetoxi)piridin-3-il}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 20 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-{[4-(fluorotetrahydro-2H-piran-4-il)metoxi]-3-[(trifluorometil)sulfonil]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-{[4-(metiltetrahydro-2H-piran-4-il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 25 4-(4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil}sulfamoil]-2-nitrofenil}piperazin-1-carboxilato de etilo;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[4-(morfolin-4-il)piperidin-1-il]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{[(3R)-1-(oxetan-3-il)pirrolidin-3-il]amino}fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-{[(3R)-1-(1,3-difluoropropan-2-il)pirrolidin-3-il]amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
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- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(1-isopropilpiperidin-4-il)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
N-({4-[(1-tert-butilpiperidin-4-il)amino]-3-nitrofenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 5 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(1-(2-metoxietil)piperidin-3-il]metil}amino)-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(1-(cianometil)piperidin-3-il]metil}amino)-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 10 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-fluoro-1-metilpiperidin-4-il)metoxi]-3-[(trifluorometil)sulfonil]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-[(5-cloro-6-[(3R)-1-(1,3-difluoropropan-2-il)pirrolidin-3-il]amino}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 15 4-[(4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil}sulfamoi]-2-nitrofenil)amino]piperazin-1-carboxilato de tert-butilo;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-(pentafluoro- $\square^6$ -sulfanil)-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 20 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-metoxitetrahidro-2H-piran-4-il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 25 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-[(3R)-1-(1,3-difluoropropan-2-il)pirrolidin-3-il]oxi)-3-nitrofenil}sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-[(4-(oxetan-3-il)piperazin-1-il]amino)fenil}sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-[(4-(tetrahidro-2H-piran-4-il)piperazin-1-il]amino)fenil}sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(3R)-tetrahidrofurano-3-ilamino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 5 N-[(4-{[1-tert-butilpiperidin-4-il]amino}-3-[(trifluorometil)sulfonil]fenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[4-(oxetan-3-il)morfolin-2-il]metil}amino)-3-[(trifluorometil)sulfonil]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 10 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-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 15 N-[(5-cloro-6-{[(2S)-4-(cianometil)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-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 20 N-[(5-cloro-6-{[(2R)-4-(cianometil)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-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 25 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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 30 N-[(5-cloro-6-[3-hidroxi-2-(hidroximetil)-2-metilpropoxi]piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-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}piridin-3-il)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 35

- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[4-(1,3-difluoropropan-2-il)morfolin-2-il]metil}amino]-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5 N-[(5-cloro-6-{[1-(cianometil)piperidin-4-il]metoksi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[(3R)-1-[2-(2-metoxietoksi)etil]pirrolidin-3-il]amino}-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 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]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-nitro-4-{[1-(oxetan-3-il)azetidin-3-il]amino}fenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 N-[(5-cloro-6-{[1-(cianometil)-4-fluoropiperidin-4-il]metoksi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 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]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 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]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-[(5-cloro-6-{[1-(N,N-dimetilglicil)piperidin-4-il]metoksi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 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]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 N-[(5-cloro-6-{[4-fluoro-1-metilpiperidin-4-il]metoksi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 35 N-[(5-cloro-6-{[1-(N,N-dimetilglicil)-4-fluoropiperidin-4-il]metoksi}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

- N-[(5-cloro-6-[(3R)-1-(1,3-difluoropropan-2-il)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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[2-(tetrahydrofurano-3-iloxi)etoxi]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5 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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({5-ciano-6-[2-(tetrahydro-2H-piran-4-il)etoxi]piridin-3-il}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-(3-furilmetoxi)-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 N-[(5-cloro-6-[(3R)-1-(1,3-difluoropropan-2-il)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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-[(5-cloro-6-{[1-(1,3-difluoropropan-2-il)-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-({3-cloro-4-[(4-fluoro-1-metilpiperidin-4-il)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-ciano-4-(tetrahydro-2H-piran-4-ilmetoxi)fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-[(5-cloro-6-{[1-(2,2-difluoroetil)-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-({3-cloro-4-[(4-fluorotetrahydro-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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[6-{[1-(1,3-difluoropropan-2-il)-4-fluoropiperidin-4-il]metoxi}-5-(trifluorometil)piridin-3-il]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[5-cloro-6-[2-(tetrahidrofurano-2-il)etoxi]piridin-3-il]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[3-(ciclopropilamino)propil]amino}-3-nitrofenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-{[5-cloro-6-(2-metoxietoxi)piridin-3-il]sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-{[3-cloro-4-{[1-(metoxiacetil)piperidin-4-il]metoxi]fenil]sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-{[3-cloro-4-{[1-(N,N-dimetilglicil)piperidin-4-il]metoxi]fenil]sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)-N-{[6-(tetrahidro-2H-piran-4-ilmetoxi)-5-(trifluorometil)piridin-3-il]sulfonil]benzamida;
- N-{[5-cloro-6-[(trans-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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[6-[(trans-4-metoxiciclohexil)metoxi]-5-(trifluorometil)piridin-3-il]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[6-[(cis-4-metoxiciclohexil)metoxi]-5-(trifluorometil)piridin-3-il]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-{[3-cloro-4-{[trans-4-(morfolin-4-il)ciclohexil]metoxi]fenil]sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[3-(ciclopropil(1,3-tiazol-5-ilmetil)amino)propil]amino}-3-nitrofenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

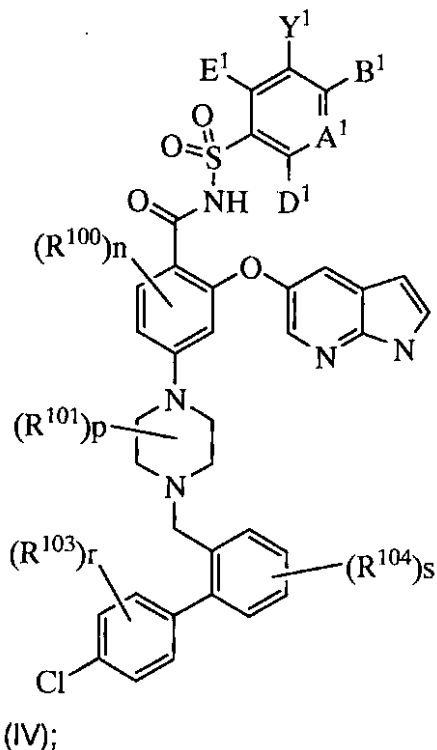
- N-({3-cloro-4-[(trans-4-hidroxiciclohexil)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-cloro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)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-(trifluorometil)fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-({3-[ciclopropil(2,2,2-trifluoroetil)amino]propil}amino)-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 N-[(3-cloro-4-[(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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3,5-difluoro-4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-({3-[ciclopropil(oxetan-3-il)amino]propil}amino)-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 N-[(3-cloro-4-[(1-(1-metil-L-prolil)piperidin-4-il]metoxi)fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3,4-difluoro-5-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 2-{{[(4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]sulfamoil}-2-nitrofenil)amino]metil}morfolina-4-carboxilato de metilo;
 2-{{[(4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]sulfamoil}-2-nitrofenil)amino]metil}-N-etil-N-metilmorfolina-4-carboxamida;
 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)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[3-(ciclobutil(ciclopropil)amino)propil]amino)-3-nitrofenil]sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 N-[(3-cloro-4-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoksi}fenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 5 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-cloro-4-(tetrahidrofurano-3-ilmetoksi)fenil]sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[(2R)-4-ciclopropilmorfolin-2-il]metil]amino)-3-nitrofenil]sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 10 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[5-(4-clorofenil)espiro[2,5]oct-5-en-6-il]metil}piperazin-1-il)-N-{[3-nitro-4-{(tetraidro-2H-piran-4-ilmetil)amino]fenil]sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 15 N-{[5-cloro-6-{[4-[ciclopropil(oxetan-3-il)amino]ciclohexil]metoksi}piridin-3-il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[5-(4-clorofenil)espiro[2,5]oct-5-en-6-il]metil}piperazin-1-il)-N-{[4-{[(4-ciclopropilmorfolin-2-il)metil]amino)-3-nitrofenil]sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 20 N-{[3-cloro-4-{[(4-ciclopropilmorfolin-2-il)metoksi]fenil]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 N-[(3-cloro-4-{[(4-ciclopropilmorfolin-2-il)metil]amino}fenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 25 2-{[(2-cloro-4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzoil]sulfamoil}fenil)amino]metil}-N-etil-N-metilmorfolina-4-carboxamida;
 (2S)-2-{[(3-cloro-5-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzoil]sulfamoil}piridin-2-il)oxi]metil}-N-etil-N-metilmorfolina-4-carboxamida;
 30 carboxamida;
 N-[(5-cloro-6-{[(4-ciclopropilmorfolin-2-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 2-{[(3-cloro-5-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzoil]sulfamoil}piridin-2-il)amino]metil}-N-etil-N-metilmorfolina-4-carboxamida;
 35 carboxamida;

- 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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(2-cianoetil)(ciclopropil)amino]ciclohexil}amino)-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 N-[(5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il)sulfonil]-4-(4-{[5-(4-clorofenil)espiro[2,5]oct-5-en-6-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 N-[(5-cloro-6-[(1R,2S,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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-[(5-cloro-6-[(4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi]piridin-3-il)sulfonil]-4-(4-{[5-(4-clorofenil)espiro[2,5]oct-5-en-6-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3,3-difluoropirrolidin-1-il)ciclohexil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(2,2-difluorociclopropil)amino]ciclohexil}amino)-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 35

- N-({5-cloro-6-[(cis-1-fluoro-4-idroxiciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-(2-oxaespiro[3,5]non-7-ilmetoxi)fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 5 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(trans-4-idroxi-4-metilciclohexil)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-ciclopropilmorfolin-2-il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 10 N-({5-cloro-6-[(trans-1-fluoro-4-idroxi-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 N-({5-cloro-6-[(cis-1-fluoro-4-idroxi-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 15 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(trans-4-etil-4-idroxiciclohexil)metil]amino}-3-nitrofenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 20 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(cis-4-etil-4-idroxiciclohexil)metil]amino}-3-nitrofenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 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)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 25 N-({3-cloro-4-[(trans-4-idroxi-4-metilciclohexil)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(2-cianoetil)(ciclopropil)amino]-1-fluorociclohexil)metoxi}-3-nitrofenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 30 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({5-nitro-6-[(tetrahidro-2H-piran-4-ilmetil)amino]piridin-3-il}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(2-oxaespiro[3,5]non-7-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
 35 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-ciano-4-metilciclohexil)metil]amino}-3-nitrofenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)-N-([3-(tetrahidro-2H-piran-4-ilmetil)-3H-[1,2,3]triazolo[4,5-b]piridin-6-il]sulfonil)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([6-([trans-4-hidroxi-4-metilciclohexil]metil)amino]-5-nitropiridin-3-il)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 10 N-(4-([4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]sulfamoi]-2-nitrofenil)morfolina-4-carboxamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-(metoximetil)ciclohexil]metil)amino]-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 15 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-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida; y sus sales terapéuticamente aceptables, y sus metabolitos.
- 20 En otro aspecto, la presente invención provee compuestos de fórmula (IV)



y sus sales terapéuticamente aceptables, y sus metabolitos,

donde A^1 , B^1 , D^1 , E^1 , y Y^1 tienen los valores definidos para la Fórmula (I); R^{100} tiene los valores que se describen para los sustituyentes de R^{26} ; n es 0, 1, 2, o 3; R^{101} tiene los valores que se describen para los sustituyentes de R^{30} ; p es 0, 1, 2, 3, 4, 5, o 6; R^{104} tiene los valores que se describen para los sustituyentes de R^{38} ; s es 0, 1, 2, 3, 4, 5, o 6; R^{103} tiene los valores que se describen para los sustituyentes de R^{58} ; y r es 0, 1, 2, 3, o 4.

En una forma de realización de Fórmula (IV), n , p , r , y s son cada uno 0.

En una forma de 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, F, Cl, Br, o I. En otra forma de realización de Fórmula (IV), A^1 es $C(A^2)$; y A^2 es H.

En una forma de realización de Fórmula (IV), B^1 es R^1 , OR^1 , NHR^1 , $NHC(O)R^1$, F, Cl, Br, o I. En otra forma de realización de Fórmula (IV), A^1 es $C(A^2)$; A^2 es H; y B^1 es NHR^1 . En otra forma de realización de Fórmula (IV), A^1 es $C(A^2)$; A^2 es H; y B^1 es OR^1 . En otra forma de realización de Fórmula (IV), A^1 es $C(A^2)$; A^2 es H; y B^1 es Cl. En otra forma de realización de Fórmula (IV), A^1 es $C(A^2)$; A^2 es H; y B^1 es R^1 . En otra forma de realización de Fórmula (IV), A^1 es N; y B^1 es NHR^1 . En otra forma de realización de Fórmula (IV), A^1 es N; y B^1 es OR^1 . En otra forma de realización de Fórmula (IV), A^1 es N; y B^1 es Cl. En otra forma de realización de Fórmula (IV), A^1 es N; y B^1 es R^1 .

En una forma de realización de Fórmula (IV), D^1 es H o Cl. En otra forma de realización de Fórmula (IV), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 ; y D^1 es H. En otra forma de realización de Fórmula (IV), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 ; y D^1 es Cl. En otra forma de realización de Fórmula (IV), A^1 es $C(A^2)$; A^2 es H; B^1 es OR^1 ; y D^1 es H. En otra forma de realización de Fórmula (IV), A^1 es $C(A^2)$; A^2 es H; B^1 es Cl; y D^1 es H. En otra forma de realización de Fórmula (IV), A^1 es $C(A^2)$; A^2 es H; B^1 es R^1 ; y D^1 es H. En otra forma de realización de Fórmula (IV), A^1 es N; B^1 es NHR^1 ; y D^1 es H. En otra forma de realización de Fórmula (IV), A^1 es N; B^1 es NHR^1 ; y D^1 es Cl. En otra forma de realización de Fórmula (IV), A^1 es N; B^1 es OR^1 ; y D^1 es H. En otra forma de realización de Fórmula (IV), A^1 es N; B^1 es Cl; y D^1 es H. En otra forma de realización de Fórmula (IV), A^1 es N; B^1 es R^1 ; y D^1 es H.

En una forma de realización de Fórmula (IV), E^1 es H. En otra forma de realización de Fórmula (IV), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 ; D^1 es H; y E^1 es H. En otra forma de realización de Fórmula (IV), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 ; E^1 es H; y D^1 es Cl. En otra forma de realización de Fórmula (IV), A^1 es $C(A^2)$; A^2 es H; B^1 es OR^1 ; D^1 es H; y E^1 es H. En otra forma de realización de Fórmula (IV), A^1 es $C(A^2)$; A^2 es H; B^1 es Cl; D^1 es H; y E^1 es H. En otra forma de realización de Fórmula (IV), A^1 es $C(A^2)$; A^2 es H; B^1 es R^1 ; D^1 es H; y E^1 es H. En otra forma de realización de Fórmula (IV), A^1 es N; B^1 es NHR^1 ; D^1 es H; y E^1 es H. En otra forma de realización de Fórmula (IV), A^1 es N; B^1 es NHR^1 ; E^1 es H; y D^1 es Cl. En otra forma de realización de Fórmula (IV), A^1 es N; B^1 es OR^1 ; D^1 es H; y E^1 es H. En otra forma

de realización de Fórmula (IV), A¹ es N; B¹ es Cl; D¹ es H; y E¹ es H. En otra forma de realización de Fórmula (IV), A¹ es N; B¹ es R¹; D¹ es H; y E¹ es H.

- En una forma de realización de Fórmula (IV), Y¹ es H, CN, NO₂, F, Cl, Br, I, CF₃, R¹⁷, OR¹⁷, SR¹⁷, SO₂R¹⁷, o C(O)NH₂. En otra forma de realización de Fórmula (IV), Y¹ es H.
- 5 En otra forma de realización de Fórmula (IV), Y¹ es CN. En otra forma de realización de Fórmula (IV), Y¹ es F, Cl, Br, o I. En otra forma de realización de Fórmula (IV), Y¹ es CF₃. En otra forma de realización de Fórmula (IV), Y¹ es SR¹⁷. En otra forma de realización de Fórmula (IV), Y¹ es OR¹⁷. En otra forma de realización de Fórmula (IV), Y¹ es NO₂. En otra forma de realización de Fórmula (IV), Y¹ es SO₂R¹⁷; donde R¹⁷ es como se ha definido. En otra forma
- 10 de realización de Fórmula (IV), Y¹ es SO₂R¹⁷; donde R¹⁷ es alquilo. En otra forma de realización de Fórmula (IV), Y¹ es R¹⁷; donde R¹⁷ es alquínilo. En otra forma de realización de Fórmula (IV), A¹ es C(A²); A² es H; B¹ es NHR¹; D¹ es H; E¹ es H; y Y¹ es NO₂ o SO₂R¹⁷; donde R¹⁷ es alquilo o alquínilo. En otra forma de realización de Fórmula (IV), A¹ es C(A²); A² es H; B¹ es NHR¹; D¹ es H; E¹ es H; y Y¹ es NO₂. En otra forma de realización de Fórmula
- 15 (IV), A¹ es C(A²); A² es H; B¹ es NHR¹; D¹ es H; E¹ es H; y Y¹ es SO₂R¹⁷; donde R¹⁷ es alquilo sustituido con tres F. En otra forma de realización de Fórmula (IV), A¹ es N; B¹ es NHR¹; D¹ es H; E¹ es H; y Y¹ es NO₂ o SO₂R¹⁷; donde R¹⁷ es alquilo o alquínilo. En otra forma de realización de Fórmula (IV), A¹ es N; B¹ es NHR¹; D¹ es H; E¹ es H; y Y¹ es NO₂. En otra forma de realización de Fórmula (IV), A¹ es N; B¹ es NHR¹; D¹ es H; E¹ es H; y Y¹ es SO₂R¹⁷; donde R¹⁷ es alquilo sustituido con tres F.
- 20

- En una forma de realización de Fórmula (IV), Y¹ y B¹, junto con los átomos a los cuales están unidos, son benceno. En otra forma de realización de Fórmula (IV), Y¹ y B¹, junto con los átomos a los cuales están unidos, son heteroareno. En otra forma de realización de Fórmula (IV), A¹ es C(A²); A², G¹, E¹, y D¹ se seleccionan en forma
- 25 independiente entre H; y Y¹ y B¹, junto con los átomos a los cuales están unidos, son benceno. En otra forma de realización de Fórmula (IV), A¹ es C(A²); A², G¹, E¹, y D¹ se seleccionan en forma independiente entre H; y Y¹ y B¹, junto con los átomos a los cuales están unidos, son heteroareno.

- En una forma de realización de Fórmula (IV), R¹ es R⁴ o R⁵. En una forma de realización de Fórmula (IV), R¹ es R⁴. En una forma de realización de Fórmula (IV), R¹ es R⁵. En una forma de realización de Fórmula (IV), R¹ es R⁴; y R⁴ es cicloalquilo, cicloalquénilo, heterocicloalquilo o heterocicloalquénilo. En una forma de realización de Fórmula (IV), R¹ es R⁴; y R⁴ es cicloalquilo o heterocicloalquilo. En una forma de realización de Fórmula (IV), R¹ es R⁴; y R⁴ es cicloalquilo. En una forma de realización de Fórmula (IV), R¹ es R⁴; y R⁴ es
- 30 heterocicloalquilo.
- 35

En una forma de realización de Fórmula (IV), R^1 es R^4 ; y R^4 es cicloalquilo; donde R^4 no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (IV), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo está sustituido como se ha definido. En otra forma de realización de Fórmula (IV), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo está sustituido con R^{57} o $N(R^{57})_2$. En otra forma de realización de Fórmula (IV), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con R^{57} ; y R^{57} es R^{60} . En otra forma de realización de Fórmula (IV), R^1 es R^4 ; R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con R^{57} ; R^{57} es R^{60} ; y R^{60} es heterocicloalquilo. En otra forma de realización de Fórmula (IV), R^1 es R^4 ; R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con R^{57} ; R^{57} es R^{60} ; R^{60} es heterocicloalquilo; donde el anillo heterocicloalquilo es morfolinilo. En otra forma de realización de Fórmula (IV), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo está sustituido con $N(R^{57})_2$. En otra forma de realización de Fórmula (IV), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con $N(R^{57})_2$. En otra forma de realización de Fórmula (IV), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con $N(R^{57})_2$; R^{57} es R^{61} ; y R^{61} es alquilo que no está sustituido o está sustituido con R^{62} . En otra forma de realización de Fórmula (IV), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con R^{57} ; R^{57} es R^{61} ; y R^{61} es alquilo que no está sustituido o está sustituido con R^{62} , R^{62} es R^{65} ; y R^{65} es cicloalquilo. En otra forma de realización de Fórmula (IV), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con R^{57} ; R^{57} es R^{61} ; y R^{61} es alquilo el cual está sustituido con R^{62} ; R^{62} es R^{65} ; y R^{65} es ciclopropilo.

En una forma de realización de Fórmula (IV), R^1 es R^4 ; y R^4 es heterocicloalquilo; donde R^4 no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (IV), R^1 es R^4 ; y R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo está sustituido como se ha definido. En otra forma de realización de Fórmula (IV), R^1 es R^4 ; y R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo está sustituido con R^{57} . En otra forma de realización de Fórmula (IV), R^1 es R^4 ; y R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo es piperidinilo o piperizinilo; y donde el anillo heterocicloalquilo está sustituido con R^{57} ; y R^{57} es R^{60} o R^{61} . En otra forma de realización de Fórmula (IV), R^1 es R^4 ; R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo es piperidinilo o piperizinilo; y donde el anillo piperidinilo o piperizinilo está sustituido con R^{57} ; R^{57} es R^{60} o R^{61} ; R^{60} es heterocicloalquilo; y R^{61} es alquilo. En otra forma de realización de Fórmula (IV), R^1 es R^4 ; R^4 es heterocicloalquilo; donde el anillo

heterocicloalquilo es piperdinilo o piperizinilo; y donde el anillo piperidinilo o piperizinilo está sustituido con R^{57} ; R^{57} es R^{60} ; R^{60} es heterocicloalquilo; donde el heterocicloalquilo es tetrahidropiranilo. En otra forma de realización de Fórmula (IV), R^1 es R^4 ; R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo es piperdinilo o piperizinilo; y donde el anillo piperidinilo o piperizinilo está sustituido con R^{57} ; R^{57} es R^{61} ; R^{61} es alquilo; y el alquilo es metilo. En otra forma de realización de Fórmula (IV), R^1 es R^4 ; R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo es piperdinilo o piperizinilo; y donde el anillo piperidinilo o piperizinilo está sustituido con $C(O)OR^{57}$; R^{57} es R^{61} ; R^{61} es alquilo; y el alquilo es metilo.

En una forma de realización de Fórmula (IV), R^1 es R^5 ; y R^5 es alquilo que no está sustituido o está sustituido. En una forma de realización de Fórmula (IV), R^1 es R^5 ; y R^5 es alquilo que no está sustituido o está sustituido con R^7 , OR^7 , OH , CN , o F . En otra forma de realización de Fórmula (IV), R^1 es R^5 ; y R^5 es alquilo el cual está sustituido con R^7 , OR^7 , NHR^7 , o $N(R^7)_2$.

En una forma de realización de Fórmula (IV), R^7 es R^8 , R^9 , R^{10} o R^{11} que no están sustituidos o están sustituidos como se ha definido. En otra forma de realización de Fórmula (IV), R^7 es R^8 que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (IV), R^7 es R^9 que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (IV), R^7 es R^{10} que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (IV), R^7 es R^{11} que no está sustituido o está sustituido como se ha definido.

En una forma de realización de Fórmula (IV), R^8 es fenilo que no está sustituido o está sustituido como se ha definido.

En una forma de realización de Fórmula (IV), R^9 es heteroarilo que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (IV), R^9 es furanilo; que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (IV), R^9 es furanilo; que no está sustituido.

En una forma de realización de Fórmula (IV), R^{10} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, heterocicloalquilo que no están sustituidos o están sustituidos como se ha definido. En otra forma de realización de Fórmula (IV), R^{10} es heterocicloalquilo que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (IV), R^{10} es tetrahidrofuranilo, tetrahidropiranilo, morfolinilo, dioxanilo, oxetanilo, piperdinilo, o pirrolidinilo, que no están sustituidos o están sustituidos como se ha definido. En otra forma de realización de Fórmula (IV), R^{10} es tetrahidropiranilo; que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (IV), R^{10} es morfolinilo; que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (IV), R^{10} es cicloalquilo que no está sustituido o está

sustituido como se ha definido. En otra forma de realización de Fórmula (IV), R^{10} es cicloalquilo que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (IV), R^{10} es ciclohexilo, ciclopropilo, ciclobutilo, o biciclo[2,2,1]heptanilo, que no está sustituido o está sustituido como se ha definido. En otra
 5 forma de realización de Fórmula (IV), R^{10} es heterocicloalquilo que está fusionado con R^{10A} ; y R^{10A} es heteroareno. En otra forma de realización de Fórmula (IV), R^{10} es 5,6,7,8-tetrahidroimidazo[1,2-a]piridinilo.

En una forma de realización de Fórmula (IV), R^{11} es alquilo, alquenilo o alquinilo que no están sustituidos o están sustituidos como se ha definido. En otra forma de realización de
 10 Fórmula (IV), R^{11} es alquilo. En otra forma de realización de Fórmula (IV), R^{11} es metilo; que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (IV), R^{11} es alquilo; que está sustituido como se ha definido. En otra forma de realización de Fórmula (IV), R^{11} es alquilo; que está sustituido con R^{12} , OR^{12} , o CF_3 . En otra forma de realización de Fórmula (IV), R^{11} es alquilo; que está sustituido con OR^{12} ; R^{12} es R^{16} ;
 15 y R^{16} es alquilo. En otra forma de realización de Fórmula (IV), R^{11} es alquilo; que está sustituido con CF_3 . En otra forma de realización de Fórmula (IV), R^{11} es alquilo; que está sustituido con R^{12} , R^{12} es R^{14} , y R^{14} es heteroarilo.

En una forma de realización de Fórmula (IV),
 n, p, r, y s son cada uno 0;
 20 A^1 es N o $C(A^2)$;
 A^2 es H, F, Br, I, o Cl;
 B^1 es R^1 , OR^1 , NHR^1 , $NHC(O)R^1$, F, Br, I o Cl;
 D^1 es H, F, Br, I, o Cl;
 E^1 es H; y
 25 Y^1 es H, CN, NO_2 , F, Cl, Br, I, CF_3 , R^{17} , OR^{17} , SR^{17} , SO_2R^{17} , o $C(O)NH_2$; o
 Y^1 y B^1 , junto con los átomos a los cuales están unidos, son benceno, heteroareno, o heterocicloalqueno; y

A^2 , D^1 , y E^1 se seleccionan en forma independiente entre H;
 R^1 es R^4 o R^5 ;
 30 R^4 es cicloalquilo, o heterocicloalquilo;
 R^5 es alquilo, 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^7 , OR^7 , NHR^7 , $N(R^7)_2$, CN, OH, F, Cl, Br o I;
 R^7 es R^8 , R^9 , R^{10} , o R^{11} ;
 35 R^8 es fenilo;
 R^9 es heteroarilo;

R^{10} es cicloalquilo, cicloalquenilo, o heterocicloalquilo; cada uno de los cuales no está fusionado o está fusionado con R^{10A} , R^{10A} es heteroareno;

R^{11} es alquilo cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre R^{12} , OR^{12} or CF_3 ;

5 R^{12} es R^{14} o R^{16} ;

R^{14} es heteroarilo;

R^{16} es alquilo;

R^{17} es R^{21} ;

10 R^{21} es alquilo, 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^{22} , F, Cl, Br o I;

R^{22} es R^{25} ;

R^{25} es heterocicloalquilo;

15 donde las unidades cíclicas representadas por Y^1 y B^1 juntos, R^4 , R^8 , R^{10} , y R^{25} , no están sustituidas, no están adicionalmente sustituidas, están sustituidas o adicionalmente sustituidas en forma independiente con uno o dos o tres o cuatro o cinco sustituyentes seleccionados en forma independiente entre R^{57A} , R^{57} , OR^{57} , SO_2R^{57} , $C(O)R^{57}$, $CO(O)R^{57}$, $C(O)N(R^{57})_2$, NH_2 , NHR^{57} , $N(R^{57})_2$, $NHC(O)R^{57}$, $NHS(O)_2R^{57}$, OH, CN, (O), F, Cl, Br o I;

20 R^{57A} es espiroalquilo, o espiroheteroalquilo;

R^{57} es R^{58} , R^{60} o R^{61} ;

R^{58} es fenilo;

R^{60} es cicloalquilo, o heterocicloalquilo;

25 R^{61} es alquilo que no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre R^{62} , OR^{62} , $N(R^{62})_2$, $C(O)OH$, CN, F, Cl, Br o I;

R^{62} es R^{65} , o R^{66} ;

R^{65} es cicloalquilo, o heterocicloalquilo;

R^{66} es alquilo que no está sustituido o está sustituido con OR^{67} ;

30 R^{67} es alquilo;

donde las unidades cíclicas representadas por R^{57A} , R^{58} , y R^{60} no están sustituidas o están sustituidas con uno o dos o tres o cuatro sustituyentes seleccionados en forma independiente entre R^{68} , F, Cl, Br o I;

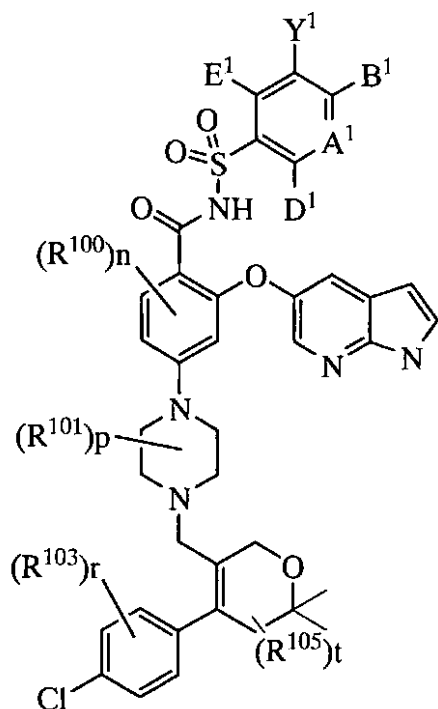
R^{68} es R^{71} o R^{72} ;

35 R^{71} es heterocicloalquilo; y

R^{72} es alquilo, que no está sustituido o está sustituido con uno o dos F.

- Aún otra forma de realización se refiere a compuestos de fórmula (IV), 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-(1H-pirrolo[2,3-b]piridin-5-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-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5 y sus sales terapéuticamente aceptables, y sus metabolitos.

En otro aspecto, la presente invención provee compuestos de fórmula (V)



- (V);
- 10 y sus sales terapéuticamente aceptables, y sus metabolitos,
- donde A¹, B¹, D¹, E¹, y Y¹ tienen los valores definidos para la Fórmula (I); R¹⁰⁰ tiene los valores que se describen para los sustituyentes de R²⁶; n es 0, 1, 2, o 3; R¹⁰¹ tiene los valores que se describen para los sustituyentes de R³⁰; p es 0, 1, 2, 3, 4, 5, o 6; R¹⁰⁵ tiene los valores que se describen para los sustituyentes de R⁴⁰; t es 0, 1, 2, 3, o 4; R¹⁰³ tiene los valores que se describen para los sustituyentes de R⁵⁸; y r es 0, 1, 2, 3, o 4.
- 15

En una forma de realización de Fórmula (V), n, p, r, y t son cada uno 0.

En una forma de realización de Fórmula (V), A¹ es N. En otra forma de realización de Fórmula (V), A¹ es C(A²). En otra forma de realización de Fórmula (V), A¹ es C(A²); y A² es H, F, Cl, Br, o I. En otra forma de realización de Fórmula (V), A¹ es C(A²); y A² es H.

- 20 En una forma de realización de Fórmula (V), B¹ es R¹, OR¹, NHR¹, NHC(O)R¹, F, Cl, Br, o I. En otra forma de realización de Fórmula (V), A¹ es C(A²); A² es H; y B¹ es NHR¹. En otra forma de realización de Fórmula (V), A¹ es C(A²); A² es H; y B¹ es OR¹. En otra forma de realización de Fórmula (V), A¹ es C(A²); A² es H; y B¹ es Cl. En otra forma de realización de

Fórmula (V), A^1 es $C(A^2)$; A^2 es H; y B^1 es R^1 . En otra forma de realización de Fórmula (V), A^1 es N; y B^1 es NHR^1 . En otra forma de realización de Fórmula (V), A^1 es N; y B^1 es OR^1 . En otra forma de realización de Fórmula (V), A^1 es N; y B^1 es Cl. En otra forma de realización de Fórmula (V), A^1 es N; y B^1 es R^1 .

5 En una forma de realización de Fórmula (V), D^1 es H o Cl. En otra forma de realización de Fórmula (V), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 ; y D^1 es H. En otra forma de realización de Fórmula (V), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 ; y D^1 es Cl. En otra forma de realización de Fórmula (V), A^1 es $C(A^2)$; A^2 es H; B^1 es OR^1 ; y D^1 es H. En otra forma de realización de Fórmula (V), A^1 es $C(A^2)$; A^2 es H; B^1 es Cl; y D^1 es H. En otra forma de realización de Fórmula (V), A^1 es $C(A^2)$; A^2 es H; B^1 es R^1 ; y D^1 es H. En otra forma de realización de Fórmula (V), A^1 es N; B^1 es NHR^1 ; y D^1 es H. En otra forma de realización de Fórmula (V), A^1 es N; B^1 es NHR^1 ; y D^1 es Cl. En otra forma de realización de Fórmula (V), A^1 es N; B^1 es OR^1 ; y D^1 es H. En otra forma de realización de Fórmula (V), A^1 es N; B^1 es Cl; y D^1 es H. En otra forma de realización de Fórmula (V), A^1 es N; B^1 es R^1 ; y D^1 es H.

15 En una forma de realización de Fórmula (V), E^1 es H. En otra forma de realización de Fórmula (V), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 ; D^1 es H; y E^1 es H. En otra forma de realización de Fórmula (V), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 ; E^1 es H; y D^1 es Cl. En otra forma de realización de Fórmula (V), A^1 es $C(A^2)$; A^2 es H; B^1 es OR^1 ; D^1 es H; y E^1 es H. En otra forma de realización de Fórmula (V), A^1 es $C(A^2)$; A^2 es H; B^1 es Cl; D^1 es H; y E^1 es H. En otra forma de realización de Fórmula (V), A^1 es $C(A^2)$; A^2 es H; B^1 es R^1 ; D^1 es H; y E^1 es H. En otra forma de realización de Fórmula (V), A^1 es N; B^1 es NHR^1 ; D^1 es H; y E^1 es H. En otra forma de realización de Fórmula (V), A^1 es N; B^1 es NHR^1 ; E^1 es H; y D^1 es Cl. En otra forma de realización de Fórmula (V), A^1 es N; B^1 es OR^1 ; D^1 es H; y E^1 es H. En otra forma de realización de Fórmula (V), A^1 es N; B^1 es Cl; D^1 es H; y E^1 es H. En otra forma de realización de Fórmula (V), A^1 es N; B^1 es R^1 ; D^1 es H; y E^1 es H.

25 En una forma de realización de Fórmula (V), Y^1 es H, CN, NO_2 , F, Cl, Br, I, CF_3 , R^{17} , OR^{17} , SR^{17} , SO_2R^{17} , o $C(O)NH_2$. En otra forma de realización de Fórmula (V), Y^1 es H. En otra forma de realización de Fórmula (V), Y^1 es CN. En otra forma de realización de Fórmula (V), Y^1 es F, Cl, Br, o I. En otra forma de realización de Fórmula (V), Y^1 es CF_3 . En otra forma de realización de Fórmula (V), Y^1 es SR^{17} . En otra forma de realización de Fórmula (V), Y^1 es OR^{17} . En otra forma de realización de Fórmula (V), Y^1 es NO_2 . En otra forma de realización de Fórmula (V), Y^1 es SO_2R^{17} ; donde R^{17} es como se ha definido. En otra forma de realización de Fórmula (V), Y^1 es SO_2R^{17} ; donde R^{17} es alquilo. En otra forma de realización de Fórmula (V), Y^1 es R^{17} ; donde R^{17} es alquínilo. En otra forma de realización de Fórmula (V), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 ; D^1 es H; E^1 es H; y Y^1 es NO_2 o SO_2R^{17} ; donde R^{17} es alquilo o alquínilo. En otra forma de realización de Fórmula (V), A^1 es $C(A^2)$; A^2 es H; B^1 es

NHR¹; D¹ es H; E¹ es H; y Y¹ es NO₂. En otra forma de realización de Fórmula (V), A¹ es C(A²); A² es H; B¹ es NHR¹; D¹ es H; E¹ es H; y Y¹ es SO₂R¹⁷; donde R¹⁷ es alquilo sustituido con tres F. En otra forma de realización de Fórmula (V), A¹ es N; B¹ es NHR¹; D¹ es H; E¹ es H; y Y¹ es NO₂ o SO₂R¹⁷; donde R¹⁷ es alquilo o alquínilo. En otra forma de realización de
 5 Fórmula (V), A¹ es N; B¹ es NHR¹; D¹ es H; E¹ es H; y Y¹ es NO₂. En otra forma de realización de Fórmula (V), A¹ es N; B¹ es NHR¹; D¹ es H; E¹ es H; y Y¹ es SO₂R¹⁷; donde R¹⁷ es alquilo sustituido con tres F.

En una forma de realización de Fórmula (V), Y¹ y B¹, junto con los átomos a los cuales están unidos, son benceno. En otra forma de realización de Fórmula (V), Y¹ y B¹,
 10 junto con los átomos a los cuales están unidos, son heteroareno. En otra forma de realización de Fórmula (V), A¹ es C(A²); A², G¹, E¹, y D¹ se seleccionan en forma independiente entre H; y Y¹ y B¹, junto con los átomos a los cuales están unidos, son benceno. En otra forma de realización de Fórmula (V), A¹ es C(A²); A², G¹, E¹, y D¹ se seleccionan en forma independiente entre H; y Y¹ y B¹, junto con los átomos a los cuales
 15 están unidos, son heteroareno.

En una forma de realización de Fórmula (V), R¹ es R⁴ o R⁵. En una forma de realización de Fórmula (V), R¹ es R⁴. En una forma de realización de Fórmula (V), R¹ es R⁵. En una forma de realización de Fórmula (V), R¹ es R⁴; y R⁴ es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo. En una forma de realización de Fórmula (V), R¹ es
 20 R⁴; y R⁴ es cicloalquilo o heterocicloalquilo. En una forma de realización de Fórmula (V), R¹ es R⁴; y R⁴ es cicloalquilo. En una forma de realización de Fórmula (V), R¹ es R⁴; y R⁴ es heterocicloalquilo.

En una forma de realización de Fórmula (V), R¹ es R⁴; y R⁴ es cicloalquilo; donde R⁴ no está sustituido o está sustituido como se ha definido. En otra forma de realización de
 25 Fórmula (V), R¹ es R⁴; y R⁴ es cicloalquilo; donde el anillo cicloalquilo está sustituido como se ha definido. En otra forma de realización de Fórmula (V), R¹ es R⁴; y R⁴ es cicloalquilo; donde el anillo cicloalquilo está sustituido con R⁵⁷ o N(R⁵⁷)₂. En otra forma de realización de Fórmula (V), R¹ es R⁴; y R⁴ es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con R⁵⁷; y R⁵⁷ es R⁶⁰. En otra forma de realización de
 30 Fórmula (V), R¹ es R⁴; R⁴ es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con R⁵⁷; R⁵⁷ es R⁶⁰; y R⁶⁰ es heterocicloalquilo. En otra forma de realización de Fórmula (V), R¹ es R⁴; R⁴ es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con R⁵⁷; R⁵⁷ es R⁶⁰; R⁶⁰ es heterocicloalquilo; donde el anillo heterocicloalquilo es morfolinilo. En otra forma de
 35 realización de Fórmula (V), R¹ es R⁴; y R⁴ es cicloalquilo; donde el anillo cicloalquilo está sustituido con N(R⁵⁷)₂. En otra forma de realización de Fórmula (V), R¹ es R⁴; y R⁴ es

cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con $N(R^{57})_2$. En otra forma de realización de Fórmula (V), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con $N(R^{57})_2$; R^{57} es R^{61} ; y R^{61} es alquilo que no está sustituido o está sustituido con R^{62} . En otra forma de realización de Fórmula (V), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con R^{57} ; R^{57} es R^{61} ; y R^{61} es alquilo que no está sustituido o está sustituido con R^{62} ; R^{62} es R^{65} ; y R^{65} es cicloalquilo. En otra forma de realización de Fórmula (V), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con R^{57} ; R^{57} es R^{61} ; y R^{61} es alquilo el cual está sustituido con R^{62} ; R^{62} es R^{65} ; y R^{65} es ciclopropilo

En una forma de realización de Fórmula (V), R^1 es R^4 ; y R^4 es heterocicloalquilo; donde R^4 no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (V), R^1 es R^4 ; y R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo está sustituido como se ha definido. En otra forma de realización de Fórmula (V), R^1 es R^4 ; y R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo está sustituido con R^{57} . En otra forma de realización de Fórmula (V), R^1 es R^4 ; y R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo es piperidinilo o piperizinilo; y donde el anillo heterocicloalquilo está sustituido con R^{57} ; y R^{57} es R^{60} o R^{61} . En otra forma de realización de Fórmula (V), R^1 es R^4 ; R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo es piperidinilo o piperizinilo; y donde el anillo piperidinilo o piperizinilo está sustituido con R^{57} ; R^{57} es R^{60} o R^{61} ; R^{60} es heterocicloalquilo; y R^{61} es alquilo. En otra forma de realización de Fórmula (V), R^1 es R^4 ; R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo es piperidinilo o piperizinilo; y donde el anillo piperidinilo o piperizinilo está sustituido con R^{57} ; R^{57} es R^{60} ; R^{60} es heterocicloalquilo; donde el heterocicloalquilo es tetrahidropiranilo. En otra forma de realización de Fórmula (V), R^1 es R^4 ; R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo es piperidinilo o piperizinilo; y donde el anillo piperidinilo o piperizinilo está sustituido con R^{57} ; R^{57} es R^{61} ; R^{61} es alquilo; y el alquilo es metilo. En otra forma de realización de Fórmula (V), R^1 es R^4 ; R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo es piperidinilo o piperizinilo; y donde el anillo piperidinilo o piperizinilo está sustituido con $C(O)OR^{57}$; R^{57} es R^{61} ; R^{61} es alquilo; y el alquilo es metilo.

En una forma de realización de Fórmula (V), R^1 es R^5 ; y R^5 es alquilo que no está sustituido o está sustituido. En una forma de realización de Fórmula (V), R^1 es R^5 ; y R^5 es alquilo que no está sustituido o está sustituido con R^7 , OR^7 , OH , CN , o F . En otra forma de realización de Fórmula (V), R^1 es R^5 ; y R^5 es alquilo el cual está sustituido con R^7 , OR^7 , NHR^7 , o $N(R^7)_2$.

En una forma de realización de Fórmula (V), R^7 es R^8 , R^9 , R^{10} o R^{11} que no están sustituidos o están sustituidos como se ha definido. En otra forma de realización de Fórmula (V), R^7 es R^8 que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (V), R^7 es R^9 que no está sustituido o está sustituido como se ha
5 definido. En otra forma de realización de Fórmula (V), R^7 es R^{10} que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (V), R^7 es R^{11} que no está sustituido o está sustituido como se ha definido.

En una forma de realización de Fórmula (V), R^8 es fenilo que no está sustituido o está sustituido como se ha definido.

10 En una forma de realización de Fórmula (V), R^9 es heteroarilo que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (V), R^9 es furanilo; que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (V), R^9 es furanilo; que no está sustituido.

En una forma de realización de Fórmula (V), R^{10} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, heterocicloalquilo que no están sustituidos o están sustituidos como se ha definido. En otra forma de realización de Fórmula (V), R^{10} es heterocicloalquilo que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (V), R^{10} es tetrahidrofuranilo, tetrahidropiranilo, morfolinilo, dioxanilo, oxetanilo, piperdinilo, o pirrolidinilo, que no están sustituidos o están sustituidos
15 como se ha definido. En otra forma de realización de Fórmula (V), R^{10} es tetrahidropiranilo; que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (V), R^{10} es morfolinilo; que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (V), R^{10} es cicloalquilo que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (V), R^{10} es cicloalquilo que no está sustituido o está sustituido como se ha definido. En otra forma de
25 realización de Fórmula (V), R^{10} es ciclohexilo, ciclopropilo, ciclobutilo, o biciclo[2,2,1]heptanilo; que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (V), R^{10} es heterocicloalquilo que está fusionado con R^{10A} ; y R^{10A} es heteroareno. En otra forma de realización de Fórmula (V), R^{10} es 5,6,7,8-
30 tetrahidroimidazo[1,2-a]piridinilo.

En una forma de realización de Fórmula (V), R^{11} es alquilo, alquenilo o alquinilo que no están sustituidos o están sustituidos como se ha definido. En otra forma de realización de Fórmula (V), R^{11} es alquilo. En otra forma de realización de Fórmula (V), R^{11} es metilo; que no está sustituido o está sustituido como se ha definido. En otra forma de realización de
35 Fórmula (V), R^{11} es alquilo; que está sustituido como se ha definido. En otra forma de realización de Fórmula (V), R^{11} es alquilo; que está sustituido con R^{12} , OR^{12} , o CF_3 . En otra

forma de realización de Fórmula (V), R^{11} es alquilo; que está sustituido con OR^{12} ; R^{12} es R^{16} ; y R^{16} es alquilo. En otra forma de realización de Fórmula (V), R^{11} es alquilo; que está sustituido con CF_3 . En otra forma de realización de Fórmula (V), R^{11} es alquilo; que está sustituido con R^{12} ; R^{12} es R^{14} ; y R^{14} es heteroarilo.

- 5 En una forma de realización de Fórmula (V),
 n , p , r , y t son cada uno 0;
 A^1 es N o $C(A^2)$;
 A^2 es H, F, Br, I, o Cl;
 B^1 es R^1 , OR^1 , NHR^1 , $NHC(O)R^1$, F, Br, I o Cl;
10 D^1 es H, F, Br, I, o Cl;
 E^1 es H; y
 Y^1 es H, CN, NO_2 , F, Cl, Br, I, CF_3 , R^{17} , OR^{17} , SR^{17} , SO_2R^{17} , o $C(O)NH_2$; o
 Y^1 y B^1 , junto con los átomos a los cuales están unidos, son benceno, heteroareno, o heterocicloalqueno; y
- 15 A^2 , D^1 , y E^1 se seleccionan en forma independiente entre H;
 R^1 es R^4 o R^5 ;
 R^4 es cicloalquilo, o heterocicloalquilo;
 R^5 es alquilo, 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^7 , OR^7 , NHR^7 , $N(R^7)_2$, CN, OH, F, Cl, Br o I;
20 R^7 es R^8 , R^9 , R^{10} , o R^{11} ;
 R^8 es fenilo;
 R^9 es heteroarilo;
 R^{10} es cicloalquilo, cicloalquenilo, o heterocicloalquilo; cada uno de los cuales no está fusionado o está fusionado con R^{10A} , R^{10A} es heteroareno;
25 R^{11} es alquilo cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre R^{12} , OR^{12} or CF_3 ;
 R^{12} es R^{14} o R^{16} ;
 R^{14} es heteroarilo;
30 R^{16} es alquilo;
 R^{17} es R^{21} ;
 R^{21} es alquilo, 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^{22} , F, Cl, Br o I;
- 35 R^{22} es R^{25} ;
 R^{25} es heterocicloalquilo;

donde las unidades cíclicas representadas por Y^1 y B^1 juntos, R^4 , R^8 , R^{10} , y R^{25} , no están sustituidas, no están adicionalmente sustituidas, están sustituidas o adicionalmente sustituidas en forma independiente con uno o dos o tres o cuatro o cinco sustituyentes seleccionados en forma independiente entre R^{57A} , R^{57} , OR^{57} , SO_2R^{57} , $C(O)R^{57}$, $CO(O)R^{57}$, $C(O)N(R^{57})_2$, NH_2 , NHR^{57} , $N(R^{57})_2$, $NHC(O)R^{57}$, $NHS(O)_2R^{57}$, OH , CN , (O) , F , Cl , Br o I ;

R^{57A} es espiroalquilo, o espiroheteroalquilo;

R^{57} es R^{58} , R^{60} o R^{61} ;

R^{58} es fenilo;

10 R^{60} es cicloalquilo, o heterocicloalquilo;

R^{61} es alquilo que no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre R^{62} , OR^{62} , $N(R^{62})_2$, $C(O)OH$, CN , F , Cl , Br o I ;

R^{62} es R^{65} , o R^{66} ;

15 R^{65} es cicloalquilo, o heterocicloalquilo;

R^{66} es alquilo que no está sustituido o está sustituido con OR^{67} ;

R^{67} es alquilo;

donde las unidades cíclicas representadas por R^{57A} , R^{58} , y R^{60} no están sustituidas o están sustituidas con uno o dos o tres o cuatro sustituyentes seleccionados en forma independiente entre R^{68} , F , Cl , Br o I ;

20 R^{68} es R^{71} o R^{72} ;

R^{71} es heterocicloalquilo; y

R^{72} es alquilo, que no está sustituido o está sustituido con uno o dos F .

Aún otra forma de realización se refiere a un compuesto de fórmula (V), which es

25 4-(4-([4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil)piperazin-1-il)-N-([3-nitro-4-([tetrahidro-2H-piran-4-ilmetil]amino)fenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

4-(4-([4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil)piperazin-1-il)-N-([4-([1,4-dioxan-2-ilmetil]amino)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

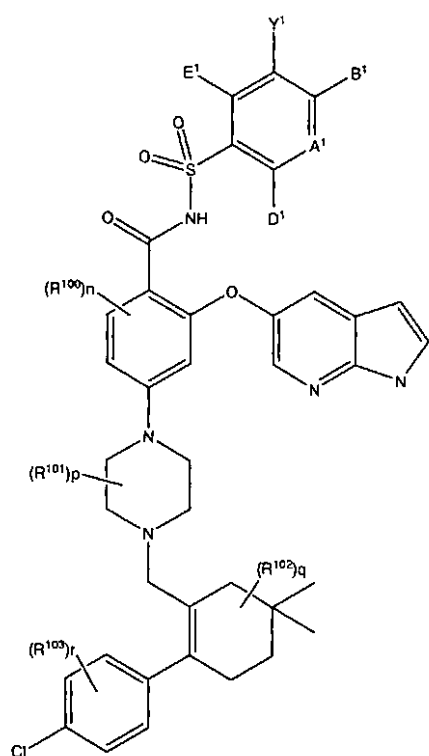
30 4-(4-([4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil)piperazin-1-il)-N-([4-(1,4-dioxan-2-ilmetoxi)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

Trans-4-(4-([4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil)piperazin-1-il)-N-([4-([4-morfolin-4-ilciclohexil]amino)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

35 4-(4-([4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil)piperazin-1-il)-N-([5-ciano-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-N-{[5-cloro-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)-N-{[4-{(tetrahidro-2H-piran-4-ilmetil)amino]-3-(trifluorometil)fenil}sulfonil}benzamida;
- 4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)-N-{[4-{(tetrahidro-2H-piran-4-ilmetil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil}benzamida;
- 4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-N-{[4-{[4-morfolin-4-ilciclohexil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-N-{[4-{[1-metilpiperidin-4-il)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- Cis-4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-N-{[4-{[4-morfolin-4-ilciclohexil)amino]-3-nitrofenil}sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-N-{[4-{[4-metilpiperazin-1-il)amino]-3-nitrofenil}sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-N-{[4-{[4-metoxiciclohexil)metil]amino]-3-nitrofenil}sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- y sus sales terapéuticamente aceptables, y sus metabolitos.

En otro aspecto, la presente invención provee compuestos de fórmula (VI)



(VI);

y sus sales terapéuticamente aceptables, y sus metabolitos,

- 5 donde A¹, B¹, D¹, E¹, y Y¹ tienen los valores definidos para la Fórmula (I); R¹⁰⁰ tiene los valores que se describen para los sustituyentes de R²⁶; n es 0, 1, 2, o 3; R¹⁰¹ tiene los valores que se describen para los sustituyentes de R³⁰; p es 0, 1, 2, 3, 4, 5, o 6; R¹⁰² tiene los valores que se describen para los sustituyentes de R⁴⁰; q es 0, 1, 2, 3, 4, 5, o 6; R¹⁰³ tiene los valores que se describen para los sustituyentes de R⁵⁸; y r es 0, 1, 2, 3, o 4.

En una forma de realización de Fórmula (VI), n, p, r, y q son cada uno 0.

- 10 En una forma de realización de Fórmula (VI), A¹ es N. En otra forma de realización de Fórmula (VI), A¹ es C(A²). En otra forma de realización de Fórmula (VI), A¹ es C(A²); y A² es H, F, Cl, Br, o I. En otra forma de realización de Fórmula (VI), A¹ es C(A²); y A² es H.

- En una forma de realización de Fórmula (VI), B¹ es R¹, OR¹, NHR¹, NHC(O)R¹, F, Cl, Br, o I. En otra forma de realización de Fórmula (VI), A¹ es C(A²); A² es H; y B¹ es NHR¹. En
 15 otra forma de realización de Fórmula (VI), A¹ es C(A²); A² es H; y B¹ es OR¹. En otra forma de realización de Fórmula (VI), A¹ es C(A²); A² es H; y B¹ es Cl. En otra forma de realización de Fórmula (VI), A¹ es C(A²); A² es H; y B¹ es R¹. En otra forma de realización de Fórmula (VI), A¹ es N; y B¹ es NHR¹. En otra forma de realización de Fórmula (VI), A¹ es N; y B¹ es OR¹. En otra forma de realización de Fórmula (VI), A¹ es N; y B¹ es Cl. En otra forma de
 20 realización de Fórmula (VI), A¹ es N; y B¹ es R¹.

En una forma de realización de Fórmula (VI), D¹ es H o Cl. En otra forma de realización de Fórmula (VI), A¹ es C(A²); A² es H; B¹ es NHR¹; y D¹ es H. En otra forma de

- realización de Fórmula (VI), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 ; y D^1 es Cl. En otra forma de realización de Fórmula (VI), A^1 es $C(A^2)$; A^2 es H; B^1 es OR^1 ; y D^1 es H. En otra forma de realización de Fórmula (VI), A^1 es $C(A^2)$; A^2 es H; B^1 es Cl; y D^1 es H. En otra forma de realización de Fórmula (VI), A^1 es $C(A^2)$; A^2 es H; B^1 es R^1 ; y D^1 es H. En otra forma de
- 5 realización de Fórmula (VI), A^1 es N; B^1 es NHR^1 ; y D^1 es H. En otra forma de realización de Fórmula (VI), A^1 es N; B^1 es NHR^1 ; y D^1 es Cl. En otra forma de realización de Fórmula (VI), A^1 es N; B^1 es OR^1 ; y D^1 es H. En otra forma de realización de Fórmula (VI), A^1 es N; B^1 es Cl; y D^1 es H. En otra forma de realización de Fórmula (VI), A^1 es N; B^1 es R^1 ; y D^1 es H.
- 10 En una forma de realización de Fórmula (VI), E^1 es H. En otra forma de realización de Fórmula (VI), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 ; D^1 es H; y E^1 es H. En otra forma de realización de Fórmula (VI), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 ; E^1 es H; y D^1 es Cl. En otra forma de realización de Fórmula (VI), A^1 es $C(A^2)$; A^2 es H; B^1 es OR^1 ; D^1 es H; y E^1 es H. En otra forma de realización de Fórmula (VI), A^1 es $C(A^2)$; A^2 es H; B^1 es Cl; D^1 es H; y E^1 es H. En otra forma de realización de Fórmula (VI), A^1 es $C(A^2)$; A^2 es H; B^1 es R^1 ; D^1 es H; y E^1 es
- 15 H. En otra forma de realización de Fórmula (VI), A^1 es N; B^1 es NHR^1 ; D^1 es H; y E^1 es H. En otra forma de realización de Fórmula (VI), A^1 es N; B^1 es NHR^1 ; E^1 es H; y D^1 es Cl. En otra forma de realización de Fórmula (VI), A^1 es N; B^1 es OR^1 ; D^1 es H; y E^1 es H. En otra forma de realización de Fórmula (VI), A^1 es N; B^1 es Cl; D^1 es H; y E^1 es H. En otra forma de realización de Fórmula (VI), A^1 es N; B^1 es R^1 ; D^1 es H; y E^1 es H.
- 20 En una forma de realización de Fórmula (VI), Y^1 es H, CN, NO_2 , F, Cl, Br, I, CF_3 , R^{17} , OR^{17} , SR^{17} , SO_2R^{17} , o $C(O)NH_2$. En otra forma de realización de Fórmula (VI), Y^1 es H. En otra forma de realización de Fórmula (VI), Y^1 es CN. En otra forma de realización de Fórmula (VI), Y^1 es F, Cl, Br, o I. En otra forma de realización de Fórmula (VI), Y^1 es CF_3 . En otra forma de realización de Fórmula (VI), Y^1 es SR^{17} . En otra forma de realización de Fórmula
- 25 (VI), Y^1 es OR^{17} . En otra forma de realización de Fórmula (VI), Y^1 es NO_2 . En otra forma de realización de Fórmula (VI), Y^1 es SO_2R^{17} ; donde R^{17} es como se ha definido. En otra forma de realización de Fórmula (VI), Y^1 es SO_2R^{17} ; donde R^{17} es alquilo. En otra forma de realización de Fórmula (VI), Y^1 es R^{17} ; donde R^{17} es alquinilo. En otra forma de realización de Fórmula (VI), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 ; D^1 es H; E^1 es H; y Y^1 es NO_2 o SO_2R^{17} ; donde R^{17} es alquilo o alquinilo. En otra forma de realización de Fórmula (VI), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 ; D^1 es H; E^1 es H; y Y^1 es NO_2 . En otra forma de realización de Fórmula (VI), A^1 es $C(A^2)$; A^2 es H; B^1 es NHR^1 ; D^1 es H; E^1 es H; y Y^1 es SO_2R^{17} ; donde R^{17} es alquilo sustituido con tres F. En otra forma de realización de Fórmula (VI), A^1 es N; B^1 es NHR^1 ; D^1 es H; E^1 es H; y Y^1 es NO_2 o SO_2R^{17} ; donde R^{17} es alquilo o alquinilo. En otra forma de
- 30 realización de Fórmula (VI), A^1 es N; B^1 es NHR^1 ; D^1 es H; E^1 es H; y Y^1 es NO_2 . En otra
- 35 realización de Fórmula (VI), A^1 es N; B^1 es NHR^1 ; D^1 es H; E^1 es H; y Y^1 es NO_2 . En otra

forma de realización de Fórmula (VI), A^1 es N; B^1 es NHR^1 ; D^1 es H; E^1 es H; y Y^1 es SO_2R^{17} ; donde R^{17} es alquilo sustituido con tres F.

En una forma de realización de Fórmula (IV), Y^1 y B^1 , junto con los átomos a los cuales están unidos, son benceno. En otra forma de realización de Fórmula (IV), Y^1 y B^1 ,
5 junto con los átomos a los cuales están unidos, son heteroareno. En otra forma de realización de Fórmula (IV), A^1 es $C(A^2)$; A^2 , G^1 , E^1 , y D^1 se seleccionan en forma independiente entre H; y Y^1 y B^1 , junto con los átomos a los cuales están unidos, son benceno. En otra forma de realización de Fórmula (IV), A^1 es $C(A^2)$; A^2 , G^1 , E^1 , y D^1 se seleccionan en forma independiente entre H; y Y^1 y B^1 , junto con los átomos a los cuales
10 están unidos, son heteroareno.

En una forma de realización de Fórmula (VI), R^1 es R^4 o R^5 . En una forma de realización de Fórmula (VI), R^1 es R^4 . En una forma de realización de Fórmula (VI), R^1 es R^5 . En una forma de realización de Fórmula (VI), R^1 es R^4 ; y R^4 es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo. En una forma de realización de Fórmula (VI), R^1 es
15 R^4 ; y R^4 es cicloalquilo o heterocicloalquilo. En una forma de realización de Fórmula (VI), R^1 es R^4 ; y R^4 es cicloalquilo. En una forma de realización de Fórmula (VI), R^1 es R^4 ; y R^4 es heterocicloalquilo.

En una forma de realización de Fórmula (VI), R^1 es R^4 ; y R^4 es cicloalquilo; donde R^4 no está sustituido o está sustituido como se ha definido. En otra forma de realización de
20 Fórmula (VI), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo está sustituido como se ha definido. En otra forma de realización de Fórmula (VI), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo está sustituido con R^{57} o $N(R^{57})_2$. En otra forma de realización de Fórmula (VI), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con R^{57} ; y R^{57} es R^{60} . En otra forma de realización de
25 Fórmula (VI), R^1 es R^4 ; R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con R^{57} ; R^{57} es R^{60} ; y R^{60} es heterocicloalquilo. En otra forma de realización de Fórmula (VI), R^1 es R^4 ; R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con R^{57} ; R^{57} es R^{60} ; R^{60} es heterocicloalquilo; donde el anillo heterocicloalquilo es morfolinilo. En otra forma de
30 realización de Fórmula (VI), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo está sustituido con $N(R^{57})_2$. En otra forma de realización de Fórmula (VI), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con $N(R^{57})_2$. En otra forma de realización de Fórmula (VI), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está
35 sustituido con $N(R^{57})_2$; R^{57} es R^{61} ; y R^{61} es alquilo que no está sustituido o está sustituido con R^{62} . En otra forma de realización de Fórmula (VI), R^1 es R^4 ; y R^4 es cicloalquilo; donde el

anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con R^{57} ; R^{57} es R^{61} ; y R^{61} es alquilo que no está sustituido o está sustituido con R^{62} ; R^{62} es R^{65} ; y R^{65} es cicloalquilo. En otra forma de realización de Fórmula (VI), R^1 es R^4 ; y R^4 es cicloalquilo; donde el anillo cicloalquilo es ciclohexilo; y donde el anillo ciclohexilo está sustituido con R^{57} ; R^{57} es R^{61} ; y R^{61} es alquilo el cual está sustituido con R^{62} ; R^{62} es R^{65} ; y R^{65} es ciclopropilo.

En una forma de realización de Fórmula (VI), R^1 es R^4 ; y R^4 es heterocicloalquilo; donde R^4 no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (VI), R^1 es R^4 ; y R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo está sustituido como se ha definido. En otra forma de realización de Fórmula (VI), R^1 es R^4 ; y R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo está sustituido con R^{57} . En otra forma de realización de Fórmula (VI), R^1 es R^4 ; y R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo es piperidinilo o piperizinilo; y donde el anillo heterocicloalquilo está sustituido con R^{57} ; y R^{57} es R^{60} o R^{61} . En otra forma de realización de Fórmula (VI), R^1 es R^4 ; R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo es piperidinilo o piperizinilo; y donde el anillo piperidinilo o piperizinilo está sustituido con R^{57} ; R^{57} es R^{60} o R^{61} ; R^{60} es heterocicloalquilo; y R^{61} es alquilo. En otra forma de realización de Fórmula (VI), R^1 es R^4 ; R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo es piperidinilo o piperizinilo; y donde el anillo piperidinilo o piperizinilo está sustituido con R^{57} ; R^{57} es R^{60} ; R^{60} es heterocicloalquilo; donde el heterocicloalquilo es tetrahidropiranilo. En otra forma de realización de Fórmula (VI), R^1 es R^4 ; R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo es piperidinilo o piperizinilo; y donde el anillo piperidinilo o piperizinilo está sustituido con R^{57} ; R^{57} es R^{61} ; R^{61} es alquilo; y el alquilo es metilo. En otra forma de realización de Fórmula (VI), R^1 es R^4 ; R^4 es heterocicloalquilo; donde el anillo heterocicloalquilo es piperidinilo o piperizinilo; y donde el anillo piperidinilo o piperizinilo está sustituido con $C(O)OR^{57}$; R^{57} es R^{61} ; R^{61} es alquilo; y el alquilo es metilo.

En una forma de realización de Fórmula (VI), R^1 es R^5 ; y R^5 es alquilo que no está sustituido o está sustituido. En una forma de realización de Fórmula (VI), R^1 es R^5 ; y R^5 es alquilo que no está sustituido o está sustituido con R^7 , OR^7 , OH , CN , o F . En otra forma de realización de Fórmula (VI), R^1 es R^5 ; y R^5 es alquilo el cual está sustituido con R^7 , OR^7 , NHR^7 , o $N(R^7)_2$.

En una forma de realización de Fórmula (VI), R^7 es R^8 , R^9 , R^{10} o R^{11} que no están sustituidos o están sustituidos como se ha definido. En otra forma de realización de Fórmula (VI), R^7 es R^8 que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (VI), R^7 es R^9 que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (VI), R^7 es R^{10} que no está sustituido o

está sustituido como se ha definido. En otra forma de realización de Fórmula (VI), R^7 es R^{11} que no está sustituido o está sustituido como se ha definido.

En una forma de realización de Fórmula (VI), R^8 es fenilo que no está sustituido o está sustituido como se ha definido.

5 En una forma de realización de Fórmula (VI), R^9 es heteroarilo que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (VI), R^9 es furanilo; que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (VI), R^9 es furanilo; que no está sustituido.

10 En una forma de realización de Fórmula (VI), R^{10} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, heterocicloalquilo que no están sustituidos o están sustituidos como se ha definido. En otra forma de realización de Fórmula (VI), R^{10} es heterocicloalquilo que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (VI), R^{10} es tetrahidrofuranilo, tetrahidropiranilo, morfolinilo, dioxanilo, oxetanilo, piperdinilo, o pirrolidinilo; que no están sustituidos o están sustituidos
15 como se ha definido. En otra forma de realización de Fórmula (VI), R^{10} es tetrahidropiranilo; que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (VI), R^{10} es morfolinilo; que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (VI), R^{10} es cicloalquilo que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (VI), R^{10} es cicloalquilo que no está sustituido o está sustituido como se ha definido. En otra forma de
20 realización de Fórmula (VI), R^{10} es ciclohexilo, ciclopropilo, ciclobutilo, o biciclo[2,2,1]heptanilo, que no está sustituido o está sustituido como se ha definido. En otra forma de realización de Fórmula (VI), R^{10} es heterocicloalquilo que está fusionado con R^{10A} ; y R^{10A} es heteroareno. En otra forma de realización de Fórmula (VI), R^{10} es 5,6,7,8-
25 tetrahidroimidazo[1,2-a]piridinilo.

En una forma de realización de Fórmula (VI), R^{11} es alquilo, alquenilo o alquinilo que no están sustituidos o están sustituidos como se ha definido. En otra forma de realización de Fórmula (VI), R^{11} es alquilo. En otra forma de realización de Fórmula (VI), R^{11} es metilo; que no está sustituido o está sustituido como se ha definido. En otra forma de realización de
30 Fórmula (VI), R^{11} es alquilo; que está sustituido como se ha definido. En otra forma de realización de Fórmula (VI), R^{11} es alquilo; que está sustituido con R^{12} , OR^{12} , o CF_3 . En otra forma de realización de Fórmula (VI), R^{11} es alquilo, que está sustituido con OR^{12} ; R^{12} es R^{16} , y R^{16} es alquilo. En otra forma de realización de Fórmula (VI), R^{11} es alquilo; que está sustituido con CF_3 . En otra forma de realización de Fórmula (VI), R^{11} es alquilo, que está
35 sustituido con R^{12} ; R^{12} es R^{14} ; y R^{14} es heteroarilo.

En una forma de realización de Fórmula (VI),

- n, p, r, y q son cada uno 0;
 A^1 es N o $C(A^2)$;
 A^2 es H, F, Br, I, o Cl;
 B^1 es R^1 , OR^1 , NHR^1 , $NHC(O)R^1$, F, Br, I o Cl;
5 D^1 es H, F, Br, I, o Cl;
 E^1 es H; y
 Y^1 es H, CN, NO_2 , F, Cl, Br, I, CF_3 , R^{17} , OR^{17} , SR^{17} , SO_2R^{17} , o $C(O)NH_2$; o
 Y^1 y B^1 , junto con los átomos a los cuales están unidos, son benceno, heteroareno, o heterocicloalqueno; y
10 A^2 , D^1 , y E^1 se seleccionan en forma independiente entre H;
 R^1 es R^4 o R^5 ;
 R^4 es cicloalquilo, o heterocicloalquilo;
 R^5 es alquilo, o alquínilo, cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre R^7 , OR^7 ,
15 NHR^7 , $N(R^7)_2$, CN, OH, F, Cl, Br o I;
 R^7 es R^8 , R^9 , R^{10} , o R^{11} ;
 R^8 es fenilo;
 R^9 es heteroarilo;
 R^{10} es cicloalquilo, cicloalquenilo, o heterocicloalquilo; cada uno de los cuales no está fusionado o está fusionado con R^{10A} , R^{10A} es heteroareno;
20 R^{11} es alquilo cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre R^{12} , OR^{12} or CF_3 ;
 R^{12} es R^{14} o R^{16} ;
 R^{14} es heteroarilo;
25 R^{16} es alquilo;
 R^{17} es R^{21} ;
 R^{21} es alquilo, o alquínilo, cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre R^{22} , F, Cl, Br o I;
30 R^{22} es R^{25} ;
 R^{25} es heterocicloalquilo;
donde las unidades cíclicas representadas por Y^1 y B^1 juntos, R^4 , R^8 , R^{10} , y R^{25} , no están sustituidas, no están adicionalmente sustituidas, están sustituidas o adicionalmente sustituidas en forma independiente con uno o dos o tres o cuatro o cinco sustituyentes
35 seleccionados en forma independiente entre R^{57A} , R^{57} , OR^{57} , SO_2R^{57} , $C(O)R^{57}$,

$\text{CO(O)R}^{57}, \text{C(O)N(R}^{57})_2, \text{NH}_2, \text{NHR}^{57}, \text{N(R}^{57})_2, \text{NHC(O)R}^{57}, \text{NHS(O)}_2\text{R}^{57}, \text{OH}, \text{CN}, (\text{O}), \text{F}, \text{Cl}, \text{Br}$
o I;

$\text{R}^{57\text{A}}$ es espiroalquilo, o espiroheteroalquilo;

R^{57} es R^{58} , R^{60} o R^{61} ;

5 R^{58} es fenilo;

R^{60} es cicloalquilo, o heterocicloalquilo;

R^{61} es alquilo que no está sustituido o está sustituido con uno o dos o tres
sustituyentes seleccionados en forma independiente entre R^{62} , OR^{62} , $\text{N(R}^{62})_2$, C(O)OH , CN ,
F, Cl, Br o I;

10 R^{62} es R^{65} , o R^{66} ;

R^{65} es cicloalquilo, o heterocicloalquilo;

R^{66} es alquilo que no está sustituido o está sustituido con OR^{67} ;

R^{67} es alquilo;

15 donde las unidades cíclicas representadas por $\text{R}^{57\text{A}}$, R^{58} , y R^{60} no están sustituidas o
están sustituidas con uno o dos o tres o cuatro sustituyentes seleccionados en forma
independiente entre R^{68} , F, Cl, Br o I;

R^{68} es R^{71} o R^{72} ;

R^{71} es heterocicloalquilo; y

R^{72} es alquilo, que no está sustituido o está sustituido con uno o dos F.

20 Aún otra forma de realización se refiere a un compuesto de fórmula (VI), which es

4-(4-([2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({3-nitro-4-
[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-
iloxi)benzamida;

25 4-(4-([2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([5-ciano-6-
(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-
iloxi)benzamida;

4-(4-([2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-
fluorotetrahidro-2H-piran-4-il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-
iloxi)benzamida;

30 y sus sales terapéuticamente aceptables, y sus metabolitos.

*Composiciones farmacéuticas, terapias combinadas, 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 de tratamiento de cáncer en un mamífero, que comprende administrarle al mismo una cantidad terapéuticamente aceptable de un compuesto de la fórmula (I).

5 Aún otra realización comprende métodos de tratamiento de una enfermedad autoinmune en un mamífero, que comprende administrarle al mismo una cantidad terapéuticamente aceptable de un compuesto de la fórmula (I).

10 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 la 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 la fórmula (I).

15 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
20 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 la 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
25 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
30 cantidad terapéuticamente efectiva de un compuesto de la 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
35 compuesto de la 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 la 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 la 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 la 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 zwitteriones. 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 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 droga o no. La cantidad de un compuesto de la invención de la 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 de 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, carbómeros, aceite de ricino, 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 safrán, 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-droga, 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, drogas antiinflamatorias no esteroideas (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 la célula de cáncer de interés. 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 siARN son moléculas con bases de ARN endógeno 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'-OCH₃, 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 multivalentes son proteínas de unión que comprenden dos o más sitios de unión a antígenos. 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 natura. El término "proteína de unión multiespecífica" significa una proteína de unión con la capacidad de unir 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 cadena pesada y un dominio variable de cadena liviana, con la participación de un total de 6 CDR en la unión al antígeno por sitio de unión al antígeno.

Los agentes alquilantes incluyen altretamina, AMD-473, AP-5280, apazicuona, bendamustina, brostalicina, busulfano, carbocuna, carmustina (BCNU), clorambucilo, CLORETAZINA™ (laromustina, VNP 40101M), ciclofosfamida, decarbacina, estramustina, fotemustina, glufosfamida, ifosfamida, KW-2170, lomustina (CCNU), mafosfamida, melfalano, mitobronitol, mitolactol, nimustina, N-óxido de mostaza nitrógenoada, ranimustina, temozolomida, tiotepa, TREANDA® (bendamustina), treosulfano, rofosfamida y semejantes.

Los inhibidores de angiogénesis 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 metaloproteínasa de matriz-2 (MMP-2), inhibidores de metaloproteínasa 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 semejantes.

Los antimetabolitos incluyen ALIMTA® (pemetrexed 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, ALKERAN® (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.

5 Los antivirales incluyen ritonavir, hidroxiclороquina 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 e inhibidores de pan-aurora quinasa y semejantes.

10 Los inhibidores de proteínas Bcl-2 incluyen AT-101 ((-)gospol), 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)sulfonyl) bencenosulfonamida (ABT-15 263), GX-070 (obatoclax) y semejantes.

Los inhibidores de la Bcr-Abl quinasa incluyen DASATINIB® (BMS-354825), GLEEVEC® (imatinib) y semejantes.

Los inhibidores de CDK incluyen AZD-5438, BMI-1040, BMS-032, BMS-387, CVT-2584, 20 flavopiridol, GPC-286199, MCS-5A, PD0332991, PHA-690509, seliciclib (CYC-202, R-roscovitine), ZK-304709 y semejantes.

Los inhibidores de la COX-2 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), 25 MK-663 (etoricoxib), NS-398, parecoxib, RS-57067, SC-58125, SD-8381, SVT-2016, S-2474, T-614, VIOXX® (rofecoxib) y semejantes.

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 30 semejantes.

Los inhibidores de ErbB2 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 35 trifuncionales AS HER2, anticuerpo monoclonal AR-209, anticuerpo monoclonal 2B-1 y semejantes.

Los inhibidores de histona desacetilasa incluyen depsipéptido, LAQ-824, MS-275, trapoxina, ácido hidroxámico suberoilánilida (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
5 recombinante humano para HSP-90), NCS-683664, PU24FCI, PU-3, radicol, 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-droga incluyen anti-CD22-MC-MMAF, anti-CD22-MC-
10 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,
15 (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.

20 Los inhibidores de MEK incluyen ARRY-142886, ARRY-438162 PD-325901, PD-98059 y semejantes.

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.

25 Las drogas antiinflamatorias no esteroideas incluyen AMIGESIC[®] (salsalato), DOLOBID[®] (diflunisal), MOTRIN[®] (ibuprofeno), ORUDIS[®] (quetoprofeno), RELAFEN[®] (nabumetona), FELDENE[®] (piroxicam) crema ibuprofin, ALEVE[®] y NAPROSYN[®] (naproxeno), VOLTAREN[®] (diclofenac), INDOCIN[®] (indometacina), CLINORIL[®] (sulindac), TOLECTIN[®] (tolmetin), LODINE[®] (etodolac), TORADOL[®] (quetorolac), DAYPRO[®] (oxaprozin)
30 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.

35 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.

Los análogos de trombospondina incluyen ABT-510, ABT-567, ABT-898, TSP-1 y
5 semejantes.

Los inhibidores de VEGFR incluyen AVASTIN® (bevacizumab), ABT-869, AEE-788, ANGIÓZIMA™ (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-10
10 786034), vatalanib (PTK-787, ZK-222584), SUTENT® (sunitinib, SU-11248), trampa de VEGF, ZACTIMA™ (vandetanib, ZD-6474) y semejantes.

Los antibióticos incluyen antibióticos intercalantes aclarubicina, actinomicina D, amrubicina, anamicina, adriamicina, BLENOXANE® (bleomicina), daunorubicina, CAELYX® o MYOCET® (doxorubicina liposómica), elsamitrucina, epirubicina, glarubicina, ZAVEDOS®
15 (idarubicina), mitomicina C, nemorubicina, neocarzinostatina, peplomicina, pirarubicina, rebecamicina, stimalamer, estreptozocina, VALSTAR® (valrubicina), zinostatina y semejantes.

Los inhibidores de topoisomerasa 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-hidroxycamptotecina, gimatecan, lurtotecan, mitoxantrona, oratecina, pirarbutin, pixantrona, rubitecan, sobuzoxan, SN-38, taflupósido, topotecan y semejantes.

Los anticuerpos incluyen AVASTIN® (bevacizumab), anticuerpos específicos para
25 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® (cetorelix), 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),
35 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® (alitretinoína), ATRAGEN® (tretinoína liposomal),
5 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.

10 Los inhibidores de proteasoma incluyen VELCADE® (bortezomib), MG132, NPI-0052, PR-171 y semejantes.

Los ejemplos de sustancias inmunológicas incluyen interferones y otros agentes inmunopotenciadores. Los interferones incluyen interferón alfa, interferón alfa-2a, interferón alfa-2b, interferón beta, interferón gamma-1a, ACTIMMUNE® (interferón gamma-1b) o
15 interferón gamma-n1, combinaciones de los mismos y semejantes. Otros agentes incluyen ALFAFERONE® (IFN-α), BAM-002 (glutación 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,
20 mitumomab, molgramostim, MILOTARG™ (gemtuzumab ozogamicina), NEUPOGEN® (filgrastim), OncoVAC-CL, OVAREX® (oregovomab), pentumomab (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)),
25 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 dirigir las hacia una
30 actividad antitumoral e incluyen creстина, lentinano, sizofirano, picibanilo PF-3512676 (CpG-8954), ubenimex y semejantes.

Los análogos de pirimidina incluyen citarabina (ara C o Arabinósido C), arabinósido de citosina, doxifluridina, FLUDARA® (fludarabina), 5-FU (5-fluorouracilo), floxuridina, GEMZAR® (gemcitabina), TOMUDEX® (ratitrexed), TROXATYL™ (triacetiluridina
35 troxacitabina) y semejantes.

Los análogos de purina incluyen LANVIS® (tioguanina) y PURI-NETHOL® (mercaptipurina).

Los agentes antimicóticos incluyen batabulina, epotilona D (KOS-862), N-(2-((4-hidroxifenil)amino)piridin-3-il)-4-metoxibencensulfonamida, ixabepilona (BMS 247550),
 5 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 esta invención también se pueden usar como
 10 radiosensibilizadores que mejoran la eficacia de una radioterapia. Los ejemplos de
 radioterapia incluyen radioterapia de haz externo, teleterapia, braquiterapia y radioterapia de
 fuente sellada, no sellada, 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
 15 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™
 20 (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), combreastatina A4P, DAB(389)EGF (dominios
 catalítico y de traslocación de la toxina de la difteria fusionados por medio de un ligador His-
 25 Ala al factor de crecimiento epidérmico humano) 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,
 30 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), Ionafarnib, 5,10-metilentetrahidrofolato, miltefosina (hexadecilfosfocolina),
 35 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, procarbazona, 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®, ukráína (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 zolendróico), zorubicina y semejantes.

Datos

La determinación de la utilidad de los compuestos con la Fórmula I como ligantes para proteínas anti-apoptóticas Bcl-2 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 de otra manera. 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-Fluorenilmetiloxycarbonilo (Fmoc) y aminoácidos (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, Fmoc-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 (1x DCM y 1x 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 crudo.

Procedimiento general para la purificación de péptidos

Los péptidos crudos 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 indican más adelante. Se purificaron entre uno y dos mililitros de solución del péptido crudo (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 N°: 1)GQVGRQLAIIIGDK(6-FAM)-(SEQ ID N°: 2) INR-NH₂

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 crudo 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 la sonda del péptido F-Bak: Acetil--(SEQ ID N°: 1)GQVGRQLAIIIGDK(6-FAM)- (SEQ ID N°: 2)INR-NH₂

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 acoplado 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 crudo se recuperó por precipitación con dietil éter. El péptido crudo 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 (2x 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 indica en la tabla 1. A continuación, las muestras se mezclan sobre un agitador durante 1 minuto y se incuban durante otras 3 horas a 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 disociación (K_i) se muestran en la siguiente tabla 2 y se determinaron usando la ecuación de Wang (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).

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	Sonda del péptido F-Bak acetil-(SEQ ID	1	100	Tb-anti-GST	1

	Nº: 1 GQVGRQLAIIGDK(6-FAM) SEQ ID Nº: 2 INR-amida)				
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6-FAM = 6- carboxifluoresceína.; Tb = terbio; GST = glutatión 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 se muestran más adelante en la tabla 2. Cuando 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 Two Different Ligands To A Protein Molecule. FEBS Lett.* **1995**, 360:111-4).

TABLA 2. K_i de unión de Bcl-2 TR-FRET (μ M)

Nº EJEMPLO	K_i	Nº EJEMPLO	K_i
1	0,000225	190	0,000026
2	< 0,000010	191	< 0,000010
3	0,000013	192	< 0,000010
4	< 0,000010	193	< 0,000010
5	< 0,000010	194	< 0,000010
6	0,000018	195	< 0,000010
7	0,00492	196	< 0,000010
8	0,000153	197	< 0,000010
9	< 0,000010	198	< 0,000010
10	< 0,000010	199	< 0,000010
11	0,000016	200	< 0,000010
12	< 0,000010	201	0,000014
13	< 0,000010	202	< 0,000010
14	0,002798	203	< 0,000010

15	< 0,000010	204	< 0,000010
16	0,000219	205	< 0,000010
17	0,00009	206	0,000036
18	0,000017	207	0,00003
19	0,000226	208	0,000104
20	0,000181	209	< 0,000010
21	0,000912	210	0,000011
22	0,000291	211	0,000058
23	0,000083	212	0,0001330
24	< 0,000010	213	< 0,000010
25	< 0,000010	214	< 0,000010
26	0,000011	215	< 0,000010
27	0,000134	216	< 0,000010
28	< 0,000010	217	< 0,000010
29	< 0,000010	218	0,000013
30	< 0,000010	219	0,001192
31	< 0,000010	220	0,000988
32	< 0,000010	221	0,000049
33	< 0,000010	222	0,000938
34	0,00001	223	0,000053
35	< 0,000010	224	< 0,000010
36	0,000017	225	0,000196
37	< 0,000010	226	0,000139
38	0,0003	227	< 0,000010
39	0,000012	228	0,026761
40	< 0,000010	229	0,002109
41	< 0,000010	230	0,000031
42	0,000439	231	0,000770
43	0,000012	232	0,001631
44	< 0,000010	233	0,001654
45	< 0,000010	234	0,000115
46	0,000935	235	0,000023
47	< 0,000010	236	0,000033
48	< 0,000010	237	0,000024

49	0,000074	238	< 0,000010
50	0,000021	239	0,000026
51	< 0,000010	240	< 0,000010
52	0,000114	241	< 0,000010
53	< 0,000010	242	0,000057
54	0,002071	243	0,000546
55	< 0,000010	244	0,000281
56	0,000037	245	0,000015
57	0,000063	246	0,000144
58	< 0,000010	247	0,000019
59	0,000203	248	0,000029
60	< 0,000010	250	0,000412
61	0,000091	251	0,000571
62	< 0,000010	252	< 0,000010
63	< 0,000010	253	0,000052
64	< 0,000010	254	< 0,000010
65	< 0,000010	255	< 0,000010
66	< 0,000010	256	< 0,000010
67	< 0,000010	257	0,000052
68	0,000012	258	< 0,000010
69	0,001157	259	< 0,000010
70	0,003964	260	0,000016
71	0,00001	261	0,000134
72	< 0,000010	262	< 0,000010
73	< 0,000010	263	0,000156
74	0,000029	264	0,000036
75	< 0,000010	265	< 0,000010
76	0,000196	266	< 0,000010
77	0,000213	267	0,000035
78	< 0,000010	268	< 0,000010
79	< 0,000010	269	0,000016
80	< 0,000010	270	< 0,000010
81	< 0,000010	271	0,000039
82	0,000328	272	0,000031

83	0,000071	273	0,000035
84	0,000123	274	0,000040
85	0,000391	275	< 0,000010
86	0,000498	276	< 0,000010
87	0,000618	277	< 0,000010
88	0,000672	278	0,000252
89	0,000073	279	0,000035
90	0,000013	280	0,000071
91	0,000487	281	0,000145
92	0,000128	282	< 0,000010
93	0,003461	283	< 0,000010
94	0,000678	284	0,000024
95	0,000014	285	< 0,000010
96	0,000014	286	< 0,000010
97	0,000017	287	0,000081
98	< 0,000010	288	0,000251
99	0,000233	289	0,000090
100	< 0,000010	290	< 0,000010
101	0,000021	291	< 0,000010
102	0,000094	292	0,000190
103	< 0,000010	293	0,000093
104	0,000016	294	0,000046
105	< 0,000010	295	< 0,000010
106	0,000895	296	0,000512
107	0,000035	297	0,000174
108	< 0,000010	298	< 0,000010
109	0,000127	299	0,000039
110	0,000557	300	0,001627
111	< 0,000010	301	0,002065
112	< 0,000010	302	0,000332
113	< 0,000010	303	0,000044
114	< 0,000010	304	nd
115	< 0,000010	305	0,000033
116	< 0,000010	306	0,002067

117	< 0,000010	307	0,000130
118	< 0,000010	308	0,000141
119	< 0,000010	309	0,000023
120	< 0,000010	310	0,000165
121	< 0,000010	311	< 0,000010
122	< 0,000010	312	< 0,000010
123	< 0,000010	313	0,001102
124	< 0,000010	314	0,000042
125	< 0,000010	315	0,000052
126	< 0,000010	316	0,000601
127	< 0,000010	317	< 0,000010
128	< 0,000010	318	< 0,000010
129	0,000002	319	< 0,000010
130	< 0,000010	320	< 0,000010
131	< 0,000010	321	< 0,000010
132	< 0,000010	322	< 0,000010
133	< 0,000010	323	0,000104
134	< 0,000010	324	< 0,000010
135	< 0,000010	325	< 0,000010
136	< 0,000010	326	< 0,000010
137	< 0,000010	327	< 0,000010
138	< 0,000010	328	< 0,000010
139	< 0,000010	329	0,000030
140	< 0,000010	330	< 0,000010
141	< 0,000010	331	0,001086
142	0,00013	332	0,000621
143	< 0,000010	333	0,000511
144	< 0,000010	334	0,000572
145	< 0,000010	335	0,000150
146	< 0,000010	336	0,000198
147	< 0,000010	337	< 0,000010
148	< 0,000010	338	0,000013
149	< 0,000010	339	0,000036
150	< 0,000010	340	< 0,000010

151	0,000017	341	< 0,000010
152	< 0,000010	342	< 0,000010
153	< 0,000010	343	< 0,000010
154	< 0,000010	344	< 0,000010
155	0,000059	345	< 0,000010
156	< 0,000010	346	0,000042
157	< 0,000010	347	0,000013
158	< 0,000010	348	0,000034
159	< 0,000010	349	0,000023
160	< 0,000010	350	< 0,000010
161	< 0,000010	351	< 0,000010
162	< 0,000010	352	0,000014
163	< 0,000010	353	< 0,000010
164	< 0,000010	354	0,000010
165	< 0,000010	355	0,000014
166	< 0,000010	356	0,000039
167	< 0,000010	357	< 0,000010
168	< 0,000010	358	< 0,000010
169	0,000021	359	< 0,000010
170	0,000022	360	< 0,000010
171	< 0,000010	361	< 0,000010
172	< 0,000010	362	0,000016
173	< 0,000010	363	0,000017
174	< 0,000010	364	< 0,000010
175	0,000119	365	< 0,000010
176	0,000023	366	0,000024
177	0,000111	367	nd
178	0,000076	368	nd
179	< 0,000010	369	< 0,000010
180	< 0,000010	370	0,000285
181	0,000017	371	< 0,0000010
182	0,000068	372	nd
183	< 0,000010	373	< 0,0000010
184	< 0,000010	374	< 0,0000010

185	0,000022	375	0,00010999
186	0,000047	376	< 0,0000010
187	0,00008	377	< 0,0000010
188	< 0,000010	378	< 0,0000010
189	0,000018		

nd = no determinado

La constante de inhibición (K_i) es la constante de disociación de un complejo de enzima-inhibidor o de un complejo de proteína/molécula pequeña, en donde la molécula pequeña está inhibiendo la unión de una proteína a otra proteína o péptido. Entonces, un valor de K_i elevado indica una afinidad de unión baja y un valor de K_i pequeño indica una gran afinidad de unión.

En la tabla 2 se muestran las constantes de inhibición para la inhibición de una sonda del péptido Bak BH3 a la proteína Bcl-2 e indican que los compuestos de acuerdo con la invención tienen afinidades de unión elevadas para las proteínas anti-apoptóticas Bcl-2. Se espera entonces que los compuestos sean de utilidad en el tratamiento de enfermedades durante cuyo transcurso se expresan proteínas anti-apoptóticas Bcl-2.

Ensayo de viabilidad celular RS4;11

Se usó la línea celular RS4;11 de leucemia linfoblástica aguda (ALL) como la línea celular humana primaria para evaluar la actividad celular de agentes selectivos para Bcl-2 *in vitro* y su eficacia *in vivo*. Estudios previos han demostrado por determinación del perfil de BH3, un ensayo en mitocondrias que clasifica bloques en la vía apoptótica intrínseca, que las células RS4;11 eran muy dependientes de BCL-2 para la sobrevivida y que son muy sensibles al inhibidor ABT-737 que es un miembro de la familia Bcl-2 (*Blood*, 2008, Volumen 111, 2300-2309). La prevalencia de Bcl-2 en complejos con la proteína proapoptóticas BH3 Bim en las células RS4;11 sugiere que estas células están "sensibilizadas" o más susceptibles a muerte celular por antagonismo de la proteína antiapoptótica Bcl-2 de la cual dependen para su sobrevivida.

Las células RS4;11 se cultivaron en RPMI-1640 suplementado con L-glutamina 2 mM, FBS 10%, piruvato de sodio 1 mM, HEPES 2 mM, penicilina/estreptomicina 1% (Invitrogen), glucosa 4,5 g/l y se mantuvieron a 37 C con 5% de CO₂. Para evaluar la actividad celular de los compuestos *in vitro*, las células fueron tratadas a razón de 50.000 células por cavidad en placas para microtitulación de 96 cavidades en la presencia de suero humano 10% durante 48 horas en una cámara húmeda con 5% de CO₂. Los valores de EC₅₀ para citotoxicidad celular fueron evaluados usando CellTiter Glo (Promega) de acuerdo con las recomendaciones del proveedor. Los valores de EC₅₀ se determinaron como un

porcentaje de células viables después del tratamiento en comparación con las células control no tratadas.

Tabla 3. Valores de EC₅₀ para RS4;11 (μM)

N° EJEMPLO	EC50	N° EJEMPLO	EC50
1	0,712	190	0,55068
2	0,783	191	0,00691
3	0,0142	192	0,00241
4	0,01854	193	0,00076
5	0,01241	194	0,00819
6	0,03487	195	0,00207
7	0,192	196	0,00172
8	0,158	197	0,0125
9	0,01476	198	0,03619
10	0,05202	199	0,00506
11	0,01393	200	0,01099
12	0,03471	201	0,59132
13	0,0232	202	0,0438
14	3,8947	203	0,02208
15	0,01276	204	0,16475
16	1,2098	205	0,01059
17	0,475	206	0,05291
18	0,086	207	0,00376
19	0,465	208	0,12121
20	0,191	209	0,0045
21	0,062	210	0,06022
22	0,085	211	0,3073
23	0,045	212	0,01283
24	0,00983	213	0,0060976
25	0,007	214	0,0043751
26	0,05888	215	0,0005603
			8
27	0,33237	216	0,68263
28	0,0419	217	0,0015528
29	0,02047	218	0,0072907

30	0,01529	219	> 1
31	0,01565	220	> 1
32	0,08147	221	0,094771
33	0,00711	222	> 1
34	0,00748	223	0,18208
35	0,29147	224	0,013887
36	0,18137	225	0,56001
37	0,00118	226	0,1178
38	3,5092	227	0,0073566
39	0,01974	228	> 1
40	0,09974	229	> 1
41	0,05801	230	0,052821
42	0,53412	231	0,52301
43	0,27208	232	> 1
44	0,05309	233	> 1
45	0,00992	234	0,13532
46	> 5	235	0,03232
47	0,03265	236	0,04292
48	0,00333	237	0,05316
49	0,35161	238	0,10303
50	0,31264	239	0,023699
51	0,02308	240	0,017266
52	0,19964	241	0,11377
53	0,06674	242	0,22275
54	1,9158	243	0,80718
55	0,0132	244	0,79378
56	0,08654	245	0,083614
57	0,42611	246	0,40218
58	> 5	247	0,092976
59	0,7215	248	0,099588
60	0,05948	250	> 1
61	0,18337	251	0,91782
62	0,02506	252	0,003475
63	0,00751	253	0,049586

64	0,00025	254	0,019908
65	0,00025	255	0,009004
66	0,01893	256	0,017997
67	0,04954	257	0,026002
68	0,10846	258	0,0005534 5
69	1,7243	259	0,0003879 5
70	> 5	260	0,0054323
71	0,09165	261	0,18366
72	0,00751	262	0,016346
73	0,02369	263	> 1
74	0,057	264	0,68866
75	0,01509	265	0,0071718
76	0,51131	266	0,0072924
77	0,76196	267	0,06944
78	0,01252	268	0,048792
79	0,0649	269	0,0072346
80	0,06863	270	0,0025216
81	0,04814	271	0,43657
82	0,68383	272	0,84006
83	0,197	273	0,20925
84	0,158	274	0,21418
85	1,95	275	0,14303
86	1,02	276	0,0035006
87	1,18	277	0,0081845
88	0,447	278	0,79393
89	0,06446	279	0,22492
90	0,06299	280	0,45923
91	0,18296	281	0,65371
92	0,08089	282	0,032187
93	> 5	283	0,013096
94	1,6946	284	0,16213
95	0,02954	285	0,057413

96	0,04356	286	0,034464
97	0,05557	287	0,59312
98	0,0229	288	0,39042
99	1,3923	289	0,6687
100	0,13666	290	0,10663
101	0,2991	291	0,016079
102	0,62178	292	0,88938
103	0,03917	293	0,28715
104	0,07125	294	0,12525
105	0,05357	295	0,014803
106	0,82639	296	0,76869
107	0,06117	297	0,59157
108	0,02407	298	0,070305
109	0,18339	299	0,067981
110	0,53638	300	0,76334
111	0,01451	301	> 1
112	0,02063	302	0,38106
113	0,00136	303	0,04776
114	0,01078	304	0,29755
115	0,01184	305	0,032539
116	0,02853	306	0,55348
117	0,0182	307	0,12767
118	0,01294	308	0,257
119	0,01138	309	0,052421
120	0,00147	310	> 1
121	0,05972	311	0,035835
122	0,00185	312	0,016178
123	0,00333	313	> 1
124	0,21224	314	0,66006
125	0,00838	315	0,21027
126	0,05359	316	> 1
127	0,00975	317	0,013313
128	0,00589	318	0,011566
129	0,01484	319	0,0044972

130	0,01059	320	0,050974
131	0,01266	321	0,0188
132	0,02209	322	0,012367
133	0,03186	323	0,71689
134	0,00251	324	0,0045254
135	0,00237	325	0,012319
136	0,00296	326	0,023133
137	0,01272	327	0,0027224
138	0,00152	328	0,0098808
139	0,01681	329	0,42369
140	0,01275	330	0,0097843
141	0,02044	331	0,92638
142	0,34531	332	0,45738
143	0,01914	333	0,46292
144	0,0212	334	> 1
145	0,004	335	0,26951
146	0,01916	336	0,35134
147	0,02618	337	0,001759
148	0,00938	338	0,003399
149	0,01347	339	0,45016
150	0,05103	340	0,05646
151	0,03372	341	0,031652
152	0,02037	342	0,050891
153	0,01723	343	0,12664
154	0,02647	344	0,0066616
155	0,59421	345	0,0092536
156	0,00805	346	0,19003
157	0,01086	347	0,018849
158	0,01793	348	0,050263
159	0,01179	349	0,023086
160	0,08363	350	0,0058378
161	0,03465	351	0,0020618
162	0,01297	352	0,0011961
163	0,00432	353	0,0050512

164	0,01476	354	0,053231
165	0,0051	355	0,018771
166	0,01185	356	0,026623
167	0,00093	357	0,013235
168	0,08867	358	0,0038131
169	0,07626	359	0,0059243
170	0,12515	360	0,0098968
171	0,05272	361	0,0005375 5
172	0,02053	362	0,031726
173	0,00516	363	0,02643
174	0,12621	364	0,011244
175	> 1	365	0,0030168
176	0,13353	366	0,016548
177	0,15936	367	nd
178	0,20234	368	nd
179	0,04273	369	0,0079974
180	0,0118	370	nd
181	0,10612	371	0,007165
182	0,1234	372	nd
183	0,01753	373	nd
184	0,02323	374	0,015475
185	0,02747	375	0,56013
186	0,06443	376	0,008765
187	0,21494	377	0,002377
188	0,01638	378	0,006764
189	0,14397		

nd = no determinado.

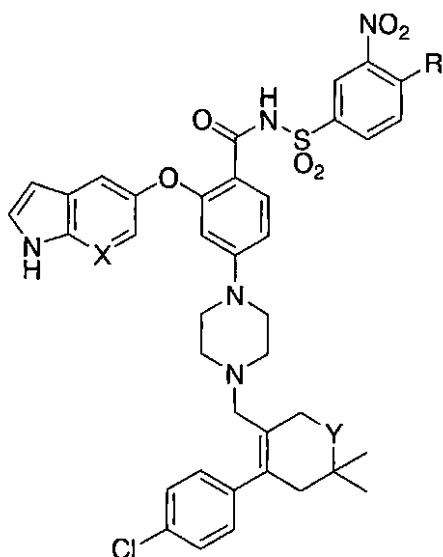
5 En la tabla 3 se muestra la utilidad de los compuestos de la fórmula I para inhibir funcionalmente la proteína anti-apoptótica Bcl-2 en un contexto celular. Se ha demostrado por determinación del perfil de BH3, un ensayo en mitocondrias que clasifica bloques en la vía apoptótica intrínseca, que la línea celular RS4;11 de leucemia linfoblástica aguda (ALL) es muy dependiente de Bcl-2 para la sobrevivida y que es sensible al inhibidor ABT-737 que es un miembro de la familia Bcl-2 (*Blood*, 2008, Vol. 111, 2300-2309). La capacidad de los compuestos para matar las células RS4;11 es una medida directa de la capacidad de los

compuestos para inhibir la función de la proteína anti-apoptótica Bcl-2. Los compuestos de la fórmula I son muy eficaces matar las células RS4;11 como lo demuestran los bajo valores de EC₅₀.

Los compuestos divulgados en la Solicitud de Patente de los EE.UU. N°: 12/631404, con el título "BCL-2-SELECTIVE APOPTOSIS-INDUCING AGENTS FOR THE TREATMENT OF CANCER AND IMMUNE DISEASES", presentada el 4 de diciembre, 2009, son de utilidad para el tratamiento de diversos tipos de cáncer y enfermedades autoinmunes debido a su actividad contra las proteínas de la familia Bcl-2 y, más específicamente, Bcl-2. Estos compuestos se unen a Bcl-2 con gran afinidad en un ensayo basado en FRET que se describe en 12/631404. La administración de uno o más de estos compuestos a las células que dependen de la proteína Bcl-2 o de proteínas de la familia Bcl-2 para su supervivencia, tal como la línea celular tumoral humana de leucemia de células B RS4;11, da como resultado apoptosis, también conocida como muerte celular programada. La cantidad de apoptosis causada por administración del compuesto está representada por la EC₅₀ en el ensayo de viabilidad celular, que es una medida de la cantidad de células vivas después de la administración del compuesto.

En la tabla 4 se identifican determinados compuestos (que se describen más adelante en los Ejemplos 19, 20, 23 y 92 y que se describe con más detalle en 12/631404, cuya divulgación se incorpora en la presente a modo de referencia), donde los diversos sustituyentes se definen por R, X e Y según se indica. Como se puede observar en la tabla 4, estos compuestos exhiben la tendencia de una afinidad de unión (K_d) creciente por Bcl-2 con niveles crecientes de apoptosis, o muerte celular, en la línea celular tumoral RS4;11 dependiente de Bcl-2. Sobre esta base, los inventores esperan que compuestos con aún mayor afinidad por Bcl-2 que los compuestos que se muestran en la Tabla 4 exhibirán una tendencia similar, provocando potencialmente niveles aún mayores de apoptosis, cuando son administrados a células que dependen de Bcl-2 para la supervivencia.

Tabla 4. Compuestos seleccionados en la Solicitud de Patente de los EE.UU. N°: 12/631404



EJEMPLO	R	X	Y	K _i de Bcl-2 FRET (μM)	EC50 de RS4;11 (μM)
(23)		C	O	0,000083	0,045
(92)		C	C	0,000128	0,081
(20)		C	C	0,000181	0,191
(19)		C	C	0,000226	0,465

Para tal fin, se comparó la afinidad de unión y la actividad celular de los compuestos de acuerdo con la presente invención con compuestos indol de estructura similar. En particular, se compararon los compuestos de la presente invención, en donde hay un nitrógeno en una posición específica dentro del heteroareno fusionado al anillo heteroarilo, con los correspondientes compuestos indol, donde estos últimos compuestos solamente carecen de la sustitución de nitrógeno específica incluida en los compuestos de la presente invención.

Como se puede observar en la tabla 5, los compuestos de la presente invención que contienen las sustituciones de nitrógeno específicas indicadas (es decir, los compuestos de los Ejemplos 1, 2, 3, 4, 5, 6, 9, 10, 11, 12, 13, 15, 16 y 17, donde Z = N) de hecho permiten

lograr niveles relativamente mayores de apoptosis cuando son administrados a células que dependen de Bcl-2 para su sobrevivencia y que tienen una mayor afinidad por Bcl-2 con relación a los correspondientes análogos estructurales que no contienen una sustitución de nitrógeno específica (es decir, los compuestos de los Ejemplos 87, 88, 89, 90, 91, 19, 20, 21, 92, 22, 23, 93, y 94, respectivamente, donde Z = C, descritos en 9696USL2, cuya divulgación se incorpora en la presente a modo de referencia).

Específicamente, la séptima columna de la tabla 5 compara la afinidad de unión de los compuestos de la presente invención (el compuesto identificado por los sustituyentes designados en la fila más superior en cada par de filas separado por filas en blanco) con los correspondientes compuestos que carecen de la sustitución de nitrógeno descrita. En cada comparación, los compuestos de la presente solicitud (fila superior de cada par de filas separado por una fila en blanco) se unen a Bcl-2 con mayor afinidad por Bcl-2 que los análogos correspondientes (fila inferior de cada par de filas separado por una fila en blanco).

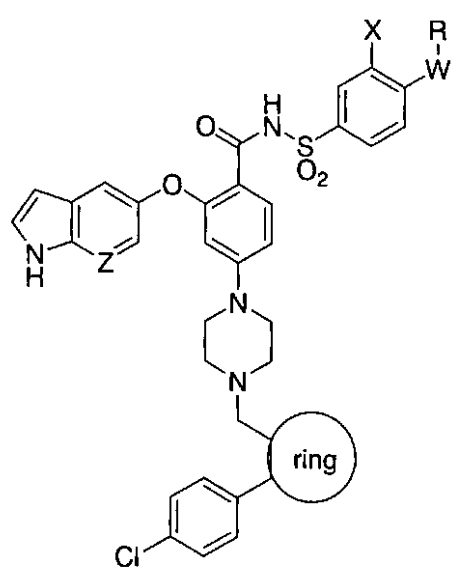
Además, en la columna 8 de la tabla 5 se compara la cantidad de apoptosis en la línea celular RS4;11 dependiente de Bcl-2 lograda usando los compuestos de la presente invención (nuevamente el compuesto identificado por los sustituyentes designados en la fila más superior en cada par de filas separado por filas en blanco) con la obtenida usando los compuestos de los Ejemplos 87, 88, 89, 90, 91, 19, 20, 21, 92, 22, 23, 93 y 94, donde Z = C. En cada comparación, los compuestos de la presente invención (fila superior de cada par de filas separado por una fila en blanco) logran un mayor grado de apoptosis en las células RS4;11 dependientes de Bcl-2 que los correspondientes análogos (fila inferior de cada par de filas separado por una fila en blanco).

El incremento en la afinidad de unión entre los compuestos de la presente invención y los análogos correspondientes varía en un rango entre 2,7x y más de 100x, y la mayor potencia en las células RS4;11 varía en un rango entre un incremento de 1,65x y un incremento de más de 10x.

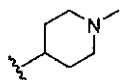
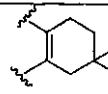
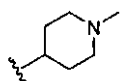
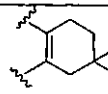
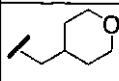
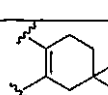
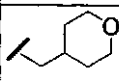
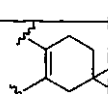
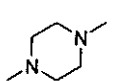
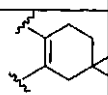
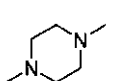
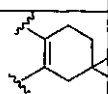
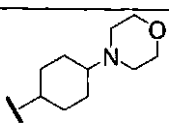
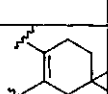
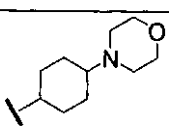
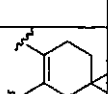
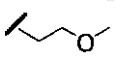
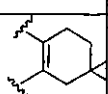
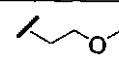
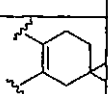
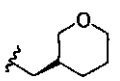
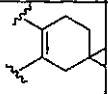
Según se indicará con detalle más adelante, una sustitución específica de un átomo de nitrógeno por un átomo de carbono conduce a un incremento inesperado en la afinidad de unión a la Bcl-2 anti-apoptótica y a un incremento en la potencia en ensayos de viabilidad celular que evalúan la apoptosis en líneas celulares dependientes de Bcl-2.

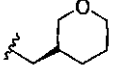
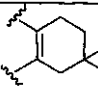
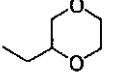
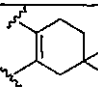
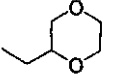
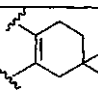
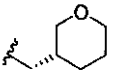
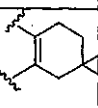
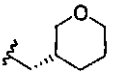
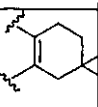
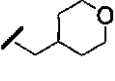
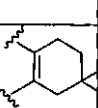
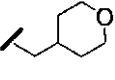
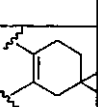
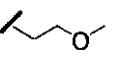
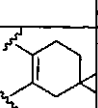
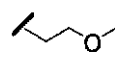
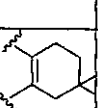
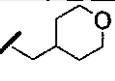
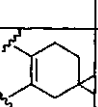
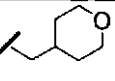
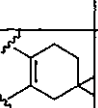
Por ello, esta invención comprende una serie de compuestos que demuestran propiedades inesperadas con respecto a su unión e inhibición de la actividad de proteínas anti-apoptóticas Bcl-2 hasta un grado significativamente mayor que los correspondientes compuestos análogos.

TABLA 5. Comparación directa de los compuestos de la presente invención con los análogos correspondientes.

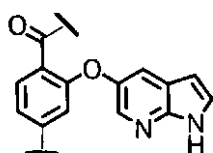


EJEMPLO	R	S	X	Anill o	Z	ki de Bcl-2 FRET (μM)	EC50 de RS4;11 (μM)
(1)		NH	NO ₂		N	0,000225	0,712
(87)		NH	NO ₂		C	0,000618	1,180
(2)		NH	NO ₂		N	< 0,000010	0,783
(88)		NH	NO ₂		C	0,672	0,447
(3)		NH	NO ₂		N	0,000013	0,0142
(89)		NH	NO ₂		C	0,000074	0,064

(4)		NH	NO ₂		N	< 0,00001	0,019
(90)		NH	NO ₂		C	0,000013	0,063
(5)		NH	NO ₂		N	< 0,00001	0,012
(18)		NH	NO ₂		C	0,000017	0,086
(6)		NH	NO ₂		N	0,000018	0,035
(91)		NH	NO ₂		C	0,000487	0,183
(9)		NH	NO ₂		N	< 0,00001	0,015
(19)		NH	NO ₂		C	0,000226	0,465
(10)		NH	NO ₂		N	< 0,00001	0,052
(20)		NH	NO ₂		C	0,000181	0,191
(11)		NH	NO ₂		N	0,000016	0,014

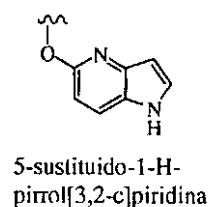
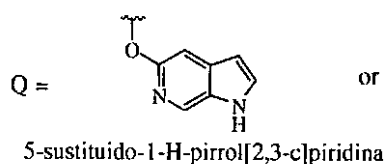
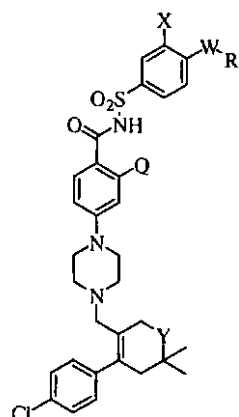
(21)		NH	NO ₂		C	0,000912	0,062
(12)		O	NO ₂		N	< 0,00001	0,035
(92)		O	NO ₂		C	0,000128	0,081
(13)		NH	NO ₂		N	< 0,00001	0,023
(22)		NH	NO ₂		C	0,000291	0,085
(15)		NH	NO ₂		N	< 0,00001	0,013
(23)		NH	NO ₂		C	0,000083	0,045
(16)		NH	SO ₂ C F ₃		N	0,000219	1,210
(93)		NH	SO ₂ C F ₃		C	0,035	> 5,000
(17)		NH	SO ₂ C F ₃		N	0,000090	0,475
(94)		NH	SO ₂ C F ₃		C	0,000678	1,690

Más específicamente, los compuestos de la presente invención contienen un patrón de sustitución que se muestra más adelante en el diagrama.



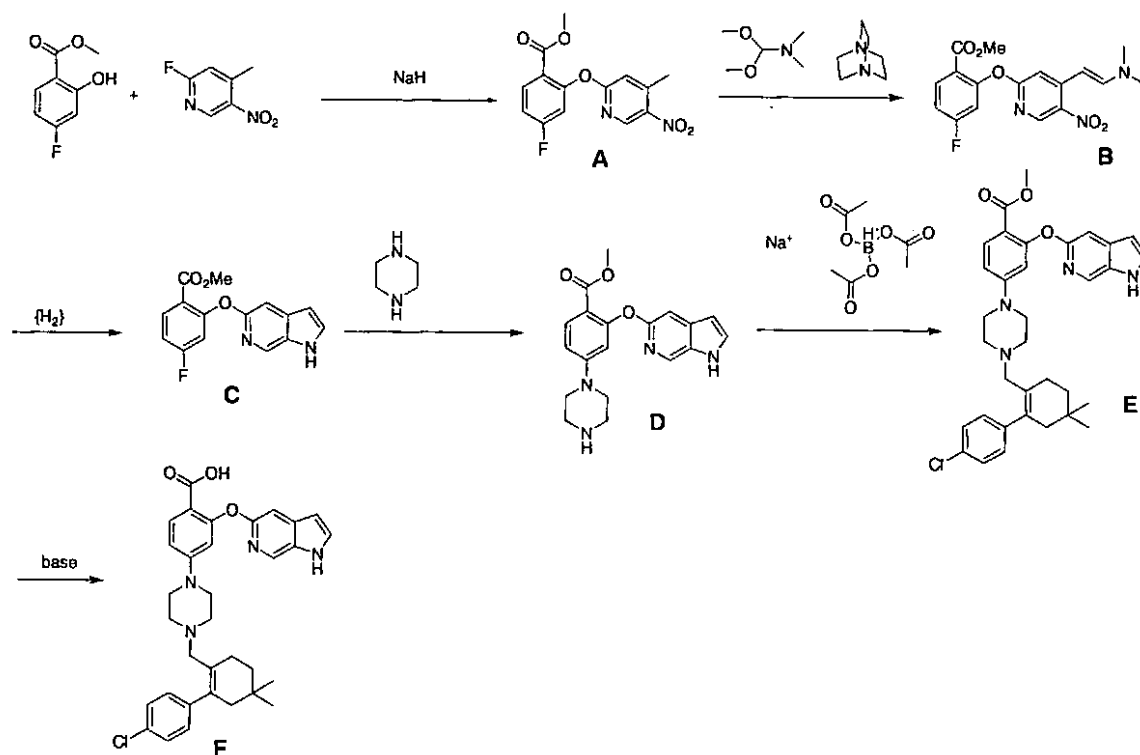
Otros compuestos que contienen sistemas de anillos isoméricos con respecto a los indicados previamente, tales como aquellos sistemas de anillos que contienen un nitrógeno adyacente al carbono oxigenado dentro del anillo, como se muestra a continuación, están

5 comprometidos por su inestabilidad.

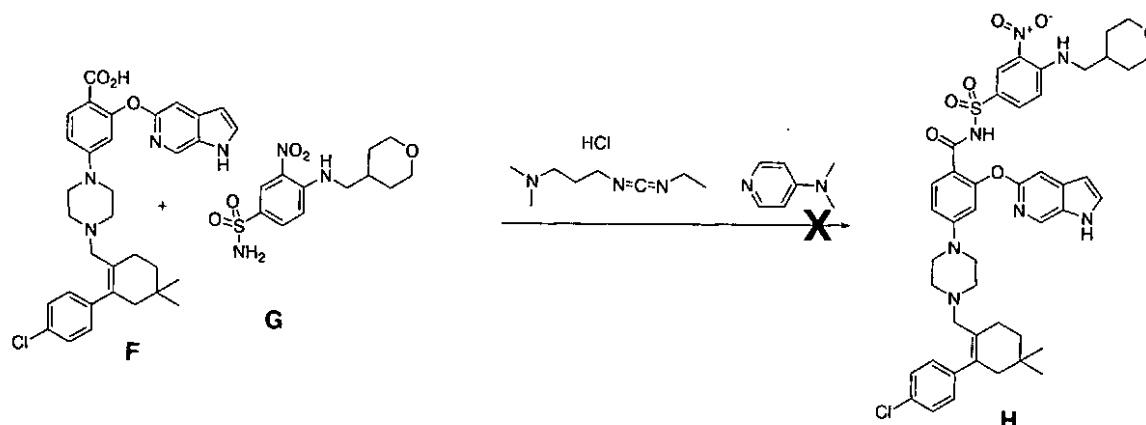


Específicamente, esto fue descubierto por los inventores en la siguiente preparación del compuesto. La estructura intermedia F, que precede directamente al producto final del compuesto inestable, se preparó de acuerdo con la ruta indicada a continuación. Todos los

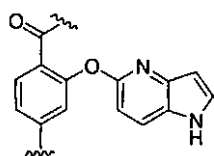
10 intermediarios A-F eran estables y se pudieron aislar usando técnicas conocidas por los especialistas en el arte.



El intermediario **F**, indicado en el esquema anterior, se hizo reaccionar con el intermediario **G** usando las condiciones de acoplamiento estándar que son conocidas por los especialistas en el arte. La mezcla de reacción se analizó por HPLC/MS para monitorear la formación de un pico correspondiente al compuesto **H**. Si bien este pico se formó dentro de las horas de iniciada la siguiente reacción, el pico desaparecía progresivamente durante los procesos de aislamiento y purificación y cromatografía, hasta que ya no estaba presente. La falta de estabilidad del compuesto putativo se origina en la posición del nitrógeno dentro del sistema de anillos fusionados que se describió previamente. Esta posición, que es adyacente al carbono que lleva al oxígeno en el sistema de anillos 5-sustituido-1H-pirrol[2,3-c]piridina que se muestra a continuación y se describió previamente, vuelve inestable al compuesto **H**.



Se espera que un compuesto que contiene al sistema de anillos fusionado 5-sustituido-1H-pirrol[3,2-b]piridina indicado a continuación sería similarmente inestable, dado que la posición del nitrógeno es adyacente al carbono que lleva al oxígeno dentro del anillo.



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Por ello, se prefieren los compuestos con las 5-sustituido-1H-pirrol[2,3-b]piridinas frente a los compuestos isoméricos.

Se espera que, dado que los compuestos de la Fórmula (I) se unen a Bcl-2, también serían de utilidad como moléculas de unión a proteínas anti-apoptóticas que presentan una homología estructural estrecha con Bcl-2, tal como, por ejemplo, las proteínas anti-apoptóticas Bcl-X_L, Bcl-w, Mcl-1 y Bfl-1/A1.

La relación de las proteínas 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

25

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.

- 5 La relación de las proteínas Bcl-2 con las enfermedades inmunes y autoinmunes ha sido descrita en *Current Allergy and 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.

- 10 La relación de las proteínas Bcl-2 con la artritis se divulga en la Solicitud Provisional de Patente de los EE.UU. N° de Acta 60/988.479 de propiedad conjunta.

La relación de las proteínas Bcl-2 con el rechazo de trasplantes de médula ósea se divulga en la Solicitud de Patente de los EE.UU. N° de Acta 11/941.196 de propiedad conjunta.

- 15 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 inmune. 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, 25 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, 30 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- 35 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,
 5 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, rhabdomyosarcoma, sarcoma, carcinoma de glándula sebácea, seminoma, cáncer de piel, carcinoma de pulmón
 10 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.

15 También se espera que los compuestos con la Fórmula I puedan inhibir el crecimiento de las células que expresan las proteínas Bcl-2 derivada de un cáncer pediátrico o neoplasma incluyendo rhabdomyosarcoma embrionario, leucemia linfoblástica aguda pediátrica, leucemia mielógena aguda pediátrica, rhabdomyosarcoma alveolar pediátrico, ependimoma anaplástico pediátrico, linfoma anaplástico de células grandes pediátrico,
 20 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,
 25 neuroblastoma pediátrico, mielocitomatosis derivada de neuroblastoma pediátrica, tipos de cáncer pediátricos en estadio pre-células B (tales como leucemia), osteosarcoma pediátrico, tumor rabdoide de riñón pediátrico, rhabdomyosarcoma 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
 30 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, alopecia, alopecia areata, enfermedad ateromatosa/arteriosclerosis, aterosclerosis, artritis (que incluye osteoartritis, artritis crónica juvenil, artritis séptica, artritis de Lyme, artritis psoriásica y artritis
 35 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,
- 5 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-1- 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
- 10 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
- 15 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
- 20 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,
- 25 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,
- 30 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
- 35 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 drogas, hepatitis inducida por drogas, trastornos del movimiento inducidos por drogas que bloquean los receptores de dopamina del SNC, sensibilidad a drogas, eccema, encefalomiелitis, endocarditis, 5 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, 10 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 15 de células pilosas, enfermedad de Hallerorden-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, 20 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 25 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, 30 enfermedad de IgA lineal, lipidema, rechazo en trasplante de hígado, enfermedad de Lyme, linfedema, 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 35 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, 5 síndrome nefrótico, enfermedades neurodegenerativas, atrofas 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 10 parasitarias, rechazo en trasplante de paratiroides, enfermedad de Parkinson, enfermedad inflamatoria pélvica, pénfigo vulgar, pénfigo foliáceo, penfigoide, rinitis perenne, enfermedad del pericardio, enfermedad ateroesclerótica periférica, trastornos vasculares periféricos, peritonitis, anemia perniciosa, uveitis facogénica, neumonía por *Pneumocystis carinii*, neumonía, síndrome POEMS (polineuropatía, organomegalia, endocrinopatía, gammapatía 15 monoclonal, y síndrome de cambios en la piel), síndrome posterior a perfusión, síndrome post-bomba, síndrome de cardiectomía 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 20 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, 25 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 30 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 35 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.

15 *Esquemas y experimentos*

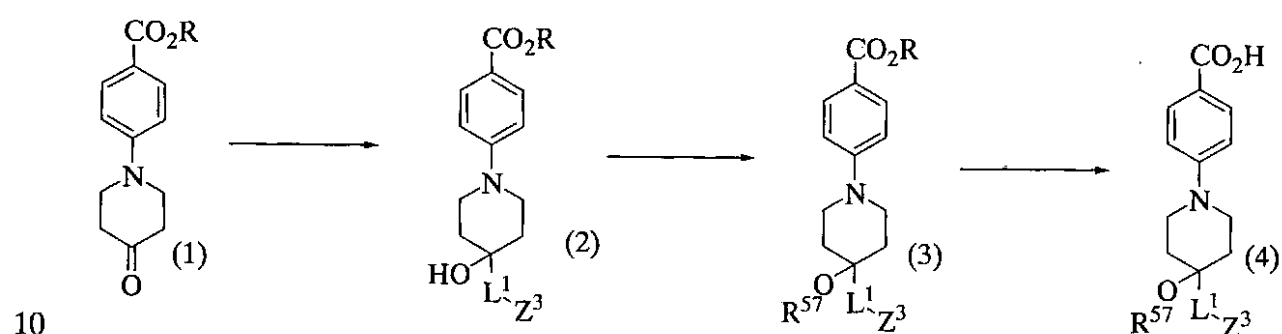
Las siguientes abreviaturas tienen los significados indicados. ADDP significa 1,1'-(azodicarbonil)dipiperidina; AD-mix- β significa una mezcla de (DHQD)₂PHAL, K₃Fe(CN)₆, K₂CO₃, y K₂SO₄; 9-BBN significa 9-borabicyclo(3.3.1)nonano; Boc significa tert-butoxicarbonilo; (DHQD)₂PHAL significa hidroquinidina 1,4-ftalazinediilo dietil éter; DBU significa 1,8-diazabicyclo(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 fluorenilmetoxycarbonilo; HATU significa hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N',N'-tetrametiluronio; HMPA significa hexametilfosforamida; IPA significa alcohol isopropílico; MP-BH₃ 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; PPh₃ significa trifenilfosfina.

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 esta invención se pueden obtener mediante procesos de síntesis química, de los cuales se ofrecen ejemplos en la presente. Se comprenderá que es posible variar el orden de los pasos en los procesos, que los reactivos, solventes y

condiciones de reacción se pueden sustituir por los que se mencionan específicamente y que los grupos vulnerables se pueden proteger y desproteger, según necesidad.

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ESQUEMA 1

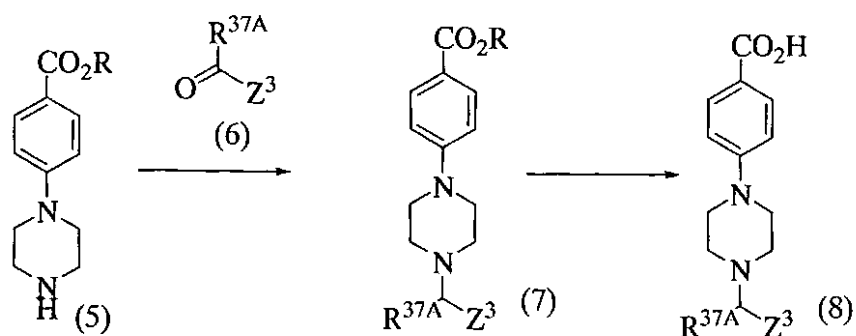


Los compuestos de la fórmula (4) se pueden preparar como se muestra en el esquema 1, y se pueden usar como se describe en el esquema 8 para preparar los compuestos de la fórmula (I), que son representativos de los compuestos de la presente invención. Los compuestos de la fórmula (1) en donde R es alquilo, se pueden convertir en los compuestos de la fórmula (2) usando $Z^3L^1MgX^1$, en donde X^1 es un haluro, en un solvente, tal como, pero en un sentido no taxativo, éter o tetrahydrofurano. Los compuestos de la fórmula (3) se pueden preparar a partir de los compuestos de la fórmula (2) usando una base fuerte tal como NaH y $R^{57}X^2$, en donde X^2 es un haluro y R^{57} es como se describe en la presente. Los compuestos de la fórmula (3), cuando son tratados con NaOH o LiOH acuoso, proporcionarán los compuestos de la fórmula (4).

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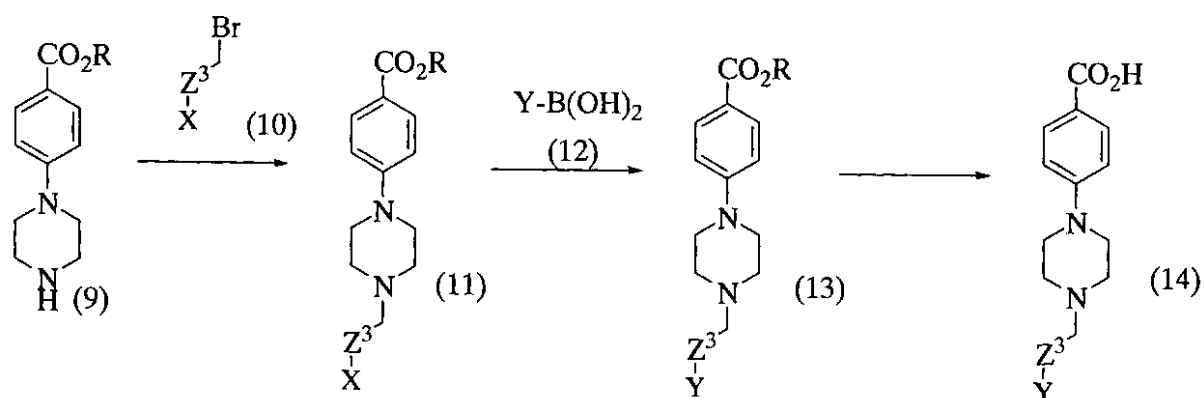
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ESQUEMA 2



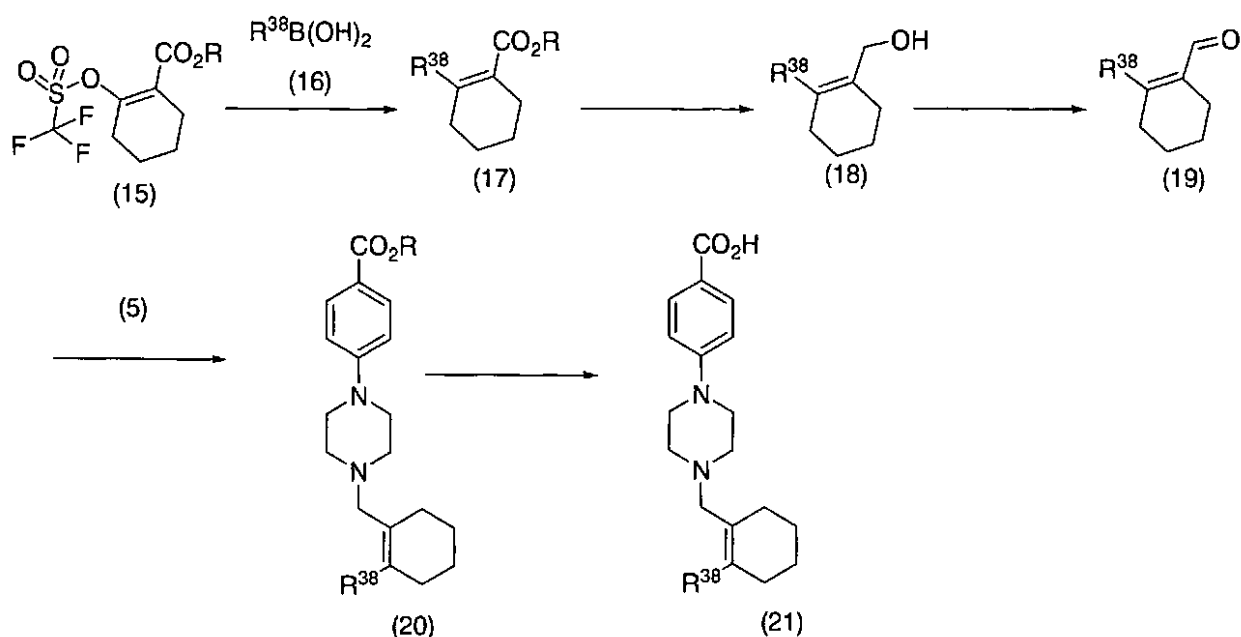
Como se muestra en el esquema 2, los compuestos de la fórmula (5) se pueden hacer reaccionar con los compuestos de la fórmula (6) y un agente reductor para proveer los compuestos de la fórmula (7). Los ejemplos de agentes reductores incluyen borohidruro de sodio, cianoborohidruro de sodio, triacetoxiborohidruro de sodio, cianoborohidruro sobre soporte de polímero supported y semejantes. La reacción se conduce típicamente en un solvente tal como, pero en un sentido no taxativo, metanol, tetrahidrofurano y diclorometano o mezclas de los mismos. Los compuestos de la fórmula (8) se pueden preparar a partir de compuestos de la fórmula (7) descritos en el esquema 1, y se pueden usar como se describe en el esquema 8 para preparar los compuestos de la fórmula (I).

ESQUEMA 3



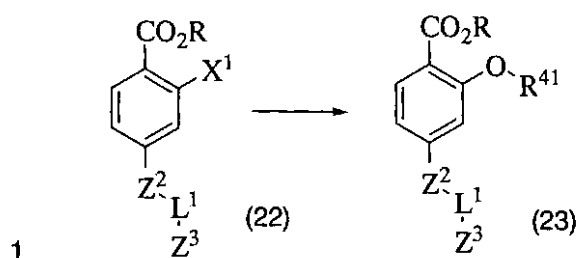
Los compuestos de la fórmula (9), cuando se hacen reaccionar con un compuesto de la fórmula (10), en donde X es un haluro o triflato, y una base proporcionarán un compuesto de la fórmula (11). Las bases que son de utilidad en la reacción incluyen trietilamina, diisopropilamina y semejantes. Los compuestos de la fórmula (13), en donde Y es como se describe en la presente para los sustituyentes sobre Z^3 , se pueden preparar a partir de los compuestos de la fórmula (11) y los compuestos de la fórmula (12) usando condiciones de acoplamiento de Suzuki conocidas por los especialistas en el arte y fácilmente disponibles en la literatura. Los compuestos de la fórmula (14) se pueden preparar a partir de compuestos de la fórmula (13) descritos en el esquema 1, y se pueden usar como se describe en el esquema 8 para preparar los compuestos de la fórmula (I).

ESQUEMA 4



Como se muestra en el esquema 4, los compuestos de la fórmula (17) se pueden preparar a partir de los compuestos de la fórmula (15) y los compuestos de la fórmula (16), en donde R es alquilo y R^{38} es como se describe en la presente, usando condiciones de acoplamiento de Suzuki conocidas por los especialistas en el arte y fácilmente disponibles en la literatura. Los compuestos de la fórmula (17) se pueden reducir en los compuestos de la fórmula (18) usando un agente reductor, tal como LiAlH_4 , en un solvente tal como pero en un sentido no taxativo dietil éter o THF. Los compuestos de la fórmula (19) se pueden preparar a partir de los compuestos de la fórmula (18) usando las condiciones de oxidación de Swern o periodinano de Dess-Martin conocidas por los especialistas en el arte y fácilmente disponibles en la literatura. Los compuestos de la fórmula (19) se pueden hacer reaccionar con un compuesto de la fórmula (5) y un agente reductor para proveer los compuestos de la fórmula (20). Los ejemplos de agentes reductores incluyen borohidruro de sodio, cianoborohidruro de sodio, triacetoxiborohidruro de sodio, cianoborohidruro sobre soporte de polímero y semejantes. La reacción se conduce típicamente en un solvente tal como pero en un sentido no taxativo metanol, tetrahidrofurano, 1,2-dicloroetano y diclorometano o mezclas de los mismos. Los compuestos de la fórmula (21) se pueden preparar a partir de compuestos de la fórmula (20) descritos en el esquema 1, y se pueden usar como se describe en el esquema 8 para preparar los compuestos de la fórmula (I).

ESQUEMA 5

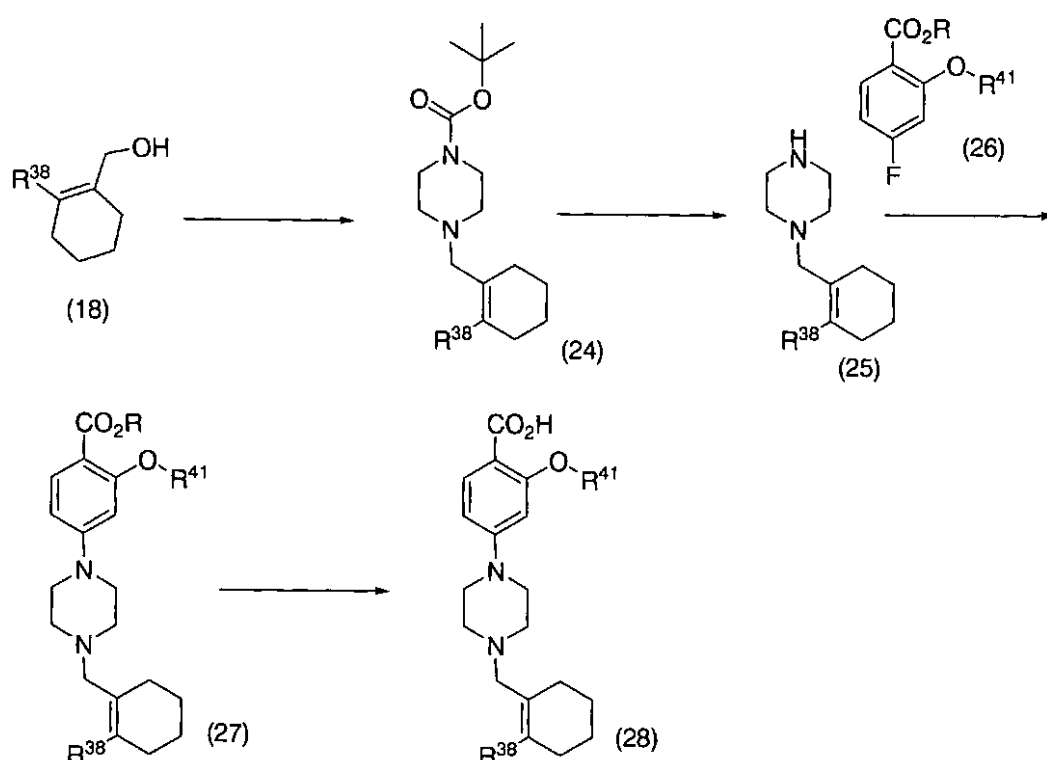


5 Como se muestra en el esquema 5, los compuestos de la fórmula (22), en donde R es alquilo, se pueden convertir en los compuestos de la fórmula (23) por reacción del primero, en donde X¹ es Cl, Br, I o CF₃SO₃⁻, y los compuestos de la fórmula R⁴¹-OH y un catalizador, con o sin una primera base. Los ejemplos de catalizadores incluyen un complejo de tolueno trifluorometansulfonato de cobre(I), PdCl₂, Pd(OAc)₂ y Pd₂(dba)₃. Los ejemplos de primeras bases incluyen trietilamina, N,N-diisopropiletilamina, Cs₂CO₃, Na₂CO₃, K₃PO₄ y mezclas de los mismos.

10 Los compuestos de la fórmula (22) también se pueden convertir en los compuestos de la fórmula (23) por reacción del primero, cuando X¹ es Cl, F, o NO₂, y compuestos de la fórmula R⁴¹-OH con una primera base. Los ejemplos de primeras bases incluyen trietilamina, N,N-diisopropiletilamina, Cs₂CO₃, Na₂CO₃, K₃PO₄ y mezclas de los mismos.

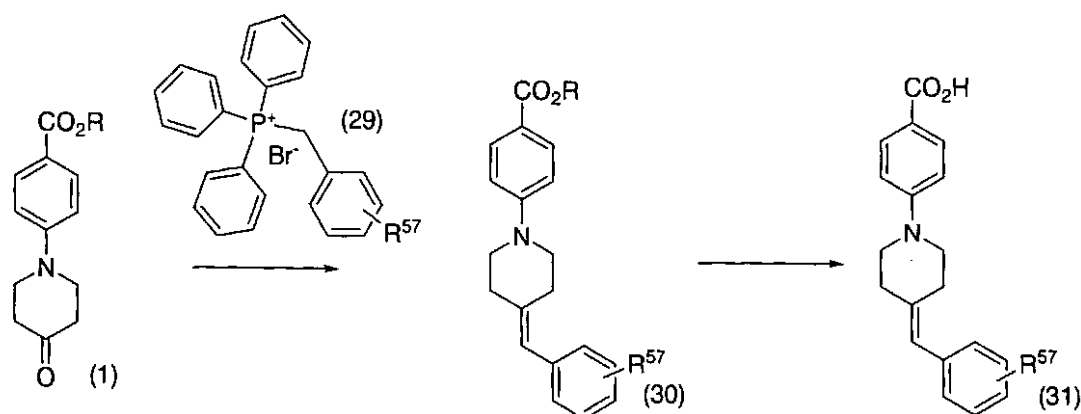
15

ESQUEMA 6



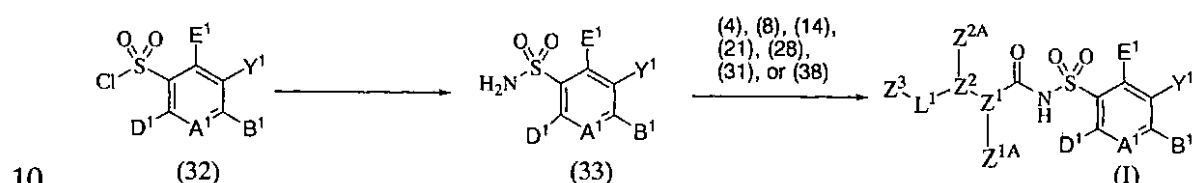
- Los compuestos de la fórmula (18) se pueden hacer reaccionar con cloruro de mesilo y una base tal como, pero en un sentido no taxativo, trietilamina, seguido por N-t-butoxicarbonilpiperazina, para proveer los compuestos de la fórmula (24). Los compuestos de la fórmula (25) se pueden preparar por reacción de los compuestos de la fórmula (24) con trietilsilano y ácido trifluoroacético. Los compuestos de la fórmula (25) se pueden hacer reaccionar con los compuestos de la fórmula (26) y HK_2PO_4 para proveer los compuestos de la fórmula (27) en un solvente tal como, pero en un sentido no taxativo, dimetilsulfóxido. Los compuestos de la fórmula (28) se pueden preparar a partir de los compuestos de la fórmula (27) descritos en el esquema 1, y se pueden usar como se describe en el esquema 8 para preparar los compuestos de la fórmula (I).

ESQUEMA 7



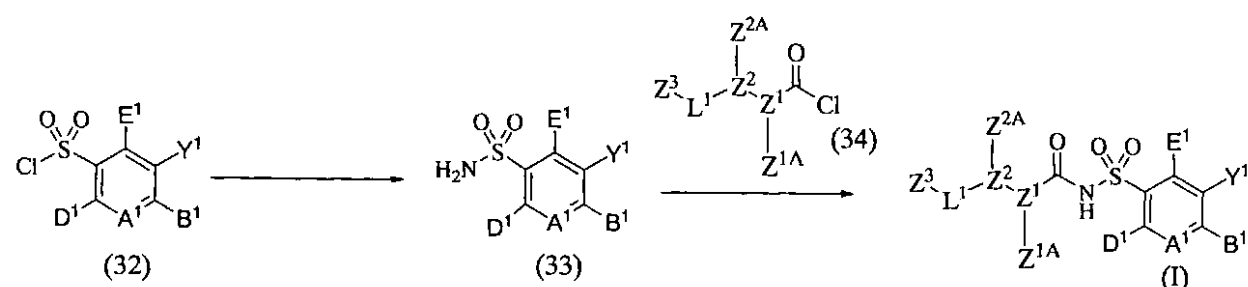
Como se muestra en el esquema 7, los compuestos de la fórmula (1) se pueden hacer reaccionar con un bromuro de trifenilfosfonio apropiado de la fórmula (29) y una base tal como, pero en un sentido no taxativo, hidruro de sodio o n-butilitio para proveer los compuestos de la fórmula (30). La reacción se conduce típicamente en un solvente tal como THF o DMSO. Los compuestos de la fórmula (31) se pueden preparar a partir de compuestos de la fórmula (30) descritos en el esquema 1, y se pueden usar como se describe en el esquema 8 para preparar los compuestos de la fórmula (I).

ESQUEMA 8



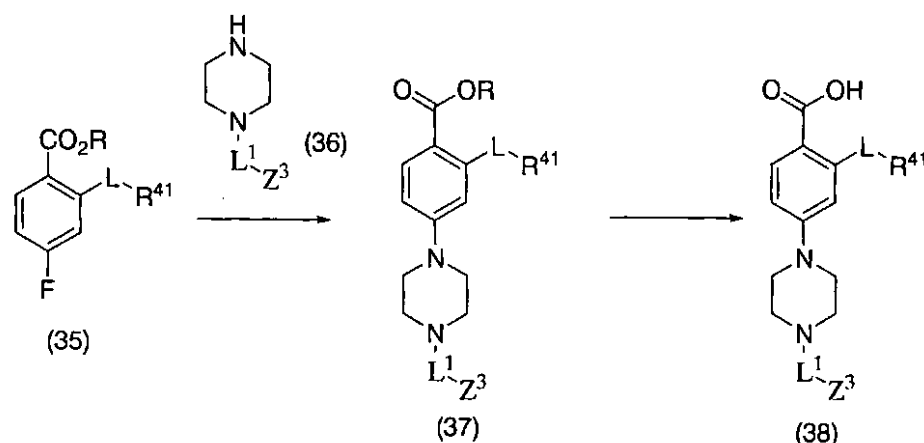
Como se muestra en el esquema 8, los compuestos de la fórmula (32), que se pueden preparar como se describe en la presente, se pueden convertir en los compuestos de la fórmula (33) por reacción del primero con amoníaco. Los compuestos de la fórmula (33) se pueden convertir en los compuestos de la fórmula (I) por reacción del primero y compuestos de la fórmula (4), (8), (14), (21), (28), (31) o (38) y un agente de acoplamiento, con o sin una primera base. Los ejemplos de agentes de acoplamiento incluyen clorhidrato de 1-etil-3-[3-(dimetilamino)propil]-carbodiimida, 1,1'-carbonildiimidazol y hexafluorofosfato de benzotriazol-1-il-oxitripirrolidinofosfonio. Los ejemplos de primeras bases incluyen trietilamina, N,N-diisopropiletilamina, 4-(dimetilamino)piridina y mezclas de los mismos.

ESQUEMA 9



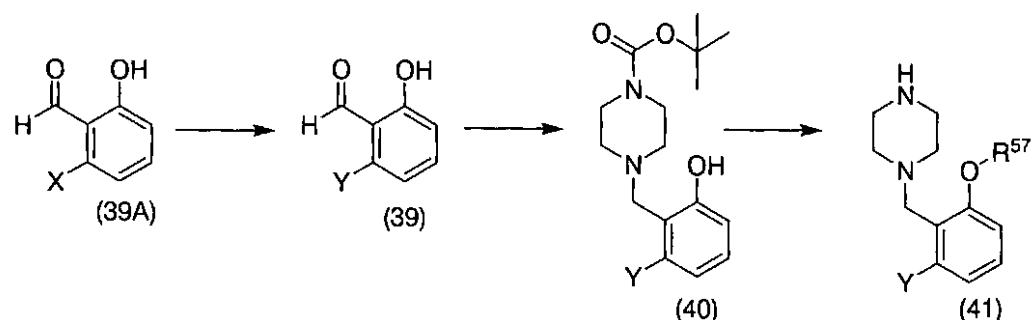
Los compuestos de la fórmula (33), preparados como se describe en el esquema 8, también se pueden convertir en compuestos de la fórmula (I) por reacción del primero y compuestos de la fórmula (34) y una primera base. Los ejemplos de primeras bases incluyen, pero en un sentido no taxativo, hidruro de sodio, trietilamina, N,N-diisopropiletilamina, 4-(dimetilamino)piridina y mezclas de los mismos.

ESQUEMA 10



Como se muestra en el esquema 10, los compuestos de la fórmula (35), en donde L es un enlace, alquilo, O, S, S(O), S(O)₂, NH, etc., se pueden hacer reaccionar con compuestos de la fórmula (36), para proveer los compuestos de la fórmula (37). La reacción se conduce típicamente a temperaturas elevadas en un solvente tal como, pero en un sentido no taxativo, dimetilsulfóxido, y puede requerir el uso de una base tal como, pero en un sentido no taxativo, fosfato de potasio, carbonato de potasio y semejantes. Los compuestos de la fórmula (38) se pueden preparar a partir de compuestos de la fórmula (37) descritos en el esquema 1, y se pueden usar como se describe en el esquema 8 para preparar los compuestos de la fórmula (I).

ESQUEMA 11

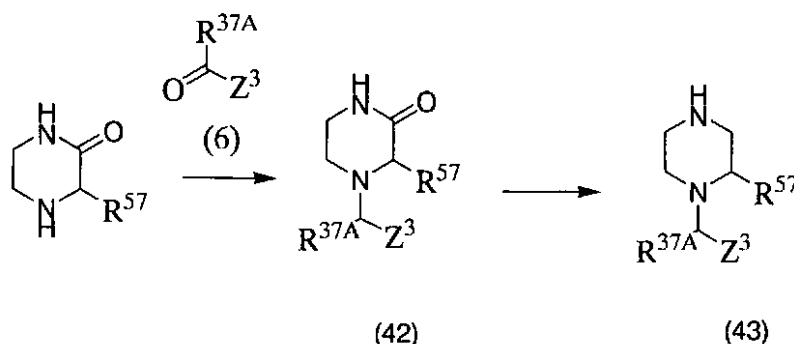


Los compuestos de la fórmula (39), en donde Y es como se describe en la presente para los sustituyentes sobre Z³, se pueden preparar a partir de los compuestos de la fórmula (39A), en donde X es un haluro o triflato, y Y-B(OH)₂ usando condiciones de acoplamiento de Suzuki conocidas por los especialistas en el arte y fácilmente disponibles en la literatura. Los compuestos de la fórmula (39) se pueden hacer reaccionar con piperazin-1-carboxilato de tert-butilo y un agente reductor, tal como triacetoxiborohidruro de sodio, para proveer los compuestos de la fórmula (40). La reacción se conduce típicamente en un solvente tal como, pero en un sentido no taxativo, cloruro de metileno. Los compuestos de la fórmula (41) se

pueden preparar a partir de los compuestos de la fórmula (40) por reacción del último con $R^{57}X$, en donde X es un haluro, y NaH en un solvente tal como N,N-dimetilformamida, y luego se puede tratar el material resultante con trietilsilano y ácido trifluoroacético en diclorometano. Los compuestos de fórmula (41) se pueden utilizar según se describe en el

5 esquema 10 donde L^1-Z^3 es según se muestra en la Fórmula (41).

ESQUEMA 12



Tal como se muestra en el esquema 12, se pueden hacer reaccionar piperazin-2-onas sustituidas donde R^{57} es alquilo, con compuestos de la fórmula (6a) y un agente reductor tal como triacetoxiborohidruro de sodio en diclorometano para dar los compuestos de la fórmula (42). Los compuestos de la fórmula (42) se pueden reducir a compuestos de la 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

10 la fórmula (43) se pueden utilizar según se describe en el esquema 10 donde L^1-Z^3 es según se muestra en la fórmula (43).

15

Los siguientes ejemplos se presentan para proveer la descripción que se considera más útil y fácil de entender de los procedimientos y los aspectos conceptuales de esta invención. Los compuestos que se ejemplifican se nombraron usando el programa

20 ACD/ChemSketch Versión 5.06 (05 de Junio de 2001, Advanced Chemistry Development Inc., Toronto, Ontario), ACD/ChemSketch Versión 12.01 (13 May 2009), Advanced Chemistry Development Inc., Toronto, Ontario) o ChemDraw® Versión 9.0.5 (CambridgeSoft, Cambridge, MA) Los intermediarios se nombraron usando ChemDraw® Versión 9.0.5 (CambridgeSoft, Cambridge, MA).

25 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-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 1A

30 4-((4'-clorobifenil-2-il)metil)piperazin-1-carboxilato de tert-butilo

Se agitó 4'-clorobifenil-2-carboxaldehído (4,1 g), piperazin-1-carboxilato de tert-butilo (4,23 g), y triacetoxiborhidruro de sodio (5,61 g) en CH_2Cl_2 (60 mL) por 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.

5

EJEMPLO 1B

1-((4'-clorobifenil-2-il)metil)piperazina

Se agitó EJEMPLO 1A (3,0 g) y trietilsilano (1 mL) en CH_2Cl_2 (30 mL) y ácido trifluoroacético (30 mL) por 2 horas, y la reacción se concentró, y luego se recogió con éter y se concentró nuevamente. El material se colocó en diclorometano (200 mL) y NaHCO_3 solución (100 mL), y se particionó. La capa orgánica se secó sobre Na_2SO_4 , y se condensó para dar el compuesto del título.

10

EJEMPLO 1C

4-(4-((4'-clorobifenil-2-il)metil)piperazin-1-il)-2-fluorobenzoato de tert-butilo

Se agitó 4-bromo-2-fluorobenzoato de tert-butilo (14,0 g), EJEMPLO 1B (16,05 g), $\text{Pd}_2(\text{dba})_3$ (tris(dibencilidenacetona)dipaladio(0)) (1,40 g), 2-(di-tert-butilfosfino)bifenilo (1,82 g), y K_3PO_4 (16,2 g) en 1,2-dimetoxietano (300 mL) a 80°C por 24 horas. La reacción se enfrió y se concentró. El producto crudo se cromatografió sobre gel de sílice con 10-20% acetato de etilo/hexanos.

20

EJEMPLO 1D

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((4'-clorobifenil-2-il)metil)piperazin-1-il)benzoato de tert-butilo

Se agitó 1H-Pirrol[2,3-B]piridin-5-ol (167 mg), EJEMPLO 1C (500 mg), y Cs_2CO_3 (508 mg) en sulfóxido de dimetilo (5 mL) a 130°C por 24 horas. La mezcla se enfrió, se diluyó con acetato de etilo, se lavó tres veces con agua, y salmuera, y se secó (Na_2SO_4), se filtró y se concentró. El producto crudo se cromatografió sobre gel de sílice con 25% acetato de etilo/hexanos.

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30

EJEMPLO 1E

Ácido 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((4'-clorobifenil-2-il)metil)piperazin-1-il)benzoico

Se agitó EJEMPLO 1D (200 mg) y trietilsilano (1 mL) en diclorometano (15 mL) y ácido trifluoroacético (15 mL) por 1 hora. La mezcla se concentró, se recogió con acetato de etilo, se lavó dos veces con NaH_2PO_4 , y salmuera, y se secó (Na_2SO_4), se filtró y se concentró.

35

EJEMPLO 1F

3-nitro-4-((tetrahidro-2H-piran-4-il)metilamino)bencenosulfonamida

- Se agitó 4-Fluoro-3-nitrobencenosulfonamida (2,18 g), 1-(tetrahidropiran-4-il)metilamina (1,14 g), y trietilamina (1 g) en tetrahidrofurano (30 mL) por 24 horas. La
 5 solución se diluyó con acetato de etilo, se lavó con NaH_2PO_4 solución y salmuera, y se secó (Na_2SO_4), se filtró y se concentró. El producto se trituró con 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-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida
 10

- Se agitó EJEMPLO 1E (115 mg), EJEMPLO 1F (67 mg), clorhidrato de 1-etil-3-[3-(dimetilamino)propil]-carbodiimida (82 mg), y 4-dimetilaminopiridina (26 mg) en CH_2Cl_2 (3 mL) por 24 horas. La reacción se enfrió y se cromatografió sobre gel de sílice con 0-5% metanol/acetato de etilo. ^1H NMR (300MHz, sulfóxido de dimetilo- d_6) δ 11,48 (brs, 1H), 8,34
 15 (br s, 1H), 8,31 (m, 1H), 7,90 (d, 1H), 7,68 (m, 1H), 7,58 (m, 2H), 7,46 (m, 4H), 7,35 (m, 2H), 7,21 (dd, 1H), 6,76 (m, 4H), 6,28 (m, 2H), 3,02 (m, 2H), 2,89 (m, 4H), 2,80 (m, 4H), 2,40 (m, 3H), 1,59 (m, 2H), 1,25 (m, 4H), 0,87 (m, 2H).

EJEMPLO 2

- 4-{4-[(4'-cloro-1,1'-bifenil-2-il)metil]piperazin-1-il}-N-({4-[(3-morfolin-4-ilpropil)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida
 20

EJEMPLO 2A

4-(3-morfolinopropilamino)-3-nitrobencenosulfonamida

- 25 Este EJEMPLO se preparó utilizando 3-(N-morfolinil)-propilamina en lugar de 1-(tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

EJEMPLO 2B

- 4-{4-[(4'-cloro-1,1'-bifenil-2-il)metil]piperazin-1-il}-N-({4-[(3-morfolin-4-ilpropil)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida
 30

- Este EJEMPLO se preparó utilizando el EJEMPLO 2A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ^1H NMR (300MHz, sulfóxido de dimetilo- d_6) δ 11,60 (brs, 1H), 8,60 (m, 1H), 8,43 (d, 1H), 7,94 (d, 1H), 7,64 (m, 2H), 7,54 (d, 1H), 7,45 (m, 4H), 7,33 (m, 2H), 7,23 (dd, 1H), 6,96 (d, 1H), 6,85 (m, 2H), 6,32 (d, 1H), 6,26 (d, 1H), 3,60 (m, 4H), 3,10 (m, 4H), 3,05
 35 (m, 10H), 2,40 (m, 2H), 2,33 (m, 2H), 1,77 (m, 2H).

EJEMPLO 3

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-il)piperidin-4-il]amino]fenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

5

EJEMPLO 3A

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-metoxycarbonilciclohexanona (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 trifluoroacético (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 (Na₂SO₄), se filtró, y se concentró para dar el producto.

15 EJEMPLO 3B

2-(4-clorofenil)-4,4-dimetilciclohex-1-encarboxilato de metilo

Se calentó EJEMPLO 3A (62,15g), ácido 4-clorofenilborónico (32,24 g), CsF (64 g) y tetrakis(trifenilfosfin)paladio(0) (2g) en 2:1 dimetoxietano /metanol (600 mL) a 70°C 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.

20

EJEMPLO 3C

25 (2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metanol

A una mezcla de LiBH₄ (13g), EJEMPLO 3B (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 1N con enfriamiento con hielo. La mezcla se diluyó con agua y se extrajo con éter (3x 100 mL). Los extractos se secaron (Na₂SO₄), se filtró, y se concentró. El producto crudo se cromatografió sobre gel de sílice con acetato de etilo al 0-30%/hexanos.

30

EJEMPLO 3D

4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-carboxilato de tert-butilo

Se agregó cloruro de mesilo (7,5 mL) mediante una jeringa a EJEMPLO 3C (29,3 g) y trietilamina (30 mL) en CH₂Cl₂ (500 mL) a 0°C, y la mezcla se agitó por 1 minuto. Se agregó

35

N-t-butoxicarbonilpiperazina (25 g) y la mezcla se agitó a temperatura ambiente por 24 horas. La suspensión se lavó con salmuera, se secó, (Na_2SO_4), se filtró, y se concentró. El producto crudo se cromatografió sobre gel de sílice con 10-20% acetato de etilo/hexanos.

5 EJEMPLO 3E

1-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazina

Se agitó EJEMPLO 3D (1 g) en diclorometano (10 mL), ácido trifluoroacético (10 mL), y trietilsilano (1 mL) por 1 hora. La mezcla se concentró, se recogió con una mezcla de diclorometano (100 mL) y solución acuosa saturada de Na_2CO_3 (20 mL) y se agitó por 10 minutos. Las capas se separaron, y la capa orgánica se secó sobre Na_2SO_4 , se filtró, y se concentró para dar el producto.

EJEMPLO 3F

5-bromo-1-(triisopropilsilil)-1H-pirrollo[2,3-b]piridina

15 A una mezcla de 5-bromo-1H-pirrollo[2,3-b]piridina (15,4 g) en tetrahidrofurano (250 mL) se agregó hexametildisilazida de litio 1M en tetrahidrofurano (86 mL), y luego de 10 minutos, se agregó TIPS-Cl (triisopropilclorosilano) (18,2 mL). La mezcla se agitó a temperatura ambiente por 24 horas. La reacción se diluyó con éter, y la solución resultante se lavó dos veces con agua. Los extractos se secaron (Na_2SO_4), se filtró, y se concentró. El producto
20 crudo se cromatografió sobre gel de sílice con 10% acetato de etilo/hexanos.

EJEMPLO 3G

1-(triisopropilsilil)-1H-pirrollo[2,3-b]piridin-5-ol

A una mezcla de EJEMPLO 3F (24,3 g) en tetrahidrofurano (500 mL) a -78°C se agregó BuLi
25 2,5M (30,3 mL). Luego de 2 minutos, se agregó trimetilborato (11,5 mL), y la mezcla se dejó calentar a temperatura ambiente durante 1 hora. La reacción se vertió en agua, se extrajo tres veces con acetato de etilo, y los extractos combinados se lavaron con salmuera y se concentró. El producto crudo se colocó en tetrahidrofurano (200 mL) a 0°C , y se agregó
30 NaOH 1M (69 mL), seguido por H_2O_2 al 30% (8,43 mL), y la solución se agitó por 1 hora. Se agregó $\text{Na}_2\text{S}_2\text{O}_3$ (10 g), y el pH se ajustó a 4-5 con HCl concentrado y NaH_2PO_4 sólido. La solución se extrajo dos veces con acetato de etilo, y los extractos combinados se lavaron con salmuera, se secó (Na_2SO_4), se filtró, y se concentró. El producto crudo se cromatografió sobre gel de sílice con 5-25% acetato de etilo/hexanos.

35 EJEMPLO 3H

2-(1H-pirrollo[2,3-b]piridin-5-iloxi)-4-fluorobenzoato de metilo

Una mezcla de EJEMPLO 3G (8,5 g), 2,4-difluorobenzoato de metilo (7,05 g), y K_3PO_4 (9,32 g) en diglima (40 mL) a $115^\circ C$ se agitó por 24 horas. La reacción se enfrió, se diluyó con éter (600 mL), y se lavó dos veces con agua, y salmuera, y se concentró. El producto crudo se cromatografió sobre gel de sílice con acetato de etilo al 2-50%/hexanos.

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EJEMPLO 3I

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoato de metilo

Una mezcla de EJEMPLO 3H (1,55 g), EJEMPLO 3E (2,42 g), y HK_2PO_4 (1,42 g) en sulfóxido de dimetilo (20 mL) a $135^\circ C$ se agitó por 24 horas. La reacción se enfrió, se diluyó con éter (400 mL), y se lavó con 3x NaOH 1M, y salmuera, y se concentró. El producto crudo se cromatografió sobre gel de sílice con acetato de etilo al 10-50%/hexanos.

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EJEMPLO 3J

ácido 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoico

Se agitó EJEMPLO 3I (200 mg) en dioxano (10 mL) y NaOH 1M (6 mL) a $50^\circ C$ por 24 horas. La reacción se enfrió, se agregó a una solución de NaH_2PO_4 , y se extrajo tres veces con acetato de etilo. Los extractos combinados se lavaron con salmuera, y se concentró para dar el producto puro.

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EJEMPLO 3K

1-(tetrahidro-2H-piran-4-il)piperidin-4-ilcarbamato de tert-butilo

Se agregó piperidin-4-ilcarbamato de tert-butilo (45,00 g, 225 mmol) y dihidro-2H-piran-4(3H)-ona (24,74 g, 247 mmol) a diclorometano (1000 mL). Se agregó triacetoxiborhidruro de sodio (61,90 g, 292 mmol), y la solución se agitó a temperatura ambiente por 16 horas. La solución se extrajo con hidróxido de sodio 1M y se secó sobre sulfato de sodio anhidro. La solución se filtró y se concentró y se purificó mediante cromatografía flash de columna sobre gel de sílice con 10% metanol (en diclorometano) elevando a 20% metanol (en diclorometano).

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EJEMPLO 3L

35 diclorhidrato de 1-(tetrahidro-2H-piran-4-il)piperidin-4-amina

Una solución de EJEMPLO 3K (52,57 g, 185 mmol) en diclorometano (900 mL) se trató con HCl acuoso 4M (462 mL), y la solución se mezcló enérgicamente a temperatura ambiente por 16 horas. El solvente se eliminó bajo vacío para dar producto crudo como la sal diclorhidrato, la cual se usó sin purificación adicional.

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EJEMPLO 3M

3-nitro-4-(1-(tetrahydro-2H-piran-4-il)piperidin-4-ilamino)benzenosulfonamida

Se agregó EJEMPLO 3L (22,12 g, 86 mmol) a 1,4-dioxano (300 mL) y agua (43 mL). Se agregó trietilamina (43,6 mL, 31,6 g, 313 mmol), y la mezcla se agitó a temperatura ambiente hasta que EJEMPLO 3L se disolvió completamente. Se agregó 4-cloro-3-nitrobenzenosulfonamida y la mezcla se calentó a 90°C por 16 horas. La mezcla se enfrió, y los solventes se eliminaron bajo vacío. Se agregó 10% metanol (en diclorometano) y la solución se agitó enérgicamente a temperatura ambiente hasta que se obtuvo una suspensión fina. El sólido se aisló mediante filtración al vacío y se lavó con diclorometano para dar producto puro.

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EJEMPLO 3N

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-(1-tetrahydro-2H-piran-4-il)piperidin-4-il)amino]fenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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Este EJEMPLO se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 3M en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300MHz, sulfóxido de dimetilo-d₆) δ 11,65 (brs, 1H), 8,53 (br s, 1H), 8,18 (m, 1H), 8,00 (br s, 1H), 7,63 (m, 1H), 7,49 (m, 3H), 7,34 (d, 2H), 7,12 (m, 1H), 7,04 (d, 2H), 6,67 (dd, 1H), 6,37 (d, 1H), 6,20 (d, 1H), 3,95 (m, 2H), 3,05 (m, 10H), 2,73 (m, 4H), 2,17 (m, 10H), 1,95 (m, 2H), 1,80 (m, 2H), 1,63 (m, 2H), 1,39 (t, 2H), 0,93 (s, 6H).

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EJEMPLO 4

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-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 4A

4-(1-metilpiperidin-4-ilamino)-3-nitrobenzenosulfonamida

Este EJEMPLO se preparó utilizando 4-amino-N-metilpiperidina en lugar de 1-(tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

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EJEMPLO 4B

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-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

Este EJEMPLO se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 4A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300MHz, sulfóxido de dimetilo-d₆) □ 11,65 (brs, 1H), 8,55 (br s, 1H), 8,17 (m, 1H), 8,02 (d, 1H), 7,85 (dd, 1H), 7,51 (m, 3H), 7,35 (m, 2H), 7,18 (dd, 1H), 7,05 (d, 2H), 6,68 (dd, 1H), 6,38 (d, 1H), 6,20 (d, 1H), 3,90 (m, 1H), 3,09 (m, 8H), 2,77 (m, 2H), 2,05-2,30 (m, 10H), 1,95 (s, 3H), 1,39 (t, 2H), 1,24 (m, 2H), 0,93 (s, 6H).

EJEMPLO 5

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-[(tetrahydro-2H-piran-4-ilmetil)amino]fenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 5A

3-nitro-4-((tetrahydro-2H-piran-4-il)metilamino)bencenosulfonamida

Una mezcla de 4-fluoro-3-nitrobencenosulfonamida (2,18 g), 1-(tetrahidropiran-4-il)metilamina (1,14 g), y trietilamina (1 g) en tetrahidrofurano (30 mL) se agitaron durante la noche, se neutralizó con HCl concentrado y se concentró. El residuo se suspendió en acetato de etilo y los precipitados se recogieron, se lavó con agua y se secó para dar el compuesto del título.

EJEMPLO 5B

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-metoxycarbonilciclohexanona (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 trifluoroacético (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 (Na₂SO₄), se filtró, y se concentró para dar el producto.

EJEMPLO 5C

2-(4-clorofenil)-4,4-dimetilciclohex-1-encarboxilato de metilo

Se calentó EJEMPLO 5B (62,15g), ácido 4-clorofenilborónico (32,24 g), CsF (64 g) y tetrakis(trifenilfosfin)paladio(0) (2g) en 2:1 dimetoxietano /metanol (600 mL) a 70°C 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 5D

(2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metanol

- 5 A una mezcla de LiBH_4 (13g), EJEMPLO 5C (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 1N con enfriamiento con hielo. La mezcla se diluyó con agua y se extrajo con éter (3x 100 mL). Los extractos se secaron (Na_2SO_4), se filtró, y se concentró. El producto crudo se cromatografió sobre gel de sílice con acetato de etilo al 0-30%/hexanos.

10 EJEMPLO 5E

4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-carboxilato de tert-butilo

- Se agregó cloruro de mesilo (7,5 mL) mediante una jeringa a EJEMPLO 5D (29,3 g) y trietilamina (30 mL) en CH_2Cl_2 (500 mL) a 0°C , y la mezcla se agitó por 1 minuto. Se agregó N-t-butoxicarbonilpiperazina (25 g) y la mezcla se agitó a temperatura ambiente por 24 horas.
- 15 La suspensión se lavó con salmuera, se secó, (Na_2SO_4), se filtró, y se concentró. El producto crudo se cromatografió sobre gel de sílice con 10-20% acetato de etilo/hexanos.

EJEMPLO 5F

1-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazina

- 20 Se agitó EJEMPLO 5E (200 mg) y trietilsilano (1 mL) en diclorometano (15 mL) y ácido trifluoroacético (15 mL) por 1 hora. La mezcla se concentró, se recogió con acetato de etilo, se lavó dos veces con NaH_2PO_4 , y salmuera, y se secó (Na_2SO_4), se filtró y se concentró.

25 EJEMPLO 5G

5-bromo-1-(triisopropilsilil)-1H-pirrol[2,3-b]piridina

- A una mezcla de 5-bromo-1H-pirrol[2,3-b]piridina (15,4 g) en tetrahidrofurano (250 mL) se agregó hexametildisilazida de litio 1M en tetrahidrofurano (86 mL), y luego de 10 minutos, se agregó TIPS-Cl (triisopropilclorosilano) (18,2 mL). La mezcla se agitó a temperatura ambiente por 24 horas. La reacción se diluyó con éter, y la solución resultante se lavó dos veces con agua. Los extractos se secaron (Na_2SO_4), se filtró, y se concentró. El producto crudo se cromatografió sobre gel de sílice con 10% acetato de etilo/hexanos.
- 30

EJEMPLO 5H

- 35 1-(triisopropilsilil)-1H-pirrol[2,3-b]piridin-5-ol

A una mezcla de EJEMPLO 5G (24,3 g) en tetrahidrofurano (500 mL) a -78°C se agregó BuLi 2,5M (30,3 mL). Luego de 2 minutos, se agregó trimetilborato (11,5 mL), y la mezcla se dejó calentar a temperatura ambiente durante 1 hora. La reacción se vertió en agua, se extrajo tres veces con acetato de etilo, y los extractos combinados se lavaron con salmuera y se concentró. El producto crudo se colocó en tetrahidrofurano (200 mL) a 0°C , y se agregó NaOH 1M (69 mL), seguido por H_2O_2 al 30% (8,43 mL), y la solución se agitó por 1 hora. Se agregó $\text{Na}_2\text{S}_2\text{O}_3$ (10 g), y el pH se ajustó a 4-5 con HCl concentrado y NaH_2PO_4 sólido. La solución se extrajo dos veces con acetato de etilo, y los extractos combinados se lavaron con salmuera, se secó (Na_2SO_4), se filtró, y se concentró. El producto crudo se cromatografió sobre gel de sílice con 5-25% acetato de etilo/hexanos.

EJEMPLO 5I

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-fluorobenzoato de metilo

Una mezcla de EJEMPLO 5H (8,5 g), 2,4-difluorobenzoato de metilo (7,05 g), y K_3PO_4 (9,32 g) en diglima (40 mL) a 115°C se agitó por 24 horas. La reacción se enfrió, se diluyó con éter (600 mL), y se lavó dos veces con agua, y salmuera, y se concentró. El producto crudo se cromatografió sobre gel de sílice con acetato de etilo al 2-50%/hexanos.

EJEMPLO 5J

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoato de metilo

Una mezcla de EJEMPLO 5I (1,55 g), EJEMPLO 5F (2,42 g), y HK_2PO_4 (1,42 g) en sulfóxido de dimetilo (20 mL) a 135°C se agitó por 24 horas. La reacción se enfrió, se diluyó con éter (400 mL), y se lavó con 3x NaOH 1M, y salmuera, y se concentró. El producto crudo se cromatografió sobre gel de sílice con acetato de etilo al 10-50%/hexanos.

EJEMPLO 5K

ácido 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoico

Se agitó EJEMPLO 5J (200 mg) en dioxano (10 mL) y NaOH 1M (6 mL) a 50°C por 24 horas. La reacción se enfrió, se agregó una solución de NaH_2PO_4 , y se extrajo tres veces con acetato de etilo. Los extractos combinados se lavaron con salmuera, y se concentró para dar el producto puro.

EJEMPLO 5L

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({3-nitro-4-
[(tetrahydro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

Se agitó EJEMPLO 5K (3,39 g), EJEMPLO 5A (1,87 g), clorhidrato de 1-etil-3-[3-(dimetilamino)propil]-carbodiimida (2,39 g), y 4-dimetilaminopiridina (1,09 g) en CH₂Cl₂ (40 mL) por 24 horas. La reacción se enfrió y se cromatografió sobre gel de sílice con 25-100% acetato de etilo/hexanos, luego 10% metanol/acetato de etilo con 1% ácido acético, para dar el producto (1,62 g, 32%) como un sólido blanco. ¹H NMR (300MHz, sulfóxido de dimetilo-d₆) 11,65 (brs, 1H), 8,55 (br s, 1H), 8,04 (d, 1H), 7,89 (dd, 1H), 7,51 (m, 3H), 7,33 (d, 2H), 7,08 (m, 1H), 7,04 (d, 2H), 6,68 (dd, 1H), 6,39 (d, 1H), 6,19 (d, 1H), 3,84 (m, 1H), 3,30 (m, 4H), 3,07 (m, 4H), 2,73(m, 2H), 2,18 (m, 6H), 1,95 (m, 2H), 1,61 (dd, 2H), 1,38 (m, 2H), 1,24 (m, 4H), 0,92 (s, 6H).

EJEMPLO 6

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)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 6A

4-(4-metilpiperazin-1-ilamino)-3-nitrobencenosulfonamida

Un balón de 50 mL se cargó con 4-cloro-3-nitrobencenosulfonamida (1 g, 4,23 mmol), diclorhidrato de 4-metilpiperazin-1-amina (1 g, 5,32 mmol), y N¹,N¹,N²,N²-tetrametiletan-1,2-diamina (3 mL, 20,01 mmol) en dioxano (10 mL). La mezcla de la reacción se sometió a reflujo por 12 horas. Luego de este tiempo, la mezcla de la reacción se enfrió a temperatura ambiente, la sal se retiró por filtración a través de un embudo Buchner, y el solvente se eliminó al vacío. El producto crudo se agregó a una columna de gel de sílice (Analogix, SF65-200g) y se purificó mediante eluyendo con 0-5% metanol en diclorometano.

EJEMPLO 6B

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)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

Este EJEMPLO se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 6A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300MHz, sulfóxido de dimetilo-d₆) □ 11,65 (brs, 1H), 9,09 (br s, 1H), 8,47 (d, 1H), 8,24 (dd, 1H), 7,99 (d, 1H), 7,50 (m, 4H), 7,34 (d, 2H), 7,04 (d, 2H), 6,64 (dd, 1H), 6,35 (d, 1H), 6,20 (d, 1H), 3,04 (m, 4H), 2,89 (m, 4H), 2,73 (m, 2H), 2,34 (s, 3H), 2,17 (m, 6H), 1,95 (br s, 2H), 1,38 (t, 2H), 1,05 (m, 4H), 0,93 (s, 6H).

EJEMPLO 7

2-(9H-carbazol-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

5 EJEMPLO 7A

2-(9H-carbazol-4-iloxi)-4-fluorobenzoato de etilo

Este EJEMPLO se preparó utilizando 2,4-difluorobenzoato de etilo en lugar de 2,4-difluorobenzoato de metilo y 4-hidroxicarbazol en lugar del EJEMPLO 3G en el EJEMPLO 3H.

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EJEMPLO 7B

2-(9H-carbazol-4-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoato de etilo

15 Este EJEMPLO se preparó utilizando el EJEMPLO 7A en lugar del EJEMPLO 3H en el EJEMPLO 3I.

EJEMPLO 7C

ácido 2-(9H-carbazol-4-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoico

20 Este EJEMPLO se preparó utilizando el EJEMPLO 7B en lugar del EJEMPLO 3I en el EJEMPLO 3J, excepto que aquí al completarse la reacción, se agregó agua y HCl 2N para ajustar el pH a 2, y la sal HCl del producto se extrajo usando $\text{CHCl}_3/\text{CH}_3\text{OH}$.

EJEMPLO 7D

25 2-(9H-carbazol-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

Este EJEMPLO se preparó utilizando el EJEMPLO 7C en lugar del EJEMPLO 1E y EJEMPLO 4A en lugar del EJEMPLO 1F en el EJEMPLO 1G, excepto que aquí la purificación se realizó mediante HPLC preparativa usando una columna C18, 250 x 50 mm, 10 μ , 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 bistrifluoroacetato. ^1H NMR (300 MHz, sulfóxido de dimetilo - d_6) δ 11,82 (br s, 1H), 11,40 (s, 1H), 9,70, 9,40 (ambos v br s, total 2H), 8,40 (d, 1H), 8,10 (br d, 1H), 7,90 (br d, 1H), 7,72 (dd, 1H), 7,60 (d, 1H), 7,48 (d, 1H), 7,38 (m, 3H), 7,22 (m, 2H), 7,07 (m, 4H), 6,78 (dd, 1H), 6,43 (dd, 1H), 6,19 (s, 1H), 3,97 (m, 1H), 3,80 (m, 2H), 3,60, 3,30, 3,10, 2,80 (todos br m, total 11H), 2,20, 2,10, 2,00 (todos br m, total 8H), 1,78 (m, 2H), 1,42 (m, 2H), 1,25 (m, 2H), 0,92 (s, 6H).

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EJEMPLO 8

2-(9H-carbazol-4-iloxi)-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([3-pirrolidin-1-ilpropil)amino]fenil)sulfonil)benzamida

5 EJEMPLO 8A

3-nitro-4-(3-(pirrolidin-1-il)propilamino)bencenosulfonamida

Este EJEMPLO se preparó utilizando 3-(pirrolidin-1-il)propan-1-amina en lugar de 1-(tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

10 EJEMPLO 8B

2-(9H-carbazol-4-iloxi)-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([3-pirrolidin-1-ilpropil)amino]fenil)sulfonil)benzamida

Este EJEMPLO se preparó utilizando el EJEMPLO 7C en lugar del EJEMPLO 1E y EJEMPLO 8A en lugar del EJEMPLO 1F en el EJEMPLO 1G, excepto que aquí la purificación se realizó mediante HPLC preparativa usando una columna C18, 250 x 50 mm, 10 μ , y eluyendo con un gradiente de 20-100% CH₃CN vs. ácido trifluoroacético al 0,1% en agua, para dar el producto como una sal bistrifluoroacetato.. ¹H NMR (300 MHz, sulfóxido de dimetilo -d₆) δ 11,80 (br s, 1H), 11,42 (s, 1H), 9,50, 9,25 (ambos v br s, total 2H), 8,58 (br t, 1H), 8,43 (d, 1H), 7,91 (d, 1H), 7,72 (dd, 1H), 7,60 (d, 1H), 7,50 (d, 1H), 7,38 (m, 3H), 7,23 (m, 2H), 7,07 (m, 3H), 6,93 (d, 1H), 6,78 (dd, 1H), 6,44 (dd, 1H), 6,18 (s, 1H), 3,70, 3,60, 3,20, 3,00 (todos br m, total 18H), 2,18 (br m, 2H), 2,00-180 (envolvente, 8H), 1,42 (m, 2H), 0,92 (s, 6H).

EJEMPLO 9

25 Trans-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)-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 9A

Trans-4-morfolinociclohexilcarbamato de tert-butilo

30 Una solución de 4-aminociclohexilcarbamato de tert-butilo (20,32 g, 95 mmol), éter bis(2-bromoetilico) (14,30 ml, 114 mmol) y trietilamina (33,0 ml, 237 mmol) en N,N-dimetilformamida (200 ml) se agitó por 16 horas a 70 °C. La mezcla de la reacción se enfrió hasta la temperatura ambiente, se concentró y el producto se extrajo con acetato de etilo. La capa orgánica se lavó con solución de carbonato de sodio (15% ac.), se secó y se concentró.

35 El producto se usó en el siguiente paso sin purificación.

EJEMPLO 9B

diclorhidrato de Trans-4-morfolinociclohexanamina

A una solución de trans-4-morfolinociclohexilcarbamato de tert-butilo (19,2 g, 67,5 mmol) en diclorometano (100 ml) se agregó HCl (100 ml, 400 mmol) (4M en dioxano) y la
 5 mezcla de la reacción se agitó por 16 horas a temperatura ambiente. La mezcla de la reacción se diluyó con éter y la sal sólida se retiró por filtración, y se secó en un horno.

EJEMPLO 9C

Trans-4-(4-morfolinociclohexilamino)-3-nitrobencenosulfonamida

Una solución de diclorhidrato de trans-4-morfolinociclohexanamina (5 g, 19,44 mmol),
 4-fluoro-3-nitrobencenosulfonamida (4,32 g, 19,63 mmol) y trietilamina (20 ml, 143 mmol) en
 tetrahidrofurano (60 ml) se agitó por 16 horas a temperatura ambiente. El producto sólido se
 retiró por filtración, se lavó con tetrahidrofurano, éter, diclorometano (3 x) y se secó bajo
 vacío.

15

EJEMPLO 9D

Trans-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)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

Este EJEMPLO se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y
 20 EJEMPLO 9C en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300MHz, sulfóxido
 de dimetilo-d₆) δ 11,61 (brs, 1H), 8,49 (br s, 1H), 8,12 (m, 1H), 7,99 (br s, 1H), 7,71 (m, 1H),
 7,50 (m, 3H), 7,35 (d, 2H), 7,04 (d, 2H), 7,01 (m, 1H), 6,65 (dd, 1H), 6,36 (d, 1H), 6,21
 (d, 1H), 3,60 (m, 4H), 3,04 (m, 4H), 2,73 (m, 2H), 2,57 (m, 2H), 2,42 (m, 1H), 2,18 (m, 6H),
 2,05 (m, 2H), 1,95 (m, 2H), 1,90 (m, 2H), 1,38 (m, 6H), 1,15 (m, 3H), 0,92 (s, 6H).

25

EJEMPLO 10

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(2-
 metoxietil)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

30 EJEMPLO 10A

4-(2-metoxietilamino)-3-nitrobencenosulfonamida

Este EJEMPLO se preparó utilizando 2-metoxietilamina en lugar de 1-(tetrahidropiran-4-
 il)metilamina en el EJEMPLO 1F.

35 EJEMPLO 10B

4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{2-metoxietil}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

Este EJEMPLO se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 10A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300MHz, sulfóxido de dimetilo-d₆) □ 11,65 (brs, 1H), 8,58-8,49 (m, 1H), 8,55 (d, 1H), 8,03 (d, 1H), 7,79 (m, 1H), 7,49 (m, 3H), 7,34 (m, 2H), 7,06 (m, 1H), 7,04 (d, 2H), 6,68 (dd, 1H), 6,38 (m, 1H), 6,20 (d, 1H), 3,61-3,51 (m, 4H), 3,31 (s, 3H), 3,07 (m, 4H), 2,74 (m, 2H), 2,17 (m, 6H), 1,95 (br s, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

10 EJEMPLO 11

4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-{{(3S)-tetrahydro-2H-piran-3-il}metil}amino}fenil}sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 11A

15 (S)-3-nitro-4-((tetrahydro-2H-piran-3-il)metilamino)bencenosulfonamida y
(R)-3-nitro-4-((tetrahydro-2H-piran-3-il)metilamino)bencenosulfonamida

Este EJEMPLO se preparó utilizando (tetrahydro-2H-piran-3-il)metanamina en lugar de 1-(tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

20 EJEMPLO 11B

(S)-3-nitro-4-((tetrahydro-2H-piran-3-il)metilamino)bencenosulfonamida

La mezcla racémica de EJEMPLO 11A se resolvió mediante SFC quiral en una columna AD (21mm i.d.x 250 mm de longitud) usando un gradiente de 10-30% 0,1% dietilamina metanol en CO₂ a lo largo de 15 minutos (temperatura del horno: 40°C; velocidad de flujo: 40 mL/minuto) para dar el compuesto del título.

EJEMPLO 11C

(R)-3-nitro-4-((tetrahydro-2H-piran-3-il)metilamino)bencenosulfonamida

La mezcla racémica de EJEMPLO 11A se resolvió mediante SFC quiral en una columna AD (21mm i.d.x 250 mm de longitud) usando un gradiente de 10-30% 0,1% dietilamina metanol en CO₂ a lo largo de 15 minutos (temperatura del horno: 40°C; velocidad de flujo: 40 mL/minuto) para dar el compuesto del título.

EJEMPLO 11D

35 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-{{(3S)-tetrahydro-2H-piran-3-il}metil}amino}fenil}sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

A una mezcla de EJEMPLO 3J (59,8 mg, 0,105 mmol), EJEMPLO 11B (33mg, 0,105 mmol) y N,N-dimetilpiridin-4-amina (38,4 mg, 0,314 mmol) en diclorometano (5 ml) se agregó clorhidrato de 1-etil-3-[3-(dimetilamino)propil]-carbodiimida (24,07 mg, 0,13 mmol). La mezcla de la reacción se agitó a temperatura ambiente durante la noche y se concentró. 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 NaHCO₃ acuoso al 50%. La capa orgánica se secó sobre Na₂SO₄ anhidro y se concentró para dar el compuesto del título. ¹H NMR (500 MHz, sulfóxido de dimetilo -d₆) □
11,68 (s, 1 H), 11,40 (s, br, 1 H), 8,53 - 8,58 (m, 2 H), 8,04 (d, 1 H), 7,80 (dd, 1 H), 7,47 - 7,54 (m, 3 H), 7,34 (d, 2 H), 7,02 - 7,09 (m, 3 H), 6,67 (dd, 1 H), 6,39 (dd, 1 H), 6,19 (d, 1 H), 3,79 (dd, 1 H), 3,69 - 3,73 (m, 1 H), 3,22 - 3,37 (m, 3 H), 3,16 - 3,21 (m, 1 H), 3,07 (s, 4 H), 2,74 (s, 2 H), 2,09 - 2,24 (m, 6 H), 1,95 (s, 2 H), 1,86 - 1,93 (m, 1 H), 1,79 - 1,85 (m, 1 H), 1,58 - 1,64 (m, 1 H), 1,42 - 1,51 (m, 1 H), 1,38 (t, 2 H), 1,25 - 1,34 (m, 1 H), 0,92 (s, 6 H).

EJEMPLO 12

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 12A

4-((1,4-dioxan-2-il)metoxi)-3-nitrobencenosulfonamida

Se trató (1,4-dioxan-2-il)metanol (380 mg, 3,22 mmol) en tetrahidrofurano (30 ml) con hidruro de sodio (60%) (245 mg, 6,13 mmol) a temperatura ambiente por 30 minutos. La mezcla de la reacción se enfrió en un baño de hielo y se agregó 4-fluoro-3-nitrobencenosulfonamida (675 mg, 3,06 mmol). La mezcla resultante se agitó a temperatura ambiente por 2 horas y se agregó otra porción de hidruro de sodio (60%) (245 mg, 6,13 mmol). La mezcla de la reacción se agitó durante la noche y se detuvo con agua helada (3 ml). La mezcla turbia se filtró y el material filtrado se concentró. El residuo se trituroó con metanol para dar el compuesto del título.

EJEMPLO 12B

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 11D usando EJEMPLO 12A en lugar de EJEMPLO 11B. ^1H NMR (500 MHz, sulfóxido de dimetilo - d_6) $\square$ 11,67 (s, 1 H), 11,42 (s, br, 1 H), 8,34 (s, 1 H), 8,03 (d, 2 H), 7,48 - 7,55 (m, 3 H), 7,41 (d, 1 H), 7,35 (d, 2 H), 7,04 (d, 2 H), 6,67 (dd, 1 H), 6,39 (dd, 1 H), 6,21 (d, 1 H), 4,20 - 4,28 (m, 2 H), 3,85 - 3,91 (m, 1 H), 3,82 (dd, 1 H), 3,74 - 3,78 (m, 1 H), 3,59 - 3,69 (m, 2 H), 3,41 - 3,51 (m, 2 H), 3,05 - 3,17 (m, 4 H), 2,83 (s, br, 2 H), 2,27 (s, br, 4 H), 2,15 (s, 2 H), 1,96 (s, 2 H), 1,39 (t, 2 H), 0,93 (s, 6 H).

EJEMPLO 13

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(3-nitro-4-((3R)-tetrahydro-2H-piran-3-ilmetil)amino)fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 11D usando EJEMPLO 11C en lugar de EJEMPLO 11B. Los espectros de NMR protónicos del EJEMPLO 13 y el EJEMPLO 11D son idénticos. ^1H NMR (500 MHz, sulfóxido de dimetilo - d_6) $\square$ 11,68 (s, 1 H), 11,40 (s, br, 1 H), 8,53 - 8,58 (m, 2 H), 8,04 (d, 1 H), 7,80 (dd, 1 H), 7,47 - 7,54 (m, 3 H), 7,34 (d, 2 H), 7,02 - 7,09 (m, 3 H), 6,67 (dd, 1 H), 6,39 (dd, 1 H), 6,19 (d, 1 H), 3,79 (dd, 1 H), 3,69 - 3,73 (m, 1 H), 3,22 - 3,37 (m, 3 H), 3,16 - 3,21 (m, 1 H), 3,07 (s, 4 H), 2,74 (s, 2 H), 2,09 - 2,24 (m, 6 H), 1,95 (s, 2 H), 1,86 - 1,93 (m, 1 H), 1,79 - 1,85 (m, 1 H), 1,58 - 1,64 (m, 1 H), 1,42 - 1,51 (m, 1 H), 1,38 (t, 2 H), 1,25 - 1,34 (m, 1 H), 0,92 (s, 6 H).

EJEMPLO 14

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-(2-naftilsulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 11D usando naftalen-2-sulfonamida (47 mg, 0,227 mmol) en lugar de EJEMPLO 11B. ^1H NMR (500 MHz, sulfóxido de dimetilo - d_6) $\square$ 11,82 (s, 1 H), 11,69 (s, 1 H), 8,51 (s, 1 H), 8,08 (d, 1 H), 8,05 (d, 1 H), 7,97 (dd, 2 H), 7,82 (dd, 1 H), 7,66 - 7,71 (m, 1 H), 7,63 (t, 1 H), 7,54 (d, 1 H), 7,47 - 7,52 (m, 2 H), 7,34 (d, 2 H), 7,04 (d, 2 H), 6,65 (dd, 1 H), 6,39 (dd, 1 H), 6,18 (s, 1 H), 3,04 (s, 4 H), 2,72 (s, 2 H), 2,10 - 2,20 (m, 6 H), 1,95 (s, 2 H), 1,38 (t, 2 H), 0,92 (s, 6 H).

EJEMPLO 15

4-(4-([4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil)piperazin-1-il)-N-[(3-nitro-4-[(tetrahydro-2H-piran-4-ilmetil)amino]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 15A

6,6-dimetil-4-oxotetrahydro-2H-piran-3-carboxilato de metilo

A una suspensión de NaH lavado con hexano (0,72 g, 60% en aceite mineral) en tetrahidrofurano (30 mL) se agregó una solución de 2,2-dimetildihidro-2H-piran-4(3H)-ona (2,0 g) en tetrahidrofurano (20mL). La suspensión se agitó a temperatura ambiente por 30 minutos. El carbonato de dimetilo (6,31 mL) se agregó por goteo mediante una jeringa. La
5 mezcla se calentó a reflujo por 4h. LC/MS mostró el producto esperado como el producto mayoritario. La mezcla se acidificó con HCl al 5% y se extrajo con diclorometano (100 mL x 3) y se lavó con agua, salmuera y se secó sobre Na₂SO₄. Luego de la evaporación, el producto crudo se cargó en una columna y se eluyó con 10% acetato de etilo en hexano para dar el producto.

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EJEMPLO 15B

6,6-dimetil-4-(trifluorometilsulfonilo)-5,6-dihidro-2H-piran-3-carboxilato de metilo

A una suspensión en agitación enfriada (0°C) de NaH (0,983 g, 60% en aceite mineral) en éter (50 mL) se agregó EJEMPLO 15A (3,2 g). La mezcla se agitó a 0°C por 30
15 minutos antes de la adición de Tf₂O (4,2 mL). La mezcla luego se agitó a temperatura ambiente durante la noche. La mezcla se diluyó con éter (200 mL) y se lavó con HCl al 5% , agua y salmuera. Luego de secar sobre Na₂SO₄, la evaporación del solvente dio el producto crudo el cual se usó en el siguiente paso sin purificación adicional.

20 EJEMPLO 15C

4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-carboxilato de metilo

A una solución de EJEMPLO 15B (2,88 g), ácido 4-clorofenilborónico (1,88 g) y Pd(Ph₃P)₄ (0,578 g) en tolueno (40 mL) y etanol (10 mL) se agregó Na₂CO₃ 2N (10 mL). La
mezcla se agitó a reflujo durante la noche. La mezcla se diluyó éter (300 mL) y se lavó con
25 agua, salmuera y se secó sobre Na₂SO₄. Luego de la evaporación del solvente, el residuo se cargó en una columna y se eluyó con 3% acetato de etilo en hexano para dar el producto.

EJEMPLO 15D

(4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il)metanol

A una solución de EJEMPLO 15C (1,6 g) en éter (20 mL) se agregó LiAlH₄ (1,2 g). La
mezcla se agitó por 4 horas. La mezcla se acidificó cuidadosamente con HCl al 5% y se
extrajo con acetato de etilo (100 mL x 3) y se lavó con agua, salmuera y se secó sobre
Na₂SO₄. Luego de la concentración, el producto crudo se cargó en una columna y se eluyó
30 con 10% acetato de etilo en hexano para dar el producto.

EJEMPLO 15E

4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-carbaldehído

5 A una solución de cloruro de oxalilo (1,1 g) en diclorometano (30 mL) a -78°C se agregó sulfóxido de dimetilo (6,12 mL). La mezcla se agitó a la temperatura por 30 minutos, y luego se agregó una solución de EJEMPLO 15D (1,2 g) en diclorometano (10 mL). La mezcla se agitó a -78°C por 2 horas antes de la adición de 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 . La concentración del solvente y purificación de columna (5% acetato de etilo en hexano) dio el
10 producto.

EJEMPLO 15F

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(piperazin-1-il)benzoato de metilo

15 Una mezcla de EJEMPLO 3H (20,5 g) y piperazina (37,0 g) en sulfóxido de dimetilo (200 mL) se calentó a 110°C por 24 horas, y la mezcla se dejó enfriar a temperatura ambiente. La mezcla se vertió en agua (1 L), se extrajo tres veces con diclorometano, y los extractos combinados se lavaron con 2x agua, y salmuera y se filtró y se concentró para dar el producto puro.

20 EJEMPLO 15G

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il)metil)piperazin-1-il)benzoato de metilo

25 A una solución de EJEMPLO 15E (100 mg) y EJEMPLO 15F (177 mg) en diclorometano (10 mL) se agregó triacetoxiborhidruro de sodio (154 mg). La mezcla se agitó durante la noche. La mezcla se diluyó con acetato de etilo (200 mL) y se lavó con 2%NaOH, agua y salmuera. Luego de secar sobre Na_2SO_4 , la mezcla se filtró y el solvente se evaporó bajo vacío. El residuo se cargó en una columna y se eluyó con acetato de etilo al 30% en hexano para dar el producto puro.

30 EJEMPLO 15H

ácido 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il)metil)piperazin-1-il)benzoico

35 A una solución de EJEMPLO 15G (254 mg) en tetrahidrofurano (4 mL), metanol (2 mL) y agua (2 mL) se agregó LiOH H_2O (126mg). 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 Na₂SO₄. La filtración y evaporación del solvente dio el producto.

EJEMPLO 15I

5 4-(4-[[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil]piperazin-1-il)-N-({3-nitro-4-
[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 1G, sustituyendo EJEMPLO 1E con EJEMPLO 15H. ¹H NMR (300 MHz, sulfóxido de dimetilo -d₆)
□ 11,68 (br s, 1H), 11,42 (s, 1H), 8,60 (m, 1H), 8,57 (d, 1H), 8,05(d, 1H), 7,80 (dd, 1H), 7,48-
10 7,54 (m, 3H), 7,38 (d, 2H), 7,12 (m, 3H), 6,68 (dd, 1H), 6,40 (dd, 1H), 6,20 (s, 1H), 4,11(s,
2H), 3,85(m, 2H), 3,27(m, 6H), 3,07 (m, 2H), 2,84 (m, 2H), 2,14 (m, 5H), 1,92(m, 1H), 1,42
(m, 2H), 1,24(m, 2H), 1,10 (s, 6H).

EJEMPLO 16

15 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({4-[(2-
metoxietil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-
iloxi)benzamida

20 EJEMPLO 16A

4-(2-metoxietilamino)-3-(trifluorometilsulfonil)bencenosulfonamida

Se calentó 4-fluoro-3-(trifluorometilsulfonil)bencenosulfonamida (1,536 g, 5 mmol), 2-
metoxietanamina (0,376 g, 5mmol), y trietilamina (1,939 g, 15 mmol) en solución de
tetrahidrofurano anhidro (30 mL) a 55°C por 3 horas. La solución se diluyó con acetato de
25 etilo, se lavó con agua y salmuera, y se secó (Na₂SO₄), se filtró y el material filtrado se
concentró. El material crudo se usó en el siguiente paso sin purificación adicional.

EJEMPLO 16B

30 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({4-[(2-
metoxietil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-
iloxi)benzamida

Este EJEMPLO se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y
EJEMPLO 16A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (400MHz, sulfóxido
de dimetilo-d₆) □ 11,67 (brs, 1H), 8,14 (m 1H), 8,03 (d, 1H), 7,91 (d, 1H), 7,50 (m, 3H), 7,34
35 (d, 2H), 7,19 (s, 1H), 7,04 (m, 3H), 6,67 (dd, 1H), 6,39 (m, 1H), 6,19 (d, 1H), 3,51 (m, 4H),
3,28 (s, 3H), 3,06 (m, 4H), 2,75 (m, 2H), 2,17 (m, 6H), 1,95 (m, 2H), 1,39 (t, 2H), 0,93 (s, 6H).

EJEMPLO 17

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol-2,3-b)piridin-5-iloxi)-N-([4-([tetrahydro-2H-piran-4-ilmetil]amino)-3-[(trifluorometil)sulfonyl]fenil)sulfonyl)benzamida

5

EJEMPLO 17A

4-((tetrahydro-2H-piran-4-il)metilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida

Este EJEMPLO se preparó utilizando 1-(tetrahidropiran-4-il)metilamina en lugar de 2-metoxietanamina en el EJEMPLO 16A.

10

EJEMPLO 17B

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol-2,3-b)piridin-5-iloxi)-N-([4-([tetrahydro-2H-piran-4-ilmetil]amino)-3-[(trifluorometil)sulfonyl]fenil)sulfonyl)benzamida

15

Este EJEMPLO se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 17A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (400MHz, sulfóxido de dimetilo-d₆) □ 11,70 (brs, 1H), 8,15 (m, 1H), 8,04 (d, 1H), 7,92 (d, 1H), 7,51 (m, 3H), 7,34 (d, 2H), 7,19 (s, 1H), 7,05 (m, 3H), 6,68 (dd, 1H), 6,40 (m, 1H), 6,18 (d, 1H), 3,85 (m, 2H), 3,25 (m, 4H), 3,07 (m, 4H), 2,77 (m, 2H), 2,17 (m, 6H), 1,95 (m, 2H), 1,84 (m, 1H), 1,54 (m, 2H), 1,39 (t, 2H), 1,24 (m, 2H), 0,93 (s, 6H).

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EJEMPLO 18

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-([tetrahydro-2H-piran-4-ilmetil]amino)fenil]sulfonyl)benzamida

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EJEMPLO 18A

2-(1H-indol-5-iloxi)-4-fluorobenzoato de metilo

Una mezcla de 5-hidroxiindol (8,5 g), 2,4-difluorobenzoato de metilo (7,05 g), y K₃PO₄ (9,32 g) en diglima (40 mL) a 115°C se agitó por 24 horas. La reacción se enfrió, se diluyó con éter (600 mL), y se lavó dos veces con agua, y salmuera, y se concentró. El producto crudo se cromatografió sobre gel de sílice con acetato de etilo al 2-50%/hexanos.

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EJEMPLO 18B

2-(1H-indol-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoato de metilo

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Una mezcla de EJEMPLO 18A (1,7 g), EJEMPLO 3E (1,8 g), y HK_2PO_4 (1,21 g) en sulfóxido de dimetilo (20 mL) a 135°C se agitó por 24 horas. La reacción se enfrió, se diluyó con éter (400 mL), y se lavó con 3x NaOH 1M, y salmuera, y se concentró. El producto crudo se cromatografió sobre gel de sílice con acetato de etilo al 10-50%/hexanos.

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EJEMPLO 18C

ácido 2-(1H-indol-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoico

Se agitó EJEMPLO 18B (200 mg) en dioxano (10 mL) y NaOH 1M (6 mL) a 50°C por 24 horas. La reacción se enfrió, se agregó una solución de NaH_2PO_4 , y se extrajo tres veces con acetato de etilo. Los extractos combinados se lavaron con salmuera, y se concentró para dar el producto puro.

15 EJEMPLO 18D

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}sulfonyl)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 11D reemplazando EJEMPLO 3J con EJEMPLO 18C, y EJEMPLO 1F en lugar del EJEMPLO 11B. ^1H NMR (300MHz, sulfóxido de dimetilo- 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).

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EJEMPLO 19

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}sulfonyl)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 11D reemplazando EJEMPLO 11B con EJEMPLO 9B y EJEMPLO 3J con EJEMPLO 18C. ^1H NMR (500 MHz, piridin- d_5) $\square$ 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),

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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 20

- 5 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-indol-5-iloxi)-N-
 10 {4-[(2-metoxietil)amino]-3-nitrofenil)sulfonil]benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 11D reemplazando EJEMPLO 11B con EJEMPLO 10A y EJEMPLO 3J con EJEMPLO 18C. ^1H NMR (400 MHz, sulfóxido de dimetilo - 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 21

- 15 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 se describe en el EJEMPLO 11D reemplazando EJEMPLO 3J con EJEMPLO 18C. ^1H NMR (400 MHz, sulfóxido de dimetilo - d_6) $\square$ 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).

25 EJEMPLO 22

- 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 se describe en el EJEMPLO 11D usando EJEMPLO 11C en lugar de EJEMPLO 11B, y EJEMPLO 18C en lugar de EJEMPLO 3J. ^1H NMR (400 MHz, sulfóxido de dimetilo - d_6) $\square$ 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 23

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

5 EJEMPLO 23A

2-(1H-indol-5-iloxi)-4-(piperazin-1-il)benzoato de metilo

El compuesto del título se preparó como se describe en el EJEMPLO 15F reemplazando EJEMPLO 3H con EJEMPLO 18A.

10 EJEMPLO 23B

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 como se describe en el EJEMPLO 15G reemplazando EJEMPLO 15F con EJEMPLO 23A.

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EJEMPLO 23C

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 como se describe en el EJEMPLO 15H reemplazando EJEMPLO 15G con EJEMPLO 23B.

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EJEMPLO 23D

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

25 El compuesto del título se preparó como se describe en el EJEMPLO 11D reemplazando EJEMPLO 11B con EJEMPLO 1F, y EJEMPLO 3J con EJEMPLO 23C. ¹H NMR (400 MHz, sulfóxido de dimetilo -d₆) □ 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).

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EJEMPLO 24

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-(tetrahidro-2H-piran-4-ilmetoxi)fenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 24A

3-nitro-4-((tetrahidro-2H-piran-4-il)metoxi)bencenosulfonamida

Se trató (tetrahidro-2H-piran-4-il)metanol (2,0 g) en tetrahidrofurano (20 mL) con NaH al 60% (1,377 g). La solución se agitó por 20 minutos a temperatura ambiente. A esta solución se agregó 4-fluoro-3-nitrobencenosulfonamida (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 MgSO₄, se filtró, y se concentró. El residuo se purificó con cromatografía flash de columna sobre gel de sílice eluyendo con 20-60% acetato de etilo en hexanos.

EJEMPLO 24B

4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-(tetrahidro-2H-piran-4-ilmetoxi)fenil}sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 24A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,67 (s, 1H), 8,33 (s, 1H), 8,00-8,02 (m, 2H), 7,50-7,53 (m, 3H), 7,34-7,36 (m, 3H), 7,04 (d, 2H), 6,67 (dd, 1H), 6,38 (d, 1H), 6,21 (s, 1H), 4,06 (d, 2H), 3,88 (dd, 2H), 3,08 (s, 4H), 2,80 (s, 2H), 2,25 (s, 4H), 2,15 (s, 2H), 1,96 (s, 2H), 1,63-1,66 (m, 2H), 1,52-1,55 (m, 1 H), 1,33-1,40 (m, 4H), 0,92 (s, 6H).

EJEMPLO 25

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 25A

4-((1,4-dioxan-2-il)metilamino)-3-nitrobencenosulfonamida

El compuesto del título se preparó como se describe en el EJEMPLO 1F usando (1,4-dioxan-2-il)metanamina en lugar de (tetrahidropiran-4-il)metanamina.

EJEMPLO 25B

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 11D usando EJEMPLO 25A en lugar de EJEMPLO 11B. ¹H NMR (500 MHz, sulfóxido de dimetilo-d₆) □ 11,66 (s, 1H), 11,38 (s, 1H), 8,53 - 8,59 (m, 2H), 8,03 (d, 1H), 7,81 (dd, 1H), 7,46 - 7,54 (m, 3H), 7,34 (d, 2H), 7,09 (d, 1H), 7,04 (d, 2H), 6,68 (dd, 1H), 6,38 (dd, 1H), 6,19 (d, 1H), 3,75 -

3,86 (m, 3H), 3,58 - 3,68 (m, 2H), 3,45 - 3,52 (m, 2H), 3,35 - 3,43 (m, 2H), 3,07 (s, 4H), 2,75 (s, 2H), 2,17 (d, 6H), 1,95 (s, 2H), 1,38 (t, 2H), 0,92 (s, 6H)

EJEMPLO 26

5 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({3-nitro-4-[(2,2,2-trifluoroetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 26A

3-nitro-4-(2,2,2-trifluoroetilamino)bencenosulfonamida

10 El compuesto del título se preparó utilizando 2,2,2-trifluoroetanamina en lugar de (tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

EJEMPLO 26B

15 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({3-nitro-4-[(2,2,2-trifluoroetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 26A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500 MHz, sulfóxido de dimetilo-d₆) δ 11,48 (s, 1H), 8,40 (m, 2H), 7,90 (d, 1H), 7,71 (dd, 1H), 7,59 (d, 1H), 7,40 (t, 1H), 7,34 (d, 2H), 7,25 (d, 1H), 7,06 (m, 3H), 6,61 (dd, 1H), 6,26 (m, 2H), 4,32 (m, 2H), 3,00 (m, 4H), 2,73 (s, 2H), 2,19 (m, 6H),
20 1,96 (s, 2H), 1,39 (t, 2H), 0,93 (s, 6H).

EJEMPLO 27

25 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({3-nitro-4-[(3,3,3-trifluoropropil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 27A

3-nitro-4-(3,3,3-trifluoropropilamino)bencenosulfonamida

El compuesto del título se preparó utilizando 3,3,3-trifluoropropan-1-amina en lugar de (tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

EJEMPLO 27B

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({3-nitro-4-[(3,3,3-trifluoropropil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 27A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500 MHz, sulfóxido de dimetilo-d₆) δ 11,47 (s, 1H), 8,37 (d, 1H), 8,29 (m, 1H), 7,89 (d, 1H), 7,61 (m, 2H), 7,39 (t, 1H), 7,35 (d, 2H), 7,22 (d, 1H), 7,05

(d, 2H), 6,75 (d, 1H), 6,62 (dd, 1H), 6,27 (m, 2H), 3,59 (q, 2H), 3,00 (m, 4H), 2,73 (s, 2H), 2,66 (m, 2H), 2,18 (m, 6H), 1,96 (s, 2H), 1,39 (t, 2H), 0,93 (m, 6H).

EJEMPLO 28

- 5 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-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 28A

(S)-4-((1,4-dioxan-2-il)metoxi)-3-nitrobencenosulfonamida

- 10 La mezcla racémica de EJEMPLO 12A se resolvió en una columna AD de SFC quiral para dar el compuesto del título.

EJEMPLO 28B

- 15 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-pirrol[2,3-b]piridin-5-iloxi)benzamida

- El compuesto del título se preparó como se describe en el EJEMPLO 11D usando EJEMPLO 28A en lugar de EJEMPLO 11B. ¹H NMR (500 MHz, sulfóxido de dimetilo-d₆) □
 11,67 (s, 2H), 8,35 (s, 1H), 8,03 (d, 2H), 7,48 - 7,57 (m, 3H), 7,42 (d, 1H), 7,35 (d, 2H), 7,05 (d, 2H), 6,68 (dd, 1H), 6,39 (dd, 1H), 6,21 (s, 1H), 4,19 - 4,30 (m, 2H), 3,85 - 3,92 (m, 1H),
 20 3,73 - 3,85 (m, 2H), 3,58 - 3,70 (m, 2H), 3,40 - 3,52 (m, 2H), 3,10 (s, 4H), 2,85 (s, 2H), 2,18 - 2,39 (m, 3H), 2,15 (s, 2H), 1,96 (s, 2H), 1,39 (t, 2H), 0,93 (s, 6H).

EJEMPLO 29

- 25 Cis-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]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 29A

Cis-4-((4-metoxiciclohexil)metilamino)-3-nitrobencenosulfonamida

- 30 4-Fluoro-3-nitrobencenosulfonamida (1,098 g) y EJEMPLO 34A (1 g) en tetrahidrofurano (20 mL) se trató con N,N-diisopropiletilamina (0,871 mL) durante la noche. La mezcla de la reacción se concentró y el residuo se purificó mediante cromatografía de fase inversa, se eluyó con 40-55% acetonitrilo en ácido trifluoroacético al 0,1% en agua durante 25 min para dar el isómero *cis* EJEMPLO 29A y el isómero *trans* EJEMPLO 34B.

- 35 EJEMPLO 29B

Cis-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4-metoxiciclohexil)metil]amino}-3-nitrofenil)sulfonyl]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 11D usando EJEMPLO 29A en lugar de EJEMPLO 11B. ¹H NMR (500 MHz, sulfóxido de dimetilo-d₆) □

5 11,69 (s, 1H), 11,36 (s, 1H), 8,53 - 8,63 (m, 2H), 8,04 (d, 1H), 7,79 (dd, 1H), 7,47 - 7,56 (m, 3H), 7,34 (d, 2H), 7,00 - 7,12 (m, 3H), 6,68 (dd, 1H), 6,39 (dd, 1H), 6,19 (d, 1H), 3,37 (s, 1H), 3,26 (t, 2H), 3,20 (s, 3H), 3,07 (s, 4H), 2,75 (s, 2H), 2,17 (d, 6H), 1,95 (s, 2H), 1,81 (dd, 2H), 1,64 - 1,74 (m, 1H), 1,48 (dd, 2H), 1,23 - 1,42 (m, 6H), 0,92 (s, 6H).

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EJEMPLO 30

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}sulfonyl]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 30A

(R)-4-((1,4-dioxan-2-il)metoxi)-3-nitrobencenosulfonamida

La mezcla racémica de EJEMPLO 12A se resolvió en una columna AD de SFC quiral para dar el compuesto del título.

EJEMPLO 30B

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}sulfonyl]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

25 El compuesto del título se preparó como se describe en el EJEMPLO 11D usando EJEMPLO 30A en lugar de EJEMPLO 11B. ¹H NMR (500 MHz, sulfóxido de dimetilo-d₆) □
11,67 (s, 2H), 8,35 (s, 1H), 8,03 (d, 2H), 7,48 - 7,57 (m, 3H), 7,42 (d, 1H), 7,35 (d, 2H), 7,05 (d, 2H), 6,68 (dd, 1H), 6,39 (dd, 1H), 6,21 (s, 1H), 4,19 - 4,30 (m, 2H), 3,85 - 3,92 (m, 1H), 3,73 - 3,85 (m, 2H), 3,58 - 3,70 (m, 2H), 3,40 - 3,52 (m, 2H), 3,10 (s, 4H), 2,85 (s, 2H), 2,18 -
30 2,39 (m, 3H), 2,15 (s, 2H), 1,96 (s, 2H), 1,39 (t, 2H), 0,93 (s, 6H).

EJEMPLO 31

4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-N-[(4-{[(1,4-dioxan-2-ilmetil)amino]-3-nitrofenil}sulfonyl]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

35 El compuesto del título se preparó como se describe en el EJEMPLO 1G reemplazando EJEMPLO 1E y EJEMPLO 1F con EJEMPLO 15H y EJEMPLO 25A,

respectivamente. ^1H NMR (300 MHz, sulfóxido de dimetilo- d_6) δ 11,66 (s, 1H), 11,46 (m, 1H), 8,54 (m, 2H), 8,45 (m, 1H), 8,03 (d, 1H), 7,83 (m, 2H), 7,50 (m, 3H), 7,34 (m, 3H), 7,12 (m, 2H), 6,68 (dd, 1H), 6,38 (dd, 1H), 6,20 (d, 1H), 4,11 (s, 2H), 3,79 (m, 4H), 3,51 (m, 6H), 3,05 (m, 4H), 2,17 (m, 3H), 1,17 (s, 6H).

5

EJEMPLO 32

4-(4-([4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil)piperazin-1-il)-N-([4-(1,4-dioxan-2-ilmetoxi)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 1G reemplazando EJEMPLO 1E y EJEMPLO 1F con EJEMPLO 15H y EJEMPLO 12A, respectivamente. ^1H NMR (300 MHz, sulfóxido de dimetilo- d_6) δ 11,67 (s, 1H), 8,37 (d, 1H), 8,03 (m, 2H), 7,50 (m, 3H), 7,37 (d, 2H), 7,13 (d, 2H), 6,68 (dd, 1H), 6,40 (dd, 1H), 6,20 (d, 1H), 4,25 (m, 2H), 4,12 (s, 2H), 3,84 (m, 3H), 3,63 (m, 2H), 3,45 (m, 2H), 3,06 (m, 4H), 2,86 (m, 2H), 2,24 (m, 6H), 1,20 (m, 6H).

15

EJEMPLO 33

Trans-4-(4-([4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil)piperazin-1-il)-N-([4-([4-morfolin-4-ilciclohexil]amino)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 1G reemplazando EJEMPLO 1E y EJEMPLO 1F con EJEMPLO 15H y EJEMPLO 9C, respectivamente. ^1H NMR (300 MHz, sulfóxido de dimetilo- d_6) δ 11,63 (s, 1H), 8,51 (d, 1H), 8,15 (d, 1H), 8,01 (d, 1H), 7,76 (dd, 1H), 7,48 (m, 3H), 7,38 (d, 2H), 7,13 (d, 2H), 7,06 (d, 1H), 6,66 (dd, 1H), 6,36 (dd, 1H), 6,21 (d, 1H), 4,11 (s, 2H), 3,63 (m, 5H), 3,05 (m, 4H), 2,83 (s, 2H), 2,64 (m, 4H), 2,17 (m, 6H), 2,05 (m, 2H), 1,91 (s, 2H), 1,43 (m, 6H), 1,17 (m, 6H).

25

EJEMPLO 34

Trans-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)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 34A

(4-metoxiciclohexil)metanamina

Se trató (4-metoxifenil)metanamina (1 g, 1,29 mmol) en etanol (10 ml) con Rh- Al_2O_3 al 5% (99,8 mg, 0,048 mmol) bajo una atmósfera de H_2 (500 psi) a 50°C por 16 horas. Se agregó más Rh- Al_2O_3 al 5% (0,4 g). La mezcla resultante se agitó bajo una atmósfera de H_2 (500 psi) a 60°C por 2 horas. el material insoluble se retiró por filtración y el material filtrado

35

se concentró para dar una mezcla de producto *cis* y *trans* como un aceite, el cual se usó en el siguiente paso sin purificación adicional.

EJEMPLO 34B

5 Trans-4-((4-metoxiciclohexil)metilamino)-3-nitrobencenosulfonamida

Se trató 4-fluoro-3-nitrobencenosulfonamida (1,098 g) y EJEMPLO 34A (1 g) en tetrahidrofurano (20 mL) con N,N-diisopropiletilamina (0,871 mL) durante la noche. La mezcla de la reacción se concentró y el residuo se purificó mediante cromatografía de fase inversa, y se eluyó con 40-55% acetonitrilo en ácido trifluoroacético al 0,1% en agua a lo largo de 25 minutos.

EJEMPLO 34C

Trans-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]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

15 El compuesto del título se preparó como se describe en el EJEMPLO 11D usando EJEMPLO 34B en lugar de EJEMPLO 11B. ¹H NMR (500 MHz, sulfóxido de dimetilo-d₆) □ 11,69 (s, 1 H), 11,37 (s, 1 H), 8,52 - 8,62 (m, 2 H), 8,04 (d, 1 H), 7,79 (dd, 1 H), 7,47 - 7,55 (m, 3 H), 7,34 (d, 2 H), 7,02 - 7,09 (m, 3 H), 6,68 (dd, 1 H), 6,39 (dd, 1 H), 6,19 (d, 1 H), 3,21 - 3,27 (m, 5 H), 3,02 - 3,12 (m, 5 H), 2,75 (s, 2 H), 2,20 (s, 4 H), 2,14 (s, 2 H), 1,93 - 2,04 (m, 20 4 H), 1,79 (d, 2 H), 1,55 - 1,65 (m, 1 H), 1,38 (t, 2 H), 0,97 - 1,12 (m, 4 H), 0,92 (s, 6 H).

EJEMPLO 35

4-(4-([4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil)piperazin-1-il)-N-([5-ciano-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

25 El compuesto del título se preparó como se describe en el EJEMPLO 1G reemplazando EJEMPLO 1E y EJEMPLO 1F con EJEMPLO 15H y EJEMPLO 36C, respectivamente. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) □ 11,65 (s, 1H), 8,78 (s, 1H), 8,58 (s, 1H), 8,00 (d, 1H), 7,51 (m, 3H), 7,38 (d, 2H), 7,14 (d, 2H), 6,68 (dd, 1H), 6,37 (dd, 1H), 6,23 (d, 1H), 4,31 (d, 2H), 4,13 (s, 2H), 3,88 (dd, 2H), 3,11 (m, 5H), 2,16 (m, 6H), 1,65 30 (m, 2H), 1,35 (m, 2H), 1,19 (s, 6H).

EJEMPLO 36

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

35

EJEMPLO 36A

Se enfrió cloruro de 5-bromo-6-cloropiridin-3-sulfonilo (8,2 g) en metanol (20 mL) a 0 °C. A esta solución se agregó NH₃ 7N en metanol (80 mL). La mezcla de la 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 (MgSO₄), se filtró, y se concentró. El sólido se purificó mediante cromatografía flash de columna sobre gel de sílice usando 20-100% acetato de etilo en hexanos para dar el compuesto del título.

EJEMPLO 36B

El compuesto del título se preparó utilizando el EJEMPLO 36A en lugar de 4-fluoro-3-nitrobencenosulfonamida en el EJEMPLO 24A.

EJEMPLO 36C

Una mezcla de EJEMPLO 36B (0,702 g), dicianocinc (0,129 g), y tetrakis(trifenilfosfin)paladio(0) (0,231 g) en N,N-dimetilformamida (2 mL) se desgasificó mediante un ciclo de vacío/nitrógeno tres veces. La mezcla de la reacción se calentó a 120 °C por 3 horas. Luego de enfriar, se vertió en agua y se extrajo con acetato de etilo tres veces. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre MgSO₄, se filtró, y se concentró. El residuo se purificó con cromatografía flash de columna sobre gel de sílice eluyendo con 20%-60% acetato de etilo en hexanos para dar el compuesto del título.

EJEMPLO 36D

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([5-ciano-6-(tetrahydro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 36C en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,56 (s, 1H), 8,66 (s, 1H), 8,44 (s, 1H), 7,94 (d, 1H), 7,55 (d, 1H), 7,44 (t, 1H), 7,34-7,35 (m, 3H), 7,04 (d, 2H), 6,65 (dd, 1H), 6,32 (s, 1H), 6,24 (s, 1H), 4,26 (d, 2H), 3,86 (dd, 2H), 3,10 (s, 4H), 2,75 (s, 2H), 2,31-2,35 (m, 2H), 2,01-2,05 (m, 1H), 2,15 (s, 2H), 1,96 (s, 2H), 1,63-1,66 (m, 2H), 1,33-1,40 (m, 4H), 0,92 (s, 6H).

EJEMPLO 37

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-fluorotetrahydro-2H-piran-4-il]metoxi)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 37A

1,6-dioxaespiro[2,5]octan-2-carbonitrilo

Una mezcla de tetrahidropiran-4-ona (10 mL) y cloroacetonitrilo (6,4 mL) en tert-butanol (10 mL) se agitó por 10 minutos. A esta solución se agregó una solución de tert-butóxido de potasio (12,11 g) en 200 mL de tert-butanol a temperatura ambiente durante 40 minutos. La mezcla de la reacción se agitó por 16 horas, se diluyó con agua y se detuvo lentamente con HCl 1 N. El solvente se eliminó parcialmente por evaporación por rotación. Luego se extrajo con éter (5x 200 mL). Los extractos combinados se lavó con salmuera, se secó sobre MgSO_4 , se filtró, y el material filtrado se concentró y se purificó mediante cromatografía flash sobre sílice con acetato de etilo:hexanos 3:7 a 1:1 para dar el compuesto del título.

EJEMPLO 37B

2-(4-fluorotetrahidro-2H-piran-4-il)-2-hidroxiacetonitrilo

Se trató EJEMPLO 37A (11,5 g) en diclorometano (40 mL) en una botella de polipropileno con fluoruro de hidrógeno al 70%-piridina (10,4 mL) por goteo a 0 °C. La solución se dejó calentar a temperatura ambiente durante 3 horas, y se agitó por otras 1,5 horas. La mezcla de la reacción se diluyó con acetato de etilo (200 mL) y se vertió en NaHCO_3 acuoso saturado. Se usó NaHCO_3 sólido adicional cuidadosamente hasta que se detuvo el burbujeo. La capa orgánica se aisló, y la capa acuosa se extrajo con acetato de etilo adicional tres veces (150 mL cada vez). Las capas orgánicas combinadas se lavaron con HCl al 5% (50 mL cada vez, dos veces), salmuera, se secó sobre MgSO_4 , se filtró y se concentró para dar el producto deseado el cual se usó directamente en el siguiente paso.

25

EJEMPLO 37C

(4-fluorotetrahidro-2H-piran-4-il)metanol

Se enfrió EJEMPLO 37B (11,7 g, 74 mmol) en 2-propanol (150 mL) y agua (37,5 mL) a 0 °C. A esta solución se agregó NaBH_4 (4,20 g, 111 mmol). La solución se agitó y se dejó calentar a temperatura ambiente durante 3 horas. Se detuvo con acetona, y se agitó por otra 1 hora. El líquido traslúcido se separó del sólido mediante decantación. Se usó acetato de etilo adicional (2x 100 mL) para lavar el sólido, y la mezcla se decantó. Las soluciones orgánicas combinadas se concentraron. El residuo se purificó mediante cromatografía flash, eluyendo con 1:1 acetato de etilo:hexanos para dar el compuesto del título.

35

EJEMPLO 37D

4-((4-fluorotetrahidro-2H-piran-4-il)metoxi)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 37C en lugar de (tetrahidro-2H-piran-4-il)metanol en el EJEMPLO 24A.

5 EJEMPLO 37E

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 11D usando EJEMPLO 37D en lugar de EJEMPLO 11B. ¹H NMR (sulfóxido de dimetilo-d₆). 11,64 (s, 2H), 8,33 (s, 1H), 8,00-8,01 (m, 2H), 7,39-7,57 (m, 4H), 7,33 (d, J = 8,24 Hz, 2H), 7,03 (d, J = 8,54 Hz, 2H), 6,65 (dd, J = 9, 1,98 Hz, 1H), 6,37-6,38 (m, 1H), 6,19 (d, J = 1,53 Hz, 1H), 4,35 (d, J = 20,75 Hz, 2H), 3,74-3,78 (m, 2H), 3,55-3,60 (m, 2H), 3,07 (br, 4H), 2,80 (br, 2H), 2,25 (br, 4H), 2,13 (br, 2H), 1,81-1,94 (m, 6H), 1,38 (t, J = 6,26 Hz, 2H), 0,91 (s, 6H).

15

EJEMPLO 38

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

20 EJEMPLO 38A

3-ciano-4-((tetrahidro-2H-piran-4-il)metoxi)bencenosulfonamida

El compuesto del título se preparó utilizando 3-ciano-4-fluorobencenosulfonamida en lugar de 4-fluoro-3-nitrobencenosulfonamida en el EJEMPLO 24A.

25 EJEMPLO 38B

5-sulfamoil-2-((tetrahidro-2H-piran-4-il)metoxi)benzamida

A una solución de EJEMPLO 38A (0,455 g) en etanol (3 mL) y tetrahidrofurano (1 mL) se agregó peróxido de hidrógeno (30% en agua, 2 mL) seguido por NaOH acuoso 1 N (1,024 ml) y se calentó a 35°C por 3 horas. La reacción se vertió en diclorometano (50 mL) y HCl acuoso 1N (25 mL). La capa acuosa se extrajo con diclorometano (3 x 50 mL). El precipitado contenido en las capas orgánicas combinadas se recogió mediante filtración para dar el compuesto del título.

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EJEMPLO 38C

35 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-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 38B en lugar del EJEMPLO 1F y EJEMPLO 3J en lugar del EJEMPLO 1E en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) δ 11,79 - 11,70 (m, 1H), 11,66 - 11,54 (m, 1H), 9,29 - 9,08 (m, 1H), 8,27 (d, 1H), 8,08 (d, 1H), 7,97 - 7,90 (m, 1H), 7,76 - 7,72 (m, 1H), 7,62 (s, 1H), 7,54 (s, 1H), 7,50 (d, 1H), 7,39 (d, 1H), 7,23 (d, 1H), 7,08 (d, 1H), 6,74 - 6,67 (m, 1H), 6,44 (s, 1H), 6,22 (s, 1H), 4,03 (d, 6H), 3,74 - 3,52 (m, 4H), 3,33 (s, 4H), 3,11 - 2,90 (m, 2H), 2,01 (s, 4H), 1,79 - 1,58 (m, 2H), 1,24 (s, 5H), 0,94 (s, 6H).

EJEMPLO 39

10 Cis-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)-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 39A

Cis-4-morfolinociclohexilcarbamato de tert-butilo

15 A una solución de morfolina (4,08 g) y 4-oxociclohexilcarbamato de tert-butilo (10 g) agitada por 24 horas a temperatura ambiente en isopropóxido de titanio (IV) (27,5 mL), se agregó metanol (10 mL) seguido por la adición cuidadosa de borhidruro de sodio (3,55 g). La mezcla de la reacción se detuvo con solución de agua/NaOH, se extrajo con éter, se secó sobre sulfato de magnesio, se filtró, y se concentró. El producto se separó del isómero trans y se purificó mediante cromatografía flash (gel de sílice, 50% - 100% acetona en hexanos) para dar el compuesto del título.

EJEMPLO 39B

bis(2,2,2-trifluoroacetato) de cis-4-morfolinociclohexanamina

25 A una solución de EJEMPLO 39A (2,43 g) en diclorometano (15 ml) se agregó ácido trifluoroacético (5 ml) y la mezcla de la reacción se agitó por 16 horas a temperatura ambiente. La mezcla de la reacción se concentró y el producto crudo se usó sin purificación.

EJEMPLO 39C

30 4-(cis-4-morfolinociclohexilamino)-3-nitrobenzenosulfonamida

Una solución de EJEMPLO 39B (0,40 g), 4-fluoro-3-nitrobenzenosulfonamida (0,478 g) y trietilamina (2 mL) en tetrahidrofurano (10 mL) se agitó por 3 días a temperatura ambiente. La mezcla de la reacción se concentró y se purificó mediante cromatografía flash (gel de sílice, 0-30% metanol / diclorometano) para dar el producto.

35

EJEMPLO 39D

Cis-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)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 39C en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500 MHz, piridin-d₅) □ 13,07 (s, 1H), 9,30 (d, 1H), 8,64 (d, 1H), 8,43 (d, 1H), 8,38 (dd, 1H), 8,11 (d, 1H), 7,67 (t, 2H), 7,44 (d, 2H), 7,06 (d, 2H), 6,91 (d, 1H), 6,74 (dd, 1H), 6,48 - 6,55 (m, 2H), 3,65 - 3,73 (m, 5H), 3,02 - 3,09 (m, 4H), 2,76 (s, 2H), 2,41 - 2,48 (m, 4H), 2,25 (t, 2H), 2,09 - 2,16 (m, 5H), 1,97 (s, 2H), 1,77 - 1,86 (m, 2H), 1,55 - 1,63 (m, 6H), 1,39 (t, 2H), 0,93 (s, 6H).

10 EJEMPLO 40

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-pirrolo[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 40A

15 5,6-dicloropiridin-3-sulfonamida

El compuesto del título se preparó utilizando cloruro de 5,6-dicloropiridin-3-sulfonilo en lugar de cloruro de 5-bromo-6-cloropiridin-3-sulfonilo en el EJEMPLO 36A.

EJEMPLO 40B

20 5-cloro-6-((tetrahidro-2H-piran-4-il)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 40A en lugar de 4-fluoro-3-nitrobencenosulfonamida en el EJEMPLO 24A.

EJEMPLO 40C

25 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 40B en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,67 (s, 1H), 8,52 (s, 1H), 8,39 (d, 1H), 8,03 (d, 1H), 7,54 (d, 1H), 7,52 (d, 1H), 7,50 (dd, 1H), 7,35 (d, 2H), 7,04 (d, 2H), 6,67 (dd, 1H), 6,39 (m, 1H), 6,21 (d, 1H), 4,25 (d, 2H), 3,87 (dd, 2H), 3,30 (m, 2H), 3,10 (v br s, 4H), 2,90 (v br s, 2H), 2,35 (v br s, 4H), 2,17 (br m, 2H), 2,05 (m, 1H), 1,96 (s, 2H), 1,64 (d, 2H), 1,40 (t, 2H), 1,35 (ddd, 2H), 0,93 (s, 6H).

EJEMPLO 41

35 4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-N-([5-cloro-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 15H en lugar del EJEMPLO 3J y EJEMPLO 40B en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,68 (s, 1H), 8,55 (d, 1H), 8,41 (d, 1H), 8,04 (d, 1H), 7,54 (m, 2H), 7,50 (dd, 1H), 7,38 (d, 2H), 7,14 (d, 2H), 6,68 (dd, 1H), 6,40 (m, 1H), 6,20 (d, 1H), 4,25 (d, 2H), 4,12 (s, 2H), 3,87 (dd, 2H), 3,30 (m, 2H), 3,10 (v br s, 4H), 2,90 (v br s, 2H), 2,27 (v br s, 4H), 2,17 (br m, 2H), 2,05 (m, 1H), 1,96 (s, 2H), 1,64 (d, 2H), 1,35 (ddd, 2H), 0,97 (s, 6H).

EJEMPLO 42

10 4-(4-{{4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il}metil}piperazin-1-il)-2-(1H-pirroló[2,3-b]piridin-5-iloxi)-N-{{4-{{tetrahidro-2H-piran-4-ilmetil}amino}-3-(trifluorometil)fenil}sulfonil}benzamida

EJEMPLO 42A

15 4-((tetrahidro-2H-piran-4-il)metilamino)-3-(trifluorometil)bencenosulfonamida

Una mezcla de 4-fluoro-3-(trifluorometil)bencenosulfonamida (1,056 g), (tetrahidro-2H-piran-4-il)metanamina (0,5 g) y N,N-diisopropiletilamina (1,68 g) en solución de sulfóxido de dimetilo anhidro (15 mL) se calentó a 90°C durante la noche. La mezcla de la 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 42B

25 4-(4-{{4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il}metil}piperazin-1-il)-2-(1H-pirroló[2,3-b]piridin-5-iloxi)-N-{{4-{{tetrahidro-2H-piran-4-ilmetil}amino}-3-(trifluorometil)fenil}sulfonil}benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 1G reemplazando EJEMPLO 1E y EJEMPLO 1F con EJEMPLO 15H y EJEMPLO 42A, respectivamente. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) □ 11,73 (s, 1H), 11,25 (s, 1H), 8,08 (d, 1H), 7,89 (d, 1H), 7,77 (m, 1H), 7,61 (d, 1H), 7,51 (m, 2H), 7,37 (d, 2H), 7,13 (d, 2H), 6,88 (d, 1H), 6,67 (dd, 1H), 6,53 (m, 1H), 6,43 (m, 1H), 6,15 (d, 1H), 4,11 (s, 2H), 3,82 (dd, 2H), 3,19 (m, 5H), 3,05 (m, 4H), 2,82 (s, 2H), 2,20 (m, 7H), 1,85 (m, 1H), 1,56 (m, 2H), 1,18 (s, 6H).

35 EJEMPLO 43

4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)-N-({4-[(tetrahidro-2H-piran-4-ilmetil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 1G reemplazando EJEMPLO 1E y EJEMPLO 1F con EJEMPLO 15H y EJEMPLO 17A, respectivamente. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) □ 11,69 (s, 1H), 11,48 (m, 1H), 8,16 (d, 1H), 8,05 (d, 1H), 7,92 (dd, 1H), 7,52 (m, 3H), 7,37 (d, 2H), 7,27 (m, 1H), 7,11 (m, 3H), 6,68 (dd, 1H), 6,41 (dd, 1H), 6,18 (d, 1H), 4,11 (s, 2H), 3,84 (dd, 2H), 3,25 (m, 4H), 3,07 (m, 4H), 2,84 (m, 2H), 2,23 (m, 5H), 1,84 (m, 1H), 1,55 (m, 2H), 1,25 (m, 3H), 1,18 (s, 6H).

EJEMPLO 44

Trans-4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-N-({4-[(4-morfolin-4-ilciclohexil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 44A

Trans-4-(4-morfolinociclohexilamino)-3-(trifluorometilsulfonil)bencenosulfonamida

El compuesto del título se preparó como se describe en el EJEMPLO 16A reemplazando 2-metoxietanamina con EJEMPLO 9B.

EJEMPLO 44B

Trans-4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-N-({4-[(4-morfolin-4-ilciclohexil)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 1G reemplazando EJEMPLO 1E y EJEMPLO 1F con EJEMPLO 15H y EJEMPLO 44A, respectivamente. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) □ 11,62 (s, 1H), 8,08 (s, 1H), 8,00 (d, 1H), 7,85 (d, 1H), 7,47 (m, 3H), 7,38 (d, 2H), 7,14 (d, 2H), 6,98 (d, 1H), 6,65 (dd, 1H), 6,55 (m, 1H), 6,37 (m, 1H), 6,21 (d, 1H), 4,12 (s, 2H), 3,54 (m, 6H), 3,04 (m, 4H), 2,83 (s, 2H), 2,57 (m, 3H), 2,24 (m, 6H), 1,91 (m, 5H), 1,34 (m, 4H), 1,20 (s, 6H).

EJEMPLO 45

4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-N-({4-[(1-metilpiperidin-4-il)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 45A

4-(1-metilpiperidin-4-ilamino)-3-(trifluorometilsulfonil)bencenosulfonamida

El compuesto del título se preparó como se describe en el EJEMPLO 16A reemplazando 2-metoxietanamina con 1-metil-4-aminopiperidina.

5

EJEMPLO 45B

4-(4-([4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil)piperazin-1-il)-N-([4-([1-metilpiperidin-4-il)amino]-3-[(trifluorometil)sulfonil]fenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

10 El compuesto del título se preparó como se describe en el EJEMPLO 1G reemplazando EJEMPLO 1E y EJEMPLO 1F con EJEMPLO 15H y EJEMPLO 45A, respectivamente. ^1H NMR (300 MHz, sulfóxido de dimetilo- d_6) δ 11,59 (s, 1H), 8,10 (s, 1H), 7,98 (d, 1H), 7,90 (dd, 1H), 7,49 (m, 3H), 7,39 (m, 3H), 7,14 (d, 2H), 7,02 (d, 1H), 6,65 (dd, 2H), 6,36 (dd, 1H), 6,22 (d, 1H), 4,12 (s, 2H), 3,75 (m, 1H), 3,16 (m, 4H), 2,98 (m, 5H), 2,88
15 (m, 5H), 2,67 (s, 2H), 2,22 (m, 6H), 1,68 (m, 1H), 1,18 (s, 6H).

EJEMPLO 46

5-([4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]amino)sulfonil)-2-(tetrahydro-2H-piran-4-ilmetoxi)nicotinamida

20 5-sulfamoil-2-((tetrahydro-2H-piran-4-il)metoxi)nicotinamida

A EJEMPLO 36C (0,025 g) en etanol (1 mL) y tetrahydrofurano (1 mL) se agregó peróxido de hidrógeno (30% en agua, 0,5 mL) seguido por hidróxido de sodio acuoso 1M (0,056 mL) luego otro 1 mL de tetrahydrofurano. La reacción se calentó a 45°C por 2 horas, se enfrió, se detuvo con HCl acuoso 1N (5 mL), y el producto se extrajo en diclorometano (10
25 mL). La capa orgánica se secó sobre sulfato de magnesio, se filtró y se concentró para dar el compuesto del título.

EJEMPLO 46B

5-([4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]amino)sulfonil)-2-(tetrahydro-2H-piran-4-ilmetoxi)nicotinamida

30 El compuesto del título se preparó utilizando el EJEMPLO 46A en lugar del EJEMPLO 1F y EJEMPLO 3J en lugar del EJEMPLO 1E en el EJEMPLO 1G. ^1H NMR (300 MHz, CDCl_3) δ 10,31 – 10,09 (m, 1H), 9,09 (s, 2H), 8,93 – 8,81 (m, 1H), 8,28 – 8,18 (m, 1H), 8,03 – 7,87 (m, 1H), 7,77 – 7,68 (m, 1H), 7,59 – 7,51 (m, 1H), 7,48 – 7,41 (m, 1H), 6,91 (d, 2H), 6,59
35 – 6,48 (m, 2H), 5,97 (s, 2H), 4,50 (d, 2H), 4,08 – 3,98 (m, 2H), 3,45 (s, 4H), 3,13 – 2,99 (m, 4H), 2,82 – 2,68 (m, 2H), 2,19 (s, 4H), 1,86 (s, 5H), 1,61 – 1,35 (m, 4H), 0,94 (s, 6H).

EJEMPLO 47

N-({5-bromo-6-[(1-metilpiperidin-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-pirrol[2,3-b]piridin-5-iloxi)benzamida

5 EJEMPLO 47A

5-bromo-6-((1-metilpiperidin-4-il)metoxi)piridin-3-sulfonamida

A (1-metilpiperidin-4-il)metanol (0,109 g) en tetrahidrofurano (2 mL) se agregó hidruro de sodio (0,136 g). Luego de 30 minutos, se agregó EJEMPLO 36A (0,230 g) como una solución en tetrahidrofurano (1 mL) y la reacción se calentó a 50°C. Luego de 4 horas, la
10 reacción se enfrió, se vertió en agua (10 mL) y diclorometano (50 mL), y el pH se ajustó a pH~8. La capa acuosa se extrajo con diclorometano (3 x 50 mL), y las capas orgánicas se combinaron, se lavó con salmuera (30 mL), se secó sobre sulfato de magnesio, se filtró, y se concentró para dar el compuesto del título.

15 EJEMPLO 47B

N-({5-bromo-6-[(1-metilpiperidin-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-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 47A en lugar del EJEMPLO 1F y EJEMPLO 3J en lugar del EJEMPLO 1E en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) δ 11,51 (s, 1H), 8,35 (d, 1H), 8,17 (d, 1H), 7,93 (d, 1H), 7,60 (d, 1H), 7,44 – 7,40 (m, 1H), 7,33 (dd, 3H), 7,05 (d, 2H), 6,61 (d, 1H), 6,31 (dd, 1H), 6,24 (s, 1H), 4,25 (d, 2H), 3,40 (s, 4H), 3,01 (s, 4H), 2,73 (d, J = 8,2, 5H), 2,20 (s, 6H), 1,93 (d, 4H), 1,54 (s, 1H), 1,39 (s, 2H), 1,24 (s, 2H), 0,93 (s, 6H).

25

EJEMPLO 48

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(1-metilpiperidin-4-il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

30 EJEMPLO 48A

4-((1-metilpiperidin-4-il)metoxi)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando (1-metilpiperidin-4-il)metanol por (tetrahidro-2H-piran-4-il)metanol en el EJEMPLO 24A.

35 EJEMPLO 48B

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-metilpiperidin-4-il]metoxi)-3-nitrofenil]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 48A en lugar del EJEMPLO 1F y EJEMPLO 3J en lugar del EJEMPLO 1E en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) δ 11,54 (s, 1H), 8,17 (s, 1H), 7,92 (s, 1H), 7,87 – 7,77 (m, 1H), 7,58 (d, 1H), 7,43 (s, 1H), 7,40 – 7,00 (m, 7H), 6,70 – 6,56 (m, 1H), 6,31 (s, 1H), 6,24 (s, 1H), 4,05 (s, 2H), 3,46 – 3,33 (m, 2H), 3,02 (s, 6H), 2,72 (d, 5H), 2,21 (s, 6H), 1,96 (s, 5H), 1,70 – 1,48 (m, 2H), 1,39 (s, 2H), 0,93 (s, 6H).

10 EJEMPLO 49

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([5-ciano-6-(1,4-dioxan-2-ilmetoxi)piridin-3-il]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 49A

15 6-((1, 4-dioxan-2-il)metoxi)-5-bromopiridin-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 36A en lugar de 4-fluoro-3-nitrobencenosulfonamida en el EJEMPLO 24A.

20 EJEMPLO 49B

6-((1,4-dioxan-2-il)metoxi)-5-cianopiridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 49A en lugar del EJEMPLO 36B en el EJEMPLO 36C.

25 EJEMPLO 49C

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([5-ciano-6-(1,4-dioxan-2-ilmetoxi)piridin-3-il]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 49B en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (400MHz, sulfóxido de dimetilo-d₆) δ 11,50 (s, 1H), 8,60 (s, 1H), 8,40 (s, 1H), 7,91 (d, 1H), 7,58 (d, 1H), 7,42 (t, 1H), 7,35 (d, 2H), 7,28 (s, 1H), 7,06 (d, 2H), 6,64 (dd, 1H), 6,29 (m, 2H), 4,40 (d, 2H), 3,90 (m, 1H), 3,79 (m, 2H), 3,63 (m, 2H), 3,46 (m, 4H), 3,07 (s, 4H), 2,85 (m, 2H), 2,34 (m, 4H), 2,16 (m, 2H), 1,40 (t, 2H), 0,93 (s, 6H).

EJEMPLO 50

35 N-([5-bromo-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 49A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (400MHz, sulfóxido de dimetilo-d₆) δ 11,60 (s, 1H), 8,46 (s, 1H), 8,27 (s, 1H), 7,99 (d, 1H), 7,56 (d, 1H), 7,46 (m, 2H), 7,35 (d, 2H), 7,05 (d, 2H), 6,65 (dd, 1H), 6,36 (dd, 1H), 6,22 (d, 1H), 4,34 (m, 2H), 3,88 (m, 1H), 3,79 (m, 2H), 3,63 (m, 2H), 3,46 (m, 2H), 3,06 (s, 4H), 2,81 (s, 2H), 2,26 (m, 4H), 2,15 (s, 2H), 1,96 (s, 2H), 1,38 (m, 2H), 0,93 (s, 6H).

EJEMPLO 51

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([2,2-dimetiltetrahydro-2H-piran-4-il]metoxi)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 51A

El compuesto del título se preparó como se describe en el EJEMPLO 12A reemplazando (1,4-dioxan-2-il)metanol con (2,2-dimetiltetrahydro-2H-piran-4-il)metanol.

EJEMPLO 51B

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([2,2-dimetiltetrahydro-2H-piran-4-il]metoxi)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 11D usando EJEMPLO 51A en lugar de EJEMPLO 11B. ¹H NMR (400 MHz, sulfóxido de dimetilo-d₆) □ 11,69 (s, 2H), 8,35 (s, 2H), 8,03 (d, 4H), 7,47 - 7,58 (m, 6H), 7,31 - 7,42 (m, 6H), 7,04 (d, 4H), 6,68 (dd, 2H), 6,40 (s, 2H), 6,20 (d, 2H), 3,96 - 4,09 (m, 2H), 3,54 - 3,68 (m, 2H), 3,09 (s, 4H), 2,83 (s, 2H), 2,09 - 2,37 (m, 7H), 1,96 (s, 2H), 1,55 - 1,69 (m, 2H), 1,39 (t, 2H), 1,19 (m, 8H), 0,92 (s, 6H).

EJEMPLO 52

N-([3-cloro-5-ciano-4-([tetrahydro-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-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 52A

3-ciano-4-fluorobencenosulfonamida

Se trató cloruro de 3-ciano-4-fluorobencen-1-sulfonilo (1,1 g) en 1,4-dioxano (10 mL) a 0 °C se trató por goteo con una solución 7M de amoníaco en metanol (3,57 mL) y se agitó por 30 minutos. Se retiró una pequeña cantidad de sólido mediante filtración y se descartó.

El material filtrado se concentró, se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó (MgSO_4), se filtró, se concentró y se trituró con éter dietílico para dar el producto.

EJEMPLO 52B

5 3-ciano-4-((tetrahydro-2H-piran-4-il)metilamino)bencenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 52A en lugar de 4-cloro-3-nitrobencenosulfonamida y (tetrahydro-2H-piran-4-il)metanamina en lugar de diclorhidrato de 4-metilpiperazin-1-amina en el EJEMPLO 6A.

10 EJEMPLO 52C

3-cloro-5-ciano-4-((tetrahydro-2H-piran-4-il)metilamino)bencenosulfonamida

Se trató EJEMPLO 52B (0,148 g) en acetonitrilo (5 mL) con N-clorosuccinimida (0,080 g), se calentó a 60 °C por 3 horas y se filtró para eliminar una pequeña cantidad de sólido. El material filtrado se concentró y se cromatografió sobre gel de sílice con 3-15% acetato de etilo en diclorometano como eluyente. Se formó una lechada con el sólido obtenido en agua, se filtró, se enjuagó con agua adicional y se secó bajo vacío para dar el producto.

EJEMPLO 52D

20 N-({3-cloro-5-ciano-4-[(tetrahydro-2H-piran-4-il)metil]amino}fenil)sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 52C en lugar del EJEMPLO 11B en el EJEMPLO 11D. ^1H NMR (300 MHz, sulfóxido de dimetilo- d_6) δ 11,70 (s, 1H), 11,41 (br s, 1H), 8,07 (d, 1H), 7,89 (s, 2H), 7,61 (m, 1H), 7,53 (m, 2H), 7,35 (d, 2H), 7,18 (m, 1H), 7,05 (d, 2H), 6,69 (m, 1H), 6,42 (dd, 1H), 6,18 (dd, 1H), 3,83 (m, 2H), 3,55 (t, 2H), 3,23 (m, 3H), 3,06 (m, 4H), 2,15 (m, 4H), 1,92 (m, 4H), 1,60 (m, 2H), 1,40 (m, 2H), 1,19 (m, 4H), 0,93 (s, 6H).

EJEMPLO 53

30 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-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 53A

N-[(4-cloro-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y 4-cloro-3-nitrobencenosulfonamida en lugar del EJEMPLO 1F en el EJEMPLO 1G.

EJEMPLO 53B

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

Un balón de 5 mL se cargó con EJEMPLO 53A (120 mg), 1-acetilpiperidin-4-amina (28 mg), y trietilamina (0,064 mL) en dioxano (2 ml). La mezcla de la reacción se calentó a 90°C por 24 horas. La mezcla de la reacción se enfrió a temperatura ambiente, y se agregó a una columna de gel de sílice y se purificó mediante eluyendo con 0-5% metanol en diclorometano. ¹H NMR (300MHz, sulfóxido de dimetilo-d₆) □ 11,66 (br s, 1H), 8,65 (d, 1H), 8,24 (d, 1H), 8,03 (d, 1H), 7,83 (dd, 1H), 7,54-7,46 (m, 3H), 7,35 (d, 2H), 7,19 (d, 1H), 7,04 (d, 2H), 6,68 (dd, 1H), 6,39 (m, 1H), 6,20 (d, 1H), 4,28 (d, 1H), 3,97-3,75 (m, 2H), 3,07 (br s, 4H), 2,87-2,70 (m, 4H), 2,29-2,10 (m, 6H), 2,02 (s, 3H), 2,00-1,89 (m, 4H), 1,66-1,54 (m, 2H), 1,39 (t, 2H), 0,92 (s, 6H).

EJEMPLO 54

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 54A

2-cloro-5-fluoro-4-((tetrahidro-2H-piran-4-il)metilamino)bencenosulfonamida

El compuesto del título se preparó utilizando 2-cloro-4,5-difluorobencenosulfonamida en lugar de 4-cloro-3-nitrobencenosulfonamida y (tetrahidro-2H-piran-4-il)metanamina en lugar de diclorhidrato de 4-metilpiperazin-1-amina en el EJEMPLO 6A.

EJEMPLO 54

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 54A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500 MHz, sulfóxido de dimetilo-d₆) □ 11,76 (s, 1H), 11,31 (s, 1H), 8,08 (d, 1H), 7,69 (d, 1H), 7,60 (d, 1H), 7,55 (m, 2H), 7,34 (d, 2H), 7,04 (d, 2H), 6,90 (s, 1H), 6,84 (d, 1H), 6,69 (dd, 1H), 6,45 (dd, 1H), 6,13 (d, 1H), 3,82 (dd, 2H), 3,24 (t, 2H), 3,05 (m, 6H), 2,73 (s, 2H), 2,14 (m, 6H), 1,95 (s, 2H), 1,81 (m, 1H), 1,61 (m, 2H), 1,38 (t, 2H), 1,17 (m, 2H), 0,92 (s, 6H).

EJEMPLO 55

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-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 2A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300MHz, sulfóxido de dimetilo-d₆) □ 11,66 (br s, 1H), 8,75 (t, 1H), 8,54 (d, 1H), 8,03 (d, 1H), 7,79 (dd, 1H), 7,54-7,48 (m, 3H), 7,35 (d, 2H), 7,08-7,02 (m, 3H), 6,67 (dd, 1H), 6,38 (m, 1H), 6,20 (d, 1H), 3,61 (t, 4H), 3,43 (q, 2H), 3,29 (m, 2H), 3,06 (br s, 4H), 2,73 (br s, 2H), 2,47 (br s, 4H), 2,18 (m, 6H), 1,95 (br s, 2H), 1,80 (m, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

10 EJEMPLO 56

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({5-ciano-6-[(4-fluorotetrahydro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

15 EJEMPLO 56A

5-bromo-6-((4-fluorotetrahydro-2H-piran-4-il)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 37C en lugar de tetrahydro-2H-piran-4-il)metanol y EJEMPLO 36A en lugar de 4-fluoro-3-nitrobenzenosulfonamida en el EJEMPLO 24A.

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EJEMPLO 56B

El compuesto del título se preparó utilizando el EJEMPLO 56A en lugar del EJEMPLO 36B en el EJEMPLO 36C.

25 EJEMPLO 56C

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({5-ciano-6-[(4-fluorotetrahydro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 56B en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,58 (s, 1H), 8,70 (s, 1H), 8,51 (s, 1H), 7,96 (d, 1H), 7,57 (d, 1H), 7,45 (t, 1H), 7,35-7,37 (m, 3H), 7,06 (d, 2H), 6,67 (dd, 1H), 6,33 (d, 1H), 6,26 (s, 1H), 4,56 (d, 2H), 3,76-3,80 (s, 2H), 3,56-3,62 (m, 2H), 3,01-3,10 (m, 4H), 2,14-2,18 (m, 2H), 1,96 (s, 2H), 1,80-1,87 (m, 4H), 1,41 (t, 2H), 0,93 (s, 6H).

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EJEMPLO 57

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 57A

5 5-bromo-6-(2-morfolinoetoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando 2-morfolinoetanol en lugar de tetrahidro-2H-piran-4-il)metanol y EJEMPLO 36A en lugar de 4-fluoro-3-nitrobenzenosulfonamida en el EJEMPLO 24A.

10 EJEMPLO 57B

5-ciano-6-(2-morfolinoetoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 57A en lugar del EJEMPLO 36A en el EJEMPLO 36B.

15 EJEMPLO 57C

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 57B en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,56 (s, 1H), 8,64 (s, 1H), 8,41 (s, 1H), 7,92 (d, 1H), 7,58 (d, 1H), 7,44 (t, 1H), 7,36 (d, 2H), 7,31 (s, 1H), 7,06 (d, 2H), 6,65 (dd, 1H), 6,31 (d, 1H), 6,27 (d, 1H), 4,59 (t, 2H), 3,59 (s, 4H), 3,08 (s, 4H), 2,89 (s, 2H), 2,65 (s, 4H), 2,16-2,18 (m, 2H), 1,97 (s, 2H), 1,41 (t, 2H), 0,93 (s, 6H).

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EJEMPLO 58

N-[(3-cloro-4-([2-(2-metoxietoxi)etil]sulfonil)fenil)sulfonil]-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 58A

3-cloro-4-(2-(2-metoxietoxi)etiltio)benzenosulfonamida

En un tubo de microondas de 25 mL se agregó hidruro de sodio (0,6 g) en tetrahidrofurano (10 mL) para dar una suspensión. Se agregó 2-(2-Metoxietoxi)etantiol (1 g) lentamente. Luego de agitar por 30 minutos, se agregó 3-cloro-4-fluorobenzenosulfonamida (1,54 g) disuelta en 10 mL de tetrahidrofurano lentamente. La mezcla se calentó a 110°C por

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30 minutos en un reactor de microondas Biotage Initiator. Se agregó agua, el producto se extrajo con éter (20 mL x3), se secó sobre Na₂SO₄, se filtró, y el solvente se eliminó bajo presión reducida. El producto crudo se purificó mediante cromatografía flash sobre sílice eluyendo con 0-25% acetato de etilo en hexano.

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EJEMPLO 58B

3-cloro-4-(2-(2-metoxietoxi)etilsulfonil)bencenosulfonamida

Se suspendió EJEMPLO 58A (0,15 g) en ácido acético (3 mL). Se agregó ácido peracético (0,4 mL) lentamente. La mezcla se agitó a temperatura ambiente durante la noche, luego se vertió en Solución de Na₂S₂O₃, y el producto precipitó. Luego de la filtración y el lavado con agua, el producto se secó bajo vacío.

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EJEMPLO 58C

N-[(3-cloro-4-([2-(2-metoxietoxi)etil]sulfonil)fenil)sulfonil]-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-ilo)benzamida

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El compuesto del título se preparó utilizando el EJEMPLO 58B en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500 MHz, sulfóxido de dimetilo-d₆) δ 11,52 (s, 1H), 7,92 (d, 1H), 7,84 (m, 2H), 7,68 (m, 1H), 7,62 (d, 1H), 7,42 (t, 1H), 7,35 (d, 2H), 7,29 (m, 1H), 7,05 (d, 2H), 6,62 (dd, 1H), 6,32 (m, 1H), 6,26 (d, 1H), 3,74 (t, 2H), 3,68 (t, 2H), 3,24 (m, 2H), 3,06 (m, 5H), 3,01 (m, 4H), 2,74 (s, 2H), 2,19 (m, 6H), 1,96 (s, 2H), 1,39 (t, 2H), 0,93 (s, 6H).

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EJEMPLO 59

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(4-([2-(2-metoxietoxi)etil]sulfonil)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-ilo)benzamida

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EJEMPLO 59A

4-(2-(2-metoxietoxi)etiltio)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando 4-fluoro-3-nitrobencenosulfonamida en lugar de 3-cloro-4-fluorobencenosulfonamida en el EJEMPLO 58A.

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EJEMPLO 59B

4-(2-(2-metoxietoxi)etilsulfonil)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 59A en lugar del EJEMPLO 58A en el EJEMPLO 58B.

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EJEMPLO 59C

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(4-([2-(2-metoxietoxi)etil]sulfonil)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 59B en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500 MHz, sulfóxido de dimetilo-d₆) δ 11,51 (s, 1H), 8,17 (m, 1H), 7,94 (m, 3H), 7,64 (d, 1H), 7,42 (m, 1H), 7,35 (d, 2H), 7,28 (d, 1H), 7,05 (d, 2H), 6,62 (m, 1H), 6,28 (m, 2H), 3,83 (m, 4H), 3,16 (m, 2H), 3,08 (s, 3H), 3,01 (m, 4H), 2,73 (s, 2H), 2,18 (m, 6H), 1,96 (m, 4H), 1,39 (t, 2H), 0,93 (s, 6H)

EJEMPLO 60

10 Trans-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-morfolin-4-ilciclohexil]oxi)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 60A

Trans-4-(4-aminociclohexiloxi)-3-nitrobencenosulfonamida

15 A una solución de 4-hidroxiciclohexilcarbamato de tert-butilo (0,250 g) en tetrahidrofurano (5 mL) se agregó hidruro de sodio (0,186 g). Luego de agitar por 15 minutos, se agregó 4-fluoro-3-nitrobencenosulfonamida (0,256 g) como una solución en tetrahidrofurano (1 mL). La reacción se calentó a 60°C por 1,5 horas, se enfrió, y se vertió en una mezcla de diclorometano (100 mL) y agua (25 ml). La capa acuosa se ajustó a pH~4 con
20 HCl acuoso 1N y la capa orgánica se separó, se lavó con salmuera (50 ml), se secó sobre sulfato de magnesio, se filtró, y se concentró. El residuo se cargó sobre gel de sílice (GraceResolv 40 g) y se eluyó usando un gradiente de 0,5% a 7,5% metanol/diclorometano a lo largo de 30 minutos. Este sólido se trató con HCl (4,0M en dioxano, 5 ml) a temperatura ambiente por 1 hora y se concentró para dar el compuesto del título.

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EJEMPLO 60B

4-(trans-4-morfolinociclohexiloxi)-3-nitrobencenosulfonamida

A EJEMPLO 60A (0,220 g) y 1-bromo-2-(2-bromoetoxi)etano (0,177 g) en N,N-dimetilformamida (3 mL) se agregó trietilamina (0,338 ml) y la reacción se calentó a 70°C por
30 5 horas. La reacción se enfrió y el precipitado resultante se retiró mediante filtración. La reacción se concentró y se cargó en gel de sílice y se eluyó usando un gradiente de 0,5% a 7,5% metanol/diclorometano para dar el compuesto del título.

EJEMPLO 60C

35 Trans-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-morfolin-4-ilciclohexil]oxi)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 60B en lugar del EJEMPLO 1F y EJEMPLO 3J en lugar del EJEMPLO 1E en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) δ 11,62 (s, 1H), 8,23 (s, 1H), 7,99 (s, 1H), 7,96 – 7,88 (m, 1H), 7,54 (d, 1H), 7,48 (s, 2H), 7,34 (d, 3H), 7,04 (d, 2H), 6,72 – 6,58 (m, 1H), 6,37 (s, 1H), 6,21 (s, 1H), 4,69 – 4,47 (m, 1H), 3,66 (s, 4H), 3,05 (s, 4H), 2,76 (s, 6H), 2,22 (s, 9H), 1,96 (s, 4H), 1,39 (s, 6H), 0,92 (s, 6H).

EJEMPLO 61

N-({5-bromo-6-[(1-tetrahidro-2H-piran-4-il)piperidin-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-pirroló[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 61A

5-bromo-6-(1-(tetrahidro-2H-piran-4-il)piperidin-4-ilamino)piridin-3-sulfonamida

Una mezcla de EJEMPLO 36A (1,0 g), EJEMPLO 3L (0,95 g) y trietilamina (3,08 mL) en dioxano anhidro (20 mL) se calentó a 110°C durante la noche. El solvente orgánico se eliminó bajo vacío. El residuo se purificó con cromatografía flash de columna sobre gel de sílice eluyendo con 2%-8% metanol/diclorometano para dar el compuesto del título.

EJEMPLO 61B

N-({5-bromo-6-[(1-tetrahidro-2H-piran-4-il)piperidin-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-pirroló[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 61A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (400MHz, sulfóxido de dimetilo-d₆) δ 11,59 (s, 1H), 8,35 (s, 1H), 8,00 (s, 2H), 7,55 (d, 1H), 7,46 (m, 2H), 7,34 (d, 2H), 7,04 (d, 2H), 6,63 (dd, 1H), 6,49 (m, 1H), 6,36 (s, 1H), 6,20 (s, 1H), 4,05 (m, 1H), 3,94 (d, 2H), 3,28 (m, 6H), 3,01 (s, 4H), 2,72 (s, 2H), 2,16 (m, 6H), 1,93 (m, 4H), 1,80 (m, 4H), 1,57 (m, 2H), 1,38 (t, 2H), 1,17 (t, 2H), 0,90 (s, 6H).

EJEMPLO 62

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-pirroló[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 62A

4-(2-cianoetilamino)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando 3-aminopropanonitrilo en lugar del EJEMPLO 39B en el EJEMPLO 39C.

EJEMPLO 62B

- 5 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-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 62A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (501 MHz, piridin-d₅) □ 13,04 (s, 1H), 9,24 (d, 1H), 9,04 (t, 1H), 8,43 (d, 1H), 8,38 (dd, 1H), 8,13 (d, 1H), 7,64 - 7,68 (m, 2H), 7,44 (ddd, 2H), 7,07 (ddd, 2H), 7,02 (d, 1H), 6,76 (dd, 1H), 6,55 (d, 1H), 6,48 (dd, 1H), 3,83 (q, 2H), 3,07 (d, 4H), 2,98 (t, 2H), 2,77 (s, 2H), 2,26 (s, 2H), 2,11 - 2,17 (m, 4H), 1,97 (s, 2H), 1,39 (t, 2H), 0,93 (s, 6H).

EJEMPLO 63

- 15 Cis-4-(4-([4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil)piperazin-1-il)-N-([4-([4-morfolin-4-ilciclohexil)amino]-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 15H en lugar del EJEMPLO 3J y EJEMPLO 39C en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (501 MHz, piridin-d₅) □ 13,09 (s, 1H), 9,30 (d, 1H), 8,64 (d, 1H), 8,43 (d, 1H), 8,38 (dd, 1H), 8,10 (d, 1H), 7,68 (dt, 2H), 7,46 (ddd, 2H), 7,12 (ddd, 2H), 6,91 (d, 1H), 6,72 (dd, 1H), 6,51 (dd, 1H), 6,49 (d, 1H), 5,69 (s, 2H), 4,40 (s, 2H), 3,69 - 3,73 (m, 4H), 3,68 (s, 1H), 2,95 - 3,02 (m, 4H), 2,84 (s, 2H), 2,40 - 2,46 (m, 4H), 2,21 (s, 2H), 2,08 - 2,15 (m, 5H), 1,76 - 1,84 (m, 2H), 1,55 - 1,63 (m, 6H), 1,29 (s, 6H).

- 25 EJEMPLO 64

Trans-N-([4-([4-[bis(ciclopropilmetil)amino]ciclohexil)amino]-3-nitrofenil]sulfonil)-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

- 30 EJEMPLO 64A

(trans)-4-(bis(ciclopropilmetil)amino)ciclohexilcarbamato de tert-butilo

El compuesto del título se preparó utilizando ciclopropancarbaldehído en lugar de 4'-clorobifenil-2-carboxaldehído y (trans)-4-aminociclohexilcarbamato de tert-butilo en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

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EJEMPLO 64B

diclorhidrato de (trans)-N1,N1-bis(ciclopropilmetil)ciclohexano-1,4-diamina

A una solución de EJEMPLO 64A (1,4 g) en diclorometano (10 ml) se agregó cloruro de hidrógeno (10 ml, 4M en dioxano) y la reacción se agitó por 16 horas a temperatura ambiente. La mezcla de la reacción se diluyó con éter y producto puro se retiró por filtración.

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EJEMPLO 64C

Trans-4-(4-(bis(ciclopropilmetil)amino)ciclohexilamino)-3-nitrobenzenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 64B en lugar del EJEMPLO 39B en el EJEMPLO 39C.

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EJEMPLO 64D

Trans-N-[[4-[[4-(bis(ciclopropilmetil)amino)ciclohexil]amino]-3-nitrofenil]sulfonil]-4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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El compuesto del título se preparó utilizando el EJEMPLO 64C en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500 MHz, piridin-d₅) □ 13,06 (s, 1H), 9,30 (d, 1H), 8,44 (d, 1H), 8,41 (dd, 1H), 8,37 (d, 1H), 8,12 (d, 1H), 7,67 (d, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 7,00 (d, 1H), 6,75 (dd, 1H), 6,53 (d, 1H), 6,49 (dd, 1H), 3,36 - 3,43 (m, 1H), 3,02 - 3,09 (m, 4H), 2,87 - 2,94 (m, 1H), 2,77 (s, 2H), 2,47 (d, 4H), 2,25 (t, 2H), 2,11 - 2,16 (m, 4H), 2,08 (d, 2H), 1,97 (s, 2H), 1,84 (d, 2H), 1,39 (t, 2H), 1,26 - 1,35 (m, 4H), 0,90 - 0,98 (m, 8H), 0,50 - 0,56 (m, 4H), 0,18 - 0,23 (m, 4H).

20

EJEMPLO 65

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]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 65A

4-((1-metilpiperidin-4-il)metilamino)-3-nitrobenzenosulfonamida

El compuesto del título se preparó utilizando 4-aminometil-1-metilpiperidina en lugar de (tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

30

EJEMPLO 65B

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]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

35

El compuesto del título se preparó utilizando el EJEMPLO 65A en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, diclorometano-d₂) □ 9,57 (bs, 1H), 8,78 (d, 1H), 8,41 (d, 1H), 8,14 (d, 1H), 7,90 (m, 2H), 7,64 (d, 1H), 7,45 (d, 1H), 7,23 (d, 2H), 6,95 (d, 2H), 6,76 (d, 1H), 6,59 (dd, 1H), 6,51 (d, 1H), 6,09 (d, 1H), 3,21 (m, 2H), 3,08 (m, 4H), 3,02 (m, 2H), 2,74 (s, 2H), 2,33 (s, 3H), 2,21-2,17 (m, 6H), 2,16-2,02 (m, 3H), 1,97 (br.s, 2H), 1,78 (m, 4H), 1,41 (t, 2H), 0,94 (s, 6H).

EJEMPLO 66

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({4-([morfolin-3-ilmetil]amino)-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 66A

3-((2-nitro-4-sulfamoilfenilamino)metil)morfolina-4-carboxilato de tert-butilo

El compuesto del título se preparó utilizando 3-(aminometil)morfolina-4-carboxilato de tert-butilo en lugar de (tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

EJEMPLO 66B

3-((4-(N-(2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoil)sulfamoil)-2-nitrofenilamino)metil)morfolina-4-carboxilato de tert-butilo

El compuesto del título se preparó utilizando el EJEMPLO 66A en lugar del EJEMPLO 1F y EJEMPLO 3J en lugar del EJEMPLO 1E en el EJEMPLO 1F, con la excepción de que el producto se purificó sobre una columna de gel de sílice eluyendo con 4% metanol en diclorometano.

EJEMPLO 66C

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({4-([morfolin-3-ilmetil]amino)-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

Una solución de EJEMPLO 66B en una mezcla de ácido trifluoroacético al 50% y diclorometano se agitó a temperatura ambiente por 2 horas. Los solventes se evaporaron y el residuo se purificó con una HPLC de fase inversa usando un gradiente de 20-80% acetonitrilo en agua con acetato de amonio al 10 mM. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,61 (s, 1H), 8,52 (bs, 1H), 8,49 (d, 1H), 7,98 (d, 1H), 7,78 (d, 1H), 7,54 (d, 1H), 7,46 (s, 1H), 7,42 (s, 1H), 7,34 (d, 2H), 7,04 (m, 3H), 6,65 (dd, 1H), 6,34 (s, 1H), 6,21 (d, 1H), 3,89 (d, 1H), 3,76 (d, 1H), 3,55-3,46 (m, 2H), 3,40-3,35 (m, 4H), 3,04 (m, 4H), 2,91 (t, 1H), 2,73 (s, 2H), 2,20-2,12 (m, 6H), 1,95 (s, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 67

4-(4-([4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil)piperazin-1-il)-N-([4-([4-metilpiperazin-1-il)amino]-3-nitrofenil)sulfonil)-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 1G reemplazando EJEMPLO 1E y EJEMPLO 1F con EJEMPLO 15H y EJEMPLO 6A, respectivamente. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) □ 11,58 (s, 1H), 9,04 (s, 1H), 8,44 (d, 1H), 7,97 (d, 1H), 7,76 (dd, 1H), 7,49 (m, 4H), 7,38 (d, 2H), 7,14 (d, 2H), 6,64 (dd, 1H), 6,34 (d, 1H), 6,21 (d, 1H), 4,12 (s, 2H), 3,03 (m, 6H), 2,85 (m, 5H), 2,29 (m, 4H), 2,18 (m, 6H), 1,20 (s, 6H).

EJEMPLO 68

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-morfolin-4-ilbut-2-inil)oxi]-3-nitrofenil)sulfonil)-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 68A

4-morfolinobut-2-in-1-ol

A una solución 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 solución se agitó a 85 °C por 3 horas. Luego de enfriar, el sólido se retiró por filtración. El material filtrado se sometió a destilación al vacío para dar el compuesto del título puro.

EJEMPLO 68B

4-(4-morfolinobut-2-iniloxi)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 68A en lugar de (tetrahidro-2H-piran-4-il)metanol en el EJEMPLO 24A.

EJEMPLO 68C

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-morfolin-4-ilbut-2-inil)oxi]-3-nitrofenil)sulfonil)-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 68B en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,68 (s, 1H), 8,36 (s, 1H), 8,08 (d, 1H), 8,03 (d, 1H), 7,47-7,53 (m, 4H), 7,35 (d, 2H), 7,04 (d, 2H), 6,67 (dd, 1H), 6,40 (dd, 1H), 6,20 (d, 1H), 5,15 (s, 2H), 3,52-3,55 (m, 4H), 3,09 (s, 4H), 2,84 (br s, 2H), 2,23-2,40 (m, 6H), 2,12-2,18 (m, 2H), 1,96 (s, 2H), 1,39 (t, 2H), 0,92 (s, 6H).

EJEMPLO 69

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([5-etinil-6-(tetrahydro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

5 EJEMPLO 69A

6-((tetrahydro-2H-piran-4-il)metoxi)-5-((triisopropilsilil)etinil)piridin-3-sulfonamida

Se combinó EJEMPLO 36B (0,176 g), cloruro de bis(trifenilfosfin)paladio(II) (0,176 g), yoduro de cobre(I) (0,010 g), N,N-dimetilacetamida (2,5 mL) y trietilamina (0,105 mL), se hizo pasar nitrógeno y se agitó por 2 minutos. Se agregó (triisopropilsilil)acetileno (0,135 mL) y a la mezcla de la reacción se hizo pasar nitrógeno nuevamente, se calentó a 60 °C durante la noche, se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó (MgSO₄), se filtró, se concentró y se cromatografió sobre gel de sílice con acetato de etilo al 10-30% en hexanos como eluyente para dar el producto.

15 EJEMPLO 69B

5-etinil-6-((tetrahydro-2H-piran-4-il)metoxi)piridin-3-sulfonamida

Se trató EJEMPLO 69A (0,205 g) en tetrahydrofurano (3 mL) a temperatura ambiente con fluoruro de tetrabutilamonio (1 M en tetrahydrofurano, 0,906 mL) y se agitó a temperatura ambiente por 4 horas. Se agregó fluoruro de tetrabutilamonio adicional (1 M en tetrahydrofurano, 1,8 mL) y la mezcla se calentó a 40 °C por 45 minutos. Se agregó fluoruro de tetrabutilamonio sólido (0,253 g) y el calentamiento se continuó por 30 minutos. La mezcla de la reacción se concentró y luego se cromatografió sobre gel de sílice usando 0-2% metanol en diclorometano como eluyente para dar el producto.

25 EJEMPLO 69

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([5-etinil-6-(tetrahydro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 69B en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) δ 11,69 (s, 1H), 11,41 (s, 1H), 8,58 (d, 1H), 8,19 (d, 1H), 8,05 (d, 1H), 7,53 (m, 3H), 7,35 (d, 2H), 7,04 (d, 2H), 6,67 (dd, 1H), 6,41 (dd, 1H), 6,18 (d, 1H), 4,56 (s, 1H), 4,24 (d, 2H), 3,87 (dd, 2H), 3,38 (m, 3H), 3,07 (m, 4H), 2,86 (m, 2H), 2,29 (m, 5H), 2,04 (m, 3H), 1,64 (dd, 2H), 1,34 (m, 4H), 0,93 (s, 6H).

35 EJEMPLO 70

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(4-oxo-3,4-dihidroquinazolin-6-il)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 70A

5 4-amino-3-cianobencenosulfonamida

Se disolvió cloruro de 3-ciano-4-fluorobencen-1-sulfonilo (1,1 g) en dioxano (4 mL). La solución se enfrió a 0°C y se agregó 7 mL de una solución de amoníaco (7N en metanol). Luego de completarse la adición, el baño de hielo se retiró y la reacción se agitó a temperatura ambiente por 24 horas. Luego de la concentración de la mezcla de la reacción, el material crudo se purificó mediante cromatografía flash eluyendo con un gradiente de 30-100% acetato de etilo/hexanos.

EJEMPLO 70B

15 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-N-(4-amino-3-cianofenilsulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 70A en lugar del EJEMPLO 1F y EJEMPLO 3J en lugar del EJEMPLO 1E en el EJEMPLO 1G.

20 EJEMPLO 70C

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-N-(4-amino-3-carbamoilfenilsulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzamida

A una solución de EJEMPLO 70B (90 mg) en etanol (2 mL) se agregó tetrahidrofurano (2 mL), peróxido de hidrógeno (30%, 1 mL) y hidróxido de sodio 1M solución (0,48 mL), seguido por 2 mL adicionales de tetrahidrofurano. La reacción se calentó a 45°C por 30 minutos, se enfrió, y luego se detuvo con Solución de HCl al 5% y se extrajo dos veces con diclorometano. Los extractos se combinaron y se concentró para obtener el producto.

30 EJEMPLO 70D

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(4-oxo-3,4-dihidroquinazolin-6-il)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

Se combinó EJEMPLO 70C (80 mg) con ortoformato de trimetilo (2,3 mL) y ácido trifluoroacético (0,03 mL) y la solución resultante se agitó a temperatura ambiente por 4 horas. La mezcla se purificó mediante cromatografía flash, eluyendo con un gradiente de 3-10% metanol/diclorometano. ¹H NMR (300MHz, sulfóxido de dimetilo-d₆) □ 12,61 (s, 1H),

11,71 (s, 1H), 8,65 (d, 1H), 8,24 (s, 1H), 8,17 (dd, 1H), 8,04 (m, 1H), 7,73 (d, 1H), 7,57 (d, 1H), 7,51 (m, 2H), 7,39 (d, 2H), 7,07 (d, 2H), 6,70 (dd, 1H), 6,40 (m, 1H), 6,24 (br s, 1H), 3,61 (m, 6H), 3,03 (m, 2H), 2,75 (m, 2H), 2,17 (m, 2H), 2,01 (m, 2H), 1,44 (m, 2H), 0,94 (s, 6H).

5 EJEMPLO 71

Trans-4-(4-([8-(4-clorofenil)espiro[4,5]dec-7-en-7-il]metil)piperazin-1-il)-N-({4-[(4-morfolin-4-ilciclohexil)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 71A

10 8-cloro-espiro[4,5]dec-7-en-7-carbaldehido

A una solución de N,N-dimetilformamida (2,81 mL) en diclorometano (40 mL) se agregó por goteo POCl_3 (2,78 mL) a 0°C. La mezcla de la reacción se calentó a temperatura ambiente y se agregó espiro[4,5]decan-8-ona (3,95 g) en diclorometano (5 mL) por goteo. La mezcla se agitó durante la noche. La reacción se detuvo con acetato de sodio acuoso frío
15 y la mezcla resultante se extrajo con éter y la capa orgánica se secó sobre Na_2SO_4 , se filtró, y se concentró para dar el compuesto del título.

EJEMPLO 71B

8-(4-clorofenil)espiro[4,5]dec-7-en-7-carbaldehido

20 A una suspensión de EJEMPLO 71A (3 g) en agua (50 mL) se agregó ácido 4-clorofenilborónico (2,83 g), tetrabutilamonio (4,87 g), carbonato de potasio (6,26 g) y acetato de paladio(II) (0,169 g). La mezcla de la reacción se agitó a 45°C por 5 horas y se extrajo con diclorometano. La capa orgánica se concentró y el residuo se cargó sobre una columna de gel de sílice, y se eluyó con 5-20% acetato de etilo en hexano para dar el compuesto del
25 título.

EJEMPLO 71C

2-(1H-pirrolo[2,3-b]piridin-5-iloxi)-4-(4-((8-(4-clorofenil)espiro[4,5]dec-7-en-7-il]metil)piperazin-1-il)benzoato de metilo

30 A una solución de EJEMPLO 71B (274 mg) en dicloroetano (3,5 mL) se agregó EJEMPLO 15F (387 mg) y triacetoxiborhidruro de sodio (317 mg). La mezcla de la reacción se agitó durante la noche. Se agregó cianoborohidruro de sodio (37,6 mg) y la mezcla resultante se agitó durante la noche. La reacción se detuvo con agua y se diluyó con diclorometano. La mezcla se lavó con agua profundamente y la capa orgánica se secó sobre
35 Na_2SO_4 , se filtró, y se concentró para dar el compuesto del título.

EJEMPLO 71D

ácido 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((8-(4-clorofenil)espiro[4,5]dec-7-en-7-il)metil)piperazin-1-il)benzoico

El compuesto del título se preparó como se describe en el EJEMPLO 3J usando
5 EJEMPLO 71C en lugar de EJEMPLO 3I.

EJEMPLO 71E

10 Trans-4-(4-([8-(4-clorofenil)espiro[4,5]dec-7-en-7-il]metil)piperazin-1-il)-N-([4-([4-morfolin-4-ilciclohexil)amino]-3-nitrofenil)sulfonyl)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 11D usando
EJEMPLO 71D y EJEMPLO 9C en lugar de EJEMPLO 3J y EJEMPLO 11B,
respectivamente. ¹H NMR (500 MHz, sulfóxido de dimetilo-d₆) □ 11,64 (s, 1H), 8,51 (s, 1H),
15 8,15 (d, 1H), 8,01 (d, 1H), 7,76 (d, 1H), 7,44 - 7,53 (m, 3H), 7,34 (d, 2H), 7,07 (d, 3H), 6,66
(dd, 1H), 6,37 (dd, 1H), 6,20 (d, 1H), 3,50 - 3,70 (m, 5H), 3,04 (s, 4H), 2,55 - 2,76 (m, 5H),
2,34 - 2,39 (m, 1H), 2,20 (d, 6H), 2,03 (s, 4H), 1,91 (s, 2H), 1,61 (q, 4H), 1,51 (t, 2H), 1,36 -
1,46 (m, 8H).

20 EJEMPLO 72

Cis-4-(4-([4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil)piperazin-1-il)-N-([4-([4-metoxiciclohexil)metil]amino]-3-nitrofenil)sulfonyl)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 11D usando
EJEMPLO 15H y 29A en lugar de EJEMPLO 3J y EJEMPLO 11B, respectivamente. ¹H NMR
25 (500 MHz, sulfóxido de dimetilo-d₆) □ 11,69 (s, 1H), 11,45 (s, 1H), 8,59 (t, 1H), 8,56 (d, 1H),
8,04 (d, 1H), 7,79 (dd, 1H), 7,54 (d, 1H), 7,47 - 7,52 (m, 2H), 7,37 (d, 2H), 7,13 (d, 2H), 7,08
(d, 1H), 6,68 (dd, 1H), 6,35 - 6,42 (m, 1H), 6,19 (d, 1H), 4,11 (s, 2H), 3,37 (s, 1H), 3,26 (t,
2H), 3,20 (s, 3H), 3,07 (s, 4H), 2,83 (s, 2H), 2,17 (d, 6H), 1,81 (dd, 2H), 1,64 - 1,73 (m, 1H),
1,48 (dd, 2H), 1,23 - 1,41 (m, 4H), 1,18 (s, 6H).

30

EJEMPLO 73

4-(4-([8-(4-clorofenil)espiro[4,5]dec-7-en-7-il]metil)piperazin-1-il)-N-([4-([4-fluorotetrahydro-2H-piran-4-il)metoxi]-3-nitrofenil)sulfonyl)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 11D usando
35 EJEMPLO 71D y EJEMPLO 37D en lugar de EJEMPLO 3J y EJEMPLO 11B,
respectivamente. ¹H NMR (500 MHz, sulfóxido de dimetilo-d₆) □ 11,68 (s, 1H), 8,37 (s, 1H),

7,98 - 8,11 (m, 2H), 4,38 (d, 2H), 3,74 - 3,82 (m, 2H), 3,54 - 3,64 (m, 2H), 3,44 (s, 1H), 3,08 (s, 3H), 2,58 - 2,89 (m, 2H), 2,13 - 2,35 (m, 4H), 2,04 (s, 2H), 1,78 - 1,93 (m, 4H), 1,57 - 1,65 (m, 4H), 1,52 (t, 2H), 1,36 - 1,47 (m, 4H).

5 EJEMPLO 74

Trans-4-(4-([8-(4-clorofenil)espiro[4,5]dec-7-en-7-il]metil)piperazin-1-il)-N-[(4-((4-metoxiciclohexil)metil)amino)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 11D usando EJEMPLO 71D y EJEMPLO 34B en lugar de EJEMPLO 3J y EJEMPLO 11B, respectivamente. ¹H NMR (500 MHz, sulfóxido de dimetilo-d₆) □ 11,69 (s, 1H), 11,39 (s, 1H), 8,58 (t, 1H), 8,56 (d, 1H), 8,04 (d, 1H), 7,79 (dd, 1H), 7,47 - 7,55 (m, 3H), 7,34 (d, 2H), 7,07 (d, 3H), 6,68 (dd, 1H), 6,39 (dd, 1H), 6,19 (d, 1H), 3,25 (t, 2H), 3,22 (s, 3H), 3,06 (s, 5H), 2,71 (s, 2H), 2,21 (s, 6H), 1,94 - 2,06 (m, 4H), 1,79 (d, 2H), 1,57 - 1,65 (m, 5H), 1,51 (t, 2H), 1,39 (t, 4H), 0,95 - 1,11 (m, 4H).

15

EJEMPLO 75

4-(4-([2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

20 EJEMPLO 75A

5,5-dimetil-2-(trifluorometilsulfoniloxi)ciclohex-1-encarboxilato de metilo

El compuesto del título se preparó utilizando 4,4-dimetil-2-metoxycarbonilciclohexanona en lugar de 5,5-dimetil-2-metoxycarbonilciclohexanona en el EJEMPLO 3A.

25

EJEMPLO 75B

2-(4-clorofenil)-5,5-dimetilciclohex-1-encarboxilato de metilo

El compuesto del título se preparó utilizando el EJEMPLO 75A en lugar del EJEMPLO 3A en el EJEMPLO 3B.

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EJEMPLO 75C

(2-(4-clorofenil)-5,5-dimetilciclohex-1-enil)metanol

El compuesto del título se preparó utilizando el EJEMPLO 75B en lugar del EJEMPLO 3B en el EJEMPLO 3C.

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EJEMPLO 75D

2-(4-clorofenil)-5,5-dimetilciclohex-1-encarbaldehido

A una solución de EJEMPLO 75C (2,8 g) en diclorometano (50 mL) se agregó Periodinano de Dess-Martin (5,68 g). La mezcla de la reacción se agitó a temperatura ambiente por 3 horas y se diluyó con éter y se lavó con NaOH al 5% y salmuera. La capa orgánica se secó sobre Na₂SO₄, se filtró, y se concentró. El residuo se purificó mediante cromatografía flash usando acetato de etilo al 20% en hexanos para dar el compuesto del título.

10 EJEMPLO 75E

2-(1H-pirrol[2,3-b]piridin-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 reemplazando 4'-clorobifenil-2-carboxaldehido con EJEMPLO 75D y piperazin-1-carboxilato de tert-butilo con EJEMPLO 15F en el EJEMPLO 1A.

EJEMPLO 75F

ácido 2-(1H-pirrol[2,3-b]piridin-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 15H reemplazando EJEMPLO 15G con EJEMPLO 75E.

EJEMPLO 75G

4-(4-([2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-[(tetrahydro-2H-piran-4-ilmetil)amino]fenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 11D usando EJEMPLO 75F y EJEMPLO 1F en lugar de EJEMPLO 3J y EJEMPLO 11B, respectivamente. ¹H NMR (400 MHz, sulfóxido de dimetilo-d₆) δ 11,69 (s, 1H), 11,38 (s, 1H), 8,60 (t, 1H), 8,56 (d, 1H), 8,04 (d, 1H), 7,80 (dd, 1H), 7,47 - 7,55 (m, 3H), 7,31 - 7,36 (m, 2H), 7,05 - 7,13 (m, 3H), 6,68 (dd, 1H), 6,39 (dd, 1H), 6,18 (d, 1H), 3,85 (dd, 2H), 3,22 - 3,31 (m, 4H), 3,07 (s, 4H), 2,67 - 2,78 (m, 2H), 2,19 (s, 6H), 1,82 - 1,98 (m, 3H), 1,56 - 1,66 (m, 2H), 1,39 (t, 2H), 1,17 - 1,33 (m, 3H), 0,93 (s, 6H).

EJEMPLO 76

35 4-(4-([2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([5-ciano-6-(tetrahydro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 11D usando EJEMPLO 75F y EJEMPLO 36C en lugar de EJEMPLO 3J y EJEMPLO 11B, respectivamente. ¹H NMR (400 MHz, sulfóxido de dimetilo-d₆) □ 11,62 (s, 1H), 8,73 (s, 1H), 8,52 (s, 1H), 7,98 (d, 1H), 7,56 (d, 1H), 7,45 - 7,51 (m, 1H), 7,43 (s, 1H), 7,37 (d, 2H), 7,10 (d, 2H), 6,68 (dd, 1H), 6,35 (dd, 1H), 6,25 (s, 1H), 4,29 (d, 2H), 3,88 (dd, 2H), 3,12 (d, 4H), 2,21 (s, 2H), 2,00 - 2,11 (m, 1H), 1,95 (s, 2H), 1,64 (dd, 2H), 1,27 - 1,46 (m, 4H), 0,95 (s, 6 H)

EJEMPLO 77

3-{{4-([4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzoil]amino)sulfonil}-2-nitrofenoxi]metil}morfolina-4-carboxilato de tert-butilo

EJEMPLO 77A

3-((2-nitro-4-sulfamoilfenoxi)metil)morfolina-4-carboxilato de tert-butilo

El compuesto del título se preparó como se describe en el EJEMPLO 12A reemplazando (1,4-dioxan-2-il)metanol con 3-(hidroximetil)morfolina-4-carboxilato de tert-butilo.

EJEMPLO 77B

3-{{4-([4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzoil]amino)sulfonil}-2-nitrofenoxi]metil}morfolina-4-carboxilato de tert-butilo

El compuesto del título se preparó como se describe en el EJEMPLO 11D usando EJEMPLO 77A en lugar de EJEMPLO 11B. ¹H NMR (400 MHz, sulfóxido de dimetilo-d₆) □ 11,67 (s, 1H), 8,36 (s, 1H), 8,01 - 8,11 (m, 2H), 7,47 - 7,61 (m, 4H), 7,35 (d, 2H), 7,04 (d, 2H), 6,68 (dd, 1H), 6,39 (d, 1H), 6,20 (s, 1H), 4,41 - 4,52 (m, 2H), 4,15 - 4,28 (m, 1H), 3,59 - 3,95 (m, 3H), 3,51 (d, 1H), 3,34 - 3,43 (m, 1H), 3,10 (s, 5H), 2,84 (s, 2H), 2,28 (s, 4H), 2,15 (s, 2H), 1,96 (s, 2H), 1,20 - 1,45 (m, 12H), 0,92 (s, 6H).

EJEMPLO 78

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-(morfolin-3-ilmetoxi)-3-nitrofenil]sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

Se trató EJEMPLO 77B (100 mg) en diclorometano (10 mL) a 0°C con ácido trifluoroacético (5 mL) por 20 minutos. La mezcla de la reacción se concentró. El residuo se purificó mediante HPLC de fase inversa en una columna C18 usando un gradiente de 35-60% acetonitrilo en ácido trifluoroacético al 0,1% agua para dar el compuesto del título como

una sal trifluoroacetato. La sal de ácido trifluoroacético se disolvió en diclorometano (10 mL) y se lavó con NaHCO₃ acuoso al 50%. La capa orgánica se secó sobre Na₂SO₄ anhidro y se concentró para dar el compuesto del título. ¹H NMR (400 MHz, sulfóxido de dimetilo-d₆) □ 11,56 (s, 1H), 8,23 (d, 1H), 7,94 (d, 1H), 7,90 (dd, 1H), 7,57 (d, 1H), 7,42 - 7,46 (m, 1H), 7,31 - 7,37 (m, 3H), 7,25 (d, 1H), 7,01 - 7,09 (m, 2H), 6,64 (dd, 1H), 6,29 - 6,37 (m, 1H), 6,24 (d, 1H), 4,17 - 4,31 (m, 2H), 3,90 - 4,05 (m, 1H), 3,77 - 3,85 (m, 1H), 3,45 - 3,59 (m, 4H), 2,94 - 3,13 (m, 6H), 2,76 (s, 2H), 2,18 (d, 6H), 1,96 (s, 2H), 1,39 (t, 2H), 0,93 (s, 6H).

EJEMPLO 79

10 4-(4-{[8-(4-clorofenil)espiro[4,5]dec-7-en-7-il]metil}piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 11D usando EJEMPLO 71D y EJEMPLO 1F en lugar de EJEMPLO 3J y EJEMPLO 11B, respectivamente.

15 ¹H NMR (400 MHz, sulfóxido de dimetilo-d₆) □ 11,69 (s, 1H), 11,38 (s, 1H), 8,60 (t, 1H), 8,56 (d, 1H), 8,04 (d, 1H), 7,77 - 7,84 (m, 1H), 7,45 - 7,56 (m, 3H), 7,34 (d, 2H), 7,04 - 7,13 (m, 3H), 6,68 (dd, 1H), 6,39 (d, 1H), 6,19 (d, 1H), 3,85 (dd, 2H), 3,22 - 3,31 (m, 4H), 3,07 (s, 4H), 2,71 (s, 2H), 2,21 (s, 6H), 2,03 (s, 2H), 1,81 - 1,94 (m, 1H), 1,56 - 1,68 (m, 6H), 1,51 (t, 2H), 1,34 - 1,45 (m, 4H), 1,20 - 1,33 (m, 2H).

20

EJEMPLO 80

25 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[1-(metilsulfonil)piperidin-4-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando 1-(metilsulfonil)piperidin-4-amina en lugar de 1-acetilpiperidin-4-amina en el EJEMPLO 53B. ¹H NMR (300MHz, sulfóxido de dimetilo-d₆) □ 11,67 (br s, 1H), 8,57 (d, 1H), 8,25 (d, 1H), 8,04 (d, 1H), 7,83 (dd, 1H), 7,54-7,46 (m, 3H), 7,35 (d, 2H), 7,17 (d, 1H), 7,04 (d, 2H), 6,68 (dd, 1H), 6,39 (m, 1H), 6,20 (d, 1H), 3,80 (m, 1H), 3,57 (m, 2H), 3,08 (br s, 4H), 2,95 (td, 2H), 2,92 (s, 3H), 2,85-2,72 (m, 2H), 2,30-2,10 (m, 6H), 2,07-1,93 (m, 4H), 1,70 (m, 2H), 1,39 (t, 2H), 0,93 (s, 6H).

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EJEMPLO 81

35 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)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 81A

1,1-Dioxotetrahydro-2H-tiopiran-4-amina

Se agregó N-Bencil-1,1-dioxotetrahydro-2H-tiopiran-4-amina (2,00 g) a etanol (40 mL) en una botella a presión. Se agregó hidróxido de paladio sobre carbono (0,587 g,) y la
 5 solución se agitó bajo 30 psi de hidrógeno a temperatura ambiente por 2 horas. La mezcla se filtró a través de una membrana de nylon y el solvente se eliminó bajo vacío.

EJEMPLO 81B

4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{1,1-
 10 dioxidotetrahydro-2H-tiopiran-4-il}amino}-3-nitrofenil}sulfonyl)-2-(1H-pirrol[2,3-b]piridin-5-
 iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 81A en lugar de 1-acetilpiperidin-4-amina en el EJEMPLO 53B. ¹H NMR (300MHz, sulfóxido de dimetilo-d₆) □
 11,65 (br s, 1H), 8,55 (d, 1H), 8,25 (d, 1H), 8,03 (d, 1H), 7,86 (dd, 1H), 7,52-7,47 (m, 3H),
 15 7,35 (d, 2H), 7,17 (d, 1H), 7,04 (d, 2H), 6,68 (dd, 1H), 6,39 (m, 1H), 6,21 (d, 1H), 4,05 (m,
 1H), 3,22-3,00 (m, 8H), 2,79 (br s, 2H), 2,31-2,11 (m, 10H), 1,96 (br s, 2H), 1,39 (t, 2H), 0,93
 (s, 6H).

EJEMPLO 82

20 N-[(4-cloro-3-nitrofenil)sulfonyl]-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-
 il}metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y 4-cloro-3-nitrobencenosulfonamida en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H
 NMR (300MHz, sulfóxido de dimetilo-d₆) □ 11,60 (br s, 1H), 8,38 (br s, 1H), 7,96 (d, 1H), 7,91
 25 (d, 1H), 7,68 (d, 1H), 7,58 (d, 1H), 7,46 (t, 1H), 7,39-7,35 (m, 3H), 7,07 (d, 2H), 6,67 (dd, 1H),
 6,34 (m, 1H), 6,28 (d, 1H), 3,31 (br s, 2H), 3,17 (br s, 8H), 2,18 (m, 2H), 1,98 (br s, 2H), 1,42
 (t, 2H), 0,94 (s, 6H).

EJEMPLO 83

30 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(3-nitro-4-{{1-(2,2,2-
 trifluoroetil)piperidin-4-il}amino}fenil)sulfonyl]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 83A

3-Nitro-4-[1-(2,2,2-trifluoro-etil)-piperidin-4-ilamino]-bencenosulfonamida

35 El compuesto del título se preparó utilizando clorhidrato de 1-(2,2,2-trifluoroetil)piperidin-4-amina en lugar de (tetrahidropiran-4-il)metilamina en el EJEMPLO 6A.

EJEMPLO 83B

4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(3-nitro-4-{{1-(2,2,2-trifluoroetil)piperidin-4-il}amino}fenil)sulfonyl]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 82A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300MHz, sulfóxido de dimetilo-d₆) δ 11,66 (br s, 1H), 8,56 (d, 1H), 8,24 (d, 1H), 8,04 (d, 1H), 7,81 (dd, 1H), 7,52 (dd, 2H), 7,48 (d, 1H), 7,35 (d, 2H), 7,15 (d, 1H), 7,04 (d, 2H), 6,68 (dd, 1H), 6,38 (m, 1H), 6,20 (d, 1H), 3,68 (m, 1H), 3,22 (q, 2H), 3,07 (br s, 4H), 2,90 (m, 2H), 2,75 (br s, 2H), 2,29-2,12 (m, 8H), 1,97-1,86 (m, 4H), 1,63 (m, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 84

4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{5-ciano-6-{{1-tetrahydro-2H-piran-4-il}piperidin-4-il}oxi}piridin-3-il}sulfonyl)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 84A

1-(tetrahydro-2H-piran-4-il)piperidin-4-ol

Se disolvió piperidin-4-ol (7,8 g) y dihidro-2H-piran-4(3H)-ona (5,0 g) en isopropóxido de titanio(IV) (30 mL) y la reacción se agitó a temperatura ambiente durante la noche. Se agregó metanol (40 mL) y la reacción se enfrió a 0°C. Luego se agregó NaBH₄ (3,8 g) en porciones durante una hora. Luego de 2 horas se agregó NaOH acuoso 1N, seguido por la adición de acetato de etilo. Luego de la filtración a través de celite las capas se separaron, la capa acuosa se extrajo con acetato de etilo, y las capas orgánicas combinadas se secaron sobre Na₂SO₄. El crudo se purificó mediante cromatografía de columna usando diclorometano con 5-10% NH₃ 7N en metanol.

EJEMPLO 84B

5-bromo-6-(1-(tetrahydro-2H-piran-4-il)piperidin-4-iloxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 84A en lugar de (tetrahydro-2H-piran-4-il)metanol y EJEMPLO 36A en lugar de 4-fluoro-3-nitrobenzenosulfonamida en el EJEMPLO 24A.

EJEMPLO 84C

5-ciano-6-(1-(tetrahydro-2H-piran-4-il)piperidin-4-iloxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 84B en lugar del EJEMPLO 36B en el EJEMPLO 36C.

EJEMPLO 84D

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([5-ciano-6-([1-tetrahidro-2H-piran-4-ilpiperidin-4-il]oxi)piridin-3-il]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

- 5 El compuesto del título se preparó utilizando el EJEMPLO 84C en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,50 (s, 1H), 8,60 (d, 1H), 8,37 (d, 1H), 7,90 (d, 1H), 7,60 (d, 1H), 7,42 (dd, 1H), 7,35 (d, 2H), 7,25 (d, 1H), 7,04 (d, 2H), 6,63 (dd, 1H), 6,28 (m, 1H), 6,24 (d, 1H), 5,30 (br s, 1H), 4,50 (d, 2H), 3,95 (dd, 2H), 3,30 (m, 5H), 3,02 (br s, 4H), 2,95 (br s, 2H), 2,24 (br s, 4H), 2,17 (br m, 4H), 1,96
10 (s, 2H), 1,90 (br m, 4H), 1,60 (br m, 2H), 1,39 (t, 2H), 0,93 (s, 6H).

EJEMPLO 85

- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([5-isopropil-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida
15

EJEMPLO 85A

5-isopropil-6-((tetrahidro-2H-piran-4-il)metoxi)piridin-3-sulfonamida

- Se combinó EJEMPLO 36B (0,176 g), 2-diciclohexilfosfino-2',6'-dimetoxibifenilo (0,041 g), y acetato de paladio(II) (0,011 g) en un recipiente de 10 mL secado en un horno.
20 Se agregó tetrahidrofurano (1 mL) y a la mezcla se hizo pasar nitrógeno y se agitó a temperatura ambiente por 5 minutos. Se agregó solución de bromuro de 2-propilcinc (0,5 M en tetrahidrofurano) (1,5 mL) y la agitación se continuó bajo nitrógeno durante la noche. Se agregó más 2-2-diciclohexilfosfino-2',6'-dimetoxibifenilo (0,041 g) y acetato de paladio(II) (0,011 g). A la mezcla se hizo pasar nitrógeno y se agitó a temperatura ambiente por 5
25 minutos. Se agregó solución de bromuro de 2-propilcinc (0,5 M en tetrahidrofurano) (1,5 mL) y la agitación se continuó bajo nitrógeno por 2,5 días. La mezcla de la reacción se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó (MgSO₄), se filtró, se concentró, y se cromatografió sobre gel de sílice con metanol entre 0 y 3% en CH₂Cl₂ como eluyente. El material obtenido se cromatografió sobre gel de sílice una segunda vez con acetato de etilo
30 al 10-40% en CH₂Cl₂ como eluyente, se trituroó con éter dietílico y se secó bajo vacío a 45 °C para dar el producto.

EJEMPLO 85B

- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([5-isopropil-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida
35

El compuesto del título se preparó utilizando el EJEMPLO 85A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ^1H NMR (500 MHz, sulfóxido de dimetilo- d_6) δ 11,70 (s, 1H), 8,49 (m, 1H), 8,04 (d, 1H), 7,90 (m, 1H), 7,57 (m, 1H), 7,52 (t, 1H), 7,48 (dd, 1H), 7,34 (d, 2H), 7,04 (d, 2H), 6,67 (dd, 1H), 6,41 (dd, 1H), 6,17 (s, 1H), 4,19 (m, 2H), 3,88 (m, 2H), 3,30 (m, 2H), 3,05 (m, 5H), 2,77 (s, 2H), 2,21 (s, 4H), 2,14 (s, 2H), 2,03 (m, 1H), 1,95 (s, 2H), 1,64 (m, 2H), 1,34 (m, 4H), 1,12 (d, 6H), 0,92 (s, 6H).

EJEMPLO 86

N-({3-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-pirrol-2-il)piridin-5-iloxi)benzamida

EJEMPLO 86A

3-fluoro-4-((tetrahidro-2H-piran-4-il)metilamino)bencenosulfonamida

El compuesto del título se preparó utilizando 3,4-difluorobencenosulfonamida en lugar de 4-cloro-3-nitrobencenosulfonamida y (tetrahidro-2H-piran-4-il)metanamina en lugar de diclorhidrato de 4-metilpiperazin-1-amina en el EJEMPLO 6A.

EJEMPLO 86B

3-cloro-5-fluoro-4-((tetrahidro-2H-piran-4-il)metilamino)bencenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 86A en lugar del EJEMPLO 52B en el EJEMPLO 52C.

EJEMPLO 86C

N-({3-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-pirrol-2-il)piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 86B en lugar del EJEMPLO 11B en el EJEMPLO 11D. ^1H NMR (500 MHz, sulfóxido de dimetilo- d_6) δ 11,72 (s, 1H), 11,20 (s, 1H), 8,08 (d, 1H), 7,61 (m, 2H), 7,50 (m, 3H), 7,34 (d, 2H), 7,04 (d, 2H), 6,68 (dd, 1H), 6,42 (dd, 1H), 6,16 (d, 1H), 6,09 (m, 1H), 3,81 (dd, 2H), 3,25 (m, 4H), 3,07 (m, 4H), 2,76 (s, 2H), 2,18 (m, 6H), 1,95 (s, 2H), 1,72 (m, 1H), 1,53 (d, 2H), 1,38 (t, 2H), 1,16 (m, 2H), 0,92 (s, 6H).

EJEMPLO 87

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 87A

2-(1H-indol-5-iloxi)-4-fluorobenzoato de metilo

El compuesto del título se preparó utilizando 5-hidroxiindol en lugar del EJEMPLO 3G en el EJEMPLO 3H.

5 EJEMPLO 87B

2-(1H-indol-5-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 el EJEMPLO 87A en lugar del EJEMPLO 3H en el EJEMPLO 3I.

10

EJEMPLO 87C

ácido 2-(1H-indol-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoico

15 El compuesto del título se preparó utilizando el EJEMPLO 87B en lugar del EJEMPLO 3I en el EJEMPLO 3J.

EJEMPLO 87D

4-{4-[(4'-cloro-1,1'-bifenil-2-il)metil]piperazin-1-il}-2-(1H-indol-5-iloxi)-N-({3-nitro-4-[(tetrahydro-2H-piran-4-ilmetil)amino]fenil}sulfonil)benzamida

20 El compuesto del título se preparó utilizando el EJEMPLO 87C en lugar del EJEMPLO 1E en el EJEMPLO 1G, excepto que aquí el crudo se purificó mediante HPLC preparativa usando una columna 250 x 50 mm C18 y eluyendo con 20-100% CH₃CN vs. ácido trifluoroacético al 0,1% en agua, para dar el producto como una sal trifluoroacetato. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) □ 11,40 (br s, 1H), 11,17 (s, 1H), 9,50 (v br s, 1H),
25 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 (todos br s, total 6H), 1,86 (m, 1H), 1,60 (m, 2H), 1,25 (m, 2H).

30 EJEMPLO 88

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

35 El compuesto del título se preparó utilizando el EJEMPLO 87C en lugar del EJEMPLO 1E y EJEMPLO 2A en lugar del EJEMPLO 1F en el EJEMPLO 1G, excepto que aquí el crudo se purificó mediante HPLC preparativa usando una columna 250 x 50 mm C18 y eluyendo con 20-100% CH₃CN vs. ácido trifluoroacético al 0,1% en agua, para dar el

producto como una sal trifluoroacetato. ^1H NMR (300 MHz, sulfóxido de dimetilo- 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 89

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-il)piperidin-4-il]amino]fenil)sulfonil)benzamida

Este EJEMPLO se preparó utilizando el EJEMPLO 87C en lugar del EJEMPLO 1E y EJEMPLO 3M en lugar del EJEMPLO 1F en el EJEMPLO 1G. ^1H NMR (300MHz, sulfóxido de dimetilo- d_6) δ 11,15 (s, 1H), 8,56 (d, 1H), 8,20 (d, 1H), 7,84 (dd, 1H), 7,52 (d, 1H), 7,39 – 7,31 (m, 4H), 7,12 (d, 2H), 7,04 (d, 2H), 6,84 (dd, 1H), 6,65 (dd, 1H), 6,38 (t, 1H), 6,14 (d, 1H), 3,94 (m, 2H), 3,84 (m, 1H), 3,02 (m, 8H), 2,79 (m, 3H), 2,72 (s, 2H), 2,20-2,02 (m, 8H), 1,85 (m, 6H), 1,60 (m, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 90

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 el EJEMPLO 87C en lugar del EJEMPLO 1E y EJEMPLO 4A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ^1H NMR (300MHz, sulfóxido de dimetilo- 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 91

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

El compuesto del título se preparó utilizando el EJEMPLO 6A en lugar del EJEMPLO 11B y EJEMPLO 87C en lugar del EJEMPLO 3J en el EJEMPLO 11D. ^1H NMR (500 MHz, sulfóxido de dimetilo- d_6) δ 11,14 (s, 1H), 9,18 (s, 1H), 8,53 (d, 1H), 7,84 (dd, 1H), 7,56 (d, 1H), 7,51 (d, 1H), 7,39 (m, 2H), 7,33 (d, 2H), 7,12 (d, 1H), 7,03 (d, 2H), 6,84 (dd, 1H), 6,62 (dd, 1H), 6,38 (m, 1H), 6,13 (d, 1H), 3,00 (m, 4H), 2,90 (m, 4H), 2,71 (s, 2H), 2,33 (s, 3H), 2,15 (m, 6H), 1,94 (s, 2H), 1,37 (t, 2H), 0,92 (s, 6H).

EJEMPLO 92

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 11D usando
 5 EJEMPLO 87C y EJEMPLO 12A en lugar de EJEMPLO 3J y EJEMPLO 11B, respectivamente. ¹H NMR (500 MHz, sulfóxido de dimetilo-d₆) 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
 10 (s, 2H), 2,23 (s, 4H), 2,14 (s, 2H), 1,95 (s, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 93

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 el EJEMPLO 87C en lugar del
 15 EJEMPLO 3J y EJEMPLO 16A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (400MHz, sulfóxido de dimetilo-d₆) 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 (s, 1H), 6,14 (d, 1H), 3,51 (m, 4H), 3,28 (s, 3H), 3,03 (s, 4H), 2,74 (s, 2H), 2,16 (m,
 20 6H), 1,95 (s, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 94

25 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 el EJEMPLO 87C en lugar del
 EJEMPLO 3J y EJEMPLO 17A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (400MHz, sulfóxido de dimetilo-d₆) δ 11,20 (s, 1H), 8,19 (d, 1H), 7,90 (dd, 1H), 7,53 (d, 1H),
 30 7,40 (m, 4H), 7,33 (t, 1H), 7,17 (d, 1H), 7,07 (m, 3H), 6,86 (dd, 1H), 6,70 (dd, 1H), 6,41 (s, 1H), 6,21 (d, 1H), 3,84 (dd, 2H), 3,59 (m, 2H), 3,25 (m, 6H), 3,00 (m, 2H), 2,74 (s, 2H), 2,54 (m, 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).

35 EJEMPLO 95

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-[2-fluoro-1-(fluorometil)etil]piperidin-4-il]amino)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

5 EJEMPLO 95A

1-(1,3-difluoropropan-2-il)piperidin-4-amina

Se agitó piperidin-4-ilcarbamato de tert-butilo (0,212 g), 1,3-difluoropropan-2-ona (0,149 g) y triacetoxiborhidruro de sodio (0,337 g) conjuntamente en dicloroetano a temperatura ambiente. Luego de agitar durante la noche la reacción se detuvo con agua (10 mL) y se extrajo con diclorometano (2 x 20 mL). La capa orgánica se secó sobre sulfato de magnesio, se filtró, y se concentró. El residuo se trató con cloruro de hidrógeno (4,0M en dioxano, 1,323 ml) por 1 hora para dar el compuesto del título como la sal HCl luego de la concentración.

15 EJEMPLO 95B

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-[2-fluoro-1-(fluorometil)etil]piperidin-4-il]amino)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

Se suspendió EJEMPLO 95A (0,057 g) y EJEMPLO 53A (0,162 g) en dioxano (3 mL) y se calentó a 105°C durante la noche. La reacción se concentró, se cargó sobre gel de sílice (GraceResolv 12 g) y se eluyó con un gradiente de 0,5% a 4% metanol/diclorometano. Las fracciones que contenían producto se concentraron y se cargó en C18 (columna SF25-75g analogix) y se eluyó usando un gradiente de 30% a 60% acetonitrilo/agua. El producto se particionó entre diclorometano (20 mL) y Solución acuosa saturada de NaHCO₃ (20 mL). La capa orgánica se secó sobre sulfato de magnesio, se filtró, y se concentró para dar el compuesto del título. ¹H NMR (300 MHz, CDCl₃) δ 10,10 (s, 1H), 8,88 (d, 2H), 8,45 (d, 1H), 8,20 (s, 1H), 8,18 - 8,09 (m, 1H), 7,95 (d, 1H), 7,68 (d, 1H), 7,44 (s, 1H), 7,23 - 7,19 (m, 1H), 6,91 (d, 3H), 6,53 (d, 2H), 5,98 (d, 1H), 4,64 (dd, 4H), 3,68 - 3,50 (m, 1H), 3,01 (d, 6H), 2,72 (d, 4H), 2,19 (s, 11H), 1,69 (s, 2H), 1,41 (s, 2H), 0,94 (s, 6H).

30

EJEMPLO 96

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 96A

5-cloro-6-((4-fluorotetrahydro-2H-piran-4-il)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 40A en lugar de 4-fluoro-3-nitrobencenosulfonamida y EJEMPLO 37C en lugar de (tetrahydro-2H-piran-4-il)metanol en el EJEMPLO 24A.

5

EJEMPLO 96B

N-({5-cloro-6-[(4-fluorotetrahydro-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-pirrol[2,3-b]piridin-5-iloxi)benzamida

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El compuesto del título se preparó utilizando el EJEMPLO 96A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,67 (s, 1H), 8,52 (s, 1H), 8,41 (s, 1H), 8,03 (d, 1H), 7,56 (d, 1H), 7,50 (m, 2H), 7,35 (d, 2H), 7,04 (d, 2H), 6,67 (dd, 1H), 6,39 (m, 1H), 6,22 (s, 1H), 4,50 (d, 2H), 3,78 (m, 2H), 3,60 (m, 2H), 3,12 (v br s, 4H), 2,93 (v br s, 2H), 2,38 (v br s, 4H), 2,17 (br m, 2H), 1,96 (s, 2H), 1,86 (m, 4H), 1,40 (t, 2H), 0,93 (s, 6H).

15

EJEMPLO 97

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[1-(2,2-difluoroetil)piperidin-4-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

20

EJEMPLO 97A

4-(2-nitro-4-sulfamoilfenilamino)piperidin-1-carboxilato de tert-butilo

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El compuesto del título se preparó utilizando 4-aminopiperidin-1-carboxilato de tert-butilo en lugar de diclorhidrato de 4-metilpiperazin-1-amina en el EJEMPLO 6A.

EJEMPLO 97B

3-nitro-4-(piperidin-4-ilamino)bencenosulfonamida

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Se disolvió 4-(2-nitro-4-sulfamoilfenilamino)piperidin-1-carboxilato de tert-butilo en diclorometano (3 mL) y se trató con HCl 1N en éter (4 mL). La reacción se agitó durante la noche y luego se concentró para dar el compuesto del título.

EJEMPLO 97C

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4-(1-(2,2-difluoroetil)piperidin-4-ilamino)-3-nitrobencenosulfonamida

Se agitó clorhidrato de 3-nitro-4-(piperidin-4-ilamino)bencenosulfonamida (0,100g), 1,1-difluoro-2-yodoetano (0,063 mL) y diisopropilamina (0,156 mL) conjuntamente en N,N-dimetilformamida (3 ml) y se calentó a 85°C. La reacción se diluyó con diclorometano (50 mL) y se lavó con agua (50 mL), salmuera (50 mL), se secó sobre sulfato de magnesio, se
 5 filtró, y se concentró. El residuo se cargó sobre gel de sílice (GraceResolve 12g) y se eluyó usando un gradiente de 0,5% metanol/diclorometano a 3% metanol/diclorometano a lo largo de 30 minutos para dar el compuesto del título.

EJEMPLO 97D

10 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-(2,2-difluoroetil)piperidin-4-il]amino)-3-nitrofenil]sulfonil]-2-(1H-pirrólo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 97B en lugar del EJEMPLO 1F y EJEMPLO 3J en lugar del EJEMPLO 1E en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) δ 11,67 (s, 1H), 11,54 - 11,27 (m, 1H), 8,55 (d, 1H), 8,24 (d, 1H), 8,03 (d, 1H), 7,81 (d, 1H), 7,50 (dd, 3H), 7,34 (d, 2H), 7,13 (d, 1H), 7,04 (d, 2H), 6,68 (d, 1H), 6,38 (dd, 1H), 6,15 (dt, 2H), 3,64 (s, 1H), 3,07 (s, 4H), 2,79 (ddd, 6H), 2,41 (t, 2H), 2,17 (d, 6H), 1,92 (d, 4H), 1,61 (d, 2H), 1,38 (s, 2H), 0,92 (s, 6H).

20 EJEMPLO 98

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-pirrólo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 53B reemplazando 1-acetilpiperidin-4-amina con 4-amino-1-ciclopropilpiperidina. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) □ 11,65 (s, 1H), 8,54 (d, 1H), 8,22 (d, 1H), 8,02 (d, 1H), 7,80 (dd, 1H), 7,49 (m, 3H), 7,34 (d, 2H), 7,11 (d, 1H), 7,04 (d, 2H), 6,67 (dd, 1H), 6,38 (dd, 1H), 6,19 (d, 1H), 3,69 (m, 1H), 3,06 (m, 4H), 2,92 (m, 2H), 2,74 (s, 2H), 2,23 (m, 7H), 1,93 (m, 5H), 1,77 (m, 1H), 1,55 (m, 3H), 1,38 (t, 2H), 0,92 (s, 6H), 0,43 (m, 4H).

30

EJEMPLO 99

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-morfolin-4-ilciclohexil]metil]amino)-3-nitrofenil]sulfonil]-2-(1H-pirrólo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 53B reemplazando 1-acetilpiperidin-4-amina con 1-(4-morfolino)ciclohexanometilamina. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) □ 11,70 (s, 1H), 9,06 (s, 1H), 8,59 (d, 1H), 8,06 (d, 1H),

35

7,83 (dd, 1H), 7,57 (d, 1H), 7,50 (m, 2H), 7,34 (m, 3H), 7,19 (d, 1H), 7,04 (d, 2H), 6,67 (dd, 1H), 6,41 (dd, 1H), 6,17 (d, 1H), 3,56 (m, 6H), 3,44 (m, 2H), 3,07 (m, 5H), 2,57 (m, 5H), 2,24 (m, 6H), 1,95 (s, 3H), 1,45 (m, 6H), 1,23 (m, 3H), 0,92 (s, 6H).

5 EJEMPLO 100

Trans-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(4-([4-(díciclopropilamino)ciclohexil]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

10 EJEMPLO 100A

Trans-4-(díciclopropilamino)ciclohexilcarbamato de tert-butilo

Una suspensión de trans-4-aminociclohexilcarbamato de tert-butilo (1 g), tamices moleculares de 3A (1 g), ácido acético (2,67 ml), (1-etoxiciclopropoxi)trimetilsilano (3,74 ml) y cianoborohidruro de sodio (0,880 g) en metanol seco (10 ml) se calentó a reflujo por 3 horas.

- 15 Los insolubles se retiraron por filtración, la solución resultante se basificó con NaOH acuoso (6 M) a pH 14, y se extrajo con éter. Los extractos combinados se lavaron con salmuera, se secó sobre Na₂SO₄, se filtró, y se concentró. El residuo se purificó mediante cromatografía flash (gel de sílice 80 g, 30 - 100% acetona/hexanos) para dar el compuesto del título.

20 EJEMPLO 100B

bis(2,2,2-trifluoroacetato) de (trans)-N1,N1-díciclopropilciclohexano-1,4-diamina

El compuesto del título se preparó utilizando el EJEMPLO 100A en lugar del EJEMPLO 39A en el EJEMPLO 39B.

25 EJEMPLO 100C

Trans-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(4-([4-(díciclopropilamino)ciclohexil]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

Una suspensión de EJEMPLO 53A (0,14 g), EJEMPLO 100B (0,112 g) y N,N-30diisopropiletilamina (0,310 mL) en dioxano (10 mL) se agitó por 3 días a 100 °C. El producto se concentró y se purificó mediante RP HPLC(C8, 30% - 100% CH₃CN/agua/ácido trifluoroacético al 0,1%). ¹H NMR (500 MHz, piridina-d₅) □ 13,07 (s, 1H), 9,28 (d, 1H), 8,41 - 8,45 (m, 2H), 8,37 (d, 1H), 8,12 (d, 1H), 7,67 (d, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 7,01 (d, 1H), 6,75 (dd, 1H), 6,53 (d, 1H), 6,48 - 6,51 (m, 1H), 3,43 (ddd, 1H), 3,03 - 3,09 (m, 4H), 2,72 - 2,79 (m, 3H), 2,22 - 2,28 (m, 352H), 2,11 - 2,16 (m, 4H), 2,10 (s, 2H), 2,00 - 2,05 (m, 2H), 1,97 (s, 2H), 1,89 (s, 1H), 1,86 (s, 3H), 1,62 - 1,71 (m, 2H), 1,39 (t, 2H), 1,19 - 1,29 (m, 2H), 0,93 (s, 6H), 0,48 (d, 8H).

EJEMPLO 101

4-(4-([2-(4-clorofenil)-6,6-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({3-nitro-4-
[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

5

EJEMPLO 101A

2-hidroxi-6,6-dimetilciclohex-1-encarboxilato de etilo

En un balón de 500 mL secado bajo llama se agregó yoduro de cobre(I) (18 g) en éter
(200 mL) para dar una suspensión. Luego de enfriar a -5°C, se agregó metilitio (120 mL,
10 1,6M en éter) por goteo. Luego de agitar a -5°C por 1 hora, se agregó 3-metilciclohex-2-
enona (5,15 mL) en 15 ml de éter por goteo, y la mezcla se agitó a -5°C por 1 hora. Luego de
enfriar a -78°C, se agregó hexametilfosforamida (60 mL) por goteo. Se agregó
carbonocianidato de etilo (23,74 mL). Luego de agitar a -78 °C por 20 minutos, la mezcla se
calentó hasta la temperatura ambiente, y se agitó por 1 hora. La mezcla se vertió en agua
15 fría, y las capas se separaron. La capa acuosa se extrajo con éter (3x 20 mL). Las capas
orgánicas combinadas se lavaron con NH₄Cl acuoso saturado (3x 20 mL), se secó sobre
Na₂SO₄, se filtró, y se secó bajo vacío. El producto crudo se agregó a una columna de gel de
sílice y se purificó mediante eluyendo con 0-10% acetato de etilo en hexano.

20 EJEMPLO 101B

6,6-dimetil-2-(trifluorometilsulfoniloxi)ciclohex-1-encarboxilato de etilo

En un balón de 500 mL se agregó hidruro de sodio lavado con hexano (0,5 g) en
diclorometano (100 mL) para dar una suspensión. Luego de enfriar a -5 °C, se agregó
EJEMPLO 101A (2,0 g). Luego de agitar a -5 °C por 30 minutos, la mezcla se enfrió a -78°C.
25 Se agregó anhídrido trifluorometansulfónico (2,2 mL). La mezcla se calentó a temperatura
ambiente y se agitó durante la noche. Se agregó agua lentamente a la mezcla, la capa
acuosa luego se extrajo con diclorometano (2x 20 mL). Las capas orgánicas combinadas se
lavarón con NH₄Cl saturado y salmuera, se secó sobre Na₂SO₄, se filtró, y se concentró.

30 EJEMPLO 101C

2-(4-clorofenil)-6,6-dimetilciclohex-1-encarboxilato de etilo

En un tubo de microondas de 25 mL se agregó EJEMPLO 101B (2,9 g), ácido 4-
clorofenilborónico (2,2 g), y tetrakis(trifenilfosfin)paladio (0,05 g) en 1,2-
dimetoxietano/metanol(2:1, 10 mL) para dar una solución. Luego se agregó fluoruro de cesio
35 (4 g). La mezcla de la reacción se agitó a 150°C bajo (100W) en un reactor de microondas
Biotage Initiator por 30 minutos. Luego de eliminar los solventes, se agregó agua, y la

mezcla se extrajo con acetato de etilo (2x). Las capas orgánicas combinadas se secaron con MgSO_4 . Luego de filtrar, el producto crudo se purificó mediante cromatografía de fase inversa eluyendo con 50-100% acetonitrilo/agua con ácido trifluoroacético al 0,1%.

EJEMPLO 101D

5 (2-(4-clorofenil)-6,6-dimetilciclohex-1-enil)metanol

En un balón de 100 mL se colocó hidruro de litio y aluminio (1 g) en éter (20 mL) para dar una suspensión. Se agregó EJEMPLO 101C (1 g) disuelto en éter (5 mL) lentamente mediante una jeringa. La mezcla se agitó a temperatura ambiente durante la noche. Luego de enfriar a 0°C, la reacción se detuvo mediante agua. Se usó éter (2x 10 mL) para extraer el
10 producto. El producto crudo se purificó mediante cromatografía flash sobre sílice eluyendo con 0-15% acetato de etilo en hexano.

EJEMPLO 101E

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-6,6-dimetilciclohex-1-
15 enil)metil)piperazin-1-il)benzoato de metilo

A una solución a 0°C de EJEMPLO 101D (0,43 g) en diclorometano (5 mL) se agregó trietilamina (1 mL). Luego se agregó cloruro de metansulfonilo (0,134 mL) lentamente. Luego de 5 minutos, se agregó EJEMPLO 15F (0,61 g). La mezcla se agitó a temperatura ambiente durante la noche. El producto crudo se purificó mediante cromatografía flash sobre sílice con
20 acetato de etilo 0 a 25% en hexanos para dar el compuesto del título.

EJEMPLO 101F

ácido 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-6,6-dimetilciclohex-1-
enil)metil)piperazin-1-il)benzoico

En un tubo de microondas de 5 mL se agregó hidróxido de litio hidratado (15 mg) y EJEMPLO 101E (45 mg) en dioxano/agua(2:1) (2 mL) para dar una suspensión. La mezcla se calentó a 130°C en un reactor de microondas Biotage Initiator por 20 minutos. Luego de enfriar y neutralizar mediante HCl, el producto crudo se agregó a una columna de HPLC preparativa y se eluyó con 20-80% acetonitrilo/agua con ácido trifluoroacético al 0,1%.
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30

EJEMPLO 101G

4-(4-[[2-(4-clorofenil)-6,6-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({3-nitro-4-
[(tetrahydro-2H-piran-4-ilmetil)amino]fenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 101F en lugar del EJEMPLO 3J y EJEMPLO 1F en lugar del EJEMPLO 11B en el EJEMPLO 11D. ^1H NMR (500 MHz, sulfóxido de dimetilo- d_6) δ 11,68 (s, 1H), 11,47 (s, 1H), 8,58 (m, 2H), 8,03 (m, 1H),
35

7,79 (m, 1H), 7,51 (m, 3H), 7,31 (d, 2H), 7,10 (m, 1H), 7,02 (d, 2H), 6,65 (m, 1H), 6,39 (m, 1H), 6,15 (m, 1H), 3,85 (m, 2H), 3,27 (m, 4H), 2,97 (m, 4H), 2,76 (s, 2H), 2,14 (m, 6H), 1,70 (m, 2H), 1,61 (m, 2H), 1,44 (m, 2H), 1,26 (m, 3H), 1,16 (m, 6H)

5 EJEMPLO 102

N-({5-bromo-6-[(4-etilmorfolin-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-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 102A

10 (4-etilmorfolin-3-il)metanol

Se trató morfolin-3-ilmetanol (500 mg) y iodoetano (666 mg) en N,N-dimetilformamida con K_2CO_3 (1,1 g) durante la noche. La mezcla de la reacción se diluyó con agua y se extrajo con acetato de etilo. La capa orgánica se secó sobre Na_2SO_4 , se filtró, y se concentró para dar el compuesto del título.

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EJEMPLO 102B

5-bromo-6-((4-etilmorfolin-3-il)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó como se describe en el EJEMPLO 12A reemplazando 4-fluoro-3-nitrobencenosulfonamida y (1,4-dioxan-2-il)metanol con 5-bromo-6-fluoropiridin-3-sulfonamida y EJEMPLO 102A, respectivamente.

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EJEMPLO 102C

N-({5-bromo-6-[(4-etilmorfolin-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-pirrol[2,3-b]piridin-5-iloxi)benzamida

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El compuesto del título se preparó como se describe en el EJEMPLO 11D usando EJEMPLO 102B en lugar de EJEMPLO 11B. 1H NMR (500 MHz, sulfóxido de dimetilo- d_6) □ 11,62 (s, 1H), 8,51 (s, 1H), 8,30 (s, 1H), 8,00 (d, 1H), 7,55 (d, 1H), 7,45 - 7,50 (m, 2H), 7,35 (d, 2H), 7,05 (d, 2H), 6,66 (dd, 1H), 6,37 (s, 1H), 6,21 (d, 1H), 4,58 (dd, 1H), 4,39 - 4,50 (m, 1H), 3,78 - 3,90 (m, 1H), 3,67 - 3,77 (m, 1H), 3,50 - 3,65 (m, 2H), 3,08 (s, 4H), 2,59 - 3,00 (m, 4H), 2,20 - 2,39 (m, 2H), 2,15 (s, 2H), 1,96 (s, 2H), 1,39 (t, 2H), 0,99 - 1,11 (m, 3H), 0,93 (s, 6H)

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EJEMPLO 103

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-etilmorfolin-3-il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 103A

4-((4-etilmorfolin-3-il)metoxi)-3-nitrobencenosulfonamida

El compuesto del título se preparó como se describe en el EJEMPLO 12A reemplazando (1,4-dioxan-2-il)metanol con EJEMPLO 102A.

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EJEMPLO 103B

4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({4-[(4-etilmorfolin-3-il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 11D usando EJEMPLO 103A en lugar de EJEMPLO 11B. ¹H NMR (500 MHz, sulfóxido de dimetilo-d₆) □ 11,66 (s, 1H), 8,33 (s, 1H), 7,99 - 8,06 (m, 2H), 7,47 - 7,57 (m, 3H), 7,45 (d, 1H), 7,35 (d, 2H), 7,04 (d, 2H), 6,67 (dd, 1H), 6,38 (dd, 1H), 6,20 (d, 1H), 4,42 (dd, 1H), 4,23 (dd, 1H), 3,81 (d, 1H), 3,69 (d, 1H), 3,49 - 3,63 (m, 2H), 3,08 (s, 4H), 2,92 (s, 1H), 2,81 (s, 4H), 2,54 (s, 1H), 2,25 (s, 4H), 2,15 (s, 2H), 1,96 (s, 2H), 1,39 (t, 2H), 1,00 (t, 3H), 0,92 (s, 6H)

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EJEMPLO 104

4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({3-nitro-4-[(4-tetrahydro-2H-piran-4-ilmorfolin-3-il)metoxi]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

Se trató EJEMPLO 78 (20 mg) y dihidro-2H-piran-4(3H)-ona (10 mg) en dicloroetano (2 mL) con NaCNBH₃ (9,74 mg) durante la noche. Se agregó más dihidro-2H-piran-4(3H)-ona (20 mg) e isopropóxido de titanio (IV) (0,05 mL). La mezcla resultante se agitó a temperatura ambiente durante la noche y se concentró. El residuo se purificó mediante HPLC de fase inversa en una columna C18 usando un gradiente de 35-60% acetonitrilo en ácido trifluoroacético al 0,1% agua para dar el compuesto del título como una sal trifluoroacetato. La sal de ácido trifluoroacético se disolvió en diclorometano (6 mL) y se lavó con NaHCO₃ acuoso al 50%. La capa orgánica se secó sobre Na₂SO₄ anhidro y se concentró para dar el compuesto del título. ¹H NMR (500 MHz, sulfóxido de dimetilo-d₆) □ 11,68 (s, 1H), 8,35 (s, 1H), 8,04 (s, 2H), 7,44 - 7,58 (m, 4H), 7,35 (d, 2H), 7,04 (d, 2H), 6,67 (dd, 1H), 6,40 (s, 1H), 6,20 (s, 1H), 4,44 (s, 1H), 4,28 (s, 1H), 3,85 (d, 2H), 3,71 (d, 1H), 3,61 (s, 3H), 3,20 - 3,29 (m, 2H), 3,08 (s, 5H), 2,54 - 2,96 (m, 5H), 2,06 - 2,42 (m, 5H), 1,96 (s, 2H), 1,77 (d, 1H), 1,53 - 1,66 (m, 1H), 1,29 - 1,51 (m, 4H), 0,92 (s, 6H)

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EJEMPLO 105

4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(3-nitro-4-[(3S)-1-tetrahydro-2H-piran-4-ilpiperidin-3-il]amino]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 105A

(S)-1-(tetrahydro-2H-piran-4-il)piperidin-3-ilcarbamato de tert-butilo

El compuesto del título se preparó utilizando (S)-piperidin-3-ilcarbamato de tert-butilo en lugar de piperazin-1-carboxilato de tert-butilo y dihidro-2H-piran-4(3H)-ona en lugar de 4'-clorobifenil-2-carboxaldehido en el EJEMPLO 1A.

EJEMPLO 105B

(S)-1-(tetrahydro-2H-piran-4-il)piperidin-3-amina

El compuesto del título se preparó utilizando el EJEMPLO 105A en lugar del EJEMPLO 1A en el EJEMPLO 1B.

EJEMPLO 105C

4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(3-nitro-4-{{(3S)-1-tetrahydro-2H-piran-4-ilpiperidin-3-il}amino}fenil)sulfonil]-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 105B en lugar de 1-acetilpiperidin-4-amina en el EJEMPLO 53B. ¹H NMR (300MHz, sulfóxido de dimetilo-d₆) □ 8,68 (br s, 1H), 8,54 (br s, 1H), 8,02 (d, 1H), 7,77 (m, 1H), 7,50 (m, 3H), 7,34 (d, 2H), 7,03 (m, 3H), 6,67 (dd, 1H), 6,38 (m, 1H), 6,19 (d, 1H), 3,98 (m, 2H), 3,90 (m, 2H), 3,52 (m, 2H), 3,09 (s, 2H), 3,05 (m, 4H), 2,77 (m, 2H), 2,60 (m, 2H), 2,16 (m, 6H), 1,95 (m, 2H), 1,65 (m, 5H), 1,50 (m, 3H), 1,38 (m, 2H), 0,94 (s, 6H).

EJEMPLO 106

4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{5-ciano-6-[(tetrahydro-2H-piran-4-ilmetil)amino]piridin-3-il}sulfonil}-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 106 A

5-Bromo-6-((tetrahydro-2H-piran-4-il)metilamino)piridin-3-sulfonamida

El compuesto del título se preparó utilizando (tetrahydro-2H-piran-4-il)metanamina en lugar del EJEMPLO 3L en el EJEMPLO 61A.

EJEMPLO 106B

5-ciano-6-((tetrahydro-2H-piran-4-il)metilamino)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 106A en lugar del EJEMPLO 36B en el EJEMPLO 36C.

EJEMPLO 106C

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-pirrol[2,3-b]piridin-5-
iloxi)benzamida

- 5 El compuesto del título se preparó utilizando el EJEMPLO 106B en lugar del
EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (400MHz, sulfóxido de dimetilo-d₆) δ 11,62 (s,
1H), 8,55 (s, 1H), 8,14 (s, 1H), 8,01 (d, 1H), 7,87 (s, 1H), 7,56 (d, 1H), 7,48 (d, 2H), 7,34 (d,
2H), 7,04 (d, 2H), 6,64 (m, 1H), 6,37 (s, 1H), 6,19 (d, 1H), 3,81 (dd, 2H), 3,25 (m, 4H), 3,04
(s, 4H), 2,74 (s, 2H), 2,17 (m, 6H), 1,95 (s, 2H), 1,87 (m, 1H), 1,53 (m, 2H), 1,37 (t, 2H), 1,18
10 (m, 2H), 0,91 (s, 6H).

EJEMPLO 107

Trans-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-pirrol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 107A

3-nitro-4-(4-aminotiomorfolina-1,1-dióxido)bencenosulfonamida

El compuesto del título se preparó utilizando 4-aminotiomorfolina-1,1-dióxido en
lugar de (tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

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EJEMPLO 107B

Trans-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-pirrol[2,3-b]piridin-5-iloxi)benzamida

- 25 El compuesto del título se preparó utilizando el EJEMPLO 107A en lugar del
EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (400MHz, sulfóxido de dimetilo-d₆) δ 11,64 (s,
1H), 9,58 (s, 1H), 8,50 (s, 1H), 8,02 (d, 1H), 7,78 (m, 2H), 7,50 (m, 3H), 7,34 (d, 2H), 7,04 (d,
2H), 6,66 (dd, 1H), 6,38 (s, 1H), 6,19 (d, 1H), 3,48 (m, 4H), 3,23 (m, 4H), 3,05 (s, 4H), 2,73
(d, 2H), 2,16 (m, 6H), 1,95 (s, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

30 EJEMPLO 108

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-pirrol[2,3-b]piridin-5-
iloxi)benzamida

35 EJEMPLO 108A

4-((4-aminotetrahidro-2H-piran-4-il)metilamino)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando 4-(aminometil)tetrahidro-2H-piran-4-amina en lugar de (tetrahidro-2H-piran-4-il)metanamina en el EJEMPLO 1F.

EJEMPLO 108B

- 5 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-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 108A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,55 (s, 1H), 8,45 (s, 2H), 7,95 (d, 1H), 7,75-7,77 (m, 1H), 7,57 (d, 2H), 7,44 (s, 1H), 7,34 (d, 2H), 7,09 (d, J = 8,85 Hz, 1H), 7,05 (d, 2H), 6,69 (dd, 1H), 6,33 (d, 1H), 6,22 (d, 1H), 3,59-3,71 (m, 6H), 3,01 (s, 4H), 2,73 (s, 2H), 2,15-2,19 (m, 6H), 1,95 (s, 2H), 1,71-1,74 (m, 2H), 1,59-1,61 (m, 1H), 1,38 (t, 2H), 0,93 (s, 6H).

15 EJEMPLO 109

Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({5-ciano-6-[(4-morfolin-4-ilciclohexil)amino]piridin-3-il}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 109A

- 20 Trans-5-bromo-6-(4-morfolinociclohexiloxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 9B en lugar del EJEMPLO 3L en el EJEMPLO 61A.

EJEMPLO 109B

- 25 Trans-5-ciano-6-(4-morfolinociclohexilamino)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 109A en lugar del EJEMPLO 36B en el EJEMPLO 36C.

EJEMPLO 109C

- 30 Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({5-ciano-6-[(4-morfolin-4-ilciclohexil)amino]piridin-3-il}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 109B en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (400MHz, sulfóxido de dimetilo-d₆) □ 11,59 (s, 1H), 8,56 (d, 1H), 8,13 (s, 1H), 8,00 (d, 1H), 7,55 (d, 1H), 7,47 (m, 2H), 7,34 (d, 2H), 7,04 (d, 2H), 6,64 (dd, 1H), 6,36 (d, 1H), 6,19 (d, 1H), 4,00 (m, 1H), 3,65 (m, 4H), 3,28 (m, 4H), 3,03 (m, 4H), 2,73 (m, 4H), 2,16 (m, 6H), 1,90 (m, 6H), 1,40 (m, 6H), 0,93 (s, 6H).

EJEMPLO 110

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 52B en lugar del EJEMPLO
5 11B en el EJEMPLO 11D. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) □ 11,71 (s, 1H), 11,23
(s, 1H), 8,08 (d, 1H), 7,91 (d, 1H), 7,74 (dd, 1H), 7,60 (d, 1H), 7,52 (m, 2H), 7,34 (m, 2H),
7,16 (s, 1H), 7,04 (m, 2H), 6,83 (d, 1H), 6,68 (dd, 1H), 6,43 (dd, 1H), 6,16 (d, 1H), 3,83 (dd,
2H), 3,23 (m, 2H), 3,12 (t, 2H), 3,06 (m, 4H), 2,73 (m, 2H), 2,15 (m, 6H), 1,95 (s, 2H), 1,82
(m, 1H), 1,58 (m, 2H), 1,38 (m, 2H), 1,18 (m, 2H), 0,92 (s, 6H).

10

EJEMPLO 111

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(1S,3R)-3-
morfolin-4-ilciclopentil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

15 EJEMPLO 111A

(1S,3R)-3-(tert-butoxicarbonilamino)ciclopentilcarbamato de bencilo

Se combinó ácido (1S,3R)-3-(tert-butoxicarbonilamino)ciclopentancarboxílico
(1,03 g), azida de difenilfosforilo (DPPA, 1,00 mL), trietilamina (0,929 mL), y alcohol bencílico
(0,931 mL) en tolueno (10 mL) y se agitó a 100°C por 24 horas. La solución se enfrió y se
20 cromatografió sobre gel de sílice usando 10% acetato de etilo/ hexanos para dar el producto
puro.

EJEMPLO 111B

(1S,3R)-3-aminociclopentilcarbamato de bencilo

25 El compuesto del título se preparó utilizando el EJEMPLO 111A en lugar del
EJEMPLO 1A en el EJEMPLO 1B.

EJEMPLO 111C

30 (1S,3R)-3-morfolinociclopentilcarbamato de bencilo

Una solución de EJEMPLO 111B (400 mg), 1-bromo-2-(2-bromoetoxi)etano
(0,246 mL), y trietilamina (0,595 mL) en N,N-dimetilformamida (6 mL) se agitó a 70°C por 24
horas. La solución se enfrió y se vertió en acetato de etilo (200 mL). La solución se extrajo
con 3x agua, se lavó con salmuera, se concentró, y se cromatografió sobre gel de sílice
35 usando 10% metanol/acetato de etilo para dar el producto puro.

EJEMPLO 111D

(1S,3R)-3-morfolinociclopentanamina

Se agregó EJEMPLO 111C (300 mg) y etanol (20 ml) a Pd(OH)₂-C húmedo al 20% (60,0 mg) en una botella de presión de 50 mL y se agitó por 8 horas a 30 psi. La mezcla se filtró a través de una membrana de nylon y se condensó para dar el producto.

EJEMPLO 111E

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(1S,3R)-3-morfolin-4-ilciclopentil]amino}-3-nitrofenil)sulfonyl]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 111D en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (sulfóxido de dimetilo-d₆) □ 11,65 (s, 1H), 8,45 (d, 1H), 8,28 (dd, 1H), 7,97 (d, 1H), 7,68 (d, 1H), 7,52 (d, 1H), 7,44 (d, 2H), 7,35 (d, 2H), 7,05 (d, 2H), 6,92 (dd, 1H), 6,85 (dd, 1H), 6,33 (s, 1H), 6,22 (s, 1H), 4,08 (m, 1H), 3,60 (br s, 4H), 3,06 (br s, 4H), 2,73 (br s, 3H), 2,48 (m, 4H), 2,28 (m, 1H), 2,18 (m, 6H), 2,07 (m, 1H), 1,95 (s, 2H), 1,79 (m, 2H), 1,63 (m, 2H), 1,38 (t, 2H), 0,93 (s, 6H).

EJEMPLO 112

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(1R,3S)-3-morfolin-4-ilciclopentil]amino}-3-nitrofenil)sulfonyl]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 112A

(1R,3S)-3-aminociclopentilcarbamato de tert-butilo

El compuesto del título se preparó utilizando el EJEMPLO 111A en lugar del EJEMPLO 111C en el EJEMPLO 111D.

EJEMPLO 112B

(1R,3S)-3-morfolinociclopentilcarbamato de tert-butilo

El compuesto del título se preparó utilizando el EJEMPLO 112A en lugar del EJEMPLO 111B en el EJEMPLO 111C.

EJEMPLO 112C

(1R,3S)-3-morfolinociclopentanamina

El compuesto del título se preparó utilizando el EJEMPLO 112B en lugar del EJEMPLO 1A en el EJEMPLO 1B.

EJEMPLO 112D

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1R,3S)-3-morfolin-4-ilciclopentil]amino)-3-nitrofenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 112C en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (sulfóxido de dimetilo -d₆) □ 11,35 (s, 1H), 8,51 (d, 1H), 8,44 (dd, 1H), 8,00 (d, 1H), 7,77 (d, 1H), 7,50 (d, 1H), 7,48 (s, 2H), 7,34 (d, 2H), 7,04 (d, 2H), 7,02 (dd, 1H), 6,67 (dd, 1H), 6,37 (dd, 1H), 6,21 (d, 1H), 4,11 (m, 1H), 3,61 (br s, 4H), 3,06 (br s, 4H), 2,73 (br s, 3H), 2,50 (m, 4H), 2,28 (m, 1H), 2,18 (m, 6H), 2,06 (m, 1H), 1,95 (s, 2H), 1,77 (m, 2H), 1,66 (m, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 113

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([morfolin-2-ilmetil]amino)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 113A

2-((2-nitro-4-sulfamoilfenilamino)metil)morfolina-4-carboxilato de tert-butilo

El compuesto del título se preparó utilizando 2-(aminometil)morfolina-4-carboxilato de tert-butilo en lugar de (tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

EJEMPLO 113B

2-((4-(N-(2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoil)sulfamoil)-2-nitrofenilamino)metil)morfolina-4-carboxilato de tert-butilo

El compuesto del título se preparó utilizando el EJEMPLO 113A en lugar del EJEMPLO 1F y EJEMPLO 3J en lugar del EJEMPLO 1E en el EJEMPLO 1G, con la excepción de que el producto se purificó sobre una columna de gel de sílice eluyendo con 4% metanol en diclorometano.

EJEMPLO 113C

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([morfolin-2-ilmetil]amino)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 113B en lugar del EJEMPLO 66B en el EJEMPLO 66C. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,60 (s, 1H), 8,55 (br, s, 1H), 8,51 (s, 1H), 8,00 (d, 1H), 7,80 (d, 1H), 7,52 (d, 1H), 7,49-7,46 (m, 2H), 7,34 (d, 2H), 7,07 (d, 1H), 7,04(d, 2H), 6,66 (dd, 1H), 6,36 (s, 1H), 6,20 (d, 1H), 4,00 (dd, 1H),

3,91 (m, 1H), 3,70 (t, 1H), 3,60 (m, 1H), 3,58 (m, 1H), 3,32 (m, 1H), 3,16 (d, 1H), 3,05 (m, 4H), 2,98 (td, 1H), 2,86 (t, 1H), 2,73 (s, 2H), 2,20-2,12 (m, 6H), 1,95 (s, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

5 EJEMPLO 114

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-[(tetrahydrofurano-3-ilmetil)amino]fenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 114A

10 3-nitro-4-((tetrahydrofurano-3-il)metilamino)bencenosulfonamida

El compuesto del título se preparó utilizando 3-aminometil-tetrahydrofurano en lugar de (tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

EJEMPLO 114B

15 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-[(tetrahydrofurano-3-ilmetil)amino]fenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 114A en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,68 (s, 1H), 11,42 (bs, 1H), 8,63 (t, 1H), 8,56 (d, 1H), 8,04 (d, 1H), 7,80 (dd, 1H), 7,53-7,48 (m, 3H), 7,34 (d, 2H), 7,10 (d, 1H), 7,04 (d, 2H), 6,68 (dd, 1H), 6,39 (m, 1H), 6,19 (d, 1H), 3,82-3,79 (m, 1H), 3,71 (t, 1H), 3,62 (dd, 1H), 3,50 (dd, 1H), 3,38 (m, 1H), 3,32 (m, 1H), 3,07 (m, 4H), 2,76 (s, 2H), 2,58 (m, 1H), 2,25-2,00 (m, 6H), 1,98 (m, 1H), 1,95 (s, 2H), 1,65 (m, 1H), 1,38 (t, 2H), 0,92 (s, 6H).

25 EJEMPLO 115

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-[cis-3-fluorotetrahydro-2H-piran-4-il]piperidin-4-il]amino)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

30 EJEMPLO 115A

Cis-1-(3-fluorotetrahydro-2H-piran-4-il)piperidin-4-ilcarbamato de tert-butilo

El compuesto del título se preparó como el racemato del diastereómero cis utilizando piperidin-4-ilcarbamato de tert-butilo en lugar de piperidin-4-ol y 3-fluorodihidro-2H-piran-4(3H)-ona (preparada de acuerdo al método descrito en US2005/0101628A1) en lugar de dihidro-2H-piran-4(3H)-ona en el EJEMPLO 84A.

EJEMPLO 115B

Cis-1-(3-fluorotetrahydro-2H-piran-4-il)piperidin-4-amina

Se disolvió EJEMPLO 115A (0,29 g) en CH₂Cl₂ (9 mL), luego se agregó HCl 4N en dioxano (4 mL) y la reacción se agitó a temperatura ambiente por 16 horas. La reacción se diluyó con CH₂Cl₂ (30 mL), luego se agregó NaOH acuoso 4N (5 mL). Luego de agitar y separar las capas la capa acuosa se saturó con NaCl sólido y se extrajo con más CH₂Cl₂ (10 mL). Las capas orgánicas combinadas se secaron sobre Na₂SO₄. Luego de la filtración y concentración la amina se usó sin purificación adicional.

10 EJEMPLO 115C

4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{1-[cis-3-fluorotetrahydro-2H-piran-4-il]piperidin-4-il}amino)-3-nitrofenil}sulfonil}-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 115B en lugar de 1-acetilpiperidin-4-amina en el EJEMPLO 53B. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,64 (s, 1H), 8,54 (d, 1H), 8,43 (br d, 1H), 8,03 (d, 1H), 7,80 (dd, 1H), 7,50 (m, 3H), 7,35 (d, 2H), 7,11 (d, 1H), 7,05 (d, 2H), 6,66 (dd, 1H), 6,38 (m, 1H), 6,20 (d, 1H), 4,92 (d, 1H), 3,95 (m, 2H), 3,70 (v br m, 1H), 3,50, 3,40, 3,30 todos m, total 5H), 3,05, 3,00 (ambos v br m, total 5H), 2,74 (s, 2H), 2,55 (v br m, 1H), 2,18 (br m, 6H), 1,95 (m, 4H), 1,88 (ddd, 1H), 1,63 (v br m, 3H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 116

4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-{{1-tetrahydro-2H-piran-4-ilazetidin-3-il}amino}fenil}sulfonil}-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 116A

1-(tetrahydro-2H-piran-4-il)azetidin-3-amina

Se agitó azetidin-3-ilcarbamato de tert-butilo (0,46 g), dihidro-2H-piran-4(3H)-ona (0,29 g) y triacetoxiborhidruro de sodio (0,85 g) conjuntamente en diclorometano (5 mL) durante la noche. La reacción se vertió en diclorometano (50 mL) y solución acuosa saturada de NaHCO₃ (25 mL). La capa orgánica se separó, se lavó con salmuera (25 mL), se secó sobre Na₂SO₄, se filtró, y se concentró. Cromatografía sobre gel de sílice (GraceResolv 12 g) eluyendo con un gradiente de 0,75% a 7,5% metanol/diclorometano a lo largo de 20 minutos dio el intermediario protegido con Boc. El tratamiento con HCl (4,0M en dioxano, 2 mL) y

metanol (1 mL) por 1 hora dio el compuesto del título luego de la concentración como la sal di-HCl.

EJEMPLO 116B

5 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-il)azetidín-3-il)amino]fenil}sulfonil)-2-(1H-pirrólo[2,3-b]piridin-5-iloxi)benzamida

Una suspensión de 2-(1H-pirrólo[2,3-b]piridin-5-iloxi)-N-(4-cloro-3-nitrofenilsulfonil)-4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-enil]metil]piperazin-1-il)benzamida (0,180 g), 1-(tetrahidro-2H-piran-4-il)azetidín-3-amina (0,078 g), y trietilamina (0,159 mL) en dioxano (2 mL) se desgasificó con nitrógeno por 30 segundos y luego se selló. La reacción se calentó a 110°C. Luego de agitar por 16 horas, se agregó más trietilamina (10 equivalentes en total) y sulfóxido de dimetilo (1 mL) y la reacción se agitó por otras 18 horas a 110°C. La reacción se enfrió, se diluyó con agua (50 mL) y se extrajo con diclorometano (2 x 150 mL). La capa orgánica se secó sobre sulfato de magnesio, se filtró y se concentró. La cromatografía sobre gel de sílice (GraceResolv 12 g) eluyendo con un gradiente de 0,75% a 7,5% metanol/diclorometano (Velocidad de flujo = 36 mL/minutos) dio el compuesto del título. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) δ 11,59 (s, 1H), 8,49 (d, 1H), 8,40 (s, 1H), 7,97 (d, 1H), 7,77 (s, 1H), 7,47 (dd, 3H), 7,34 (d, 2H), 7,04 (d, 2H), 6,90 – 6,78 (m, 1H), 6,65 (d, 1H), 6,35 (s, 1H), 6,21 (s, 1H), 4,47 – 4,23 (m, 1H), 3,83 (s, 3H), 3,05 (s, 6H), 2,73 (s, 2H), 2,18 (s, 8H), 1,95 (s, 2H), 1,68 (s, 2H), 1,38 (s, 2H), 1,24 (s, 4H), 0,92 (s, 6H).

EJEMPLO 117

25 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({3-nitro-4-[(1-tetrahydrofurano-3-il)azetidín-3-il)amino]fenil}sulfonil)-2-(1H-pirrólo[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 117A

1-(tetrahydrofurano-3-il)azetidín-3-amina

30 Se agitó azetidín-3-ilcarbamato de tert-butilo (0,550 g), dihidrofurano-3(2H)-ona (0,412 g) y triacetoxiborhidruro de sodio (1,015 g) conjuntamente en diclorometano (5 mL). Luego de agitar durante la noche, la reacción se vertió en solución acuosa saturada de NaHCO₃ (25 mL) y se extrajo con diclorometano (50 mL). La capa orgánica se lavó con salmuera (25 mL), se secó sobre sulfato de magnesio, se filtró, y se concentró. La cromatografía sobre gel de sílice* (GraceResolv 12 g) eluyendo con un gradiente de 0,5% a 7,5% metanol/diclorometano a lo largo de 30 minutos dio 1-(tetrahydrofurano-3-il)azetidín-3-ilcarbamato de tert-butilo. El

material resultante se trató con HCl/dioxano por 1 hora, y luego se concentró para dar el compuesto del título.

5 EJEMPLO 117B

3-nitro-4-(1-(tetrahydrofurano-3-il)azetidin-3-ilamino)bencenosulfonamida

Se calentó 4-fluoro-3-nitrobencenosulfonamida (0,084 g), 1-(tetrahydrofurano-3-il)azetidin-3-amina (0,090 g) y trietilamina (0,266 ml) en tetrahydrofurano (3 mL) a 60°C. Luego de agitar por 4 horas, la reacción se enfrió, el tetrahydrofurano se retiró y el residuo se
10 particionó entre diclorometano (200 mL) y agua (20 mL). La capa orgánica se separó, se lavó con salmuera (25 mL), se secó sobre sulfato de magnesio, se filtró, y se concentró para dar el compuesto del título.

15

EJEMPLO 117C

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-(1-tetrahydrofurano-3-ilazetidin-3-il)amino]fenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-
20 iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 117B en lugar del EJEMPLO 1F y EJEMPLO 3J en lugar del EJEMPLO 1E en el EJEMPLO 1G. ¹H NMR (300 MHz, CDCl₃) δ 10,39 - 9,79 (m, 1H), 9,17 (s, 1H), 8,87 (d, 1H), 8,51 (d, 1H), 8,15 (dd, 2H), 7,94 (d, 1H), 7,68 (d, 1H), 7,48 - 7,42 (m, 1H), 7,23 (d, 2H), 6,91 (d, 2H), 6,69 (d, 1H), 6,54
25 (dd, 2H), 5,99 (d, 1H), 4,29 (d, 1H), 4,01 - 3,73 (m, 4H), 3,66 (d, 2H), 3,08 (s, 6H), 2,76 (s, 2H), 2,21 (s, 6H), 2,03 - 1,83 (m, 3H), 1,64 (s, 2H), 1,42 (d, 2H), 0,93 (s, 6H).

EJEMPLO 118

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([(3R)-1-tetrahydro-2H-piran-4-ilpirrolidin-3-il]metil)amino]fenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-
30 iloxi)benzamida

EJEMPLO 118A

(R)-(1-(tetrahydro-2H-piran-4-il)pirrolidin-3-il)metilcarbamato de tert-butilo

El compuesto del título se preparó utilizando (S)-pirrolidin-3-ilmetilcarbamato de tert-butilo en lugar de piperazin-1-carboxilato de tert-butilo y dihidro-2H-piran-4(3H)-ona en lugar de 4'-clorobifenil-2-carboxaldehído en el EJEMPLO 1A.

5 EJEMPLO 118B

(R)-(1-(tetrahidro-2H-piran-4-il)pirrolidin-3-il)metanamina

El compuesto del título se preparó utilizando el EJEMPLO 118A en lugar del EJEMPLO 1A en el EJEMPLO 1B.

10 EJEMPLO 118C

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-(((3R)-1-tetrahidro-2H-piran-4-ilpirrolidin-3-il)metil)amino)fenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 118B en lugar de 1-acetilpiperidin-4-amina en el EJEMPLO 53B. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,57 (s, 1H), 8,59 (br s, 1H), 8,45 (br s, 1H), 8,02 (d, 1H), 7,95 (m, 1H), 7,71 (m, 1H), 7,56 (d, 1H), 7,45 (m, 1H), 7,35 (m, 3H), 7,05 (m, 2H), 6,90 (br s, 1H), 6,64 (d, 1H), 6,33 (m, 1H), 6,22 (m, 1H), 3,90 (m, 2H), 3,44 (m, 2H), 3,27 (m, 4H), 3,02 (m, 5H), 2,73 (m, 3H), 2,59 (m, 2H), 2,19 (m, 6H), 1,95 (m, 2H), 1,85 (m, 2H), 1,64 (m, 1H), 1,50 (m, 2H), 1,39 (m, 2H), 1,23 (m, 1H), 0,94 (s, 6H).

EJEMPLO 119

4-(4-([2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-fluorotetrahidro-2H-piran-4-il)metoxi]-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 11D usando EJEMPLO 75F y EJEMPLO 37D en lugar de EJEMPLO 3J y EJEMPLO 11B, respectivamente. ¹H NMR (500 MHz, sulfóxido de dimetilo-d₆) □ 11,69 (s, 1H), 8,39 (s, 1H), 8,08 (d, 1H), 8,04 (d, 1H), 7,41 - 7,59 (m, 4H), 7,35 (d, 2H), 7,08 (d, 2H), 6,68 (dd, 1H), 6,37 - 6,43 (m, 1H), 6,20 (s, 1H), 4,38 (d, 2H), 3,73 - 3,82 (m, 2H), 3,54 - 3,63 (m, 2H), 3,09 (s, 4H), 2,81 (s, 2H), 2,16 - 2,39 (m, 5H), 1,94 (s, 2H), 1,79 - 1,93 (m, 4H), 1,40 (t, 2H), 0,94 (s, 6H).

EJEMPLO 120

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-N-(4-((trans-4-hidroxiciclohexil)metoxi)-3-nitrofenilsulfonil)benzamida

EJEMPLO 120A

Trans-4-(aminometil)ciclohexanol

Se trató ((1r,4r)-4-hidroxiciclohexil)metilcarbamato de tert-butilo (1 g) en diclorometano (10 mL) con ácido trifluoroacético (5 mL) a 0°C por 10 minutos y a temperatura ambiente por 30 minutos. La mezcla de la reacción se concentró y se secó al vacío para dar el compuesto del título como una sal de ácido trifluoroacético.

EJEMPLO 120B

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-N-(4-((trans-4-hidroxiciclohexil)metoxi)-3-nitrofenilsulfonil)benzamida

Una mezcla de EJEMPLO 53A (211 mg), EJEMPLO 120A (104 mg) y N-etil-N-isopropilpropan-2-amina (0,3 mL) en sulfóxido de dimetilo (2 mL) se calentó a 150°C en un sintetizador de microondas Biotage Initiator por 1,5 horas y se concentró. El residuo se purificó mediante HPLC de fase inversa en una columna C18 usando un gradiente de 40-60% acetonitrilo en ácido trifluoroacético al 0,1% agua para dar el compuesto del título como una sal trifluoroacetato. La sal de ácido trifluoroacético se disolvió en diclorometano (30 mL) y se lavó con NaHCO₃ acuoso al 50%. La capa orgánica se secó sobre Na₂SO₄ anhidro, se filtró, y se concentró para dar el compuesto del título. ¹H NMR (500 MHz, sulfóxido de dimetilo-d₆) δ 11,69 (s, 1H), 11,41 (s, 1H), 8,61 (t, 1H), 8,53 - 8,58 (m, 1H), 8,04 (d, 1H), 7,76 - 7,83 (m, 1H), 7,47 - 7,56 (m, 3H), 7,34 (d, 2H), 7,07 - 7,11 (m, 1H), 7,04 (d, 2H), 6,68 (dd, 1H), 6,39 (dd, 1H), 6,19 (d, 1H), 4,82 - 4,99 (m, 1H), 4,50 (d, 1H), 3,26 - 3,31 (m, 2H), 3,23 (t, 1H), 3,07 (s, 4H), 2,76 (s, 2H), 2,10 - 2,28 (m, 6H), 2,05 (dd, 1H), 1,95 (s, 2H), 1,84 (t, 2H), 1,52 - 1,76 (m, 2H), 1,41 - 1,51 (m, 1H), 1,38 (t, 2H), 0,95 - 1,25 (m, 4H), 0,92 (s, 6H)

EJEMPLO 121

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-N-(4-((cis-4-metoxiciclohexil)metoxi)-3-nitrofenilsulfonil)benzamida

EJEMPLO 121A

(4-metoxiciclohexil)metanol

Se trató ácido 4-metoxiciclohexanocarboxílico (7 g) en tetrahidrofurano (20 mL) con complejo borano-tetrahidrofurano 1 M (en tetrahidrofurano) (100 mL) durante la noche. La mezcla se concentró y el residuo se disolvió en metanol (100 mL) y HCl concentrado (10 mL). La mezcla resultante se agitó por 1 hora y se concentró. El residuo se disolvió en diclorometano y se lavó con agua. La capa orgánica se secó sobre Na₂SO₄, se filtró, y se concentró para dar el compuesto del título.

EJEMPLO 121B

4-((4-metoxiciclohexil)metoxi)-3-nitrobenzenosulfonamida

El compuesto del título se preparó como se describe en el EJEMPLO 12A reemplazando (1,4-dioxan-2-il)metanol con EJEMPLO 121A.

5

EJEMPLO 121C

4-((cis-4-metoxiciclohexil)metoxi)-3-nitrobenzenosulfonamida

La separación de la mezcla cis y trans de EJEMPLO 121B en una HPLC de fase inversa (gradiente: 40-55% acetonitrilo en 0,1% TFA en agua a lo largo de 25 minutos) dio el

10 compuesto del título.

EJEMPLO 121D

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-N-(4-((cis-4-metoxiciclohexil)metoxi)-3-nitrofenilsulfonil)benzamida

15 El compuesto del título se preparó como se describe en el EJEMPLO 11D usando EJEMPLO 121C en lugar de EJEMPLO 11B. ¹H NMR (500 MHz, sulfóxido de dimetilo-d₆) □ 11,69 (s, 1H), 11,39 (s, 1H), 8,34 (s, 1H), 7,96 - 8,07 (m, 2H), 7,48 - 7,56 (m, 3H), 7,31 - 7,42 (m, 3H), 7,04 (d, 2H), 6,68 (dd, 1H), 6,40 (dd, 1H), 6,20 (d, 1H), 4,02 (d, 2H), 3,39 (s, 1H), 3,20 (s, 3H), 3,09 (s, 4H), 2,82 (s, 2H), 2,09 - 2,34 (m, 6H), 1,96 (s, 2H), 1,78 - 1,86 (m, 3H),
20 1,54 (dd, 2H), 1,28 - 1,46 (m, 6H), 0,92 (s, 6H)

EJEMPLO 122

Cis-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(4-([4-(ciclopropilamino)ciclohexil]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

25

EJEMPLO 122A

Cis-4-(ciclopropilamino)ciclohexilcarbamato de tert-butilo

El compuesto del título se preparó utilizando 4-oxociclohexilcarbamato de tert-butilo en lugar de 4'-clorobifenil-2-carboxaldehído y ciclopropilamina en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

30

EJEMPLO 122B

bis(2,2,2-trifluoroacetato) de cis-N1-ciclopropilciclohexano-1,4-diamina

El compuesto del título se preparó utilizando el EJEMPLO 122A en lugar del EJEMPLO 39A en el EJEMPLO 39B.

35

EJEMPLO 122C

Cis-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[4-(ciclopropilamino)ciclohexil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

5 El compuesto del título se preparó utilizando el EJEMPLO 122B en lugar del EJEMPLO 100B en el EJEMPLO 100C. ¹H NMR (500 MHz, piridin-d₅) □ 13,06 (s, 1H), 9,28 (d, 1H), 8,59 (d, 1H), 8,44 (d, 1H), 8,37 (dd, 1H), 8,12 (d, 1H), 7,67 (t, 2H), 7,43 (t, 2H), 7,07 (d, 2H), 6,90 (d, 1H), 6,75 (dd, 1H), 6,53 (d, 1H), 6,50 (dd, 1H), 3,56 - 3,63 (m, 1H), 3,02 - 3,08 (m, 4H), 2,77 (s, 3H), 2,26 (t, 2H), 2,10 - 2,16 (m, 4H), 2,06 (ddd, 1H), 1,97 (s, 2H), 1,74
10 - 1,82 (m, 2H), 1,61 - 1,71 (m, 5H), 1,39 (t, 2H), 0,93 (s, 6H), 0,39 - 0,44 (m, 4H).

EJEMPLO 123

Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{[4-(tetrahydro-2H-piran-4-ilamino)ciclohexil]amino}fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida
15

EJEMPLO 123A

Trans-4-(tetrahydro-2H-piran-4-ilamino)ciclohexilcarbamato de tert-butilo

El compuesto del título se preparó utilizando trans-4-aminociclohexilcarbamato de tert-butilo en lugar de piperazin-1-carboxilato de tert-butilo y dihidro-2H-piran-4(3H)-ona en lugar de 4'-clorobifenil-2-carboxaldehído en el EJEMPLO 1A.
20

EJEMPLO 123B

bis(2,2,2-trifluoroacetato) de trans-N1-(tetrahydro-2H-piran-4-il)ciclohexano-1,4-diamina

25 El compuesto del título se preparó utilizando el EJEMPLO 123A en lugar del EJEMPLO 39A en el EJEMPLO 39B.

EJEMPLO 123C

Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{[4-(tetrahydro-2H-piran-4-ilamino)ciclohexil]amino}fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida
30

El compuesto del título se preparó utilizando el EJEMPLO 123B en lugar del EJEMPLO 100B en el EJEMPLO 100C. ¹H NMR (500 MHz, piridin-d₅) □ 13,01 (s, 1H), 9,28 (d, 1H), 8,48 (d, 1H), 8,38 (dd, 1H), 8,32 (d, 1H), 8,24 (d, 1H), 7,67 - 7,69 (m, 2H), 7,44 (d, 2H), 7,08 (d, 2H), 6,91 (d, 1H), 6,78 (dd, 1H), 6,59 (d, 1H), 6,48 (dd, 1H), 4,01 (d, 2H), 3,44 - 3,49 (m, 1H), 3,37 - 3,43 (m, 2H), 3,01 - 3,09 (m, 5H), 2,85 (t, 1H), 2,78 (s, 2H), 2,27 (t, 2H),
35

2,13 - 2,18 (m, 4H), 2,05 (t, 4H), 1,97 (s, 2H), 1,93 (d, 2H), 1,52 - 1,60 (m, 2H), 1,44 - 1,50 (m, 2H), 1,39 (t, 2H), 1,25 - 1,34 (m, 2H), 0,94 (s, 6H).

EJEMPLO 124

- 5 Trans-N-({5-bromo-6-[(4-morfolin-4-ilciclohexil)oxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 124A

Trans-4-morfolinociclohexanol

- 10 Se disolvió trans-4-aminociclohexanol (0,5 g), 1-bromo-2-(2-bromoetoxi)etano (1,07 g) y trietilamina (2,42 mL) en acetonitrilo anhidro (20 mL). La mezcla de la reacción se calentó a 60°C durante la noche. El solvente orgánico se eliminó bajo vacío. El residuo se purificó con cromatografía flash de columna sobre gel de sílice eluyendo con 7%-10% metanol en diclorometano para dar el compuesto del título.

15

EJEMPLO 124B

Trans-5-bromo-6-(4-morfolinociclohexiloxi)piridin-3-sulfonamida

- El compuesto del título se preparó utilizando el EJEMPLO 124A por (tetrahydro-2H-piran-4-il)metanol y EJEMPLO 36A en lugar de 4-fluoro-3-nitrobenzenosulfonamida en el EJEMPLO 24A.

20

EJEMPLO 124C

Trans-N-({5-bromo-6-[(4-morfolin-4-ilciclohexil)oxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

- 25 El compuesto del título se preparó utilizando el EJEMPLO 124B en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (400MHz, sulfóxido de dimetilo-d₆) □ 11,67 (s, 1H), 8,56 (m, 2H), 8,03 (d, 1H), 7,80 (m, 1H), 7,50 (m, 3H), 7,34 (d, 2H), 7,12 (m, 1H), 7,04 (d, 2H), 6,67 (dd, 1H), 6,39 (dd, 1H), 6,19 (d, 1H), 3,99 (m, 1H), 3,67 (m, 1H), 3,37 (m, 2H), 3,24 (m, 2H), 3,07 (m, 4H), 2,89 (m, 1H), 2,71 (m, 2H), 2,16 (m, 6H), 1,96 (s, 3H), 1,80 (m, 4H), 1,38 (t, 2H), 1,27 (m, 2H), 0,92 (s, 6H).

30

EJEMPLO 125

Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-metoxiciclohexil)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

35

EJEMPLO 125A

4-(((trans)-4-metoxiciclohexil)metoxi)-3-nitrobenzenosulfonamida

La separación de la mezcla cis y trans de EJEMPLO 121B en una HPLC de fase inversa dio el compuesto del título.

5 EJEMPLO 125B

Trans-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-(4-metoxiciclohexil)metoxi]-3-nitrofenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 11D usando EJEMPLO 125A en lugar de EJEMPLO 11B. ¹H NMR (500 MHz, sulfóxido de dimetilo-d₆) □

10 11,68 (s, 1H), 8,34 (s, 1H), 7,96 - 8,09 (m, 2H), 7,51 (dd, 3H), 7,32 - 7,39 (m, 3H), 7,04 (d, 2H), 6,68 (dd, 1H), 6,39 (dd, 1H), 6,20 (d, 1H), 4,02 (d, 2H), 3,24 (s, 3H), 3,00 - 3,15 (m, 5H), 2,83 (s, 2H), 2,09 - 2,36 (m, 6H), 2,03 (d, 2H), 1,96 (s, 2H), 1,77 - 1,86 (m, 2H), 1,73 (s, 1H), 1,39 (t, 2H), 1,02 - 1,17 (m, 4H), 0,92 (s, 6H)

15 EJEMPLO 126

4-([4-([4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]amino)sulfonil)-2-nitrofenoxi]metil]-4-fluoropiperidin-1-carboxilato de tert-butilo

20 EJEMPLO 126A

4-fluoro-4-(hidroximetil)piperidin-1-carboxilato de tert-butilo

Se trató 4-fluoropiperidin-1,4-dicarboxilato de 1-tert-butilo 4-etilo (1,0 g) en tetrahidrofurano (5 mL) con LiAlH₄ 1,0 N en THF (2,54 mL) a 0 °C. La mezcla de la reacción se agitó a temperatura ambiente por 2 horas. Se agregó agua (0,6 mL) a la mezcla de la
25 reacción por goteo, seguido por NaOH acuoso 2 N (0,2 mL). La reacción se agitó por otra 1 hora. El sólido se retiró mediante filtración a travé de un tapón de Celite y se lavó con acetato de etilo. El material filtrado se lavó con salmuera, se secó sobre MgSO₄, se filtró, y se concentró para dar el producto.

EJEMPLO 126B

30 4-fluoro-4-((2-nitro-4-sulfamoilfenoxi)metil)piperidin-1-carboxilato de tert-butilo

El compuesto del título se preparó utilizando el EJEMPLO 126A en lugar de (tetrahidro-2H-piran-4-il)metanol en el EJEMPLO 24A.

EJEMPLO 126C

4-{{4-([4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]amino)sulfonil}-2-nitrofenoxi]metil)-4-fluoropiperidin-1-carboxilato de tert-butiloil)oxi]benzamida

El compuesto del título se preparó utilizando el EJEMPLO 126B en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,67 (s, 1H), 8,36 (s, 2H), 8,02-8,06 (m, 2H), 7,49-7,53 (m, 3H), 7,40 (d, 1H), 7,35 (d, 2H), 7,04 (d, 1H), 6,67 (dd, 1H), 6,39 (dd, 1H), 6,21 (d, 1H), 4,36 (d, 2H), 3,83-3,85 (m, 2H), 3,09 (s, 4H), 2,33 (s, 2H), 2,27-2,32 (m, 4H), 2,13-2,16 (m, 2H), 1,96 (s, 2H), 1,83-1,92 (m, 2H), 1,67-1,75 (m, 2H), 1,38-1,41 (m, 11H), 0,92 (s, 6H).

EJEMPLO 127

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-fluoropiperidin-4-il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 126C en lugar del EJEMPLO 1A en el EJEMPLO 1B. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,50 (s, 1H), 8,14 (d, 1H), 7,90 (d, 2H), 7,80 (dd, 1H), 7,60 (d, 1H), 7,40 (t, 1H), 7,35 (d, 2H), 7,25 (t, 1H), 7,13 (d, 1H), 7,05 (d, 2H), 6,61 (dd, 1H), 6,30 (dd, 1H), 6,26 (d, 1H), 4,28 (d, 2H), 3,10-3,13 (m, 2H), 2,91-3,00 (m, 6H), 2,73 (s, 2H), 1,96-2,02 (m, 4H), 1,77-1,89 (m, 2H), 1,39 (t, 2H), 0,93 (s, 6H).

EJEMPLO 128

Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{[4-(4-tetrahidro-2H-piran-4-il)piperazin-1-il]ciclohexil}amino)fenil}sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 128A

4-(tetrahidro-2H-piran-4-il)piperazin-1-carboxilato de tert-butilo

El compuesto del título se preparó utilizando piperazin-1-carboxilato de tert-butilo en lugar de morfolina y dihidro-2H-piran-4(3H)-ona en lugar de 4-oxociclohexilcarbamato de tert-butilo en el EJEMPLO 39A.

EJEMPLO 128B

diclorhidrato de 1-(tetrahidro-2H-piran-4-il)piperazina

A una solución de EJEMPLO 128A (3,92 g) en éter se agregó HCl (25 ml, 2M en éter) y la mezcla de la reacción se agitó por 16 horas a temperatura ambiente. El producto sólido se retiró por filtración, se secó y se usó en el siguiente paso sin purificación adicional.

EJEMPLO 128C

Trans-4-(4-(tetrahydro-2H-piran-4-il)piperazin-1-il)ciclohexilcarbamato de tert-butilo

El compuesto del título se preparó utilizando el EJEMPLO 128B en lugar de morfolina en el EJEMPLO 39A.

5 EJEMPLO 128D

tris(2,2,2-trifluoroacetato) de trans-4-(4-(tetrahydro-2H-piran-4-il)piperazin-1-il)ciclohexanamina

El compuesto del título se preparó utilizando el EJEMPLO 128C en lugar del EJEMPLO 39A en el EJEMPLO 39B.

10

EJEMPLO 128E

Trans-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(3-nitro-4-([4-(4-tetrahydro-2H-piran-4-il)piperazin-1-il)ciclohexil]amino)fenil)sulfonil]-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

15

El compuesto del título se preparó utilizando el EJEMPLO 128D en lugar del EJEMPLO 100B en el EJEMPLO 100C. ¹H NMR (500 MHz, piridin-d₅) δ 13,07 (s, 1H), 9,28 - 9,32 (m, 1H), 8,44 (t, 1H), 8,34 - 8,39 (m, 2H), 8,10 - 8,14 (m, 1H), 7,66 - 7,69 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,92 (t, 1H), 6,73 - 6,77 (m, 1H), 6,52 - 6,55 (m, 1H), 6,49 - 6,52 (m, 1H), 3,99 - 4,06 (m, 2H), 3,29 - 3,36 (m, 2H), 3,03 - 3,09 (m, 4H), 2,77 (s, 2H), 2,62 (s, 8H), 2,24 - 2,29 (m, 3H), 2,10 - 2,16 (m, 5H), 2,05 (s, 2H), 1,97 (s, 2H), 1,92 (s, 2H), 1,70 (d, 2H), 1,57 (td, 2H), 1,34 - 1,43 (m, 4H), 1,20 - 1,30 (m, 2H), 0,93 (s, 6H).

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EJEMPLO 129

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-[2-fluoro-1-(fluorometil)etil]piperidin-4-il]metoxi)-3-nitrofenil]sulfonil]-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 129A

(1-(1,3-difluoropropan-2-il)piperidin-4-il)metanol

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Una suspensión de piperidin-4-ilmetanol (0,250 g), triacetoxiborhidruro de sodio (0,690 g) y 1,3-difluoropropan-2-ona (0,245 g) se agitaron conjuntamente en diclorometano. Luego de agitar durante la noche la reacción se vertió en solución acuosa saturada de NaHCO₃ (10 mL) y se agitó por 15 minutos. La reacción se extrajo con diclorometano (3 x 25 mL), se secó sobre sulfato de magnesio, se filtró, y se concentró. Cromatografía sobre gel de sílice (GraceResolv 12 g) eluyendo con un gradiente de metanol entre 0,75% y 3%/diclorometano dio el compuesto del título.

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EJEMPLO 129B

4-((1-(1,3-difluoropropan-2-il)piperidin-4-il)metoxi)-3-nitrobencenosulfonamida

A una solución de (1-(1,3-difluoropropan-2-il)piperidin-4-il)metanol (0,068 g) en tetrahidrofurano (1 mL) se agregó hidruro de sodio (0,056 g) y la reacción se agitó por 30 minutos a temperatura ambiente. Se agregó 4-Fluoro-3-nitrobencenosulfonamida (0,077 g) en una porción y la agitación se continuó por 1 hora. La reacción se vertió en agua (20 mL) y se extrajo con diclorometano. El pH de la capa acuosa se ajustó a pH~8 y se extrajo con diclorometano (50 mL). La capa orgánica se secó sobre sulfato de magnesio, se filtró, y se concentró para dar el compuesto del título.

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EJEMPLO 129C

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-({1-[2-fluoro-1-(fluorometil)etil]piperidin-4-il}metoxi)-3-nitrofenil]sulfonil)-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 129B en lugar del EJEMPLO 1F y EJEMPLO 3J en lugar del EJEMPLO 1E en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) δ 11,67 (s, 1H), 11,47 - 10,98 (m, 1H), 8,33 (d, 1H), 8,03 (d, 2H), 7,50 (dd, 3H), 7,36 (t, 3H), 7,04 (d, 2H), 6,67 (d, 1H), 6,39 (dd, 1H), 6,20 (s, 1H), 4,62 (dd, 4H), 4,06 (d, 2H), 3,18 - 2,71 (m, 11H), 2,20 (d, 6H), 1,96 (s, 2H), 1,73 (d, 3H), 1,35 (d, 4H), 0,92 (s, 6H).

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EJEMPLO 130

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(3-nitro-4-([(3R)-1-tetrahydro-2H-piran-4-ilpirrolidin-3-il]amino)fenil)sulfonil]-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 130A

(R)-1-(tetrahydro-2H-piran-4-il)pirrolidin-3-ilcarbamato de tert-butilo

El compuesto del título se preparó utilizando dihidro-2H-piran-4(3H)-ona en lugar de 4'-clorobifenil-2-carboxaldehído y (R)-pirrolidin-3-ilcarbamato de tert-butilo en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

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EJEMPLO 130B

(R)-1-(tetrahydro-2H-piran-4-il)pirrolidin-3-amina

Una solución de EJEMPLO 130A (550 mg) en diclorometano (25 ml) se enfrió en un baño de hielo bajo nitrógeno. Se agregó ácido 2,2,2-trifluoroacético (8,333 ml) y la reacción se agitó por 2 horas. El producto se obtuvo mediante concentración y secado con alto vacío.

5 EJEMPLO 130C

(R)-3-nitro-4-(1-(tetrahydro-2H-piran-4-il)pirrolidin-3-ilamino)bencenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 130B en lugar de (tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

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EJEMPLO 130D

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(3-nitro-4-([(3R)-1-tetrahydro-2H-piran-4-ilpirrolidin-3-il]amino)fenil)sulfonyl]-2-(1H-pirrololo[2,3-b]piridin-5-iloxy)benzamida

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A una solución de EJEMPLO 3J (90 mg), EJEMPLO 130C (64,2 mg), trietilamina (0,077 ml), N,N-dimetilpiridin-4-amina (38,5 mg) en una mezcla de diclorometano (5 ml) y N,N-dimetilformamida (0,5 ml) se agregó N¹-(etilimino)metilen)-N³,N³-dimetilpropan-1,3-diamina, ácido clorhídrico (60,4 mg) y la mezcla se agitó 18 horas. Esto se concentró en alto vacío y el crudo se purificó mediante cromatografía de fase inversa con solución amortiguadora acetato de amonio / acetonitrilo. ¹H NMR (500 MHz, piridin-d₅) δ 13,03 (s, 1H), 9,27 (d, 1H), 8,59 (d, 1H), 8,43 (d, 1H), 8,37 (dd, 1H), 8,11 (d, 1H), 7,65 - 7,67 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,88 (d, 1H), 6,76 (dd, 1H), 6,54 (d, 1H), 6,48 (m, 1H), 4,06 (m, 1H), 3,98 (d, 2H), 3,35 (t, 2H), 3,07 (m, 4H), 2,73 - 2,80 (m, 4H), 2,68 - 2,72 (m, 1H), 2,36 (q, 1H), 2,11 - 2,30 (m, 9H), 1,97 (m, 2H), 1,62 - 1,71 (m, 3H), 1,48 - 1,58 (m, 2H), 1,39 (t, 2H), 0,94 (s, 6H).

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EJEMPLO 131

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(4-([(3R)-1-(2,2-dimetiltetrahydro-2H-piran-4-il)pirrolidin-3-il]amino)-3-nitrofenil)sulfonyl]-2-(1H-pirrololo[2,3-b]piridin-5-iloxy)benzamida

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EJEMPLO 131A

(3R)-1-(2,2-dimetiltetrahydro-2H-piran-4-il)pirrolidin-3-ilcarbamato de tert-butilo

El compuesto del título se preparó utilizando 2,2-dimetildihidro-2H-piran-4(3H)-ona en lugar de 4'-clorobifenil-2-carboxaldehído y (R)-pirrolidin-3-ilcarbamato de tert-butilo en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

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EJEMPLO 131B

(3R)-1-(2,2-dimetiltetrahydro-2H-piran-4-il)pirrolidin-3-amina

El compuesto del título se preparó utilizando el EJEMPLO 131A en lugar del EJEMPLO 130A en el EJEMPLO 130B.

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EJEMPLO 131C

4-((3R)-1-(2,2-dimetiltetrahydro-2H-piran-4-il)pirrolidin-3-ilamino)-3-nitrobenzenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 131B en lugar de (tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

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EJEMPLO 131D

4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[[4-{{(3R)-1-(2,2-dimetiltetrahydro-2H-piran-4-il)pirrolidin-3-il}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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El compuesto del título se preparó utilizando el EJEMPLO 131C en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500 MHz, piridin-d₅) δ 13,03 (d, 1H), 9,28 (m, 1H), 8,61 (m, 1H), 8,44 (d, 1H), 8,38 (dd, 1H), 8,11 (d, 1H), 7,64 - 7,68 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,89 (m, 1H), 6,76 (dd, 1H), 6,54 (m, 1H), 6,49 (m, 1H), 4,08 (m, 1H), 3,78 (m, 1H), 3,61 (m, 1H), 3,07 (m, 4H), 2,71 - 2,82 (m, 5H), 2,37 - 2,44 (m, 2H), 2,19 - 2,29 (m, 3H), 2,14 (m, 5H), 1,97 (s, 2H), 1,76 (m, 1H), 1,66 (m, 2H), 1,32 - 1,49 (m, 4H), 1,28 (d, 3H), 1,20 (s, 3H), 0,94 (s, 6H).

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EJEMPLO 132

4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(3-nitro-4-{{(3S)-1-tetrahydro-2H-piran-4-ilpirrolidin-3-il}amino}fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 132A

(S)-1-(tetrahydro-2H-piran-4-il)pirrolidin-3-ilcarbamato de tert-butilo

El compuesto del título se preparó utilizando dihidro-2H-piran-4(3H)-ona en lugar de 4'-clorobifenil-2-carboxaldehído y (S)-pirrolidin-3-ilcarbamato de tert-butilo en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

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EJEMPLO 132B

(S)-1-(tetrahydro-2H-piran-4-il)pirrolidin-3-amina

El compuesto del título se preparó utilizando el EJEMPLO 132A en lugar del EJEMPLO 130A en el EJEMPLO 130B.

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EJEMPLO 132C

(S)-3-nitro-4-(1-(tetrahydro-2H-piran-4-il)pirrolidin-3-ilamino)bencenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 132B en lugar de (tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

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EXAMPLE 132D

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(3-nitro-4-((3S)-1-tetrahydro-2H-piran-4-ilpirrolidin-3-il)amino)fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

15

El compuesto del título se preparó utilizando el EJEMPLO 132C en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500 MHz, piridin- d₅) □ 13,04 (m, 1H), 9,27 (d, 1H), 8,58 (d, 1H), 8,43 (d, 1H), 8,37 (dd, 1H), 8,11 (d, 1H), 7,64 - 7,68 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,88 (d, 1H), 6,75 (dd, 1H), 6,54 (m, 1H), 6,49 (m, 1H), 4,06 (m, 1H), 3,98 (d, 2H), 3,36 (t, 2H), 3,07 (m, 4H), 2,68 - 2,80 (m, 5H), 2,36 (m, 1H), 2,09 - 2,29 (m, 9H), 1,97 (s, 2H), 1,62 - 1,72 (m, 3H), 1,48 - 1,60 (m, 2H), 1,39 (t, 2H), 0,94 (s, 6H).

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EJEMPLO 133

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(4-((3S)-1-(2,2-dimetiltetrahydro-2H-piran-4-il)pirrolidin-3-il)amino)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 133A

(3S)-1-(2,2-dimetiltetrahydro-2H-piran-4-il)pirrolidin-3-ilcarbamato de tert-butilo

El compuesto del título se preparó utilizando 2,2-dimetildihidro-2H-piran-4(3H)-ona en lugar de 4'-clorobifenil-2-carboxaldehído y (S)-pirrolidin-3-ilcarbamato de tert-butilo en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

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EJEMPLO 133B

(3S)-1-(2,2-dimetiltetrahydro-2H-piran-4-il)pirrolidin-3-amina

El compuesto del título se preparó utilizando el EJEMPLO 133A en lugar del EJEMPLO 130A en el EJEMPLO 130B.

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EJEMPLO 133C

4-(3S)-(1-(2,2-dimetiltetrahydro-2H-piran-4-il)pirrolidin-3-ilamino)-3-nitro bencenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 133B en lugar de (tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

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EJEMPLO 133D

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(4-([(3S)-1-(2,2-dimetiltetrahydro-2H-piran-4-il)pirrolidin-3-il]amino)-3-nitrofenil)sulfonyl]-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida

10 El compuesto del título se preparó utilizando el EJEMPLO 133C en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500 MHz, piridin- d₅) □ 13,03 (d, 1H), 9,28 (m, 1H), 8,61 (m, 1H), 8,43 (d, 1H), 8,38 (dd, 1H), 8,11 (d, 1H), 7,64 - 7,68 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,89 (m, 1H), 6,76 (dd, 1H), 6,54 (m, 1H), 6,49 (m, 1H), 4,08 (m, 1H), 3,78 (m, 1H), 3,61 (m, 1H), 3,07 (m, 4H), 2,71 - 2,82 (m, 5H), 2,37 - 2,44 (m, 2H), 2,19 - 2,29 (m, 15 3H), 2,14 (m, 5H), 1,97 (s, 2H), 1,76 (m, 1H), 1,66 (m, 2H), 1,33 - 1,48 (m, 4H), 1,28 (d, 3H), 1,20 (s, 3H), 0,94 (s, 6H).

EJEMPLO 134

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(4-([(4-metilmorfolin-2-il)metil]amino)-3-nitrofenil)sulfonyl]-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 134A

4-(morfolin-2-ilmetilamino)-3-nitrobencenosulfonamida

25 Una solución de EJEMPLO 113A (0,8 g) en diclorometano (10 mL) y ácido trifluoroacético (10 mL) se agitó a temperatura ambiente por 2 horas. Los solventes se evaporaron y el residuo se trituró con éter dietílico. El sólido resultante se disolvió en solución acuosa al 5% de carbonato de sodio (20 mL). La solución se concentró hasta secar y el sólido resultante se trituró con una solución de metanol al 10% en diclorometano varias veces. La evaporación de los solventes orgánicos dio el compuesto del título.

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EJEMPLO 134B

4-((4-metilmorfolin-2-il)metilamino)-3-nitrobencenosulfonamida

35 A una solución de EJEMPLO 134A (158 mg) en *N,N*-dimetilformamida anhidra (4 mL) se agregó carbonato de sodio (64 mg) y yoduro de metilo (78 mg). Luego de agitar durante la noche a temperatura ambiente, la mezcla se evaporó hasta secar. El producto crudo luego

se adsorbió sobre gel de sílice (6 g) y se purificó en una columna de gel de sílice eluyendo con metanol al 10% en diclorometano para dar el compuesto del título.

EJEMPLO 134C

- 5 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-metilmorfolin-2-il]metil)amino]-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 134B en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridin-d₅) □ 13,00 (s, 1H), 9,27 (d, 1H), 8,87 (t, 1H), 8,43 (d, 1H), 8,32 (dd, 1H), 8,11 (d, 1H), 7,65 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,91 (d, 1H), 6,75 (dd, 1H), 6,54 (d, 1H), 6,48 (m, 1H), 3,92 (m, 1H), 3,86 (d, 1H), 3,67 (dt, 1H), 3,49-3,39 (m, 2H), 3,07 (m, 4H), 2,77 (s, 2H), 3,71 (m, 1H), 2,49 (d, 1H), 2,26 (m, 2H), 2,16 (s, 3H), 2,14 (m, 4H), 2,03 (dt, 1H), 1,97 (s, 2H), 1,90 (t, 1H), 1,39 (t, 2H), 0,94 (s, 6H).

15 EJEMPLO 135

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-(2-metoxietil)morfolin-2-il]metil)amino]-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

20 EJEMPLO 135A

4-((4-(2-metoxietil)morfolin-2-il)metilamino)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando bromuro de 2-metoxietilo en lugar de yoduro de metilo en el EJEMPLO 134B.

EJEMPLO 135B

- 25 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-(2-metoxietil)morfolin-2-il]metil)amino]-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 135A en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridin-d₅) □ 12,98 (s, 1H), 9,26 (d, 1H), 8,88 (t, 1H), 8,43 (d, 1H), 8,32 (dd, 1H), 8,11 (d, 1H), 7,66 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,91 (d, 1H), 6,75 (dd, 1H), 6,54 (d, 1H), 6,48 (m, 1H), 3,93 (m, 1H), 3,87 (d, 1H), 3,70 (dt, 1H), 3,51 (t, 2H), 3,48-3,38 (m, 2H), 3,27 (s, 3H), 3,07 (m, 4H), 2,95 (d, 1H), 2,77 (s, 2H), 2,70 (m, 1H), 2,57 (t, 2H), 2,27-2,07 (m, 8H), 1,97 (s, 2H), 1,39 (t, 2H), 0,94 (s, 6H).

35 EJEMPLO 136

N-[(4-{[(4-acetilmorfolin-2-il)metil]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 136A

5 4-((4-acetilmorfolin-2-il)metilamino)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando anhídrido acético en lugar de yoduro de metilo en el EJEMPLO 134B.

EJEMPLO 136B

10 N-[(4-{[(4-acetilmorfolin-2-il)metil]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 136A en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridina-d₅) □ 13,00 (s, 1H), 9,26 (s, 1H), 8,85 (s, 1H), 8,43 (d, 1H), 8,32 (dd, 1H), 8,10 (d, 1H), 7,65 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,91 (dd, 1H), 6,75 (dd, 1H), 6,54 (s, 1H), 6,48 (s, 1H), 4,73 (dd, 1H), 3,93-3,65 (m, 2H), 3,60-3,40 (m, 4H), 3,12 (m, 1H), 3,07 (m, 4H), 2,77 (s, 2H), 2,70 (m, 1H), 2,57 (t, 2H), 2,14 (s, 3H), 2,27-2,07 (m, 4H), 1,97 (s, 2H), 1,39 (t, 2H), 0,93 (s, 6H).

EJEMPLO 137

20 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[trans-4-(fluorometil)-1-oxetan-3-ilpirrolidin-3-il]metoxi}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 137A

4-fluorobut-2-enoato de etilo

25 Se trató 2-fluoroacetato de etilo (21,0 g) en CH₂Cl₂ (200 mL) a -78 °C por goteo a lo largo de 45 min con una solución 1,0 M de hidruro de diisobutilaluminio en CH₂Cl₂ (200 mL) manteniendo la temperatura interna por debajo de -70 °C. La agitación se continuó a -78 °C por 30 minutos y luego se agregó (carbetoximetilen)trifenilfosforano (70,0 g) en una porción. La mezcla de la reacción de dejó alcanzar lentamente temperatura ambiente mientras se agitaba durante la noche. Luego se detuvo con metanol, se filtró y se concentró para dar el producto como una mezcla de isómeros (E/Z = 3:1).

EJEMPLO 137B

Trans-1-bencil-4-(fluorometil)pirrolidin-3-carboxilato de etilo

35 Una mezcla de N-bencil-1-metoxi-N-((trimetilsilil)metil)metanamina (4,5 g) y EJEMPLO 137A (2,5 g) en diclorometano (50 mL) se enfrió a 0 °C, se trató por goteo con

ácido trifluoroacético (0,15 mL), se agitó por 4 horas a 0 °C y se neutralizó con solución acuosa saturada de Na_2CO_3 . La mezcla se vertió en un embudo de separación y las capas se separaron. La capa orgánica se lavó con agua y salmuera, se secó (MgSO_4), se filtró, se concentró y se cromatografió sobre gel de sílice con acetato de etilo al 0-20% en hexanos como eluyente para dar ambos isómeros cis y trans del producto. Sólo los diastereómeros trans se llevaron a los siguientes pasos.

EJEMPLO 137C

Trans-4-(fluorometil)pirrolidin-3-carboxilato de etilo

Se trató EJEMPLO 137B (0,83 g) en etanol (9 mL) con Pd/C al 10% (0,208 g) y formato de amonio (1,97 g), se sometió a reflujo por 1,5 horas, se concentró, se disolvió en diclorometano, se filtró a través de una almohadilla de celite enjuagando con diclorometano, y se concentró para dar el producto.

EJEMPLO 137D

Trans-4-(fluorometil)pirrolidin-1,3-dicarboxilato de 1-bencilo 3-etilo

Se trató EJEMPLO 137C (0,44 g) en dioxano (4 mL) y agua (4 mL) a 0 °C en forma secuencial con Na_2CO_3 (0,89 g) y cloroformato de bencilo (0,48 mL). La mezcla de la reacción se agitó a 0 °C por 3 horas y luego se dejó calentar lentamente a temperatura ambiente durante 1,5 horas. La mezcla de la reacción 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 10-25% acetato de etilo en hexanos como eluyente para dar el producto.

EJEMPLO 137E

ácido trans-1-(benciloxicarbonil)-4-(fluorometil)pirrolidin-3-carboxílico

El compuesto del título se preparó utilizando el EJEMPLO 137D en lugar del EJEMPLO 15G en el EJEMPLO 15H.

EJEMPLO 137F

Trans-3-(fluorometil)-4-(hidroximetil)pirrolidin-1-carboxilato de bencilo

Se trató EJEMPLO 137E (0,563 g) en tetrahidrofurano (10 mL) a 0 °C por goteo con una solución 1 M de borano en tetrahidrofurano (4 mL), se agitó por 3 horas y luego se detuvo lentamente con solución acuosa saturada de NH_4Cl . La mezcla de la reacción se

diluyó con acetato de etilo, se lavó con agua y salmuera, se secó (MgSO_4), se filtró y se concentró para dar el producto.

EJEMPLO 137G

- 5 Trans-3-(fluorometil)-4-((2-nitro-4-sulfamoilfenoxi)metil)pirrolidin-1-carboxilato de bencilo

El compuesto del título se preparó utilizando el EJEMPLO 137F en lugar de (tetrahidro-2H-piran-4-il)metanol en el EJEMPLO 24A.

EJEMPLO 137H

- 10 Trans-4-((4-(fluorometil)pirrolidin-3-il)metoxi)-3-nitrobenzenosulfonamida

Se trató EJEMPLO 137G (0,232g) en ácido acético (2,5 ml) con ácido bromhídrico (33 % en peso en ácido acético) (0,875 mL) a temperatura ambiente, se agitó por 1 hora y se concentró. El producto se liberó de su base usando una columna MEGA BE-SCX con 1:1 CH_2Cl_2 /metanol como eluyente para el ácido bromhídrico y ácido acético. El producto se liberó de la columna con (amoníaco 7 M en metanol) al 10% en CH_2Cl_2 como eluyente.

EJEMPLO 137I

Trans-4-((4-(fluorometil)-1-(oxetan-3-il)pirrolidin-3-il)metoxi)-3-nitrobenzenosulfonamida

- 20 El compuesto del título se preparó utilizando el EJEMPLO 137H en lugar de piperazin-1-carboxilato de tert-butilo y 3-oxetanona en lugar de 4'-clorobifenil-2-carboxaldehído en el EJEMPLO 1A.

EJEMPLO 137J

- 25 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([trans-4-(fluorometil)-1-oxetan-3-ilpirrolidin-3-il]metoxi)-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

- 30 El compuesto del título se preparó utilizando el EJEMPLO 137I en lugar del EJEMPLO 11B en el EJEMPLO 11D. ^1H NMR (300 MHz, sulfóxido de dimetilo- d_6) δ 11,67 (s, 1H), 8,35 (d, 1H), 8,03 (m, 2H), 7,51 (m, 3H), 7,37 (m, 3H), 7,04 (m, 2H), 6,67 (dd, 1H), 6,39 (dd, 1H), 6,21 (d, 1H), 4,45 (m, 6H), 4,21 (d, 2H), 3,62 (m, 1H), 3,08 (m, 4H), 2,72 (m, 5H), 2,31 (m, 9H), 1,96 (s, 2H), 1,39 (t, 2H), 0,93 (s, 6H).

EJEMPLO 138

- 35 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-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 138A

metansulfonato de (4-fluorotetrahidro-2H-piran-4-il)metilo

Una mezcla de EJEMPLO 37C (1,4 g), cloruro de metansulfonilo (1,054 mL), trietilamina (2,99 mL), y 4-dimetilaminopiridina (0,051 g) en CH_2Cl_2 (20 mL) se agitó a 0 °C por 2 horas, se concentró y se cromatografió sobre gel de sílice eluyendo con acetato de etilo al 30% en hexanos para dar el producto.

EJEMPLO 138B

2-((4-fluorotetrahidro-2H-piran-4-il)metil)isoindolin-1,3-diona

Una mezcla de EJEMPLO 138A (1,8 g) y ftalimida de potasio (2,356 g) en N,N-dimetilformamida (30 mL) se calentó a 150 °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 cromatografió sobre gel de sílice eluyendo con acetato de etilo al 30% en hexanos para dar el producto.

EJEMPLO 138C

(4-fluorotetrahidro-2H-piran-4-il)metanamina

Una mezcla de EJEMPLO 138B (1,4 g) e hidrazina (1,548 mL) en etanol (40 mL) se calentó a 70 °C durante la noche, se enfrió a temperatura ambiente, se formó una lechada con CH_2Cl_2 (200 mL) y el sólido se retiró mediante filtración. El material filtrado se concentró y se cromatografió sobre gel de sílice eluyendo con 100:5:1 acetato de etilo/metanol/ NH_4OH para dar el producto.

EJEMPLO 138D

4-((4-fluorotetrahidro-2H-piran-4-il)metilamino)-3-nitrobencenosulfonamida

Una mezcla de 4-fluoro-3-nitrobencenosulfonamida (0,44 g), EJEMPLO 138C (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 cromatografió sobre gel de sílice eluyendo con acetato de etilo al 50% en hexanos para dar el producto.

EJEMPLO 138E

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 138D en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) δ 11,68 (s, 1H), 8,62 (t, 1H), 8,56 (d, 1H), 8,04 (d, 1H), 7,82 (dd, 1H), 7,48-7,54 (m, 3H), 7,34 (d, 2H), 7,24 (d, 1H), 7,04 (d, 2H), 6,68 (dd, 1H), 6,39 (dd, 1H), 6,19 (d, 1H), 3,70-3,77 (m, 4H), 3,50-3,55 (m, 2H), 3,07 (s, 4H), 2,76 (s, 2H), 2,14-2,20 (m, 6H), 1,76-1,84 (m, 4H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 139

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([1-oxetan-3-ilpiperidin-4-il)amino]fenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 139A

4-(4-(N-(2-(1H-pirrolo[2,3-b]piridin-5-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 como se describe en el EJEMPLO 53B reemplazando 1-acetilpiperidin-4-amina con éster tert-butílico del ácido 4-amino-piperidin-1-carboxílico.

20 EJEMPLO 139B

2-(1H-pirrolo[2,3-b]piridin-5-iloxi)-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-N-(3-nitro-4-(piperidin-4-ilamino)fenilsulfonil)benzamida

A una solución fría (0°C) de EJEMPLO 139A (960 mg) en diclorometano (10 mL) se agregó por goteo ácido trifluoracético (5 mL). La mezcla se agitó a la temperatura por 3 horas. Luego, la mezcla se concentró bajo vacío y el residuo se disolvió en diclorometano (200 mL) y se lavó con NaHCO₃ acuoso y salmuera. Luego de secar sobre Na₂SO₄, la mezcla se filtró, y la evaporación del solvente a partir del material filtrado dio el compuesto del título.

30 EJEMPLO 139C

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([1-oxetan-3-ilpiperidin-4-il)amino]fenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

A una solución de EJEMPLO 139B (120 mg) en tetrahidrofurano (3 mL) y ácido acético (1 mL) se agregó oxetan-3-ona (50,8 mg) y MP-cianoborohidruro (2,15 mmol/g, 150 mg). La mezcla se agitó a temperatura ambiente durante la noche. La mezcla se filtró. El material filtrado se concentró y el residuo se cargó en un cartucho de gel de sílice y se eluyó

con NH_3 7N al 5-10% en metanol en diclorometano para dar el compuesto del título. ^1H NMR (300 MHz, sulfóxido de dimetilo- d_6) $\square$ 11,62 (s, 1H), 8,51 (d, 1H), 8,20 (d, 1H), 7,99 (d, 1H), 7,74 (m, 1H), 7,48 (m, 3H), 7,35 (d, 2H), 7,05 (d, 2H), 6,66 (dd, 1H), 6,36 (dd, 1H), 6,20 (d, 1H), 4,54 (t, 2H), 4,43 (t, 2H), 3,66 (m, 1H), 3,44 (m, 3H), 3,04 (m, 5H), 2,73 (s, 2H), 2,61 (m, 2H), 2,12 (m, 11H), 1,61 (m, 2H), 1,38 (t, 2H), 0,93 (m, 6H).

EJEMPLO 140

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-(ciclobutilpiperidin-4-il)amino]-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 139C reemplazando oxetan-3-ona con ciclobutanona. ^1H NMR (300 MHz, sulfóxido de dimetilo- d_6) $\square$ 11,58 (s, 1H), 8,47 (d, 1H), 8,12 (d, 1H), 7,97 (d, 1H), 7,74 (d, 1H), 7,53 (d, 1H), 7,45 (m, 1H), 7,36 (m, 3H), 7,02 (m, 3H), 6,64 (dd, 1H), 6,33 (m, 1H), 6,22 (d, 1H), 3,74 (m, 1H), 2,97 (m, 6H), 2,73 (s, 3H), 2,15 (m, 15H), 1,67 (m, 4H), 1,38 (t, 2H), 0,93 (s, 6H).

EJEMPLO 141

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-(2,2-dimetiltetrahidro-2H-piran-4-il)piperidin-4-il]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 139C reemplazando oxetan-3-ona con 2,2-dimetiltetrahidropiran-4-ona. ^1H NMR (300 MHz, sulfóxido de dimetilo- d_6) $\square$ 11,60 (s, 1H), 8,50 (d, 1H), 8,15 (m, 1H), 7,99 (d, 1H), 7,78 (m, 1H), 7,62 (m, 1H), 7,47 (m, 3H), 7,34 (m, 3H), 7,05 (m, 3H), 6,65 (m, 2H), 6,35 (dd, 1H), 6,21 (d, 1H), 4,56 (d, 3H), 3,89 (m, 3H), 3,67 (m, 6H), 3,45 (m, 2H), 3,04 (m, 3H), 2,75 (m, 3H), 2,14 (m, 3H), 1,71 (m, 5H), 1,16 (s, 9H).

EJEMPLO 142

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([(3S)-1-ciclopropilpirrolidin-3-il]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 142A

(S)-1-ciclopropilpirrolidin-3-ilcarbamato de tert-butilo

Se combinó (S)-pirrolidin-3-ilcarbamato de tert-butilo (415 mg), (1-etoxiciclopropoxi)trimetilsilano (1,8 mL) y tamices moleculares (500 mg) en metanol (4,5 mL). Se agregó ácido acético (1,3 mL), seguido por cianoborohidruro de sodio (420 mg). La

mezcla resultante se calentó a reflujo por 4 horas. El material insoluble se retiró por filtración y la reacción se basificó a pH 14 con la adición de solución acuosa 6M de NaOH. La solución se extrajo tres veces con éter dietílico, y los extractos combinados se secaron sobre MgSO₄, se filtró y se concentró para obtener un aceite, el cual se purificó mediante cromatografía flash, eluyendo primero con diclorometano al 100%, seguido por metanol al 5%/diclorometano y metanol al 10%/diclorometano.

EJEMPLO 142B

(S)-1-ciclopropilpirrolidin-3-amina

El compuesto del título se preparó utilizando el EJEMPLO 142A en lugar del EJEMPLO 1A en el EJEMPLO 1B.

EJEMPLO 142C

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([(3S)-1-ciclopropilpirrolidin-3-il]amino)-3-nitrofenil]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 142B en lugar de 1-acetilpiperidin-4-amina en el EJEMPLO 53B. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,64 (s, 1H), 8,51 (m, 2H), 8,30 (m, 1H), 8,00 (br s, 1H), 7,77 (m, 1H), 7,49 (m, 3H), 7,34 (d, 2H), 7,04 (d, 2H), 6,97 (br s, 1H), 6,67 (dd, 1H), 6,36 (m, 1H), 6,21 (m, 1H), 4,19 (m, 1H), 3,00 (m, 5H), 2,74 (m, 3H), 2,64 (m, 1H), 2,36 (m, 1H), 2,15 (m, 6H), 1,95 (s, 2H), 1,78 (br s, 1H), 1,68 (m, 1H), 1,38 (t, 2H), 1,23 (m, 1H), 0,92 (s, 6H), 0,39 (m, 4H).

EJEMPLO 143

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-[(1-tetrahidrofurano-3-il)piperidin-4-il]amino]fenil]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 139C reemplazando oxetan-3-ona con 3-oxotetrahidrofurano. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) □ 11,65 (s, 1H), 8,53 (d, 1H), 8,21 (m, 1H), 8,02 (m, 1H), 7,80 (dd, 1H), 7,49 (m, 3H), 7,34 (m, 3H), 7,05 (m, 3H), 6,67 (dd, 1H), 6,37 (m, 1H), 6,19 (d, 1H), 4,29 (m, 3H), 3,73 (m, 6H), 3,09 (m, 4H), 2,76 (m, 2H), 2,05 (m, 8H), 1,68 (m, 2H), 1,37 (m, 2H), 0,94 (s, 6H).

EJEMPLO 144

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([(3R)-1-ciclopropilpirrolidin-3-il]amino)-3-nitrofenil]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 144A

(R)-1-ciclopropilpirrolidin-3-ilcarbamato de tert-butilo

El compuesto del título se preparó utilizando (R)-pirrolidin-3-ilcarbamato de tert-butilo en lugar de (S)-pirrolidin-3-ilcarbamato de tert-butilo en el EJEMPLO 142A.

5

EJEMPLO 144B

(R)-1-ciclopropilpirrolidin-3-amina

El compuesto del título se preparó utilizando el EJEMPLO 144A en lugar del EJEMPLO 1A en el EJEMPLO 1B.

10

EJEMPLO 144C

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(4-([[(3R)-1-ciclopropilpirrolidin-3-il]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida

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El compuesto del título se preparó utilizando el EJEMPLO 144B en lugar de 1-acetilpiperidin-4-amina en el EJEMPLO 53B. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,66 (s, 1H), 8,53 (d, 2H), 8,32 (d, 1H), 8,02 (d, 1H), 7,81 (m, 1H), 7,49 (m, 3H), 7,34 (d, 2H), 7,03 (m, 3H), 6,67 (dd, 1H), 6,37 (m, 1H), 6,20 (d, 1H), 4,21 (m, 1H), 3,00 (m, 5H), 2,74 (m, 3H), 2,64 (m, 1H), 2,36 (m, 1H), 2,15 (m, 6H), 1,95 (s, 2H), 1,74 (br s, 1H), 1,66 (m, 1H), 20 1,38 (t, 2H), 1,23 (m, 1H), 0,92 (s, 6H), 0,39 (m, 4H).

EJEMPLO 145

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-([[(3S)-1-tetrahydro-2H-piran-4-ilpirrolidin-3-il]metil]amino)fenil]sulfonil)-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida

25

EJEMPLO 145A

30 (S)-(1-(tetrahydro-2H-piran-4-il)pirrolidin-3-il)metilcarbamato de tert-butilo

El compuesto del título se preparó utilizando (R)-pirrolidin-3-ilmetilcarbamato de tert-butilo en lugar de piperazin-1-carboxilato de tert-butilo y dihidro-2H-piran-4(3H)-ona en lugar de 4'-clorobifenil-2-carboxaldehído en el EJEMPLO 1A.

35

EJEMPLO 145B

(S)-(1-(tetrahydro-2H-piran-4-il)pirrolidin-3-il)metanamina

El compuesto del título se preparó utilizando el EJEMPLO 145A en lugar del EJEMPLO 1A en el EJEMPLO 1B.

EJEMPLO 145C

5 (S)-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-N-(3-nitro-4-((1-(tetrahidro-2H-piran-4-il)pirrolidin-3-il)metilamino)fenilsulfonil)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 145B en lugar de 1-acetilpiperidin-4-amina en el EJEMPLO 53B. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □
 10 11,58 (s, 1H), 8,61 (br s, 1H), 8,46 (s, 1H), 7,96 (d, 1H), 7,72 (m, 1H), 7,54 (d, 1H), 7,45 (t, 1H), 7,37 (br s, 2H), 7,34 (d, 2H), 7,04 (m, 2H), 6,94 (m, 1H), 6,64 (dd, 1H), 6,34 (m, 1H), 6,22 (d, 1H), 3,89 (m, 2H), 3,38 (m, 4H), 3,27 (m, 4H), 3,02 (m, 5H), 2,73 (s, 2H), 2,61 (m, 1H), 2,18 (m, 6H), 2,05 (m, 1H), 1,95 (m, 2H), 1,85 (m, 2H), 1,64 (m, 1H), 1,50 (m, 2H), 1,38 (m, 2H), 0,94 (s, 6H).

15

EJEMPLO 146

4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({4-{{3-hidroxi-2,2-dimetilpropil}amino}-3-nitrofenil}sulfonil)-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 120B usando 3-amino-2,2-dimetilpropan-1-ol en lugar de EJEMPLO 120A. ¹H NMR (500 MHz, sulfóxido de dimetilo-d₆) □ 11,68 (s, 1H), 11,35 (s, 1H), 8,96 (t, 1H), 8,56 (d, 1H), 8,05 (d, 1H), 7,79 (dd, 1H), 7,46 - 7,56 (m, 3H), 7,34 (d, 2H), 7,10 (d, 1H), 7,04 (d, 2H), 6,68 (dd, 1H), 6,39 (dd, 1H), 6,19 (d, 1H), 5,10 (t, 1H), 3,29 (d, 1H), 3,24 (d, 1H), 3,07 (s, 4H), 2,75 (s, 2H), 2,17 (d, 6H), 1,95 (s, 2H), 1,38 (t, 2H), 0,93 (d, 12H).

25

EJEMPLO 147

4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{1-(metilsulfonil)piperidin-3-il}metil}amino}-3-nitrofenil}sulfonil)-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 147A

(1-(metilsulfonil)piperidin-3-il)metilcarbamato de tert-butilo

Se disolvió piperidin-3-ilmetilcarbamato de tert-butilo (500 mg) en diclorometano anhidro (10 mL), y se agregó cloruro de metansulfonilo (0,181 mL) seguido por la adición de trietilamina (1,3 mL). La mezcla de la reacción se agitó a temperatura ambiente durante la
 35 noche. El solvente orgánico se eliminó bajo vacío. El residuo se purificó con cromatografía

flash de columna sobre gel de sílice eluyendo con 0-70% acetato de etilo en hexano para dar el compuesto del título.

EJEMPLO 147B

5 (1-(metilsulfonil)piperidin-3-il)metanamina

Se suspendió EJEMPLO 147A (400 mg) en HCl 4N en dioxano (10 mL) seguido por la adición de metanol anhidro (1 mL). La solución traslúcida se agitó a temperatura ambiente por 2 horas. El solvente orgánico se eliminó bajo vacío. El residuo sólido se usó en el siguiente paso sin purificación adicional.

10

EJEMPLO 147C

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-(metilsulfonil)piperidin-3-il]metil)amino]-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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Se disolvió EJEMPLO 53A (50 mg), EJEMPLO 147B (26 mg) y trietilamina (0,088 mL) en dioxano anhidro (1 mL) y N,N-dimetilformamida (0,2 mL). El vial de la reacción se calentó en un reactor de microondas Biotage Initiator a 130°C por 25 minutos. El solvente se eliminó bajo vacío. 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 (6 mL) y se lavó con NaHCO₃ acuoso al 50%. La capa orgánica se secó sobre Na₂SO₄ anhidro y se concentró para dar el compuesto del título. ¹H NMR (400MHz, sulfóxido de dimetilo-d₆) □ 11,65 (s, 1H), 8,56 (m, 2H), 8,03 (d, 1H), 7,80 (m, 1H), 7,50 (m, 3H), 7,35 (d, 2H), 7,12 (m, 1H), 7,04 (d, 2H), 6,67 (dd, 1H), 6,38 (dd, 1H), 6,19 (d, 1H), 3,52 (m, 1H), 3,40 (m, 2H), 3,06 (m, 4H), 2,84 (s, 3H), 2,75 (m, 2H), 2,75 (m, 4H), 2,58 (m, 1H), 2,16 (m, 6H), 1,95 (s, 3H), 1,76 (m, 2H), 1,52 (m, 1H), 1,37 (m, 2H), 0,92 (s, 6H).

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EJEMPLO 148

N-([4-([1-(1-acetilpiperidin-3-il)metil]amino)-3-nitrofenil)sulfonil]-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 148A

(1-acetilpiperidin-3-il)metilcarbamato de tert-butilo

El compuesto del título se preparó utilizando cloruro de acetilo en lugar de cloruro de metansulfonilo en el EJEMPLO 147A.

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EJEMPLO 148B

1-(3-(aminometil)piperidin-1-il)etanona

El compuesto del título se preparó utilizando el EJEMPLO 148A en lugar del EJEMPLO 147A en el EJEMPLO 147B.

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EJEMPLO 148C

N-[(4-[(1-acetilpiperidin-3-il)metil]amino)-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 148B en lugar del EJEMPLO 147B en el EJEMPLO 147C. ¹H NMR (400MHz, sulfóxido de dimetilo-d₆) δ 11,67 (s, 1H), 8,56 (m, 2H), 8,03 (d, 1H), 7,80 (m, 1H), 7,50 (m, 3H), 7,34 (d, 2H), 7,12 (m, 1H), 7,04 (d, 2H), 6,67 (dd, 1H), 6,39 (dd, 1H), 6,19 (d, 1H), 3,99 (m, 1H), 3,67 (m, 1H), 3,37 (m, 2H), 3,24 (m, 2H), 3,07 (m, 4H), 2,89 (m, 1H), 2,71 (m, 2H), 2,16 (m, 6H), 1,96 (s, 3H), 1,80 (m, 4H), 1,38 (t, 2H), 1,27 (m, 2H), 0,92 (s, 6H).

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EJEMPLO 149

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-[(3R)-1-(metilsulfonil)pirrolidin-3-il]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 149A

(R)-1-(metilsulfonil)pirrolidin-3-ilcarbamato de tert-butilo

El compuesto del título se preparó utilizando (R)-pirrolidin-3-ilcarbamato de tert-butilo en lugar de piperidin-3-ilmetilcarbamato de tert-butilo en el EJEMPLO 147A.

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EJEMPLO 149B

(R)-1-(metilsulfonil)pirrolidin-3-amina

El compuesto del título se preparó utilizando el EJEMPLO 149A en lugar del EJEMPLO 147A en el EJEMPLO 147B.

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EJEMPLO 149C

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-[(3R)-1-(metilsulfonil)pirrolidin-3-il]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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El compuesto del título se preparó utilizando el EJEMPLO 149B en lugar del EJEMPLO 147B en el EJEMPLO 147C. ^1H NMR (400MHz, sulfóxido de dimetilo- d_6) δ 11,65 (s, 1H), 8,55 (d, 1H), 8,29 (d, 1H), 8,02 (d, 1H), 7,86 (dd, 1H), 7,49 (m, 3H), 7,33 (d, 2H), 7,17 (d, 1H), 7,04 (d, 2H), 6,68 (dd, 1H), 6,38 (dd, 1H), 6,20 (d, 1H), 4,41 (m, 1H), 3,69 (m, 1H), 3,39 (m, 3H), 3,06 (m, 4H), 2,97 (s, 3H), 2,76 (m, 2H), 2,27 (m, 8H), 1,93 (m, 2H), 1,54 (m, 1H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 150

4-(4-([2-(4-clorofenil)-3,3-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida
EJEMPLO 150A

2-hidroxi-3,3-dimetilciclohex-1-encarboxilato de etilo

En un balón de 500 mL se agregó diisopropilamina (3,5 mL) en éter (200 mL). Luego de enfriar a -30°C , se agregó butillitio (16 mL) (1,6M en hexano) lentamente. Luego de agitar 30 minutos, la temperatura se enfrió a -5°C . Se agregó 2,2-dimetilciclohexanona (3 g) lentamente. La mezcla se calentó hasta 0°C y se agitó por 1 hora. Luego de enfriar a -5°C , se agregó hexametilfosforamida (8 mL) y carbonocianidato de etilo (2,5 mL). Luego de agitar a -5°C por 20 minutos, y calentar a temperatura ambiente, la reacción se agitó por 1 hora. La mezcla se vertió en agua fría, y las capas se separaron. La capa acuosa se extrajo con éter (3x 20 mL). Las capas orgánicas combinadas se lavaron con NH_4Cl acuoso saturado (3x 20 mL). Luego de secar sobre Na_2SO_4 , la mezcla se filtró y el material filtrado se concentró. El producto crudo se purificó mediante cromatografía flash sobre sílice con 0-10% acetato de etilo en hexanos para dar el compuesto del título.

EJEMPLO 150B

3,3-dimetil-2-(trifluorometilsulfoniloxi)ciclohex-1-encarboxilato de etilo

El compuesto del título se preparó utilizando el EJEMPLO 150A en lugar del EJEMPLO 101A en el EJEMPLO 101B.

EJEMPLO 150C

2-(4-clorofenil)-3,3-dimetilciclohex-1-encarboxilato de etilo

El compuesto del título se preparó utilizando el EJEMPLO 150B en lugar del EJEMPLO 101B en el EJEMPLO 101C.

EJEMPLO 150D

(2-(4-clorofenil)-3,3-dimetilciclohex-1-enil)metanol

En un balón de 200 mL se agregó EJEMPLO 150C (0,97 g) y borhidruro de litio (0,47 g) en éter (20 mL) para dar una suspensión. Se agregó metanol (2,2 mL) lentamente. La mezcla se sometió a reflujo durante la noche. La reacción luego se enfrió, y metanol se agregó para detener la reacción. Luego se agregó HCl acuoso 1N hasta pH<7, y se usó éter (3x 30 mL) para extraer el producto. Las capas orgánicas combinadas se secaron sobre Na₂SO₄, se filtró, y se concentró. El material crudo se purificó mediante cromatografía flash sobre sílice con 0-25% acetato de etilo en hexanos para dar el compuesto del título.

EJEMPLO 150E

2-(4-clorofenil)-3,3-dimetilciclohex-1-encarbaldehido

En un balón de 100 mL se agregó EJEMPLO 150D (0,3 g) y Periodinano de Dess-Martin (0,6 g) en diclorometano (10 mL) para dar una suspensión. La mezcla se agitó a temperatura ambiente durante la noche. Luego de la filtración, la mezcla se lavó con NaHCO₃ acuoso saturado (2x 20 mL), se secó sobre Na₂SO₄, se filtró, y se concentró. El producto crudo se purificó mediante cromatografía flash sobre sílice con 0-25% acetato de etilo en hexanos para dar el compuesto del título.

EJEMPLO 150F

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-3,3-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoato de metilo

El compuesto del título se preparó utilizando el EJEMPLO 150E en lugar de 4'-clorobifenil-2-carboxaldehido y EJEMPLO 15F en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 150G

ácido 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-3,3-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoico

El compuesto del título se preparó utilizando el EJEMPLO 150F en lugar del EJEMPLO 101E en el EJEMPLO 101F.

EJEMPLO 150H

4-(4-([2-(4-clorofenil)-3,3-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 150G en lugar del EJEMPLO 3J y EJEMPLO 1F en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500 MHz, sulfóxido de dimetilo-d₆) δ 11,50 (s, 1H), 8,36 (m, 1H), 8,32 (m, 1H), 7,91 (d, 1H), 7,59 (m, 2H), 7,40 (t, 1H), 7,35 (d, 2H), 7,25 (m, 1H), 6,94 (d, 2H), 6,79 (d, 1H), 6,60 (m, 1H),

6,29 (m, 1H), 6,24 (d, 1H), 3,83 (m, 2H), 3,25 (m, 4H), 2,98 (m, 4H), 2,42 (s, 2H), 2,14 (m, 6H), 1,60 (m, 6H), 1,25 (m, 3H), 0,86 (s, 6H)

EJEMPLO 151

- 5 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-[2-fluoro-1-(fluorometil)etil]azetidin-3-il]amino)-3-nitrofenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 151A

- 10 1-(1,3-difluoropropan-2-il)azetidin-3-amina

A una solución de azetidin-3-ilcarbamato de tert-butilo (0,256 g) y 1,3-difluoropropan-2-ona (0,154 g) en diclorometano (2 mL) se agregó triacetoxiborhidruro de sodio (0,473 g) y la reacción se dejó agitar a temperatura ambiente. Luego de 16 horas, la reacción se detuvo con solución saturada de NaHCO₃ (10 mL) y se extrajo en diclorometano (25 mL). La capa orgánica se secó y se concentró. La cromatografía sobre gel de sílice (GraceResolv 12 g) eluyendo con un gradiente de metanol al 0,5% a 3,5%/diclorometano seguido por tratamiento con HCl (4,0M en dioxano, 3 mL) y metanol (0,5 mL) por 2 horas dio el compuesto del título luego de la concentración.

- 20 EJEMPLO 151B

4-(1-(1,3-difluoropropan-2-il)azetidin-3-ilamino)-3-nitrobencenosulfonamida

A una suspensión de 4-cloro-3-nitrobencenosulfonamida (0,225 g) y 1-(1,3-difluoropropan-2-il)azetidin-3-amina (0,193 g) en dioxano (5 mL) se agregó diisopropilamina (0,832 mL). La reacción se sonicó y luego se calentó a 100°C. Luego de agitar durante la noche, la reacción se concentró y se cargó en gel de sílice (GraceResolv 12 g) y se eluyó con un gradiente de metanol al 0,5% a 3,5%/diclorometano para dar el compuesto del título.

EJEMPLO 151C

- 30 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-[2-fluoro-1-(fluorometil)etil]azetidin-3-il]amino)-3-nitrofenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 151B en lugar del EJEMPLO 1F y EJEMPLO 3J en lugar del EJEMPLO 1E en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) δ 11,66 (s, 1H), 11,54 - 11,28 (m, 1H), 8,54 (d, 1H), 8,45 (s, 1H), 8,01 (d, 1H), 7,82 (d, 1H), 7,48 (d, 3H), 7,34 (d, 2H), 7,04 (d, 2H), 6,90 (d, 1H), 6,67 (d,

1H), 6,37 (s, 1H), 6,20 (s, 1H), 4,64 - 4,23 (m, 6H), 3,81 (s, 2H), 3,08 (s, 4H), 2,75 (s, 3H), 2,15 (s, 7H), 1,95 (s, 2H), 1,38 (s, 2H), 0,92 (s, 6H).

EJEMPLO 152

- 5 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-(metilsulfonil)pirrolidin-3-il]metil)amino)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 152A

- 10 (1-(metilsulfonil)pirrolidin-3-il)metilcarbamato de tert-butilo

El compuesto del título se preparó utilizando pirrolidin-3-ilmetilcarbamato de tert-butilo en lugar de piperidin-3-ilmetilcarbamato de tert-butilo en el EJEMPLO 147A.

- 15 EJEMPLO 152B

(1-(metilsulfonil)pirrolidin-3-il)metanamina

El compuesto del título se preparó utilizando el EJEMPLO 152A en lugar del EJEMPLO 147A en el EJEMPLO 147B.

- 20 EJEMPLO 152C

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-(metilsulfonil)pirrolidin-3-il]metil)amino)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

- 25 El compuesto del título se preparó utilizando el EJEMPLO 152B en lugar del EJEMPLO 147B en el EJEMPLO 147C. ¹H NMR (400MHz, sulfóxido de dimetilo-d₆) δ 11,60 (s, 1H), 8,49 (m, 2H), 7,99 (s, 1H), 7,73 (m, 1H), 7,53 (d, 1H), 7,47 (s, 1H), 7,42 (m, 1H), 7,34 (d, 2H), 7,04 (m, 3H), 6,65 (m, 1H), 6,35 (s, 1H), 6,22 (s, 1H), 3,41 (m, 4H), 3,22 (m, 2H), 3,03 (m, 4H), 2,89 (s, 3H), 2,73 (m, 2H), 2,59 (m, 1H), 2,17 (m, 6H), 2,00 (m, 4H), 1,68 (m, 1H), 1,38 (t, 2H), 0,92 (s, 6H).

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- 35 EJEMPLO 153

N-[(4-[(1-acetilpirrolidin-3-il)metil]amino)-3-nitrofenil]sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida
EJEMPLO 153A

(1-acetilpirrolidin-3-il)metilcarbamato de tert-butilo

- 5 El compuesto del título se preparó utilizando pirrolidin-3-ilmetilcarbamato de tert-butilo en lugar de piperidin-3-ilmetilcarbamato de tert-butilo y cloruro de acetilo en lugar de cloruro de metansulfonilo en el EJEMPLO 147A.

EJEMPLO 153B

- 10 1-(3-(aminometil)pirrolidin-1-il)etanona

El compuesto del título se preparó utilizando el EJEMPLO 153A en lugar del EJEMPLO 147A en el EJEMPLO 147B.

EJEMPLO 153C

- 15 N-[(4-[(1-acetilpirrolidin-3-il)metil]amino)-3-nitrofenil]sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 153B en lugar del EJEMPLO 147B en el EJEMPLO 147C. ¹H NMR (400MHz, sulfóxido de dimetilo-d₆) □ 11,66 (s, 1H), 8,62 (m, 1H), 8,54 (s, 1H), 8,03 (m, 1H), 7,78 (d, 1H), 7,50 (m, 3H), 7,35 (t, 2H), 7,09 (s, 1H), 7,04 (d, 2H), 6,67 (dd, 1H), 6,37 (d, 1H), 6,20 (s, 1H), 3,56 (m, 1H), 3,42 (m, 4H), 3,43 (m, 4H), 3,23 (m, 1H), 3,07 (m, 4H), 2,74 (m, 2H), 2,16 (m, 6H), 1,93 (m, 5H), 1,38 (t, 2H), 0,93 (s, 6H).

EJEMPLO 154

- 25 N-[(4-[(3R)-1-acetilpirrolidin-3-il]amino)-3-nitrofenil]sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

- 30 EJEMPLO 154A

(R)-1-acetilpirrolidin-3-ilcarbamato de tert-butilo

El compuesto del título se preparó utilizando (R)-pirrolidin-3-ilcarbamato de tert-butilo en lugar de piperidin-3-ilmetilcarbamato de tert-butilo y cloruro de acetilo en lugar de cloruro de metansulfonilo en el EJEMPLO 147A.

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EJEMPLO 154B

(R)-1-(3-aminopirrolidin-1-il)etanona

El compuesto del título se preparó utilizando el EJEMPLO 154A en lugar del EJEMPLO 147A en el EJEMPLO 147B.

5 EJEMPLO 154C

N-[(4-[(3R)-1-acetilpirrolidin-3-il]amino)-3-nitrofenil]sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 154B en lugar del EJEMPLO 147B en el EJEMPLO 147. ¹H NMR (400MHz, sulfóxido de dimetilo-d₆) □ 11,61 (s, 1H), 8,50 (s, 1H), 8,17 (d, 1H), 7,98 (s, 1H), 7,78 (s, 1H), 7,49 (m, 3H), 7,34 (d, 2H), 7,10 (m, 1H), 7,04 (d, 2H), 6,66 (dd, 1H), 6,35 (s, 1H), 6,22 (s, 1H), 4,34 (m, 1H), 3,81 (m, 1H), 3,58 (m, 1H), 3,43 (m, 1H), 3,05 (m, 4H), 2,74 (s, 2H), 2,19 (m, 9H), 1,96 (m, 5H), 1,38 (t, 2H), 0,94 (s, 6H).

15 EJEMPLO 155

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(3-metoxi-2,2-dimetilpropil)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 120B usando 3-metoxi-2,2-dimetilpropan-1-amina en lugar de EJEMPLO 120A. ¹H NMR (500 MHz, sulfóxido de dimetilo-d₆) □ 11,69 (s, 1H), 11,32 (s, 1H), 8,92 (t, 1H), 8,57 (d, 1H), 8,04 (d, 1H), 7,80 (dd, 1H), 7,46 - 7,55 (m, 3H), 7,34 (d, 2H), 7,08 (d, 1H), 7,04 (d, 2H), 6,68 (dd, 1H), 6,36 - 6,42 (m, 1H), 6,19 (d, 1H), 3,25 - 3,30 (m, 5H), 3,19 (s, 2H), 3,07 (s, 4H), 2,76 (s, 2H), 2,17 (d, 6H), 1,95 (s, 2H), 1,38 (t, 2H), 0,96 (s, 6H), 0,92 (s, 6H).

EJEMPLO 156

25 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-([4-([(1R,3R)-3-hidrox ciclopentil]metil]amino)-3-nitrofenil]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 156A

30 4-([(1R,3R)-3-hidrox ciclopentil]metilamino)-3-nitrobenzenosulfonamida

El compuesto del título se preparó utilizando (1R,3R)-3-hidrox ciclopentil]metilamina en lugar de (tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

EJEMPLO 156B

35 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-([4-([(1R,3R)-3-hidrox ciclopentil]metil]amino)-3-nitrofenil]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 156A en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridina-d₅) □ 13,05 (s, 1H), 9,29 (s, 1H), 8,62 (t, 1H), 8,43 (d, 1H), 8,32 (dd, 1H), 8,10 (d, 1H), 7,66 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,85 (d, 1H), 6,74 (dd, 1H), 6,54 (s, 1H), 6,49 (m, 1H), 4,60 (m, 1H), 3,19 (dd, 2H),
 5 3,06 (m, 4H), 2,77 (s, 2H), 2,70 (m, 1H), 2,26 (t, 2H), 2,20-2,07 (m, 6H), 2,00 (m, 1H), 1,97 (s, 2H), 1,90 (m, 1H), 1,56 (m, 1H), 1,39 (t, 2H), 1,34 (m, 1H), 0,93 (s, 6H).

EJEMPLO 157

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-{[4-(((1S,3S)-3-
 10 hidroxiciclopentil]metil)amino)-3-nitrofenil]sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 157A

4-(((1S,3S)-3-hidroxiciclopentil)metilamino)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando (1S, 3S)-3-hidroxiciclopentil)metilamina
 15 en lugar de (tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

EJEMPLO 157B

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-{[4-(((1S,3S)-3-
 hidroxiciclopentil]metil)amino)-3-nitrofenil]sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 157A en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridina-d₅) □ 13,03 (s, 1H), 9,29 (s, 1H), 8,60 (t, 1H), 8,44 (d, 1H), 8,32 (dd, 1H), 8,14 (d, 1H), 7,66 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,83 (d, 1H), 6,75 (dd, 1H), 6,55 (s, 1H), 6,49 (m, 1H), 4,60 (m, 1H), 3,19 (dd, 2H),
 20 3,06 (m, 4H), 2,77 (s, 2H), 2,70 (m, 1H), 2,26 (t, 2H), 2,20-2,07 (m, 6H), 2,00 (m, 1H), 1,97 (s, 2H), 1,90 (m, 1H), 1,56 (m, 1H), 1,39 (t, 2H), 1,34 (m, 1H), 0,93 (s, 6H).

EJEMPLO 158

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-{[4-(((1S,3R)-3-
 hidroxiciclopentil]metil)amino)-3-nitrofenil]sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

30

EJEMPLO 158A

4-(((1S,3R)-3-hidroxiciclopentil)metilamino)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando (1S, 3R)-3-hidroxiciclopentil)metilamina
 en lugar de (tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

35

EJEMPLO 158B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-(((1S,3R)-3-hidroxiciclopentil]metil)amino)-3-nitrofenil]sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 158A en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridina-d₅) □ 12,94 (s, 1H), 9,25 (d, 1H), 8,59 (t, 1H), 8,48 (d, 1H), 8,27 (m, 2H), 7,66 (m, 2H), 7,45 (d, 2H), 7,08 (d, 2H), 6,77 (dd, 1H), 6,72 (d, 1H), 6,60 (d, 1H), 6,47 (m, 1H), 4,53 (m, 1H), 3,30 (m, 2H), 3,06 (m, 4H), 2,78 (s, 2H), 2,27 (m, 3H), 2,19-2,10 (m, 5H), 1,98 (m, 3H), 1,85-1,66 (m, 4H), 1,39 (t, 2H), 0,94 (s, 6H).

10 EJEMPLO 159

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-(((1R,3S)-3-hidroxiciclopentil]metil)amino)-3-nitrofenil]sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 159A

15 4-(((1R,3S)-3-hidroxiciclopentil)metilamino)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando (1R, 3S)-3-hidroxiciclopentil)metilamina en lugar de (tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

EJEMPLO 159B

20 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-(((1R,3S)-3-hidroxiciclopentil]metil)amino)-3-nitrofenil]sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 158A en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridina-d₅) □ 13,02 (s, 1H), 9,28 (d, 1H), 8,59 (t, 1H), 8,44 (d, 1H), 8,29 (d, 1H), 8,13 (d, 1H), 7,66 (m, 2H), 7,44 (d, 2H), 7,08 (d, 2H), 6,82 (dd, 1H), 6,74 (d, 1H), 6,55 (d, 1H), 6,48 (m, 1H), 4,53 (m, 1H), 3,34 (m, 2H), 3,06 (m, 4H), 2,77 (s, 2H), 2,27 (m, 3H), 2,19-2,10 (m, 5H), 1,97 (m, 3H), 1,85-1,66 (m, 4H), 1,39 (t, 2H), 0,93 (s, 6H).

EJEMPLO 160

30 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-((3S)-2-oxopiperidin-3-il)amino)fenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando (S)-3-aminopiperidin-2-ona en lugar de 1-acetilpiperidin-4-amina en el EJEMPLO 53B. ¹H NMR (300MHz, sulfóxido de dimetilo-d₆) □ 11,68 (br s, 1H), 8,88 (d, 1H), 8,57 (d, 1H), 8,04 (d, 1H), 7,95 (br s, 1H), 7,83 (dd, 1H), 7,55-7,46 (m, 3H), 7,35 (d, 2H), 7,16 (d, 1H), 7,05 (d, 2H), 6,68 (dd, 1H), 6,38 (m, 1H), 6,21 (d,

1H), 4,41 (m, 1H), 3,22 (m, 2H), 3,09 (br s, 4H), 2,78 (br s, 2H), 2,35-2,09 (m, 8H), 1,96 (br s, 2H), 1,86 (m, 2H), 1,39 (t, 2H), 0,93 (s, 6H).

EJEMPLO 161

- 5 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({4-([1-[2-fluoro-1-(fluorometil)etil]azetidin-3-il]metil)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 161A

- 10 3-((4-(N-(2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoil)sulfamoil)-2-nitrofenilamino)metil)azetidin-1-carboxilato de tert-butilo

- Se calentó EJEMPLO 82 (305 mg), 3-(aminometil)azetidin-1-carboxilato de tert-butilo (86 mg) y diisopropilamina (0,202 mL) en dioxano (3 mL) a 110°C. Luego de agitar durante la noche, la reacción se concentró. La cromatografía sobre gel de sílice (Reveleris, 12 g) eluyendo con un gradiente de metanol al 0,5% a 3%/diclorometano (Velocidad de flujo = 36 ml/minuto) dio el compuesto del título.

EJEMPLO 161B

- 20 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-N-(4-(azetidin-3-ilmetilamino)-3-nitrofenilsulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzamida

- A una solución de EJEMPLO 161A (0,257 g) en diclorometano (5 mL) se agregó ácido trifluoroacético (0,211 mL). Luego de 30 minutos se agregó 0,2 ml adicionales de ácido trifluoroacético. Luego de 3 horas, la reacción se concentró para dar el compuesto del título.

EJEMPLO 161C

- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({4-([1-[2-fluoro-1-(fluorometil)etil]azetidin-3-il]metil)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

- 30 Una solución de EJEMPLO 161B (0,118 g), triacetoxiborhidruro de sodio (0,035 g) y 1,3-difluoropropan-2-ona (0,012 g) se agitaron conjuntamente en diclorometano (1 mL) durante la noche. La reacción se detuvo con solución acuosa saturada de NaHCO₃ (10 mL) y se extrajo con diclorometano (30 mL). La capa orgánica se secó y se concentró. La cromatografía sobre gel de sílice (Reveleris 12 g) eluyendo con un gradiente de metanol al 0,5% a 3,5%/diclorometano a lo largo de 30 minutos (Velocidad de flujo = 36 ml/min) dio el compuesto del título. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) δ 11,67 (s, 1H), 11,47 -

11,21 (m, 1H), 8,85 (s, 1H), 8,55 (d, 1H), 8,03 (d, 1H), 7,80 (dd, 1H), 7,54 - 7,45 (m, 3H), 7,33 (s, 2H), 7,04 (d, 3H), 6,67 (d, 1H), 6,38 (dd, 1H), 6,20 (d, 1H), 4,43 (dt, 4H), 3,56 (t, 2H), 3,46 (s, 2H), 3,12 (m, 6H), 2,74 (m, 3H), 2,17 (m, 7H), 1,95 (s, 2H), 1,39 (d, 2H), 0,92 (s, 6H).

5

EJEMPLO 162

4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(3-nitro-4-[(1-oxetan-3-ilazetidín-3-il)metil]amino}fenil)sulfonil]-2-(1H-pirrólo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando oxetan-3-ona en lugar de 1,3-difluoropropan-2-ona en el EJEMPLO 161C. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) δ 11,66 (s, 1H), 11,51 - 11,03 (m, 1H), 8,81 (s, 1H), 8,54 (d, 1H), 8,02 (d, 1H), 7,79 (dd, 1H), 7,50 (dd, 3H), 7,34 (d, 2H), 7,04 (d, 3H), 6,67 (d, 1H), 6,38 (dd, 1H), 6,20 (d, 1H), 4,57 (s, 2H), 4,43 - 4,35 (m, 2H), 3,82 (s, 1H), 3,59 (t, 2H), 3,44 (t, 2H), 3,20 (s, 2H), 3,06 (s, 4H), 2,73 (s, 3H), 2,18 (s, 6H), 1,95 (s, 2H), 1,39 (d, 2H), 0,92 (s, 6H).

15

EJEMPLO 163

4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(3-nitro-4-[(1-oxetan-3-ilpiperidin-4-il)metil]amino}fenil)sulfonil]-2-(1H-pirrólo[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 163A

4-((4-(N-(2-(1H-pirrólo[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoil)sulfamoil)-2-nitrofenilamino)metil)piperidin-1-carboxilato de tert-butilo

El compuesto del título se preparó utilizando 4-(aminometil)piperidin-1-carboxilato de tert-butilo en lugar de 1-acetilpiperidin-4-amina en el EJEMPLO 53B.

25

EJEMPLO 163B

2-(1H-pirrólo[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-N-(3-nitro-4-(piperidin-4-ilmetilamino)fenilsulfonil)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 163A en lugar del EJEMPLO 1A en el EJEMPLO 1B.

30

EJEMPLO 163C

4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(3-nitro-4-[(1-oxetan-3-ilpiperidin-4-il)metil]amino}fenil)sulfonil]-2-(1H-pirrólo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 163B en lugar del EJEMPLO 161B y oxetan-3-ona en lugar de 1,3-difluoropropan-2-ona en el EJEMPLO 161C.

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¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,68 (s, 1H), 8,60 (t, 1H), 8,54 (d, 1H), 8,03 (d, 1H), 7,79 (dd, 1H), 7,50 (m, 3H), 7,34 (d, 2H), 7,09 (d, 1H), 7,04 (d, 2H), 6,67 (dd, 1H), 6,39 (m, 1H), 6,19 (d, 1H), 4,55 (t, 2H), 4,46 (t, 2H), 3,52 (br s, 1H), 3,28 (m, 2H), 3,17 (d, 1H), 3,06 (m, 4H), 2,82 (m, 2H), 2,74 (m, 2H), 2,17 (m, 6H), 1,95 (m, 3H), 1,72 (m, 3H), 1,38 (t, 2H), 1,28 (m, 2H), 0,92 (s, 6H).

EJEMPLO 164

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[1-ciclopropilpiperidin-4-il]metil}amino)-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando EJEMPLO 163B en lugar de (S)-pirrolidin-3-ilcarbamato de tert-butilo en el EJEMPLO 142A. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,96 (br s, 1H), 11,62 (br s, 1H), 8,50 (m, 2H), 7,98 (d, 1H), 7,72 (m, 1H), 7,52 (d, 1H), 7,45 (m, 2H), 7,34 (d, 2H), 7,04 (m, 2H), 6,94 (m, 1H), 6,64 (dd, 1H), 6,34 (m, 1H), 6,22 (d, 1H), 3,28 (m, 3H), 3,04 (m, 5H), 2,72 (s, 2H), 2,64 (m, 1H), 2,64 (m, 1H), 2,36 (m, 1H), 2,16 (m, 7H), 1,95 (s, 2H), 1,68 (m, 3H), 1,38 (t, 2H), 1,18 (m, 3H), 0,94 (s, 6H), 0,35 (m, 3H).

EJEMPLO 165

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[4-(2-fluoroetil)morfolin-2-il]metil}amino)-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 165A

4-((4-(2-fluoroetil)morfolin-2-il)metilamino)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando bromuro de 2-fluoro-etilo en lugar de yoduro de metilo en el EJEMPLO 134B.

EJEMPLO 165B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[4-(2-fluoroetil)morfolin-2-il]metil}amino)-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 165A en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridina-d₅) □ 13,00 (s, 1H), 9,26 (d, 1H), 8,87 (t, 1H), 8,43 (d, 1H), 8,32 (dd, 1H), 8,11 (d, 1H), 7,66 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,92 (d, 1H), 6,75 (dd, 1H), 6,54 (d, 1H), 6,48 (dd, 1H), 3,93 (m, 1H), 4,63, 4,51 (dt,

2H), 3,95-3,85 (m, 2H), 3,68 (dt, 1H), 3,43-3,37 (m, 2H), 3,07 (m, 4H), 2,92 (d, 1H), 2,77 (s, 2H), 2,65 (m, 2H), 2,59 (m, 1H), 2,26 (m, 2H), 2,17-2,08 (m, 5H), 1,97 (s, 2H), 1,39 (t, 2H), 0,93 (s, 6H).

5 EJEMPLO 166

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)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 166A

10 4-((4-(2,2-difluoroetil)morfolin-2-il)metilamino)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando bromuro de 2,2-difluoro-etilo en lugar de yoduro de metilo en el EJEMPLO 134B.

EJEMPLO 166B

15 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)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 166A en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridina-d₅) □ 13,01 (s, 1H), 9,26 (d, 1H), 8,86 (t, 1H), 8,43 (d, 1H), 8,34 (dd, 1H), 8,11 (d, 1H), 7,66 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,93 (d, 1H), 6,75 (dd, 1H), 6,54 (d, 1H), 6,48 (m, 1H), 6,31, 6,20, 6,09 (tt, 1H), 3,90 (m, 1H), 3,85 (d, 1H), 3,67 (dt, 1H), 3,49-3,30 (m, 2H), 3,07 (m, 4H), 2,84 (d, 1H), 2,82-2,75 (m, 4H), 2,69 (d, 1H), 2,33 (dt, 1H), 2,27-2,20 (m, 3H), 2,14 (m, 4H), 1,97 (s, 2H), 1,39 (t, 2H), 0,93 (s, 6H).

25

EJEMPLO 167

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-fluoro-1-oxetan-3-il]piperidin-4-il)metoxi]-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 167A

4-((4-fluoro-1-(oxetan-3-il)piperidin-4-il)metoxi)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 173A en lugar de piperazin-1-carboxilato de tert-butilo y 3-oxetanona en lugar de 4'-clorobifenil-2-carboxaldehído en el EJEMPLO 1A.

35

EJEMPLO 167B

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-fluoro-1-oxetan-3-ilpiperidin-4-il]metoxi)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

5 El compuesto del título se preparó utilizando el EJEMPLO 167A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) δ 11,69 (s, 1H), 8,39 (s, 1H), 8,09 (d, 1H), 8,04 (d, 1H), 7,52 (m, 4H), 7,35 (d, 2H), 7,05 (m, 2H), 6,68 (dd, 1H), 6,40 (dd, 1H), 6,20 (s, 1H), 4,57 (t, 2H), 4,48 (m, 2H), 4,38 (d, 2H), 4,02 (m, 1H), 3,63 (m, 2H), 3,08 (m, 4H), 2,74 (m, 4H), 2,17 (m, 6H), 1,88 (m, 6H), 1,40 (t, 2H), 0,93 (s, 10 6H).

EJEMPLO 168

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([(2S)-4,4-difluoro-1-oxetan-3-ilpirrolidin-2-il]metoxi)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

15

EJEMPLO 168A

(S)-4,4-difluoropirrolidin-2-carboxilato de metilo

Se trató (S)-4,4-difluoropirrolidin-1,2-dicarboxilato de 1-tert-butilo 2-metilo (0,472 g) en 20 CH₂Cl₂ (1 mL) se trató con ácido trifluoroacético (1,4 mL), se agitó a temperatura ambiente por 4 horas, y se concentró. El producto se liberó de su base usando una columna MEGA BE-SCX con 1:1 CH₂Cl₂/metanol como eluyente para el ácido trifluoroacético. El producto se liberó de la columna con (amoníaco 7 M en metanol) al 5% en CH₂Cl₂ como eluyente.

25 EJEMPLO 168B

(S)-4,4-difluoro-1-(oxetan-3-il)pirrolidin-2-carboxilato de metilo

El compuesto del título se preparó utilizando el EJEMPLO 168A en lugar de piperazin-1-carboxilato de tert-butilo y 3-oxetanona en lugar de 4'-clorobifenil-2-carboxaldehído en el EJEMPLO 1A.

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EJEMPLO 168C

(S)-(4,4-difluoro-1-(oxetan-3-il)pirrolidin-2-il)metanol

Se trató EJEMPLO 168B (0,180 g) en tetrahidrofurano (3 mL) en forma secuencial con una solución de cloruro de calcio (0,245 g) en etanol (3 mL) y NaBH₄ (0,167 g) y luego 35 se agitó a temperatura ambiente por 7 horas. La reacción se detuvo con solución acuosa saturada de NH₄Cl y se extrajo con acetato de etilo. Los extractos combinados se lavaron

con salmuera, se secó (MgSO_4), se filtró, se concentró y se cromatografió sobre gel de sílice con acetato de etilo al 50% en hexanos como eluyente para dar el producto.

EJEMPLO 168D

(S)-4-((4,4-difluoro-1-(oxetan-3-il)pirrolidin-2-il)metoxi)-3-nitrobencenosulfonamida

- 5 El compuesto del título se preparó utilizando el EJEMPLO 168C en lugar de (tetrahidro-2H-piran-4-il)metanol en el EJEMPLO 24A.

EJEMPLO 168E

- 10 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(4-((2S)-4,4-difluoro-1-oxetan-3-ilpirrolidin-2-il)metoxi)-3-nitrofenil)sulfonyl]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

- 15 El compuesto del título se preparó utilizando el EJEMPLO 168D en lugar del EJEMPLO 11B en el EJEMPLO 11D. ^1H NMR (300 MHz, sulfóxido de dimetilo- d_6) δ 11,69 (s, 1H), 8,38 (s, 1H), 8,06 (m, 2H), 7,49 (m, 4H), 7,35 (d, 2H), 7,05 (d, 2H), 6,68 (dd, 1H), 6,40 (m, 1H), 6,21 (s, 1H), 4,54 (m, 3H), 4,43 (t, 1H), 4,23 (m, 1H), 4,12 (m, 2H), 3,44 (m, 2H), 3,12 (m, 7H), 2,58 (m, 1H), 2,29 (m, 7H), 1,97 (s, 2H), 1,40 (t, 2H), 0,93 (s, 6H).

20

EJEMPLO 169

- 25 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(3-nitro-4-((4-tetrahidro-2H-piran-4-il)morfolin-3-il)metil)amino]fenil)sulfonyl]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 169A

- 30 3-((4-(N-(2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoil)sulfamoyl)-2-nitrofenilamino)metil)morfolina-4-carboxilato de tert-butilo

El compuesto del título se preparó como se describe en el EJEMPLO 53B reemplazando 1-acetilpiperidin-4-amina con 3-(aminometil)morfolina-4-carboxilato de tert-butilo.

- 35 EJEMPLO 169B

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-N-(4-(morfolin-3-ilmetilamino)-3-nitrofenilsulfonil)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 139B reemplazando EJEMPLO 139A con EJEMPLO 169A.

5

EJEMPLO 169C

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(3-nitro-4-((4-tetrahidro-2H-piran-4-ilmorfolin-3-il)metil)amino)fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

10 El compuesto del título se preparó como se describe en el EJEMPLO 139C reemplazando EJEMPLO 139B y oxetan-3-ona con EJEMPLO 169B y tetrahidropiran-4-ona, respectivamente. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) □ 11,69 (s, 1H), 8,77 (m, 1H), 8,57 (d, 1H), 8,05 (d, 1H), 7,84 (dd, 1H), 7,52 (m, 3H), 7,34 (m, 2H), 7,03 (m, 3H), 6,68 (dd, 1H), 6,40 (dd, 1H), 6,18 (d, 1H), 3,86 (m, 2H), 3,72 (m, 2H), 3,11 (m, 6H), 2,74 (m, 4H), 2,20
15 (m, 6H), 1,95 (m, 3H), 1,51 (m, 7H), 0,92 (s, 6H).

20 EJEMPLO 170

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(4-((4-ciclobutilmorfolin-3-il)metil)amino)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

25 El compuesto del título se preparó como se describe en el EJEMPLO 139C reemplazando EJEMPLO 139B y oxetan-3-ona con EJEMPLO 169B y ciclobutanona. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) □ 11,68 (s, 1H), 8,72 (s, 1H), 8,57 (d, 1H), 8,04 (d, 1H), 7,84 (dd, 1H), 7,52 (m, 3H), 7,34 (m, 3H), 7,03 (m, 4H), 6,67 (dd, 1H), 6,39 (dd, 1H), 6,18 (d, 1H), 3,47 (m, 3H), 3,10 (m, 6H), 2,72 (m, 6H), 2,25 (m, 8H), 1,95 (m, 4H), 1,56 (m, 3H), 1,38 (m, 2H), 0,92 (s, 6H).

30

EJEMPLO 171

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(3-nitro-4-((4-tetrahidrofurano-3-ilmorfolin-3-il)metil)amino)fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

35 El compuesto del título se preparó como se describe en el EJEMPLO 139C reemplazando EJEMPLO 139B y oxetan-3-ona con EJEMPLO 169B y 3-oxotetrahidrofurano,

respectivamente. ^1H NMR (300 MHz, sulfóxido de dimetilo- d_6) δ 11,64 (s, 1H), 8,66 (s, 1H), 8,53 (d, 1H), 8,01 (d, 1H), 7,80 (d, 1H), 7,50 (m, 3H), 7,35 (d, 2H), 7,05 (d, 2H), 6,98 (d, 1H), 6,66 (dd, 1H), 6,37 (d, 1H), 6,19 (d, 1H), 3,68 (m, 8H), 3,05 (m, 6H), 2,85 (m, 3H), 2,73 (s, 2H), 2,25 (m, 6H), 1,91 (m, 3H), 1,37 (m, 3H), 0,95 (m, 6H).

5

EJEMPLO 172

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({4-([1-[2-fluoro-1-(fluorometil)etil]piperidin-4-il]metil)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

10 El compuesto del título se preparó utilizando el EJEMPLO 163B en lugar de piperazin-1-carboxilato de tert-butilo y 1,3-difluoropropan-2-ona en lugar de 4'-clorobifenil-2-carboxaldehído en el EJEMPLO 1A. ^1H NMR (500MHz, sulfóxido de dimetilo- d_6) δ 11,67 (s, 1H), 11,40 (br s, 1H), 8,57 (m, 2H), 8,03 (d, 1H), 7,78 (d, 1H), 7,50 (m, 3H), 7,34 (d, 2H), 7,07 (d, 1H), 7,04 (d, 2H), 6,67 (dd, 1H), 6,38 (m 1H), 6,19 (d, 1H), 4,63 (d, 2H), 4,53 (d, 2H), 3,28
15 (m, 2H), 3,07 (m, 4H), 2,89 (m, 2H), 2,74 (m, 2H), 2,40 (m, 2H), 2,16 (m, 6H), 1,95 (s, 2H), 1,67 (m, 3H), 1,38 (t, 2H), 1,23 (m, 3H), 0,94 (s, 6H).

EJEMPLO 173

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({4-([1-ciclopropil-4-fluoropiperidin-4-il]metoxi)-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida
20

EJEMPLO 173A

4-((4-fluoropiperidin-4-il)metoxi)-3-nitrobencenosulfonamida

25 El compuesto del título se preparó utilizando el EJEMPLO 126B en lugar del EJEMPLO 1A en el EJEMPLO 1B.

EJEMPLO 173B

4-((1-ciclopropil-4-fluoropiperidin-4-il)metoxi)-3-nitrobencenosulfonamida

30 A EJEMPLO 173A (0,24 g) en metanol (3 mL) se agregó tamices moleculares de 3Å (0,1 g), seguido en forma secuencial por ácido acético (0,31 mL), (1-etoxiciclopropoxi)trimetilsilano (0,64 mL), y cianoborohidruro de sodio (0,148 g). La reacción se calentó bajo reflujo durante la noche. Luego de enfriar, la mezcla de la reacción se cargó sobre una columna de gel de sílice. Luego de secar, la columna se eluyó con 100:2:0,2 acetato de etilo/metanol/ NH_4OH para dar el compuesto del título.

35 EJEMPLO173C

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({4-[(1-ciclopropil-4-fluoropiperidin-4-il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 173B en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,65 (s, 1H), 8,33 (s, 1H), 8,01 (m, 2H), 7,53 (d, 1H), 7,48-7,49 (m, 2H), 7,34-7,38 (m, 3H), 7,04 (d, 2H), 6,66 (dd, 1H), 6,38 (dd, 1H), 6,21 (d, 1H), 4,32 (d, 2H), 3,70-3,77 (m, 2H), 3,07 (s, 4H), 2,92 (s, 2H), 2,80 (s, 2H), 2,58 (s, 2H), 2,25 (s, 4H), 2,13-2,16 (m 2H), 1,38 (t, 2H), 0,92 (s, 6H), 0,40-0,49 (m, 4H).

10

EJEMPLO 174

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({4-[(4-metoxibencil)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

Una suspensión de EJEMPLO 53A (120 mg), (4-metoxifenil)metanamina (31 mg) y Base de Hunig (0,159 mL) en sulfóxido de dimetilo (2 mL) se calentó por 2 horas a 150 °C en un reactor de microondas Biotage Initiator. La mezcla de la reacción se diluyó con metanol (2 mL) y se purificó mediante HPLC de fase inversa (C8, 30% - 100% CH₃CN/agua/ácido trifluoroacético al 0,1%). ¹H NMR (500 MHz, piridina-d₅) □ 13,07 (s, 1H), 9,32 (d, 1H), 9,17 (t, 1H), 8,43 (d, 1H), 8,28 (dd, 1H), 8,08 (d, 1H), 7,64 - 7,68 (m, 2H), 7,44 (d, 2H), 7,38 (d, 2H), 7,07 (d, 2H), 6,97 - 7,02 (m, 2H), 6,90 (d, 1H), 6,74 (dd, 1H), 6,52 (d, 1H), 6,49 (dd, 1H), 4,55 (d, 2H), 3,68 (s, 3H), 3,03 - 3,09 (m, 4H), 2,77 (s, 2H), 2,26 (t, 2H), 2,10 - 2,17 (m, 4H), 1,97 (s, 2H), 1,39 (t, 2H), 0,93 (s, 6H).

20

EJEMPLO 175

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(3-nitro-4-[(3-trifluorometoxi)bencil]amino)fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando (3-trifluorometoxifenil)metanamina en lugar de (4-metoxifenil)metanamina en el EJEMPLO 174. ¹H NMR (500 MHz, piridina-d₅) □ 13,06 (s, 1H), 9,38 (t, 1H), 9,31 (d, 1H), 8,42 (d, 1H), 8,28 (dd, 1H), 8,08 (d, 1H), 7,65 (ddd, 2H), 7,41 - 7,46 (m, 3H), 7,36 - 7,40 (m, 2H), 7,07 (d, 2H), 6,88 (d, 1H), 6,74 (dd, 1H), 6,52 (d, 1H), 6,49 (d, 1H), 4,73 (d, 2H), 3,02 - 3,08 (m, 4H), 2,77 (s, 2H), 2,22 - 2,28 (m, 2H), 2,09 - 2,16 (m, 4H), 1,97 (s, 2H), 1,39 (t, 2H), 0,93 (s, 6H).

30

EJEMPLO 176

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({4-[(3-metoxibencil)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

35

El compuesto del título se preparó utilizando (3-metoxifenil)metanamina en lugar de (4-metoxifenil)metanamina en el EJEMPLO 174. ^1H NMR (500 MHz, piridina- d_5) δ 13,06 (s, 1H), 9,27 - 9,32 (m, 2H), 8,42 (d, 1H), 8,26 (dd, 1H), 8,08 (d, 1H), 7,64 - 7,67 (m, 2H), 7,44 (d, 2H), 7,32 (t, 1H), 7,14 (s, 1H), 7,04 - 7,09 (m, 3H), 6,88 - 6,94 (m, 2H), 6,74 (dd, 1H), 6,52 (d, 1H), 6,48 - 6,50 (m, 1H), 4,64 (d, 2H), 3,68 (s, 3H), 3,03 - 3,09 (m, 4H), 2,77 (s, 2H), 2,26 (t, 2H), 2,10 - 2,18 (m, 4H), 1,97 (s, 2H), 1,39 (t, 2H), 0,93 (s, 6H).

EJEMPLO 177

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-(4-(difluorometoxi)bencil]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando (4-difluorometoxifenil)metanamina en lugar de (4-metoxifenil)metanamina en el EJEMPLO 174. ^1H NMR (500 MHz, piridina- d_5) δ 13,06 (s, 1H), 9,32 (d, 1H), 9,28 (t, 1H), 8,42 (d, 1H), 8,28 (dd, 1H), 8,07 (d, 1H), 7,66 (t, 1H), 7,64 (d, 1H), 7,58 (s, 1H), 7,44 (s, 2H), 7,26 (s, 1H), 7,25 (d, 1H), 7,07 (d, 2H), 6,87 (d, 1H), 6,74 (dd, 1H), 6,52 (d, 1H), 6,49 (dd, 1H), 4,64 (d, 2H), 3,03 - 3,10 (m, 4H), 2,77 (s, 2H), 2,26 (t, 2H), 2,11 - 2,17 (m, 4H), 1,97 (s, 2H), 1,39 (t, 2H), 0,93 (s, 6H).

EJEMPLO 178

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-(1,4-dioxaespiro[4,5]dec-8-ilamino)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando 1,4-dioxa-espiro[4,5]dec-8-ilamina en lugar de 1-acetilpiperidin-4-amina en el EJEMPLO 53B. ^1H NMR (300MHz, sulfóxido de dimetilo- d_6) δ 11,67 (br s, 1H), 8,55 (d, 1H), 8,26 (d, 1H), 8,04 (d, 1H), 7,81 (dd, 1H), 7,54-7,46 (m, 3H), 7,35 (d, 2H), 7,15 (d, 1H), 7,04 (d, 2H), 6,68 (dd, 1H), 6,38 (m, 1H), 6,19 (d, 1H), 3,89 (s, 4H), 3,78 (m, 1H), 3,07 (br s, 4H), 2,78 (br s, 2H), 2,28-2,11 (m, 6H), 2,00-1,88 (m, 4H), 1,75-1,57 (m, 4H), 1,54-1,35 (m, 4H), 0,92 (s, 6H).

EJEMPLO 179

Trans-N-([4-([4-(acetilamino)ciclohexil]amino)-3-nitrofenil)sulfonil]-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 179A

trans-4-acetamidociclohexilcarbamato de tert-butilo

Se agregó (trans)-4-aminociclohexilcarbamato de tert-butilo (1,500 g) y trietilamina (2,93 mL, 2,125 g) a diclorometano y se agitó hasta que el (trans)-4-aminociclohexilcarbamato de tert-butilo se disolvió completamente. Se agregó cloruro de acetilo (0,577 g) lentamente, y la solución se agitó a temperatura ambiente por 16 horas. El solvente se eliminó, y el residuo se colocó en acetato de etilo, se lavó con solución amortiguadora de pH 4, se lavó con salmuera, se secó con sulfato de sodio anhidro, y se filtró. El material filtrado se concentró bajo vacío.

EJEMPLO 179B

10 N-(trans-4-aminociclohexil)acetamida

El compuesto del título se preparó utilizando el EJEMPLO 179A en lugar del EJEMPLO 1A en el EJEMPLO 1B.

EJEMPLO 179C

15 Trans-N-[(4-[[4-(acetilamino)ciclohexil]amino]-3-nitrofenil)sulfonil]-4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 179B en lugar de 1-acetilpiperidin-4-amina en el EJEMPLO 53B. ¹H NMR (300MHz, sulfóxido de dimetilo-d₆) □ 11,67 (br s, 1H), 8,55 (d, 1H), 8,20 (d, 1H), 8,04 (d, 1H), 7,82-7,76 (m, 2H), 7,53-7,46 (m, 3H), 7,35 (d, 2H), 7,16 (d, 1H), 7,04 (d, 2H), 6,68 (dd, 1H), 6,39 (m, 1H), 6,19 (d, 1H), 3,57 (m, 2H), 3,07 (br s, 4H), 2,75 (br s, 2H), 2,28-2,10 (m, 6H), 2,03-1,94 (m, 4H), 1,83 (d, 2H), 1,80 (s, 3H), 1,55-1,24 (m, 6H), 0,92 (s, 6H).

EJEMPLO 180

25 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]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 180A

30 (R)-1-(2,2-difluoroetil)pirrolidin-3-ilcarbamato de tert-butilo

A una solución de (R)-pirrolidin-3-ilcarbamato de tert-butilo (500 mg) y 1,1-difluoro-2-yodoetano (618 mg) en N,N-dimetilformamida (6 mL) se agregó N-etil-N-isopropilpropan-2-amina (1,403 ml) y la mezcla se agitó a 70 °C por 72 horas. La mezcla de la reacción se concentró y el producto crudo se purificó sobre gel de sílice con metanol / diclorometano.

EJEMPLO 180B

(R)-1-(2,2-difluoroetil)pirrolidin-3-amina

A una solución de EJEMPLO 180A (525 mg) en una mezcla de diclorometano (3 mL) y metanol (4,0 mL) se agregó cloruro de hidrógeno, 4M en dioxano (5,24 mL) y la reacción se agitó por 1,5 horas. La reacción se concentró y el material crudo se colocó en diclorometano y el solvente se evaporó, luego se recogió con éter y el solvente se evaporó, y luego se secó en alto vacío.

EJEMPLO 180C

(R)-4-(1-(2,2-difluoroetil)pirrolidin-3-ilamino)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 180B en lugar de (tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

EJEMPLO 180D

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]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 180C en lugar del EJEMPLO 130C en el EJEMPLO 130D. ^1H NMR (500 MHz, piridin- d_5) δ 13,02 (m, 1H), 9,27 (d, 1H), 8,55 (d, 1H), 8,43 (d, 1H), 8,35 (dd, 1H), 8,10 (d, 1H), 7,64 - 7,68 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,83 (d, 1H), 6,75 (dd, 1H), 6,54 (m, 1H), 6,48 (m, 1H), 6,04 - 6,29 (m, 1H), 4,06 (m, 1H), 3,07 (m, 4H), 2,83 - 2,95 (m, 4H), 2,74 - 2,82 (m, 3H), 2,47 (m, 1H), 2,09 - 2,30 (m, 8H), 1,97 (s, 2H), 1,67 (m, 1H), 1,39 (t, 2H), 0,93 (s, 6H).

EJEMPLO 181

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([(3S)-1-(2-fluoroetil)pirrolidin-3-il]amino)-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 181A

(S)-1-(2-fluoroetil)pirrolidin-3-ilcarbamato de tert-butilo

El compuesto del título se preparó utilizando 1-fluoro-2-yodoetano en lugar de 1,1-difluoro-2-yodoetano y (S)-pirrolidin-3-ilcarbamato de tert-butilo en lugar de (R)-pirrolidin-3-ilcarbamato de tert-butilo en el EJEMPLO 180A.

EJEMPLO 181B

(S)-1-(2-fluoroetil)pirrolidin-3-amina

El compuesto del título se preparó utilizando el EJEMPLO 181A en lugar del EJEMPLO 180A en el EJEMPLO 180B.

EJEMPLO 181C

(S)-4-(1-(2-fluoroetil)pirrolidin-3-ilamino)-3-nitrobenzenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 181B en lugar de (tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

5

EJEMPLO 181D

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(4-((3S)-1-(2-fluoroetil)pirrolidin-3-il)amino)-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 181C en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500 MHz, piridin- d₅) □ 13,00 (m, 1H), 9,26 (d, 1H), 8,56 (d, 1H), 8,43 (d, 1H), 8,34 (dd, 1H), 8,10 (d, 1H), 7,63 - 7,66 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,82 (d, 1H), 6,75 (dd, 1H), 6,54 (d, 1H), 6,48 (m, 1H), 4,60 (t, 1H), 4,51 (t, 1H), 4,05 (m, 1H), 3,07 (m, 4H), 2,84 (m, 1H), 2,66 - 2,79 (m, 6H), 2,39 (q, 1H), 2,20 - 2,29 (m, 3H), 2,15 (m, 5H), 1,97 (s, 2H), 1,66 (m, 1H), 1,39 (t, 2H), 0,94 (s, 6H).

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EJEMPLO 182

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(4-((3S)-1-(2,2-difluoroetil)pirrolidin-3-il)amino)-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 182A

(S)-1-(2,2-difluoroetil)pirrolidin-3-ilcarbamato de tert-butilo

El compuesto del título se preparó utilizando (S)-pirrolidin-3-ilcarbamato de tert-butilo en lugar de (R)-pirrolidin-3-ilcarbamato de tert-butilo en el EJEMPLO 180A.

25

EJEMPLO 182B

(S)-1-(2,2-difluoroetil)pirrolidin-3-amina

El compuesto del título se preparó utilizando el EJEMPLO 182A en lugar del EJEMPLO 180A en el EJEMPLO 180B.

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EJEMPLO 182C

(S)-4-(1-(2,2-difluoroetil)pirrolidin-3-ilamino)-3-nitrobenzenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 182B en lugar de (tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

35

EJEMPLO 182D

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3S)-1-(2,2-difluoroetil)pirrolidin-3-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida

5 El compuesto del título se preparó utilizando el EJEMPLO 182C en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500 MHz, piridin- d₅) □ 13,02 (m, 1H), 9,27 (d, 1H), 8,54 (d, 1H), 8,43 (d, 1H), 8,35 (dd, 1H), 8,11 (d, 1H), 7,64 - 7,68 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,82 (d, 1H), 6,75 (dd, 1H), 6,54 (m, 1H), 6,48 (m, 1H), 6,04 - 6,29 (m, 1H), 4,06 (m, 1H), 3,07 (m, 4H), 2,83 - 2,95 (m, 4H), 2,74 - 2,82 (m, 3H), 2,47 (m, 1H), 2,09 - 2,30
10 (m, 8H), 1,97 (s, 2H), 1,67 (m, 1H), 1,39 (t, 2H), 0,93 (s, 6H).

EJEMPLO 183

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3R)-1-(2-fluoroetil)pirrolidin-3-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrololo[2,b]piridin-5-iloxi)benzamida

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EJEMPLO 183A

(R)-1-(2-fluoroetil)pirrolidin-3-ilcarbamato de tert-butilo

El compuesto del título se preparó utilizando 1-fluoro-2-yodoetano en lugar de 1,1-difluoro-2-yodoetano en el EJEMPLO 180A.

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EJEMPLO 183B

(R)-1-(2-fluoroetil)pirrolidin-3-amina

El compuesto del título se preparó utilizando el EJEMPLO 183A en lugar del EJEMPLO 180A en el EJEMPLO 180B.

25

EJEMPLO 183C

(R)-4-(1-(2-fluoroetil)pirrolidin-3-ilamino)-3-nitrobenzenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 183B en lugar de (tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

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EJEMPLO 183D

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3R)-1-(2-fluoroetil)pirrolidin-3-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida

35 El compuesto del título se preparó utilizando el EJEMPLO 183C en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500 MHz, piridin- d₅) □ 13,00 (m, 1H), 9,26 (d, 1H), 8,56 (d, 1H), 8,43 (d, 1H), 8,34 (dd, 1H), 8,10 (d, 1H), 7,63 - 7,66 (m, 2H), 7,44 (d,

2H), 7,07 (d, 2H), 6,83 (d, 1H), 6,75 (dd, 1H), 6,54 (d, 1H), 6,48 (m, 1H), 4,60 (t, 1H), 4,50 (t, 1H), 4,04 (m, 1H), 3,07 (m, 4H), 2,84 (m, 1H), 2,66 - 2,79 (m, 6H), 2,39 (q, 1H), 2,19 - 2,28 (m, 3H), 2,14 (m, 5H), 1,97 (s, 2H), 1,66 (m, 1H), 1,39 (t, 2H), 0,94 (s, 6H).

5 EJEMPLO 184

4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(3-nitro-4-[(3S)-1-oxetan-3-ilpirrolidin-3-il]metoxi}fenil)sulfonyl]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 184A

10 (S)-3-((2-nitro-4-sulfamoilfenoxi)metil)pirrolidin-1-carboxilato de tert-butilo

A una solución de (S)-3-(hidroximetil)pirrolidin-1-carboxilato de tert-butilo (0,300 g) en tetrahidrofurano (5 mL) se agregó hidruro de sodio (0,238 g). Luego de agitar por 15 minutos, se agregó 4-fluoro-3-nitrobencenosulfonamida (0,295 g) y la reacción se agitó a temperatura ambiente. Luego de 1 hora, la reacción se particionó entre agua (25 mL) y diclorometano (50 mL) y la reacción se detuvo con HCl acuoso 1N (5,96 mL). La capa orgánica se separó, se secó sobre sulfato de magnesio, se filtró, y se concentró. La cromatografía sobre gel de sílice (Reveleris 12 g) eluyendo con un gradiente de 0,2% a 2% metanol/diclorometano a lo largo de 30 minutos (velocidad de flujo = 36 mL/minuto) dio el compuesto del título.

EJEMPLO 184B

20 (S)-3-nitro-4-((1-(oxetan-3-il)pirrolidin-3-il)metoxi)bencenosulfonamida

A (S)-3-((2-nitro-4-sulfamoilfenoxi)metil)pirrolidin-1-carboxilato de tert-butilo (0,433 g) se agregó cloruro de hidrógeno (4,0M en dioxano, 1,0 mL). Luego de agitar por 1 hora, la reacción se concentró y se particionó entre diclorometano (50 mL) y solución acuosa saturada de NaHCO₃ (50 mL). La capa acuosa se separó y se concentró. El residuo se trituró con metanol (100 mL), se filtró y se concentró y se trató con cianoborohidruro de sodio (0,068 g) y ciclobutanona (0,078 g) y se agitó durante la noche. La reacción se particionó entre diclorometano (50 mL) y agua (25 mL) y NaHCO₃ acuoso saturado (10 mL). La capa orgánica se secó sobre sulfato de magnesio, se filtró, y se concentró para dar el compuesto del título.

30

EJEMPLO 184C

4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(3-nitro-4-[(3S)-1-oxetan-3-ilpirrolidin-3-il]metoxi}fenil)sulfonyl]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 184B en lugar del EJEMPLO 1F y EJEMPLO 3J en lugar del EJEMPLO 1E en el EJEMPLO 1G ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) δ 11,64 (s, 1H), 11,45 - 11,01 (m, 1H), 8,30 (d, 1H), 7,98 (dd,

35

2H), 7,60 – 7,43 (m, 3H), 7,33 (t, 3H), 7,04 (d, 2H), 6,74 – 6,59 (m, 1H), 6,37 (dd, 1H), 6,21 (d, 1H), 4,49 (td, 2H), 4,33 (s, 1H), 4,13 (dd, 2H), 3,79 (s, 2H), 3,44 (dd, 2H), 3,07 (s, 4H), 2,74 (d, 6H), 2,19 (d, 6H), 1,98 (d, 2H), 1,74 – 1,52 (m, 1H), 1,39 (t, 2H), 0,92 (s, 6H).

5 EJEMPLO 185

4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({4-{{4-hidroxi**ben**cil}amino}-3-nitrofenil}sulfonil)-2-(1H-pirrol**o**[2,3-b]piridin-5-ilo**xi**)benzamida

El compuesto del título se preparó utilizando (4-hidroxifenil)metanamina en lugar de (4-metoxifenil)metanamina en el EJEMPLO 174. ¹H NMR (500 MHz, piridina-d₅) □ 13,06 (s, 1H), 11,67 (bs, 1H), 9,32 (d, 1H), 9,14 (s, 1H), 8,44 (d, 1H), 8,28 (dd, 1H), 8,09 (d, 1H), 7,65 - 7,68 (m, 2H), 7,44 (d, 2H), 7,37 - 7,41 (m, 2H), 7,19 (s, 2H), 7,07 (d, 2H), 6,93 (d, 1H), 6,75 (dd, 1H), 6,53 (d, 1H), 6,49 (dd, 1H), 4,54 (d, 2H), 3,02 - 3,09 (m, 4H), 2,77 (s, 2H), 2,22 - 2,29 (m, 2H), 2,10 - 2,17 (m, 4H), 1,97 (d, 2H), 1,39 (t, 2H), 0,94 (s, 6H).

15 EJEMPLO 186

4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({4-{{3-hidroxi**ben**cil}amino}-3-nitrofenil}sulfonil)-2-(1H-pirrol**o**[2,3-b]piridin-5-ilo**xi**)benzamida

El compuesto del título se preparó utilizando (3-hidroxifenil)metanamina en lugar de (4-metoxifenil)metanamina en el EJEMPLO 174. ¹H NMR (500 MHz, piridina-d₅) □ 13,06 (s, 1H), 11,67 (bs, 1H), 9,27 - 9,32 (m, 2H), 8,43 (d, 1H), 8,20 (dd, 1H), 8,08 (d, 1H), 7,66 (t, 2H), 7,44 (d, 2H), 7,33 (t, 1H), 7,25 (s, 1H), 7,13 (dd, 1H), 7,07 (d, 2H), 6,98 (d, 1H), 6,88 (d, 1H), 6,74 (dd, 1H), 6,52 (d, 1H), 6,49 (dd, 1H), 4,64 (d, 2H), 3,02 - 3,09 (m, 4H), 2,77 (s, 2H), 2,22 - 2,28 (m, 2H), 2,09 - 2,16 (m, 4H), 1,97 (s, 2H), 1,39 (t, 2H), 0,93 (s, 6H).

25 EJEMPLO 187

4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({4-{{3-(difluorometoxi)**ben**cil}amino}-3-nitrofenil}sulfonil)-2-(1H-pirrol**o**[2,3-b]piridin-5-ilo**xi**)benzamida

El compuesto del título se preparó utilizando (3-difluorometoxifenil)metanamina en lugar de (4-metoxifenil)metanamina en el EJEMPLO 174. ¹H NMR (500 MHz, piridina-d₅) □ 13,06 (s, 1H), 9,34 (t, 1H), 9,30 (d, 1H), 8,42 (d, 1H), 8,26 (dd, 1H), 8,08 (d, 1H), 7,66 (ddd, 2H), 7,40 - 7,45 (m, 3H), 7,36 (t, 1H), 7,27 - 7,30 (m, 2H), 7,19 (d, 1H), 7,07 (d, 2H), 6,87 (d, 1H), 6,74 (dd, 1H), 6,52 (d, 1H), 6,49 (dd, 1H), 4,69 (d, 2H), 3,02 - 3,08 (m, 4H), 2,77 (s, 2H), 2,26 (t, 2H), 2,09 - 2,16 (m, 4H), 1,97 (s, 2H), 1,39 (t, 2H), 0,93 (s, 6H).

EJEMPLO 188

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([cis-3-morfolin-4-ilciclopentil]metil)amino)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

5 EJEMPLO 188A

Cis-3-morfolinociclopentancarboxilato de metilo

El compuesto del título se preparó utilizando 3-oxociclopentancarboxilato de metilo en lugar de 4'-clorobifenil-2-carboxaldehido y morfolina en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

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EJEMPLO 188B

Cis-3-morfolinociclopentil)metanol

El compuesto del título se preparó utilizando el EJEMPLO 188A en lugar del EJEMPLO 101C en el EJEMPLO 101D.

EJEMPLO 188C

4-((Cis-3-morfolinociclopentil)metoxi)-3-nitrobenzenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 188B en lugar de (1,4-dioxan-2-il)metanol en el EJEMPLO 12A.

5

EJEMPLO 188D

4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{cis-3-morfolin-4-ilciclopentil}metil}amino)-3-nitrofenil}sulfonil}-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 188C en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500 MHz, sulfóxido de dimetilo-d₆) δ 11,57 (s, 1H), 8,17 (m, 1H), 7,94 (m, 1H), 7,82 (m, 1H), 7,56 (d, 1H), 7,44 (t, 1H), 7,34 (m, 3H), 7,16 (m, 1H), 7,05 (d, 2H), 6,64 (dd, 1H), 6,33 (m, 1H), 6,24 (d, 1H), 4,06 (m, 2H), 3,62 (m, 4H), 3,03 (m, 4H), 2,75 (s, 2H), 2,35 (m, 2H), 2,19 (m, 6H), 2,03 (m, 2H), 1,96 (s, 2H), 1,78 (m, 2H), 1,51 (m, 4H), 1,39 (t, 2H), 0,93 (s, 6H)

15

EJEMPLO 189

Trans-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{4-[(metilsulfonil)amino]ciclohexil}amino)-3-nitrofenil}sulfonil}-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 189A

éster tert-butílico del ácido trans-(4-Metansulfonilamino-ciclohexil)-carbámico

25

El compuesto del título se preparó utilizando cloruro de metansulfonilo en lugar de cloruro de acetilo en el EJEMPLO 179A.

EJEMPLO 189B

Trans-N-(4-Aminociclohexil)-metansulfonamida

30

El compuesto del título se preparó utilizando el EJEMPLO 189A en lugar del EJEMPLO 1A en el EJEMPLO 1B.

EJEMPLO 189C

Trans-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{4-[(metilsulfonil)amino]ciclohexil}amino)-3-nitrofenil}sulfonil}-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

35

El compuesto del título se preparó utilizando el EJEMPLO 189B en lugar de 1-acetilpiperidin-4-amina en el EJEMPLO 53B. ^1H NMR (300MHz, sulfóxido de dimetilo- d_6) δ 11,68 (br s, 1H), 8,55 (d, 1H), 8,18 (d, 1H), 8,04 (d, 1H), 7,84 (d, 1H), 7,79 (dd, 1H), 7,56-7,47 (m, 3H), 7,34 (d, 2H), 7,16 (d, 1H), 7,04 (d, 2H), 6,68 (dd, 1H), 6,39 (m, 1H), 6,19 (d, 1H), 3,56 (m, 1H), 3,17 (m, 1H), 3,07 (br s, 4H), 2,93 (s, 3H), 2,75 (br s, 2H), 2,28-2,10 (m, 6H), 2,05-1,90 (m, 6H), 1,55-1,32 (m, 6H), 0,92 (s, 6H).

EJEMPLO 190

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-ciclopropilpiperidin-4-il)amino]-3-[(trifluorometil)sulfonil]fenil)sulfonil)-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 190A

4-(1-ciclopropilpiperidin-4-ilamino)-3-(trifluorometilsulfonil)bencenosulfonamida

El compuesto del título se preparó como se describe en el EJEMPLO 17A reemplazando (tetrahidropiran-4-il)metilamina con 4-amino-1-ciclopropilpiperidina.

EJEMPLO 190B

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-ciclopropilpiperidin-4-il)amino]-3-[(trifluorometil)sulfonil]fenil)sulfonil)-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 1G reemplazando EJEMPLO 1E y EJEMPLO 1F con EJEMPLO 3J y EJEMPLO 190A, respectivamente. ^1H NMR (300 MHz, sulfóxido de dimetilo- d_6) δ 11,66 (s, 1H), 8,13 (d, 1H), 8,02 (d, 1H), 7,91 (m, 1H), 7,48 (m, 3H), 7,34 (d, 2H), 7,04 (d, 2H), 6,67 (m, 2H), 6,38 (dd, 1H), 6,19 (d, 1H), 3,64 (m, 1H), 3,13 (m, 5H), 2,73 (m, 5H), 2,22 (m, 6H), 1,92 (m, 5H), 1,70 (m, 1H), 1,41 (m, 5H), 0,94 (s, 6H), 0,41 (m, 4H).

EJEMPLO 191

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-[(1-oxetan-3-ilpiperidin-4-il)metoxi]fenil)sulfonil)-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 191A

3-nitro-4-(piperidin-4-ilmetoxi)bencenosulfonamida

A una solución de 4-(hidroximetil)piperidin-1-carboxilato de tert-butilo (0,300 g) en tetrahidrofurano (5 mL) se agregó hidruro de sodio (0,223 g). Luego de agitar por 15 minutos, se agregó 4-fluoro-3-nitrobencenosulfonamida (0,276 g) y la reacción se agitó a temperatura

ambiente. Luego de 1 hora la reacción se particionó entre agua (25 mL) y diclorometano (50 mL) y la reacción se detuvo con HCl acuoso 1N (5,57 mL). La capa orgánica se separó, se secó sobre sulfato de magnesio, se filtró, y se concentró. El tratamiento con HCl (4,0M en dioxano, 2 mL) y metanol (2 mL) por 1 hora, seguido por concentración, trituración con
 5 diclorometano y filtrado dio el compuesto del título.

EJEMPLO 191B

3-nitro-4-((1-(oxetan-3-il)piperidin-4-il)metoxi)bencenosulfonamida

A una suspensión de 3-nitro-4-(piperidin-4-ilmetoxi)bencenosulfonamida (0,100 g) y
 10 ciclobutanona (0,030 g) en metanol (1 mL) se agregó cianoborohidruro de sodio (0,027 g). Luego de agitar durante la noche, la reacción se detuvo con NaHCO₃ saturado (5 mL) y se extrajo con diclorometano (2 x 10 mL). La capa orgánica se secó sobre sulfato de magnesio, se filtró, y se concentró para dar el compuesto del título.

15 EJEMPLO 191C

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({3-nitro-4-[(1-oxetan-3-ilpiperidin-4-il)metoxi]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 191B en lugar del EJEMPLO 1F y EJEMPLO 3J en lugar del EJEMPLO 1E en el EJEMPLO 1G ¹H NMR (300
 20 MHz, sulfóxido de dimetilo-d₆) δ 11,64 (s, 1H), 11,46 - 10,46 (m, 1H), 8,29 (s, 1H), 8,00 (d, 2H), 7,61 - 7,41 (m, 3H), 7,35 (d, 3H), 7,04 (d, 2H), 6,66 (d, 1H), 6,37 (s, 1H), 6,21 (s, 1H), 4,67 - 4,40 (m, 4H), 4,08 (d, 2H), 3,06 (s, 4H), 2,78 (s, 4H), 2,19 (m, 6H), 1,96 (s, 4H), 1,79 (m, 4H), 1,39 (s, 4H), 0,93 (s, 6H).

25 EJEMPLO 192

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({4-[(4-fluoro-1-tetrahidro-2H-piran-4-il)piperidin-4-il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 192A

4-((4-fluoro-1-(tetrahidro-2H-piran-4-il)piperidin-4-il)metoxi)-3-nitrobencenosulfonamida

Una mezcla de EJEMPLO 173A (0,4 g), dihidro-2H-piran-4(3H)-ona (0,179 g), cianoborohidruro de sodio (0,112 g), y ácido acético (0,5 mL) en tetrahidrofurano (3 mL) se
 35 agitó durante la noche. Los solventes se eliminaron bajo presión reducida. El residuo se

purificó con cromatografía flash de columna sobre gel de sílice eluyendo con 100:5:0,5 acetato de etilo/metanol/NH₄OH para dar el producto deseado.

EJEMPLO 192B

- 5 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({4-[(4-fluoro-1-tetrahidro-2H-piran-4-il)piperidin-4-il]metoxi}-3-nitrofenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 192A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,58 (s, 1H), 8,25 (s, 1H), 7,96 (d, 1H), 7,93 (d, 1H), 7,57 (d, 1H), 7,45 (t, 1H), 7,34-7,37 (m, 3H), 7,26 (d, 1H), 7,05 (d, 2H), 6,64 (dd, 1H), 6,34 (dd, 1H), 6,23 (d, 1H), 4,34 (d, 2H), 3,93 (dd, 2H), 3,03 (s, 6H), 2,76 (s, 4H), 2,09-2,22 (m, 6H), 1,96 (s, 2H), 1,52-1,27 (m, 2H), 1,39 (t, 2H), 0,93 (s, 6H).

15 EJEMPLO 193

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({4-[(4-fluoro-1-tetrahidrofurano-3-il)piperidin-4-il]metoxi}-3-nitrofenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

20 EJEMPLO 193A

4-((4-fluoro-1-(tetrahidrofurano-3-il)piperidin-4-il)metoxi)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando dihidrofuran-3(2H)-ona en lugar de dihidro-2H-piran-4(3H)-ona en el EJEMPLO 192A.

25 EJEMPLO 193B

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({4-[(4-fluoro-1-tetrahidrofurano-3-il)piperidin-4-il]metoxi}-3-nitrofenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 193A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,63 (s, 1H), 8,31 (s, 1H), 7,99-8,00 (m, 2H), 7,54 (d, 1H), 7,46-7,48 (m, 2H), 7,34-7,35 (m, 3H), 7,05 (d, 2H), 6,66 (dd, 1H), 6,37 (dd, 1H), 6,21 (d, 1H), 4,34 (d, 2H), 3,76-3,83 (m, 3H), 3,62-3,65 (m, 2H), 3,03 (s, 4H), 2,79 (s, 4H), 2,24 (s, 2H), 2,15 (s, 2H), 1,84-1,99 (m, 8H), 1,52-1,27 (m, 2H), 1,39 (t, 2H), 0,93 (s, 6H).

35

EJEMPLO 194

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[4-fluoro-1-(metilsulfonil)piperidin-4-il]metoxi}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

5 EJEMPLO 194A

4-((4-fluoro-1-(metilsulfonil)piperidin-4-il)metoxi)-3-nitrobencenosulfonamida

Una mezcla de EJEMPLO 173A (0,4 g), cloruro de metansulfonilo (0,113 g), y trietilamina (0,64 mL) en diclorometano (5 mL) se agitó durante la noche. La mezcla de la reacción se cargó sobre una columna de gel de sílice y se eluyó con 100:1 acetato de etilo:metanol para dar el producto límpido.

EJEMPLO 194B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[4-fluoro-1-(metilsulfonil)piperidin-4-il]metoxi}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 194A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) δ 11,66 (s, 1H), 8,37 (s, 1H), 8,06 (d, 1H), 8,02 (d, 1H), 7,49-7,53 (m, 3H), 7,42 (d, 1H), 7,35 (d, 2H), 7,05 (d, 2H), 6,67 (dd, 1H), 6,38-6,39 (m, 1H), 6,21 (d, 1H), 4,40 (d, 2H), 3,51-3,54 (m, 2H), 3,09 (s, 4H), 2,96-3,01 (m, 4H), 2,92 (s, 3H), 2,82 (s, 2H), 2,25-2,34 (m, 4H), 2,13-2,16 (m, 6H), 2,01-2,07 (m, 2H), 1,99 (s, 2H), 1,39 (t, 2H), 0,93 (s, 6H).

EJEMPLO 195

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[[3-nitro-4-(((3R)-1-oxetan-3-ilpirrolidin-3-il)metil)amino)fenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 195A

(R)-3-((4-(N-(2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoil)sulfamoil)-2-nitrofenilamino)metil)pirrolidin-1-carboxilato de tert-butilo

El compuesto del título se preparó utilizando (R)-3-(aminometil)pirrolidin-1-carboxilato de tert-butilo en lugar de 1-acetilpiperidin-4-amina en el EJEMPLO 53B.

EJEMPLO 195B

(S)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-N-(3-nitro-4-(pirrolidin-3-ilmetilamino)fenilsulfonil)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 195A en lugar del EJEMPLO 1A en el EJEMPLO 1B.

EJEMPLO 195C

- 5 (R)-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-N-(3-nitro-4-((1-(oxetan-3-il)pirrolidin-3-il)metilamino)fenilsulfonil)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 195B en lugar de piperazin-1-carboxilato de tert-butilo y oxetan-3-ona en lugar de 4'-clorobifenil-2-
10 carboxaldehído en el EJEMPLO 1A. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) 11,67 (s, 1H), 8,81 (t, 1H), 8,55 (d, 1H), 8,02 (d, 1H), 7,79 (dd, 1H), 7,50 (m, 3H), 7,35 (m, 2H), 7,04 (m, 3H), 6,67 (dd, 1H), 6,39 (m, 1H), 6,19 (d, 1H), 4,57 (m, 2H), 4,48 (m, 2H), 3,68 (m, 2H), 3,30 (m, 2H), 3,06 (m, 4H), 2,74 (m, 3H), 2,56 (m, 3H), 2,44 (m, 1H), 2,18 (m, 5H), 1,95 (m, 3H), 1,58 (m, 1H), 1,36 (m, 2H), 0,94 (s, 6H).

15 EJEMPLO 196

Trans-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-hidroxiciclohexil)metoxi]-3-nitrofenil]sulfonil)-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida
EJEMPLO 196A

Trans-4-(4-(tert-butildimetilsililoxi)ciclohexil)metoxi)-3-nitrobencenosulfonamida

- 20 El compuesto del título se preparó como se describe en el EJEMPLO 12A reemplazando (1,4-dioxan-2-il)metanol con trans-(4-(tert-butildimetilsililoxi)ciclohexil)metanol (realizado de acuerdo a los procedimientos en WO 2008/124878).

EJEMPLO 196B

- 25 Trans-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)-N-(4-(((1r,4r)-4-(tert-butildimetilsililoxi)ciclohexil)metoxi)-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 usando EJEMPLO 196A en lugar de EJEMPLO 1F y EJEMPLO 3J en lugar de EJEMPLO 1E.

30

EJEMPLO 196C

Trans-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-hidroxiciclohexil)metoxi]-3-nitrofenil]sulfonil)-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida

- 35 EJEMPLO 196B (150 mg) en diclorometano (5 mL) y metanol (2 mL) se trató con HCl acuoso al 10% (3 mL) por 1 hora y se concentró. El residuo se purificó mediante HPLC de fase inversa en una columna C18 usando un gradiente de 40-60% acetonitrilo en ácido

trifluoroacético al 0,1% en agua para dar el compuesto del título como una sal trifluoroacetato. La sal de ácido trifluoroacético se disolvió en diclorometano (30 mL) y se lavó con NaHCO₃ acuoso al 50%. La capa orgánica se secó sobre Na₂SO₄ anhidro, se filtró, y se concentró para dar el compuesto del título. ¹H NMR (400 MHz, sulfóxido de dimetilo-d₆)

5 □ 11,69 (s, 1H), 11,27 (s, 1H), 8,34 (d, 1H), 7,95 - 8,08 (m, 2H), 7,47 - 7,55 (m, 3H), 7,32 - 7,40 (m, 3H), 7,01 - 7,07 (m, 2H), 6,68 (dd, 1H), 6,39 (dd, 1H), 6,20 (d, 1H), 4,54 (d, 1H), 3,96 - 4,06 (m, 2H), 3,10 (s, 4H), 2,84 (s, 2H), 2,05 - 2,39 (m, 6H), 1,96 (s, 2H), 1,46 - 1,93 (m, 5H), 1,39 (t, 2H), 0,98 - 1,29 (m, 4H), 0,92 (s, 6H)

10 EJEMPLO 197

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-[3-(dimetilamino)propoxi]bencil]amino)-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

15 EJEMPLO 197A

3-(4-(aminometil)fenoxi)-N,N-dimetilpropan-1-amina

4-(3-(Dimetilamino)propoxi)benzonitrilo (300 mg) en metanol (20 mL) se trató con níquel de Raney (húmedo, 1,5 g) bajo H₂ (30 psi) por 4 hora. El material insoluble se retiró por filtración y el material filtrado se concentró para dar el compuesto del título.

20 EJEMPLO 197B

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-[3-(dimetilamino)propoxi]bencil]amino)-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 120B usando

25 EJEMPLO 197A en lugar de EJEMPLO 120A. ¹H NMR (400 MHz, sulfóxido de dimetilo-d₆) □ 11,56 (s, 1H), 8,80 (t, 1H), 8,42 (d, 1H), 7,93 (d, 1H), 7,52 - 7,61 (m, 2H), 7,41 - 7,47 (m, 1H), 7,26 - 7,36 (m, 5H), 7,03 - 7,08 (m, 2H), 6,89 (d, 2H), 6,73 (d, 1H), 6,61 (dd, 1H), 6,31 (dd, 1H), 6,22 (d, 1H), 4,52 (d, 2H), 3,99 (t, 2H), 2,90 - 3,05 (m, 7H), 2,72 (s, 2H), 2,61 (s, 6H), 2,09 - 2,24 (m, 6H), 1,89 - 2,04 (m, 5H), 1,38 (t, 2H), 0,92 (s, 6H)

30

EJEMPLO 198

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-(2-morfolin-4-iletoxi)bencil]amino)-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

35 EJEMPLO 198A

(4-(2-morfolinoetoxi)fenil)metanamina

El compuesto del título se preparó como se describe en el EJEMPLO 197A usando 4-(2-morfolinoetoxi)benzonitrilo en lugar de 4-(3-(dimetilamino)propoxi)benzonitrilo.

EJEMPLO 198B

5 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-(2-morfolin-4-iletoxi)bencil]amino)-3-nitrofenil]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 120B usando EJEMPLO 198A en lugar de EJEMPLO 120A. ¹H NMR (400 MHz, sulfóxido de dimetilo-d₆) □
11,69 (s, 1H), 9,00 (t, 1H), 8,56 (d, 1H), 8,02 (d, 1H), 7,72 (dd, 1H), 7,46 - 7,54 (m, 3H), 7,27 -
10 7,36 (m, 4H), 7,01 - 7,07 (m, 2H), 6,89 - 6,95 (m, 3H), 6,66 (dd, 1H), 6,38 (dd, 1H), 6,18 (d, 1H), 4,56 (d, 2H), 4,07 (t, 2H), 3,54 - 3,61 (m, 4H), 3,06 (s, 4H), 2,71 - 2,78 (m, 4H), 2,07 - 2,24 (m, 6H), 1,95 (s, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 199

15 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([[(E)-4-hidroxi-1-adamantil]metil]amino)-3-nitrofenil]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 199A

4-([[(E)-4-Hidroxi-adamantan-1-ilmetil]-amino]-3-nitro-bencenosulfonamida

20 Se trató 4-fluoro-3-nitrobencenosulfonamida (0,5 g) y 5-(aminometil)adamantan-2-ol (0,6 g) en tetrahidrofurano (10 mL) con trietilamina (1 mL) durante la noche. La mezcla de la reacción se concentró y el residuo se purificó mediante HPLC de fase inversa, eluyendo con 40-60% acetonitrilo en ácido trifluoroacético al 0,1% en agua para dar dos isómeros, los cuales se designaron temporalmente como EJEMPLO 199A y EJEMPLO 199B,
25 respectivamente.

EJEMPLO 199B

4-([[(Z)-4-Hidroxi-adamantan-1-ilmetil]-amino]-3-nitro-bencenosulfonamida

30 Se trató 4-fluoro-3-nitrobencenosulfonamida (0,5 g) y 5-(aminometil)adamantan-2-ol (0,6 g) en tetrahidrofurano (10 mL) con trietilamina (1 mL) durante la noche. La mezcla de la reacción se concentró y el residuo se purificó mediante HPLC de fase inversa, eluyendo con 40-60% acetonitrilo en ácido trifluoroacético al 0,1% en agua para dar dos isómeros, los cuales se designaron temporalmente como EJEMPLO 199A y EJEMPLO 199B, respectivamente.

35

EJEMPLO 199C

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([[(E)-4-hidroxi-1-adamantil]metil]amino)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 11D usando EJEMPLO 199A en lugar de EJEMPLO 11B. ¹H NMR (400 MHz, sulfóxido de dimetilo-d₆) □

5 11,68 (s, 1H), 11,40 (s, 1H), 8,55 (d, 1H), 8,50 (t, 1H), 8,03 (d, 1H), 7,77 (dd, 1H), 7,46 - 7,54 (m, 3H), 7,31 - 7,38 (m, 2H), 7,14 (d, 1H), 7,01 - 7,06 (m, 2H), 6,68 (dd, 1H), 6,38 (dd, 1H), 6,19 (d, 1H), 4,61 (d, 1H), 3,63 (d, 1H), 3,02 - 3,16 (m, 6H), 2,75 (s, 2H), 2,17 (d, 6H), 2,04 (d, 2H), 1,95 (s, 2H), 1,76 - 1,88 (m, 3H), 1,49 - 1,61 (m, 6H), 1,38 (t, 2H), 1,29 (d, 2H), 0,92 (s, 6H).

10 EJEMPLO 200

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([[(Z)-4-hidroxi-1-adamantil]metil]amino)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 11D usando EJEMPLO 199B en lugar de EJEMPLO 11B. ¹H NMR (400 MHz, sulfóxido de dimetilo-d₆) □

15 11,68 (s, 1H), 11,39 (s, 1H), 8,55 (d, 1H), 8,51 (t, 1H), 8,04 (d, 1H), 7,77 (dd, 1H), 7,46 - 7,55 (m, 3H), 7,31 - 7,37 (m, 2H), 7,14 (d, 1H), 7,01 - 7,06 (m, 2H), 6,68 (dd, 1H), 6,39 (dd, 1H), 6,19 (d, 1H), 4,61 (d, 1H), 3,61 (d, 1H), 3,08 (d, 6H), 2,75 (s, 2H), 2,17 (d, 6H), 1,79 - 1,99 (m, 7H), 1,55 - 1,69 (m, 4H), 1,49 (s, 2H), 1,38 (t, 2H), 1,22 (d, 2H), 0,92 (s, 6H).

20 EJEMPLO 201

N-([4-([1S,4S)-biciclo[2,2,1]hept-5-en-2-ilmetoxi]-3-nitrofenil]sulfonil)-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 201A

25 4-([1S,4S)-biciclo[2,2,1]hept-5-en-2-ilmetoxi)-3-nitrobencenosulfonamida

El compuesto del título se preparó como se describe en el EJEMPLO 12A reemplazando (1,4-dioxan-2-il)metanol con (1S,4S)-biciclo[2,2,1]hept-5-en-2-ilmetanol.

EJEMPLO 201B

30 N-([4-([1S,4S)-biciclo[2,2,1]hept-5-en-2-ilmetoxi]-3-nitrofenil]sulfonil)-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 11D usando EJEMPLO 201A en lugar de EJEMPLO 11B. ¹H NMR (500 MHz, sulfóxido de dimetilo-d₆) □

35 11,69 (s, 1H), 8,35 (d, 1H), 7,95 - 8,10 (m, 2H), 7,47 - 7,58 (m, 3H), 7,30 - 7,45 (m, 3H), 7,04 (d, 2H), 6,68 (dd, 1H), 6,40 (d, 1H), 5,92 - 6,23 (m, 3H), 3,65 - 4,39 (m, 3H), 3,00 - 3,22 (m,

4H), 2,76 - 2,98 (m, 4H), 2,28 (s, 4H), 2,15 (s, 2H), 1,96 (s, 2H), 1,71 - 1,91 (m, 1H), 1,33 - 1,47 (m, 3H), 1,20 - 1,32 (m, 2H), 0,92 (s, 6H), 0,50 - 0,66 (m, 1H).

EJEMPLO 202

5 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({4-[(1-metil-5-oxopirrolidin-3-il)amino]-3-nitrofenil)sulfonyl)-2-(1H-pirrol-2,3-b)piridin-5-il)benzamida

Se disolvió EJEMPLO 82 (140 mg) en dioxano (3,0 mL), y se agregó clorhidrato de 4-amino-1-metilpirrolidin-2-ona (30 mg) y trietilamina (0,100 mL). La mezcla de la reacción se calentó a 110°C por 40 horas. La reacción se concentró y el material crudo se purificó
10 mediante HPLC preparativa usando una columna C18, 250 x 50 mm, 10µ, y eluyendo con un gradiente de 20-100% CH₃CN 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 NaHCO₃ acuoso al 50%. La capa orgánica se secó sobre Na₂SO₄ anhidro y se concentró para dar el compuesto del título. ¹H NMR (400 MHz, sulfóxido de dimetilo-d₆) δ 11,65 (s, 1H),
15 8,74 (d, 1H), 8,37 (br d, 1H), 8,02 (d, 1H), 7,83 (dd, 1H), 7,49 (m, 3H), 7,34 (d, 2H), 7,07 (d, 1H), 7,04 (d, 2H), 6,68 (dd, 1H), 6,38 (m, 1H), 6,21 (d, 1H), 4,46 (m, 1H), 3,81 (dd, 1H), 3,38 (dd, 1H), 3,08 (br m, 4H), 2,82 (dd, 1H), 2,75 (s, 5H), 2,43 (dd, 1H), 2,21 (br m, 4H), 2,16 (br t, 2H), 1,95 (s, 2H), 1,39 (t, 2H), 0,94 (s, 6H).

20 EJEMPLO 203

4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(4-[(1R,4R,5R,6S)-5,6-dihidroxibiciclo[2,2,1]hept-2-il]metoxi)-3-nitrofenil)sulfonyl]-2-(1H-pirrol-2,3-b)piridin-5-il)benzamida

25 EJEMPLO 203A

4-(((1R,4R,5R,6S)-5,6-dihidroxibiciclo[2,2,1]heptan-2-il)metoxi)-3-nitrobencenosulfonamida

A una solución de EJEMPLO 201A (340 mg) en tetrahidrofurano (10 mL) y agua (1 mL) se agregó N-óxido de N-metilmorfolina (184 mg) y OsO₄ (2,5% en 2-metil-2-propanol) (1,05 mL). La mezcla de la reacción se agitó durante la noche y se purificó mediante HPLC
30 de fase inversa para dar dos isómeros, los cuales se designaron temporalmente como EJEMPLO 203A y EAMPLE 203B, respectivamente.

EJEMPLO 203B

4-(((1R,4R,5S,6R)-5,6-dihidroxibiciclo[2,2,1]heptan-2-il)metoxi)-3-nitrobencenosulfonamida

35 A una solución de EJEMPLO 201A (340 mg) en tetrahidrofurano (10 mL) y agua (1 mL) se agregó N-óxido de N-metilmorfolina (184 mg) y OsO₄ (2,5% en 2-metil-2-propanol)

(1,05 mL). La mezcla de la reacción se agitó durante la noche y se purificó mediante HPLC de fase inversa para dar dos isómeros, los cuales se designaron temporalmente como EJEMPLO 203A y EJEMPLO 203B, respectivamente.

5 EJEMPLO 203C

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1R,4R,5R,6S]-5,6-dihidroxiciclo[2,2,1]hept-2-il]metoxi)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 11D usando
 10 EJEMPLO 203A en lugar de EJEMPLO 11B. ¹H NMR (400 MHz, sulfóxido de dimetilo-d₆) □
 11,68 (s, 1H), 8,33 (s, 1H), 7,97 - 8,07 (m, 2H), 7,48 - 7,55 (m, 3H), 7,41 (d, 1H), 7,32 - 7,37
 (m, 2H), 7,02 - 7,07 (m, 2H), 6,67 (dd, 1H), 6,40 (dd, 1H), 6,20 (d, 1H), 4,58 (dd, 2H), 4,07 -
 4,19 (m, 2H), 3,82 (t, 1H), 3,51 (t, 1H), 3,09 (s, 4H), 2,81 (s, 2H), 2,09 - 2,34 (m, 8H), 2,04 -
 2,09 (m, 2H), 1,93 - 2,01 (m, 3H), 1,62 - 1,77 (m, 2H), 1,39 (t, 2H), 1,11 (d, 1H), 0,92 (s, 6H),
 15 0,67 - 0,76 (m, 1H).

EJEMPLO 204

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1R,4R,5S,6R]-5,6-dihidroxiciclo[2,2,1]hept-2-il]metoxi)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida
 20

El compuesto del título se preparó como se describe en el EJEMPLO 11D usando
 EJEMPLO 203B en lugar de EJEMPLO 11B. ¹H NMR (400 MHz, sulfóxido de dimetilo-d₆) □
 11,68 (s, 1H), 8,33 (s, 1H), 7,98 - 8,07 (m, 2H), 7,49 - 7,54 (m, 3H), 7,41 (d, 1H), 7,32 - 7,36
 (m, 2H), 7,02 - 7,07 (m, 2H), 6,67 (dd, 1H), 6,40 (dd, 1H), 6,20 (d, 1H), 4,58 (dd, 2H), 4,13
 25 (dd, 2H), 3,82 (t, 1H), 3,51 (t, 1H), 3,09 (s, 4H), 2,81 (s, 2H), 2,09 - 2,35 (m, 8H), 2,07 (s, 2H),
 1,93 - 2,02 (m, 3H), 1,61 - 1,80 (m, 2H), 1,39 (t, 2H), 1,11 (d, 1H), 0,92 (s, 6H), 0,66 - 0,78
 (m, 1H).

EJEMPLO 205

30 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-[(3-oxociclohexil)metoxi]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 205A

1,4-dioxaspiro[4,5]decan-7-carboxilato de metilo

35 A una solución de trifluorometansulfonato de trimetilsililo (0,034 mL) en diclorometano seco (5 mL) se agregó 1,2-bis(trimetilsiloxi)etano (4,55 mL) seguido por 3-

oxociclohexanocarboxilato de metilo (2,9 g). La mezcla de la reacción se agitó por 3 horas a -78 °C. La mezcla de la reacción se detuvo con piridina seca (0,5 mL), se vertió en NaHCO₃ acuoso saturado, y se extrajo con éter. La capa de éter se secó sobre Na₂CO₃ / Na₂SO₄. La mezcla de la reacción se concentró y se purificó mediante cromatografía flash sobre sílice con acetato de etilo entre 5 y 30% en hexanos para dar el compuesto del título.

EJEMPLO 205B

1,4-dioxaespiro[4,5]decan-7-ilmetanol

El compuesto del título se preparó utilizando el EJEMPLO 205A en lugar del EJEMPLO 101C en el EJEMPLO 101D.

EJEMPLO 205C

3-nitro-4-((3-oxociclohexil)metoxi)bencenosulfonamida

En un balón de 250 mL se agregó hidruro de sodio (0,5 g) en tetrahidrofurano (10 mL) y luego se agregó 1,4-dioxaespiro[4,5]decan-7-ilmetanol (0,5 g). Luego la mezcla se agitó a temperatura ambiente por 20 minutos, se agregó 4-fluoro-3-nitrobencenosulfonamida (0,65 g). La mezcla se agitó a temperatura ambiente por durante la noche. Se agregó agua (20 mL) lentamente. La capa acuosa se extrajo con diclorometano (3x 20 mL). Las capas orgánicas combinadas se secaron sobre Na₂SO₄. Luego de la filtración, y concentración del material filtrado, el residuo se purificó mediante cromatografía de fase inversa, eluyendo con 30-60% acetonitrilo en agua con ácido trifluoroacético al 0,1%.

EJEMPLO 205D

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-((3-nitro-4-((3-oxociclohexil)metoxi)fenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 205C en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (400 MHz, sulfóxido de dimetilo-d₆) δ 11,59 (s, 1H), 8,22 (s, 1H), 7,96 (d, 1H), 7,87 (m, 1H), 7,55 (d, 1H), 7,45 (t, 1H), 7,35 (m, 3H), 7,20 (m, 1H), 7,04 (d, 2H), 6,64 (dd, 1H), 6,34 (m, 1H), 6,23 (d, 1H), 4,07 (d, 2H), 3,04 (m, 4H), 2,76 (s, 2H), 2,35 (m, 2H), 2,20 (m, 8H), 1,96 (m, 4H), 1,58 (m, 2H), 1,39 (t, 2H), 0,93 (s, 6H).

EJEMPLO 206

4-(4-([2-(4-clorofenil)-5,5-dimetilciclohexa-1,3-dien-1-il]metil)piperazin-1-il)-N-((3-nitro-4-((tetrahidro-2H-piran-4-ilmetil)amino)fenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 206A

2-cloro-5,5-dimetilciclohexa-1,3-dienecarbaldehido

En un balón de 250 mL se agregó N,N-dimetilformamida (3,5 mL) en diclorometano (30 mL), y la mezcla se enfrió a -10 °C. Se agregó tricloruro de fosforilo (4 mL) por goteo, y la solución se calentó hasta temperatura ambiente. Luego se agregó 4,4-dimetilciclohex-2-enona (5,5 mL) lentamente, y la mezcla se calentó a reflujo durante la noche. La mezcla de la reacción se enfrió y se detuvo con una solución a 0°C de acetato de sodio (25 g en 50 mL agua). La capa acuosa se extrajo con éter dietílico (200 mL x3). Las capas orgánicas combinadas se secaron sobre Na₂SO₄, se filtró, y se concentró para dar el producto.

EJEMPLO 206B

10 2-(4-clorofenil)-5,5-dimetilciclohexa-1,3-dienecarbaldehido

En un balón de 1 L se agregó EJEMPLO 206A (6,8 g), ácido 4-clorofenilborónico (6,5 g), y acetato de paladio (II) (0,2 g) en agua (100 mL) para dar una suspensión. Se agregó carbonato de potasio (15 g) y bromuro de tetrabutilamonio (10 g). Luego de desgasificar, la mezcla se agitó a 45°C por 4 horas. Luego de enfriar y filtrar a través de gel de sílice en un embudo, se usó éter dietílico (4x 200mL) para extraer el producto. Las capas orgánicas combinadas se secaron sobre Na₂SO₄, y se filtró. El material filtrado se concentró y se purificó mediante cromatografía flash sobre sílice con 0-10% acetato de etilo en hexanos para dar el compuesto del título.

20 EJEMPLO 206C

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-5,5-dimetilciclohexa-1,3-dienil)metil)piperazin-1-il)benzoato de metilo

El compuesto del título se preparó utilizando el EJEMPLO 206B en lugar de 4'-clorobifenil-2-carboxaldehido y EJEMPLO 15F en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 206D

ácido 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-5,5-dimetilciclohexa-1,3-dienil)metil)piperazin-1-il)benzoico

El compuesto del título se preparó utilizando el EJEMPLO 206C en lugar del EJEMPLO 101E en el EJEMPLO 101F.

EJEMPLO 206E

4-(4-{{2-(4-clorofenil)-5,5-dimetilciclohexa-1,3-dien-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-[[tetrahidro-2H-piran-4-ilmetil]amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 206D en lugar del EJEMPLO 3J y EJEMPLO 1F en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR

(400 MHz, sulfóxido de dimetilo- d_6) δ 11,61 (s, 1H), 8,49 (m, 2H), 7,99 (m, 1H), 7,72 (m, 1H), 7,53 (d, 1H), 7,41 (m, 4H), 7,12 (d, 2H), 6,99 (m, 1H), 6,66 (dd, 1H), 6,35 (m, 1H), 6,23 (d, 1H), 5,74 (d, 1H), 5,58 (d, 1H), 3,84 (m, 2H), 3,26 (m, 4H), 3,06 (m, 4H), 2,88 (s, 2H), 2,24 (m, 6H), 1,61 (m, 2H), 1,26 (m, 3H), 1,00 (s, 6H).

5

EJEMPLO 207

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

10

EJEMPLO 207A

(R)-1-(1,3-difluoropropan-2-il)pirrolidin-3-amina

El compuesto del título se preparó utilizando (R)-pirrolidin-3-ilcarbamato de tert-butilo en lugar de azetidín-3-ilcarbamato de tert-butilo en el EJEMPLO 151A.

15

EJEMPLO 207B

(R)-4-(1-(1,3-difluoropropan-2-il)pirrolidin-3-ilamino)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 207A en lugar del EJEMPLO 151A en el EJEMPLO 151B.

20

EJEMPLO 207C

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

25

El compuesto del título se preparó utilizando el EJEMPLO 207B en lugar del EJEMPLO 1F y EJEMPLO 3J en lugar del EJEMPLO 1E en el EJEMPLO 1G. ^1H NMR (300 MHz, sulfóxido de dimetilo- d_6) δ 11,67 (s, 1H), 11,52 - 11,24 (m, 1H), 8,55 (d, 1H), 8,37 (d, 1H), 8,03 (d, 1H), 7,83 (dd, 1H), 7,57 - 7,45 (m, 3H), 7,34 (d, 2H), 7,06 (t, 3H), 6,67 (d, 1H), 6,38 (dd, 1H), 6,20 (d, 1H), 4,70 (d, 2H), 4,54 (d, 2H), 4,23 (s, 1H), 3,11 - 2,87 (m, 7H), 2,74 (dd, 4H), 2,35 - 2,13 (m, 7H), 1,95 (s, 2H), 1,70 (s, 1H), 1,39 (d, 2H), 0,92 (s, 6H).

30

EJEMPLO 208

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]sulfoni]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

35

EJEMPLO 208A

2-((4-fluorotetrahidro-2H-piran-4-il)metoxi)-5-yodo-3-(trifluorometil)piridina

Una mezcla de EJEMPLO 37C (0,537 g), 5-yodo-3-(trifluorometil)piridin-2-ol (1,156 g), y trifenilfosfina (1,574 g) en tetrahidrofurano (20 mL) se enfrió a 0 °C. A esta solución se
 5 agregó (E)-diazén-1,2-dicarboxilato de di-tert-butilo (0,921 g). La mezcla de la reacción se agitó durante la noche. El solvente se eliminó, y el residuo se purificó con cromatografía flash de columna sobre gel de sílice eluyendo con 4:1 hexanos/acetato de etilo para dar el producto deseado.

10 EJEMPLO 208B

6-((4-fluorotetrahidro-2H-piran-4-il)metoxi)-5-(trifluorometil)piridin-3-sulfonamida

Se enfrió EJEMPLO 207A (1,3 g) en tetrahidrofurano (10 mL) a -42°C con un baño frío de CH₃CN/hielo seco. A esta solución se agregó cloruro de isopropilmagnesio al 2,0 M (1,6 mL) por goteo a lo largo de 5 minutos. La mezcla de la reacción se agitó por 30 minutos
 15 a -42°C, luego se dejó calentar a 0°C durante 10 minutos. La mezcla de la reacción se enfrió nuevamente a -42°C, y se burbujeó SO₂ a través de la misma por 10 minutos. La mezcla de la reacción se agitó por otros 30 minutos. A esta solución se agregó dicloruro de sulfurilo (0,433 g). Al calentar a temperatura ambiente, se agregó NH₄OH concentrado (10 mL) y la mezcla de la reacción se agitó por otras 2 horas. La mezcla de la reacción se particionó entre
 20 agua y acetato de etilo. La capa acuosa se extrajo con acetato de etilo adicional tres veces. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre MgSO₄, se filtró, y se concentró. El residuo se purificó mediante cromatografía flash de columna sobre gel de sílice eluyendo con 3:1 hexanos/ acetato de etilo para dar el compuesto del título.

25

EJEMPLO 208C

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-pirrol[2,3-
 30 b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 208B en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,61 (s, 1H), 8,72 (s, 1H), 8,36 (s, 1H), 7,98 (d, 1H), 7,55 (d, 1H), 7,42-7,47 (m, 2H), 7,36 (d, 2H), 7,05 (d, 2H), 6,66 (dd, 1H), 6,35 (s, 1H), 6,23 (s, 1H), 4,56 (d, 2H), 3,75-3,79 (m, 2H), 3,56-
 35 3,61 (m, 2H), 3,09 (s, 4H), 2,32-2,37 (m, 2H), 2,16(s, 2H), 1,97-1,99 (m, 2H), 1,79-1,86 (m, 4H), 1,40 (t, 2H), 0,93 (s, 6H).

EJEMPLO 209

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-(((3S)-1-oxetan-3-ilpirrolidin-3-il]metil)amino)fenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

5 EJEMPLO 209A

(S)-(1-(oxetan-3-il)pirrolidin-3-il)metilcarbamato de tert-butilo

El compuesto del título se preparó utilizando (R)-pirrolidin-3-ilmetilcarbamato de tert-butilo en lugar de piperazin-1-carboxilato de tert-butilo y 3-oxetanona en lugar de 4'-clorobifenil-2-carboxaldehído en el EJEMPLO 1A.

10

EJEMPLO 209B

(S)-(1-(oxetan-3-il)pirrolidin-3-il)metanamina

El compuesto del título se preparó utilizando el EJEMPLO 209A en lugar de (S)-4,4-difluoropirrolidin-1,2-dicarboxilato de 1-tert-butilo 2-metilo en el EJEMPLO 168A.

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EJEMPLO 209C

(S)-3-nitro-4-((1-(oxetan-3-il)pirrolidin-3-il)metilamino)bencenosulfonamida

El compuesto del título se preparó utilizando 4-fluoro-3-nitrobencenosulfonamida en lugar de 4-cloro-3-nitrobencenosulfonamida y EJEMPLO 209B en lugar de diclorhidrato de 4-metilpiperazin-1-amina en el EJEMPLO 6A.

20

EJEMPLO 209D

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-(((3S)-1-oxetan-3-ilpirrolidin-3-il]metil)amino)fenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 209C en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500 MHz, piridina-d₅) □ 13,05 (s, 1H), 9,30 (d, 1H), 9,02 (t, 1H), 8,42 (d, 1H), 8,34 (dd, 1H), 8,10 (d, 1H), 7,67 (dd, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,82 (d, 1H), 6,75 (m, 1H), 6,52 (m, 2H), 4,82 (t, 1H), 4,75 (t, 1H), 4,67 (t, 2H), 3,57 (m, 1H), 3,24 (t, 2H), 3,07 (m, 4H), 2,75 (m, 3H), 2,57 (dd, 1H), 2,45 (s, 1H), 2,36 (t, 1H), 2,26 (s, 2H), 2,18 (m, 5H), 1,93 (m, 3H), 1,56 (m, 1H), 1,39 (t, 2H), 0,93 (s, 6H).

30

EJEMPLO 210

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

35 EJEMPLO 210A

(4-metoxiciclohexil)metanol

El compuesto del título se preparó utilizando ácido 4-metoxiciclohexanocarboxílico en lugar de 4-fluoropiperidin-1,4-dicarboxilato de 1-tert-butilo 4-etilo en el EJEMPLO 126A.

EJEMPLO 210B

5 Trans-5-cloro-6-((4-metoxiciclohexil)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 210A en lugar de tetrahidro-2H-piran-4-il)metanol y EJEMPLO 40A en lugar de 4-fluoro-3-nitrobencenosulfonamida en el EJEMPLO 24A.

10 EJEMPLO 210C

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-pirrolol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 210C en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,67 (s, 1H), 8,50 (s, 1H), 8,17 (s, 1H), 8,02 (d, 1H), 7,49-7,54 (m, 3H), 7,35 (d, 2H), 7,05 (d, 2H), 6,67 (dd, J 1H), 6,39 (s, 1H), 6,21 (s, 1H), 4,20 (d, 2H), 3,23 (s, 3H), 3,06-3,09 (m, 4H), 2,15-2,37 (m, 4H), 1,96-2,03 (m, 4H), 1,74-1,84 (m, 2H), 1,40 (t, 2H), 1,04-1,13 (m, 4H), 0,93 (s, 6H).

20 EJEMPLO 211

Cis-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-pirrolol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 211A

25 Cis-5-cloro-6-((4-metoxiciclohexil)metoxi)piridin-3-sulfonamida

El compuesto del título se aisló como un subproducto en la síntesis de EJEMPLO 210B.

EJEMPLO 211B

30 Cis-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-pirrolol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 211A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,67 (s, 1H), 8,51 (s, 1H), 8,17 (s, 1H), 8,03 (d, 1H), 7,49-7,54 (m, 3H), 7,35 (d, 2H), 7,05 (d, 2H), 6,68 (dd, 1H), 6,39 (s, 1H), 6,21 (s, 1H), 4,21 (d, 2H), 3,20 (s, 3H), 3,06 (s, 4H), 2,15-2,37 (m, 4H), 1,96 (s, 2H), 1,80-1,84 (m, 2H), 1,50-1,54 (m, 2H), 1,34-1,44 (m, 6H), 0,93 (s, 6H).

EJEMPLO 212

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(3-nitro-4-((3S)-1-oxetan-3-ilpirrolidin-3-il)amino)fenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

5 EJEMPLO 212A

(S)-1-(oxetan-3-il)pirrolidin-3-ilcarbamato de tert-butilo

El compuesto del título se preparó utilizando (S)-pirrolidin-3-ilcarbamato de tert-butilo en lugar de piperazin-1-carboxilato de tert-butilo y 3-oxetanona en lugar de 4'-clorobifenil-2-carboxaldehído en el EJEMPLO 1A.

10

EJEMPLO 212B

(S)-1-(oxetan-3-il)pirrolidin-3-amina

El compuesto del título se preparó utilizando el EJEMPLO 212A en lugar de (S)-4,4-difluoropirrolidin-1,2-dicarboxilato de 1-tert-butilo 2-metilo en el EJEMPLO 168A.

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EJEMPLO 212C

(S)-3-nitro-4-(1-(oxetan-3-il)pirrolidin-3-ilamino)benzenosulfonamida

El compuesto del título se preparó utilizando 4-fluoro-3-nitrobenzenosulfonamida en lugar de 4-cloro-3-nitrobenzenosulfonamida y EJEMPLO 212B en lugar de diclorhidrato de 4-metilpiperazin-1-amina en el EJEMPLO 6A.

20

EJEMPLO 212D

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(3-nitro-4-((3S)-1-oxetan-3-ilpirrolidin-3-il)amino)fenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

25

El compuesto del título se preparó utilizando el EJEMPLO 212C en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500 MHz, piridina-d₅) □ 13,03 (s, 1H), 9,27 (d, 1H), 8,58 (d, 1H), 8,42 (d, 1H), 8,37 (dd, 1H), 8,09 (d, 1H), 7,67 (t, 1H), 7,64 (d, 1H), 7,44 (d, 2H), 7,07 (d, 2H), 6,86 (d, 1H), 6,75 (dd, 1H), 6,54 (d, 1H), 6,48 (dd, 1H), 4,67 (m, 4H), 4,09 (m, 1H), 3,59 (m, 1H), 3,07 (m, 4H), 2,77 (s, 2H), 2,69 (m, 2H), 2,62 (dd, 1H), 2,28 (m, 4H), 2,14 (m, 4H), 1,97 (s, 2H), 1,68 (m, 1H), 1,39 (t, 2H), 0,93 (s, 6H).

30

EJEMPLO 213

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({4-[(4-[2-(2-metoxietoxi)etil]morfolin-2-il)metil]amino]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

35

EJEMPLO 213A

4-((4-(2-(2-metoxietoxi)etil)morfolin-2-il)metilamino)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando bromuro de 2-(2'-metoxietoxi)etilo en lugar de yoduro de metilo en el EJEMPLO 134B.

5

EJEMPLO 213B

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({4-([4-(2-(2-metoxietoxi)etil)morfolin-2-il]metil)amino}-3-nitrofenil)sulfonil)-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

10 El compuesto del título se preparó utilizando el EJEMPLO 213A en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridina-d₅) □ 12,98 (s, 1H), 9,26 (d, 1H), 8,87 (t, 1H), 8,43 (d, 1H), 8,32 (dd, 1H), 8,11 (d, 1H), 7,66 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,91 (d, 1H), 6,75 (dd, 1H), 6,54 (d, 1H), 6,48 (m, 1H), 3,96-3,86 (m, 2H), 3,72 (dd, 1H), 3,67-3,61 (m, 4H), 3,51 (t, 2H), 3,48-3,38 (m, 2H), 3,28 (s, 3H), 3,07 (m, 4H), 2,95 (d, 15 1H), 2,77 (s, 2H), 2,70 (m, 1H), 2,60 (t, 2H), 2,30-2,05 (m, 8H), 1,97 (s, 2H), 1,39 (t, 2H), 0,94 (s, 6H).

EJEMPLO 214

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)-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

20

EJEMPLO 214A

4-((4-(4-(cianometil)morfolin-2-il)metilamino)-3-nitrobencenosulfonamida

25 El compuesto del título se preparó utilizando 2-bromoacetónitrilo en lugar de yoduro de metilo en el EJEMPLO 134B.

EJEMPLO 214B

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)-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

30

El compuesto del título se preparó utilizando el EJEMPLO 214A en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridina-d₅) □ 13,01 (s, 1H), 9,26 (d, 1H), 8,86 (t, 1H), 8,43 (d, 1H), 8,35 (dd, 1H), 8,11 (d, 1H), 7,66 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,94 (d, 1H), 6,75 (dd, 1H), 6,54 (d, 1H), 6,48 (m, 1H), 3,93 (m, 1H), 3,87 (d, 1H), 3,77 (s, 2H), 3,65 (dt, 1H), 3,51-3,40 (m, 2H), 3,07 (m, 4H), 2,87 (d, 1H), 2,77 (s, 2H), 2,60 (d, 1H), 35 2,50 (m, 1H), 2,38 (t, 1H), 2,26 (m, 2H), 2,14 (m, 4H), 1,97 (s, 2H), 1,39 (t, 2H), 0,94 (s, 6H).

EJEMPLO 215

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-(N,N-dimetilglicil)morfolin-2-il]metil)amino]-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

5

EJEMPLO 215A

4-((4-(2-(dimetilamino)acetil)morfolin-2-il)metilamino)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando clorhidrato de cloruro de 2-dimetilaminoacetilo en lugar de yoduro de metilo en el EJEMPLO 134B.

10

EJEMPLO 215B

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-(N,N-dimetilglicil)morfolin-2-il]metil)amino]-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

15

El compuesto del título se preparó utilizando el EJEMPLO 215A en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridina-d₅) □ 13,00 (s, 1H), 9,27 (d, 1H), 8,87 (bs, 1H), 8,43 (d, 1H), 8,34 (dd, 1H), 8,10 (dd, 1H), 7,66 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,94 (dd, 1H), 6,75 (d, 1H), 6,54 (s, 1H), 6,48 (s, 1H), 4,55 (dd, 1H), 4,20 (dd, 1H), 3,95-3,76 (m, 2H), 3,60-3,40 (m, 3H), 3,32 (dd, 1H), 3,25-3,12 (m, 2H), 3,07 (m, 4H), 2,80 (m, 1H), 2,77 (s, 2H), 2,26 (s, 6H), 2,23 (s, 2H), 2,14 (m, 4H), 1,97 (s, 2H), 1,39 (t, 2H), 0,94 (s, 6H).

20

EJEMPLO 216

ácido (2-([4-([4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil)sulfamoil]-2-nitrofenil)amino]metil)morfolin-4-il)acético

25

EJEMPLO 216A

2-(2-((2-nitro-4-sulfamoilfenilamino)metil)morfolino)acetato de tert-butilo

El compuesto del título se preparó utilizando 2-bromoacetato de tert-butilo en lugar de yoduro de metilo en el EJEMPLO 134B.

30

EJEMPLO 216B

2-(2-((4-(N-(2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoil)sulfamoil)-2-nitrofenilamino)metil)morfolino)acetato de tert-butilo

35

El compuesto del título se preparó utilizando el EJEMPLO 216A en lugar del EJEMPLO 130C en el EJEMPLO 130D.

EJEMPLO 216C

- 5 ácido (2-[[[4-([4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzoil]sulfamoil]-2-nitrofenil)amino]metil]morfolin-4-il)acético

El compuesto del título se preparó tratando EJEMPLO 216B con ácido trifluoroacético al 50% en diclorometano. ¹H NMR (500MHz, piridina-d₅) □ 12,97 (s, 1H), 9,26 (d, 1H), 8,87 (t, 1H), 8,43 (d, 1H), 8,30 (dd, 1H), 8,12 (d, 1H), 7,69 (t, 1H), 7,64 (d, 1H), 7,43 (d, 2H), 7,08 (d, 2H), 6,88 (d, 1H), 6,76 (dd, 1H), 6,55 (d, 1H), 6,47 (m, 1H), 4,05-4,00 (m, 1H), 3,91 (d, 1H), 3,79 (dt, 1H), 3,50 (s, 2H), 3,45 (m, 2H), 3,13 (d, 1H), 3,07 (m, 4H), 2,88 (d, 1H), 2,78 (s, 2H), 2,57 (dt, 1H), 2,43 (t, 1H), 2,26 (m, 2H), 2,14 (m, 4H), 1,97 (s, 2H), 1,39 (t, 2H), 0,94 (s, 6H).

EJEMPLO 217

- 15 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[3-nitro-4-([4-(oxetan-3-il)morfolin-2-il]metil)amino]fenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 217A

- 20 El compuesto del título se preparó utilizando el EJEMPLO 134A en lugar de piperazin-1-carboxilato de tert-butilo y 3-oxetanona en lugar de 4'-clorobifenil-2-carboxaldehído en el EJEMPLO 1A.

25 EJEMPLO 217B

4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[3-nitro-4-([4-(oxetan-3-il)morfolin-2-il]metil)amino]fenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

- El compuesto del título se preparó utilizando el EJEMPLO 217A en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridina-d₅) □ 13,00 (s, 1H), 9,26 (d, 1H), 8,87 (t, 1H), 8,44 (d, 1H), 8,34 (dd, 1H), 8,12 (d, 1H), 7,66 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,94 (d, 1H), 6,75 (dd, 1H), 6,54 (d, 1H), 6,48 (m, 1H), 4,64 (m, 4H), 3,93 (m, 1H), 3,89 (d, 1H), 3,68 (dt, 1H), 3,53-3,35 (m, 3H), 3,07 (m, 4H), 2,77 (s, 2H), 2,72 (d, 1H), 2,44 (d, 1H), 2,26 (m, 2H), 2,14 (m, 4H), 1,97 (s, 2H), 1,85 (t, 1H), 1,39 (t, 2H), 0,94 (s, 6H).

35 EJEMPLO 218

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

5 EJEMPLO 218A

4-((4-ciclopropilmorfolin-2-il)metilamino)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 134A en lugar del EJEMPLO 173A en el EJEMPLO 173B.

10 EJEMPLO 218B

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 218A en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridina-d₅) □ 13,00 (s, 1H), 9,26 (d, 1H), 8,88 (t, 1H), 8,44 (d, 1H), 8,34 (dd, 1H), 8,12 (d, 1H), 7,66 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,94 (d, 1H), 6,75 (dd, 1H), 6,54 (d, 1H), 6,48 (m, 1H), 3,88 (d, 1H), 3,84-3,81 (m, 1H), 3,59 (dt, 1H), 3,50-3,40 (m, 2H), 3,07 (m, 4H), 2,93 (d, 1H), 2,77 (s, 2H), 2,69 (d, 1H), 2,34 (dt, 1H), 2,26 (m, 2H), 2,21 (t, 1H), 2,14 (m, 4H), 1,97 (s, 2H), 1,58 (m, 1H), 1,39 (t, 2H), 0,94 (s, 6H), 0,45-0,39 (m, 4H).

EJEMPLO 219

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([5-(metilsulfonil)-6-(tetrahydro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 219A

5-(metiltio)-6-((tetrahydro-2H-piran-4-il)metoxi)piridin-3-sulfonamida

Una mezcla de EJEMPLO 36B (0,1 g) y metantioato de sodio (0,04 g) en N,N-dimetilformamida (2 mL) se calentó a 80°C durante la noche. Luego de enfriar, 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 MgSO₄, 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 para dar el compuesto del título.

EJEMPLO 219B

5-(metilsulfonil)-6-((tetrahidro-2H-piran-4-il)metoxi)piridin-3-sulfonamida

Una mezcla de EJEMPLO 219A (0,15 g) y ácido meta-cloroperoxibenzoico al 75% (0,217 g) en cloroformo (4 mL) se agitó a temperatura ambiente. La mezcla de la reacción se agitó durante la noche. La mezcla de la reacción luego 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 MgSO₄, 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 para dar el compuesto del título.

EJEMPLO 219C

4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{5-(metilsulfonil)-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il}sulfonil}-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 219B en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,65 (s, 1H), 8,81 (s, 1H), 8,55 (d, 1H), 8,01 (d, 1H), 7,55 (d, 1H), 7,49-7,50 (m, 2H), 7,37 (d, 2H), 7,05 (d, 2H), 6,67 (dd, 1H), 6,38 (dd, 1H), 6,21 (d, 1H), 4,36 (d, 2H), 3,88 (dd, 2H), 3,13 (s, 4H), 2,95 (s, 2H), 2,36-2,38 (m, 2H), 2,03-2,16 (m, 4H), 1,97 (s, 3H), 1,66-1,69 (m, 2H), 1,38-1,402 (m, 4H), 0,93 (s, 6H).

EJEMPLO 220

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)sulfonil]fenil}sulfonil}-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 220A

4-((4-fluorotetrahidro-2H-piran-4-il)metoxi)-3-(trifluorometilsulfonil)bencenosulfonamida

A una solución de EJEMPLO 37C (0,500 g) en tetrahidrofurano (5 mL) se agregó hidruro de sodio (0,596 g). Se agregó tetrahidrofurano adicional (25 mL) y la mezcla se agitó por 30 minutos, luego se agregó 4-fluoro-3-(trifluorometilsulfonil)bencenosulfonamida (1,145 g) como una solución en tetrahidrofurano (5 mL). Luego de agitar por 2 horas, la mezcla de la reacción se particionó entre HCl acuoso 1N (50 mL) y diclorometano (200 mL). La capa orgánica se secó sobre sulfato de magnesio, se filtró, y se concentró. El sólido resultante se cromatografió sobre gel de sílice (Reveleris 80g) eluyendo con un gradiente de metanol entre

0,5% y 7,5%/diclorometano a lo largo de 30 minutos (velocidad de flujo = 40 mL/min) para dar el compuesto del título.

EJEMPLO 220B

5 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({4-([4-fluorotetrahydro-2H-piran-4-il]metoxi)-3-[(trifluorometil)sulfonil]fenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 220A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) δ 11,66 (s, 1H), 8,42 (s, 1H), 8,35 - 8,22 (m, 1H), 8,01 (s, 1H), 7,49 (d, 4H), 7,35 (d, 2H), 7,05 (d, 2H), 6,68 (s, 1H), 6,38 (s, 1H), 6,21 (s, 1H), 4,42 (d, 2H), 3,76 (s, 2H), 3,59 (s, 2H), 3,10 (s, 6H), 2,15 (s, 6H), 2,02 - 1,74 (m, 6H), 1,40 (s, 2H), 0,93 (s, 6H).

15

EJEMPLO 221

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({4-([4-metiltetrahydro-2H-piran-4-il]metoxi)-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

20

EJEMPLO 221A

4-((4-metiltetrahydro-2H-piran-4-il]metoxi)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando (4-metiltetrahydro-2H-piran-4-il]metanol en lugar de (tetrahydro-2H-piran-4-il]metanol en el EJEMPLO 24A.

25

EJEMPLO 221B

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({4-([4-metiltetrahydro-2H-piran-4-il]metoxi)-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

30

El compuesto del título se preparó utilizando el EJEMPLO 221A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,69 (s, 1H), 8,36 (s, 1H), 8,04-8,06 (m, 2H), 7,50-7,53 (m, 3H), 7,41 (d, 1H), 7,35 (d, 2H), 7,04 (d, 2H), 6,67 (dd, 1H), 6,40 (dd, 1H), 6,20 (d, 1H), 4,00 (s, 2H), 3,63-3,67 (m, 2H), 3,53-3,58 (m, 2H), 3,09 (s, 4H), 2,82 (s, 2H), 2,27 (s, 2H), 2,15 (s, 2H), 1,58-1,63 (m, 2H), 1,39 (t, 2H), 1,30-1,34 (m, 2H), 1,09 (s, 3H), 0,92 (s, 6H).

35

EJEMPLO 222

4-(4-([4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]sulfamoil)-2-nitrofenil)piperazin-1-carboxilato de etilo

5 EJEMPLO 222A

4-(2-nitro-4-sulfamoilfenil)piperazin-1-carboxilato de etilo

El compuesto del título se preparó utilizando piperazin-1-carboxilato de etilo en lugar de 1-(tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

10 EJEMPLO 222B

4-(4-([4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]sulfamoil)-2-nitrofenil)piperazin-1-carboxilato de etilo

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 222A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (500 MHz, sulfóxido de dimetilo-d₆) □ 11,52 (br. s, 1H), 8,08 (d, 1H), 7,89 (d, 1H), 7,59 (m, 2H), 7,43 (t, 1H), 7,35 (d, 2H), 7,23 (d, 1H), 7,05 (d, 2H), 6,94 (d, 1H), 6,63 (dd, 1H), 6,29 (m, 2H), 4,07 (q, 2H), 3,47 (m, 4H), 3,17 (d, 2H), 3,00 (m, 8H), 2,73 (s, 2H), 2,18 (m, 6H), 1,96 (s, 2H), 1,39 (t, 2H), 1,20 (t, 3H), 0,93 (s, 6H).

20 EJEMPLO 223

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-(4-(morfolin-4-il)piperidin-1-il]-3-nitrofenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 223A

25 El compuesto del título se preparó utilizando 4-(piperidin-4-il)morfolina en lugar de 1-(tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

EJEMPLO 223B

30 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-(4-(morfolin-4-il)piperidin-1-il]-3-nitrofenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 223A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (500 MHz, sulfóxido de dimetilo-d₆) □ 11,53 (br. s, 1H), 8,05 (d, 1H), 7,91 (d, 1H), 7,58 (m, 2H), 7,43 (t, 1H), 7,35 (d, 2H), 7,26 (d, 1H), 7,05 (d, 2H), 6,91 (d, 1H), 6,62 (dd, 1H), 6,29 (m, 2H), 5,76 (s, 1H), 3,57 (m, 4H), 3,20 (m, 2H), 3,01 (m, 4H), 2,80 (t, 2H), 2,73 (s, 2H), 2,47 (m, 4H), 2,32 (m, 1H), 2,18 (m, 6H), 1,96 (m, 3H), 1,82 (m, 2H), 1,44 (m, 4H), 0,93 (s, 6H).

EJEMPLO 224

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(3-nitro-4-((3R)-1-(oxetan-3-il)pirrolidin-3-il)amino)fenil)sulfonyl]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

5 EJEMPLO 224A

(R)-1-(oxetan-3-il)pirrolidin-3-ilcarbamato de tert-butilo

El compuesto del título se preparó utilizando (R)-pirrolidin-3-ilcarbamato de tert-butilo en lugar de piperazin-1-carboxilato de tert-butilo y 3-oxetanona en lugar de 4'-clorobifenil-2-carboxaldehído en el EJEMPLO 1A.

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EJEMPLO 224B

(R)-1-(oxetan-3-il)pirrolidin-3-amina

El compuesto del título se preparó utilizando el EJEMPLO 224A en lugar de (S)-4,4-difluoropirrolidin-1,2-dicarboxilato de 1-tert-butilo 2-metilo en el EJEMPLO 168A.

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EJEMPLO 224C

(R)-3-nitro-4-(1-(oxetan-3-il)pirrolidin-3-ilamino)bencenosulfonamida

El compuesto del título se preparó utilizando 4-fluoro-3-nitrobencenosulfonamida en lugar de 4-cloro-3-nitrobencenosulfonamida y EJEMPLO 224B en lugar de diclorhidrato de 4-metilpiperazin-1-amina en el EJEMPLO 6A.

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224D

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(3-nitro-4-((3R)-1-(oxetan-3-il)pirrolidin-3-il)amino)fenil)sulfonyl]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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El compuesto del título se preparó utilizando el EJEMPLO 224C en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (400 MHz, piridina-d₅) δ 13,03 (s, 1H), 9,26 (d, 1H), 8,57 (d, 1H), 8,42 (d, 1H), 8,36 (dd, 1H), 8,09 (d, 1H), 7,66 (m, 1H), 7,64 (d, 1H), 7,44 (m, 2H), 7,07 (m, 2H), 6,86 (d, 1H), 6,75 (dd, 1H), 6,54 (d, 1H), 6,48 (dd, 1H), 4,67 (m, 4H), 3,58 (m, 1H), 3,07 (m, 4H), 2,77 (m, 2H), 2,68 (m, 2H), 2,61 (m, 1H), 2,28 (m, 4H), 2,14 (m, 4H), 1,97 (m, 2H), 1,67 (m, 1H), 1,39 (t, 2H), 0,93 (s, 6H).

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EJEMPLO 225

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(4-((3R)-1-(1,3-difluoropropan-2-il)pirrolidin-3-il)amino)-3-[(trifluorometil)sulfonyl]fenil)sulfonyl]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 225A

(R)-4-(1-(1,3-difluoropropan-2-il)pirrolidin-3-ilamino)-3-(trifluorometilsulfonyl)bencenosulfonamida

A EJEMPLO 207A (0,217 g) y 4-fluoro-3-(trifluorometilsulfonyl)bencenosulfonamida (0,281 g) en tetrahidrofurano (5 mL) se agregó diisopropiletilamina (0,559 mL) y la reacción se dejó agitar a temperatura ambiente por 1 hora y luego se calentó a 50°C por 1 hora. La reacción se concentró, el residuo se cargó sobre gel de sílice (Reveleris 40 g) y se eluyó con un gradiente de 0,75% metanol/diclorometano a 7,5% metanol/diclorometano para dar el compuesto del título.

EJEMPLO 225B

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-((3R)-1-(1,3-difluoropropan-2-il)pirrolidin-3-il]amino)-3-((trifluorometil)sulfonyl]fenil)sulfonyl]-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 225A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) δ 11,69 (s, 1H), 11,52 - 11,23 (m, 1H), 8,17 (d, 1H), 8,04 (d, 1H), 7,95 (d, 1H), 7,54 (d, 1H), 7,53 - 7,50 (m, 1H), 7,48 (d, 1H), 7,34 (d, 2H), 7,10 - 6,97 (m, 4H), 6,67 (d, 1H), 6,40 (dd, 1H), 6,18 (d, 1H), 4,60 (dd, 4H), 4,20 (s, 1H), 3,11 - 2,63 (m, 12H), 2,19 (d, 6H), 1,95 (s, 2H), 1,58 (s, 1H), 1,40 (d, 2H), 0,92 (s, 6H).

EJEMPLO 226

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-((1-isopropilpiperidin-4-il)amino)-3-nitrofenil]sulfonyl]-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 226A

4-(4-(N-(2-(1H-pirrololo[2,3-b]piridin-5-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

A una solución de EJEMPLO 82 (800 mg) y 4-aminopiperidin-1-carboxilato de tert-butilo (203 mg) en dioxano (10 mL) se agregó Base de Hunig (1 mL). La mezcla se agitó a 120°C durante la noche. La mezcla se diluyó con acetato de etilo (200 mL) y se lavó con agua, salmuera y se secó sobre Na₂SO₄. Luego de la filtración y evaporación del solvente, el residuo se cargó en un cartucho de gel de sílice y se eluyó con metanol al 3% en diclorometano para dar el compuesto del título.

EJEMPLO 226B

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-N-(3-nitro-4-(piperidin-4-ilamino)fenilsulfonil)benzamida

A una solución de EJEMPLO 226A (902 mg) en diclorometano (10 mL) se agregó ácido trifluoroacético (5 mL). La mezcla se agitó a temperatura ambiente por 3 horas. La
5 mezcla se concentró bajo vacío y se co-concentró con diclorometano dos veces para dar el producto crudo el cual se usó en el siguiente paso sin purificación adicional.

EJEMPLO 226C

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-
10 isopropilpiperidin-4-il)amino]-3-nitrofenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

A una solución de EJEMPLO 226B (79 mg) en tetrahidrofurano (3 mL) y ácido acético (1 mL) se agregó acetona (54 mg) y MP-cianoborohidruro (150 mg, 2,25mmol/g). La mezcla se agitó durante la noche. La mezcla se filtró. El material filtrado se concentró y el residuo se cargó en un cartucho de gel de sílice y se eluyó con NH₃ 7N entre 5 y 10% en metanol en
15 diclorometano para dar el compuesto del título. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) □ 12,09 (s, 1 H), 8,34 (m, 1 H), 7,93 (m, 2 H), 7,66 (m, 4 H), 7,35 (d, 2 H), 7,06 (d, 2 H), 6,89 (m, 1 H), 6,74 (dd, 1 H), 6,59 (dd, 1 H), 6,50 (d, 1 H), 3,11 (m, 6 H), 2,73 (m, 4 H), 2,26 (m, 9 H), 1,97 (s, 3 H), 1,40 (t, 2 H), 1,23 (s, 8 H), 0,94 (s, 6 H).

20 EJEMPLO 227

N-([4-([1-tert-butilpiperidin-4-il)amino]-3-nitrofenil)sulfonil)-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 227A

25 1-tert-butilpiperidin-4-amina

A una solución de 1-tert-butilpiperidin-4-ona (5,0 g) en metanol (100 mL) y agua (10 mL) se agregó formato de amonio (20,3 g) y 0,5 g de Pd/C (10%). La mezcla se agitó durante la noche. La mezcla se filtró y el material filtrado se concentró bajo vacío y el residuo se diluyó con acetato de etilo (500 mL) y se lavó con agua y salmuera. Luego de secar sobre
30 Na₂SO₄ y filtrar, el solvente se evaporó bajo vacío para dar el compuesto del título.

EJEMPLO 227B

4-(1-tert-butilpiperidin-4-ilamino)-3-nitrobencenosulfonamida

A una mezcla de 4-fluoro-3-nitrobencenosulfonamida (2,2 g) y EJEMPLO 227A (1,56
35 g) en tetrahidrofurano (20 mL) se agregó Base de Hunig (6 mL). La mezcla se agitó por 3 días. La mezcla se diluyó con acetato de etilo (300 mL) y agua (100 mL) y se agitó hasta que

el sólido desapareció en la solución. Las capas se separaron y la fase orgánica se lavó con agua y salmuera, se secó sobre Na_2SO_4 , y se filtró. Las capas acuosas combinadas se extrajeron nuevamente con acetato de etilo y las fases orgánicas combinadas se secaron sobre Na_2SO_4 . Luego de la filtración, el solvente se evaporó para dar el compuesto del título.

5

EJEMPLO 227C

N-({4-[(1-*tert*-butilpiperidin-4-il)amino]-3-nitrofenil}sulfonil)-4-{4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 227B en lugar del EJEMPLO 1F en el EJEMPLO 1G. ^1H NMR (300 MHz, sulfóxido de dimetilo- d_6) δ 11,51 (s, 1 H), 8,43 (d, 1 H), 8,04 (m, 1 H), 7,93 (d, 1 H), 7,72 (m, 1 H), 7,56 (dd, 1 H), 7,42 (m, 1 H), 7,34 (m, 3 H), 7,05 (d, 2 H), 6,93 (dd, 1 H), 6,62 (dd, 1 H), 6,28 (m, 1 H), 3,04 (m, 6 H), 2,73 (s, 3 H), 2,25 (m, 9 H), 1,95 (s, 2 H), 1,68 (m, 2 H), 1,32 (m, 9 H), 0,93 (s, 6 H).

15 EJEMPLO 228

4-{4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il}-N-{{4-[[1-(2-metoxietil)piperidin-3-il]metil]amino]-3-nitrofenil}sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

20 EJEMPLO 228A

3-((2-nitro-4-sulfamoilfenilamino)metil)piperidin-1-carboxilato de *tert*-butilo

El compuesto del título se preparó utilizando 3-(aminometil)piperidin-1-carboxilato de *tert*-butilo en lugar de (tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

25 EJEMPLO 228B

3-nitro-4-(piperidin-3-ilmetilamino)bencenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 228A en lugar del EJEMPLO 113A en el EJEMPLO 134A.

30 EJEMPLO 228C

4-((1-(2-metoxietil)piperidin-3-il)metilamino)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 228B en lugar del EJEMPLO 134A y bromuro de 2-metoxietilo en lugar de yoduro de metilo en el EJEMPLO 134B.

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EJEMPLO 228D

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-(2-metoxietil)piperidin-3-il]metil)amino)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 228C en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridina-d₅, 90 °C) □ 12,40 (s, 1H), 8,52 (s, 1H), 8,43 (s, 1H), 8,20 (m, 2H), 7,95 (bs, 1H), 7,80 (s, 1H), 7,46 (d, 1H), 7,36 (d, 2H), 7,07 (d, 2H), 7,05 (s, 1H), 6,75 (d, 1H), 6,59 (s, 1H), 6,47 (s, 1H), 3,65-3,50 (m, 5H), 3,20 (s, 3H), 3,04 (m, 5H), 2,81 (s, 3H), 2,74 (m, 1H), 2,24 (m, 7H), 2,06 (s, 2H), 2,00 (s, 2H), 1,75 (m, 1H), 1,57 (m, 2H), 1,42 (t, 2H), 1,15 (m, 1H), 0,95 (s, 6H).

EJEMPLO 229

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-(cianometil)piperidin-3-il]metil)amino)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 229A

4-((1-(cianometil)piperidin-3-il)metilamino)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 228B en lugar del EJEMPLO 134A y 2-bromoacetónitrilo en lugar de yoduro de metilo en el EJEMPLO 134B.

EJEMPLO 229B

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-(cianometil)piperidin-3-il]metil)amino)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 229A en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridina-d₅) □ 13,06 (s, 1H), 9,03 (s, 1H), 8,42 (s, 1H), 8,30 (d, 1H), 8,10 (d, 1H), 7,68 (m, 2H), 7,44 (d, 2H), 7,08 (m, 3H), 6,99 (d, 1H), 6,75 (d, 1H), 6,51 (m, 2H), 3,78 (m, 2H), 3,43 (d, 1H), 3,13 (m, 1H), 3,04 (m, 4H), 2,76 (s, 2H), 2,71-2,65 (m, 3H), 2,52 (m, 1H), 2,25 (m, 2H), 2,14 (m, 4H), 1,97 (s, 2H), 1,84 (m, 1H), 1,68 (m, 1H), 1,50 (m, 2H), 1,39 (t, 2H), 1,07-0,99 (m, 1H), 0,93 (s, 6H).

EJEMPLO 230

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-fluoro-1-metilpiperidin-4-il]metoxi)-3-[(trifluorometil)sulfonil]fenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 230A

4-((4-fluoro-1-metilpiperidin-4-il)metoxi)-3-(trifluorometilsulfonil)bencenosulfonamida

A una solución de (4-fluoro-1-metilpiperidin-4-il)metanol (0,315 g) en tetrahidrofurano (5 mL) se agregó hidruro de sodio (0,342 g). Luego de agitar por 15 minutos, se agregó 4-fluoro-3-(trifluorometilsulfonil)bencenosulfonamida (0,658 g) como una solución en tetrahidrofurano (2 mL) seguido por tetrahidrofurano adicional (5 mL). Luego de agitar por 1 hora, la reacción se vertió en diclorometano (50 mL) y agua (25 mL) y el pH de la capa acuosa se ajustó a 8. La capa orgánica se secó sobre sulfato de magnesio, se filtró, y se concentró. El aceite resultante se cromatografió sobre gel de sílice (Reveleris 40 g) eluyendo con un gradiente de NH₃ 7N entre 1,0% y 10% en metanol/diclorometano a lo largo de 20 minutos luego manteniendo NH₃ 7N al 10% en metanol/diclorometano por 5 minutos (velocidad de flujo = 30 mL/min) para dar el compuesto del título.

EJEMPLO 230B

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-[(4-fluoro-1-metilpiperidin-4-il)metoxi]-3-[(trifluorometil)sulfonil]fenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 230A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) δ 11,63 - 11,57 (m, 1H), 8,40 - 8,36 (m, 1H), 8,28 - 8,17 (m, 1H), 7,97 (s, 1H), 7,53 (d, 1H), 7,50 - 7,32 (m, 5H), 7,05 (d, 1H), 7,05 (d, 1H), 6,68 - 6,61 (m, 1H), 6,35 (s, 1H), 6,22 (s, 1H), 4,55 - 4,40 (m, 2H), 3,06 (s, 8H), 2,79 (s, 4H), 2,06 (d, 13H), 1,39 (s, 2H), 0,93 (s, 6H).

EJEMPLO 231

N-[(5-cloro-6-([(3R)-1-(1,3-difluoropropan-2-il)pirrolidin-3-il]amino)piridin-3-il)sulfonil]-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 231A

(R)-5-cloro-6-(1-(1,3-difluoropropan-2-il)pirrolidin-3-ilamino)piridin-3-sulfonamida

A EJEMPLO 207A (0,051 g) y EJEMPLO 40A (0,049 g) en dioxano (5 mL) se agregó diisopropiletilamina (0,131 mL) y la reacción se calentó a 75°C por 1 hora luego 85°C por 2 días. La reacción se concentró, se cargó sobre gel de sílice (Reveleris 12 g) y se eluyó con un gradiente de 0,75% metanol/diclorometano a 7,5% metanol/diclorometano para dar el compuesto del título.

EJEMPLO 231B

N-[(5-cloro-6-[(3R)-1-(1,3-difluoropropan-2-il)pirrolidin-3-il]amino)piridin-3-il)sulfonil]-4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

- 5 El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 231A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo- d₆) δ 11,71 (s, 1H), 11,44 - 11,11 (m, 1H), 8,44 (d, 1H), 8,07 (d, 1H), 7,90 (d, 1H), 7,61 (d, 1H), 7,52 (dd, 2H), 7,34 (d, 2H), 7,19 (s, 1H), 7,04 (d, 2H), 6,67 (d, 1H), 6,42 (dd, 1H), 6,16 (s, 1H), 4,77 - 4,39 (m, 5H), 3,19 - 2,63 (m, 11H), 2,19 (s, 7H), 1,91 (d, 3H), 1,38 (s, 2H), 0,92 (s, 6H).

EJEMPLO 232

4-[[4-[[4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]sulfamoil]-2-nitrofenil]amino]piperazin-1-carboxilato de tert-butilo

15 EJEMPLO 232A

4-nitrosopiperazin-1-carboxilato de tert-butilo

- En un balón de 500 mL, se enfrió HCl acuoso 6N (30 mL) a -10 °C, y se agregó piperazin-1-carboxilato de tert-butilo (10 g). Se agregó nitrito de sodio (4,5 g) disuelto en 35 ml de agua lentamente. Se usó NaOH (10 g en 20 mL agua) para neutralizar la solución. Se usó diclorometano (3x 50 mL) para extraer el producto. Luego de secar sobre Na₂SO₄ y filtrar, la solución se concentró. El producto crudo se agregó a una columna de gel de sílice (Analogix, SF65-400 g,) y se purificó mediante eluyendo con acetato de etilo al 0-30% en hexano.

EJEMPLO 232B

25 4-aminopiperazin-1-carboxilato de tert-butilo

- En un balón de 100 mL se agregó EJEMPLO 232A (0,15 g) y cinc (1 g) en agua/metanol (1:1, 10 mL) para dar una suspensión. La mezcla se enfrió a 0°C. Se agregó HCl acuoso 12N (2 ml) lentamente, y la mezcla se agitó a 0 °C por 30 minutos. Se usó solución acuosa 2N de NaOH para ajustar la mezcla a pH básico. La mezcla se filtró, y se extrajo con éter (3x 30 mL). Luego de secar sobre Na₂SO₄, filtrar y concentrar, el producto crudo se agregó a una columna de gel de sílice (Analogix, SF15-12g,) y se purificó eluyendo con 0-25% acetato de etilo en hexano.

35 EJEMPLO 232C

4-(2-nitro-4-sulfamoilfenilamino)piperazin-1-carboxilato de tert-butilo

El compuesto del título se preparó utilizando el EJEMPLO 232B en lugar de 1-(tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

EJEMPLO 232D

- 5 4-[(4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil}sulfamoil]-2-nitrofenil)amino]piperazin-1-carboxilato de tert-butilo

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 232C en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) □ 11,47 (br. s, 1H), 8,86 (s, 1H), 8,34 (d, 1H), 7,90 (d, 1H), 7,59 (m, 2H), 7,36 (m, 4H), 7,23 (m, 1H), 7,05 (d, 2H), 6,61 (dd, 1H), 6,27 (m, 2H), 2,99 (m, 5H), 2,76 (m, 6H), 2,19 (m, 6H), 1,96 (s, 2H), 1,41 (m, 11H), 1,24 (m, 4H), 0,93 (s, 6H).

EJEMPLO 233

- 15 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-(pentafluoro-lambda~6~-sulfanil)-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 233A

pentafluoruro de 2-(5-bromo-2-nitrofenil)azufre

- 20 A una solución de pentafluoruro de 3-bromofenilazufre (2,18 g) en H₂SO₄ concentrado (5 mL) se agregó KNO₃ (780 mg). La mezcla se agitó durante la noche. La mezcla se diluyó con éter dietílico (100 mL) y se lavó con agua y salmuera. Luego de secar sobre Na₂SO₄ y filtrar, el solvente se evaporó bajo vacío para dar el compuesto del título.

25 EJEMPLO 233B

pentafluoruro de 2-(5-bromo-2-aminofenil)azufre

- Se agregó EJEMPLO 233A (6,4g) y tetrahidrofurano (300 mL) a Ra-Ni, (12,80 g) en una botella de presión de 50 mL y la mezcla se agitó por 2 horas a 30 psi y temperatura ambiente. La mezcla se filtró a través de una membrana de nylon y el material filtrado se
30 concentró bajo vacío para dar el compuesto del título.

EJEMPLO 233C

4-bromo-2-pentafluorosulfanil-N-(tetrahidro-2H-piran-4-ilmetil)anilina

- A una solución de EJEMPLO 233B (4,4 g) en metanol (50 mL) se agregó tetrahidro-
35 2H-piran-4-carbaldehído (1,68 g) y decaborano (1,1 g). La mezcla se agitó y se monitoreó mediante cromatografía de capa fina. Se agregó más tetrahidro-2H-piran-4-carbaldehído

(500 mg) a la mezcla en agitación para hacer completar la reacción. La mezcla de la reacción se concentró bajo vacío y se agregó acetato de etilo (500 mL) y salmuera (200 mL). La fase orgánica se secó sobre Na_2SO_4 . La filtración y evaporación del solvente y cromatografía flash (acetato de etilo al 20% en hexano) dio el compuesto del título.

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EJEMPLO 233D

4-tioacetoxi-2-pentafluorosulfanil-N-((tetrahydro-2H-piran-4-ilmetil)anilina

A una solución de EJEMPLO 233C (456 mg) y etantioato de potasio (197 mg) en dioxano (4 mL) se agregó tris(dibencilidenacetona)dipaladio(0) (27 mg) y xantphos (33 mg) seguido por N,N-diisopropiletilamina (0,5 mL). La mezcla se purgó con argón, se selló y se agitó bajo irradiación de microondas por 60 minutos a 120°C. La mezcla se disolvió en acetato de etilo (300 mL) y agua (100 mL). La fase orgánica se lavó con salmuera y se secó sobre Na_2SO_4 . La filtración y evaporación del solvente seguido por cromatografía flash (acetato de etilo al 20% en hexano) dio el compuesto del título.

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EJEMPLO 233E

3-pentafluorosulfanil-4-[(tetrahydro-2H-piran-4-ilmetil)amino]fenilsulfonamida

Se agregó N-clorosuccinimida (527 mg) a una mezcla de HCl acuoso 2N (1,5 mL) y acetonitrilo (12 mL) y luego se enfrió a 0°C. Se agregó una solución de EJEMPLO 233D (386 mg) en acetonitrilo (3 mL) a la mezcla la cual luego se agitó a 0°C por 2 horas, y luego se diluyó con acetato de etilo (300 mL) y se lavó con salmuera y se secó sobre Na_2SO_4 . Luego de la filtración y evaporación del solvente, el residuo se disolvió en alcohol isopropílico (20 mL) y se enfrió a 0°C con agitación. Luego, se agregó hidróxido de amonio (conc. 10 mL) a la mezcla. Luego de agitar por 2 horas, la mezcla se concentró bajo vacío y el residuo se agregó a acetato de etilo (400 mL) y agua (150 mL). La capa orgánica se lavó con salmuera y se secó sobre Na_2SO_4 . Luego de la filtración y evaporación del solvente, el residuo se purificó mediante columna flash (acetato de etilo al 20% en diclorometano) para dar el compuesto del título.

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30 EJEMPLO 233F

4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({3-(pentafluoro-lambda~6~-sulfanil)-4-[(tetrahydro-2H-piran-4-ilmetil)amino]fenil)sulfonil)-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 233E en lugar del EJEMPLO 1F en el EJEMPLO 1G. ^1H NMR (300 MHz,

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sulfóxido de dimetilo- d_6) $\square$ 11,71 (s, 1 H), 11,33 (m, 1 H), 8,12 (m, 2 H), 7,72 (d, 1 H), 7,54 (m, 3 H), 7,33 (m, 2 H), 7,02 (m, 3 H), 6,67 (m, 2 H), 6,42 (m, 1 H), 6,16 (d, 1 H), 3,82 (m, 2 H), 3,21 (m, 4 H), 3,05 (m, 4 H), 2,73 (s, 2 H), 2,21 (m, 8 H), 1,97 (m, 3 H), 1,29 (m, 4 H), 0,92 (s, 6 H).

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EJEMPLO 234

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-metoxitetrahydro-2H-piran-4-il]metoxi)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 234A

4-viniltetrahydro-2H-piran-4-ol

Se trató dihidro-2H-piran-4(3H)-ona (8,01 g) en éter anhidro etílico (50 mL) con bromuro de vinilmagnesio 1,0 M (104 mL) a lo largo de 20 minutos a 0°C. La mezcla de la reacción se agitó a temperatura ambiente durante la noche. La reacción se detuvo con NH_4Cl saturado, y la capa orgánica se separó. La capa acuosa se extrajo con éter etílico adicional tres veces. Las capas orgánicas combinadas se lavaron con salmuera, se secó, se filtró, y se concentró. El residuo se purificó mediante cromatografía flash de columna sobre gel de sílice usando acetato de etilo al 20% en hexanos para dar el compuesto del título.

EJEMPLO 234B

4-metoxi-4-viniltetrahydro-2H-piran

A una solución de EJEMPLO 234A (9,4 g) en tetrahydrofurano (150 mL) se agregó hidruro de sodio al 60 % (5,28 g) a 0°C por porciones. Luego de completarse la adición, la solución se calentó bajo reflujo por tres horas. Luego de enfriar, a esta suspensión se agregó sulfato de dimetilo (8,41 mL) lentamente. La solución se calentó bajo reflujo durante la noche, se enfrió a temperatura ambiente, y se hidrolizó con NH_4Cl acuoso saturado frío. Luego de la extracción con éter dietílico varias 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 1-10% acetato de etilo en hexanos para dar el compuesto del título.

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EJEMPLO 234C

4-metoxitetrahydro-2H-piran-4-carbaldehído

Se trató EJEMPLO 234B (4,3 g) en tetrahydrofurano (200 mL) y agua (67 mL) con tetróxido de osmio al 4% en agua (9,24 mL). A esta solución se agregó periodato de potasio (13,91 g) por porciones a lo largo de 2 horas. La solución se agitó durante la noche a

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temperatura ambiente. Se agregó agua a la mezcla seguido por varias extracciones con éter dietílico. Las capas orgánicas combinadas se secaron sobre MgSO_4 , se filtró, y se concentró. El residuo se purificó mediante cromatografía flash de columna sobre gel de sílice usando 5-acetato de etilo al 20% en hexanos para dar el compuesto del título.

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EJEMPLO 234D

(4-metoxitetrahydro-2H-piran-4-il)metanol

Se enfrió EJEMPLO 234C (1,8 g) en 2-propanol (28 mL) y agua (7 mL) a 0 °C. A esta solución se agregó borhidruro de sodio (0,709 g). La solución se agitó y se dejó calentar a temperatura ambiente durante 3 horas. La reacción se detuvo con acetona, y se agitó por otra 1 hora. El líquido traslúcido se separó del sólido mediante decantación. Se usó acetato de etilo adicional para lavar el sólido, y la mezcla se decantó. Las soluciones orgánicas combinadas se concentraron. El residuo se purificó mediante cromatografía flash sobre gel de sílice eluyendo 1:1 acetato de etilo: hexano para dar el compuesto del título.

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EJEMPLO 234E

4-((4-metoxitetrahydro-2H-piran-4-il)metoxi)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 234D en lugar de (tetrahydro-2H-piran-4-il)metanol en el EJEMPLO 24A.

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EJEMPLO 234F

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-metoxitetrahydro-2H-piran-4-il)metoxi]-3-nitrofenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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El compuesto del título se preparó utilizando el EJEMPLO 234E en lugar del EJEMPLO 11B en el EJEMPLO 11D. ^1H NMR (500MHz, sulfóxido de dimetilo- d_6) δ 11,68 (s, 1H), 8,36 (s, 1H), 8,04-8,07 (m, 2H), 7,50-7,53 (m, 3H), 7,45 (d, 1H), 7,35 (d, 2H), 7,05 (d, 2H), 6,68 (dd, 1H), 6,40 (dd, 1H), 6,20 (d, 1H), 4,21 (s, 2H), 3,65-3,67 (m, 2H), 3,53-3,56 (m, 2H), 3,19 (s, 3H), 3,10 (s, 4H), 2,86 (s, 2H), 2,30 (s, 4H), 2,15 (s, 2H), 1,96 (s, 2H), 1,61-1,74 (m, 4H), 1,39 (t, 2H), 0,93 (s, 6H).

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EJEMPLO 235

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([3R]-1-(1,3-difluoropropan-2-il)pirrolidin-3-il)oxi]-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 235A

(R)-3-(2-nitro-4-sulfamoilfenoxi)pirrolidin-1-carboxilato de *tert*-butilo

El compuesto del título se preparó utilizando (R)-3-hidroxi-pirrolidin-1-carboxilato de *tert*-butilo en lugar de (tetrahydro-2H-piran-4-il)metanol en el EJEMPLO 24A.

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EJEMPLO 235B

(R)- 3-(4-(N-(2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoil)sulfamoil)-2-nitrofenoxi)pirrolidin-1-carboxilato de *tert*-butilo

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 235A en lugar del EJEMPLO 1F en el EJEMPLO 1G.

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EJEMPLO 235C

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([(3R)-1-(1,3-difluoropropan-2-il)pirrolidin-3-il]oxi)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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A una solución de EJEMPLO 235B (0,230 g) en diclorometano (3 mL) se agregó ácido trifluoroacético (0,377 mL). Luego de agitar por 4 horas, la reacción se concentró y luego se disolvió en diclorometano (3 mL) y se trató con 1,3-difluoropropan-2-ona (0,028 g) seguido por triacetoxiborhidruro de sodio (0,078 g). Luego de agitar por 4 horas, la reacción se detuvo mediante la adición de NaHCO₃ acuoso saturado y diclorometano (5 mL). La reacción se diluyó con diclorometano (250 mL) y se agregó NaHCO₃ acuoso saturado (100 mL). La capa orgánica se separó, se lavó con salmuera (100 mL), se secó sobre sulfato de magnesio, se filtró y se concentró. La trituración con acetonitrilo dio el compuesto del título. ¹H NMR (300 MHz, sulfóxido de dimetilo- d₆) δ 11,67 (s, 1H), 8,34 (s, 1H), 8,03 (s, 2H), 7,52 (d, 3H), 7,35 (d, 3H), 7,04 (d, 2H), 6,75 - 6,60 (m, 1H), 6,40 (s, 1H), 6,20 (s, 1H), 5,17 - 5,06 (m, 1H), 4,60 (d, 4H), 2,98 (d, 12H), 2,37 - 2,02 (m, 6H), 1,96 (s, 3H), 1,39 (s, 2H), 0,93 (s, 6H).

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EJEMPLO 236

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(3-nitro-4-([4-(oxetan-3-il)piperazin-1-il]amino)fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 236A

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-

enil)metil)piperazin-1-il)-N-(3-nitro-4-(piperazin-1-ilamino)fenilsulfonil)benzamida

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El compuesto del título se preparó utilizando el EJEMPLO 232D en lugar del EJEMPLO 1A en el EJEMPLO 1B.

EJEMPLO 236B

- 5 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(3-nitro-4-{{4-(oxetan-3-il)piperazin-1-il}amino}fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 236A en lugar de piperazin-1-carboxilato de tert-butilo y oxetan-3-ona en lugar de 4'-clorobifenil-2-carboxaldehído en el EJEMPLO 1A. ¹H NMR (400 MHz, sulfóxido de dimetilo-d₆) δ 11,67 (br. s, 1H), 9,20 (s, 1H), 8,53 (d, 1H), 8,04 (d, 1H), 7,83 (dd, 1H), 7,53 (m, 4H), 7,34 (d, 2H), 7,04 (d, 2H), 6,67 (dd, 1H), 6,39 (m, 1H), 6,18 (d, 1H), 4,55 (t, 2H), 4,44 (t, 2H), 3,47 (m, 1H), 3,06 (m, 4H), 2,88 (m, 4H), 2,74 (m, 4H), 2,09 (m, 11H), 1,38 (t, 2H), 0,91 (s, 6H).

EJEMPLO 237

- 15 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(3-nitro-4-{{4-(tetrahydro-2H-piran-4-il)piperazin-1-il}amino}fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 236A en lugar de piperazin-1-carboxilato de tert-butilo y dihidro-2H-piran-4(3H)-ona en lugar de 4'-clorobifenil-2-carboxaldehído en el EJEMPLO 1A. ¹H NMR (400 MHz, piridina-d₅) δ 13,05 (br. s, 1H), 9,27 (d, 1H), 9,23 (s, 1H), 8,44 (m, 2H), 8,12 (d, 1H), 7,68 (m, 3H), 7,44 (m, 2H), 7,06 (m, 2H), 6,75 (dd, 1H), 6,51 (m, 2H), 4,02 (m, 2H), 3,31 (m, 2H), 3,06 (m, 4H), 2,91 (m, 5H), 2,76 (s, 2H), 2,38 (m, 2H), 2,26 (m, 2H), 2,14 (m, 4H), 1,97 (s, 2H), 1,65 (m, 2H), 1,39 (m, 7H), 0,93 (s, 6H).

EJEMPLO 238

4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(3-nitro-4-[(3R)-tetrahydrofurano-3-ilamino]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

30 EJEMPLO 238A

(R)-3-nitro-4-(tetrahydrofurano-3-ilamino)bencenosulfonamida

El compuesto del título se preparó utilizando (R)-tetrahydrofurano-3-amina en lugar de diclorhidrato de 4-metilpiperazin-1-amina en el EJEMPLO 6A.

35 EJEMPLO 238B

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-((3R)-tetrahidrofurano-3-ilamino]fenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 238A en lugar del EJEMPLO 1F y EJEMPLO 3J en lugar del EJEMPLO 1E en el EJEMPLO 1G. ¹H NMR (400 MHz, sulfóxido de dimetilo-d₆) δ 11,59 (s, 1H), 8,47 (d, 1H), 8,19 (m, 2H), 7,97 (d, 1H), 7,74 (m, 1H), 7,52 (d, 1H), 7,46 (t, 1H), 7,34 (m, 2H), 7,05 (m, 2H), 6,96 (d, 1H), 6,89 (d, 1H), 6,65 (dd, 1H), 6,33 (m, 1H), 6,22 (d, 1H), 4,31 (m, 1H), 3,92 (m, 1H), 3,87 (m, 1H), 3,76 (m, 1H), 3,69 (m, 1H), 3,04 (m, 4H), 2,73 (m, 2H), 2,33 (m, 1H), 2,18 (m, 6H), 1,95 (m, 2H), 1,88 (m, 1H), 1,39 (t, 2H), 0,92 (s, 6H).

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EJEMPLO 239

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

15 EJEMPLO 239A

(4,4-difluorociclohexil)metilcarbamato de tert-butilo

Se agitó (4-oxociclohexil)metilcarbamato de tert-butilo (5 g) y trifluoruro de dietilaminoazufre (7,45 g) en diclorometano (100 mL) por 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 la capa orgánica se lavó dos veces con agua, y una vez con salmuera, y luego se concentró para dar el producto crudo y el subproducto fluoroolefina en una proporción de 3:2. El material crudo se colocó en tetrahidrofurano (70 mL) y agua (30 mL), y se agregó N-óxido de N-metilmorfolina (1,75 g), y OsO₄ (solución al 2,5 % en peso en t-butanol), y la mezcla se agitó por 24 horas. Luego se agregó Na₂S₂O₃ (10 g), y la mezcla se agitó por 30 minutos. La mezcla luego se diluyó con éter (300 mL), y la solución resultante se separó, y se enjuagó dos veces con agua, y una vez con salmuera, y se concentró. El producto crudo se cromatografió sobre gel de sílice usando 5-10% acetato de etilo en hexanos para dar el compuesto del título.

30 EJEMPLO 239B

(4,4-difluorociclohexil)metanamina

Una solución de EJEMPLO 239A (3 g) en diclorometano (35 mL), ácido trifluoroacético (15 mL), y trietilsilano (1 mL) se agitó por 2 horas. La solución se concentró, luego se concentró a partir de tolueno, y se dejó en alto vacío por 24 horas. El semisólido se colocó en éter/hexano y se filtró para dar el compuesto del título como su sal de ácido trifluoroacético.

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EJEMPLO 239C

4-((4,4-difluorociclohexil)metilamino)-3-nitrobenzenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 239B en lugar de (tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

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EJEMPLO 239D

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 239C en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300MHz, sulfóxido de dimetilo-d₆) □ 12,40 (s, 1H), 11,61 (br s, 1H), 8,53 (m, 1H), 8,50 (d, 1H), 7,99 (d, 1H), 7,73 (d, 1H), 7,49 (m, 2H), 7,32 (d, 2H), 7,04 (d, 2H), 7,00 (d, 1H), 6,65 (d, 1H), 6,32 (s, 1H), 6,21 (s, 1H), 3,37 (m, 4H), 3,06 (m, 4H), 2,73 (m, 2H), 2,18 (m, 4H), 1,97 (m, 4H), 1,81 (m, 4H), 1,38 (m, 2H), 1,20 (m, 4H), 0,92 (s, 6H).

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EJEMPLO 240

N-([4-([1-tert-butilpiperidin-4-il)amino]-3-[(trifluorometil)sulfonil]fenil)sulfonil)-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 240A

4-(1-tert-butilpiperidin-4-ilamino)-3-(trifluorometilsulfonil)benzenosulfonamida

A una mezcla de 4-fluoro-3-(trifluorometilsulfonil)benzenosulfonamida (307 mg) y EJEMPLO 227A (156 mg) en tetrahidrofurano (4 mL) se agregó Base de Hunig (1 mL). La mezcla se agitó por 3 días. La mezcla se diluyó con acetato de etilo (300 mL) y agua (100 mL) y se agitó hasta que el sólido desapareció en la solución. Las capas se separaron y la fase orgánica se lavó con agua, salmuera y se secó sobre Na₂SO₄. Luego de la filtración, las capas acuosas combinadas se extrajeron nuevamente con acetato de etilo y la fase orgánica combinada se secó sobre Na₂SO₄. Luego de la filtración, el solvente se evaporó para dar el compuesto del título.

30

EJEMPLO 240B

N-([4-([1-tert-butilpiperidin-4-il)amino]-3-[(trifluorometil)sulfonil]fenil)sulfonil)-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

35

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 240A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) □ 11,53 (s, 1 H), 8,04 (s, 1 H), 7,94 (d, 1 H), 7,86 (m, 1 H), 7,55 (d, 2 H), 7,44 (d, 1 H), 7,33 (m, 3 H), 7,05 (d, 2 H), 6,92 (m, 1 H), 6,62 (dd, 1 H), 6,43 (m, 1 H),
 5 6,29 (d, 2 H), 3,79 (m, 1 H), 3,05 (m, 6 H), 2,73 (s, 3 H), 2,19 (m, 8 H), 1,96 (s, 3 H), 1,27 (m, 12 H), 0,92 (s, 6 H).

EJEMPLO 241

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({4-([4-(oxetan-3-il)morfolin-2-il]metil)amino)-3-[(trifluorometil)sulfonil]fenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida
 10

EJEMPLO 241A

2-((4-sulfamoil-2-(trifluorometilsulfonil)fenilamino)metil)morfolina-4-carboxilato de tert-butilo
 15 El compuesto del título se preparó utilizando 2-(aminometil)morfolina-4-carboxilato de tert-butilo en lugar de (tetrahidropiran-4-il)metilamina y 4-fluoro-3-(trifluorometilsulfonil)bencenosulfonamida en lugar de 4-fluoro-3-nitrobencenosulfonamida en el EJEMPLO 1F.

20 EJEMPLO 241B

2-((4-(N-(2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoil)sulfamoil)-2-(trifluorometilsulfonil)fenilamino)metil)morfolina-4-carboxilato de tert-butilo

El compuesto del título se preparó utilizando el EJEMPLO 241A en lugar del EJEMPLO 1F y EJEMPLO 3J en lugar del EJEMPLO 1E en el EJEMPLO 1G.

EJEMPLO 241C

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-N-(4-(morfolin-2-ilmetilamino)-3-(trifluorometilsulfonil)fenilsulfonil)benzamida

30 El compuesto del título se preparó utilizando el EJEMPLO 241B en lugar del EJEMPLO 1A en el EJEMPLO 1B.

EJEMPLO 241D

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({4-([4-(oxetan-3-il)morfolin-2-il]metil)amino)-3-[(trifluorometil)sulfonil]fenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida
 35

El compuesto del título se preparó utilizando el EJEMPLO 241C en lugar de piperazin-1-carboxilato de tert-butilo y oxetan-3-ona en lugar de 4'-clorobifenil-2-carboxaldehído en el EJEMPLO 1A. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) □ 11,69 (s, 1H), 8,15 (d, 1H), 8,04 (d, 1H), 7,92 (dd, 1H), 7,54 (d, 1H), 7,51 (t, 1H), 7,48 (d, 1H), 7,34 (d, 2H), 7,25 (m, 1H), 7,04 (m, 3H), 6,68 (dd, 1H), 6,41 (m, 1H), 6,19 (d, 1H), 4,54 (t, 2H), 4,43 (m, 2H), 3,85 (m, 1H), 3,69 (m, 1H), 3,52 (m, 1H), 3,48 (m, 1H), 3,39 (m, 2H), 3,07 (m, 4H), 2,77 (br s, 2H), 2,69 (d, 1H), 2,56 (d, 1H), 2,21 (br s, 4H), 2,15 (t, 2H), 1,94 (m, 3H), 1,76 (t, 1H), 1,38 (t, 2H), 0,92 (s, 6H).

10 EJEMPLO 242

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

15 EJEMPLO 242A

5-cloro-6-((4-fluorotetrahidro-2H-piran-4-il)metilamino)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 40A en lugar de 4-fluoro-3-nitrobencenosulfonamida en el EJEMPLO 138D.

20 EJEMPLO 242B

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 242A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,71 (s, 1H), 8,41 (d, 1H), 8,07 (d, 1H), 7,93 (d, 1H), 7,60 (d, 1H), 7,51-7,53 (m, 2H), 7,40 (s, 1H), 7,33-7,35 (m, 2H), 7,03-7,05 (m, 2H), 6,68 (dd, 1H), 6,42 (dd, 1H), 6,16 (d, 1H), 3,77 (d, 1H), 3,69-3,71 (m, 3H), 3,48-3,53 (m, 2H), 3,07 (s, 4H), 2,76 (s, 2H), 2,14-2,20 (m, 6H), 1,96 (s, 2H), 1,65-1,76 (m, 4H), 1,38 (t, 2H), 0,93 (s, 6H).

30

EJEMPLO 243

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

35 EJEMPLO 243A

5-cloro-6-(1-ciclopropilpiperidin-4-ilamino)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 40A en lugar de 4-cloro-3-nitrobencenosulfonamida, 1-ciclopropilpiperidin-4-amina en lugar de diclorhidrato de 4-metilpiperazin-1-amina y Base de Hunig en lugar de N¹,N¹,N²,N²-tetrametiletan-1,2-diamina en el EJEMPLO 6A.

5

EJEMPLO 243B

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 243A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (400MHz, sulfóxido de dimetilo-d₆) □ 11,67 (s, 1H), 8,40 (d, 1H), 8,05 (d, 1H), 7,88 (d, 1H), 7,56 (d, 1H), 7,50 (m, 2H), 7,34 (d, 2H), 7,03 (d, 2H), 6,97 (br d, 1H), 6,66 (dd, 1H), 6,40 (m, 1H), 6,16 (d, 1H), 4,04 (m, 1H), 3,03 (br m, 6H), 2,73 (s, 2H), 2,42 (br m, 2H), 2,18 (br m, 6H), 1,95 (s, 2H), 1,80 (m, 3H), 1,62 (m, 2H), 1,38 (t, 2H), 0,91 (s, 6H), 0,47 (m, 2H), 0,40 (br m, 2H).

15

EJEMPLO 244

N-[(5-cloro-6-[(2S)-4-(cianometil)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-pirrol[2,3-b]piridin-5-iloxi)benzamida

20

EJEMPLO 244A

(S)-2-((3-cloro-5-sulfamoilpiridin-2-iloxi)metil)morfolina-4-carboxilato de tert-butilo

El compuesto del título se preparó utilizando (S)-2-(hidroximetil)-morfolina-4-carboxilato de tert-butilo en lugar de tetrahidro-2H-piran-4-il-metanol y EJEMPLO 40A en lugar de 4-fluoro-3-nitrobencenosulfonamida en el EJEMPLO 24A.

25

EJEMPLO 244B

(S)-5-cloro-6-(morfolin-2-ilmetoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 244A en lugar del EJEMPLO 113A en el EJEMPLO 134A.

30

EJEMPLO 244C

(S)-5-cloro-6-((4-(cianometil)morfolin-2-il)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 244B en lugar del EJEMPLO 134A y 2-bromoacetónitrilo en lugar de yoduro de metilo en el EJEMPLO 134B.

35

EJEMPLO 244D

N-[(5-cloro-6-[[[(2S)-4-(cianometil)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-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 244C en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridina-d₅) □ 12,99 (s, 1H), 9,09 (d, 1H), 8,70 (d, 1H), 8,42 (d, 1H), 8,12 (d, 1H), 7,66 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,75 (dd, 1H), 6,53 (d, 1H), 6,48 (m, 1H), 4,55 (dd, 1H), 4,43 (dd, 1H), 4,05 (m, 1H), 3,85 (d, 1H), 3,76 (s, 2H), 3,63 (dt, 1H), 3,06 (m, 4H), 2,91 (d, 1H), 2,77 (s, 2H), 2,58 (d, 1H), 2,51-2,44 (m, 2H), 2,26 (m, 2H), 2,14 (m, 4H), 1,97 (s, 2H), 1,39 (t, 2H), 0,94 (s, 6H).

EJEMPLO 245

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 245A

(S)-5-cloro-6-((4-(2-(dimetilamino)acetil)morfolin-2-il)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 244B en lugar del EJEMPLO 134A y clorhidrato de cloruro de 2-(dimetilamino)acetilo en lugar de yoduro de metilo en el EJEMPLO 134B.

EJEMPLO 245B

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 245A en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridina-d₅) □ 13,00 (s, 1H), 9,09 (d, 1H), 8,69 (s, 1H), 8,42 (s, 1H), 8,11 (t, 1H), 7,66 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,76 (s, 1H), 6,54 (s, 1H), 6,49 (s, 1H), 4,85-4,46 (m, 3H), 4,45-3,87 (m, 3H), 3,50 (m, 1H), 3,37 (dd, 1H), 3,21 (m, 2H), 3,07 (m, 4H), 2,86 (t, 1H), 2,77 (s, 2H), 2,27 (m, 8H), 2,14 (m, 4H), 1,97 (s, 2H), 1,39 (t, 2H), 0,94 (s, 6H).

EJEMPLO 246

N-[(5-cloro-6-[[[(2R)-4-(cianometil)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-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 246A

(R)-2-((3-cloro-5-sulfamoilpiridin-2-iloxi)metil)morfolina-4-carboxilato de tert-butilo

El compuesto del título se preparó utilizando (R)-2-(hidroximetil)-morfolina-4-carboxilato de tert-butilo en lugar de tetrahidro-2H-piran-4-il-metanol y EJEMPLO 40A en
5 lugar de 4-fluoro-3-nitrobenzenosulfonamida en el EJEMPLO 24A.

EJEMPLO 246B

(R)-5-cloro-6-(morfolin-2-ilmetoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 246A en lugar del
EJEMPLO 113A en el EJEMPLO 134A.

10

EJEMPLO 246C

(R)-5-cloro-6-((4-(cianometil)morfolin-2-il)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 246B en lugar del
EJEMPLO 134A y 2-bromoacetónitrilo en lugar de yoduro de metilo en el EJEMPLO 134B.

15

EJEMPLO 246D

N-[(5-cloro-6-[(2R)-4-(cianometil)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-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 246C en lugar del
EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridina-d₅) □ 12,99 (s, 1H), 9,09
(d, 1H), 8,70 (d, 1H), 8,42 (d, 1H), 8,12 (d, 1H), 7,66 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,75
(dd, 1H), 6,53 (d, 1H), 6,48 (m, 1H), 4,55 (dd, 1H), 4,43 (dd, 1H), 4,05 (m, 1H), 3,85 (d, 1H),
3,76 (s, 2H), 3,63 (dt, 1H), 3,06 (m, 4H), 2,91 (d, 1H), 2,77 (s, 2H), 2,58 (d, 1H), 2,51-2,44 (m,
25 2H), 2,26 (m, 2H), 2,14 (m, 4H), 1,97 (s, 2H), 1,39 (t, 2H), 0,94 (s, 6H).

EJEMPLO 247

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

30

EJEMPLO 247A

(R)-5-cloro-6-((4-(2-(dimetilamino)acetil)morfolin-2-il)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 246B en lugar del
EJEMPLO 134A y clorhidrato de cloruro de 2-(dimetilamino)acetilo en lugar de yoduro de
35 metilo en el EJEMPLO 134B.

EJEMPLO 247B

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

- 5 El compuesto del título se preparó utilizando el EJEMPLO 247A en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridina-d₅) □ 13,00 (s, 1H), 9,09 (d, 1H), 8,69 (s, 1H), 8,42 (s, 1H), 8,11 (t, 1H), 7,66 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,76 (s, 1H), 6,54 (s, 1H), 6,49 (s, 1H), 4,85-4,46 (m, 3H), 4,45-3,87 (m, 3H), 3,50 (m, 1H), 3,37 (dd, 1H), 3,21 (m, 2H), 3,07 (m, 4H), 2,86 (t, 1H), 2,77 (s, 2H), 2,27 (m, 8H), 2,14 (m, 4H),
10 1,97 (s, 2H), 1,39 (t, 2H), 0,94 (s, 6H).

EJEMPLO 248

- 4-(4-[(2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(5-fluoro-6-[(4-fluorotetrahydro-2H-piran-4-il)metoxi]piridin-3-il)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida
15

EJEMPLO 248A

5-bromo-3-fluoro-2-[(4-fluorotetrahydro-2H-piran-4-il)metoxi]piridina

- El compuesto del título se preparó utilizando 5-bromo-2,3-difluoropiridina en lugar de
20 4-fluoro-3-nitrobenzenosulfonamida y EJEMPLO 37C en lugar de (tetrahydro-2H-piran-4-il)metanol en el EJEMPLO 24A.

EJEMPLO 248B

5-fluoro-6-[(4-fluorotetrahydro-2H-piran-4-il)metoxi]piridin-3-ilcarbamato de tert-butilo

- 25 Se combinó EJEMPLO 248A (0,308 g), carbamato de tert-butilo (0,141 g), acetato de paladio(II) (0,011 g), Xantphos (0,043 g) y carbonato de cesio (0,489 g) con dioxano (5,0 mL) en un vial de 20 mL equipado con una barra de agitación magnética. Al vial se hizo pasar nitrógeno, se tapó y se agitó a 100°C durante la noche. Se agregó más acetato de paladio(II) (0,011 g), Xantphos (0,043 g) y carbamato de tert-butilo (0,141 g) y el calentamiento se
30 continuó a 100°C por 8 horas. La mezcla de reacción fría se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó (MgSO₄), se filtró y se concentró. El material concentrado se cromatografió sobre gel de sílice con 7-25% acetato de etilo en hexanos como eluyente.

35 EJEMPLO 248C

cloruro de 5-fluoro-6-[(4-fluorotetrahydro-2H-piran-4-il)metoxi]piridin-3-sulfonilo

Bajo enfriamiento con hielo, se agregó cloruro de tionilo (1,563 mL) por goteo a lo largo de 20 minutos a agua (9 mL). La mezcla se agitó por 12 horas para dar una solución que contenía SO₂. En forma separada, se agregó EJEMPLO 248B (0,295 g) a una mezcla de 1,4-dioxano (3,2 mL) y HCl concentrado (8 mL) a 0°C. Luego de agitar por 15 minutos, se
 5 agregó una solución de nitrito de sodio (0,065 g) en agua (2 mL) por goteo y la agitación se continuó a 0°C por 3 horas. Se agregó cloruro de cobre(I) (0,042 g) y luego la solución recién preparada de material diazotizado en forma secuencial a la solución que contenía SO₂ previamente formada. La solución resultante se agitó por 30 minutos y luego se extrajo con acetato de etilo (2 x 125 mL). Los extractos combinados se secaron (MgSO₄), se filtró y se
 10 concentró. El material concentrado se cromatografió sobre gel de sílice con 5% acetato de etilo en hexanos como eluyente.

EJEMPLO 248D

5-fluoro-6-((4-fluorotetrahidro-2H-piran-4-il)metoxi)piridin-3-sulfonamida

Se trató EJEMPLO 248C (0,08 g) en isopropanol (2 mL) a 0°C con hidróxido de
 15 amonio (1,697 mL), se agitó durante la noche y luego se concentró hasta secar. Se formó una lechada con el sólido obtenido en agua, se filtró, se enjuagó con agua y se secó bajo alto vacío para dar el compuesto del título.

EJEMPLO 248E

20 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-pirrololo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 248D en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500 MHz, piridina-d₅) □ 13,05 (s, 1H), 9,03 (d, 1H), 8,44 (dd, 1H), 8,41 (d, 1H), 8,10 (d, 1H), 7,67 (m, 1H), 7,65 (d, 1H), 7,44 (m, 2H), 7,07 (m, 2H), 6,77 (dd, 1H), 6,53 (d, 1H), 6,49 (dd, 1H), 4,55 (d, 2H), 3,80 (m, 4H), 3,08 (m, 4H), 2,77 (s, 2H), 2,26 (t, 2H), 2,14 (m, 4H), 1,97 (s, 2H), 1,88 (m, 4H), 1,39 (t, 2H), 0,94 (s, 6H).
 25

EJEMPLO 250

30 N-({5-cloro-6-[3-hidroxi-2-(hidroximetil)-2-metilpropoxi]piridin-3-il}sulfonil)-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 250A

35 5-cloro-6-((3-metiloxetan-3-il)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando (3-metiloxetan-3-il)metanol en lugar de (tetrahidro-2H-piran-4-il)metanol y EJEMPLO 40A en lugar de 4-fluoro-3-nitrobencenosulfonamida en el EJEMPLO 24A.

5 EJEMPLO 250B

N-({5-cloro-6-[3-hidroxi-2-(hidroximetil)-2-metilpropoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 250A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500 MHz, piridina-d₅) □ 13,05 (s, 1H), 9,22 (d, 1H), 8,51 (d, 1H), 8,42 (d, 1H), 8,09 (d, 1H), 7,66 (t, 2H), 7,43 - 7,46 (m, 2H), 7,04 - 7,09 (m, 2H), 6,75 (dd, 1H), 6,45 - 6,54 (m, 2H), 4,47 (s, 2H), 3,81 - 3,84 (m, 2H), 3,74 (d, 2H), 3,03 - 3,11 (m, 4H), 2,77 (s, 2H), 2,26 (t, 2H), 2,10 - 2,17 (m, 4H), 1,97 (s, 2H), 1,39 (t, 2H), 1,16 (s, 3H), 0,94 (s, 6H).

15

EJEMPLO 251

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]piridin-3-il}sulfonil)-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

20

EJEMPLO 251A

5-bromo-6-((4-fluorotetrahidro-2H-piran-4-il)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando (4-fluorotetrahidro-2H-piran-4-il)metanol en lugar de (tetrahidro-2H-piran-4-il)metanol y 5-bromo-6-cloropiridin-3-sulfonamida en lugar de 4-fluoro-3-nitrobencenosulfonamida en el EJEMPLO 24A.

25

EJEMPLO 251B

6-((4-fluorotetrahidro-2H-piran-4-il)metoxi)piridin-3-sulfonamida

A una suspensión de 5-bromo-6-((4-fluorotetrahidro-2H-piran-4-il)metoxi)piridin-3-sulfonamida (200 mg) y ciclohexeno (0,549 mL) en acetato de etilo (10 mL) se agregó paladio sobre carbono al 10% (57,6 mg). La suspensión se agitó por 60 minutos a 120°C. La mezcla de la reacción se filtró y se concentró. El producto se purificó mediante cromatografía flash de fase inversa (C18, 150g, 10%-100% acetonitrilo/H₂O/ácido trifluoroacético 0,1%).

35 EJEMPLO 251C

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)piridin-3-il]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 251B en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500 MHz, piridina-d₅) δ 13,06 (s, 1H), 9,29 (d, 1H), 8,50 (dd, 1H), 8,41 (d, 1H), 8,07 (d, 1H), 7,66 - 7,70 (m, 1H), 7,64 (d, 1H), 7,44 (d, 2H), 7,07 (d, 2H), 6,84 (d, 1H), 6,75 (dd, 1H), 6,52 (d, 1H), 6,49 (dd, 1H), 4,50 (d, 2H), 3,81 - 3,89 (m, 2H), 3,70 - 3,81 (m, 2H), 3,02 - 3,12 (m, 4H), 2,77 (s, 2H), 2,26 (t, 2H), 2,10 - 2,18 (m, 4H), 1,97 (s, 2H), 1,77 - 1,94 (m, 4H), 1,39 (t, 2H), 0,94 (s, 6H).

EJEMPLO 252

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-(1,3-difluoropropan-2-il)morfolin-2-il]metil)amino]-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 252A

(4-(1,3-difluoropropan-2-il)morfolin-2-il)metilcarbamato de tert-butilo

El compuesto del título se preparó utilizando 1,3-difluoropropan-2-ona en lugar de 4'-clorobifenil-2-carboxaldehído y morfolin-2-ilmetilcarbamato de tert-butilo en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

EJEMPLO 252B

(4-(1,3-difluoropropan-2-il)morfolin-2-il)metanamina

Una solución de EJEMPLO 252A (538 mg) en dioxano (4 mL) se trató con solución 4,0M de HCl en dioxano (1,8 mL). La reacción se agitó a temperatura ambiente durante la noche. La mezcla de la reacción se concentró bajo vacío y se usó sin purificación adicional.

EJEMPLO 252C

4-((4-(1,3-difluoropropan-2-il)morfolin-2-il)metilamino)-3-nitrobenzenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 252B en lugar de (tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

EJEMPLO 252D

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-(1,3-difluoropropan-2-il)morfolin-2-il]metil)amino]-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 252C en lugar del EJEMPLO 1F y EJEMPLO 3J en lugar del EJEMPLO 1E en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) δ 11,64 (s, 1H), 8,59 (t, 1H), 8,57 (d, 1H), 8,04 (d, 1H), 7,83 (dd, 1H), 7,51 (m, 3H), 7,33 (d, 2H), 7,07 (d, 1H), 7,03 (d, 2H), 6,66 (dd, 1H), 6,39 (m, 1H), 6,19 (d, 1H), 4,69 (t, 2H), 4,57 (t, 2H), 3,85 (m, 1H), 3,70 (m, 1H), 3,52 (m, 2H), 3,41 (m, 2H), 3,07 (br s, 4H), 2,91 (d, 1H), 2,74 (m, 3H), 2,59 (m, 1H), 2,43 (m, 1H), 2,20 (m, 4H), 2,15 (m, 2H), 1,95 (br s, 2H), 1,39 (t, 2H), 0,92 (s, 6H).

EJEMPLO 253

10 N-[(5-cloro-6-[[1-(cianometil)piperidin-4-il]metoxi]piridin-3-il)sulfonyl]-4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 253A

4-((3-cloro-5-sulfamoylpiridin-2-iloxi)metil)piperidin-1-carboxilato de tert-butilo

15 El compuesto del título se preparó utilizando 4-(hidroximetil)piperidin-1-carboxilato de tert-butilo en lugar de tetrahydro-2H-piran-4-il)metanol y EJEMPLO 40A en lugar de 4-fluoro-3-nitrobenzenosulfonamida en el EJEMPLO 24A.

EJEMPLO 253B

20 ditrifluoroacetato de 5-cloro-6-(piperidin-4-ilmetoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 253A en lugar del EJEMPLO 39A en el EJEMPLO 39B.

EJEMPLO 253C

25 5-cloro-6-((1-(cianometil)piperidin-4-il)metoxi)piridin-3-sulfonamida

Se combinó EJEMPLO 253B (0,061 g), 2-cloroacetronitrilo (0,017 g), carbonato de sodio (0,025 g) y N,N-dimetilformamida (1 mL) en un vial de 4-mL y se calentó a 60°C durante la noche. La mezcla de reacción fría se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó (MgSO₄), se filtró y se concentró. El material concentrado se 30 cromatografió sobre gel de sílice con metanol al 2-10% en CH₂Cl₂ como eluyente.

EJEMPLO 253D

N-[(5-cloro-6-[[1-(cianometil)piperidin-4-il]metoxi]piridin-3-il)sulfonyl]-4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

35 El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 253C en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (400 MHz,

piridina-d₅) □ 13,04 (s, 1H), 9,14 (d, 1H), 8,41 (d, 1H), 8,10 (d, 1H), 7,66 (t, 2H), 7,44 (m, 2H), 7,07 (m, 2H), 6,74 (dd, 1H), 6,50 (m, 2H), 4,18 (d, 2H), 3,64 (s, 2H), 3,05 (s, 4H), 2,77 (m, 4H), 2,24 (m, 4H), 2,13 (m, 4H), 1,97 (s, 2H), 1,69 (m, 3H), 1,41 (m, 4H), 0,93 (s, 6H).

5 EJEMPLO 254

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)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

10 EJEMPLO 254A

(R)-3-(2-nitro-4-sulfamoilfenilamino)pirrolidin-1-carboxilato de tert-butilo

El compuesto del título se preparó utilizando (R)-3-aminopirrolidin-1-carboxilato de tert-butilo en lugar de 1-(tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

15 EJEMPLO 254B

(R)-3-nitro-4-(pirrolidin-3-ilamino)bencenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 254A en lugar del EJEMPLO 113A en el EJEMPLO 134A.

20 EJEMPLO 254C

(R)-4-(1-(2-(2-metoxietoxi)etil)pirrolidin-3-ilamino)-3-nitrobencenosulfonamida

A una solución de (R)-3-nitro-4-(pirrolidin-3-ilamino)bencenosulfonamida (440 mg) en N,N-dimetilformamida (10 mL) se agregó carbonato de sodio (132 mg) y 1-bromo-2-(2-metoxietoxi)etano (0,155 mL). La mezcla de la reacción se calentó a 60°C por 18 horas y luego de un tratamiento acuoso posterior, el producto crudo se purificó sobre gel de sílice con un gradiente de metanol entre 2,5 y 10% en cloruro de metileno para dar el compuesto del título.

EJEMPLO 254D

30 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)-2-(1H-pirrol[2,3-b]piridin-5-il-oxi)benzamida

35 El compuesto del título se preparó utilizando el EJEMPLO 254C en lugar del EJEMPLO 130C en el EJEMPLO 130D. 1H NMR (500 MHz, piridina-d₅) □ 12,96 (m, 1H), 9,25 (m, 1H), 8,57 (d, 1H), 8,43 (d, 1H), 8,34 (dd, 1H), 8,11 (d, 1H), 7,66 (t, 1H) 7,64 (d, 1H), 7,44 (d, 2H), 7,07 (d, 2H), 6,82 (d, 1H), 6,76 (dd, 1H), 6,55 (m, 1H), 6,47 (m, 1H), 5,26 (br s,

1H), 4,02 (m, 1H), 3,63 (m, 4H), 3,53 (m, 2H), 3,28 (s, 3H), 3,07 (m, 4H), 2,89 - 2,81 (m, 2H), 2,78 (s, 2H), 2,75 - 2,66 (m, 3H), 2,37 (m, 1H), 2,26 (m, 2H), 2,24 - 2,18 (m, 1H), 2,15 (m, 4H), 1,97 (s, 2H), 1,65 (m, 1H), 1,39 (t, 2H), 0,94 (s, 6H).

EJEMPLO 255

- 5 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]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 255A

- 10 (R)-4-(1-(2-(dimetilamino)acetil)pirrolidin-3-ilamino)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando cloruro de 2-(dimetilamino)acetilo, ácido clorhídrico en lugar de 1-bromo-2-(2-metoxietoxi)etano en el EJEMPLO 254C excepto que la reacción se agitó a temperatura ambiente por 18 horas.

- 15 EJEMPLO 255B

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]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

- 20 El compuesto del título se preparó utilizando el EJEMPLO 255A en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500 MHz, piridina - d₅) □ 13,01 (d, 1H), 9,26 (m, 1H), 8,46 - 8,33 (m, 3H), 8,14 (d, 1H), 7,66 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 7,01 - 6,89 (m, 1H), 6,76 (dd, 1H), 6,55 (m, 1H), 6,48 (m, 1H), 5,32 (br s, 1H), 4,27 - 4,14 (m, 1H), 4,05 - 3,95 (m, 1H), 3,82 - 3,62 (m, 3H), 3,27 - 3,15 (m, 2H), 3,07 (m, 4H), 2,77 (s, 2H), 2,34 (2, 3H), 2,32 (s, 3H), 2,30 - 2,20 (m, 3H), 2,15 (m, 4H), 1,97 (s, 2H), 1,87 - 1,81 (m, 1H), 1,39 (t, 2H), 0,94 (s, 6H).

EJEMPLO 256

4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(3-nitro-4-{{1-(oxetan-3-il)azetidin-3-il}amino}fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

- 30 EJEMPLO 256A

3-(2-nitro-4-sulfamoilfenilamino)azetidin-1-carboxilato de tert-butilo

El compuesto del título se preparó utilizando 3-aminoazetidin-1-carboxilato de tert-butilo en lugar de diclorhidrato de 4-metilpiperazin-1-amina en el EJEMPLO 6A.

- 35 EJEMPLO 256B

4-(azetidin-3-ilamino)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 256A en lugar de (S)-4,4-difluoropirrolidin-1,2-dicarboxilato de 1-tert-butilo 2-metilo en el EJEMPLO 168A.

EJEMPLO 256C

5 3-nitro-4-(1-(oxetan-3-il)azetidin-3-ilamino)bencenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 256B en lugar de piperazin-1-carboxilato de tert-butilo y 3-oxetanona en lugar de 4'-clorobifenil-2-carboxaldehído en el EJEMPLO 1A.

10 EJEMPLO 256D

4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(3-nitro-4-{{1-(oxetan-3-il)azetidin-3-il}amino}fenil)sulfonyl]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 256C en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500 MHz, piridina-d₅) □ 13,04 (s, 1H), 9,27 (d, 1H), 8,62 (d, 1H), 8,42 (d, 1H), 8,35 (dd, 1H), 8,09 (d, 1H), 7,67 (m, 1H), 7,63 (d, 1H), 7,44 (m, 2H), 7,07 (m, 2H), 6,76 (dd, 1H), 6,67 (d, 1H), 6,55 (d, 1H), 6,48 (dd, 1H), 4,66 (t, 2H), 4,58 (m, 2H), 4,23 (m, 1H), 3,71 (m, 3H), 3,12 (dd, 2H), 3,07 (m, 4H), 2,77 (s, 2H), 2,26 (t, 2H), 2,14 (t, 4H), 1,97 (s, 2H), 1,39 (t, 2H), 0,94 (s, 6H).

20 EJEMPLO 257

N-[(5-cloro-6-{{1-(cianometil)-4-fluoropiperidin-4-il}metoxi}piridin-3-il)sulfonyl]-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

25 EJEMPLO 257A

4-((3-cloro-5-sulfamoylpiridin-2-iloxi)metil)-4-fluoropiperidin-1-carboxilato de tert-butilo

El compuesto del título se preparó utilizando el EJEMPLO 126A en lugar de (tetrahidro-2H-piran-4-il)metanol y EJEMPLO 40A en lugar de 4-fluoro-3-nitrobencenosulfonamida en el EJEMPLO 24A.

30

EJEMPLO 257B

ditrifluoroacetato de 5-cloro-6-((4-fluoropiperidin-4-il)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 257A en lugar del EJEMPLO 39A en el EJEMPLO 39B.

35

EJEMPLO 257C

5-cloro-6-((1-(cianometil)-4-fluoropiperidin-4-il)metoxi)piridin-3-sulfonamida

Se trató EJEMPLO 257B (0,166 g) en acetonitrilo (3 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 cromatografió sobre gel de sílice con metanol entre 0 y 3% en CH₂Cl₂ como eluyente. Se formó una lechada con el sólido obtenido en agua, se filtró, se enjuagó con agua y éter dietílico, y se secó en un horno de vacío a 80°C.

EJEMPLO 257D

N-[(5-cloro-6-[[1-(cianometil)-4-fluoropiperidin-4-il]metoxi]piridin-3-il)sulfonyl]-4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 257C en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (400 MHz, piridina-d₅) □ 13,05 (s, 1H), 9,12 (d, 1H), 8,72 (d, 1H), 8,41 (d, 1H), 8,10 (d, 1H), 7,66 (m, 2H), 7,44 (m, 2H), 7,07 (m, 2H), 6,75 (dd, 1H), 6,50 (m, 2H), 4,49 (d, 2H), 3,72 (s, 2H), 3,06 (m, 4H), 2,77 (s, 2H), 2,73 (m, 4H), 2,26 (t, 2H), 2,13 (m, 4H), 2,07 (m, 2H), 1,90 (m, 4H), 1,39 (t, 2H), 0,93 (s, 6H).

EJEMPLO 258

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]sulfonyl]-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 258A

(S)-2-(tosiloximetil)morfolina-4-carboxilato de tert-butilo

A una solución de (S)-2-(hidroximetil)morfolina-4-carboxilato de tert-butilo (1 g) en diclorometano (50 mL) se agregó trietilamina (1,604 mL) y cloruro de 4-metilbencen-1-sulfonyl (1,097 g). La mezcla se agitó a temperatura ambiente bajo nitrógeno por 72 horas. La reacción se diluyó con cloruro de metileno (50 mL) y salmuera (100 mL). La capa de salmuera se extrajo con cloruro de metileno (75 mL). Los orgánicos combinados se secaron sobre sulfato de sodio, se filtró y se concentró. El material crudo se purificó en una columna de gel de sílice eluyendo con un gradiente de 15-65 % acetato de etilo en hexano para dar el compuesto del título.

EJEMPLO 258B

(S)-2-(azidometil)morfolina-4-carboxilato de tert-butilo

Una solución de EJEMPLO 258A (1,66 g) y azida de sodio (0,581 g) en N,N-dimetilformamida anhidra (10 mL) se agitó a 90 °C por 4 horas. La mezcla se enfrió y se concentró hasta secar. El residuo se colocó en solución acuosa al 5% de carbonato de sodio y se extrajo con cloruro de metileno. La solución orgánica se secó (MgSO₄), se filtró y se
5 concentró para dar un sólido.

EJEMPLO 258C

(R)-2-(aminometil)morfolina-4-carboxilato de tert-butilo

Este compuesto se obtuvo mediante la hidrogenación de EJEMPLO 258B bajo 60 psi
10 de hidrógeno sobre paladio sobre carbono al 10% en metanol por 24 horas, seguido por la filtración y evaporación del solvente.

EJEMPLO 258D

(R)-2-((2-nitro-4-sulfamoilfenilamino)metil)morfolina-4-carboxilato de tert-butilo

El compuesto del título se preparó utilizando el EJEMPLO 258C en lugar de
15 (tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

EJEMPLO 258E

(S)-4-(morfolin-2-ilmetilamino)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 258D en lugar del
20 EJEMPLO 113A en el EJEMPLO 134A.

EJEMPLO 258F

(R)-4-((4-(2-(dimetilamino)acetil)morfolin-2-il)metilamino)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 258E en lugar del
25 EJEMPLO 134A y clorhidrato de cloruro de 2-(dimetilamino)acetilo en lugar de yoduro de metilo en el EJEMPLO 134B.

EJEMPLO 258G

30 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)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 258F en lugar del
EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridina-d₅) □ 13,00 (s, 1H), 9,27
35 (d, 1H), 8,87 (bs, 1H), 8,43 (d, 1H), 8,34 (dd, 1H), 8,10 (dd, 1H), 7,66 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,94 (dd, 1H), 6,75 (d, 1H), 6,54 (s, 1H), 6,48 (s, 1H), 4,55 (dd, 1H), 4,20 (dd,

1H), 3,95-3,76 (m, 2H), 3,60-3,40 (m, 3H), 3,32 (dd, 1H), 3,25-3,12 (m, 2H), 3,07 (m, 4H), 2,80 (m, 1H), 2,77 (s, 2H), 2,26 (s, 6H), 2,23 (s, 2H), 2,14 (m, 4H), 1,97 (s, 2H), 1,39 (t, 2H), 0,94 (s, 6H).

5 EJEMPLO 259

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]sulfonyl}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 259A

10 (R)-2-(tosiloximetil)morfolina-4-carboxilato de tert-butilo

El compuesto del título se preparó utilizando (R)-2-(hidroximetil)morfolina-4-carboxilato de tert-butilo en lugar de (S)-2-(hidroximetil)morfolina-4-carboxilato de tert-butilo en el EJEMPLO 258A.

15 EJEMPLO 259B

(R)-2-(azidometil)morfolina-4-carboxilato de tert-butilo

El compuesto del título se preparó utilizando el EJEMPLO 259A en lugar del EJEMPLO 258A en el EJEMPLO 258B.

20 EJEMPLO 259C

(S)-2-(aminometil)morfolina-4-carboxilato de tert-butilo

El compuesto del título se preparó utilizando el EJEMPLO 259B en lugar del EJEMPLO 258B en el EJEMPLO 258C.

25 EJEMPLO 259D

(S)-2-((2-nitro-4-sulfamoiifenilamino)metil)morfolina-4-carboxilato de tert-butilo

El compuesto del título se preparó utilizando el EJEMPLO 259C en lugar de (tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

30 EJEMPLO 259E

(R)-4-(morfolin-2-ilmetilamino)-3-nitrobenzenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 259D en lugar del EJEMPLO 113A en el EJEMPLO 134A.

35 EJEMPLO 259F

(S)-4-((4-(2-(dimetilamino)acetil)morfolin-2-il)metilamino)-3-nitrobenzenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 259E en lugar del EJEMPLO 134A y clorhidrato de cloruro de 2-(dimetilamino)acetilo en lugar de yoduro de metilo en el EJEMPLO 134B.

EJEMPLO 259G

5 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)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 259F en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridina-d₅) □ 13,00 (s, 1H), 9,27
10 (d, 1H), 8,87 (bs, 1H), 8,43 (d, 1H), 8,34 (dd, 1H), 8,10 (dd, 1H), 7,66 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,94 (dd, 1H), 6,75 (d, 1H), 6,54 (s, 1H), 6,48 (s, 1H), 4,55 (dd, 1H), 4,20 (dd, 1H), 3,95-3,76 (m, 2H), 3,60-3,40 (m, 3H), 3,32 (dd, 1H), 3,25-3,12 (m, 2H), 3,07 (m, 4H), 2,80 (m, 1H), 2,77 (s, 2H), 2,26 (s, 6H), 2,23 (s, 2H), 2,14 (m, 4H), 1,97 (s, 2H), 1,39 (t, 2H), 0,94 (s, 6H).

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EJEMPLO 260

N-[(5-cloro-6-([1-(N,N-dimetilglicil)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-pirrol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 260A

5-cloro-6-((1-(2-(dimetilamino)acetil)piperidin-4-il)metoxi)piridin-3-sulfonamida

EJEMPLO 253B (0,061 g), cloruro de 2-(dimetilamino)acetilo, ácido clorhídrico (0,061 g), y carbonato de sodio (0,032 g) se combinaron en un vial de 4 mL con N,N-dimetilformamida (2 mL). La mezcla se agitó a temperatura ambiente por 3 días. Se agregó
25 más cloruro de 2-(dimetilamino)acetilo, ácido clorhídrico (0,037 g), carbonato de sodio (0,032 g) y N,N-dimetilformamida (1 mL) y la agitación se continuó por 24 horas. La mezcla de la reacción se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó (MgSO₄), se filtró, se concentró y se cromatografió sobre gel de sílice con metanol entre 0 y 20% en
30 CH₂Cl₂ como eluyente.

35 EJEMPLO 260B

N-[(5-cloro-6-[[1-(N,N-dimetilglicil)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-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 260A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (400 MHz, piridina-d₅) □ 12,91 (s, 1H), 9,16 (d, 1H), 8,75 (d, 1H), 8,51 (d, 1H), 8,33 (d, 1H), 7,70 (d, 1H), 7,62 (d, 1H), 7,45 (m, 2H), 7,09 (m, 2H), 6,77 (dd, 1H), 6,60 (d, 1H), 6,45 (d, 1H), 4,81 (d, 1H), 4,15 (m, 3H), 3,24 (m, 2H), 3,04 (m, 4H), 2,89 (m, 1H), 2,79 (s, 2H), 2,53 (m, 1H), 2,29 (m, 6H), 2,26 (m, 2H), 2,18 (m, 4H), 1,98 (m, 2H), 1,91 (m, 1H), 1,71 (m, 2H), 1,39 (t, 2H), 1,25 (m, 2H), 0,94 (s, 6H).

EJEMPLO 261

N-[(5-cloro-6-[[3(R)-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-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 261A

(R)-3-(3-cloro-5-sulfamoilpiridin-2-iloxi)pirrolidin-1-carboxilato de tert-butilo

El compuesto del título se preparó utilizando el EJEMPLO 40A en lugar de 4-fluoro-3-nitrobenzenosulfonamida y (R)-3-hidroxipirrolidin-1-carboxilato de tert-butilo en lugar de (tetrahidro-2H-piran-4-il)metanol en el EJEMPLO 24A.

EJEMPLO 261B

(R)-5-Cloro-6-(pirrolidin-3-iloxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 261A en lugar de (4-(1,3-difluoropropan-2-il)morfolin-2-il)metilcarbarnato de tert-butilo en el EJEMPLO 252B.

EJEMPLO 261C

(R)-5-cloro-6-(1-(2,2-difluoroetil)pirrolidin-3-iloxi)piridin-3-sulfonamida

Una mezcla de EJEMPLO 261B (353 mg), 1, 1-difluoro-2-yodoetano (268 mg), carbonato de sodio (283 mg) en N,N-dimetilformamida (10mL) se calentó a 80°C durante la noche. La mezcla de la 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 magnesio, se filtró, y se concentró. El residuo se cargó sobre columna de gel de sílice y se eluyó usando un gradiente de metanol entre 0,5 y 3 % en diclorometano para dar el compuesto del título.

EJEMPLO 261D

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 261C en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (400MHz, sulfóxido de dimetilo-d₆) □ 11,55 (s, 1 H), 8,04 (s, 1 H), 7,95 (d, 1 H), 7,58 (d, 1 H), 7,44 (t, 1 H), 7,35 (m, 3 H), 7,05 (d, 2 H), 6,64 (dd, 1 H), 6,33 (m, 1 H), 6,24 (d, 1 H), 6,25-5,97 (m, 1 H), 5,39 (m, 1 H), 2,98 (m, 6 H), 2,86 (m, 6 H), 2,55 (m, 2 H), 2,24 (m, 7 H), 1,96 (s, 2 H), 1,83 (m, 1 H), 1,39 (t, 2 H), 0,93 (s, 6 H)

10 EJEMPLO 262

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]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 262A

15 (R)-4-(1-(cianometil)pirrolidin-3-ilamino)-3-nitrobenzenosulfonamida

El compuesto del título se preparó utilizando 2-bromoacetónitrilo en lugar de 1-bromo-2-(2-metoxietoxi)etano en el EJEMPLO 254C.

EJEMPLO 262B

20 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]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 262A en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (400 MHz, piridina - d₅) □ 13,03 (s, 1H), 9,27 (d, 1H), 8,53 (d, 1H), 8,43 (d, 1H), 8,35 (dd, 1H), 8,10 (d, 1H), 7,67 - 7,64 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,81 (d, 1H), 6,76 (dd, 1H), 6,54 (m, 1H), 6,48 (m, 1H), 5,15 (br s, 1H), 4,10 (m, 1H), 3,89 (s, 2H), 3,07 (m, 4H), 2,93 - 2,86 (m, 2H), 2,80 - 2,77 (m, 3H), 2,61 - 2,53 (m, 1H), 2,31 - 2,21 (m, 3H), 2,14 (m, 4H), 1,97 (s, 2H), 1,75 - 1,68 (m, 1H), 1,39 (t, 2H), 0,94 (m, 6H).

30 EJEMPLO 263

4-{4-[(4'-clorobifenil-2-il)metil]-4-metoxipiperidin-1-il}-N-[(5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 263A

35 1-oxa-6-azaespiro[2,5]octan-6-carboxilato de tert-butilo

Se agregó hidruro de sodio (6,63 g, 60% en aceite mineral) a yoduro de trifenilsulfoxonio (36,5 g) en sulfóxido de dimetilo (150 mL) y tetrahidrofurano (150 mL), y se agitó por 30 minutos. Se agregó 4-oxopiperidin-1-carboxilato de tert-butilo (25,4 g) y la reacción se agitó por 3 horas. La reacción se vertió en agua (800 mL) y se extrajo tres veces con éter. Los extractos combinados se lavaron tres veces con agua, y salmuera, se secó sobre Na_2SO_4 , se filtró, y se concentró para dar el producto crudo el cual se usó sin purificación adicional.

EJEMPLO 263B

10 4-(2-(benciloxi)bencil)-4-hidroxipiperidin-1-carboxilato de tert-butilo

Se agregó bromuro de (2-(Benciloxi)fenil)magnesio (33,8 mL, 1M) a una solución de EJEMPLO 263A (6,0 g) y CuI (1,07 g) en tetrahidrofurano (220 mL) a 0°C por 10 minutos. La reacción se detuvo con solución amortiguadora de pH 7 (20 mL), se extrajo dos veces con éter, y los extractos combinados se lavaron con salmuera, se secó sobre Na_2SO_4 , se filtró, y se concentró. El producto crudo se cromatografió sobre gel de sílice usando acetato de etilo al 2-20% en hexanos para dar el compuesto del título.

EJEMPLO 263C

4-hidróxi-4-(2-hidroxibencil)piperidin-1-carboxilato de tert-butilo

20 Se agregó EJEMPLO 263B (11,5 g) y metanol (120 mL) a Níquel de Raney (1,150 g) en una botella de presión SS de 250 mL y se agitó por 1 hora a 30 psi bajo hidrógeno. La mezcla se filtró a través de una membrana de nylon y la solución se concentró para dar el compuesto del título.

EJEMPLO 263D

25 4-hidroxi-4-(2-(trifluorometilsulfonilo)xi)bencil)piperidin-1-carboxilato de tert-butilo

Una mezcla de EJEMPLO 263C (4,6 g), N-fenilbis(trifluorometansulfonimida) (5,88 g), y Base de Hunig (2,88 mL) en diclorometano (100 mL) se agitó por 24 horas. La mezcla se concentró y se cromatografió sobre gel de sílice usando acetato de etilo al 5-50% en hexanos para dar el compuesto del título.

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EJEMPLO 263E

4-((4'-clorobifenil-2-il)metil)-4-hidroxipiperidin-1-carboxilato de tert-butilo

Una mezcla de EJEMPLO 263D (4,3 g), ácido 4-clorofenilborónico (1,84 g), K_3PO_4 (2,91 g), y [1,1'-bis(difenilfosfino)ferrocen]dicloropaladio(II) (0,36 g) en 2-metiltetrahidrofurano (50 mL) se agitó a 70°C por 24 horas. La reacción se enfrió y se detuvo con agua (50 mL), se extrajo dos veces con éter, y los extractos combinados se lavaron con salmuera, se secó

sobre Na_2SO_4 , se filtró, y se concentró. El producto crudo se cromatografió sobre gel de sílice usando acetato de etilo al 5-30% en hexanos para dar el compuesto del título.

EJEMPLO 263F

5 4-((4'-clorobifenil-2-il)metil)-4-metoxipiperidin-1-carboxilato de tert-butilo

Se agregó hidruro de sodio (0,36 g, 60% en aceite mineral) a EJEMPLO 263E (4,3 g), en tetrahidrofurano (40 mL) y la reacción se agitó por 10 minutos. Se agregó hexametilfosforamida (5 mL) y CH_3I (2,34 mL) y la reacción se agitó a 50°C por 18 horas. La reacción se enfrió y se detuvo con agua (50 mL), se extrajo dos veces con éter, y los
10 extractos combinados se lavaron con salmuera, se secó sobre Na_2SO_4 , se filtró, y se concentró. El producto crudo se cromatografió sobre gel de sílice usando 5-25% acetato de etilo en hexanos para dar el compuesto del título.

EJEMPLO 263G

15 4-((4'-clorobifenil-2-il)metil)-4-metoxipiperidina

El compuesto del título se preparó utilizando el EJEMPLO 263F en lugar del EJEMPLO 1A en el EJEMPLO 1B.

EJEMPLO 263H

20 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((4'-clorobifenil-2-il)metil)-4-metoxipiperidin-1-il)benzoato de metilo

Una solución de EJEMPLO 263G (1,4 g), EJEMPLO 3H (1,06 g) y Base de Hunig (0,75 mL) en sulfóxido de dimetilo (20 mL) se agitó a 120°C por 18 horas. La reacción se enfrió y se detuvo con agua (200 mL), se extrajo tres veces con éter, y los extractos
25 combinados se lavaron tres veces con agua, y salmuera, se secó sobre Na_2SO_4 , se filtró, y se concentró. El producto crudo se cromatografió sobre gel de sílice usando acetato de etilo al 5-50% en hexanos para dar el compuesto del título.

EJEMPLO 263I

30 ácido 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((4'-clorobifenil-2-il)metil)-4-metoxipiperidin-1-il)benzoico

El compuesto del título se preparó utilizando el EJEMPLO 263H en lugar del EJEMPLO 3I en el EJEMPLO 3J.

35 EJEMPLO 263J

4-{4-[(4'-clorobifenil-2-il)metil]-4-metoxipiperidin-1-il}-N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 263I en lugar del EJEMPLO 1E y EJEMPLO 96A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300MHz, sulfóxido de dimetilo-d₆) □ 11,71 (s, 1H), 11,58 (br s, 1H), 8,58 (d, 1H), 8,28 (d, 1H), 8,05 (d, 1H), 7,56 (d, 1H), 7,52 (m, 1H), 7,46 (d, 1H), 7,44 (d, 2H), 7,28 (m, 5H), 7,11 (dd, 1H), 6,62 (dd, 1H), 6,41 (dd, 1H), 6,11 (d, 1H), 4,54 (d, 2H), 3,75 (m, 2H), 3,59 (m, 2H), 3,20 (m, 2H), 2,97 (s, 3H), 2,81 (m, 2H), 2,74 (m, 2H), 1,89 (m, 2H), 1,83 (m, 2H), 1,36 (m, 2H), 1,09 (m, 2H).

EJEMPLO 264

4-{4-[(4'-clorobifenil-2-il)metil]-4-metoxipiperidin-1-il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 263I en lugar del EJEMPLO 1E en el EJEMPLO 1G. ¹H NMR (300MHz, sulfóxido de dimetilo-d₆) □ 11,71 (s, 1H), 11,40 (br s, 1H), 8,62 (t, 1H), 8,58 (d, 1H), 8,03 (d, 1H), 7,81 (dd, 1H), 7,54 (m, 2H), 7,44 (m, 3H), 7,28 (m, 5H), 7,13 (dd, 1H), 6,62 (dd, 1H), 6,41 (dd, 1H), 6,11 (d, 1H), 3,85 (dd, 2H), 3,31 (m, 4H), 3,20 (m, 2H), 2,97 (s, 3H), 2,81 (m, 2H), 2,73 (m, 2H), 1,89 (m, 1H), 1,62 (m, 2H), 1,38 (m, 2H), 1,25 (m, 2H), 1,09 (m, 2H).

EJEMPLO 265

4-(4-{{9-(4-clorofenil)-3-(1,3-difluoropropan-2-il)-3-azaespiro[5,5]undec-8-en-8-il}metil}piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 265A

4-(piperidin-1-ilmetil)en)piperidin-1-carboxilato de bencilo

A una solución de 4-formilpiperidin-1-carboxilato de bencilo (12,5g) en tolueno (120 mL) se agregó piperidina (6,46g). La mezcla se agitó a reflujo bajo una trampa Dean-Stark durante la noche. La mezcla luego se concentró bajo vacío y el residuo se usó directamente en el siguiente paso.

EJEMPLO 265B

9-oxo-3-azaespiro[5,5]undec-7-en-3-carboxilato de bencilo

A una solución de EJEMPLO 265A (15,88g) en etanol (300 mL) se agregó but-3-enona (3,89 g). La mezcla se agitó a reflujo durante la noche. Luego se agregó ácido acético

(30 mL) a la mezcla la cual se agitó a reflujo nuevamente durante la noche. La mezcla luego se concentró bajo vacío y el residuo se diluyó con acetato de etilo (400 mL) y se lavó con agua y salmuera y se secó sobre Na_2SO_4 . Luego de la filtración y evaporación del solvente, la purificación de columna dio el compuesto del título.

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EJEMPLO 265C

9-hidroxi-3-azaespiro[5,5]undecan-3-carboxilato de bencilo

Se agregó EJEMPLO 265B (21 g) y tetrahidrofurano (160 mL) a Pt-C al 5% húmedo (3,15 g) en una botella de presión de 250 mL y se agitó por 1 hora a 30 psi y temperatura ambiente. La mezcla se filtró a través de una membrana de nylon y el material filtrado se concentró bajo vacío para dar el compuesto del título.

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EJEMPLO 265D

9-oxo-3-azaespiro[5,5]undecan-3-carboxilato de bencilo

A una solución de EJEMPLO 265C (8,0 g) en diclorometano (200 mL) se agregó Periodinano de Dess-Martin (11,2 g). La mezcla se agitó durante la noche. La mezcla se diluyó con acetato de etilo (400 mL) y se lavó con NaOH acuoso 2N, agua, y salmuera. Luego de secar sobre Na_2SO_4 y filtrar, la concentración del solvente dio el producto crudo el cual se usó directamente en la siguiente reacción sin purificación adicional.

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EJEMPLO 265E

9-cloro-8-formil-3-azaespiro[5,5]undec-8-en-3-carboxilato de bencilo

Se agregó oxiclورو de fósforo (2,33 mL) por goteo a una solución fría (0°C) de EJEMPLO 265D (7,5 g) en N,N-dimetilformamida (10 mL) y diclorometano (30 mL). La mezcla luego se agitó durante la noche antes de diluirse con acetato de etilo (300 mL) y se lavó con acetato de sodio acuoso, agua (3x), y salmuera y se secó sobre Na_2SO_4 . Luego de la filtración y concentración, el producto crudo se usó directamente en la siguiente reacción sin purificación adicional.

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EJEMPLO 265F

9-(4-clorofenil)-8-formil-3-azaespiro[5,5]undec-8-en-3-carboxilato de bencilo

A una mezcla de ácido 4-clorofenilborónico (5,94 g), EJEMPLO 265E (11,01 g), acetato de paladio(II) (142 mg), K_2CO_3 (13,2 g) y bromuro de tetrabutilamonio (10,2 g) se agregó agua (120 mL). La mezcla se agitó a 50°C durante la noche. La mezcla se diluyó con acetato de etilo (400 mL) y se lavó con agua (3x) y salmuera y se secó sobre Na_2SO_4 . Luego

35

de la filtración y concentración, el residuo se cargó en una columna y se eluyó con acetato de etilo entre 5 y 20% en hexano para dar el compuesto del título.

EJEMPLO 265G

- 5 8-((4-(3-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(metoxicarbonil)fenil)piperazin-1-il)metil)-9-(4-clorofenil)-3-azaespiro[5,5]undec-8-en-3-carboxilato de bencilo

A una solución de EJEMPLO 15F (1,37 g) y EJEMPLO 265F (1,65 g) en diclorometano (20 mL) se agregó triacetoxiborhidruro de sodio (1,24 g). La mezcla se agitó durante la noche. La mezcla se diluyó con acetato de etilo (200 mL) y se lavó con NaOH acuoso 2N, agua y salmuera. Luego de secar sobre Na₂SO₄, la mezcla se filtró y el solvente se evaporó bajo vacío para dar el compuesto del título.

EJEMPLO 265H

- 15 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((9-(4-clorofenil)-3-azaespiro[5,5]undec-8-en-8-il)metil)piperazin-1-il)benzoato de metilo

Se agregó EJEMPLO 265G (2 g) y tetrahidrofurano (10 mL) a Pd(OH)₂-C al 20%, húmedo (0,400 g) en una botella de presión de 50 mL y se agitó por 16 horas a 30 psi y temperatura ambiente. La mezcla se filtró a través de una membrana de nylon y la evaporación del solvente dio el compuesto del título.

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EJEMPLO 265I

- 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((9-(4-clorofenil)-3-(1,3-difluoropropan-2-il)-3-azaespiro[5,5]undec-8-en-8-il)metil)piperazin-1-il)benzoato de metilo

A una solución de EJEMPLO 265H (320 mg) en diclorometano (5 mL) se agregó 1, 3-difluoroacetona (139 mg) y triacetoxiborhidruro de sodio (157 mg). La mezcla se agitó durante la noche. La mezcla se diluyó con acetato de etilo (200 mL) y se lavó con NaOH acuoso 2N, agua y salmuera. Luego de secar sobre Na₂SO₄, la mezcla se filtró y el solvente se evaporó bajo vacío para dar el compuesto del título.

EJEMPLO 265J

- 30 ácido 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((9-(4-clorofenil)-3-(1,3-difluoropropan-2-il)-3-azaespiro[5,5]undec-8-en-8-il)metil)piperazin-1-il)benzoico

A una solución de EJEMPLO 265I (320 mg) en tetrahidrofurano (4 mL) y metanol (2 mL) se agregó LiOH H₂O (120 mg) y la solución se agitó durante la noche. La reacción se enfrió, se neutralizó cuidadosamente con HCl acuoso 1N y se extrajo con diclorometano (3x

35

50 mL). Las capas orgánicas combinadas se lavaron con salmuera (25 mL), se secó sobre sulfato de sodio, se filtró y se concentró bajo vacío para dar el compuesto del título.

EJEMPLO 265K

- 5 4-(4-([9-(4-clorofenil)-3-(1,3-difluoropropan-2-il)-3-azaespiro[5,5]undec-8-en-8-il]metil)piperazin-1-il)-N-([3-nitro-4-[(tetrahydro-2H-piran-4-ilmetil)amino]fenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 265J en lugar del EJEMPLO 1E en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) δ 11,61 (s, 1 H), 8,49 (d, 2 H), 7,72 (m, 1 H), 7,49 (m, 2 H), 7,32 (d, 2 H), 7,07 (m, 3 H), 6,65 (dd, 1 H), 6,35 (d, 1 H), 6,20 (m, 1 H), 4,66 (m, 2 H), 4,50 (m, 2 H), 3,84 (m, 2 H), 3,04 (m, 5 H), 2,70 (m, 6 H), 2,23 (m, 6 H), 2,00 (m, 4 H), 1,35 (m, 12 H).

EJEMPLO 266

- 15 4-(4-([9-(4-clorofenil)-3-isopropil-3-azaespiro[5,5]undec-8-en-8-il]metil)piperazin-1-il)-N-([3-nitro-4-[(tetrahydro-2H-piran-4-ilmetil)amino]fenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 266A

- 20 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((9-(4-clorofenil)-3-isopropil-3-azaespiro[5,5]undec-8-en-8-il)metil)piperazin-1-il)benzoato de metilo

A una solución de EJEMPLO 265H (320 mg) en diclorometano (5 mL) se agregó acetona (143 mg) y triacetoxiborhidruro de sodio (157 mg). La mezcla se agitó durante la noche. La mezcla se diluyó con acetato de etilo (200 mL) y se lavó con NaOH acuoso 2N, agua y salmuera. Luego de secar sobre Na₂SO₄, la mezcla se filtró y el solvente se evaporó bajo vacío para dar el compuesto del título.

EJEMPLO 266B

- 30 ácido 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((9-(4-clorofenil)-3-isopropil-3-azaespiro[5,5]undec-8-en-8-il)metil)piperazin-1-il)benzoico

El compuesto del título se preparó utilizando el EJEMPLO 266A en lugar del EJEMPLO 265I en el EJEMPLO 265J.

EJEMPLO 266C

4-(4-([9-(4-clorofenil)-3-isopropil-3-azaespiro[5,5]undec-8-en-8-il]metil)piperazin-1-il)-N-([3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 266B en lugar del
 5 EJEMPLO 1E en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) □ 11,54 (s, 1 H), 8,38 (m, 2 H), 7,93 (d, 1 H), 7,60 (m, 3 H), 7,39 (m, 4 H), 7,09 (d, 2 H), 6,85 (d, 1 H), 6,63 (dd, 1 H), 6,27 (dd, 2 H), 3,84 (m, 3 H), 3,08 (m, 8 H), 2,71 (s, 3 H), 2,15 (m, 8 H), 1,71 (m, 9 H), 1,24 (m, 11 H)

10 EJEMPLO 267

4-(4-([9-(4-clorofenil)-3-(1,3-difluoropropan-2-il)-3-azaespiro[5,5]undec-8-en-8-il]metil)piperazin-1-il)-N-([5-cloro-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 265J en lugar del
 15 EJEMPLO 1E y EJEMPLO 40B en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) □ 11,56 (s, 1 H), 8,38 (s, 1 H), 8,06 (m, 1 H), 7,57 (d, 1 H), 7,38 (m, 5 H), 7,07 (m, 3 H), 6,64 (dd, 1 H), 6,33 (d, 1 H), 6,23 (m, 1 H), 4,68 (d, 2 H), 4,52 (d, 2 H), 4,21 (d, 2 H), 3,86 (dd, 2 H), 3,08 (m, 8 H), 2,71 (m, 6 H), 2,10 (m, 12 H), 1,42 (m, 7 H).

20 EJEMPLO 268

4-(4-([9-(4-clorofenil)-3-isopropil-3-azaespiro[5,5]undec-8-en-8-il]metil)piperazin-1-il)-N-([5-cloro-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 266B en lugar del
 25 EJEMPLO 1E y EJEMPLO 40B en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) □ 11,49 (s, 1 H), 8,28 (d, 1 H), 7,94 (dd, 2 H), 7,60 (d, 1 H), 7,35 (m, 4 H), 7,08 (m, 2 H), 6,61 (dd, 1 H), 6,28 (dd, 2 H), 4,18 (d, 2 H), 3,85 (m, 2 H), 3,05 (m, 7 H), 2,71 (s, 3 H), 2,25 (m, 6 H), 2,02 (m, 2 H), 1,63 (m, 8 H), 1,30 (m, 9 H).

30 EJEMPLO 269

N-([5-cloro-6-[(4-fluoro-1-metilpiperidin-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-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 269A

35 5-cloro-6-((4-fluoro-1-metilpiperidin-4-il)metoxi)piridin-3-sulfonamida

Se trató EJEMPLO 257B (0,131 g) en N,N-dimetilformamida (3,0 mL) con yodometano (0,043 g) y carbonato de sodio (0,079 g) y se agitó a temperatura ambiente por 3 días. La N,N-dimetilformamida se retiró en alto vacío y el material concentrado se cromatografió sobre gel de sílice funcionalizado con amina con metanol entre 0 y 2% en CH₂Cl₂ como eluyente.

EJEMPLO 269B

N-({5-cloro-6-[(4-fluoro-1-metilpiperidin-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-pirrol[2,3-b]piridin-5-ilo)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 269A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (400 MHz, piridina-d₅) δ 13,01 (s, 1H), 9,11 (d, 1H), 8,71 (d, 1H), 8,44 (d, 1H), 8,16 (d, 1H), 7,66 (m, 2H), 7,44 (m, 2H), 7,07 (m, 2H), 6,76 (dd, 1H), 6,54 (d, 1H), 6,49 (dd, 1H), 4,49 (d, 2H), 3,06 (m, 4H), 2,77 (s, 2H), 2,68 (m, 2H), 2,38 (m, 2H), 2,26 (m, 5H), 2,14 (t, 4H), 1,97 (m, 6H), 1,39 (t, 2H), 0,94 (s, 6H).

EJEMPLO 270

N-[(5-cloro-6-{[1-(N,N-dimetilglicil)-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-pirrol[2,3-b]piridin-5-ilo)benzamida

EJEMPLO 270A

5-cloro-6-((1-(2-(dimetilamino)acetil)-4-fluoropiperidin-4-il)metoxi)piridin-3-sulfonamida

Se combinó EJEMPLO 257B (0,131 g), cloruro de 2-(dimetilamino)acetilo, ácido clorhídrico (0,139 g), y carbonato de sodio (0,048 g) en un vial de 5 mL con N,N-dimetilformamida (3,0 mL) y se agitó durante la noche a temperatura ambiente. Se agregó carbonato de sodio adicional (0,048 g) seguido por cloruro de 2-(dimetilamino)acetilo, ácido clorhídrico (0,139 g) y la agitación se continuó durante una segunda noche. La mezcla de la reacción se concentró bajo alto vacío, se formó una lechada en CH₂Cl₂, se filtró, se concentró y se cromatografió sobre gel de sílice funcionalizado con amina con metanol entre 0 y 4% en CH₂Cl₂ como eluyente.

EJEMPLO 270B

N-[(5-cloro-6-{[1-(N,N-dimetilglicil)-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-pirrol[2,3-b]piridin-5-ilo)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 270A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500 MHz, piridina-d₅) δ 13,04 (s, 1H), 9,12 (d, 1H), 8,73 (d, 1H), 8,42 (d, 1H), 8,11 (d, 1H), 7,66 (m, 2H), 7,44 (m, 2H), 7,07 (m, 2H), 6,76 (dd, 1H), 6,52 (d, 1H), 6,49 (dd, 1H), 4,66 (d, 1H), 4,52 (dd, 2H), 4,07 (d, 1H), 3,46 (m, 1H),
 5 3,40 (m, 1H), 3,30 (m, 1H), 3,11 (m, 1H), 3,06 (m, 4H), 2,77 (s, 2H), 2,35 (s, 6H), 2,26 (t, 2H),
 10 2,14 (m, 4H), 2,05 (m, 2H), 1,97 (s, 2H), 1,81 (m, 2H), 1,39 (t, 2H), 0,93 (s, 6H).

EJEMPLO 271

4-{4-[(4'-clorobifenil-2-il)metil]-4-fluoropiperidin-1-il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida
 10

EJEMPLO 271A

4-[(4'-clorobifenil-2-il)metil]-4-fluoropiperidin-1-carboxilato de tert-butilo

Una solución de EJEMPLO 263E (2,0 g) y trifluoruro de dietilaminoazufre (1,39 mL)
 15 en diclorometano (40 mL) se agitó por 24 horas. La reacción se detuvo con agua (30 mL), se extrajo dos veces con éter, y los extractos combinados se lavaron con agua, y salmuera, se secó sobre Na₂SO₄, se filtró, y se concentró. El producto crudo se cromatografió sobre gel de sílice usando 5% acetato de etilo en hexanos para dar el compuesto del título.

20 EJEMPLO 271B

4-[(4'-clorobifenil-2-il)metil]-4-fluoropiperidina

El compuesto del título se preparó utilizando el EJEMPLO 271A en lugar del EJEMPLO 1A en el EJEMPLO 1B.

EJEMPLO 271C

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-[(4'-clorobifenil-2-il)metil]-4-fluoropiperidin-1-il)benzoato de metilo
 25

El compuesto del título se preparó utilizando el EJEMPLO 271B en lugar del EJEMPLO 263G en el EJEMPLO 263H.

30 EJEMPLO 271D

ácido 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-[(4'-clorobifenil-2-il)metil]-4-fluoropiperidin-1-il)benzoico

El compuesto del título se preparó utilizando el EJEMPLO 271C en lugar del EJEMPLO 3I en el EJEMPLO 3J.

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EJEMPLO 271E

4-{4-[(4'-clorobifenil-2-il)metil]-4-fluoropiperidin-1-il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 271D en lugar del EJEMPLO 1E EJEMPLO 1G. ¹H NMR (300MHz, sulfóxido de dimetilo-d₆) □ 11,66 (s, 1H), 11,46 (br s, 1H), 8,62 (t, 1H), 8,56 (d, 1H), 8,03 (d, 1H), 7,81 (dd, 1H), 7,52 (m, 3H), 7,44 (d, 2H), 7,28 (m, 5H), 7,14 (m, 1H), 6,68 (dd, 1H), 6,40 (dd, 1H), 6,19 (d, 1H), 3,84 (dd, 2H), 3,31 (m, 9H), 2,95 (d, 2H), 2,81 (m, 2H), 1,91 (m, 1H), 1,62 (m, 2H), 1,45 (m, 2H), 1,29 (m, 2H).

EJEMPLO 272

4-{4-[(4'-clorobifenil-2-il)metil]-4-fluoropiperidin-1-il}-N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 271D en lugar del EJEMPLO 1E y EJEMPLO 96A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300MHz, sulfóxido de dimetilo-d₆) □ 11,68 (s, 1H), 11,64 (br s, 1H), 8,58 (m, 1H), 8,25 (m, 1H), 8,03 (d, 1H), 7,70 (dd, 1H), 7,50 (m, 4H), 7,43 (m, 3H), 7,28 (m, 4H), 7,15 (m, 1H), 6,68 (dd, 1H), 6,40 (dd, 1H), 6,19 (d, 1H), 4,54 (d, 2H), 4,04 (m, 1H), 3,75 (m, 2H), 3,58 (m, 2H), 2,95 (d, 2H), 2,80 (m, 2H), 1,88 (m, 2H), 1,82 (m, 2H), 1,48 (m, 2H), 1,28 (m, 2H), 0,85 (m, 2H).

EJEMPLO 273

4-(4-{[9-(4-clorofenil)-3-isopropil-3-azaespiro[5,5]undec-8-en-8-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)-N-({4-[(tetrahidro-2H-piran-4-ilmetil)amino]-3-(trifluorometil)fenil}sulfonil)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 266B en lugar del EJEMPLO 1E y EJEMPLO 42A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) □ 11,57 (s, 1 H), 7,97 (d, 1 H), 7,77 (s, 1 H), 7,55 (m, 2 H), 7,45 (m, 1 H), 7,36 (m, 3 H), 7,08 (d, 2 H), 6,62 (dd, 2 H), 6,35 (dd, 1 H), 6,21 (d, 1 H), 3,82 (m, 3 H), 3,06 (m, 9 H), 2,72 (m, 3 H), 2,25 (m, 8 H), 2,09 (m, 2 H), 1,56 (m, 9 H), 1,20 (m, 10 H).

EJEMPLO 274

N-[(5-cloro-6-[(3R)-1-(1,3-difluoropropan-2-il)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-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 274A

(R)-5-cloro-6-(1-(3-fluoro-2-(fluorometil)propil)pirrolidin-3-iloxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando 1,3-difluoropropan-2-ona en lugar de 4'-clorobifenil-2-carboxaldehído y EJEMPLO 261B en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

5

EJEMPLO 274B

N-[(5-cloro-6-[[[(3R)-1-(1,3-difluoropropan-2-il)pirrolidin-3-il]oxi]piridin-3-il)sulfonyl]-4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrol-2,3-b)piridin-5-iloxi)benzamida

10 El compuesto del título se preparó utilizando el EJEMPLO 274A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (400MHz, sulfóxido de dimetilo-d₆) δ 11,52 (s, 1 H), 8,32 (d, 1 H), 8,01 (d, 1 H), 7,93 (d, 1 H), 7,59 (d, 1 H), 7,42 (m, 1 H), 7,33 (m, 3 H), 7,05 (d, 2 H), 6,63 (dd, 1 H), 6,31 (dd, 1 H), 6,25 (d, 1 H), 5,38 (m, 1 H), 4,65 (t, 2 H), 4,53 (t, 2 H), 3,02 (s, 4 H), 2,94 (m, 5 H), 2,75 (s, 2 H), 2,66 (m, 1 H), 2,23 (m, 7 H), 1,96 (s, 2 H),
15 1,82 (m, 1 H), 1,39 (t, 2 H), 0,93 (s, 6 H).

EJEMPLO 275

4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[(3-nitro-4-[2-(tetrahydrofurano-3-iloxi)etoxi]fenil)sulfonyl]-2-(1H-pirrol-2,3-b)piridin-5-iloxi)benzamida

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EJEMPLO 275A

3-(2-(benciloxi)etoxi)tetrahydrofurano

Se trató tetrahydrofurano-3-ol (0,881 g) en tetrahydrofurano (15 mL) con hidruro de sodio al 60% (0,8 g). Luego de 10 minutos, se agregó ((2-bromoetoxi)metil)benceno (3,23 g).

25 La solución se agitó por 16 horas. La mezcla de la reacción se particionó entre agua y acetato de etilo. La capa acuosa se separó, y se extrajo con acetato de etilo adicional dos veces. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre MgSO₄, se filtró, y se concentró. El residuo se purificó mediante cromatografía flash sobre gel de sílice eluyendo con 1:1 acetato de etilo: hexano para dar el compuesto del título.

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EJEMPLO 275B

2-(tetrahydrofurano-3-iloxi)etanol

Se trató EJEMPLO 275A (0,85 g) y paladio sobre carbono al 5% (0,1 g) en etanol (10 mL) con un globo de hidrógeno. La reacción se agitó durante la noche. El sólido se retiró por
35 filtración, y el material filtrado se concentró para dar el compuesto del título.

EJEMPLO 275C

3-nitro-4-(2-(tetrahidrofurano-3-iloxi)etoxi)bencenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 275B en lugar de (tetrahidro-2H-piran-4-il)metanol en el EJEMPLO 24A.

5

EJEMPLO 275D

4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-[2-(tetrahidrofurano-3-iloxi)etoxi]fenil}sulfonil}-2-(1H-pirrololo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 275C en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,65 (s, 1H), 8,32 (s, 1H), 8,00-8,02 (m, 2H), 7,49-7,52 (m, 2H), 7,39-7,41 (m, 1H), 7,38 (d, 2H), 7,04 (d, 2H), 6,68 (dd, 1H), 6,39 (dd, 1H), 6,21 (d, 1H), 4,33-4,35 (m, 2H), 4,18-4,21 (m, 1H), 3,62-3,67 (m, 4H), 3,09 (s, 4H), 2,83 (s, 2H), 2,26 (s, 2H), 2,15 (s, 2H), 1,96 (s, 2H), 1,85-1,94 (m, 2H), 1,39 (t, 2H), 0,92 (s, 6H).

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EJEMPLO 276

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-pirrololo[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 276A

trans-4-(aminometil)ciclohexanocarbonitrilo

A una solución de (trans-4-(cianometil)ciclohexil)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.

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EJEMPLO 276B

4-((trans-4-cianociclohexil)metilamino)-3-nitrobencenosulfonamida

Una mezcla de 4-fluoro-3-nitrobencenosulfonamida (347 mg) y EJEMPLO 276A (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.

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EJEMPLO 276C

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-pirrololo[2,3-b]piridin-5-iloxi)benzamida

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El compuesto del título se preparó como se describe en el EJEMPLO 11D usando EJEMPLO 276B en lugar de EJEMPLO 11B. ^1H NMR (400 MHz, sulfóxido de dimetilo- d_6) δ 11,69 (s, 1 H), 11,36 (s, 1 H), 8,60 (t, 1 H), 8,56 (d, 1 H), 8,04 (d, 1 H), 7,79 (dd, 1 H), 7,47 - 7,54 (m, 3 H), 7,34 (d, 2 H), 7,01 - 7,09 (m, 3 H), 6,68 (dd, 1 H), 6,39 (dd, 1 H), 6,19 (d, 1 H), 3,25 (t, 2 H), 3,07 (s, 4 H), 2,76 (s, 2 H), 2,57 - 2,68 (m, 1 H), 2,17 (d, 6 H), 1,92 - 2,06 (m, 4 H), 1,78 (d, 2 H), 1,66 (s, 1 H), 1,35 - 1,53 (m, 4 H), 0,96 - 1,10 (m, 2 H), 0,92 (s, 6 H).

EJEMPLO 277

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-pirrolol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 277A

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-metoxycarbonilciclohexanona (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 trifluoroacético (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 277B

2-(4-clorofenil)-4,4-dimetilciclohex-1-encarboxilato de metilo

Se calentó EJEMPLO 277A (62,15g), ácido 4-clorofenilborónico (32,24 g), CsF (64 g) y tetrakis(trifenilfosfin)paladio(0) (2g) en 2:1 dimetoxietano /metanol (600 mL) a 70°C 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 277C

(2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metanol

A una mezcla de LiBH_4 (13g), EJEMPLO 277B (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 1N con enfriamiento con hielo. La mezcla se diluyó con agua y se extrajo con éter (3x 100 mL). Los extractos se secaron (Na_2SO_4), se filtró, y se concentró. El producto crudo se cromatografió sobre gel de sílice con acetato de etilo al 0-30%/hexanos.

EJEMPLO 277D

4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-carboxilato de tert-butilo

- Se agregó cloruro de mesilo (7,5 mL) mediante una jeringa a EJEMPLO 277C (29,3 g) y trietilamina (30 mL) en CH_2Cl_2 (500 mL) a 0°C , y la mezcla se agitó por 1 minuto. Se agregó
- 5 N-t-butoxicarbonilpiperazina (25 g) y la mezcla se agitó a temperatura ambiente por 24 horas. La suspensión se lavó con salmuera, se secó, (Na_2SO_4), se filtró, y se concentró. El producto crudo se cromatografió sobre gel de sílice con acetato de etilo al 10-20%/hexanos.

EJEMPLO 277E

- 10 1-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazina

- Se agitó EJEMPLO 277D (1 g) en diclorometano (10 mL), ácido trifluoroacético (10 mL), y trietilsilano (1 mL) por 1 hora. La mezcla se concentró, se recogió con una mezcla de diclorometano (100 mL) y solución acuosa saturada de Na_2CO_3 (20 mL) y se agitó por 10 minutos. Las capas se separaron, y la capa orgánica se secó sobre Na_2SO_4 , se filtró, y se
- 15 concentró para dar el producto.

EJEMPLO 277F

5-bromo-1-(triisopropilsilil)-1H-pirrol[2,3-b]piridina

- A una mezcla de 5-bromo-1H-pirrol[2,3-b]piridina (15,4 g) en tetrahidrofurano (250 mL) se
- 20 agregó hexametildisilazida de litio 1M en tetrahidrofurano (86 mL), y luego de 10 minutos, se agregó TIPS-Cl (triisopropilclorosilano) (18,2 mL). La mezcla se agitó a temperatura ambiente por 24 horas. La reacción se diluyó con éter, y la solución resultante se lavó dos veces con agua. Los extractos se secaron (Na_2SO_4), se filtró, y se concentró. El producto
- crudo se cromatografió sobre gel de sílice con 10% acetato de etilo/hexanos.

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EJEMPLO 277G

1-(triisopropilsilil)-1H-pirrol[2,3-b]piridin-5-ol

- A una mezcla de EJEMPLO 277F (24,3 g) en tetrahidrofurano (500 mL) a -78°C se agregó BuLi 2,5M (30,3 mL). Luego de 2 minutos, se agregó borato de trimetilo (11,5 mL), y la
- 30 mezcla se dejó calentar a temperatura ambiente durante 1 hora. La reacción se vertió en agua, se extrajo tres veces con acetato de etilo, y los extractos combinados se lavaron con salmuera y se concentró. El producto crudo se colocó en tetrahidrofurano (200 mL) a 0°C , y se agregó NaOH 1M (69 mL), seguido por H_2O_2 al 30% (8,43 mL), y la solución se agitó por 1 hora. Se agregó $\text{Na}_2\text{S}_2\text{O}_3$ (10 g), y el pH se ajustó a 4-5 con HCl concentrado y NaH_2PO_4
- 35 sólido. La solución se extrajo dos veces con acetato de etilo, y los extractos combinados se

lavarón con salmuera, se secó (Na_2SO_4), se filtró, y se concentró. El producto crudo se cromatografió sobre gel de sílice con 5-25% acetato de etilo/hexanos.

EJEMPLO 277H

5 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-fluorobenzoato de metilo

Una mezcla de EJEMPLO 277G (8,5 g), 2,4-difluorobenzoato de metilo (7,05 g), y K_3PO_4 (9,32 g) en diglima (40 mL) a 115°C se agitó por 24 horas. La reacción se enfrió, se diluyó con éter (600 mL), y se lavó dos veces con agua, y salmuera, y se concentró. El producto crudo se cromatografió sobre gel de sílice con acetato de etilo al 2-50%/hexanos.

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EJEMPLO 277I

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoato de metilo

Una mezcla de EJEMPLO 277H (1,55 g), EJEMPLO 277E (2,42 g), y HK_2PO_4 (1,42 g) en sulfóxido de dimetilo (20 mL) a 135°C se agitó por 24 horas. La reacción se enfrió, se diluyó con éter (400 mL), y se lavó tres veces con NaOH 1M, y salmuera, y se concentró. El producto crudo se cromatografió sobre gel de sílice con acetato de etilo al 10-50%/hexanos.

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EJEMPLO 277J

20 ácido 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoico

Se agitó EJEMPLO 277I (200 mg) en dioxano (10 mL) y NaOH 1M (6 mL) a 50°C por 24 horas. La reacción se enfrió, se agregó una solución de NaH_2PO_4 , y se extrajo tres veces con acetato de etilo. Los extractos combinados se lavaron con salmuera, y se concentró para dar el producto puro.

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EJEMPLO 277K

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°C 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.

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EJEMPLO 277L

4-fluoro-4-(hidroximetil)piperidin-1-carboxilato de tert-butilo

Se trató 4-fluoropiperidin-1,4-dicarboxilato de 1-tert-butilo 4-etilo (1,0 g) en tetrahidrofurano (5 mL) con LiAlH_4 1,0 N en tetrahidrofurano (2,54 mL) a 0 °C. La mezcla de la reacción se agitó a temperatura ambiente por 2 horas. Se agregó agua (0,6 mL) a la mezcla de la reacción por goteo, seguido por NaOH acuoso 2 N (0,2 mL). La reacción se agitó por otra 1 hora. El sólido se retiró mediante filtración a través de un tapón de tierra diatomea y se lavó con acetato de etilo. El material filtrado se lavó con salmuera, se secó sobre MgSO_4 , se filtró, y se concentró para dar el producto.

EJEMPLO 277M

4-((3-cloro-5-sulfamoylpiridin-2-iloxi)metil)-4-fluoropiperidin-1-carboxilato de tert-butilo

A una solución de EJEMPLO 277L (1 g) en tetrahidrofurano (15 mL) se agregó NaH (dispersión al 60% en aceite mineral, 685 mg), y la solución se agitó por 10 minutos. Se agregó EJEMPLO 227K (1 g) y la reacción se agitó por 24 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 30% en hexanos.

EJEMPLO 277N

ditrifluoroacetato de 5-cloro-6-((4-fluoropiperidin-4-il)metoxi)piridin-3-sulfonamida

Se trató EJEMPLO 277M (13 mL) con ácido trifluoroacético (2,363 mL), se agitó a temperatura ambiente por 2 horas, se concentró y se secó para dar el compuesto del título.

EJEMPLO 277O

5-cloro-6-((4-fluoro-1-(oxetan-3-il)piperidin-4-il)metoxi)piridin-3-sulfonamida

Se combinó EJEMPLO 277N (0,088 g) y oxetan-3-ona (0,014 g) en diclorometano (2,0 mL) y dimetilformamida (1,0 mL) y se agitó a temperatura ambiente por 45 minutos. Se agregó triacetoxiborhidruro de sodio (0,064 g) en porciones. La agitación se continuó durante la noche a temperatura ambiente. Se agregó oxetan-3-ona adicional (0,014 g) y la agitación se continuó por 30 minutos a temperatura ambiente antes de agregar más triacetoxiborhidruro de sodio (0,064 g). La mezcla de la reacción se agitó por 72 horas a temperatura ambiente, se concentró, se cromatografió sobre gel de sílice con metanol entre 0 y 5% en diclorometano como eluyente, y se secó en un horno de vacío a 80 °C para dar el compuesto del título.

EJEMPLO 277P

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

- 5 Se combinó EJEMPLO 277J (0,063 g), EJEMPLO 277O (0,042 g), clorhidrato de 1-etil-3-[3-(dimetilamino)propil]-carbodiimida (0,032 g), y 4-dimetilaminopiridina (0,027 g) en un vial de 4 mL con diclorometano (1,0 mL) y se agitó durante la noche a temperatura ambiente. La mezcla de la reacción se cromatografió directamente si tratamiento acuoso posterior
- 10 contenían el producto deseado se concentraron, se formó una lechada en acetonitrilo, se concentró y se secó durante la noche en un horno de vacío a 80 °C para dar el compuesto del título. ¹H NMR (500 MHz, piridina-d₅) □ 13,05 (s, 1H), 9,13 (d, 1H), 8,72 (d, 1H), 8,41 (d, 1H), 8,10 (d, 1H), 7,67 (m, 1H), 7,66 (d, 1H), 7,44 (m, 2H), 7,07 (m, 2H), 6,76 (dd, 1H), 6,51 (m, 2H), 4,63 (m, 4H), 4,53 (d, 2H), 3,39 (m, 1H), 3,07 (m, 4H), 2,77 (s, 2H), 2,51 (m, 2H),
- 15 2,25 (m, 2H), 2,18 (m, 2H), 2,13 (m, 4H), 2,06 (t, 2H), 1,97 (s, 2H), 1,89 (m, 2H), 1,39 (t, 2H), 0,93 (s, 6H).

EJEMPLO 278

- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({5-ciano-6-[2-(tetrahydro-2H-piran-4-il)etoxi]piridin-3-il}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida
- 20

EJEMPLO 278A

5-bromo-6-(2-(tetrahydro-2H-piran-4-il)etoxi)piridin-3-sulfonamida

- El compuesto del título se preparó utilizando 2-(tetrahydro-2H-piran-4-il)etanol en lugar
- 25 de (tetrahydro-2H-piran-4-il)metanol en el EJEMPLO 36B.

EJEMPLO 278B

5-ciano-6-(2-(tetrahydro-2H-piran-4-il)etoxi)piridin-3-sulfonamida

- El compuesto del título se preparó utilizando el EJEMPLO 278A en lugar del
- 30 EJEMPLO 36B en el EJEMPLO 36C.

EJEMPLO 278C

4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({5-ciano-6-[2-(tetrahydro-2H-piran-4-il)etoxi]piridin-3-il}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

- 35 El compuesto del título se preparó utilizando el EJEMPLO 278B en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,60 (s,

1H), 8,70 (s, 1H), 8,48 (s, 1H), 7,96 (d, 1H), 7,56 (d, 1H), 7,45-7,47 (m, 1H), 7,40 (s, 1H), 7,36 (d, 2H), 7,06 (d, 2H), 6,67 (dd, 1H), 6,34 (dd, 1H), 6,25 (d, 1H), 4,47 (d, 2H), 3,80-3,84 (m, 2H), 3,24-3,28 (m, 2H), 3,12 (s, 2H), 2,16 (s, 2H), 1,97 (s, 2H), 1,61-1,71 (m, 4H), 1,40 (t, 2H), 1,21-1,25 (m, 2H), 0,93 (s, 6H).

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EJEMPLO 279

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-(3-furilmetoxi)-3-nitrofenil]sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

10 EJEMPLO 279A

4-(furan-3-ilmetoxi)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando furan-3-ilmetanol en lugar de (tetrahidro-2H-piran-4-il)metanol en el EJEMPLO 24A.

15 EJEMPLO 279B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-(3-furilmetoxi)-3-nitrofenil]sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 279A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,69 (s, 1H), 8,34 (s, 1H), 8,03-8,06 (m, 2H), 7,83 (s, 1H), 7,69 (t, 1H), 7,51-7,53 (m, 4H), 7,34-7,36 (m, 2H), 7,04-7,06 (m, 2H), 6,68 (dd, 1H), 6,57 (s, 1H), 6,40 (dd, 1H), 6,20 (d, 1H), 5,23 (s, 2H), 3,10 (s, 4H), 2,83 (s, 2H), 2,15-2,32 (m, 6H), 1,39 (t, 2H), 0,92 (s, 6H).

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EJEMPLO 280

N-[(5-cloro-6-{[(3R)-1-(1,3-difluoropropan-2-il)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-pirrol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 280A

(R)-3-((3-cloro-5-sulfamoilpiridin-2-iloxi)metil)pirrolidin-1-carboxilato de tert-butilo

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El compuesto del título se preparó utilizando el EJEMPLO 40A en lugar de 4-fluoro-3-nitrobencenosulfonamida y (R)-3-(hidroximetil)pirrolidin-1-carboxilato de tert-butilo en lugar de (tetrahidro-2H-piran-4-il)metanol en el EJEMPLO 24A.

EJEMPLO 280B

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(R)-5-cloro-6-(pirrolidin-3-ilmetoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 280A en lugar de (4-(1,3-difluoropropan-2-il)morfolin-2-il)metilcarbamato de tert-butilo en el EJEMPLO 252B.

EJEMPLO 280C

- 5 (R)-5-cloro-6-((1-(1,3-difluoropropan-2-il)pirrolidin-3-il)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando 1,3-difluoropropan-2-ona en lugar de 4'-clorobifenil-2-carboxaldehído y EJEMPLO 280B en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

10 EJEMPLO 280D

N-[(5-cloro-6-((3R)-1-(1,3-difluoropropan-2-il)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-pirrol[2,3-b]piridin-5-iloxi)benzamida

- 15 El compuesto del título se preparó utilizando el EJEMPLO 280C en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (400MHz, sulfóxido de dimetilo-d₆) □ 11,57 (s, 1 H), 8,38 (d, 1 H), 8,07 (d, 1 H), 7,96 (d, 1 H), 7,57 (d, 1 H), 7,44 (m, 1 H), 7,35 (m, 3 H), 7,05 (d, 2 H), 6,64 (dd, 1 H), 6,33 (dd, 1 H), 6,23 (d, 1 H), 4,65 (d, 2 H), 4,53 (dd, 2 H), 2,92 (m, 8 H), 2,75 (m, 4 H), 2,58 (m, 2 H), 2,20 (m, 6 H), 1,96 (m, 4 H), 1,53 (m, 1 H), 1,39 (t, 2 H), 0,89 (s, 6 H).

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EJEMPLO 281

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 281A

(R)-5-cloro-6-((1-(2,2-difluoroetil)pirrolidin-3-il)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 280B en lugar del EJEMPLO 261B en el EJEMPLO 261C.

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EJEMPLO 281B

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

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El compuesto del título se preparó utilizando el EJEMPLO 281A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (400MHz, sulfóxido de dimetilo-d₆) □ 11,59 (s,

1 H), 8,41 (d, 1 H), 8,10 (d, 1 H), 7,98 (d, 1 H), 7,56 (d, 1 H), 7,46 (m, 1 H), 7,41 (d, 1 H), 7,34 (d, 2 H), 7,04 (d, 2 H), 6,65 (dd, 1 H), 6,35 (dd, 1 H), 6,23 (m, 1 H), 6,03 (m, 1 H), 3,06 (s, 4 H), 2,84 (m, 6 H), 2,63 (m, 4 H), 2,20 (m, 6 H), 1,94 (m, 3 H), 1,53 (m, 1 H), 1,39 (t, 2 H), 0,91 (s, 6 H).

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EJEMPLO 282

N-[(5-cloro-6-[[1-(1,3-difluoropropan-2-il)-4-fluoropiperidin-4-il]metoxi]piridin-3-il)sulfonyl]-4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 282A

5-cloro-6-((1-(1,3-difluoropropan-2-il)-4-fluoropiperidin-4-il)metoxi)piridin-3-sulfonamida

Se combinó EJEMPLO 257B (0,088 g) y 1,3-difluoropropan-2-ona (0,028 g) en diclorometano (2 mL) y N,N-dimetilformamida (0,500 mL) y se agitó a temperatura ambiente por 45 minutos. Se agregó triacetoxiborhidruro de sodio (0,064 g) en porciones y luego la mezcla de la reacción se agitó durante la noche a temperatura ambiente. Se agregó 1,3-difluoropropan-2-ona adicional (0,028 g), seguido 30 minutos luego por la adición de más triacetoxiborhidruro de sodio (0,064 g). La mezcla de la reacción se agitó a temperatura ambiente por 72 horas. Se agregó nuevamente 1,3-difluoropropan-2-ona adicional (0,028 g), seguida 30 minutos luego por la adición de más triacetoxiborhidruro de sodio (0,064 g). La mezcla de la reacción se agitó durante la noche a temperatura ambiente. Se agregó nuevamente 1,3-difluoropropan-2-ona adicional (0,028 g), seguido 30 minutos luego por la adición de more triacetoxiborhidruro de sodio (0,064 g). La mezcla de la reacción se agitó durante la noche a temperatura ambiente. La mezcla de la reacción se concentró bajo alto vacío para eliminar N,N-dimetilformamida y luego se cromatografió sobre gel de sílice con metanol entre 0 y 4% en CH₂Cl₂ como eluyente.

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EJEMPLO 282B

N-[(5-cloro-6-[[1-(1,3-difluoropropan-2-il)-4-fluoropiperidin-4-il]metoxi]piridin-3-il)sulfonyl]-4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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El compuesto del título se preparó utilizando el EJEMPLO 282A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (400 MHz, piridina-d₅) □ 13,05 (s, 1H), 9,12 (t, 1H), 8,72 (d, 1H), 8,41 (d, 1H), 8,10 (d, 1H), 7,66 (m, 2H), 7,44 (m, 2H), 7,07 (m, 2H), 6,75 (dd, 1H), 6,50 (m, 2H), 4,77 (dd, 1H), 4,65 (dd, 1H), 4,52 (dd, 2H), 3,06 (m, 4H), 2,93 (t, 1H),

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2,80 (m, 5H), 2,52 (m, 1H), 2,26 (t, 2H), 2,13 (m, 4H), 2,04 (m, 2H), 1,97 (s, 2H), 1,85 (m, 2H), 1,39 (t, 2H), 1,28 (m, 2H), 0,93 (s, 6H).

EJEMPLO 283

- 5 N-({3-cloro-4-[(4-fluoro-1-metilpiperidin-4-il)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 283A

3-cloro-4-((4-fluoro-1-metilpiperidin-4-il)metoxi)bencenosulfonamida

- 10 A una solución de (4-fluoro-1-metilpiperidin-4-il)metanol (0,265 g) en tetrahidrofurano (2 mL) se agregó hidruro de sodio (0,288 g). Luego de 15 minutos, se agregó 3-cloro-4-fluorobencenosulfonamida (0,377 g) como una solución en tetrahidrofurano (1 mL). La reacción se agitó por 2 horas, se detuvo con agua (5 mL), se ajustó a pH~7 con HCl acuoso 1N, y se extrajo con diclorometano (2 x 25 mL). La capa orgánica se lavó con salmuera (25
15 mL), se secó sobre sulfato de magnesio, se filtró y se concentró. Cromatografía sobre gel de sílice (Reveleris 40 g) eluyendo con un gradiente de metanol entre 0,1% y 10% que contenía NH₃ 2N/diclorometano a lo largo de 30 minutos dio el compuesto del título.

EJEMPLO 283B

- 20 N-({3-cloro-4-[(4-fluoro-1-metilpiperidin-4-il)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

- El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 283A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo- d₆) δ 11,60 (s, 1H), 10,68 – 9,84 (m, 1H), 7,99 (d, 1H), 7,79 (d, 1H),
25 7,63 (t, 1H), 7,54 (d, 1H), 7,50 – 7,38 (m, 2H), 7,34 (d, 2H), 7,04 (d, 3H), 6,64 (dd, 1H), 6,36 (dd, 1H), 6,22 (s, 1H), 4,23 (d, 2H), 3,03 (s, 6H), 2,71 (m, 4H), 2,07 (m, 12H), 1,38 (s, 3H), 1,24 (s, 2H), 0,92 (s, 6H).

EJEMPLO 284

- 30 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-([3-ciano-4-(tetrahydro-2H-piran-4-ilmetoxi)fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 284A

3-ciano-4-((tetrahydro-2H-piran-4-il)metoxi)bencenosulfonamida

- 35 A una solución de (tetrahydro-2H-piran-4-il)metanol (0,258 g) en tetrahidrofurano (5 mL) se agregó hidruro de sodio (0,355 g) y la reacción se agitó a temperatura ambiente por

15 minutos. Se agregó EJEMPLO 52A (0,400 g) y la reacción se agitó por 1 hora adicional. La reacción se vertió en acetato de etilo (50 mL) y HCl acuoso 1N (35 mL). La capa orgánica se lavó con salmuera (35 mL), se secó sobre sulfato de magnesio, se filtró, y se concentró. Cromatografía sobre gel de sílice (Reveleris 40 g) eluyendo con un gradiente de acetato de etilo entre 10% y 100%/hexanos a lo largo de 30 minutos dio el compuesto del título.

EJEMPLO 284B

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-ciano-4-(tetrahydro-2H-piran-4-ilmetoxi)fenil]sulfonil)-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

10 El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 284A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo- d₆) δ 11,69 (s, 1H), 11,60 - 11,16 (m, 1H), 8,15 (s, 1H), 8,08 - 8,01 (m, 2H), 7,58 - 7,46 (m, 3H), 7,35 (d, J = 8,4, 2H), 7,29 (d, 1H), 7,04 (d, 2H), 6,68 (d, 1H), 6,40 (dd, 1H), 6,20 (s, 1H), 4,05 (d, 2H), 3,89 (d, 2H), 3,37 (d, 4H), 3,09 (s, 4H), 2,81 (s, 2H), 2,21 (d, 7H), 1,96 (s, 2H), 1,67 (d, 2H), 1,39 (s, 2H), 0,92 (s, 6H).

EJEMPLO 285

20 N-[(5-cloro-6-([1-(2,2-difluoroetil)-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-pirrolol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 285A

5-cloro-6-([1-(2,2-difluoroetil)-4-fluoropiperidin-4-il]metoxi)piridin-3-sulfonamida

25 Se combinó EJEMPLO 257B (0,263 g), 1,1-difluoro-2-yodoetano (0,23 g), y carbonato de sodio (0,254 g) en un vial de 20 mL con N,N-dimetilformamida (6 ml) y se agitó a 70 °C durante la noche. La mezcla de la reacción se concentró bajo alto vacío y luego se cromatografió sobre gel de sílice con metanol entre 0 y 5% en CH₂Cl₂ como eluyente.

EJEMPLO 285B

30 N-[(5-cloro-6-([1-(2,2-difluoroetil)-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-pirrolol[2,3-b]piridin-5-iloxi)benzamida

35 El compuesto del título se preparó utilizando el EJEMPLO 285A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (400 MHz, piridina-d₅) □ 13,05 (s, 1H), 9,12 (d, 1H), 8,72 (d, 1H), 8,41 (d, 1H), 8,10 (d, 1H), 7,66 (m, 2H), 7,43 (m, 2H), 7,06 (m, 2H), 6,75 (dd, 1H), 6,50 (m, 2H), 6,18 (tt, 2H), 4,51 (d, 2H), 3,07 (m, 4H), 2,80 (m, 6H), 2,60 (td, 2H),

2,25 (t, 2H), 2,13 (m, 4H), 2,03 (t, 2H), 1,97 (s, 2H), 1,93 (m, 1H), 1,85 (m, 1H), 1,39 (t, 2H), 0,93 (s, 6H).

EJEMPLO 286

5 N-({3-cloro-4-[(4-fluorotetrahydro-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-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 286A

3-cloro-4-((4-fluorotetrahydro-2H-piran-4-il)metoxi)bencenosulfonamida

10 El compuesto del título se preparó utilizando el EJEMPLO 37C en lugar de (4-fluoro-1-metilpiperidin-4-il)metanol en el EJEMPLO 283A.

EJEMPLO 286B

N-({3-cloro-4-[(4-fluorotetrahydro-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-pirrol[2,3-b]piridin-5-iloxi)benzamida

15 El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 286A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo- d₆) δ 11,71 (s, 1H), 11,56 - 11,16 (m, 1H), 8,06 (d, 1H), 7,90 (d, 1H), 7,81 (d, 1H), 7,64 - 7,45 (m, 3H), 7,34 (d, 2H), 7,26 (d, 1H), 7,04 (d, 2H), 6,68 (d, 1H), 6,42 (dd, 1H), 6,18 (s, 1H), 4,28 (d, 2H), 3,78 (d, 2H), 3,61 (dd, 2H), 3,07 (s, 4H), 2,76 (s, 2H),
20 2,17 (d, 6H), 1,87 (dd, 6H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 287

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 287A

(4,4-difluorociclohexil)metanol

30 Se agregó 4,4-difluorociclohexanocarboxilato de etilo (1,0 g, 5,20 mmol) en éter dietílico (2 mL) por goteo a hidruro de litio y aluminio (0,24 g) en éter dietílico (15 mL), y se calentó bajo reflujo por 4 horas. La reacción luego se enfrió a 0°C, y se agregó agua (0,24 mL), seguido por NaOH acuoso 5N (0,24 mL) y agua (0,72 mL). Luego se agregó Na₂SO₄ y más éter dietílico (40 mL), y la mezcla se agitó por 30 minutos, luego se filtró a través de celite. Luego de la concentración, el residuo se diluyó con CH₂Cl₂ y se agregó Na₂SO₄, y la mezcla se filtró y se concentró para dar el compuesto del título.

35

EJEMPLO 287B

5-cloro-6-((4,4-difluorociclohexil)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 40A en lugar de 4-fluoro-3-nitrobencenosulfonamida y EJEMPLO 287A en lugar de (tetrahydro-2H-piran-4-il)metanol en el EJEMPLO 24A.

5 EJEMPLO 287C

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 287B en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (400MHz, sulfóxido de dimetilo-d₆) □ 11,63 (s, 1H), 8,46 (d, 1H), 8,14 (d, 1H), 8,00 (d, 1H), 7,56 (d, 1H), 7,47 (m, 2H), 7,35 (d, 2H), 7,03 (d, 2H), 6,66 (dd, 1H), 6,37 (m, 1H), 6,21 (d, 1H), 4,25 (d, 2H), 3,07 (br m, 4H), 2,82 (br s, 2H), 2,30 (br m, 4H), 2,16 (br m, 2H), 2,00, 1,95, 1,85 todos m, total 9H), 1,40 (t, 2H), 1,37 (m, 2H), 0,92 (s, 6H).

15 EJEMPLO 288

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([6-([1-(1,3-difluoropropan-2-il)-4-fluoropiperidin-4-il]metoxi)-5-(trifluorometil)piridin-3-il)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

20 EJEMPLO 288A

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 °C. La mezcla se agitó a 0°C por 5 minutos. A esta solución se agregó ácido nítrico fumante (6 mL) por goteo por 5 minutos. La mezcla de la reacción se agitó a temperatura ambiente por 2 horas, y luego se calentó a 50°C por 3 horas. Luego de enfriar, la mezcla de la 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 secó sobre MgSO₄, se filtró, y se concentró bajo presión reducida para dar el compuesto del título.

30 EJEMPLO 288B

2-Cloro-5-nitro-3-(trifluorometil)piridina

Una mezcla de EJEMPLO 288A (1,69 g), pentacloruro de fósforo (2,03 g), y tricloruro de fosforilo (0,97 mL) se calentó a 90°C por 3 horas. Luego de enfriar, la mezcla de la reacción se vertió en hielo, y se extrajo con acetato de etilo tres veces. El extracto se lavó con salmuera, se secó sobre MgSO₄, se filtró, y se concentró bajo presión reducida. El

residuo se purificó mediante cromatografía flash de columna sobre gel de sílice eluyendo con 10% acetato de etilo en hexanos para dar el compuesto del título.

EJEMPLO 288C

6-Cloro-5-(trifluorometil)piridin-3-amina

- 5 Una mezcla de hierro (1,5 g) y cloruro de amonio (2,38 g) en agua (40 mL) se agitó a temperatura ambiente por 5 minutos. A esta suspensión se agregó EJEMPLO 288B en metanol (40 mL). La mezcla de la reacción se agitó a temperatura ambiente por 1 hora. Se agregó más hierro (1,8 g) a la mezcla de la reacción, y se agitó por otras 3 horas. El sólido de la mezcla de la reacción se retiró por filtración, y el material filtrado se particionó entre
- 10 agua y acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre MgSO_4 , se filtró, y se concentró bajo presión reducida. El residuo se purificó mediante cromatografía flash de columna sobre gel de sílice eluyendo con acetato de etilo al 20% en hexanos para dar el compuesto del título.

15 EJEMPLO 288D

cloruro de 6-cloro-5-(trifluorometil)piridin-3-sulfonilo

- Bajo enfriamiento con hielo, se agregó cloruro de tionilo (4 mL) por goteo a lo largo de 20 minutos a agua (27 mL). La mezcla se agitó durante la noche por 12 horas para dar una solución que contenía SO_2 . En forma separada, se agregó EJEMPLO 288C (1,14 g) en
- 20 dioxano (5 mL) a HCl concentrado (20 mL) a 0°C . La solución se agitó por 5 minutos. A esto se agregó una suspensión/solución de nitrito de sodio (0,44 g) en agua (6 mL) por goteo a 0°C . La solución se agitó a 0°C por 3 horas. Durante este tiempo, los sólidos formados se trituraron con una varilla de vidrio para asegurarse que el EJEMPLO 288C hubiese reaccionado por completo. A la solución que contenía SO_2 solución se agregó cloruro de
- 25 cobre(I) (0,115 g). Luego, a esta solución se agregó el EJEMPLO 288C diazotizado a 0°C . La solución se agitó por 30 minutos. La mezcla de la reacción se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre MgSO_4 , se filtró, y se concentró bajo presión reducida. El residuo se purificó mediante cromatografía flash de columna sobre gel de sílice eluyendo con 5% acetato de etilo en hexanos para dar el
- 30 compuesto del título.

EJEMPLO 288E

6-cloro-5-(trifluorometil)piridin-3-sulfonamida

- Se enfrió EJEMPLO 288D (2,03 g) en solución de dioxano (20 mL) a 0°C . Se agregó
- 35 solución de hidróxido de amonio por goteo. La mezcla de la reacción se agitó a 0°C por 2 horas seguido por temperatura ambiente durante la noche. El solvente se eliminó

parcialmente, y el residuo se particionó entre agua y acetato de etilo. La fase orgánica se lavó con salmuera, se secó sobre MgSO_4 , se filtró, y se concentró bajo presión reducida. El residuo se purificó mediante cromatografía flash de columna sobre gel de sílice eluyendo con metanol al 0-3% en diclorometano para dar el compuesto del título.

5

EJEMPLO 288F

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 288E en lugar de 4-fluoro-3-nitrobenzenosulfonamida y EJEMPLO 322A en lugar de (tetrahydro-2H-piran-4-il)metanol en el EJEMPLO 24A.

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EJEMPLO 288G

6-((4-fluoropiperidin-4-il)metoxi)-5-(trifluorometil)piridin-3-sulfonamida

15

El compuesto del título se preparó utilizando el EJEMPLO 288F en lugar de 4-(1,3-difluoropropan-2-il)morfolin-2-il)metilcarbamato de tert-butilo en el EJEMPLO 252B.

EJEMPLO 288H

6-((1-(1,3-difluoropropan-2-il)-4-fluoropiperidin-4-il)metoxi)-5-(trifluorometil)piridin-3-sulfonamida

20

El compuesto del título se preparó utilizando 1,3-difluoropropan-2-ona en lugar de 4'-clorobifenil-2-carboxaldehído y EJEMPLO 288G en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A.

25

EJEMPLO 288I

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([6-([1-(1,3-difluoropropan-2-il)-4-fluoropiperidin-4-il]metoxi)-5-(trifluorometil)piridin-3-il]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 288H en lugar del EJEMPLO 11B en el EJEMPLO 11D. ^1H NMR (400MHz, sulfóxido de dimetilo- d_6) δ 11,50 (s, 1 H), 8,57 (s, 1 H), 8,27 (d, 1 H), 7,91 (d, 1 H), 7,58 (d, 1 H), 7,40 (m, 1 H), 7,35 (d, 2 H), 7,28 (d, 1 H), 7,05 (d, 2 H), 6,61 (dd, 1 H), 6,29 (dd, 1 H), 6,24 (d, 1 H), 4,67 (d, 2 H), 4,55 (d, 2 H), 4,50 (s, 1 H), 4,44 (s, 1 H), 3,06 (m, 5 H), 2,73 (m, 6 H), 2,19 (d, 6 H), 1,90 (m, 7 H), 1,39 (t, 2 H), 0,93 (s, 6 H).

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EJEMPLO 289

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([5-cloro-6-[2-(tetrahydrofurano-2-il)etoxi]piridin-3-il]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 289A

5 5-cloro-6-(2-(tetrahydrofurano-2-il)etoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando 2-(tetrahydro-2H-piran-4-il)etanol en lugar de (tetrahydro-2H-piran-4-il)metanol y EJEMPLO 40A en lugar del EJEMPLO 36A en el EJEMPLO 36B.

10 EJEMPLO 289B

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([5-cloro-6-[2-(tetrahydrofurano-2-il)etoxi]piridin-3-il]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 289A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,66 (s, 1H), 8,52 (d, 1H), 8,18 (s, 1H), 8,02 (s, 1H), 7,50-7,55 (m, 3H), 7,35 (d, 2H), 7,05 (d, 2H), 6,68 (dd, 1H), 6,38 (dd, 1H), 6,21 (d, 1H), 4,39-4,51 (m, 4H), 3,87-3,94 (m, 1H), 3,73-3,78 (m, 1H), 3,57-3,62 (m, 1H), 3,11 (s, 4H), 2,89 (s, 2H), 2,33 (s, 4H), 2,15 (s, 2H), 1,77-2,01 (m, 7H), 1,45-1,54 (m, 1H), 1,40 (t, 2H), 0,93 (s, 6H).

20 EJEMPLO 290

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)-3-metilpiperazin-1-il)-N-([3-nitro-4-[(tetrahydro-2H-piran-4-ilmetil)amino]fenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 290A

25 2-cloro-4,4-dimetilciclohex-1-encarbaldehido

En un balón de 250 mL se agregó N,N-dimetilformamida (3,5 mL) en diclorometano (30 mL). La mezcla se enfrió a -10°C, y se agregó tricloruro de fosforilo (4 mL) por goteo. La solución se calentó hasta temperatura ambiente y se agregó 3,3-dimetilciclohexanona (5,5 mL) lentamente. La mezcla se calentó a reflujo durante la noche. La mezcla de la reacción se detuvo mediante solución de acetato de sodio a 0°C (25 g en 50 mL agua). La capa acuosa se extrajo con éter (3 x 200 mL). Las capas orgánicas se combinaron, se secó sobre Na₂SO₄, se filtró, y se secó bajo vacío.

EJEMPLO 290B

35 2-(4-clorofenil)-4,4-dimetilciclohex-1-encarbaldehido

En un balón de 1 L se agregó EJEMPLO 290A (6,8 g), ácido 4-clorofenilborónico (6,5 g) y acetato de paladio(II) (0,2 g) en agua (100 mL) para dar una suspensión. Se agregó carbonato de potasio (15 g) y bromuro de tetrabutilamonio (10 g). Luego de desgasificar luego de someter a vacío y nitrógeno, la mezcla se agitó a 45°C por 4 horas. Luego de filtrar a través de gel de sílice, se usó éter dietílico (4x 200 mL) para extraer el producto. Las capas orgánicas combinadas se secaron sobre Na₂SO₄ y se filtró. El material filtrado se concentró y se purificó mediante cromatografía flash sobre sílice con 0-10% acetato de etilo en hexanos para dar el compuesto del título.

10 EJEMPLO 290C

4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)-3-metilpiperazin-1-carboxilato de *tert*-butilo

A una solución de 3-metilpiperazin-1-carboxilato de *tert*-butilo (0,256 g) y EJEMPLO 290B (0,350 g) en diclorometano (2 mL) se agregó triacetoxiborhidruro de sodio (0,406 g) y la reacción se agitó a temperatura ambiente durante la noche. La reacción se detuvo con solución de NaHCO₃ (50 mL) y se extrajo con diclorometano (50 mL). La capa orgánica se secó sobre sulfato de magnesio, se filtró y se concentró. Cromatografía sobre gel de sílice (Reveleris 40 g) eluyendo con un gradiente de metanol entre 0,5 y 2,5%/diclorometano dio el compuesto del título.

20 EJEMPLO 290D

1-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)-2-metilpiperazina

Una solución de EJEMPLO 290C (0,298 g) y HCl (4,0M en dioxano, 2 mL) se agitaron por 1 hora. La reacción se concentró y se particionó entre diclorometano (100 mL) y NaHCO₃ (100 mL). La capa orgánica se lavó con salmuera (50 mL), se secó sobre sulfato de magnesio, se filtró y se concentró para dar el compuesto del título.

EJEMPLO 290E

2-(1H-pirroló[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)-3-metilpiperazin-1-il)benzoato de metilo

El compuesto del título se preparó utilizando el EJEMPLO 290D en lugar del EJEMPLO 3E en el EJEMPLO 3I.

EJEMPLO 290F

ácido 2-(1H-pirroló[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)-3-metilpiperazin-1-il)benzoico

El compuesto del título se preparó utilizando el EJEMPLO 290E en lugar del EJEMPLO 15G en el EJEMPLO 15H.

EJEMPLO 290G

- 5 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)-3-metilpiperazin-1-il)-N-([3-nitro-4-
[(tetrahidro-2H-piran-4-ilmetil)amino]fenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 290F en lugar del EJEMPLO 1E en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo- d₆) δ 11,66 (s, 1H), 11,54 - 11,30 (m, 1H), 8,62 - 8,53 (m, 2H), 8,03 (d, 1H), 7,78 (d, 1H), 7,48 (d, 3H), 7,34
10 (d, 2H), 7,06 (t, 3H), 6,68 (d, 1H), 6,38 (dd, 1H), 6,21 (s, 1H), 3,84 (d, 2H), 3,23 (s, 4H), 2,75 (s, 4H), 1,64 (s, 8H), 1,62 (d, 2H), 1,42 - 1,17 (m, 6H), 0,92 (s, 6H), 0,87 (s, 3H).

EJEMPLO 291

- 15 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([3-(
(ciclopropilamino)propil]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-
iloxi)benzamida

EJEMPLO 291A

- 20 2-cianoetil(ciclopropil)carbamato de tert-butilo

A una solución de 3-(ciclopropilamino)propanonitrilo (5,0g) en tetrahidrofurano (30 mL) se agregó dicarbonato de di-tert-butilo (9,91g) y una cantidad catalítica de 4-dimetilaminopiridina. La mezcla se agitó durante la noche. La mezcla se diluyó con acetato de etilo (400 mL) y se lavó con HCl acuoso al 5%, agua y salmuera. Luego de secar sobre
25 Na₂SO₄, la mezcla se filtró, y el solvente se evaporó bajo vacío para dar el compuesto del título.

EJEMPLO 291B

3-aminopropil(ciclopropil)carbamato de tert-butilo

- 30 Se agregó EJEMPLO 291A (9,75 g) y NH₃ 7M-metanol (25 mL) a una lecha de Ra-Ni 2800, en agua (19,50 g, 332 mmol) en una botella de presión de 250 mL y se agitó por 2 horas a 30 psi y temperatura ambiente. La mezcla se filtró a través de una membrana de nylon y la evaporación del solvente dio el compuesto del título.

- 35 EJEMPLO 291C

ciclopropil(3-(2-nitro-4-sulfamoilfenilamino)propil)carbamato de tert-butilo

A una solución de 4-cloro-3-nitrobencenosulfonamida (2,5 g), y EJEMPLO 291B (2,26 g) en dioxano (20 mL) se agregó N,N-diisopropiletilamina (5 mL). La mezcla se agitó a reflujo durante la noche. La mezcla se diluyó con acetato de etilo (400 mL) y se lavó con agua y salmuera. Luego de secar sobre Na₂SO₄, la mezcla se filtró, y el solvente se evaporó bajo vacío para dar el compuesto del título.

EJEMPLO 291D

3-(4-(N-(2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoil)sulfamoil)-2-nitrofenilamino)propil(ciclopropil)carbamato de tert-butilo

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 291C en lugar del EJEMPLO 1F en el EJEMPLO 1G.

EJEMPLO 291E

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([3-(ciclopropilamino)propil]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

A una solución de EJEMPLO 291D (2,56 g) en diclorometano (10 mL) se agregó ácido trifluoroacético(10 mL). La mezcla se agitó por 2 horas. La mezcla se concentró bajo vacío y el residuo se disolvió en diclorometano (300 mL) y se lavó con NaHCO₃ acuoso, agua, y salmuera y se secó sobre Na₂SO₄. La filtración y evaporación del solvente dio el producto crudo. El compuesto del título se obtuvo disolviendo 200 mg del material crudo en sulfóxido de dimetilo/metanol (1:1, 10 mL) y se cargó sobre Gilson, C18(100A) 250x121,2 mm(10micron), eluyendo con 30% acetonitrilo a 65% acetonitrilo a lo largo de 40 minutos. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) δ 11,54 (s, 1 H), 8,43 (m, 2 H), 7,94 (d, 1 H), 7,71 (dd, 1 H), 7,57 (d, 1 H), 7,43 (m, 1 H), 7,34 (m, 3 H), 7,05 (d, 2 H), 6,90 (d, 1 H), 6,63 (dd, 1 H), 6,29 (d, 2 H), 3,43 (m, 2 H), 2,96 (m, 6 H), 2,73 (m, 2 H), 2,22 (m, 7 H), 1,87 (m, 4 H), 1,38 (m, 3 H), 0,94 (m, 6 H), 0,62 (m, 4 H).

EJEMPLO 292

N-([5-cloro-6-(2-metoxietoxi)piridin-3-il)sulfonil]-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 292A

5-cloro-6-(2-metoxietoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 40A en lugar de 4-fluoro-3-nitrobencenosulfonamida y 2-metoxietanol en lugar de (tetrahydro-2H-piran-4-il)metanol en el EJEMPLO 24A.

5 EJEMPLO 292B

N-{{[5-cloro-6-(2-metoxietoxi)piridin-3-il]sulfonil}-4-(4-{{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 292A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (400MHz, sulfóxido de dimetilo-d₆) □ 11,63 (s, 1H), 8,48 (d, 1H), 8,17 (d, 1H), 8,01 (d, 1H), 7,56 (d, 1H), 7,49 (m, 2H), 7,35 (d, 2H), 7,04 (d, 2H), 6,66 (dd, 1H), 6,37 (m, 1H), 6,21 (d, 1H), 4,52 (m, 2H), 3,70 (m, 2H), 3,28 (s, 3H), 3,13 (br m, 4H), 2,88 (br s, 2H), 2,34 (br m, 4H), 2,16 (br m, 2H), 1,97 (s, 2H), 1,40 (t, 2H), 0,92 (s, 6H).

15 EJEMPLO 293

4-(4-{{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{{[5-fluoro-6-(tetrahydro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 293A

El compuesto del título se preparó utilizando 5-bromo-2,3-difluoropiridina en lugar de 4-fluoro-3-nitrobencenosulfonamida en el EJEMPLO 24A.

EJEMPLO 293B

5-fluoro-6-((tetrahydro-2H-piran-4-il)metoxi)piridin-3-ilcarbamato de tert-butilo

El compuesto del título se preparó utilizando el EJEMPLO 293A en lugar del EJEMPLO 248A en el EJEMPLO 248B.

EJEMPLO 293C

cloruro de 5-fluoro-6-((tetrahydro-2H-piran-4-il)metoxi)piridin-3-sulfonilo

El compuesto del título se preparó utilizando el EJEMPLO 293B en lugar del EJEMPLO 248B en el EJEMPLO 248C.

EJEMPLO 293D

5-fluoro-6-((tetrahydro-2H-piran-4-il)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 293C en lugar del EJEMPLO 248C en el EJEMPLO 248D.

EJEMPLO 293E

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 293D en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (400 MHz, piridina-d₅) δ 13,07 (s, 1H), 9,05 (d, 1H), 8,44 (dd, 1H), 8,41 (d, 1H), 8,09 (d, 1H), 7,67 (t, 1H), 7,65 (d, 1H), 7,44 (m, 2H), 7,07 (m, 2H), 6,76 (dd, 1H), 6,53 (d, 1H), 6,49 (dd, 1H), 4,21 (d, 2H), 3,96 (dd, 2H), 3,31 (td, 2H), 3,07 (m, 4H), 2,77 (s, 2H), 2,26 (t, 2H), 2,14 (m, 4H), 1,97 (m, 3H), 1,58 (dd, 2H), 1,38 (m, 4H), 0,94 (s, 6H).

10 EJEMPLO 294

N-[(3-cloro-4-([1-(metoxiacetil)piperidin-4-il]metoxi)fenil)sulfonil]-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 294A

15 4-((2-cloro-4-sulfamoilfenoxi)metil)piperidin-1-carboxilato de *tert*-butilo

El compuesto del título se preparó utilizando 4-(hidroximetil)piperidin-1-carboxilato de *tert*-butilo en lugar de (4-fluoro-1-metilpiperidin-4-il)metanol en el EJEMPLO 283A.

EJEMPLO 294B

20 4-((4-(N-(2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoil)sulfamoil)-2-clorofenoxi)metil)piperidin-1-carboxilato de *tert*-butilo

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 294A en lugar del EJEMPLO 1F en el EJEMPLO 1G.

25

EJEMPLO 294C

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-N-(3-cloro-4-(piperidin-4-ilmetoxi)fenil)sulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzamida

A EJEMPLO 294B (0,286 g) en diclorometano (3 mL) se agregó ácido trifluoroacético (1 mL) y la reacción se agitó a temperatura ambiente. Luego de 3 horas la reacción se concentró para dar el compuesto del título.

EJEMPLO 294D

35 N-[(3-cloro-4-([1-(metoxiacetil)piperidin-4-il]metoxi)fenil)sulfonil]-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

A EJEMPLO 294C (0,75 g) como una solución en diclorometano (1 mL) se agregó N,N-diisopropiletilamina (0,055 mL) seguido por cloruro de 2-metoxiacetilo (6 µl). Luego de agitar por 10 minutos la reacción se cargó sobre gel de sílice (Reveleris 40 g) y se eluyó usando un gradiente de metanol entre 0,5% y 3,5%/diclorometano a lo largo de 30 minutos (velocidad de flujo = 40 mL/minutos) para dar el compuesto del título. ¹H NMR (300 MHz, sulfóxido de dimetilo- d₆) δ 11,71 (s, 1H), 11,55 - 11,24 (m, 1H), 8,06 (d, 1H), 7,88 (d, 1H), 7,78 (d, 1H), 7,57 (s, 1H), 7,51 (s, 1H), 7,48 (d, 1H), 7,34 (d, 2H), 7,21 (d, 1H), 7,04 (d, 2H), 6,67 (d, 1H), 6,42 (dd, 1H), 6,18 (s, 1H), 4,42 - 4,32 (m, 1H), 4,03 (dd, 4H), 3,86 - 3,74 (m, 1H), 3,28 (s, 3H), 3,07 (s, 5H), 2,77 (s, 3H), 2,30 - 1,92 (m, 9H), 1,77 (s, 2H), 1,31 (d, 4H), 0,92 (s, 6H).

EJEMPLO 295

N-[(3-cloro-4-[[1-(N,N-dimetilglicil)piperidin-4-il]metoxi]fenil)sulfonil]-4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando cloruro de 2-(dimetilamino)acetilo en lugar de cloruro de 2-metoxiacetilo en el EJEMPLO 294D. ¹H NMR (300 MHz, sulfóxido de dimetilo- d₆) δ 11,58 (s, 1H), 10,35 - 9,94 (m, 1H), 7,96 (d, 1H), 7,74 (d, 1H), 7,55 (d, 2H), 7,45 (s, 1H), 7,41 - 7,29 (m, 3H), 7,05 (d, 3H), 6,63 (d, 1H), 6,37 - 6,32 (m, 1H), 6,22 (d, 1H), 4,39 (d, 1H), 3,94 (s, 6H), 3,01 (s, 6H), 2,73 (m, 4H), 2,55 (m, 5H), 2,19 (s, 6H), 1,95 (m, 2H), 1,82 (m, 2H), 1,38 (s, 4H), 0,93 (s, 6H).

EJEMPLO 296

4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohexil]metil]piperidin-1-il)-N-({3-nitro-4-[(tetrahydro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 296A

4-((4,4-dimetil-2-oxociclohexil)metil)piperidin-1-carboxilato de tert-butilo

Se agregó 3,3-dimetilciclohexanona (5,60 mL) a bis(trimetilsilil)amida de sodio (45,3 mL, 1M en tetrahidrofurano), y la reacción se agitó por 1 hora. Se agregó 4-(bromometil)piperidin-1-carboxilato de tert-butilo (11,1 g) en sulfóxido de dimetilo (30 mL), y la reacción se agitó a 50°C por 24 horas. La reacción se enfrió, se vertió en agua (300 mL), se extrajo tres veces con éter, y los extractos combinados se lavaron tres veces con agua, y salmuera, se secó sobre Na₂SO₄, se filtró, y se concentró. El producto crudo se cromatografió sobre gel de sílice usando acetato de etilo al 5-20% en hexanos para dar el compuesto del título.

EJEMPLO 296B

4-((2-(4-clorofenil)-2-hidroxi-4,4-dimetilciclohexil)metil)piperidin-1-carboxilato de tert-butilo

Se agregó bromuro de (4-clorofenil)magnesio (14,1 mL, 1M en éter) a EJEMPLO 296A (3,25 g) en tetrahidrofurano (40 mL) a -78°C, y la reacción se agitó por 20 minutos, y
5 luego se dejó calentar a temperatura ambiente durante la noche. La reacción se detuvo con solución amortiguadora de pH 7 (20 mL), se extrajo con 2x éter, y los extractos combinados se lavaron con salmuera, se secó sobre Na₂SO₄, se filtró, y se concentró. El producto crudo se cromatografió sobre gel de sílice usando acetato de etilo al 1-20% en hexanos para dar el compuesto del título.

10

EJEMPLO 296C

trans-4-((2-(4-clorofenil)-4,4-dimetilciclohexil)metil)piperidina

El compuesto del título se preparó utilizando el EJEMPLO 296B en lugar del EJEMPLO 1A en el EJEMPLO 1B.

15

EXMAPLE 296D

Trans-2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohexil)metil)piperidin-1-il)benzoato de metilo

El compuesto del título se preparó utilizando el EJEMPLO 296C en lugar del EJEMPLO 263G en el EJEMPLO 263H.

20

EJEMPLO 296E

ácido trans-2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohexil)metil)piperidin-1-il)benzoico

El compuesto del título se preparó utilizando el EJEMPLO 296D en lugar del EJEMPLO 3I en el EJEMPLO 3J.

25

EJEMPLO 296F

Trans-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohexil]metil)piperidin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

30

El compuesto del título se preparó utilizando el EJEMPLO 296E en lugar del EJEMPLO 1E en el EJEMPLO 1G. ¹H NMR (300MHz, sulfóxido de dimetilo-d₆) □ 11,69 (s, 1H), 11,36 (br s, 1H), 8,60 (t, 1H), 8,55 (d, 1H), 8,03 (d, 1H), 7,78 (dd, 1H), 7,52 (m, 3H), 7,27 (d, 2H), 7,16 (d, 2H), 7,09 (m, 1H), 6,63 (dd, 1H), 6,38 (dd, 1H), 6,11 (d, 1H), 3,83 (dd, 2H),
35 3,52 (m, 2H), 3,26 (m, 4H), 2,61 (m, 2H), 2,35 (m, 1H), 1,89 (m, 2H), 1,76 (m, 1H), 1,62 (m, 2H), 1,38 (m, 4H), 1,25 (m, 6H), 1,12 (m, 2H), 0,95 (m, 2H), 0,94 (s, 3H), 0,88 (s, 3H).

EJEMPLO 297

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)-N-([6-(tetrahidro-2H-piran-4-ilmetoxi)-5-(trifluorometil)piridin-3-il]sulfonil)benzamida

5

EJEMPLO 297A

6-((tetrahidro-2H-piran-4-il)metoxi)-5-(trifluorometil)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 288E en lugar de 4-fluoro-3-nitrobenzenosulfonamida en el EJEMPLO 24A.

10

EJEMPLO 297B

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)-N-([6-(tetrahidro-2H-piran-4-ilmetoxi)-5-(trifluorometil)piridin-3-il]sulfonil)benzamida

15

El compuesto del título se preparó utilizando el EJEMPLO 297A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (400MHz, sulfóxido de dimetilo-d₆) □ 11,49 (s, 1 H), 8,56 (d, 1 H), 8,23 (d, 1 H), 7,90 (d, 1 H), 7,58 (d, 1 H), 7,40 (m, 1 H), 7,34 (m, 2 H), 7,26 (d, 1 H), 7,05 (d, 2 H), 6,61 (dd, 1 H), 6,28 (dd, 1 H), 6,24 (d, 1 H), 4,24 (d, 2 H), 3,86 (dd, 2 H), 3,30 (m, 4 H), 3,00 (s, 4 H), 2,73 (s, 2 H), 2,16 (m, 6 H), 1,97 (m, 2 H), 1,61 (dd, 2 H), 1,33 (m, 4 H), 0,93 (s, 6 H).

20

EJEMPLO 298

N-([5-cloro-6-[(trans-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-pirrol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 298A

6-((trans-4-(tert-butildimetilsililoxi)ciclohexil)metoxi)-5-cloropiridin-3-sulfonamida

El compuesto del título se preparó utilizando (trans-4-(tert-butildimetilsililoxi)ciclohexil)metanol en lugar de (tetrahidro-2H-piran-4-il)metanol y EJEMPLO 40A en lugar del EJEMPLO 36A en el EJEMPLO 36B.

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EJEMPLO 298B

N-([5-cloro-6-[(trans-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-pirrol[2,3-b]piridin-5-iloxi)benzamida

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El compuesto del título se preparó utilizando el EJEMPLO 298A en lugar del EJEMPLO 11B en el EJEMPLO 11D. Luego de finalizar la reacción, el solvente se eliminó, y

el residuo se trató con 1:1 ácido trifluoroacético/diclorometano por dos horas. Los solventes se eliminaron, y el residuo se purificó mediante un sistema 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

5 título, ^1H NMR (500MHz, sulfóxido de dimetilo- d_6) δ 11,65 (s, 1H), 8,47 (s, 1H), 8,15 (s, 1H), 8,01 (d, 1H), 7,54 (d, 1H), 7,48-7,49 (m, 1H), 7,35 (d, 2H), 7,05 (d, 2H), 6,67 (dd, 1H), 6,37 (d, 1H), 6,21 (s, 1H), 4,53 (t, 1H), 4,18 (d, 2H), 3,08 (s, 4H), 2,84 (s, 2H), 2,29 (s, 4H), 2,15 (s, 2H), 1,96 (s, 2H), 1,79-1,83 (m, 5H), 1,39 (t, 2H), 1,08-1,13 (m, 5H), 0,93 (s, 6H).

10 EJEMPLO 299

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 299A

15 3-ciano-4-((4-fluorotetrahidro-2H-piran-4-il)metoxi)bencenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 37C en lugar de (tetrahidro-2H-piran-4-il)metanol en el EJEMPLO 284A.

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EJEMPLO 299B

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO

25 1E y EJEMPLO 299A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ^1H NMR (300 MHz, sulfóxido de dimetilo- d_6) δ 11,72 (s, 1H), 10,24 - 9,27 (m, 1H), 8,21 (d, 1H), 8,12 (dd, 1H), 8,05 (d, 1H), 7,63 - 7,46 (m, 3H), 7,45 - 7,31 (m, 3H), 7,07 (d, 2H), 6,70 (dd, 1H), 6,42 (s, 1H), 6,23 (s, 1H), 4,38 (d, 2H), 3,91 - 3,73 (m, 2H), 3,68 - 3,51 (m, 2H), 3,22 - 2,96 (m, 10H), 2,31 - 2,12 (m, 2H), 1,99 (s, 6H), 1,43 (t, 2H), 0,93 (s, 6H).

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EJEMPLO 300

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([6-[(trans-4-metoxiciclohexil)metoxi]-5-(trifluorometil)piridin-3-il]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 300A

6-((trans-4-metoxiciclohexil)metoxi)-5-(trifluorometil)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 288E en lugar de 4-fluoro-3-nitrobenzenosulfonamida y EJEMPLO 121A en lugar de (tetrahidro-2H-piran-4-il)metanol en el EJEMPLO 24A.

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EJEMPLO 300B

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({6-[(trans-4-metoxiciclohexil)metoxi]-5-(trifluorometil)piridin-3-il}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

10 El compuesto del título se preparó utilizando el EJEMPLO 300A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (400MHz, sulfóxido de dimetilo-d₆) □ 11,50 (s, 1 H), 8,56 (d, 1 H), 8,23 (d, 1 H), 7,90 (d, 1 H), 7,58 (d, 1 H), 7,40 (m, 1 H), 7,35 (d, 2 H), 7,27 (d, 1 H), 7,05 (d, , 2 H), 6,61 (dd, 1 H), 6,28 (dd, 1 H), 6,24 (d, 1 H), 4,20 (d, 2 H), 3,23 (s, 3 H), 3,03 (m, 5 H), 2,73 (s, 2 H), 2,18 (m, 6 H), 1,98 (m, 5 H), 1,80 (m, 3 H), 1,39 (t, 2 H), 1,09 (m, 4 H), 0,93 (s, 6 H).

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EJEMPLO 301

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({6-[(cis-4-metoxiciclohexil)metoxi]-5-(trifluorometil)piridin-3-il}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 301A

6-((cis-4-metoxiciclohexil)metoxi)-5-(trifluorometil)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 288E en lugar de 4-fluoro-3-nitrobenzenosulfonamida y EJEMPLO 121A en lugar de (tetrahidro-2H-piran-4-il)metanol en el EJEMPLO 24A.

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EJEMPLO 301B

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({6-[(cis-4-metoxiciclohexil)metoxi]-5-(trifluorometil)piridin-3-il}sulfonil)-2-(1H-pirrol[2,3b]piridin-5-iloxi)benzamida

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El compuesto del título se preparó utilizando el EJEMPLO 301A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (400MHz, sulfóxido de dimetilo-d₆) □ 11,49 (m, 1 H), 8,54 (m, 1 H), 8,23 (d, 1 H), 7,91 (d, 1 H), 7,59 (d, 1 H), 7,40 (m, 1 H), 7,34 (m, 2 H), 7,27 (d, 1 H), 7,04 (d, 2 H), 6,61 (dd, 1 H), 6,29 (dd, 1 H), 6,24 (d, 1 H), 4,20 (d, 2 H), 3,37 (m,

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2 H), 3,19 (s, 3 H), 3,00 (s, 4 H), 2,73 (s, 2 H), 2,18 (m, 6 H), 1,96 (s, 2 H), 1,80 (m, 3 H), 1,50 (dd, 2 H), 1,37 (m, 6 H), 0,93 (s, 6 H).

EJEMPLO 302

- 5 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]piperidin-1-il}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 302A

4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperidina

- 10 Se agitó EJEMPLO 296B (1,0 g) en diclorometano (15 mL) y ácido trifluoroacético (15 mL) a 35°C por 48 horas. La mezcla se concentró, se recogió con diclorometano (100 mL), y se agitó, y se agregó solución saturada de Na₂CO₃ (20 mL) lentamente. La solución se separó y la capa orgánica se secó sobre Na₂SO₄, se filtró, y se concentró para dar el compuesto del título.

- 15 EJEMPLO 302B

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-{4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperidin-1-il}benzoato de metilo

El compuesto del título se preparó utilizando el EJEMPLO 302A en lugar del EJEMPLO 263G en el EJEMPLO 263H.

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EJEMPLO 302C

ácido 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-{4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperidin-1-il}benzoico

El compuesto del título se preparó utilizando el EJEMPLO 302B en lugar del

- 25 EJEMPLO 3I en el EJEMPLO 3J.

EJEMPLO 302D

1,1-difluoro-4-metilciclohexano

- 30 Se agregó butillitio (12,32 mL, 2,5 M solución 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 302E

- 35 4,4-difluoro-1-(hidroximetil)ciclohexanol

A la solución del Ejemplo 302D se agregó agua (75 mL), luego N-óxido de N-metilmorfolina (6,4 mL, 50% solución en agua) y OsO₄ (14,2 g, solución al 2,5 % en peso 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 Na₂S₂O₃ (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 HCl 1M, 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.

10 EJEMPLO 302F

5-cloro-6-((4,4-difluoro-1-hidrox ciclohexil)metoxi)piridin-3-sulfonamida

Este ejemplo se preparó utilizando el EJEMPLO 302E en lugar de tetrahydro-2H-piran-4-il)metanol y EJEMPLO 40A en lugar de 4-fluoro-3-nitrobenzenosulfonamida en el EJEMPLO 24A.

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EJEMPLO 302G

N-({5-cloro-6-[(4,4-difluoro-1-hidrox ciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperidin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 302C en lugar del EJEMPLO 1E y EJEMPLO 302F en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300MHz, sulfóxido de dimetilo-d₆) □ 11,65 (br s, 2H), 8,51 (s, 1H), 8,18 (s, 1H), 8,02 (d, 1H), 7,53 (m, 3H), 7,35 (d, 2H), 7,04 (d, 2H), 6,69 (dd, 1H), 6,39 (dd, 1H), 6,21 (d, 1H), 4,88 (s, 1H), 4,27 (s, 2H), 3,10 (m, 4H), 2,88 (m, 1H), 2,33 (m, 2H), 2,15 (m, 4H), 1,97 (s, 2H), 1,91 (m, 2H), 1,73 (m, 4H), 1,52 (m, 1H), 1,40 (m, 2H), 1,31 (m, 1H), 0,93 (s, 3H), 0,91 (m, 2H).

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EJEMPLO 303

N-[(3-cloro-4-{[trans-4-(morfolin-4-il)ciclohexil]metoxi}fenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 303A

30 trans-4-morfolinociclohexil)metanol

A trans-4-(hidroximetil)ciclohexilcarbamato de *tert*-butilo (0,500 g) se agregó cloruro de hidrógeno (4,0M en dioxano, 2,2 mL) y la reacción se agitó por 1 hora y se concentró. El sólido resultante se disolvió en acetonitrilo (4 mL) y se trató con N,N-diisopropiletilamina (1,523 mL) seguido por 1-bromo-2-(2-bromoetoxi)etano (0,556 g) y se calentó a 60°C. Luego de agitar durante la noche la reacción se concentró, se cargó sobre gel de sílice (Reveleris

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40 g) y se eluyó usando un gradiente de metanol entre 1% y 10%/diclorometano a lo largo de 30 minutos (velocidad de flujo = 40 mL/min) para dar el compuesto del título.

EJEMPLO 303B

5 3-cloro-4-(((1r,4r)-4-morfolinociclohexil)metoxi)bencenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 303A en lugar de (4-fluoro-1-metilpiperidin-4-il)metanol en el EJEMPLO 283A.

EJEMPLO 303C

10 N-[(3-cloro-4-[[trans-4-(morfolin-4-il)ciclohexil]metoxi]fenil)sulfonil]-4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 303B en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo- d₆) δ 11,65 (s, 1H), 10,96 – 10,59 (m, 1H), 8,02 (d, 1H), 7,82 (d, 1H), 7,69 (s, 1H), 7,50 (dd, 3H), 7,38 – 7,30 (m, 2H), 7,15 – 6,99 (m, 3H), 6,65 (dd, 1H), 6,39 (dd, 15 1H), 6,20 (d, 1H), 3,91 (d, 2H), 3,64 (s, 4H), 3,04 (s, 4H), 2,73 (s, 7H), 2,18 (s, 6H), 1,93 (m, 6H), 1,80 – 1,65 (m, 1H), 1,32 (m, 6H), 0,92 (s, 6H).

EJEMPLO 304

20 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[4-[[3-(ciclopropil(1,3-tiazol-5-ilmetil)amino)propil]amino)-3-nitrofenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

A una solución de EJEMPLO 291E (95 mg) en diclorometano (2 mL) y ácido acético (0,5 mL) se agregó tiazol-5-carbaldehído (13 mg) seguido por triacetoxiborhidruro de sodio (35 mg). La mezcla se agitó durante la noche. La mezcla se diluyó con diclorometano (300 25 mL) y se lavó con NaHCO₃ acuoso, agua, y salmuera y se secó sobre Na₂SO₄. La filtración y evaporación del solvente dio producto crudo el cual se disolvió en sulfóxido de dimetilo/metanol (6 mL, 1:1) y se cargó sobre Gilson, C18(100A) 250x121,2 mm(10micron), con 30% acetonitrilo a 65% acetonitrilo durante 40 minutos. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) □ 11,67 (s, 1 H), 8,95 (s, 1 H), 8,57 (m, 2 H), 8,03 (d, 1 H), 7,78 (m, 2 H), 7,49 30 (m, 3 H), 7,35 (m, 2 H), 7,02 (m, 3 H), 6,67 (dd, 1 H), 6,38 (dd, 1 H), 6,19 (d, 1 H), 4,00 (s, 2 H), 3,05 (d, 4 H), 2,73 (m, 2 H), 2,60 (m, 2 H), 2,18 (m, 7 H), 1,95 (s, 2 H), 1,79 (m, 3 H), 1,37 (m, 3 H), 0,92 (s, 6 H), 0,45 (m, 4 H).

EJEMPLO 305

35 N-[(3-cloro-4-[(trans-4-hidroxiciclohexil)metoxi]fenil)sulfonil]-4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 305A

3-cloro-4-((trans-4-hidroxiciclohexil)metoxi)bencenosulfonamida

Se trató (trans-4-(tert-butildimetilsililoxi)ciclohexil)metanol (275 mg, preparado de acuerdo a procedimientos en WO 2008/124878) y 3-cloro-4-fluorobencenosulfonamida (259 mg) en tetrahidrofurano (15 mL) con hidruro de sodio (180 mg, 60%) durante la noche. La reacción se detuvo con agua (1 mL) y se agregó ácido trifluoroacético (4 mL). La mezcla resultante se agitó por 1 hora y se concentró. El residuo se trituró con agua y metanol para dar el compuesto del título.

10 EJEMPLO 305B

N-({3-cloro-4-[(trans-4-hidroxiciclohexil)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 11D usando EJEMPLO 305A en lugar de EJEMPLO 11B. ¹H NMR (500 MHz, sulfóxido de dimetilo-d₆) □
 15 11,71 (s, 1 H), 11,38 (s, 1 H), 8,06 (d, 1 H), 7,87 (d, 1 H), 7,76 (dd, 1 H), 7,57 (d, 1 H), 7,51 - 7,55 (m, 1 H), 7,49 (d, 1 H), 7,34 (d, 2 H), 7,18 (d, 1 H), 7,04 (d, 2 H), 6,67 (dd, 1 H), 6,42 (dd, 1 H), 6,18 (d, 1 H), 4,54 (d, 1 H), 3,91 (d, 2 H), 3,07 (s, 4 H), 2,75 (s, 2 H), 2,17 (d, 6 H), 1,95 (s, 2 H), 1,78 - 1,90 (m, 4 H), 1,63 - 1,75 (m, 1 H), 1,38 (t, 2 H), 1,00 - 1,25 (m, 4 H), 0,92 (s, 6 H).

20 EJEMPLO 306

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-cloro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 306A

25 3-cloro-4-((tetrahidro-2H-piran-4-il)metilamino)bencenosulfonamida

El compuesto del título se preparó utilizando 4-fluoro-3-clorobencenosulfonamida en lugar de 4-cloro-3-nitrobencenosulfonamida, (tetrahidro-2H-piran-4-il)metanamina en lugar de diclorhidrato de 4-metilpiperazin-1-amina y Base de Hunig en lugar de N¹,N¹,N²,N²-tetrametiletan-1,2-diamina en el EJEMPLO 6A.

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EJEMPLO 306B

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-cloro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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El compuesto del título se preparó utilizando el EJEMPLO 306A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (400MHz, sulfóxido de dimetilo-d₆) □ 11,80 (s, 1H), 11,17 (br s, 1H), 8,09 (d, 1H), 7,71 (d, 1H), 7,63 (d, 1H), 7,58 (dd, 1H), 7,53 (dd, 1H), 7,50 (d, 1H), 7,34 (d, 2H), 7,03 (d, 2H), 6,74 (d, 1H), 6,66 (dd, 1H), 6,42 (m, 1H), 6,40 (t, 1H),
 5 6,16 (d, 1H), 3,83 (m, 2H), 3,24 (m, 2H), 3,10 (m, 2H), 3,06 (br m, 4H), 2,72 (s, 2H), 2,17 (br m, 6H), 1,95 (s, 2H), 1,83 (m, 1H), 1,59 (br m, 2H), 1,38 (t, 2H), 1,20 (ddd, 2H), 0,92 (s, 6H).

EJEMPLO 307

4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{{4-{{4-
 10 fluorotetrahidro-2H-piran-4-il)metoxi]-3-(trifluorometil)fenil}sulfonil}-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 307A

4-((4-fluorotetrahidro-2H-piran-4-il)metoxi)-3-(trifluorometil)bencenosulfonamida
 15 El compuesto del título se preparó utilizando 4-fluoro-3-(trifluorometil)bencenosulfonamida en lugar de 4-fluoro-3-nitrobencenosulfonamida y EJEMPLO 37C en lugar de (tetrahidro-2H-piran-4-il)metanol en el EJEMPLO 24A.

EJEMPLO 307B

4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{{4-{{4-
 20 fluorotetrahidro-2H-piran-4-il)metoxi]-3-(trifluorometil)fenil}sulfonil}-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 307A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (400 MHz, piridina-d₅) □ 13,07 (s, 1H), 8,78 (d, 1H), 8,58 (dd, 1H), 8,42 (d, 1H), 8,09 (d, 1H), 7,67 (t, 1H), 7,65 (d, 1H), 7,43 (m, 2H), 7,16 (d, 1H), 7,06 (m, 2H), 6,74 (dd, 1H), 6,51 (m, 2H), 4,21 (d, 2H), 3,87 (m, 2H), 3,78 (td, 2H), 3,06 (m, 4H), 2,76 (s, 2H), 2,25 (t, 2H), 2,13 (m, 4H), 1,95 (m, 6H), 1,39 (t, 2H), 0,93 (s, 6H).

EJEMPLO 308

4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{{4-{{3-
 30 [ciclopropil(2,2,2-trifluoroetil)amino]propil}amino)-3-nitrofenil}sulfonil}-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 308A

35 4-(3-(ciclopropilamino)propilamino)-3-nitrobencenosulfonamida

A una solución de EJEMPLO 291C (4,14 g) en diclorometano (10 mL) se agregó ácido trifluoroacético (10 mL). La mezcla se agitó por 2 horas. La mezcla se concentró bajo vacío y el residuo se disolvió en diclorometano (300 mL) y se lavó con NaHCO₃ acuoso, agua, y salmuera y se secó sobre Na₂SO₄. La filtración y evaporación del solvente dio el compuesto del título.

EJEMPLO 308B

4-(3-(ciclopropil(2,2,2-trifluoroetil)amino)propilamino)-3-nitrobencenosulfonamida

A una solución de EJEMPLO 308A (314 mg) en diclorometano (6 mL) se agregó trifluorometansulfonato de 2,2,2-trifluoroetilo (255 mg) y N,N-diisopropiletilamina (258 mg). La mezcla se agitó durante la noche. La mezcla se diluyó con diclorometano (300 mL) y se lavó con NaHCO₃ acuoso, agua, salmuera y se secó sobre Na₂SO₄. La filtración y evaporación del solvente dio el compuesto del título.

15 EJEMPLO 308C

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-(3-(ciclopropil(2,2,2-trifluoroetil)amino)propil)amino)-3-nitrofenil]sulfonyl)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 308B en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) □ 11,67 (s, 1 H), 11,38 (m, 1 H), 8,55 (d, 2 H), 8,03 (d, 1 H), 7,81 (dd, 1 H), 7,50 (m, 3 H), 7,34 (d, 2 H), 7,05 (m, 3 H), 6,67 (dd, 1 H), 6,38 (dd, 1 H), 6,19 (d, 1 H), 3,07 (m, 4 H), 2,82 (m, 4 H), 2,18 (m, 7 H), 1,38 (m, 2 H), 0,92 (s, 6 H), 0,44 (m, 4 H).

25 EJEMPLO 309

N-[(3-cloro-4-([1-(oxetan-3-il)piperidin-4-il]metoxi)fenil)sulfonyl]-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

A una solución de EJEMPLO 294B (0,150 g) en diclorometano (2 mL) se agregó ácido trifluoroacético (1 mL). Luego de agitar por 1 hora la reacción se concentró y se secó bajo alto vacío. El residuo se disolvió en diclorometano (2 mL) y se trató con triacetoxiborhidruro de sodio (0,050 g) y oxetan-3-ona (0,017 g) y se agitó durante la noche a temperatura ambiente. La reacción se detuvo con NaHCO₃ acuoso saturado (20 mL) y se extrajo con diclorometano (50 mL). La capa orgánica se separó, se lavó con salmuera (25 mL), se secó sobre Na₂SO₄, se filtró, y se concentró. La cromatografía sobre gel de sílice (Reveleris 40 g) eluyendo con un gradiente de metanol entre 0,5% y 5%/diclorometano a lo largo de 30 minutos (velocidad de flujo = 40 mL/min) dio el compuesto del título. ¹H NMR

(300 MHz, sulfóxido de dimetilo- d_6) δ 11,70 (s, 1H), 11,21 (s, 1H), 8,05 (d, 1H), 7,87 (d1H), 7,75 (dd, 1H), 7,61 - 7,42 (m, 3H), 7,42 - 7,26 (m, 2H), 7,18 (d, 1H), 7,14 - 6,97 (m, 2H), 6,67 (dd, 1H), 6,41 (dd, 1H), 6,18 (d, 1H), 4,51 (dt, 4H), 3,99 (d, 2H), 3,56 - 3,32 (m, 1H), 3,06 (s, 4H), 2,89 - 2,68 (m, 4H), 2,16 (d, 6H), 2,01 - 1,69 (m, 7H), 1,50 - 1,07 (m, 4H), 0,92 (s, 6H).

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EJEMPLO 310

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({3,5-difluoro-4-[(4-fluorotetrahydro-2H-piran-4-il)metoxi]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

10 EJEMPLO 310A

3,5-difluoro-4-((4-fluorotetrahydro-2H-piran-4-il)metoxi)bencenosulfonamida

Se trató EJEMPLO 37C (0,423 g) en tetrahydrofurano (30 mL) con NaH (dispersión de aceite al 60%) (0,480 g), se agitó 20 minutos a temperatura ambiente, se trató con 3,4,5-trifluorobencenosulfonamida (0,633 g) y se agitó 30 minutos. Se agregó N,N-dimetilacetamida (15 mL) para incrementar la solubilidad de los reactivos y la agitación se continuó durante la noche a temperatura ambiente. Se agregó NaH adicional (dispersión de aceite al 60%) (0,480 g) y N,N-dimetilacetamida (15 mL) y la mezcla se calentó durante la noche a 50°C. La reacción se detuvo con solución acuosa saturada de NH_4Cl y luego se particionó entre solución acuosa saturada de NH_4Cl y acetato de etilo. La capa orgánica se lavó con agua y salmuera, se secó (MgSO_4), se filtró y se concentró. El material concentrado se cromatografió sobre gel de sílice funcionalizado con amina con metanol entre 0 y 2% en CH_2Cl_2 como eluyente. El residuo se purificó adicionalmente mediante HPLC de fase inversa en una columna C18 usando un gradiente de 10-70% acetonitrilo/ácido trifluoroacético al 0,1% en agua para dar el compuesto del título.

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EJEMPLO 310B

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-({3,5-difluoro-4-[(4-fluorotetrahydro-2H-piran-4-il)metoxi]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 310A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ^1H NMR (500 MHz, piridina- d_5) δ 13,06 (s, 1H), 8,41 (d, 1H), 8,11 (m, 2H), 8,08 (d, 1H), 7,66 (m, 2H), 7,44 (m, 2H), 7,07 (m, 2H), 6,75 (dd, 1H), 6,52 (d, 1H), 6,50 (dd, 1H), 4,26 (d, 2H), 3,85 (dd, 1H), 3,83 (dd, 1H), 3,74 (m, 2H), 3,07 (m, 4H), 2,77 (s, 2H), 2,26 (t, 2H), 2,14 (m, 4H), 1,97 (s, 2H), 1,87 (m, 4H), 1,39 (t, 2H), 0,94 (s, 6H).

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EJEMPLO 311

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([3-(ciclopropil(oxetan-3-il)amino]propil)amino)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

5 EJEMPLO 311A

4-(3-(ciclopropil(oxetan-3-il)amino)propilamino)-3-nitrobencenosulfonamida

A una solución de EJEMPLO 308A (314 mg) en diclorometano (5 mL) se agregó oxetan-3-ona (72 mg) seguido por triacetoxiborhidruro de sodio (318 mg). La mezcla se agitó durante la noche. La mezcla se diluyó con diclorometano (300 mL) y se lavó con NaHCO₃ acuoso, agua y salmuera y se secó sobre Na₂SO₄. Luego de la filtración, la evaporación del solvente dio el compuesto crudo del título.

EJEMPLO 311B

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([3-(ciclopropil(oxetan-3-il)amino]propil)amino)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 311A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) δ 11,65 (s, 1 H), 11,37 (s, 1 H), 8,68 (s, 1 H), 8,54 (d, 1 H), 8,02 (d, 1 H), 7,79 (d, 1 H), 7,49 (m, 3 H), 7,34 (d, 2 H), 7,03 (m, 3 H), 6,67 (dd, 1 H), 6,38 (dd, 1 H), 6,19 (d, 1 H), 4,62 (m, 2 H), 4,48 (t, 2 H), 3,98 (m, 1 H), 3,37 (m, 2 H), 3,06 (m, 4 H), 2,73 (d, 2 H), 2,59 (m, 2 H), 2,23 (m, 6 H), 1,95 (s, 2 H), 1,74 (m, 3 H), 1,38 (t, 2 H), 0,92 (s, 6 H), 0,41 (m, 4 H).

25 EJEMPLO 312

N-([3-cloro-4-([1-(1-metil-L-prolil)piperidin-4-il]metoxi)fenil]sulfonil)-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

A EJEMPLO 294B (0,065 g) se agregó cloruro de hidrógeno (4,0M en dioxano, 0,339 mL) y unas pocas gotas de metanol. Luego de 30 minutos, la reacción se concentró, y se agregó ácido (S)-1-metilpirrolidin-2-carboxílico (0,013 g), clorhidrato de N¹-((etilimino)metilen)-N³,N³-dimetilpropan-1,3-diamina (0,026 g), suspendido en diclorometano (0,5 mL) seguido por diisopropiletilamina (0,036 mL). La mezcla se agitó a temperatura ambiente. Luego de agitar durante la noche, la mezcla de la reacción se cargó sobre gel de sílice (Reveleris 40g) y se eluyó usando un gradiente de metanol entre 1% y 10% (con NH₃ 1N)/diclorometano a lo largo de 30 minutos (velocidad de flujo = 40 mL/minutos) para dar el compuesto del título. ¹H NMR (300 MHz, sulfóxido de dimetilo- d₆) δ 11,51 (s, 1H), 10,00 –

9,22 (m, 1H), 7,92 (d, 1H), 7,68 (d, 1H), 7,57 (d, 1H), 7,47 (dd, 1H), 7,44 – 7,38 (m, 1H), 7,38 – 7,31 (m, 2H), 7,29 (d, 1H), 7,12 – 7,01 (m, 2H), 6,90 (d, 1H), 6,61 (dd, 1H), 6,31 (dd, 1H), 6,25 (d, 1H), 5,85 (d, 1H), 4,40 (s, 1H), 3,92 (s, 4H), 3,17 – 2,89 (m, 8H), 2,73 (s, 4H), 2,38 (s, 3H), 2,18 (m, 6H), 1,96 (s, 2H), 1,80 (m, 2H), 1,57 (s, 2H), 1,39 (s, 2H), 1,22 (m, 2H), 0,96 (m, 6H).

EJEMPLO 313

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3,4-difluoro-5-([4-fluorotetrahydro-2H-piran-4-il)metoxi]fenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 313A

3,4-difluoro-5-([4-fluorotetrahydro-2H-piran-4-il)metoxi]bencenosulfonamida

El compuesto del título se obtuvo como un subproducto en el EJEMPLO 310A.

EJEMPLO 313B

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3,4-difluoro-5-([4-fluorotetrahydro-2H-piran-4-il)metoxi]fenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 313A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (400 MHz, piridina-d₅) □ 13,05 (s, 1H), 8,41 (d, 1H), 8,10 (d, 1H), 7,98 (m, 2H), 7,66 (m, 1H), 7,63 (d, 1H), 7,44 (m, 2H), 7,07 (m, 2H), 6,77 (dd, 1H), 6,54 (d, 1H), 6,48 (dd, 1H), 4,12 (d, 2H), 3,83 (m, 2H), 3,75 (m, 2H), 3,08 (m, 4H), 2,77 (s, 2H), 2,26 (t, 2H), 2,15 (m, 4H), 1,97 (s, 2H), 1,82 (m, 4H), 1,39 (t, 2H), 0,94 (s, 6H).

EJEMPLO 314

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 314A

(S)-5-cloro-6-([4-ciclopropilmorfolin-2-il]metoxi)piridin-3-sulfonamida

Una solución de EJEMPLO 244B (250 mg), metanol anhidro (6 mL), (1-etoxiciclopropoxi)trimetilsilano (0,474 mL), y ácido acético (0,509 mL) se calentó a 70 °C por 30 minutos. Luego de enfriar a temperatura ambiente, se agregó cianoborohidruro de sodio (112 mg) y la mezcla se agitó por 18 horas. Se agregó cianoborohidruro de sodio adicional (75 mg) y la agitación se continuó 18 horas. La reacción se concentró y el residuo se

particionó entre cloruro de metileno y solución de bicarbonato de sodio saturado. El producto crudo se aisló a partir de la capa de cloruro de metileno seca y se purificó sobre gel de sílice y se eluyó con un gradiente escalonado de metanol al 1, 2,5, 5, 10% en cloruro de metileno para dar el compuesto del título.

5

EJEMPLO 314B

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

10 El compuesto del título se preparó utilizando el EJEMPLO 314A en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (400 MHz, piridin- d₅) □ 12,98 (s, 1H), 9,09 (d, 1H), 8,69 (d, 1H), 8,41 (d, 1H), 8,11 (d, 1H), 7,66 - 7,64 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,75 (dd, 1H), 6,53 (m, 1H), 6,48 (m, 1H), 5,72 (br s, 1H), 4,62 - 4,57 (m, 1H), 4,51 - 4,47 (m, 1H), 3,99 (m, 1H), 3,85 (m, 1H), 3,57 (m, 1H), 3,08 - 3,01 (m, 5H), 2,77 (s, 2H), 2,69 (m, 1H),
15 2,39 - 2,24 (m, 4H), 2,14 (m, 4H), 1,97 (s, 2H), 1,57 (m, 1H), 1,39 (t, 2H), 0,94 (m, 6H), 0,48 - 0,3 (m, 4H).

EJEMPLO 315

4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperidin-1-il)-N-([3-nitro-4-[(tetrahydro-2H-piran-4-ilmetil)amino]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

20 El compuesto del título se preparó utilizando el EJEMPLO 302C en lugar del EJEMPLO 1E y EJEMPLO 3J en lugar del EJEMPLO 1E en el EJEMPLO 1G. ¹H NMR (300MHz, sulfóxido de dimetilo-d₆) □ 11,70 (s, 1H), 11,35 (br s, 1H), 8,61 (m, 1H), 8,57 (d, 1H), 8,04 (d, 1H), 7,82 (dd, 1H), 7,45-7,57 (m, 3H), 7,33 (d, 2H), 7,15 (d, 1H), 7,01 (d, 2H),
25 6,65 (dd, 1H), 6,40 (dd, 1H), 6,11 (d, 1H), 3,85 (dd, 2H), 3,53 (m, 2H), 3,27 (m, 4H), 2,63 (m, 2H), 2,04 (m, 2H), 1,91 (s, 2H), 1,77 (m, 2H), 1,62 (m, 4H), 1,45 (m, 2H), 1,38 (m, 2H), 1,27 (m, 1H), 1,23 (m, 4H), 0,92 (s, 6H).

EJEMPLO 316

30 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperidin-1-il)-N-([3-cloro-4-(tetrahydro-2H-piran-4-ilmetoxi)fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 316A

3-cloro-4-((tetrahydro-2H-piran-4-il)metoxi)bencenosulfonamida

35 El compuesto del título se preparó utilizando (tetrahydro-2H-piran-4-il)metanol en lugar de (4-fluoro-1-metilpiperidin-4-il)metanol en el EJEMPLO 283A.

EJEMPLO 316B

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperidin-1-il)-N-([3-cloro-4-(tetrahidro-2H-piran-4-ilmetoxi)fenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 302C en lugar del
 5 EJEMPLO 1E y EJEMPLO 316A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300MHz, sulfóxido de dimetilo-d₆) □ 11,77 (s, 1H), 11,35 (br s, 1H), 8,06 (m, 1H), 7,88 (d, 1H), 7,79 (dd, 1H), 7,58 (s, 1H), 7,53 (t, 1H), 7,46 (d, 1H), 7,34 (d, 2H), 7,22 (d, 1H), 7,01 (d, 2H), 6,66 (dd, 1H), 6,42 (dd, 1H), 6,11 (d, 1H), 3,99 (d, 2H), 3,88 (dd, 2H), 3,52 (m, 2H), 3,34 (m, 4H), 2,62 (m, 2H), 2,04 (m, 4H), 1,76 (m, 2H), 1,68 (m, 2H), 1,46 (m, 2H), 1,38 (m, 4H),
 10 0,92 (s, 6H), 0,75 (m, 2H).

EJEMPLO 317

2-([4-([4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]sulfamoil)-2-nitrofenil)amino]metil)morfolina-4-carboxilato
 15 de metilo

EJEMPLO 317A

2-((2-nitro-4-sulfamoilfenilamino)metil)morfolina-4-carboxilato de metilo

El compuesto del título se preparó utilizando clorofornato de metilo en lugar de
 20 yoduro de metilo en el EJEMPLO 134B.

EJEMPLO 317B

2-([4-([4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]sulfamoil)-2-nitrofenil)amino]metil)morfolina-4-carboxilato
 25 de metilo

El compuesto del título se preparó utilizando el EJEMPLO 317A en lugar del
 EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridina-d₅) □ 13,00 (s, 1H), 9,26 (d, 1H), 8,84 (t, 1H), 8,43 (d, 1H), 8,35 (d, 1H), 8,12 (d, 1H), 7,66 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,91 (bs, 1H), 6,75 (dd, 1H), 6,54 (d, 1H), 6,48 (m, 1H), 4,29-4,03 (m, 1H), 3,89-3,70 (m, 3H), 3,71 (s, 3H), 3,55-3,38 (m, 3H), 3,07 (m, 4H), 2,96 (dt, 1H), 2,86 (dd, 1H), 2,77 (s, 2H), 2,26 (m, 2H), 2,14 (m, 4H), 1,97 (s, 2H), 1,39 (t, 2H), 0,94 (s, 6H).
 30

EJEMPLO 318

2-([4-([4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]sulfamoil)-2-nitrofenil)amino]metil)-N-etil-N-metilmorfolina-4-carboxamida
 35

EJEMPLO 318A

N-etil-N-metil-2-((2-nitro-4-sulfamoilfenilamino)metil)morfolina-4-carboxamida

El compuesto del título se preparó utilizando Cloruro de N-metil-N-etilcarbamilato en lugar de yoduro de metilo en el EJEMPLO 134B.

5

EJEMPLO 318B

2-[[[4-[[4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzoil]sulfamoil]-2-nitrofenil)amino]metil]-N-etil-N-metilmorfolina-4-carboxamida

10

El compuesto del título se preparó utilizando el EJEMPLO 318A en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridina-d₅) □ 13,00 (s, 1H), 9,26 (d, 1H), 8,86 (t, 1H), 8,44 (d, 1H), 8,33 (dd, 1H), 8,12 (d, 1H), 7,67 (t, 1H), 7,64 (d, 1H), 7,44 (d, 2H), 7,07 (d, 2H), 6,91 (d, 1H), 6,75 (dd, 1H), 6,54 (d, 1H), 6,48 (m, 1H), 3,92-3,85 (m, 2H), 3,75 (d, 1H), 3,62 (dt, 1H), 3,55-3,48 (m, 1H), 3,45-3,39 (m, 2H), 3,21 (q, 2H), 3,07 (m, 4H), 2,99 (dt, 1H), 2,90 (dd, 1H), 2,77 (s, 2H), 2,76 (s, 3H), 2,26 (m, 2H), 2,14 (m, 4H), 1,97 (s, 2H), 1,39 (t, 2H), 1,06 (t, 3H), 0,93 (s, 6H).

15

EJEMPLO 319

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]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

20

EJEMPLO 319A

4-((4-(metilsulfonil)morfolin-2-il)metilamino)-3-nitrobencenosulfonamida

25

El compuesto del título se preparó utilizando cloruro de metansulfonilo en lugar de yoduro de metilo en el EJEMPLO 134B.

EJEMPLO 319B

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]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

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El compuesto del título se preparó utilizando el EJEMPLO 319A en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridina-d₅) □ 13,00 (s, 1H), 9,25 (d, 1H), 8,84 (t, 1H), 8,43 (d, 1H), 8,32 (dd, 1H), 8,13 (d, 1H), 7,67 (t, 1H), 7,65 (d, 1H), 7,44 (d, 2H), 7,07 (d, 2H), 6,92 (d, 1H), 6,75 (dd, 1H), 6,54 (d, 1H), 6,48 (m, 1H), 3,99 (m, 1H), 3,92-3,88 (m, 2H), 3,64 (m, 2H), 3,56 (m, 1H), 3,50 (m, 1H), 3,07 (m, 4H), 3,04 (s, 3H),

2,95-2,88 (m, 2H), 2,77 (s, 2H), 2,26 (m, 2H), 2,14 (m, 4H), 1,97 (s, 2H), 1,39 (t, 2H), 0,94 (s, 6H).

EJEMPLO 320

- 5 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([3-(ciclobutil(ciclopropil)amino)propil]amino)-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 320A

- 10 4-(3-(ciclobutil(ciclopropil)amino)propilamino)-3-nitrobencenosulfonamida

A una solución de EJEMPLO 308A (314 mg) en diclorometano (5 mL) se agregó ciclobutanona (70 mg) seguido por triacetoxiborhidruro de sodio (318 mg). La mezcla se agitó durante la noche. La mezcla se diluyó con diclorometano (300 mL) y se lavó con NaHCO₃ acuoso, agua y salmuera y se secó sobre Na₂SO₄. Luego de la filtración, la evaporación del
15 solvente dio el compuesto del título.

EJEMPLO 320B

- 20 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([3-(ciclobutil(ciclopropil)amino)propil]amino)-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 320A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) □ 11,65 (s, 1 H), 8,70 (m, 1 H), 8,54 (d, 1 H), 8,02 (d, 1 H), 7,79 (dd, 1 H), 7,49 (m, 3 H), 7,34 (d, 2 H), 7,03 (m, 3 H), 6,66 (dd, 1 H), 6,38 (dd, 1 H), 6,19 (d, 1 H),
25 3,37 (q, 2 H), 3,06 (m, 4 H), 2,73 (s, 2 H), 2,63 (m, 2 H), 2,21 (m, 8 H), 1,82 (m, 3 H), 1,53 (m, 2 H), 1,38 (t, 2 H), 0,94 (m, 6 H), 0,41 (m, 4 H).

EJEMPLO 321

- 30 4-(4-([2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 321A

5,5-difluoro-2-oxociclohexanocarboxilato de etilo

- 35 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.

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EJEMPLO 321B

5,5-difluoro-2-(trifluorometilsulfonilo)ciclohex-1-encarboxilato de etilo

A una solución de EJEMPLO 321A (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), y 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.

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EJEMPLO 321C

2-(4-clorofenil)-5,5-difluorociclohex-1-encarboxilato de etilo

Una solución de EJEMPLO 321B (3,47 g), ácido 4-clorofenilborónico (1,925 g) y fluoruro de cesio (3,43 g) en 30 ml de 1,2-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) y 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.

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EJEMPLO 321D

(2-(4-clorofenil)-5,5-difluorociclohex-1-enil)metanol

A una solución de EJEMPLO 321C (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.

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EJEMPLO 321E

2-(4-clorofenil)-5,5-difluorociclohex-1-encarbaldehido

A una solución de EJEMPLO 321D (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 321F

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-5,5-difluorociclohex-1-enil)metil)piperazin-1-il)benzoato de metilo

El compuesto del título se preparó utilizando el EJEMPLO 321E en lugar del EJEMPLO 15E en el EJEMPLO 15G.

EJEMPLO 321G

ácido 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-5,5-difluorociclohex-1-enil)metil)piperazin-1-il)benzoico

El compuesto del título se preparó utilizando el EJEMPLO 321F en lugar del EJEMPLO 15G en el EJEMPLO 15H.

EJEMPLO 321H

4-(4-{{2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-[[tetrahidro-2H-piran-4-ilmetil]amino]fenil}sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 321G en lugar del EJEMPLO 1E y EJEMPLO 3J en lugar del EJEMPLO 1E en el EJEMPLO 1G.. ¹H NMR (300 MHz, sulfóxido de dimetilo- d₆) δ 11,74 - 11,63 (m, 1H), 11,53 - 11,29 (m, 1H), 8,57 (d, 2H), 8,05 (d, 1H), 7,85 - 7,77 (m, 1H), 7,49 (d, 3H), 7,38 (d, 2H), 7,16 - 7,06 (m, 3H), 6,73 - 6,64 (m, 1H), 6,43 - 6,36 (m, 1H), 6,21 - 6,14 (m, 1H), 3,93 - 3,77 (m, 2H), 3,29 (d, 4H), 3,07 (s, 4H), 2,79 - 2,57 (m, 4H), 2,45 (dd, 2H), 2,19 (s, 6H), 1,99 - 1,80 (m, 1H), 1,70 - 1,54 (m, 2H), 1,38 - 1,13 (m, 2H).

EJEMPLO 322

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 322A

4-fluoro-4-(hidroximetil)piperidin-1-carboxilato de tert-butilo

Se colocó 4-fluoropiperidin-1,4-dicarboxilato de 1-tert-butilo 4-etilo (2 g) en tetrahidrofurano (20 ml) y se enfrió en un baño de hielo. Se agregó hidruro de litio y aluminio (1,0M en dioxano, 5,09 mL) por goteo. La reacción se agitó a temperatura ambiente por 2 horas. La reacción se detuvo con agua y con solución acuosa 1M de NaOH y luego se agitó otra 1 hora a temperatura ambiente. La mezcla se extrajo con acetato de etilo, y los extractos se combinaron y se lavó con agua y con salmuera, se secó sobre MgSO₄, se filtró y se concentró bajo vacío. El producto crudo se usó sin purificación adicional.

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EJEMPLO 322B

4-((2-cloro-4-sulfamoilfenoxi)metil)-4-fluoropiperidin-1-carboxilato de tert-butilo

El compuesto del título se preparó utilizando el EJEMPLO 322A en lugar de (tetrahidro-2H-piran-4-il)metanol y 3-cloro-4-fluorobencenosulfonamida en lugar de 4-fluoro-3-nitrobencenosulfonamida en el EJEMPLO 24A.

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EJEMPLO 322C

3-cloro-4-((4-fluoropiperidin-4-il)metoxi)bencenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 322B en lugar del EJEMPLO 1A en el EJEMPLO 1B.

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EJEMPLO 322D

3-cloro-4-((4-fluoro-1-(oxetan-3-il)piperidin-4-il)metoxi)bencenosulfonamida

A una solución de EJEMPLO 322C (830 mg) en tetrahidrofurano (15 mL) y ácido acético (5 mL) se agregó oxetan-3-ona (163 mg) y MP-cianoborohidruro (2,38 mmol/g, 1,9 g). La mezcla se agitó a temperatura ambiente durante la noche. La reacción luego se filtró y el material filtrado se concentró bajo vacío. Se formó una lechada con el residuo en éter y el producto sólido se recogió mediante filtración.

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30 EJEMPLO 322E

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 322D en lugar del EJEMPLO 1F y EJEMPLO 3J en lugar del EJEMPLO 1E en el EJEMPLO 1G. ¹H NMR (400 MHz, sulfóxido de dimetilo-d₆) δ 11,71 (s, 1H), 8,06 (d, 1H), 7,89 (d, 1H), 7,79 (m, 1H), 7,58 (d, 1H), 7,52 (t, 1H), 7,49 (d, 1H), 7,34 (d, 2H), 7,25 (d, 1H), 7,04 (d, 2H), 6,67 (dd, 1H), 6,42

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(m, 1H), 6,18 (d, 1H), 4,55 (t, 2H), 4,44(t, 2H), 4,24 (d, 2H), 3,44 (m, 2H), 3,07 (br s, 4H), 2,74 (m, 2H), 2,59 (m, 2H), 2,14 (m, 7H), 1,95 (m, 4H), 1,78 (m, 2H), 1,38 (t, 2H), 0,92 (s, 6H).

EJEMPLO 323

- 5 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{{3-cloro-4-(tetrahydrofurano-3-ilmetoxi)fenil}sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 323A

3-cloro-4-((tetrahydrofurano-3-il)metoxi)bencenosulfonamida

- 10 El compuesto del título se preparó utilizando 4-fluoro-3-clorobencenosulfonamida en lugar de 4-fluoro-3-nitrobencenosulfonamida y (tetrahydrofurano-3-il)metanol en lugar de (tetrahydro-2H-piran-4-il)metanol en el EJEMPLO 24A, excepto que aquí, se usó dimetilformamida en lugar de tetrahydrofurano y la reacción se calentó a 70° C por dos días.

- 15 EJEMPLO 323B

4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{{3-cloro-4-(tetrahydrofurano-3-ilmetoxi)fenil}sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

- 20 El compuesto del título se preparó utilizando el EJEMPLO 323A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,73 (s, 1H), 8,07 (d, 1H), 7,89 (d, 1H), 7,80 (dd, 1H), 7,59 (d, 1H), 7,51 (dd, 1H), 7,49 (d, 1H), 7,34 (d, 2H), 7,23 (d, 1H), 7,03 (d, 2H), 6,66 (dd, 1H), 6,42 (m, 1H), 6,19 (d, 1H), 4,07 (m, 2H), 3,80 (m, 2H), 3,68 (m, 1H) 3,56 (m, 1H), 3,10 (br m, 4H), 2,85 (br s, 2H), 2,69 (m, 1H), 2,32 (br m, 4H), 2,17 (br m, 2H), 2,02 (m, 1H), 1,96 (s, 2H), 1,69 (m, 1H), 1,40 (t, 2H), 0,92 (s, 6H).

- 25 EJEMPLO 324 4-(4-{{2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{{(trans-4-hidroxiciclohexil)metil}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 324A

4-((trans-4-hidroxiciclohexil)metilamino)-3-nitrobencenosulfonamida

- 30 El compuesto del título se preparó utilizando el EJEMPLO 120A en lugar del EJEMPLO 39B en el EJEMPLO 39C.

EJEMPLO 324B

- 35 4-(4-{{2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{{(trans-4-hidroxiciclohexil)metil}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 321G en lugar del EJEMPLO 1E y EJEMPLO 324A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo- d₆) δ 11,69 (s, 1H), 11,41 (s, 1H), 8,65 - 8,50 (m, 2H), 8,05 (d, 1H), 7,80 (dd, 1H), 7,60 - 7,44 (m, 3H), 7,41 - 7,34 (m, 2H), 7,14 - 7,02 (m, 3H), 6,68 (dd, 1H), 6,39 (dd, 1H), 6,17 (d, 1H), 4,50 (d, 1H), 3,23 (t, 2H), 3,06 (s, 4H), 2,70 (d₄H), 2,44 (s, 2H), 2,33 - 1,94 (m, 6H), 1,78 (dd, 4H), 1,51 (d, 2H), 1,23 (s, 2H), 1,16 - 0,92 (m, 2H).

EJEMPLO 325

N-({3-cloro-4-[(4-fluorotetrahydro-2H-piran-4-il)metoxi]fenil}sulfonil)-4-(4-{[9-(4-clorofenil)-3-(oxetan-3-il)-3-azaespiro[5,5]undec-8-en-8-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 325A

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((9-(4-clorofenil)-3-(oxetan-3-il)-3-azaespiro[5,5]undec-8-en-8-il)metil)piperazin-1-il)benzoato de metilo

El compuesto del título se preparó utilizando oxetan-3-ona en lugar de 1,3-difluoropropan-2-ona en el EJEMPLO 265G.

EJEMPLO 325B

ácido 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((9-(4-clorofenil)-3-(oxetan-3-il)-3-azaespiro[5,5]undec-8-en-8-il)metil)piperazin-1-il)benzoico

El compuesto del título se preparó utilizando el EJEMPLO 325A en lugar del EJEMPLO 15G en el EJEMPLO 15H.

EJEMPLO 325C

N-({3-cloro-4-[(4-fluorotetrahydro-2H-piran-4-il)metoxi]fenil}sulfonil)-4-(4-{[9-(4-clorofenil)-3-(oxetan-3-il)-3-azaespiro[5,5]undec-8-en-8-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 325B en lugar del EJEMPLO 1E y EJEMPLO 286A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo- d₆) δ 11,67 (s, 1H), 11,13 (s, 1H), 8,05 (d, 1H), 7,87 (d, 1H), 7,80 - 7,70 (m, 1H), 7,59 - 7,46 (m, 3H), 7,34 (d, 2H), 7,21 (d, 1H), 7,11 - 7,03 (m, 2H), 6,66 (d, 1H), 6,41 (dd, 1H), 6,18 (d, 1H), 4,50 (dd, 4H), 4,26 (d, 2H), 3,85 - 3,69 (m, 2H), 3,61 (d, 3H), 3,05 (s, 4H), 2,69 (s, 2H), 2,37 (s, 4H), 2,17 (s, 6H), 2,04 (s, 2H), 1,87 (d, 4H), 1,49 (d, 6H).

EJEMPLO 326

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([[(2R)-4-ciclopropilmorfolin-2-il]metil]amino)-3-nitrofenil]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 326A

(R)-4-((4-ciclopropilmorfolin-2-il)metilamino)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 258E en lugar del EJEMPLO 173A en el EJEMPLO 173B.

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EJEMPLO 326B

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([[(2R)-4-ciclopropilmorfolin-2-il]metil]amino)-3-nitrofenil]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

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El compuesto del título se preparó utilizando el EJEMPLO 326A en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridina-d₅) □ 13,00 (s, 1H), 9,26 (d, 1H), 8,88 (t, 1H), 8,44 (d, 1H), 8,34 (dd, 1H), 8,12 (d, 1H), 7,66 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,94 (d, 1H), 6,75 (dd, 1H), 6,54 (d, 1H), 6,48 (m, 1H), 3,88 (d, 1H), 3,84-3,81 (m, 1H), 3,59 (dt, 1H), 3,50-3,40 (m, 2H), 3,07 (m, 4H), 2,93 (d, 1H), 2,77 (s, 2H), 2,69 (d, 1H), 2,34 (dt, 1H), 2,26 (m, 2H), 2,21 (t, 1H), 2,14 (m, 4H), 1,97 (s, 2H), 1,58 (m, 1H), 1,39 (t, 2H), 0,94 (s, 6H), 0,45-0,39 (m, 4H).

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EJEMPLO 327

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-pirrolo[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 327A

(S)-4-((4-ciclopropilmorfolin-2-il)metilamino)-3-nitrobencenosulfonamida

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El compuesto del título se preparó utilizando el EJEMPLO 259E en lugar del EJEMPLO 173A en el EJEMPLO 173B.

EJEMPLO 327B

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-pirrolo[2,3-b]piridin-5-iloxi)benzamida

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El compuesto del título se preparó utilizando el EJEMPLO 327A en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridina-d₅) δ 13,00 (s, 1H), 9,26 (d, 1H), 8,88 (t, 1H), 8,44 (d, 1H), 8,34 (dd, 1H), 8,12 (d, 1H), 7,66 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,94 (d, 1H), 6,75 (dd, 1H), 6,54 (d, 1H), 6,48 (m, 1H), 3,88 (d, 1H), 3,84-3,81 (m, 1H), 3,59 (dt, 1H), 3,50-3,40 (m, 2H), 3,07 (m, 4H), 2,93 (d, 1H), 2,77 (s, 2H), 2,69 (d, 1H), 2,34 (dt, 1H), 2,26 (m, 2H), 2,21 (t, 1H), 2,14 (m, 4H), 1,97 (s, 2H), 1,58 (m, 1H), 1,39 (t, 2H), 0,94 (s, 6H), 0,45-0,39 (m, 4H).

EJEMPLO 328

4-(4-([5-(4-clorofenil)espiro[2,5]oct-5-en-6-il]metil)piperazin-1-il)-N-([3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil]sulfonil)-2-(1H-pirrol-2-il)piridin-5-il)benzamida

EJEMPLO 328A

espiro[2,5]octan-5-ona

A una solución de 3-etoxiciclohex-2-enona (48,1 mL) en éter (1000 mL) se agregó isopropóxido de titanio(IV) (110 mL) seguido por la adición de bromuro de etilmagnesio (357 mL) a temperatura ambiente. La mezcla de la reacción se agitó por 2 horas a temperatura ambiente y luego se detuvo con agua (500 mL). La capa orgánica se separó (decantó) y la capa acuosa se extrajo con éter (3 x 300 mL). Los extractos combinados se concentraron parcialmente a aproximadamente 300 mL. Se agregó ácido p-toluenosulfónico monohidratado (3,0 g) y la mezcla de la reacción se agitó durante la noche a temperatura ambiente. La mezcla de la reacción luego se lavó con solución acuosa saturada de NaHCO₃, se secó (MgSO₄), se filtró y se concentró. El material concentrado se purificó mediante destilación fraccional (primera fracción punto de ebullición 27°C a 23 torr (no el producto), segunda fracción (el producto) punto de ebullición 75°C a 8 torr).

EJEMPLO 328B

5-cloro-espiro[2,5]oct-5-en-6-carbaldehído

Se trató N,N-dimetilformamida (2,1 mL) en diclorometano (3,2 mL) a -5 °C lentamente con POCl₃ (2,33 mL) manteniendo la temperatura del baño por debajo de 0°C. El baño de frío se retiró y la mezcla se agitó a temperatura ambiente por 30 minutos. La mezcla de la reacción se colocó nuevamente en el baño de frío y se agregó EJEMPLO 328A (2,484 g) en diclorometano (4 mL) lentamente a la mezcla de la reacción. La mezcla de la reacción se calentó a 45°C por 15 horas, se enfrió a temperatura ambiente y luego se vertió en una mezcla de hielo y solución acuosa saturada de acetato de sodio. Luego de que el hielo se fundió, la mezcla se extrajo con éter dietílico. Los extractos combinados se lavaron con solución acuosa saturada de NaHCO₃ y salmuera, se secó (MgSO₄), se filtró y se concentró.

El material concentrado se cromatografió con CH_2Cl_2 entre 0 y 10% en hexanos, luego 25% CH_2Cl_2 en hexanos y luego 100% CH_2Cl_2 como eluyentes.

EJEMPLO 328C

5-(4-clorofenil)espiro[2,5]oct-5-en-6-carbaldehído

- 5 Se combinó EJEMPLO 328B (2,9 g), ácido 4-clorofenilborónico (2,87 g), acetato de paladio(II) (0,103 g), K_2CO_3 (5,28 g) y bromuro de tetrabutilamonio (4,93 g) en un balón de 100 mL con agua (17,0 mL). Por el recipiente se hizo pasar nitrógeno y se agitó a 45°C por 14 horas. La mezcla de la reacción 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 celite, se concentró y se cromatografió sobre gel de sílice con acetato de etilo entre 0 y 2% en hexanos como eluyente.

EJEMPLO 328D

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((5-(4-clorofenil)espiro[2,5]oct-5-en-6-il)metil)piperazin-1-il)benzoato de metilo

- 15 El compuesto del título se preparó utilizando el EJEMPLO 15F en lugar de piperazinacarboxilato de tert-butilo y EJEMPLO 328C en lugar de 4-clorobifenil-2-carboxaldehído en el EJEMPLO 1A.

EJEMPLO 328E

- 20 clorhidrato del ácido 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((5-(4-clorofenil)espiro[2,5]oct-5-en-6-il)metil)piperazin-1-il)benzoico

- Se trató EJEMPLO 328D (0,85 g) en una mezcla de tetrahidrofurano (4,8 mL), metanol (2,4 mL) y agua (2,4 mL) con $\text{LiOH}\cdot\text{H}_2\text{O}$ (0,184 g) y se calentó durante la noche a 50°C. La mezcla de la reacción se enfrió a temperatura ambiente, se concentró para eliminar tetrahidrofurano y metanol y se acidificó con HCl acuoso 1 N causando la precipitación del producto. El sólido se recogió mediante filtración, se enjuagó con agua y se secó durante la noche en un horno de vacío a 80°C para dar el compuesto del título.

EJEMPLO 328F

- 30 4-(4-([5-(4-clorofenil)espiro[2,5]oct-5-en-6-il]metil)piperazin-1-il)-N-([3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

- El compuesto del título se preparó utilizando el EJEMPLO 328E en lugar del EJEMPLO 1E en el EJEMPLO 1G. ^1H NMR (500 MHz, piridina- d_5) δ 13,07 (s, 1H), 9,32 (d, 1H), 8,68 (t, 1H), 8,44 (d, 1H), 8,38 (dd, 1H), 8,10 (d, 1H), 7,68 (m, 1H), 7,66 (d, 1H), 7,43 (m, 2H), 7,10 (m, 2H), 6,91 (d, 1H), 6,75 (dd, 1H), 6,51 (m, 2H), 3,97 (dd, 2H), 3,30 (td, 2H), 3,16 (t, 2H), 3,06 (m, 4H), 2,81 (s, 2H), 2,37 (t, 2H), 2,16 (m, 4H), 2,11 (s, 2H), 1,81 (m, 1H), 1,58 (dd, 2H), 1,45 (t, 2H), 1,32 (qd, 2H), 0,38 (s, 4H).

EJEMPLO 329

N-[[5-cloro-6-({4-[ciclopropil(oxetan-3-il)amino]ciclohexil}metoxi)piridin-3-il]sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 329A

4-(ciclopropilamino)ciclohexanocarboxilato de etilo

A una solución de 4-oxociclohexanocarboxilato de etilo (3,4 g) en diclorometano (30 mL) se agregó ciclopropanamina (1,14 g) seguido por triacetoxiborhidruro de sodio (4,24 g).

10 La mezcla se agitó durante la noche. La mezcla se diluyó con diclorometano (300 mL) y se lavó con NaOH 2N, agua, salmuera y se secó sobre Na₂SO₄. La filtración y evaporación del solvente dio el compuesto del título.

EJEMPLO 329B

15 4-(ciclopropil(oxetan-3-il)amino)ciclohexanocarboxilato de etilo

A una solución de EJEMPLO 329A (1,05g) en diclorometano (10 mL) se agregó oxetan-3-ona (0,358 g) seguido por triacetoxiborhidruro de sodio (1,05 g). La mezcla se agitó durante la noche. La mezcla se diluyó con diclorometano (300 mL) y se lavó con NaOH acuoso 2N, agua, salmuera y se secó sobre Na₂SO₄. La filtración y evaporación del solvente dio el compuesto del título.

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EJEMPLO 329C

(4-(ciclopropil(oxetan-3-il)amino)ciclohexil)metanol

A una solución de EJEMPLO 329B (1,2 g) en tetrahidrofurano (20 mL) se agregó hidruro de litio y aluminio (0,681 g). La mezcla se agitó durante la noche. Se agregó solución acuosa 2N de NaOH por goteo a la mezcla de la reacción. La mezcla luego se diluyó con acetato de etilo (300 mL) y se lavó con agua, salmuera y se secó sobre Na₂SO₄. La filtración y evaporación del solvente dio el compuesto del título.

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EJEMPLO 329D

5-cloro-6-((4-(ciclopropil(oxetan-3-il)amino)ciclohexil)metoxi)piridin-3-sulfonamida

A una solución de EJEMPLO 329C (706 mg) en N,N-dimetilformamida (6 mL) se agregó NaH (60% en aceite mineral, 300 mg) . La mezcla se agitó por 30 minutos, y luego se agregó 5,6-dicloropiridin-3-sulfonamida (706 mg). La mezcla se agitó durante la noche. La mezcla se vertió sobre NH₄Cl acuoso y se extrajo con acetato de etilo (3x 200 mL). Las capas orgánicas combinadas se lavaron con agua, salmuera y se secó sobre Na₂SO₄. Luego

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de la filtración y evaporación del solvente el residuo se cargó en un cartucho de gel de sílice y se eluyó con NH_3 7N entre 5 y 10% en metanol en diclorometano para dar el compuesto del título.

EJEMPLO 329E

- 5 N-{{[5-cloro-6-({4-[ciclopropil(oxetan-3-il)amino]ciclohexil}metoxi)piridin-3-il]sulfonil}-4-(4-{{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 329D en lugar del EJEMPLO 1F en el EJEMPLO 1G. ^1H NMR (300 MHz, sulfóxido de dimetilo- d_6) $\square$ 11,64 (s, 1 H), 8,50 (m, 1 H), 8,16 (s, 1 H), 8,02 (d, 1 H), 7,51 (m, 3 H), 7,35 (d, 2 H), 7,04 (d, 2 H), 6,67 (dd, 1 H), 6,38 (m, 1 H), 6,21 (s, 1 H), 4,70 (m, 2 H), 4,43 (t, 3 H), 4,19 (m, 2 H), 3,12 (m, 4 H), 2,84 (m, 2 H), 2,19 (m, 6 H), 1,96 (s, 3 H), 1,77 (m, 3 H), 1,38 (m, 7 H), 0,93 (s, 6 H), 0,44 (m, 4 H).

15 EJEMPLO 330

4-(4-{{[5-(4-clorofenil)espiro[2,5]oct-5-en-6-il]metil}piperazin-1-il)-N-[[4-{{[(4-ciclopropilmorfolin-2-il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 328E en lugar del EJEMPLO 3J y EJEMPLO 218A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ^1H NMR (400 MHz, piridina- d_5) $\square$ 13,01 (s, 1H), 9,26 (d, 1H), 8,88 (t, 1H), 8,43 (d, 1H), 8,34 (dd, 1H), 8,11 (d, 1H), 7,66 (m, 2H), 7,42 (m, 2H), 7,09 (m, 2H), 6,95 (d, 1H), 6,75 (dd, 1H), 6,53 (d, 1H), 6,49 (dd, 1H), 3,84 (m, 2H), 3,58 (td, 1H), 3,45 (m, 2H), 3,06 (m, 4H), 2,93 (d, 1H), 2,81 (s, 2H), 2,69 (d, 1H), 2,35 (m, 3H), 2,19 (m, 5H), 2,11 (s, 2H), 1,58 (m, 1H), 1,45 (t, 2H), 0,42 (m, 8H).

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EJEMPLO 331

N-{{[3-cloro-4-{{[4-ciclopropilmorfolin-2-il]metoxi}fenil}sulfonil]-4-(4-{{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

30 EJEMPLO 331A

2-((2-cloro-4-sulfamoilfenoxi)metil)morfolina-4-carboxilato de *tert*-butilo

A una solución de 2-(hidroximetil)morfolina-4-carboxilato de *tert*-butilo (0,478 g) en N,N-dimetilformamida anhidra (5 mL) se agregó hidruro de sodio (0,280 g). La mezcla se agitó a temperatura ambiente por 30 minutos, seguido por la adición de 3-cloro-4-fluorobencenosulfonamida (0,419 g). La mezcla se agitó a 40°C durante la noche. La reacción se detuvo con agua (10 mL), y la mezcla se ajustó a ~pH 7 y se extrajo con acetato

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de etilo. El producto crudo se purificó en una columna de gel de sílice eluyendo con 60% acetato de etilo en hexano para dar el compuesto del título.

EJEMPLO 331B

5 3-cloro-4-(morfolin-2-ilmetoxi)bencenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 331A en lugar del EJEMPLO 113A en el EJEMPLO 134A.

EJEMPLO 331C

10 3-cloro-4-((4-ciclopropilmorfolin-2-il)metoxi)bencenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 331B en lugar del EJEMPLO 173A en el EJEMPLO 173B.

EJEMPLO 331D

15 N-({3-cloro-4-[(4-ciclopropilmorfolin-2-il)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 331C en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridina-d₅) □ 13,04 (s, 1H), 8,54 (d, 1H), 8,43 (d, 1H), 8,27 (dd, 1H), 8,09 (d, 1H), 7,66 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 7,05 (d, 1H), 6,75 (dd, 1H), 6,52 (d, 1H), 6,50 (m, 1H), 4,20 (dd, 1H), 4,10 (dd, 1H), 3,94 (m, 1H), 3,86 (d, 1H), 3,58 (dt, 1H), 3,06 (m, 5H), 2,77 (s, 2H), 2,69 (d, 1H), 2,40-2,20 (m, 4H), 2,14 (m, 4H), 1,97 (s, 2H), 1,60 (m, 1H), 1,39 (t, 2H), 0,94 (s, 6H), 0,41 (m, 4H).

EJEMPLO 332

25 N-[(3-cloro-4-[(4-ciclopropilmorfolin-2-il)metil]amino)fenil}sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 332A

2-((2-cloro-4-sulfamoilfenilamino)metil)morfolina-4-carboxilato de tert-butilo

30 Se agitó una solución de 3-cloro-4-fluorobencenosulfonamida (1,0 g), 2-(aminometil)morfolina-4-carboxilato de tert-butilo (1,135 g) y N-etil-N-isopropilpropan-2-amina (1,246 mL) en sulfóxido de dimetilo (15 mL) a 115°C por 72 horas. La mezcla se concentró, y el residuo se purificó en una columna de gel de sílice eluyendo con 60% acetato de etilo para dar el compuesto del título.

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EJEMPLO 332B

3-cloro-4-(morfolin-2-ilmetilamino)bencenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 332A en lugar del EJEMPLO 113A en el EJEMPLO 134A.

5 EJEMPLO 332C

El compuesto del título se preparó utilizando el EJEMPLO 332B en lugar del EJEMPLO 173A en el EJEMPLO 173B.

EJEMPLO 332D

10 N-[(3-cloro-4-[(4-ciclopropilmorfolin-2-il)metil]amino)fenil)sulfonil]-4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 332C en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridina-d₅) □ 13,05 (s, 1H), 8,45 (m, 2H), 8,21 (dd, 1H), 8,12 (d, 1H), 7,69 (d, 1H), 7,67 (t, 1H), 7,44 (d, 2H), 7,07 (d, 2H), 6,78 (d, 1H), 6,74 (dd, 1H), 6,52 (d, 1H), 6,50 (m, 1H), 6,37 (m, 1H), 3,84 (d, 1H), 3,77 (m, 1H), 3,54 (dt, 1H), 3,35 (m, 2H), 3,05 (m, 4H), 2,94 (d, 1H), 2,77 (s, 2H), 2,68 (d, 1H), 2,32 (dt, 1H), 2,26 (m, 2H), 2,18-2,12 (m, 5H), 1,97 (s, 2H), 1,55 (m, 1H), 1,39 (t, 2H), 0,94 (s, 6H), 0,41 (m, 4H).

20 EJEMPLO 333

2-[[[(2-cloro-4-[[4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]sulfamoil]fenil)amino]metil]-N-etil-N-metilmorfolina-4-carboxamida

25 EJEMPLO 333A

2-((2-cloro-4-sulfamoilfenilamino)metil)-N-etil-N-metilmorfolina-4-carboxamida

El compuesto del título se preparó utilizando el EJEMPLO 332B en lugar del EJEMPLO 134A y cloruro de N-metil-N-etilcarbamilato en lugar de yoduro de metilo en el EJEMPLO 134B.

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EJEMPLO 333B

2-[[[(2-cloro-4-[[4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]sulfamoil]fenil)amino]metil]-N-etil-N-metilmorfolina-4-carboxamida

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El compuesto del título se preparó utilizando el EJEMPLO 333A en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridina-d₅) □ 13,05 (s, 1H), 8,46

(s, 1H), 8,45 (s, 1H), 8,20 (dd, 1H), 8,10 (d, 1H), 7,69 (d, 1H), 7,67 (t, 1H), 7,44 (d, 2H), 7,07 (d, 2H), 6,79 (d, 1H), 6,73 (dd, 1H), 6,52 (dd, 1H), 6,49 (d, 1H), 6,43 (m, 1H), 3,83 (d, 2H), 3,73 (d, 1H), 3,59 (dt, 1H), 3,41-3,35 (m, 3H), 3,20 (q, 2H), 3,05 (m, 4H), 2,95 (t, 1H), 2,84 (dd, 1H), 2,76 (s, 2H), 2,73 (s, 3H), 2,25 (m, 2H), 2,14 (m, 4H), 1,97 (s, 2H), 1,39 (t, 2H),
 5 1,04 (t, 3H), 0,94 (s, 6H).

EJEMPLO 334

(2S)-2-((3-cloro-5-([4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-
 10 (1H-pirrol[2,3-b]piridin-5-iloxi)benzoil)sulfamoil)piridin-2-il)oxi]metil)-N-etil-N-metilmorfolina-4-carboxamida

EJEMPLO 334A

(S)-2-((3-cloro-5-sulfamoilpiridin-2-iloxi)metil)-N-etil-N-metilmorfolina-4-carboxamida

15 El compuesto del título se preparó utilizando el EJEMPLO 244B en lugar del EJEMPLO 134A y cloruro de N-metil-N-etilcarbamilato en lugar de yoduro de metilo en el EJEMPLO 134B.

EJEMPLO 334B

20 (2S)-2-((3-cloro-5-([4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil)sulfamoil)piridin-2-il)oxi]metil)-N-etil-N-metilmorfolina-4-carboxamida

El compuesto del título se preparó utilizando el EJEMPLO 334A en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridina-d₅) □ 12,98 (s, 1H), 9,08
 25 (d, 1H), 8,70 (d, 1H), 8,42 (d, 1H), 8,11 (d, 1H), 7,67 (t, 1H), 7,64 (d, 1H), 7,44 (d, 2H), 7,07 (d, 2H), 6,75 (dd, 1H), 6,53 (d, 1H), 6,48 (m, 1H), 4,58 (dd, 1H), 4,47 (dd, 1H), 4,03 (m, 1H), 3,84 (m, 2H), 3,63 (dt, 1H), 3,45 (d, 1H), 3,22 (q, 2H), 3,07 (m, 4H), 3,05-2,95 (m, 2H), 2,78 (s, 3H), 2,77 (s, 2H), 2,26 (m, 2H), 2,14 (m, 4H), 1,97 (s, 2H), 1,39 (t, 2H), 1,07 (t, 3H), 0,94 (s, 6H).

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EJEMPLO 335

N-([5-cloro-6-((4-ciclopropilmorfolin-2-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-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 335A

2-((3-cloro-5-sulfamoilpiridin-2-ilamino)metil)morfolina-4-carboxilato de tert-butilo

El compuesto del título se preparó utilizando el EJEMPLO 40A en lugar de 4-fluoro-3-nitrobencenosulfonamida y 2-(aminometil)morfolina-4-carboxilato de tert-butilo en lugar de (tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

5 EJEMPLO 335B

5-cloro-6-(morfolin-2-ilmetilamino)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 335A en lugar del EJEMPLO 113A en el EJEMPLO 134A.

10 EJEMPLO 335C

5-cloro-6-((4-ciclopropilmorfolin-2-il)metilamino)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 335B en lugar del EJEMPLO 173A en el EJEMPLO 173B.

15 EJEMPLO 335D

N-[(5-cloro-6-[[[4-ciclopropilmorfolin-2-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 335C en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridina-d₅) δ 13,02 (s, 1H), 9,15 (d, 1H), 8,49 (d, 1H), 8,43 (d, 1H), 8,11 (d, 1H), 7,80 (t, 1H), 7,69 (d, 1H), 7,65 (t, 1H), 7,44 (d, 2H), 7,07 (d, 2H), 6,73 (dd, 1H), 6,52 (m, 1H), 6,49 (d, 1H), 3,92 (m, 1H), 3,84 (m, 2H), 3,70 (m, 1H), 3,54 (dt, 1H), 3,05 (m, 4H), 2,99 (d, 1H), 2,76 (s, 2H), 2,68 (d, 1H), 2,32 (dt, 1H), 2,25 (m, 2H), 2,12 (m, 5H), 1,97 (s, 2H), 1,53 (m, 1H), 1,39 (t, 2H), 0,93 (s, 6H), 0,40 (m, 4H).

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EJEMPLO 336

2-[[[(3-cloro-5-[[4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzoil]sulfamoil]piridin-2-il)amino]metil]-N-etil-N-metilmorfolina-4-carboxamida

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EJEMPLO 336A

2-((3-cloro-5-sulfamoilpiridin-2-ilamino)metil)-N-etil-N-metilmorfolina-4-carboxamida

El compuesto del título se preparó utilizando el EJEMPLO 335B en lugar del EJEMPLO 134A y Cloruro de N-metil-N-etilcarbamilo en lugar de yoduro de metilo en el EJEMPLO 134B.

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EJEMPLO 336B

2-[[[(3-cloro-5-[[4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]sulfamoil]piridin-2-il)amino]metil]-N-etil-N-metilmorfolina-4-carboxamida

- 5 El compuesto del título se preparó utilizando el EJEMPLO 336A en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridina-d₅) □ 13,03 (s, 1H), 9,14 (d, 1H), 8,51 (d, 1H), 8,43 (d, 1H), 8,11 (d, 1H), 7,89 (m, 1H), 7,69 (d, 1H), 7,66 (t, 1H), 7,44 (d, 2H), 7,07 (d, 2H), 6,74 (dd, 1H), 6,51 (m, 1H), 6,48 (d, 1H), 3,96 (m, 1H), 3,90-3,70 (m, 4H), 3,59 (dt, 1H), 3,43 (d, 1H), 3,17 (q, 2H), 3,05 (m, 4H), 2,95 (dt, 1H), 2,81 (dd, 1H), 2,76 (s, 2H), 2,72 (s, 3H), 2,25 (m, 2H), 2,13 (m, 4H), 1,97 (s, 2H), 1,39 (t, 2H), 1,03 (t, 3H), 0,93 (s, 6H).
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EJEMPLO 337

- 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-pirrol[2,3-b]piridin-5-iloxi)benzamida
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EJEMPLO 337A

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-metoxycarbonilciclohexanona (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 trifluoroacético (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 (Na₂SO₄), se filtró, y se concentró para dar el producto.
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EJEMPLO 337B

2-(4-clorofenil)-4,4-dimetilciclohex-1-encarboxilato de metilo

- Se calentó EJEMPLO 337A (62,15g), ácido 4-clorofenilborónico (32,24 g), CsF (64 g) y tetrakis(trifenilfosfin)paladio(0) (2g) en 2:1 dimetoxietano /metanol (600 mL) a 70°C 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.
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EJEMPLO 337C

(2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metanol

- 35 A una mezcla de LiBH₄ (13g), EJEMPLO 337B (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 1N con enfriamiento con hielo. La mezcla se diluyó con agua y se extrajo con éter (3x 100 mL). Los extractos se secaron (Na_2SO_4), se filtró, y se concentró. El producto crudo se cromatografió sobre gel de sílice con acetato de etilo al 0-30%/hexanos.

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EJEMPLO 337D

4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-carboxilato de tert-butilo

Se agregó cloruro de mesilo (7,5 mL) mediante una jeringa a EJEMPLO 337C (29,3 g) y trietilamina (30 mL) en CH_2Cl_2 (500 mL) a 0°C , y la mezcla se agitó por 1 minuto. Se agregó N-t-butoxicarbonilpiperazina (25 g) y la mezcla se agitó a temperatura ambiente por 24 horas. La suspensión se lavó con salmuera, se secó, (Na_2SO_4), se filtró, y se concentró. El producto crudo se cromatografió sobre gel de sílice con acetato de etilo al 10-20%/hexanos.

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EJEMPLO 337E

1-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazina

Se agitó EJEMPLO 337D (1 g) en diclorometano (10 mL), ácido trifluoroacético (10 mL), y trietilsilano (1 mL) por 1 hora. La mezcla se concentró, se recogió con una mezcla de diclorometano (100 mL) y solución acuosa saturada de Na_2CO_3 (20 mL) y se agitó por 10 minutos. Las capas se separaron, y la capa orgánica se secó sobre Na_2SO_4 , y se concentró para dar el producto.

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EJEMPLO 337F

5-bromo-1-(triisopropilsilil)-1H-pirrol[2,3-b]piridina

A una mezcla de 5-bromo-1H-pirrol[2,3-b]piridina (15,4 g) en tetrahidrofurano (250 mL) se agregó hexametildisilazida de litio 1M en tetrahidrofurano (86 mL), y luego de 10 minutos, se agregó TIPS-Cl (triisopropilclorosilano) (18,2 mL). La mezcla se agitó a temperatura ambiente por 24 horas. La reacción se diluyó con éter, y la solución resultante se lavó dos veces con agua. Los extractos se secaron (Na_2SO_4), se filtró, y se concentró. El producto crudo se cromatografió sobre gel de sílice con 10% acetato de etilo/hexanos.

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EJEMPLO 337G

1-(triisopropilsilil)-1H-pirrol[2,3-b]piridin-5-ol

A una mezcla de EJEMPLO 337F (24,3 g) en tetrahidrofurano (500 mL) a -78°C se agregó BuLi 2,5M (30,3 mL). Luego de 2 minutos, se agregó borato de trimetilo (11,5 mL), y la mezcla se dejó calentar a temperatura ambiente durante 1 hora. La reacción se vertió en agua, se extrajo tres veces con acetato de etilo, y los extractos combinados se lavaron con

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salmuera y se concentró. El producto crudo se colocó en tetrahidrofurano (200 mL) a 0°C, y se agregó NaOH acuoso 1M (69 mL), seguido por H₂O₂ acuoso al 30% (8,43 mL), y la solución se agitó por 1 hora. Se agregó Na₂S₂O₃ (10 g), y el pH se ajustó a 4-5 con HCl concentrado y NaH₂PO₄ sólido. La solución se extrajo dos veces con acetato de etilo, y los
 5 extractos combinados se lavaron con salmuera, se secó (Na₂SO₄), se filtró, y se concentró. El producto crudo se cromatografió sobre gel de sílice con 5-25% acetato de etilo/hexanos.

EJEMPLO 337H

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-fluorobenzoato de metilo

10 Una mezcla de EJEMPLO 337G (8,5 g), 2,4-difluorobenzoato de metilo (7,05 g), y K₃PO₄ (9,32 g) en diglima (40 mL) a 115°C se agitó por 24 horas. La reacción se enfrió, se diluyó con éter (600 mL), y se lavó dos veces con agua, y salmuera, y se concentró. El producto crudo se cromatografió sobre gel de sílice con acetato de etilo al 2-50%/hexanos.

EJEMPLO 337I

15 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoato de metilo

Una mezcla de EJEMPLO 337H (1,55 g), EJEMPLO 337E (2,42 g), y HK₂PO₄ (1,42 g) en sulfóxido de dimetilo (20 mL) a 135°C se agitó por 24 horas. La reacción se enfrió, se diluyó con éter (400 mL), y se lavó tres veces con NaOH acuoso 1M, y salmuera, y se concentró. El
 20 producto crudo se cromatografió sobre gel de sílice con acetato de etilo al 10-50%/hexanos.

EJEMPLO 337J

ácido 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoico
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Se agitó EJEMPLO 337I (200 mg) en dioxano (10 mL) y NaOH acuoso 1M (6 mL) a 50°C por 24 horas. La reacción se enfrió, se agregó una solución de NaH₂PO₄, y se extrajo tres veces con acetato de etilo. Los extractos combinados se lavaron con salmuera, y se concentró para dar el producto puro.

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EJEMPLO 337K

(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 metililitio 1,6 M (14,02 mL) en
 35 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 NH₄Cl. La mezcla resultante se extrajo con diclorometano (100

ml, tres veces) 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.

5 EJEMPLO 337L

4-(aminometil)-1-metilciclohexanol

Se trató EJEMPLO 337K (1,3 g) en diclorometano (5 mL) a 0°C con ácido trifluoroacético (2,1 mL) y unas pocas gotas de agua por 1 hora. La mezcla de la reacción se concentró y el residuo se usó directamente para el siguiente paso.

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EJEMPLO 337M

4-((trans-4-hidroxi-4-metilciclohexil)metilamino)-3-nitrobencenosulfonamida

Se trató EJEMPLO 337L (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 cromatografía de fase inversa, eluyendo con 30% - 50% acetonitrilo en solución acuosa de ácido trifluoroacético al 0,1% para aislar el compuesto del título.

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20 EJEMPLO 337N

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

Una mezcla de EJEMPLO 337J (3,0 g), EJEMPLO 337M (1,98 g), N, N-dimetilpiridin-4-amina (1,93 g) y clorhidrato de N^1 -((etilimino)metilen)- N^3 , N^3 -dimetilpropan-1,3-diamina (1,31 g) en diclorometano (50 ml) se agitó durante la noche y se concentró. El residuo se purificó mediante cromatografía inversa, se eluyó con 40%-70% acetonitrilo en TFA 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 concentró y se secó para dar el compuesto del título. ^1H NMR (400 MHz, sulfóxido de dimetilo- d_6) δ 11,68 (s, 1 H), 8,52 - 8,58 (m, 2 H), 8,04 (d, 1 H), 7,79 (dd, 1 H), 7,53 (d, 1 H), 7,47 - 7,52 (m, 2 H), 7,30 - 7,37 (m, 2 H), 7,07 (d, 1 H), 7,01 - 7,06 (m, 2 H), 6,68 (dd, 1 H), 6,39 (dd, 1 H), 6,19 (d, 1 H), 4,25 (s, 1 H), 3,25 - 3,32 (m, 4 H), 3,07 (s, 4 H), 2,75 (s, 2 H), 2,09 - 2,24 (m, 6 H), 1,95 (s, 2 H), 1,50 - 1,73 (m, 5 H), 1,28 - 1,43 (m, 4 H), 1,06 - 1,18 (m, 5 H), 0,92 (s, 6 H).

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EJEMPLO 338

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 338A

5 4,4-dimetil-2-(trifluorometilsulfonilo)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-metoxycarbonilciclohexanona (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 trifluoroacético (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 (Na₂SO₄), se filtró, y se concentró para dar el producto.

EJEMPLO 338B

2-(4-clorofenil)-4,4-dimetilciclohex-1-encarboxilato de metilo

15 Se calentó EJEMPLO 338A (62,15g), ácido 4-clorofenilborónico (32,24 g), CsF (64 g) y tetrakis(trifenilfosfin)paladio(0) (2g) en 2:1 dimetoxietano /metanol (600 mL) a 70°C 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.

20 EJEMPLO 338C

(2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metanol

A una mezcla de LiBH₄ (13g), EJEMPLO 338B (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 con enfriamiento con hielo. La mezcla se diluyó con agua y se extrajo con éter (3x 100 mL). Los extractos se secaron (Na₂SO₄), se filtró, y se concentró. El producto crudo se cromatografió sobre gel de sílice con acetato de etilo al 0-30%/hexanos.

EJEMPLO 338D

30 4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-carboxilato de tert-butilo

Se agregó cloruro de mesilo (7,5 mL) mediante una jeringa a EJEMPLO 338C (29,3 g) y trietilamina (30 mL) en CH₂Cl₂ (500 mL) a 0°C, y la mezcla se agitó por 1 minuto. Se agregó N-t-butoxicarbonilpiperazina (25 g) y la mezcla se agitó a temperatura ambiente por 24 horas. La suspensión se lavó con salmuera, se secó, (Na₂SO₄), se filtró, y se concentró. El producto crudo se cromatografió sobre gel de sílice con acetato de etilo al 10-20%/hexanos.

EJEMPLO 338E

1-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazina

Se agitó EJEMPLO 338D (1 g) en diclorometano (10 mL), ácido trifluoroacético (10 mL), y trietilsilano (1 mL) por 1 hora. La mezcla se concentró, se recogió con una mezcla de
5 diclorometano (100 mL) y solución acuosa saturada de Na_2CO_3 (20 mL) y se agitó por 10 minutos. Las capas se separaron, y la capa orgánica se secó sobre Na_2SO_4 , se filtró, y se concentró para dar el producto.

EJEMPLO 338F

10 5-bromo-1-(triisopropilsilil)-1H-pirrolol[2,3-b]piridina

A una mezcla de 5-bromo-1H-pirrolol[2,3-b]piridina (15,4 g) en tetrahidrofurano (250 mL) se agregó hexametildisilazida de litio 1M en tetrahidrofurano (86 mL), y luego de 10 minutos, se agregó TIPS-Cl (triisopropilclorosilano) (18,2 mL). La mezcla se agitó a temperatura ambiente por 24 horas. La reacción se diluyó con éter, y la solución resultante se lavó dos
15 veces con agua. Los extractos se secaron (Na_2SO_4), se filtró, y se concentró. El producto crudo se cromatografió sobre gel de sílice con 10% acetato de etilo/hexanos.

EJEMPLO 338G

1-(triisopropilsilil)-1H-pirrolol[2,3-b]piridin-5-ol

20 A una mezcla de EJEMPLO 338F (24,3 g) en tetrahidrofurano (500 mL) a -78°C se agregó BuLi 2,5M (30,3 mL). Luego de 2 minutos, se agregó borato de trimetilo (11,5 mL), y la mezcla se dejó calentar a temperatura ambiente durante 1 hora. La reacción se vertió en agua, se extrajo tres veces con acetato de etilo, y los extractos combinados se lavaron con salmuera y se concentró. El producto crudo se colocó en tetrahidrofurano (200 mL) a 0°C , y
25 se agregó NaOH acuoso 1M (69 mL), seguido por H_2O_2 acuoso al 30% (8,43 mL), y la solución se agitó por 1 hora. Se agregó $\text{Na}_2\text{S}_2\text{O}_3$ (10 g), y el pH se ajustó a 4-5 con HCl concentrado y NaH_2PO_4 sólido. La solución se extrajo dos veces con acetato de etilo, y los extractos combinados se lavaron con salmuera, se secó (Na_2SO_4), se filtró, y se concentró. El producto crudo se cromatografió sobre gel de sílice con 5-25% acetato de etilo/hexanos.

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EJEMPLO 338H

2-(1H-pirrolol[2,3-b]piridin-5-iloxi)-4-fluorobenzoato de metilo

Una mezcla de EJEMPLO 338G (8,5 g), 2,4-difluorobenzoato de metilo (7,05 g), y K_3PO_4 (9,32 g) en diglima (40 mL) a 115°C se agitó por 24 horas. La reacción se enfrió, se diluyó
35 con éter (600 mL), y se lavó dos veces con agua, y salmuera, y se concentró. El producto crudo se cromatografió sobre gel de sílice con acetato de etilo al 2-50%/hexanos.

EJEMPLO 338I

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoato de metilo

- 5 Una mezcla de EJEMPLO 338H (1,55 g), EJEMPLO 338E (2,42 g), y HK_2PO_4 (1,42 g) en sulfóxido de dimetilo (20 mL) a 135°C se agitó por 24 horas. La reacción se enfrió, se diluyó con éter (400 mL), y se lavó tres veces con NaOH acuoso 1M, y salmuera, y se concentró. El producto crudo se cromatografió sobre gel de sílice con acetato de etilo al 10-50%/hexanos.

EJEMPLO 338J

- 10 ácido 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoico

- 15 Se agitó EJEMPLO 338I (200 mg) en dioxano (10 mL) y NaOH 1M (6 mL) a 50°C por 24 horas. La reacción se enfrió, se agregó una solución de NaH_2PO_4 , y se extrajo tres veces con acetato de etilo. Los extractos combinados se lavaron con salmuera, y se concentró para dar el producto puro.

EJEMPLO 338K

(4-hidroxi-4-metilciclohexil)metilcarbamato de tert-butilo

- 20 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 metililitio 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 (100 ml, tres veces) y la capa orgánica se secó sobre Na_2SO_4 , se filtró, y se concentró. El residuo
- 25 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 338L

4-(aminometil)-1-metilciclohexanol

- 30 Se trató EJEMPLO 338K (1,3 g) en diclorometano (5 mL) a 0°C con ácido trifluoroacético (2,1 mL) y unas pocas gotas de agua por 1 hora. La mezcla de la reacción se concentró y el residuo se usó directamente para el siguiente paso.

EJEMPLO 338M

- 35 4-((cis-4-hidroxi-4-metilciclohexil)metilamino)-3-nitrobenzenosulfonamida

Se trató EJEMPLO 338L (732 mg) y 4-fluoro-3-nitrobenzenosulfonamida (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 a cromatografía de fase inversa, eluyendo con 30% - 50% acetonitrilo en solución acuosa de ácido trifluoroacético al 0,1% para aislar el
5 compuesto del título.

EJEMPLO 338N

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)sulfonyl]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

10 Una mezcla de EJEMPLO 338J (144 mg), EJEMPLO 338M (95 mg), N, N-dimetilpiridin-4-amina (123 mg) y clorhidrato de N¹-((etilimino)metilen)-N³,N³-dimetilpropan-1,3-diamina (62,7 mg) en diclorometano (7 ml) se agitó durante la noche y se concentró. El residuo se purificó mediante cromatografía inversa, se eluyó con 40%-70% acetonitrilo en TFA acuoso al 0,1%. Las fracciones deseadas se concentraron, se neutralizó con NaHCO₃ y
15 se extrajo con diclorometano. La capa orgánica se secó sobre Na₂SO₄, se filtró, se concentró y se secó para dar el compuesto del título. ¹H NMR (400 MHz, sulfóxido de dimetilo-d₆) □ 11,69 (s, 1 H), 11,38 (s, 1 H), 8,59 (t, 1 H), 8,55 (d, 1 H), 8,04 (d, 1 H), 7,79 (dd, 1 H), 7,54 (d, 1 H), 7,46 - 7,52 (m, 2 H), 7,30 - 7,38 (m, 2 H), 7,00 - 7,10 (m, 3 H), 6,68 (dd, 1 H), 6,39 (dd, 1 H), 6,19 (d, 1 H), 3,95 (s, 1 H), 3,25 (t, 4 H), 3,07 (s, 4 H), 2,75 (s, 2 H), 2,10 - 2,26 (m, 6
20 H), 1,95 (s, 2 H), 1,29 - 1,62 (m, 8 H), 1,16 - 1,30 (m, 2 H), 1,08 (s, 3 H), 0,92 (s, 6 H).

EJEMPLO 339

N-[(5-cloro-6-[[[(1R,2R,4R,5R)-5-hidroxi-5-metilbiciclo[2,2,1]hept-2-il]metoxi]piridin-3-il)sulfonyl]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida
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EJEMPLO 339A

(1R,4S)-espiro[biciclo[2,2,1]heptan-2,2'-[1,3]dioxolan]-5-carboxilato de metilo

30 Una mezcla de reacción de 1,4-dioxaespiro[4,4]non-6-eno (5 g), acrilato de metilo (10,24 g), e hidroquinona (0,13 g) se calentó 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 isómeros.

35 EJEMPLO 339B

(1R,4S)-espiro[biciclo[2,2,1]heptan-2,2'-[1,3]dioxolan]-5-ilmetanol

Se enfrió EJEMPLO 339A (1,0 g) en tetrahidrofurano a 0°C. 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 luego se destiló para eliminar cualquier resto de agua. El compuesto del título se usó para la siguiente reacción sin purificación adicional.

EJEMPLO 339C

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 el EJEMPLO 339B en lugar de (tetrahidro-2H-piran-4-il)metanol y EJEMPLO 40A en lugar del EJEMPLO 36A en el EJEMPLO 36B. Los dos estereoisómeros en la posición 5 se aislaron mediante Sistema Gilson de HPLC 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%. Las fracciones deseadas se recogieron, y los solventes se eliminaron bajo vacío reducido a 60°C. Durante este proceso, se formó 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 MgSO₄, se filtró y se concentró para dar el compuesto del título.

EJEMPLO 339D

5-cloro-6-(((1S,2R,4R,5R)-5-hidroxi-5-metilbiciclo[2,2,1]heptan-2-il)metoxi)piridin-3-sulfonamida

Se trató EJEMPLO 339C (0,44 g) en tetrahidrofurano (15 mL) con bromuro de metilmagnesio 3,0 M (5,3 mL) a 0 °C. La solución 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 MgSO₄, 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 para dar el compuesto del título.

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EJEMPLO 339E

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

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El compuesto del título se preparó utilizando el EJEMPLO 339D en lugar del EJEMPLO 11B en el EJEMPLO 11D, ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) δ 11,66 (s,

1H), 8,50 (s, 1H), 8,16 (s, 1H), 8,02 (d, 1H), 7,49-7,55 (m, 3H), 7,35 (d, 2H), 7,05 (d, 2H), 6,67 (dd, 1H), 6,38 (dd, 1H), 6,20 (s, 1H), 4,40-4,48 (m, 2H), 4,31 (s, 1H), 3,09 (s, 4H), 2,83 (s, 2H), 2,15-2,33 (m, 7H), 1,96 (s, 2H), 1,87 (d, 1H), 1,65-1,69 (m, 1H), 1,54-1,56 (m, 2H), 1,36-1,47 (m, 6H), 1,26-1,30 (m, 1H), 1,19 (s, 3H), 0,93 (s, 6H).

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EJEMPLO 340

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([2-cianoetil](ciclopropil)amino)ciclohexil]amino)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 340A

4-(1,4-dioxaespiro[4,5]decan-8-ilamino)-3-nitrobencenosulfonamida

A una solución de 4-fluoro-3-nitrobencenosulfonamida (1,4 g) en tetrahidrofurano (30 mL) se agregó 1,4-dioxaespiro[4,5]decan-8-amina (1,0 g) y diisopropiletilamina (5 mL). La mezcla se agitó durante la noche. La mezcla se diluyó con acetato de etilo (300 mL) y se lavó con agua, salmuera y se secó sobre Na₂SO₄. La filtración y evaporación del solvente dio el compuesto del título.

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EJEMPLO 340B

20 N-(4-(1,4-dioxaespiro[4,5]decan-8-ilamino)-3-nitrofenilsulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-enil]metil)piperazin-1-il)benzamida

A una solución de EJEMPLO 3J (617 mg) y EJEMPLO 340A (386 mg) en diclorometano (10 mL) se agregó clorhidrato de 1-etil-3-[3-(dimetilamino)propil]-carbodiimida (288 mg) y 4-(dimetilamino)piridina (183 mg). La mezcla se agitó durante la noche. La mezcla se diluyó con diclorometano (300 mL) y se lavó con NaHCO₃ acuoso, agua, salmuera y se secó sobre Na₂SO₄. La filtración y evaporación del solvente dio el compuesto del título.

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EJEMPLO 340C

30 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-enil]metil)piperazin-1-il)-N-(3-nitro-4-(4-oxociclohexilamino)fenilsulfonil)benzamida

A una solución de EJEMPLO 340B (386 mg) en acetona (10 mL) y agua (5 mL) se agregó monohidrato de ácido para-toluensulfónico (50 mg). La mezcla se agitó a 120°C en un reactor de microondas Biotage Initiator por 30 minutos. La mezcla se diluyó con diclorometano (300 mL) y se lavó con NaHCO₃ acuoso, agua, salmuera y se secó sobre Na₂SO₄. La filtración y evaporación del solvente dio el compuesto del título.

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EJEMPLO 340D

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([2-cianoetil](ciclopropil)amino)ciclohexil]amino)-3-nitrofenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

5 A una solución de EJEMPLO 340C (240 mg) y 3-(ciclopropilamino)propanonitrilo (62 mg) en tetrahidrofurano (10 mL) se agregó ácido acético (2 mL) y MP-cianoborohidruro (300 mg, 2,15mmol/g). La mezcla se agitó durante la noche. La mezcla se filtró y se concentró bajo vacío y el residuo se disolvió en sulfóxido de dimetilo/metanol (1:1, 10 mL) y se cargó sobre Gilson, C18(100A) 250x121,2 mm(10 micron), con 30% acetonitrilo a 65% acetonitrilo
10 a lo largo de 40 minutos, ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) δ 11,66 (s, 1 H), 8,55 (dd, 1 H), 8,17 (d, 1 H), 8,03 (d, 1 H), 7,79 (d, 1 H), 7,49 (m, 3 H), 7,34 (d, 2 H), 7,11 (m, 1 H), 7,04 (d, 2 H), 6,67 (dd, 1 H), 6,38 (d, 1 H), 6,19 (d, 1 H), 4,01 (m, 1 H), 3,56 (m, 1 H), 3,06 (m, 4 H), 2,88 (t, 2 H), 2,65 (m, 6 H), 2,19 (m, 6 H), 2,00 (m, 7 H), 1,51 (m, 6 H), 0,92 (s, 6 H), 0,42 (m, 4 H).

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EJEMPLO 341

N-([5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il]sulfonil)-4-(4-([5-(4-clorofenil)espiro[2,5]oct-5-en-6-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 341A

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
25 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 concentración bajo alto vacío.

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EJEMPLO 341B

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 por goteo una solución de EJEMPLO 341A (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
35 baño de hielo y se detuvo muy lentamente con agua (8 mL). Luego se agregó en forma secuencial hidróxido de sodio 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 se filtró. El compuesto del título se aisló mediante concentración del material filtrado.

EJEMPLO 341C

5 8-(benciloximetil)-1,4-dioxaspiro[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 341B (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 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.

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EJEMPLO 341D

4-(benciloximetil)ciclohexanona

A una solución de EJEMPLO 341C (43,02 g) en dioxano (500 mL) se agregó agua (125 mL) y ácido clorhídrico 2M (90 mL). La mezcla se calentó a 85°C 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 5-50% en hexanos para dar el compuesto del título.

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EJEMPLO 341E

trans-4-(benciloximetil)-1-metilciclohexanol

A 2,6-di-t-butil-4-metilfenol (83,4 g) en tolueno (1100 mL) se agregó trimetilaluminio 2,0M (en hexanos) (95 mL) para de alguna manera controlar cuidadosamente la evolución de metano y una pequeña reacción exotérmica. La mezcla de la reacción se agitó a temperatura ambiente bajo N₂ por 75 minutos y luego se enfrió a -77° C. Se agregó una solución de EJEMPLO 341D (14 g) en tolueno (15 mL) por goteo, manteniendo la temperatura bajo -74 °C. Luego se agregó metililitio (1,6M en éter dietílico, 120 mL) por goteo, manteniendo la temperatura bajo -65 °C. La mezcla resultante se agitó a -77 °C bajo N₂ 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

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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 341F

Trans-4-(hidroximetil)-1-metilciclohexanol

Se agregó EJEMPLO 341E (12,6 g) y etanol (120 ml) a $\text{Pd}(\text{OH})_2/\text{C}$ al 20%, húmedo (1,260 g) en una botella de presión SS de 500 mL. La mezcla de la reacción se agitó a temperatura ambiente bajo 30 psi gas hidrógeno. La toma de hidrógeno finalizó 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 341G

5-cloro-6-((trans-4-hidroxi-4-metilciclohexil)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 40A en lugar de 4-fluoro-3-nitrobencenosulfonamida y EJEMPLO 341F en lugar de (tetrahydro-2H-piran-4-il)metanol en el EJEMPLO 24A.

EJEMPLO 341H

N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[5-(4-clorofenil)espiro[2,5]oct-5-en-6-il]metil}piperazin-1-il)-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 328E en lugar del EJEMPLO 3J y EJEMPLO 341G en lugar del EJEMPLO 11B en el EJEMPLO 11D. ^1H NMR (500 MHz, piridina- d_5) δ 13,09 (s, 1H), 9,18 (d, 1H), 8,74 (d, 1H), 8,41 (d, 1H), 8,09 (d, 1H), 7,67 (m, 2H), 7,42 (m, 2H), 7,09 (m, 2H), 6,74 (dd, 1H), 6,52 (dd, 1H), 6,49 (d, 1H), 4,29 (d, 2H), 3,05 (m, 4H), 2,80 (s, 2H), 2,37 (t, 2H), 2,15 (m, 4H), 2,11 (s, 2H), 1,89 (m, 6H), 1,75 (m, 2H), 1,45 (t, 2H), 1,41 (s, 3H), 1,32 (m, 2H), 0,37 (m, 4H).

EJEMPLO 342

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

5 EJEMPLO 342A

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 colocó en acetato de etilo. Luego se lavó con bicarbonato de sodio saturado, salmuera, se secó sobre MgSO₄, se filtró, y se concentró. El residuo se purificó mediante cromatografía flash de columna sobre gel de sílice usando acetato de etilo al 10-100% en hexanos para dar el compuesto del título.

15 EJEMPLO 342B

(5,6,7,8-tetrahidroimidazo[1,2-a]piridin-6-il)metanol

El compuesto del título se preparó utilizando el EJEMPLO 342A en lugar del EJEMPLO 339A en el EJEMPLO 339B.

20 EJEMPLO 342C

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 el EJEMPLO 342B en lugar de (tetrahidro-2H-piran-4-il)metanol y EJEMPLO 40A en lugar del EJEMPLO 36A en el EJEMPLO 36B.

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EJEMPLO 342D

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

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El compuesto del título se preparó utilizando el EJEMPLO 342C en lugar del EJEMPLO 11B en el EJEMPLO 11D, 1H NMR (500MHz, sulfóxido de dimetilo-d₆) δ 11,54 (s, 1H), 8,36 (s, 1H), 8,06 (s, 1H), 7,93 (s, 1H), 7,58 (d, 1H), 7,41-7,44 (m, 2H), 7,2-7,36 (m, 4H), 7,05 (d, 2H), 6,63 (dd, 1H), 6,32 (dd, 1H), 6,24 (d, 1H), 4,42-4,51 (m, 1H), 4,37-4,40 (m, 1H), 4,29 (dd, 1H), 3,91 (dd, 1H), 3,03 (s, 4H), 2,90-2,95 (m, 2H), 2,77 (s, 2H), 2,51-2,52 (m, 1H), 2,07-2,23 (m, 7H), 1,96 (s, 2H), 1,76-1,82 (m, 1H), 1,65-1,69 (m, 2H), 1,54-1,56 (m, 2H), 1,39 (t, 2H), 0,93 (s, 6H).

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EJEMPLO 343

N-[(5-cloro-6-[[[(1R,2S,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-pirrol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 343A

5-cloro-6-(((1S,2S,4R)-5-oxobiciclo[2,2,1]heptan-2-il)metoxi)piridin-3-sulfonamida

El compuesto del título se aisló como otro isómero en el EJEMPLO 339C.

10 EJEMPLO 343B

5-cloro-6-(((1S,2S,4R,5R)-5-hidroxi-5-metilbiciclo[2,2,1]heptan-2-il)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 343A en lugar del EJEMPLO 339B en el EJEMPLO 339C.

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EJEMPLO 343C

N-[(5-cloro-6-[[[(1R,2S,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-pirrol[2,3-b]piridin-5-iloxi)benzamida

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El compuesto del título se preparó utilizando el EJEMPLO 343B en lugar del EJEMPLO 11B en el EJEMPLO 11D, ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) δ 11,67 (s, 1H), 8,51 (s, 1H), 8,17 (s, 1H), 8,03 (s, 1H), 7,49-7,55 (m, 3H), 7,35 (d, 2H), 7,05 (d, 2H), 6,67 (dd, 1H), 6,39 (dd, 1H), 6,20 (d, 1H), 4,27 (s, 1H), 4,11-4,19 (m, 2H), 3,11 (s, 4H), 2,87 (s, 2H), 1,96-2,23 (m, 10H), 1,88 (d, 1H), 1,50 (dd, 1H), 1,33-1,44 (m, 2H), 1,13-1,19 (m, 4H), 0,88-0,93 (m, 8H).

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EJEMPLO 344

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 344A

4-((cis-4-hidroxi-4-metilciclohexil)metoxi)-3-nitrobencenosulfonamida

Se trató EJEMPLO 347A (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 Na₂SO₄, se filtró, y se concentró. El residuo

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se purificó mediante a cromatografía de fase inversa, eluyendo con 30-50% CH₃CN en ácido trifluoroacético al 0,1% agua para dar el compuesto del título como sólo un enantiómero.

EJEMPLO 344B

- 5 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 344A en lugar del EJEMPLO 1F y EJEMPLO 3J en lugar del EJEMPLO 1E en el EJEMPLO 1G. ¹H NMR (400 MHz, sulfóxido de dimetilo-d₆) □ 11,69 (s, 1H), 8,34 (d, 1H), 8,04 (m, 2H), 7,52 (m, 3H), 7,40 (d, 1H), 7,35 (d, 2H), 7,04 (d, 2H), 6,68 (dd, 1H), 6,40 (m, 1H), 6,20 (d, 1H), 4,02 (d, 2H), 3,96 (s, 1H), 3,10 (br s, 4H), 2,85 (m, 2H), 2,29 (m, 3H), 2,15 (t, 2H), 1,96 (br s, 2H), 1,68 (m, 1H), 1,55(m, 4H), 1,42 (m, 4H), 1,27 (m, 2H), 1,10 (s, 3H), 0,92 (s, 6H).

EJEMPLO 345

- 15 N-[(5-cloro-6-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi}piridin-3-il)sulfonil]-4-(4-{[5-(4-clorofenil)espiro[2,5]oct-5-en-6-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 328E en lugar del EJEMPLO 3J y EJEMPLO 277O en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (500 MHz, piridina-d₅) □ 13,07 (s, 1H), 9,13 (d, 1H), 8,41 (d, 1H), 8,09 (d, 1H), 7,68 (t, 1H), 7,66 (d, 1H), 7,42 (m, 2H), 7,09 (m, 2H), 6,75 (dd, 1H), 6,51 (m, 2H), 4,64 (d, 4H), 4,53 (d, 2H), 3,39 (m, 1H), 3,06 (m, 4H), 2,81 (s, 2H), 2,51 (m, 2H), 2,37 (m, 2H), 2,12 (m, 10H), 1,90 (m, 2H), 1,45 (t, 2H), 0,38 (s, 4H).

25 EJEMPLO 346

- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[4-(3,3-difluoropirrolidin-1-il)ciclohexil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando clorhidrato de 3,3-difluoropirrolidina en lugar de 3-(ciclopropilamino)propanonitrilo en el EJEMPLO 340D. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) □ 11,68 (s, 1 H), 11,38 (m, 1 H), 8,55 (m, 1 H), 8,36 (d, 1 H), 8,03 (d, 1 H), 7,80 (m, 1 H), 7,50 (m, 3 H), 7,34 (d, 2 H), 7,13 (d, 1 H), 7,04 (d, 2 H), 6,83 (m, 1 H), 6,68 (m, 1 H), 6,38 (d, 1 H), 6,19 (s, 1 H), 4,02 (s, 1 H), 3,83 (m, 1 H), 3,06 (m, 4 H), 2,96 (m, 2 H), 2,73 (m, 4 H), 2,26 (m, 8 H), 1,97 (m, 4 H), 1,68 (m, 4 H), 1,37 (m, 2 H), 0,92 (s, 6 H).

35

EJEMPLO 347

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

5 EJEMPLO 347A

4-(hidroximetil)-1-metilciclohexanol

Se trató 4-(hidroximetil)ciclohexanona (800 mg) en tetrahidrofurano (15 mL) 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 347B

15 5-cloro-6-((trans-4-hidroxi-4-metilciclohexil)metoxi)piridin-3-sulfonamida

Se trató EJEMPLO 347A (970 mg) y EJEMPLO 40A (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 Na₂SO₄, se filtró, y se concentró. El residuo se purificó mediante a cromatografía de fase inversa, eluyendo con 30-45% acetonitrilo en ácido trifluoroacético al 0,1% agua para aislar el compuesto del título.

EJEMPLO 347C

5-cloro-6-((cis-4-hidroxi-4-metilciclohexil)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó y se aisló como se describe en Ejemplo 347B.

25

EJEMPLO 347D

30 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-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 11D usando EJEMPLO 347B en lugar de EJEMPLO 11B. ¹H NMR (400 MHz, sulfóxido de dimetilo-d₆) □
 35 11,67 (s, 1 H), 8,51 (d, 1 H), 8,18 (d, 1 H), 8,03 (d, 1 H), 7,48 - 7,56 (m, 3 H), 7,35 (d, 2 H), 7,05 (d, 2 H), 6,68 (dd, 1 H), 6,39 (dd, 1 H), 6,21 (d, 1 H), 4,17 - 4,34 (m, 3 H), 3,11 (s, 4 H),

2,89 (s, 2 H), 2,24 - 2,42 (m, 4 H), 2,15 (s, 2 H), 1,96 (s, 2 H), 1,66 - 1,82 (m, 3 H), 1,55 (d, 2 H), 1,31 - 1,44 (m, 4 H), 1,12 - 1,27 (m, 2 H), 1,10 (s, 3 H), 0,93 (s, 6 H).

EJEMPLO 348

- 5 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-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 11D usando EJEMPLO 347C en lugar de EJEMPLO 11B. ¹H NMR (400 MHz, sulfóxido de dimetilo-d₆) □ 11,67 (s, 1 H), 8,51 (d, 1 H), 8,18 (d, 1 H), 8,03 (d, 1 H), 7,47 - 7,58 (m, 3 H), 7,35 (d, 2 H), 10 7,05 (d, 2 H), 6,68 (dd, 1 H), 6,39 (dd, 1 H), 6,21 (d, 1 H), 4,21 (d, 2 H), 3,95 (s, 1 H), 3,11 (s, 4 H), 2,89 (s, 2 H), 2,33 (d, 4 H), 2,15 (s, 2 H), 1,96 (s, 2 H), 1,63 - 1,77 (m, 1 H), 1,48 - 1,60 (m, 4 H), 1,35 - 1,48 (m, 4 H), 1,20 - 1,33 (m, 2 H), 1,09 (s, 3 H), 0,93 (s, 6 H).

EJEMPLO 349

- 15 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-({(2,2-difluorociclopropil)amino)ciclohexil}amino]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando clorhidrato de 2,2-difluorociclopropanamina en lugar de 3-(ciclopropilamino)propanonitrilo en el EJEMPLO 20 340D. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) □ 11,60 (s, 1 H), 8,47 (m, 2 H), 8,12 (m, 1 H), 7,98 (m, 1 H), 7,72 (m, 2 H), 7,47 (m, 3 H), 7,34 (m, 3 H), 7,05 (m, 3 H), 6,65 (dd, 1 H), 6,35 (m, 1 H), 6,22 (d, 1 H), 3,54 (m, 2 H), 3,08 (m, 4 H), 2,74 (m, 4 H), 2,25 (m, 4 H), 2,01 (m, 4 H), 1,38 (m, 4 H), 0,92 (s, 6 H).

25 EJEMPLO 350

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 350A

- 30 espiro[benzo[d][1,3]dioxol-2,1'-ciclohexan]-4'-carboxilato de etilo

A una solución de 4-oxociclohexanocarboxilato de etilo (22,75 g) y pirocatecol (14,75 g) en tolueno (200 mL) se agregó una cantidad catalítica de monohidrato de ácido para-
toluensulfónico y la mezcla se agitó bajo reflujo y una trampa Dean-Stark durante la noche. La mezcla se diluyó con éter dietílico (600 mL) y se lavó con NaHCO₃ acuoso, agua y
35 salmuera. Luego de secar sobre Na₂SO₄, la mezcla se filtró y el solvente se evaporó bajo vacío para dar el compuesto del título.

EJEMPLO 350B

4'-fluoro-espiro[benzo[d][1,3]dioxol-2,1'-ciclohexan]-4'-carboxilato de etilo

Una solución de EJEMPLO 350A (5,25g) en tetrahidrofurano (40 mL) se agregó por goteo a una solución de diisopropilamida de litio (12 mL, 2,0M en tetrahidrofurano/heptano/etilbenceno) a 0°C. La solución se agitó a 0°C por 30 minutos, y luego se transfirió mediante cánulos a una solución previamente enfriada (0°C) en agitación de N-fluorobencenosulfonimida (7,89g) en tetrahidrofurano seco (20 mL). La mezcla de la reacción se agitó a 0°C por 30 minutos, y luego a 20°C por 18 horas. La mezcla de la reacción se vertió sobre NH₄Cl acuoso y se extrajo con éter dietílico (3x200 mL). Las capas orgánicas combinadas se lavaron con agua, salmuera y se secó sobre Na₂SO₄. La filtración y evaporación del solvente dio el producto crudo.

EJEMPLO 350C

(4'-fluoro-espiro[benzo[d][1,3]dioxol-2,1'-ciclohexan]-4'-il)metanol

A una solución de EJEMPLO 350B (23 g) en tetrahidrofurano (150 mL) se agregó hidruro de litio y aluminio (3,11 g). La mezcla se agitó durante la noche. Se agregó una solución acuosa 2N de NaOH por goteo a la mezcla de la reacción. La mezcla luego se diluyó con acetato de etilo (600 mL) y se lavó con agua, salmuera y se secó sobre Na₂SO₄. La filtración y evaporación del solvente dio el producto crudo el cual se cargó en una columna analógica de 600 g y se eluyó con acetato de etilo entre 10% y 20% en hexano para dar el compuesto del título.

EJEMPLO 350D

5-cloro-6-((4'-fluoro-espiro[benzo[d][1,3]dioxol-2,1'-ciclohexan]-4'-il)metoxi)piridin-3-sulfonamida

A una solución de EJEMPLO 350C (89 mg) en N,N-dimetilformamida (3 mL) se agregó NaH (65% en aceite mineral, 36 mg). La mezcla se agitó por 30 minutos, y luego se agregó 5, 6-dicloropiridin-3-sulfonamida (85 mg). La mezcla se agitó durante la noche. La mezcla se vertió sobre NH₄Cl acuoso y se extrajo con acetato de etilo (100 mL). Las capas orgánicas combinadas se lavaron con agua, salmuera y se secó sobre Na₂SO₄. 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 compuesto del título.

EJEMPLO 350E

5-cloro-6-((1-fluoro-4-oxociclohexil)metoxi)piridin-3-sulfonamida

A una solución de EJEMPLO 350D (1,6g) y p-toluensulfonato de piridinio (1,2 g) en acetona (10 mL) se agregó agua (2 mL) y la mezcla se agitó bajo radiación de microondas a 100°C por 10 minutos. La mezcla se diluyó con diclorometano (300 mL) y se lavó con

NaHCO₃ acuoso, agua, salmuera y se secó sobre Na₂SO₄. La filtración y evaporación del solvente dio el compuesto del título.

EJEMPLO 350F

5 5-cloro-6-((cis-1-fluoro-4-hidroxiciclohexil)metoxi)piridin-3-sulfonamida

A una solución de EJEMPLO 350E (336 mg) en tetrahidrofurano (10 mL) se agregó NaBH₄ (75 mg). La mezcla se agitó por 45 minutos. La mezcla se diluyó con acetato de etilo (300 mL) y se lavó con NaOH acuoso 2N, agua, y salmuera. Luego de secar sobre Na₂SO₄, la mezcla se filtró y el solvente se evaporó para dar el producto crudo.

10 EJEMPLO 350G

N-({5-cloro-6-[(cis-1-fluoro-4-hidroxiciclohexil)metoxi]piridin-3-il}sulfonyl)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol-2-il)piridin-5-il}benzamida

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 350F en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) δ 11,63 (s, 1 H), 8,48 (s, 1 H), 8,18 (s, 1 H), 8,01 (d, 1 H), 7,50 (m, 3 H), 7,35 (d, 2 H), 7,05 (d, 2 H), 6,67 (dd, 1 H), 6,37 (dd, 1 H), 6,21 (d, 1 H), 4,62 (d, 1 H), 4,47 (s, 1 H), 4,40 (s, 1 H), 3,46 (m, 1 H), 3,06 (m, 4 H), 2,88 (m, 1 H), 2,25 (m, 6 H), 1,99 (m, 4 H), 1,58 (m, 8 H), 0,93 (s, 6 H).

20 EJEMPLO 351

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-nitro-4-(2-oxaespиро[3,5]non-7-ilmetoxi)fenil}sulfonyl]-2-(1H-pirrol-2-il)piridin-5-il}benzamida

EJEMPLO 351A

25 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 N₂ y se agregó n-BuLi (2,5 M en hexanos, 44,8 mL). La reacción se agitó por 30 minutos a -78°C y se agregó 1,4-dioxaespiro[4,5]decan-8-carboxilato de etilo (20 g) como una solución de tetrahidrofurano (aprox. 10 mL). La solución se agitó a -78°C por 1 hora y se agregó clorofórmato 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 NH₄Cl 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 (Na₂SO₄), 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 351B

1,4-dioxaespiro[4,5]decan-8,8-diildimetanol

A un balón de 1 L se agregó EJEMPLO 351A (26,6 g) y tetrahidrofurano (310 mL) para dar una solución incolora. 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 y se detuvo lentamente con 4,7 mL de agua, 4,7 mL de NaOH acuoso al 10% y 14 mL de agua. La mezcla se dejó agitar hasta que se formaron sales y luego 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 351C

2,8,11-trioxa-diespiro[3,2,4]tridecano

1. A un balón de 1 L se agregó EJEMPLO 351B (13 g) en tetrahidrofurano (321 mL). La solución se enfrió a -78 °C bajo N₂ y se agregó n-BuLi (25,7 mL) por goteo mediante una jeringa. Luego de completarse la adición, la mezcla se agitó por 30 minutos y se agregó una solución de tetrahidrofurano de cloruro de 4-toluensulfonilo (12,25 g) a través de un embudo de adición. La reacción se dejó agitar durante la noche, y calentar gradualmente a temperatura ambiente. La mezcla de la reacción se enfrió a -78 °C y se agregó n-BuLi (25,7mL). La mezcla se calentó a temperatura ambiente y se agitó por 3 horas. La reacción se detuvo con NH₄Cl acuoso saturado y se diluyó con éter dietílico. Las capas se separaron, las capas acuosas se extrajeron con éter dietílico y los orgánicos combinados se secaron (Na₂SO₄), 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 351D

2-oxaespiro[3,5]nonan-7-ona

A un balón de 500 mL se agregó EJEMPLO 351C (11 g) en ácido acético acuoso 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 eliminó 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 351E

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) para dar una suspensión. La suspensión se enfrió a -15 °C. Se agregó n-BuLi (2,5 M en hexanos, 4,28 mL) por goteo y la mezcla se agitó a -15 °C por 40 minutos y se agregó EJEMPLO 351D (1 g) como una solución de 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 NH₄Cl 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 (Na₂SO₄), se filtró y se concentró por evaporación por rotación. El residuo se purificó mediante cromatografía de fase normal (Analogix, columna de gel de sílice Grace de 80 g, hexanos al 0-50%/acetato de etilo).

EJEMPLO 351F

2-oxaespiro[3,5]nonan-7-ilmetanol

A un balón de 25 mL se agregó EJEMPLO 351E (568 mg) y EJEMPLO 351F en tetrahidrofurano (4,11 mL) para dar una solución incolora. Se agregó 9-borabicyclo[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 (2,1 mL). La reacción se calentó a 50 °C por 2 horas. La mezcla se concentró por evaporación por rotación, y se diluyó con agua y acetato de etilo. La capa acuosa se extrajo con acetato de etilo (3x) y los orgánicos combinados se secaron (Na₂SO₄), se filtró y se concentró por evaporación por rotación. El residuo se purificó mediante cromatografía flash de columna de fase normal (Analogix, 80 g Grace, 0-70 % hexanos / acetato de etilo).

EJEMPLO 351G

4-(2-oxaespiro[3,5]nonan-7-ilmetoxi)-3-nitrobenzenosulfonamida

Se preparó EJEMPLO 351G utilizando EJEMPLO 351F en lugar de (tetrahidro-2H-piran-4-il)metanol en el EJEMPLO 24A.

EJEMPLO 351H

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-N-(4-(2-oxaespiro[3,5]nonan-7-ilmetoxi)-3-nitrofenilsulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 351G en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) □ 11,67 (s, 1 H) 8,34 (s, 1 H) 8,03 (d, 2 H) 7,45 - 7,57 (m, 3 H) 7,30 -

7,40 (m, 3 H) 7,04 (d, 2 H) 6,67 (dd, 1 H) 6,39 (dd, 1 H) 6,17 - 6,23 (m, 1 H) 4,29 (s, 2 H) 4,20 (s, 2 H) 4,00 (d, 2 H) 3,08 (s, 4 H) 2,73 - 2,90 (m, 2 H) 2,72 (s, 1 H) 2,01 - 2,32 (m, 6 H) 1,96 (s, 2 H) 1,64 - 1,78 (m, 4 H) 1,33 - 1,50 (m, 6 H) 0,96 - 1,15 (m, 2 H) 0,92 (s, 6 H).

5 EJEMPLO 352

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 352A

10 4-([trans-4-hidroxi-4-metilciclohexil]metoxi)-3-nitrobenzenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 341F en lugar de (tetrahydro-2H-piran-4-il)metanol en el EJEMPLO 24A.

EJEMPLO 352B

15 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-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 352A en lugar del EJEMPLO 1F y EJEMPLO 3J en lugar del EJEMPLO 1E in EJEMPLO 1G. ¹H NMR (400 MHz, sulfóxido de dimetilo-d₆) □ 11,66 (s, 1H), 8,31 (br s, 1H), 8,01 (m, 2H), 7,49 (m, 3H), 7,33 (m, 3H), 7,03 (m, 2H), 6,66 (dd, 1H), 6,37 (m, 1H), 6,19 (d, 1H), 4,27 (s, 1H), 4,05 (d, 2H), 3,40 (m, 2H), 3,17 (s, 1H), 3,07 (m, 3H), 2,79 (m, 1H), 2,24 (m, 3H), 2,14 (m, 2H), 1,94 (m, 2H), 1,71 (m, 3H), 1,52 (m, 2H), 1,38 (m, 4H), 1,22 (m, 2H), 1,09 (s, 3H), 0,91 (s, 6H).

EJEMPLO 353

25 4-(4-([2-(4-clorofenil)-5,5-bis(fluorometil)ciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-[(tetrahydro-2H-piran-4-ilmetil)amino]fenil]sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 353A

bis(4-metilbenzenosulfonato) de 1,4-dioxaespiro[4,5]decan-8,8-diilbis(metileno)

A un balón de 500 mL se agregó EJEMPLO 351B (10 g) y diclorometano (165 mL) para dar una solución incolora. Se agregó trietilamina (24,1 mL) y cloruro de tolueno-2-sulfonilo (19,8 g) seguido por 4-dimetilaminopiridina (0,604 g). La reacción se sometió a reflujo durante la noche. Se agregó NH₄Cl acuoso saturado seguido por la dilución con agua y diclorometano adicional. La capa acuosa se extrajo con diclorometano (2x) y los orgánicos combinados se secaron (MgSO₄), se filtró y se concentró por evaporación por rotación. El residuo se purificó mediante cromatografía flash de columna de fase normal (Analogix, 0-55% hexanos / acetato de etilo).

EJEMPLO 353B

8,8-bis(fluorometil)-1,4-dioxaspiro[4,5]decano

- 5 A un balón de 500 mL se agregó EJEMPLO 353A (20 g). Se agregó fluoruro de tetra-n-butilamonio (1M en tetrahidrofurano, 200 mL) y la solución resultante se sometió a reflujo por 6 días. La reacción se enfrió, se diluyó con éter dietílico y se lavó con agua (3x). Los orgánicos 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, 0-30% hexanos / acetato de etilo).

10 EJEMPLO 353C

4,4-bis(fluorometil)ciclohexanona

- 15 A un balón de 250 mL se agregó EJEMPLO 353B (1,1 g) y ácido acético acuoso al 80% (50 mL). La reacción se calentó a 65 °C por 3 horas, se enfrió y se concentró por evaporación por rotación para eliminar la mayor parte del ácido acético y el agua. El residuo se purificó mediante cromatografía flash de columna de fase normal (Analogix, hexanos al 0-50% / acetato de etilo).

EJEMPLO 353D

2-cloro-5,5-bis(fluorometil)ciclohex-1-encarbaldehido

- 20 A un recipiente en forma de pera de 100 mL se agregó N,N-dimetilformamida (498 μL) y diclorometano (8,9 mL) para dar una solución incolora. La solución se enfrió a 0 °C y se agregó POCl_3 (550 μL) por goteo y luego la mezcla se calentó a temperatura ambiente por 30 minutos. Mientras tanto, a un recipiente en forma de pera de 100 mL se agregó EJEMPLO 353C (870 mg, 5,36 mmol) en diclorometano (8941 μL) para dar una solución incolora. el reactivo de Vilsmeier luego se recogió con una jeringa y se agregó por goteo a la solución de 4,4-bis(fluorometil)ciclohexanona (870 mg) a temperatura ambiente. La solución resultante se agitó durante la noche. La reacción se vertió en NaHCO_3 acuoso saturado y hielo, se calentó a temperatura ambiente y se extrajo con diclorometano (3 x 30 mL). Los orgánicos se combinaron, se secó sobre MgSO_4 , se filtró y se concentró por evaporación por rotación. El residuo se purificó mediante cromatografía flash de columna de fase normal (Analogix (0-60% hexanos / acetato de etilo).

EJEMPLO 353E

2-(4-clorofenil)-5,5-bis(fluorometil)ciclohex-1-encarbaldehido

- 35 A un vial de 20 mL se agregó EJEMPLO 353D (460 mg), ácido 4-clorofenilborónico (414 mg), carbonato de potasio (762 mg), bromuro de tetrabutilamonio (711 mg), acetato de

paladio (II) (14,85 mg) y agua (2450 µl) para dar una suspensión la cual se desgasificó con N₂ por 2 minutos. La reacción se agitó a 45 °C durante la noche, se enfrió, y se vertió sobre un embudo Buchner de gel de sílice Supelco, lavando con acetato de etilo varias veces. El material filtrado se concentró por evaporación por rotación y el residuo se purificó mediante
5 cromatografía flash de columna de fase normal (Analogix, 0-60% hexanos / acetato de etilo).

EJEMPLO 353F

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-5,5-bis(fluorometil)ciclohex-1-enil)metil)piperazin-1-il)benzoato de metilo

10 A un vial de 20 mL se agregó EJEMPLO 353E (240 mg), EJEMPLO 15F (297 mg) y diclorometano (4,2 mL). Se agregó triacetoxiborhidruro de sodio (268 mg) y la reacción se agitó durante la noche a temperatura ambiente. La reacción se cargó directamente sobre gel de sílice y se purificó mediante cromatografía flash de columna de fase normal (Analogix, 0-80% hexanos / acetato de etilo).

15

EJEMPLO 353G

ácido 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-5,5-bis(fluorometil)ciclohex-1-enil)metil)piperazin-1-il)benzoico

20 El compuesto del título se preparó utilizando el EJEMPLO 353F en lugar del EJEMPLO 15G en el EJEMPLO 15 H.

EJEMPLO 353H

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-5,5-bis(fluorometil)ciclohex-1-enil)metil)piperazin-1-il)-N-(3-nitro-4-((tetrahidro-2H-piran-4-il)metilamino)fenilsulfonil)benzamida

25

EJEMPLO 353H se preparó reemplazando EJEMPLO 3J por EJEMPLO 353G y EJEMPLO 11B por EJEMPLO 1F en el EJEMPLO 11D. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) □ 11,69 (s, 1 H) 11,44 (s, 1 H) 8,48 - 8,70 (m, 1 H) 8,05 (d, 2 H) 7,81 (dd, 1 H) 7,46 - 7,59 (m, 3 H) 7,35 (d, 2 H) 7,12 (d, 2 H) 6,68 (dd, 1 H) 6,40 (dd, 1 H) 6,16 (d, 1 H) 4,39
30 - 4,49 (m, 2 H) 4,23 - 4,35 (m, 2 H) 3,85 (dd, J=11,87, 2,71 Hz, 2 H) 3,20 - 3,30 (m, 4 H) 2,98 - 3,10 (m, 4 H) 2,66 - 2,77 (m, 2 H) 2,11 - 2,30 (m, 6 H) 2,02 - 2,12 (m, 3 H) 1,99 (s, 1 H) 1,82 - 1,97 (m, 1 H) 1,54 - 1,67 (m, 4 H) 1,20 - 1,34 (m, 2 H).

EJEMPLO 354

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-ciclopropilmorfolin-2-il)metoxi]-3-nitrofenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

5 EJEMPLO 354A

2-((2-nitro-4-sulfamoilfenoxi)metil)morfolina-4-carboxilato de tert-butilo

El compuesto del título se preparó utilizando 2-(hidroximetil)-morfolina-4-carboxilato de tert-butilo en lugar de tetrahidro-2H-piran-4-il-metanol EJEMPLO 24A.

10 EJEMPLO 354B

4-(morfolin-2-ilmetoxi)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 354A en lugar del EJEMPLO 113A en el EJEMPLO 134A.

15 EJEMPLO 354C

4-((4-ciclopropilmorfolin-2-il)metoxi)-3-nitrobencenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 354B en lugar del EJEMPLO 173A en el EJEMPLO 173B.

20 EJEMPLO 354D

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-ciclopropilmorfolin-2-il)metoxi]-3-nitrofenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 354C en lugar del

25 EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridina-d₅) □ 12,98 (s, 1H), 9,06 (d, 1H), 8,50 (dd, 1H), 8,41 (d, 1H), 8,09 (d, 1H), 7,66 (t, 1H), 7,62 (d, 1H), 7,44 (d, 2H), 7,26 (d, 1H), 7,07 (d, 2H), 6,75 (dd, 1H), 6,54 (d, 1H), 6,48 (m, 1H), 4,31 (dd, 1H), 4,22 (dd, 1H), 3,92 (m, 1H), 3,83 (d, 1H), 3,56 (dt, 1H), 3,07 (m, 5H), 2,77 (s, 2H), 2,68 (d, 1H), 2,35 (m, 2H), 2,26 (m, 2H), 2,14 (m, 4H), 1,97 (s, 2H), 1,59 (m, 1H), 1,39 (t, 2H), 0,94 (s, 6H), 0,40 (m, 30 4H).

EJEMPLO 355

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

35

EJEMPLO 355A

5-cloro-6-((trans-1-fluoro-4-hidroxi-4-metilciclohexil)metoxi)piridin-3-sulfonamida

A una solución fría (0°C) de EJEMPLO 350E (1,2 g) en tetrahidrofurano (30 mL) se agregó por goteo una solución de bromuro de metilmagnesio (5 mL, 3,0M en éter). Luego de la adición, la mezcla de la reacción se solidificó. Se agregó más tetrahidrofurano (10 mL) a la mezcla y la agitación se continuó por 1 hora. La mezcla se vertió sobre NH₄Cl acuoso y se extrajo con acetato de etilo (3x 150 mL). Las capas orgánicas combinadas se lavaron con agua, salmuera y se secó sobre Na₂SO₄. La mezcla se filtró y se concentró. El residuo se disolvió en sulfóxido de dimetilo/metanol (20 mL, 1:1) y se cargó sobre Gilson, C18(100A) 250x121,2 mm (10 micron), con 30% acetonitrilo a 65% acetonitrilo a lo largo de 40 minutos para separar los dos isómeros y aislar el compuesto del título.

EJEMPLO 355B

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-pirroló[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 355A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) □ 11,63 (s, 1 H), 8,47 (s, 1 H), 8,17 (s, 1 H), 7,54 (d, 1 H), 7,48 (m, 2 H), 7,35 (d, 2 H), 7,05 (d, 2 H), 6,67 (dd, 1 H), 6,37 (d, 1 H), 6,22 (d, 1 H), 4,49 (s, 1 H), 4,42 (s, 1 H), 4,15 (s, 1 H), 3,06 (m, 4 H), 2,84 (m, 1 H), 2,25 (m, 6 H), 1,96 (s, 3 H), 1,83 (m, 4 H), 1,44 (m, 6 H), 1,14 (s, 3 H), 0,93 (s, 6 H).

EJEMPLO 356

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-pirroló[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 356A

5-cloro-6-((cis-1-fluoro-4-hidroxi-4-metilciclohexil)metoxi)piridin-3-sulfonamida

El compuesto del título se preparó como se describe en el EJEMPLO 355A.

EJEMPLO 356B

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-pirroló[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 356A en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) □ 11,65 (s, 1 H), 8,52 (s, 1 H), 8,20 (s, 1 H), 8,03 (d, 1 H), 7,51 (m, 3 H), 7,35 (d, 2 H), 7,05 (d, 2 H), 6,67 (dd, 1 H), 6,39 (dd, 1 H), 6,21 (d, 1 H), 4,55 (s, 1 H), 4,48 (s, 1 H), 4,34 (s, 1 H), 3,08 (m, 4 H), 2,89 (d, 2 H), 2,27 (m, 5 H), 1,93 (m, 4 H), 1,66 (m, 4 H), 1,43 (m, 4 H), 1,11 (s, 3 H), 0,93 (s, 6 H).

EJEMPLO 357

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-pirrolol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 357A

4-fluoro-1-(oxetan-3-il)piperidin-4-carboxilato de etilo

A 4-fluoropiperidin-1,4-dicarboxilato de 1-tert-butilo 4-etilo (1,000 g) se agregó HCl (4,0M en dioxano, 4,54 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 (1,155 g) y oxetan-3-ona (0,262 g) y se agitó durante la noche. La reacción se detuvo con Solución saturada de NaHCO₃ (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 = 30mL/min) dio el compuesto del título.

EJEMPLO 357B

(4-fluoro-1-(oxetan-3-il)piperidin-4-il)metanol

A una solución de EJEMPLO 357A (0,59 g) en tetrahidrofurano (5 mL) se agregó hidruro de litio y aluminio (1,80 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 acuoso 2N. La reacción se filtró a través de celite y se enjuagó con acetato de etilo (50 mL). La mezcla y el residuo se cargó sobre gel de sílice (Reveleris 40 g) y se eluyó usando un gradiente de metanol entre 0,75% y 7,5%/diclorometano a lo largo de 30 minutos (velocidad de flujo = 40 mL/minutos) para dar el compuesto del título.

EJEMPLO 357C

3-ciano-4-((4-fluoro-1-(oxetan-3-il)piperidin-4-il)metoxi)bencenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 357B en lugar de (tetrahidro-2H-piran-4-il)metanol en el EJEMPLO 284A.

EJEMPLO 357D

- 5 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)sulfonyl]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 357C en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo- d₆) δ 11,67 (s, 1H), 11,49 - 11,14 (m, 1H), 8,17 (d, 1H), 8,03 (d, 2H),
 10 7,51 (dd, 3H), 7,43 - 7,26 (m, 3H), 7,12 - 6,96 (m, 2H), 6,67 (dd, 1H), 6,40 (dd, 1H), 6,20 (d, 1H), 4,55 (t, 2H), 4,45 (t, 2H), 4,34 (d, 2H), 3,49 (s, 1H), 3,09 (s, 8H), 2,39 - 1,66 (m, 14H), 1,39 (s, 2H), 0,92 (s, 6H).

EJEMPLO 358

- 15 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{(trans-4-etil-4-hidroxyciclohexil)metil}amino}-3-nitrofenil)sulfonyl]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 358A

- 20 (4-etil-4-hidroxyciclohexil)metilcarbamato de bencilo

A una solución en agitación enérgica de (4-oxociclohexil)metilcarbamato de bencilo (1 g) en tetrahidrofurano (20 mL) a -78°C se agregó lentamente bromuro de etilmagnesio 1 M (11,48 ml, 11,48 mmol) en éter. Luego de completarse la adición, la mezcla se agitó a -78°C por 2 horas y se calentó a 0°C, y se agitó en un baño de hielo por 30 minutos. La reacción se
 25 detuvo con una solución acuosa fría de NH₄Cl. Los precipitados se retiraron por filtración y se lavó con acetato de etilo. El material filtrado 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.

- 30 EJEMPLO 358B

4-(aminometil)-1-etilciclohexanol

Una mezcla de EJEMPLO 358A (500 mg) y Pd/C al 10% (100 mg) en tetrahidrofurano (15 mL) se agitó bajo H₂ por 3 horas. El material insoluble se retiró mediante filtración, y el material filtrado se concentró para dar el compuesto del título.

35

EJEMPLO 358C

4-((trans-4-etil-4-hidroxiciclohexil)metilamino)-3-nitrobencenosulfonamida

Se trató EJEMPLO 358B (270 mg) y 4-fluoro-3-nitrobencenosulfonamida (417 mg) en tetrahidrofurano con trietilamina (0,8 mL) durante la noche. La reacción se detuvo con agua. La mezcla resultante se neutralizó con HCl acuoso diluido, y se extrajo con acetato de etilo.

- 5 La capa orgánica se secó sobre Na₂SO₄, se filtró y se concentró. El residuo se purificó mediante a cromatografía de fase inversa, eluyendo con 40-55% acetonitrilo en ácido trifluoroacético al 0,1% agua para aislar el compuesto del título.

EJEMPLO 358D

- 10 4-((cis-4-etil-4-hidroxiciclohexil)metilamino)-3-nitrobencenosulfonamida

El compuesto del título se preparó y se aisló como se describe en Ejemplo 358C.

EJEMPLO 358E

- 15 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{(trans-4-etil-4-hidroxiciclohexil)metil}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

- El compuesto del título se preparó como se describe en el EJEMPLO 11D usando EJEMPLO 358C en lugar de EJEMPLO 11B. ¹H NMR (400 MHz, sulfóxido de dimetilo-d₆) □
 11,69 (s, 1 H), 11,35 (s, 1 H), 8,56 (d, 2 H), 8,05 (d, 1 H), 7,80 (dd, 1 H), 7,45 - 7,57 (m, 3 H),
 7,34 (d, 2 H), 7,00 - 7,10 (m, 3 H), 6,68 (dd, 1 H), 6,39 (dd, 1 H), 6,19 (d, 1 H), 3,98 (s, 1 H),
 20 3,24 - 3,31 (m, 4 H), 3,07 (s, 4 H), 2,75 (s, 2 H), 2,17 (d, 6 H), 1,95 (s, 2 H), 1,54 - 1,73 (m, 5 H), 1,35 - 1,47 (m, 4 H), 1,20 - 1,32 (m, 2 H), 1,03 - 1,18 (m, 2 H), 0,92 (s, 6 H), 0,81 (t, 3 H).

EJEMPLO 359

- 25 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{(cis-4-etil-4-hidroxiciclohexil)metil}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

- El compuesto del título se preparó como se describe en el EJEMPLO 11D usando EJEMPLO 358D en lugar de EJEMPLO 11B. ¹H NMR (400 MHz, sulfóxido de dimetilo-d₆) □
 11,69 (s, 1 H), 11,34 (s, 1 H), 8,60 (t, 1 H), 8,56 (d, 1 H), 8,05 (d, 1 H), 7,80 (dd, 1 H), 7,54 (d,
 1 H), 7,47 - 7,52 (m, 2 H), 7,34 (d, 2 H), 7,01 - 7,10 (m, 3 H), 6,68 (dd, 1 H), 6,39 (dd, 1 H),
 30 6,19 (d, 1 H), 3,77 (s, 1 H), 3,26 (t, 2 H), 3,07 (s, 4 H), 2,76 (s, 2 H), 2,10 - 2,26 (m, 6 H), 1,95 (s, 2 H), 1,46 - 1,61 (m, 5 H), 1,28 - 1,46 (m, 6 H), 1,12 - 1,24 (m, 2 H), 0,92 (s, 6 H), 0,82 (t, 3 H).

EJEMPLO 360

4-(4-[[2-(4-clorofenil)-5-(metoximetil)-5-metilciclohex-1-en-1-il]metil]piperazin-1-il)-N-((3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil)sulfonil)-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

5 EJEMPLO 360A

8-metil-1,4-dioxaespiro[4,5]decan-8-carboxilato de etilo

En un balón de 500 mL se agregó diisopropilamina (7,98 mL) en tetrahidrofurano (233 mL) para dar una solución incolora. La mezcla se enfrió a -78 °C bajo N₂ y se agregó n-BuLi (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 CH₃I (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 (Na₂SO₄), 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 360B

(8-metil-1,4-dioxaespiro[4,5]decan-8-il)metanol

En un balón de 500 mL se agregó hidruro de litio y aluminio (1,772 g) en tetrahidrofurano (234 mL) para dar una suspensión. Esta suspensión se enfrió a 0 °C y se agregó 8-metil-1,4-dioxaespiro[4,5]decan-8-carboxilato de etilo (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 de 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).

30 EJEMPLO 360C

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) para dar una suspensión. Se agregó EJEMPLO 360B como una solución de tetrahidrofurano a temperatura ambiente. La suspensión se agitó por 30 minutos y se agregó luego CH₃I (0,611 mL). La reacción se agitó bajo N₂ 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).

5 EJEMPLO 360D

4-(metoximetil)-4-metilciclohexanona

El compuesto del título se preparó utilizando el EJEMPLO 360C en lugar del EJEMPLO 353B en el EJEMPLO 353C.

10 EJEMPLO 360E

2-cloro-5-(metoximetil)-5-metilciclohex-1-encarbaldehído

El compuesto del título se preparó utilizando el EJEMPLO 360D en lugar del EJEMPLO 353C en el EJEMPLO 353D.

15 EJEMPLO 360F

2-(4-clorofenil)-5-(metoximetil)-5-metilciclohex-1-encarbaldehído

El compuesto del título se preparó utilizando el EJEMPLO 360E en lugar del EJEMPLO 353D en el EJEMPLO 353E.

20 EJEMPLO 360G

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-5-(metoximetil)-5-metilciclohex-1-enil)metil)piperazin-1-il)benzoato de metilo

El compuesto del título se preparó utilizando el EJEMPLO 360F en lugar del EJEMPLO 353E en el EJEMPLO 353F.

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EJEMPLO 360H

ácido 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-5-(metoximetil)-5-metilciclohex-1-enil)metil)piperazin-1-il)benzoico

El compuesto del título se preparó utilizando el EJEMPLO 360G en lugar del

30 EJEMPLO 15G en el EJEMPLO 15H.

EJEMPLO 360I

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-5-(metoximetil)-5-metilciclohex-1-enil)metil)piperazin-1-il)-N-(3-nitro-4-((tetrahidro-2H-piran-4-

35 il)metilamino)fenilsulfonil)benzamida

El compuesto del título se preparó reemplazando EJEMPLO 3J por EJEMPLO 360H y EJEMPLO 11B por EJEMPLO 1F en el EJEMPLO 11D. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) □ 11,68 (s, 1 H) 11,43 (s, 1 H) 8,45 - 8,72 (m, 2 H) 8,04 (d, 1 H) 7,80 (dd, 1 H) 7,44 - 7,61 (m, 3 H) 7,34 (d, 2 H) 6,99 - 7,20 (m, 3 H) 6,68 (dd, 1 H) 6,39 (dd, 1 H) 6,18 (d, 1 H) 3,85 (dd, 2 H) 3,25 - 3,30 (m, 4 H) 3,24 (s, 3 H) 3,02 - 3,17 (m, 6 H) 2,72 (dd, 2 H) 2,18 (s, 5 H) 2,03 - 2,13 (m, 2 H) 1,81 - 1,93 (m, 2 H) 1,57 - 1,67 (m, 2 H) 1,47 - 1,56 (m, 1 H) 1,17 - 1,41 (m, 3 H) 0,91 (s, 3 H).

EJEMPLO 361

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}-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 361A

(S)-3-nitro-4-((4-(oxetan-3-il)morfolin-2-il)metilamino)bencenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 259E en lugar de piperazin-1-carboxilato de tert-butilo y 3-oxetanona en lugar de 4'-clorobifenil-2-carboxaldehído en el EJEMPLO 1A.

EJEMPLO 361B

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}-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 361A en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (500MHz, piridina-d₅) □ 13,00 (s, 1H), 9,26 (d, 1H), 8,87 (t, 1H), 8,43 (d, 1H), 8,35 (dd, 1H), 8,11 (d, 1H), 7,66 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,96 (d, 1H), 6,75 (dd, 1H), 6,54 (d, 1H), 6,48 (m, 1H), 4,64 (m, 4H), 3,93 (m, 1H), 3,89 (d, 1H), 3,68 (dt, 1H), 3,53-3,35 (m, 3H), 3,07 (m, 4H), 2,77 (s, 2H), 2,72 (d, 1H), 2,44 (d, 1H), 2,26 (m, 2H), 2,14 (m, 4H), 1,97 (s, 2H), 1,85 (t, 1H), 1,39 (t, 2H), 0,94 (s, 6H).

EJEMPLO 362

N-({3-cloro-4-[(trans-4-hidroxi-4-metilciclohexil)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 362A

3-cloro-4-(((1*r*, 4*r*)-4-hidroxi-4-metilciclohexil)metoxi)bencenosulfonamida

A una solución de EJEMPLO 341F (300 mg) en N,N-dimetilformamida (10 mL) se agregó hidruro de sodio (416 mg) por porciones. La suspensión resultante se agitó por 15 minutos. Se agregó 3-cloro-4-fluorobencenosulfonamida (425 mg) y la agitación se continuó por 72 horas. La reacción se detuvo con agua y el pH se ajustó a aproximadamente 7. La mezcla se diluyó con salmuera (75 mL) y se extrajo con cloruro de metileno. El producto crudo se aisló a partir de la capa de cloruro de metileno seca mediante concentración y se purificó sobre gel de sílice eluyendo con un gradiente escalonado de acetato de etilo al 10, 25, 50% en cloruro de metileno para dar el compuesto del título.

10 EJEMPLO 362B

N-({3-cloro-4-[(trans-4-hidroxi-4-metilciclohexil)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol-2,3-b)piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 362A en lugar del EJEMPLO 130C en el EJEMPLO 130D. ¹H NMR (400 MHz, piridin- d₅) □ 13,07 (m, 1H), 8,58 (d, 1H), 8,45 (d, 1H), 8,31 (dd, 1H), 8,11 (d, 1H), 7,69 - 7,67 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,97 (d, 1H), 6,74 (dd, 1H), 6,52 (m, 2H), 5,34 (br s, 2H), 3,82 (d, 2H), 3,06 (m, 4H), 2,77 (s, 2H), 2,25 (m, 2H), 2,13 (m, 4H), 1,97 - 1,85 (m, 7H), 1,82 - 1,73 (m, 2H), 1,44 - 1,32 (m, 7H), 0,94 (m, 6H).

20 EJEMPLO 363

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[2-(cianoetil)(ciclopropil)amino]-1-fluorociclohexil}metoxi]-3-nitrofenil}sulfonil}-2-(1H-pirrol-2,3-b)piridin-5-iloxi)benzamida

25 EJEMPLO 363A

4-((4'-fluoroesp[benzo[d][1,3]dioxol-2,1'-ciclohexan]-4'-il)metoxi)-3-nitrobencenosulfonamida

A una solución de EJEMPLO 350C (495 mg) en N,N-dimetilformamida (6 mL) se agregó NaH (65% en aceite mineral, 320 mg). La mezcla se agitó por 30 minutos, y luego se agregó 4-fluoro-3-nitrobencenosulfonamida (457 mg). La mezcla se agitó durante la noche. La mezcla se vertió sobre NH₄Cl acuoso y se extrajo con acetato de etilo (300 mL). Las capas orgánicas combinadas se lavaron con agua, salmuera y se secó sobre Na₂SO₄. 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 compuesto del título.

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EJEMPLO 363B

4-((1-fluoro-4-oxociclohexil)metoxi)-3-nitrobenzenosulfonamida

A una solución de EJEMPLO 363A (860 mg) en etanol (30 mL) se agregó HCl concentrado (10 mL) y la mezcla se agitó a 100°C por 3 horas. La mezcla se neutralizó con Na₂CO₃ sólido y se extrajo con diclorometano (300 mL) y se lavó con NaHCO₃ acuoso, agua, salmuera y se secó sobre Na₂SO₄. La filtración y evaporación del solvente dio el compuesto del título.

EJEMPLO 363C

4-((4-((2-cianoetil)(ciclopropil)amino)-1-fluorociclohexil)metoxi)-3-nitrobenzenosulfonamida

A una solución de EJEMPLO 363B (200 mg) en diclorometano (6 mL) se agregó 3-(ciclopropilamino)propanonitrilo (64 mg) seguido por triacetoxiborhidruro de sodio (184 mg). La mezcla se agitó durante la noche. La mezcla de la reacción se diluyó con diclorometano (400 mL) y se lavó con NaOH acuoso 2N, agua, y salmuera. Luego de secar sobre Na₂SO₄, la mezcla se filtró y la evaporación del solvente dio el compuesto del título.

EJEMPLO 363D

4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(2-cianoetil)(ciclopropil)amino]-1-fluorociclohexil}metoxi)-3-nitrofenil}sulfonil}-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 363C en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) □ 11,66 (s, 1 H), 8,35 (s, 1 H), 8,02 (d, 2 H), 7,51 (m, 3 H), 7,40 (m, 1 H), 7,35 (d, 2 H), 7,04 (d, 2 H), 6,67 (dd, 1 H), 6,39 (d, 1 H), 6,20 (s, 1 H), 4,27 (d, 2 H), 3,13 (m, 4 H), 2,88 (m, 3 H), 2,67 (m, 4 H), 2,09 (m, 10 H), 1,49 (m, 9 H), 0,93 (s, 6 H), 0,45 (m, 4 H).

EJEMPLO 364

4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{5-nitro-6-[(tetrahidro-2H-piran-4-ilmetil)amino]piridin-3-il}sulfonil}-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 364A

ácido 6-amino-5-nitropiridin-3-sulfónico

Se calentó ácido 6-aminopiridin-3-sulfónico (20 g) en H₂SO₄ concentrado (80 mL) a 50°C hasta que se disolvió completamente. A esta solución se agregó HNO₃ fumante lentamente a lo largo de 20 minutos, de modo que la temperatura interna no excediera los 55

°C. Luego de completarse la adición, la mezcla de la reacción se calentó a 50°C por 1 hora. Luego se enfrió a temperatura ambiente, se vertió en 150 g de hielo. La mezcla se agitó por otra hora. El recipiente se enfrió a 0°C, y se mantuvo a 0°C 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 364B

ácido 6-hidroxi-5-nitropiridin-3-sulfónico

10 Se trató EJEMPLO 364A (4,0 g) en HCl acuoso (37%, 12 mL) y agua (50 mL) con nitrito de sodio (1,19 g) en agua (8 mL) por goteo a 0°C. Luego de completarse la adición, la mezcla de la reacción se agitó a 0°C por 1 hora. La mezcla se calentó a reflujo por 2 horas. Se retiró el agua por destilación para dar un residuo seco. Luego de enfriar el residuo a temperatura ambiente, se agregó una solución de 1:1 etano/agua (20 mL). La suspensión
15 resultante se enfrió a 0°C, y se mantuvo a 0°C por 1 hora. El sólido se recogió mediante filtración para dar el compuesto del título.

EJEMPLO 364C

cloruro de 6-cloro-5-nitropiridin-3-sulfonilo

20 Una mezcla de EJEMPLO 364B (2,6 g), PCl_5 (5,91 g), y POCl_3 (10 mL) se calentó a 120 °C 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
25 secó sobre MgSO_4 , se filtró, y se concentró para dar producto crudo que se usó en el siguiente paso sin purificación adicional.

EJEMPLO 364D

6-cloro-5-nitropiridin-3-sulfonamida

30 Se enfrió EJEMPLO 364C en tetrahidrofurano (10 mL) a -10 °C. A esta solución se agregó hidróxido de amonio concentrado (0,82 mL) por goteo. La solución se agitó a -10 °C 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 ,
35 se filtró, y se concentró. El residuo se purificó mediante cromatografía flash de columna

sobre gel de sílice usando acetato de etilo al 5-50% en hexanos para dar el compuesto del título.

EJEMPLO 364E

5 5-nitro-6-((tetrahydro-2H-piran-4-il)metilamino)piridin-3-sulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 364D en lugar de 4-fluoro-3-nitrobenzenosulfonamida y (tetrahydro-2H-piran-4-il)metanamina en lugar de (4-fluorotetrahydro-2H-piran-4-il)metanamina en el EJEMPLO 138D.

10 EJEMPLO 364F

4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({5-nitro-6-[(tetrahydro-2H-piran-4-ilmetil)amino]piridin-3-il}sulfonil)-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 364E en lugar del

15 EJEMPLO 11B en el EJEMPLO 11D, ¹H NMR (500MHz, sulfóxido de dimetilo-d₆) δ 11,63 (s, 1H), 8,93 (s, 1H), 8,73 (d, 1H), 8,69 (d, 1H), 8,00 (d, 1H), 7,54 (d, 1H), 7,47-7,48 (m, 2H), 7,35 (d, 2H), 7,05 (d, 2H), 6,68 (dd, 1H), 6,35 (dd, 1H), 6,22 (d, 1H), 3,83 (dd, 2H), 3,51 (t, 2H), 3,21-3,27 (m, 2H), 3,10 (s, 4H), 2,83 (s, 2H), 1,90-2,27 (m, 12H), 1,58 (dd, 2H), 1,39 (t, 2H), 1,18-1,28 (m, 2H), 0,88-0,93 (m, 8H).

20

EJEMPLO 365

25 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({3-nitro-4-[(2-oxaesp[iro[3,5]non-7-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 365A

7-(azidometil)-2-oxaesp[iro[3,5]nonano

30 A un balón de 250 mL se agregó EJEMPLO 351F (350 mg) en tetrahidrofurano (75,0 mL) para dar una solución incolora. La solución se enfrió a 0 °C, se agregó trifenilfosfina (2,94 g), azodicarboxilato de diisopropilo (2,18 mL) y fosforazidato de difenilo (2,32 mL) y la reacción se agitó por 30 minutos a temperatura ambiente. La mezcla se concentró y se purificó el residuo mediante cromatografía flash de columna de fase normal (Analogix, 0-20% hexanos / acetato de etilo).

35

EJEMPLO 365B

2-oxaespiro[3,5]nonan-7-ilmetanamina

A un balón de 50 mL se agregó paladio sobre carbono al 10% (58,7 mg). Se hizo pasar N₂ por el recipiente y se agregó EJEMPLO 365A (400 mg) como una solución en metanol (10,5 mL). Luego se hizo pasar varias veces H₂ por el recipiente (mediante un globo) y se calentó a 45 °C por 2 horas. La reacción se enfrió a temperatura ambiente, se filtró a través de celite y el material filtrado se concentró por evaporación por rotación. El residuo se usó en el siguiente paso sin purificación adicional.

EJEMPLO 365C

4-(2-oxaespiro[3,5]nonan-7-ilmetilamino)-3-nitrobenzenosulfonamida

El compuesto del título se preparó utilizando el EJEMPLO 365B en lugar de 1-(tetrahidropiran-4-il)metilamina en el EJEMPLO 1F.

EJEMPLO 365D

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-N-(4-(2-oxaespiro[3,5]nonan-7-ilmetilamino)-3-nitrofenilsulfonil)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 365C en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) □ 11,67 (s, 1 H) 11,25 - 11,49 (m, 1 H) 8,48 - 8,66 (m, 2 H) 8,03 (d, 1 H) 7,79 (dd, 1 H) 7,41 - 7,61 (m, 3 H) 7,27 - 7,40 (m, 2 H) 7,05 (t, 3 H) 6,67 (dd, 1 H) 6,39 (dd, 1 H) 6,18 (d, 1 H) 4,29 (s, 2 H) 4,19 (s, 2 H) 3,17 - 3,27 (m, 2 H) 2,99 - 3,14 (m, 4 H) 2,69 - 2,79 (m, 2 H) 2,09 - 2,28 (m, 6 H) 2,04 (d, 2 H) 1,95 (s, 2 H) 1,66 (d, 2 H) 1,49 - 1,61 (m, 1 H) 1,29 - 1,45 (m, 4 H) 0,93 - 1,05 (m, 2 H) 0,92 (s, 6 H).

EJEMPLO 366

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-ciano-4-metilciclohexil]metil)amino]-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 366A

(4-ciano-4-metilciclohexil)metilcarbamato de tert-butilo

A una solución fría (-78°C) de (4-cianociclohexil)metilcarbamato de tert-butilo (500 mg) en tetrahidrofurano (10 mL) se agregó diisopropilamida de litio (2,0 mL, 2M en heptano). La mezcla se agitó a -78°C por 30 minutos antes de la adición de CH₃I (1 mL). La mezcla luego se agitó y la temperatura se dejó calentar a temperatura ambiente. La reacción se detuvo con NH₄Cl acuoso y la mezcla se extrajo con acetato de etilo (300 mL) y se lavó con

agua, salmuera y se secó sobre Na_2SO_4 . La filtración y evaporación del solvente y la cromatografía en gel de sílice (acetato de etilo al 40% en hexano) del material crudo dio el compuesto del título.

5 EJEMPLO 366B

4-(aminometil)-1-metilciclohexanocarbonitrilo

A una solución de EJEMPLO 366A (480 mg) en diclorometano (10 mL) se agregó ácido trifluoroacético (10 mL). La mezcla se agitó por 3 horas. La mezcla luego se concentró bajo vacío y se usó directamente en la siguiente reacción sin purificación adicional.

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EJEMPLO 366C

4-((4-ciano-4-metilciclohexil)metilamino)-3-nitrobenzenosulfonamida

15

A una solución de 4-fluoro-3-nitrobenzenosulfonamida (362 mg) en tetrahidrofurano (10 mL) se agregó EJEMPLO 366B (250 mg) y N,N-diisopropiletilamina (2 mL). La mezcla se agitó durante la noche. La mezcla se diluyó con acetato de etilo (300 mL) y se lavó con agua, salmuera y se secó sobre Na_2SO_4 . La filtración y evaporación del solvente dio el compuesto del título.

EJEMPLO 366D

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4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([4-ciano-4-metilciclohexil)metil]amino)-3-nitrofenil)sulfonyl-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

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El compuesto del título se preparó utilizando el EJEMPLO 3J en lugar del EJEMPLO 1E y EJEMPLO 366C en lugar del EJEMPLO 1F en el EJEMPLO 1G. ^1H NMR (300 MHz, sulfóxido de dimetilo- d_6) δ 11,67 (s, 1 H), 11,37 (m, 1 H), 8,59 (m, 2 H), 8,04 (d, 1 H), 7,80 (d, 1 H), 7,51 (m, 3 H), 7,34 (d, 2 H), 7,10 (d, 1 H), 7,04 (d, 2 H), 6,68 (dd, 1 H), 6,39 (m, 1 H), 6,19 (s, 1 H), 3,07 (m, 4 H), 2,75 (m, 2 H), 2,17 (m, 7 H), 1,76 (m, 9 H), 1,32 (m, 9 H), 0,92 (s, 6 H).

EJEMPLO 367

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pivalato de {[4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]}{4-([4-fluorotetrahidro-2H-piran-4-il)metoxi]-3-nitrofenil)sulfonyl}amino}metilo

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Este ejemplo se preparó utilizando pivalato de clorometilo en lugar de butirato de clorometilo en el EJEMPLO 368. ^1H NMR (400 MHz, sulfóxido de dimetilo- d_6) δ 11,72 (s, 1 H), 8,43 (d, 1 H), 8,22 (dd, 1 H), 8,01 (d, 1 H), 7,55 (m, 3 H), 7,36 (m, 3 H), 7,03 (d, 2 H), 6,68 (dd, 1 H), 6,41 (m, 1 H), 6,17 (d, 1 H), 5,83 (s, 2 H), 4,40 (d, 2 H), 3,78 (m, 2 H), 3,59 (m, 2 H), 3,08 (br

m, 4H), 2,73 (br s, 2H), 2,18 (br m, 6H), 1,96 (s, 2H), 1,84 (m, 4H), 1,39 (m, 2H), 1,00 (s, 9H), 0,92 (s, 6H).

EJEMPLO 368

5 butirato de {[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]}(4-{[4-fluorotetrahidro-2H-piran-4-il]metoxi]-3-nitrofenil)sulfonil)amino}metilo

Se disolvió EJEMPLO 37E (500 mg) en acetonitrilo (3,7 mL) y se agregó butirato de clorometilo (77 mg) y Base de Hunig (73 mg). La reacción se calentó bajo reflujo por un día. 10 Luego de enfriar y diluir con sulfóxido de dimetilo (4 mL) la reacción se purificó mediante HPLC preparativa usando una columna 250 x 50 mm C18 y eluyendo con 20-100% CH₃CN vs. ácido trifluoroacético al 0,1% en agua, para dar el producto como una sal trifluoroacetato. La sal de ácido trifluoroacético se disolvió en diclorometano (6 ml) y se lavó con NaHCO₃ acuoso al 50%. La capa orgánica se secó sobre Na₂SO₄ anhidro, se filtró, y se concentró 15 para dar el compuesto del título. ¹H NMR (400 MHz, sulfóxido de dimetilo-d₆) δ 11,72 (s, 1H), 8,43 (d, 1H), 8,22 (dd, 1H), 8,01 (d, 1H), 7,55 (m, 3H), 7,36 (m, 3H), 7,03 (d, 2H), 6,68 (dd, 1H), 6,41 (m, 1H), 6,17 (d, 1H), 5,83 (s, 2H), 4,40 (d, 2H), 3,78 (m, 2H), 3,59 (m, 2H), 3,08 (br m, 4H), 2,73 (br s, 2H), 2,18 (m, 8H), 1,96 (s, 2H), 1,84 (m, 4H), 1,39 (m, 4H), 0,92 (s, 6H), 0,75 (t, 3H).

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EJEMPLO 369

4-[4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}(²H₈)piperazin-1-il]-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

25 EJEMPLO 369A

4-[(2,2,3,3,5,5,6,6-²H₈)piperazin-1-il]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoato de metilo

En un vial de 40 mL se agregaron EJEMPLO 3H (1,55 g) y piperazin-d₈ (2,040 g) en sulfóxido de dimetilo (13 mL). La solución se calentó a 85°C por 2,5 horas, y luego se dejó enfriar a temperatura ambiente durante la noche. La mezcla se transfirió a un recipiente de 120 mL y se enfrió a 5-10 °C. Se agregó diclorometano (30 mL), luego se agregó agua (10 mL) mediante una jeringa a lo largo de 5 minutos manteniendo la temperatura a no más que 15°C. Las capas se separaron y la capa orgánica se lavó con agua (4x 10-15 mL) hasta que el pH de la capa acuosa fue 8-9. La capa orgánica se filtró a través de Na₂SO₄ y se enjuagó con diclorometano (5 mL), y se concentró para dar el compuesto del título.

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EJEMPLO 369B

4-[4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]⁽²H₈)piperazin-1-il]-2-(1*H*-pirrolo[2,3-*b*]piridin-5-iloxi)benzoato de metilo

En un balón de 100 mL, se agregó EJEMPLO 369A (3,4 g), EJEMPLO 290B (1,321 g) y diclorometano (3 mL) a un baló de 100 mL a temperatura ambiente. A un balón de 3
 5 cuellos de 50 mL separado, se agregó triacetoxiborohidruro de sodio (1,330 g) y diclorometano (12 mL) para dar una lechada. Luego de enfriar el balón de 50 mL a 18-20 °C, la solución de aducto piperazina/aldehído se agregó mediante una jeringa a lo largo de 5 minutos. El triacetoxiborohidruro se disolvió gradualmente para dar una solución traslúcida luego de ~5 minutos. Luego de otros 10 minutos, la solución se volvió turbia. Luego de 16
 10 horas, la reacción se enfrió a 5-10 °C. Se agregó NaHCO₃ acuoso saturado (12 mL) durante 5 minutos manteniendo la temperatura a no más que 10 °C. Las capas se separaron y la capa orgánica se lavó con NaHCO₃ acuoso saturado, y NaCl 10% (12 mL), y luego se filtró a través de Na₂SO₄ y se enjuagó con diclorometano (4 mL). La solución se concentró en un rotovap, y el producto se concentró con metanol (40 mL). La solución resultante se enfrió a 5-
 15 10 °C, y el producto precipitó. La solución se mezcló a temperatura ambiente por 30 minutos, luego se filtró y se enjuagó con metanol (5 mL), y el producto se secó con aire.

EJEMPLO 369C

ácido 4-[4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]⁽²H₈)piperazin-1-il]-2-(1*H*-
 20 pirrolo[2,3-*b*]piridin-5-iloxi)benzoico

El compuesto del título se preparó utilizando el EJEMPLO 369B en lugar del EJEMPLO 15G en el EJEMPLO 15H.

EJEMPLO 369D

25 4-[4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]⁽²H₈)piperazin-1-il]-*N*-({3-nitro-4-[(tetrahidro-2*H*-piran-4-ilmetil)amino]fenil)sulfonil}-2-(1*H*-pirrolo[2,3-*b*]piridin-5-iloxi)benzamida

A una mezcla de EJEMPLO 369C (2,0g), EJEMPLO 1F (1,1g) y *N,N*-dimetilpiridin-4-amina (0,7 g) en diclorometano (20 mL) se agregó clorhidrato de 1-etil-3-[3-(dimetilamino)propil]-carbodiimida (0,8 g). La mezcla de la reacción se agitó a temperatura ambiente durante la noche. La reacción se detuvo con *N,N*-dimetiletan-1,2-diamina (0,6g) y se agitó a temperatura ambiente por 3 horas. La mezcla se extrajo con ácido acético acuoso al 20% y se lavó con NaCl acuoso al 5%. Se agregó metanol (2 mL) y acetato de etilo (18
 30 mL) y el precipitado se recogió mediante filtración para dar el compuesto del título. ¹H NMR (400 MHz, sulfóxido de dimetilo -*d*₆) □ 11,71 (s, 1H), 11,37 (s, br, 1H), 8,60 (t, 1H), 8,55 (d, 1H), 8,04 (d, 1H), 7,80 (dd, 1H), 7,47 - 7,54 (m, 3H), 7,31 - 7,34 (m, 2H), 7,09 (d, 1H), 7,01 -

7,03 (m, 2H), 6,67 (dd, 1H), 6,39 (dd, 1H), 6,19 (d, 1H), 3,83 (dd, 2H), 3,21 - 3,30 (m, 4H), 3,00 - 3,10 (s, 4H), 2,75 (s, 2H), 2,05 - 2,24 (m, 6H), 1,95 (s, 2H), 1,80 - 1,93 (m, 1H), 1,55 - 1,64 (m, 2H), 1,37 (t, 2H), 1,18 - 1,31 (m, 2H), 0,90 (s, 6H).

5 EJEMPLO 370

4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)-N-{{3-(tetrahydro-2H-piran-4-ilmetil)-3H-[1,2,3]triazolo[4,5-b]piridin-6-il}sulfonil}benzamida

10 EJEMPLO 370A

5-amino-6-((tetrahydro-2H-piran-4-il)metilamino)piridin-3-sulfonamida

Una mezcla de EJEMPLO 364E (0,16 g) y paladio sobre carbono al 5% (0,025 g) en etanol (5 mL) se trató con un globo de hidrógeno. La mezcla de la reacción se agitó durante la noche. El sólido se retiró por filtración. El material filtrado se concentró. El residuo se purificó mediante cromatografía flash sobre gel de sílice para dar el compuesto del título.

EJEMPLO 370B

3-((tetrahydro-2H-piran-4-il)metil)-3H-[1,2,3]triazolo[4,5-b]piridin-6-sulfonamida

Se trató EJEMPLO 370A (0,085 g) en agua (10 mL) con H₂SO₄ concentrado (0,5 mL). La solución se enfrió a 0 °C. A esta solución se agregó NaNO₂ (0,023 g) en agua (1 mL) por goteo. La solución se agitó por 1 hora a 0 °C. La mezcla de la reacción se vertió en solución saturada de NaHCO₃, y se extrajo con acetato de etilo tres veces. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre MgSO₄, se filtró, y se concentró para dar el compuesto del título.

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EJEMPLO 370C

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-N-(3-((tetrahydro-2H-piran-4-il)metil)-3H-[1,2,3]triazolo[4,5-b]piridin-6-ilsulfonil)benzamida

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Este ejemplo se preparó utilizando el EJEMPLO 370B en lugar del EJEMPLO 11B en el EJEMPLO 11D, 1H NMR (500MHz, sulfóxido de dimetilo-d₆) □ 11,60 (s, 1H), 9,11 (s, 1H), 8,92 (d, 1H), 7,96 (d, 1H), 7,55 (d, 1H), 7,45-7,46 (m, 1H), 7,42 (s, 1H), 7,36 (d, 2H), 7,05 (d, 2H), 6,66 (dd, 1H), 6,32 (s, 1H), 6,22 (s, 1H), 4,63 (d, 2H), 3,80 (dd, 2H), 3,21-3,30 (m, 2H), 3,16 (s, 4H), 2,83 (s, 2H), 2,19-2,29 (m, 6H), 1,97 (s, 2H), 1,33-1,41 (m, 6H), 0,93 (s, 2H).

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EJEMPLO 371

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(6-([(trans-4-hidroxi-4-metilciclohexil)metil]amino)-5-nitropiridin-3-il)sulfonil]-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 371A

6-([(trans-4-hidroxi-4-metilciclohexil)metil]amino)-5-nitropiridin-3-sulfonamida

Este ejemplo se preparó utilizando el EJEMPLO 364D en lugar de 4-fluoro-3-nitrobencenosulfonamida y EJEMPLO 376B en lugar del EJEMPLO 138C en el EJEMPLO 138D. El compuesto del título se aisló 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 0,1% TFA.

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EJEMPLO 371B

4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-[(6-([(trans-4-hidroxi-4-metilciclohexil)metil]amino)-5-nitropiridin-3-il)sulfonil]-2-(1H-pirrolol[2,3-b]piridin-5-iloxi)benzamida

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El compuesto del título se preparó utilizando el EJEMPLO 371A en lugar del EJEMPLO 11B en el EJEMPLO 11D. ^1H NMR (300 MHz, sulfóxido de dimetilo- d_6) δ 11,63 (s, 1H), 11,53 - 10,99 (m, 1H), 8,91 (s, 1H), 8,71 (dd, 2H), 8,01 (d, 1H), 7,61 - 7,44 (m, 3H), 7,44 - 7,28 (m, 2H), 7,12 - 6,97 (m, 2H), 6,76 - 6,61 (m, 1H), 6,36 (dd, 1H), 6,21 (d, 1H), 3,92 (s, 1H), 3,48 (t, 2H), 3,10 (s, 4H), 2,83 (s, 2H), 2,24 (dd, 6H), 1,96 (s, 2H), 1,37 (ddd, 11H), 1,07 (s, 3H), 0,93 (s, 6H).

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EJEMPLO 372

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-pirrolol[2,3-b]piridin-5-iloxi)benzamida

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EJEMPLO 372A

4-fluoro-1-(oxetan-3-il)piperidin-4-carboxilato de etilo

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A 4-fluoropiperidin-1,4-dicarboxilato de 1-tert-butilo 4-etilo (1,00 g) se agregó HCl (4,0M en dioxano, 4,54 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 (1,155 g) y oxetan-3-ona (0,262 g) y se agitó durante la noche. La reacción se detuvo con solución saturada de NaHCO_3 (20 mL) y se extrajo con

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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/minuto) dio el compuesto del título.

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EJEMPLO 372B

(4-fluoro-1-(oxetan-3-il)piperidin-4-il)metanol

A una solución de EJEMPLO 372A (0,59 g) en tetrahidrofurano (5 mL) se agregó hidruro de litio y aluminio (1,80 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 acuoso 2N. La reacción se filtró a través de tierra diatomea y se enjuagó con acetato de etilo (50 mL). Los orgánicos se concentraron y se cargó en gel de sílice (Reveleris 40 g) y se eluyó usando un gradiente de metanol entre 0,75% y 7,5%/diclorometano durante 30 minutos (velocidad de flujo = 40 mL/minutos) para dar el compuesto del título.

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EJEMPLO 372C

5-bromo-6-((4-fluoro-1-(oxetan-3-il)piperidin-4-il)metoxi)piridin-3-sulfonamida

Este ejemplo se preparó utilizando el EJEMPLO 372B en lugar de (tetrahidro-2H-piran-4-il)metanol y EJEMPLO 36A en lugar de 4-fluoro-3-nitrobenzenosulfonamida en el EJEMPLO 24A.

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EJEMPLO 372D

5-ciano-6-((4-fluoro-1-(oxetan-3-il)piperidin-4-il)metoxi)piridin-3-sulfonamida

Este ejemplo se preparó utilizando el EJEMPLO 372C en lugar del EJEMPLO 36B en el EJEMPLO 36C.

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EJEMPLO 372E

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-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)benzamida

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El compuesto del título se preparó utilizando el EJEMPLO 372D en lugar del EJEMPLO 11B en el EJEMPLO 11D. ¹H NMR (300 MHz, sulfóxido de dimetilo-d₆) δ 11,58 (s, 1H), 8,71 (s, 1H), 8,52 (s, 1H), 7,96 (d, 1H), 7,57 (d, 1H), 7,48 - 7,30 (m, 4H), 7,06 (d, 2H), 6,68 (d, 1H), 6,37 - 6,22 (m, 2H), 4,65 - 4,40 (m, 6H), 3,58 (s, 1H), 3,12 (s, 6H), 2,84 - 2,59 (m, 4H), 2,17 (s, 6H), 1,96 (d, 6H), 1,41 (s, 2H), 0,93 (s, 6H).

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EJEMPLO 373

N-(4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]sulfamoil}-2-nitrofenil)morfolina-4-carboxamida

EJEMPLO 373A

5 morfolina-4-carboxamida

Una solución de cloruro de morfolina-4-carbonilo (2,0 g) en metanol (10 mL) y NH_3 7 N en metanol (5 mL) se agitó a 45 °C durante la noche. La mezcla se concentró para dar un sólido, el cual se secó bajo vacío.

10 EJEMPLO 373B

N-(2-nitro-4-sulfamoilfenil)morfolina-4-carboxamida

Este ejemplo se preparó utilizando el EJEMPLO 373A en lugar de (tetrahidro-2H-piran-4-il)metanol en el EJEMPLO 24A.

15 EJEMPLO 373C

N-(4-(N-(2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)benzoil)sulfamoil)-2-nitrofenil)morfolina-4-carboxamida

Este ejemplo se preparó utilizando el EJEMPLO 373B en lugar del EJEMPLO 130C en el EJEMPLO 130D. ^1H NMR (500MHz, piridina- d_5) $\square$ 13,02 (s, 1H), 10,41 (s, 1H), 9,27 (d, 1H), 8,81 (d, 1H), 8,50 (dd, 1H), 8,40 (d, 1H), 8,09 (d, 1H), 7,65 (m, 2H), 7,44 (d, 2H), 7,07 (d, 2H), 6,76 (dd, 1H), 6,54 (d, 1H), 6,48 (m, 1H), 3,67 (m, 4H), 3,58 (m, 4H), 3,07 (m, 4H), 2,77 (s, 2H), 2,26 (t, 2H), 2,14 (m, 4H), 1,97 (s, 2H), 1,39 (t, 2H), 0,94 (s, 6H).

25 EJEMPLO 374

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[4-(metoximetil)ciclohexil]metil}amino)-3-nitrofenil]sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

30 EJEMPLO 374A

(4,4-dietoxiciclohexil)metanol

Se trató 4, 4-dietoxiciclohexanocarboxilato de etilo (6,67 g) sintetizado de acuerdo a un procedimiento de la literatura (*European Journal of Organic Chemistry*, 2008, 5, 895) en tetrahidrofurano (60 mL) con hidruro de litio y aluminio 2 M en tetrahidrofurano (14,5 mL) a 35 0°C por 1 hora. Se agregó agua (3 mL) lentamente para detener la reacción. Los precipitados

se retiraron por filtración y se lavó con acetato de etilo. El material filtrado se secó sobre Na_2SO_4 , se filtró, y se concentró para dar el compuesto del título.

EJEMPLO 374B

5 1,1-dietoxi-4-(metoximetil)ciclohexano

Se trató EJEMPLO 374A (665 mg) en tetrahidrofurano (20 mL) con NaH (394 mg) por 30 minutos y luego se agregó CH_3I (0,267 mL) lentamente. La mezcla resultante se agitó durante la noche y la reacción se detuvo con unas pocas gotas de agua. La mezcla se concentró y el residuo se suspendió en agua y se extrajo con diclorometano. La capa orgánica se secó sobre Na_2SO_4 , se filtró y se concentró. El residuo se purificó mediante cromatografía flash, y se eluyó con acetato de etilo al 0-15% en diclorometano para dar el compuesto del título.

EJEMPLO 374C

15 4-(metoximetil)ciclohexanona

Se calentó EJEMPLO 374B (2,2 g) en una mezcla de agua (3 mL) y ácido acético (12 mL) a 65°C por 2 horas. La mezcla de la reacción se concentró. El residuo se mezcló con agua y NaHCO_3 acuoso saturado 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.

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EJEMPLO 374D

4-(metoximetil)ciclohexanocarbonitrilo

Se agregó una solución fría (-10°C) de EJEMPLO 374C (1,18 g) y isocianuro de toluenosulfonilmetilo (2,268 g) en dimetoxietano (3 mL) y etanol absoluto (0,1 mL) se agregó (en pequeñas porciones) tert-butoxido de potasio (2,235 g). La mezcla de la reacción se continuó agitando a $<5^\circ\text{C}$ por 30 minutos, se calentó a temperatura ambiente, se calentó a 35°C por 30 minutos y luego a temperatura ambiente por 2 horas. La mezcla de la reacción se concentró y el residuo se disolvió en agua-salmuera, y se extrajo con diclorometano. La capa de diclorometano se purificó mediante cromatografía flash, y se eluyó con acetato de etilo al 5% en diclorometano para dar el compuesto del título.

EJEMPLO 374E

35 (4-(metoximetil)ciclohexil)metanamina

A una solución de EJEMPLO 374D (460 mg) en tetrahidrofurano (15 mL) se agregó hidruro de litio y aluminio 2M en tetrahidrofurano (2,252 mL) lentamente. La mezcla de la reacción se agitó a temperatura ambiente por 1 hora, se mantuvo a reflujo por 1 hora y se enfrió. Se agregó 2 ml de NaOH acuoso 2M y agua (5 mL). El sólido se retiró por filtración y se lavó con éter. El material filtrado se concentró. El residuo se mezcló con diclorometano (50 mL) y la mezcla resultante se secó sobre Na₂SO₄ y se concentró para dar el compuesto del título.

EJEMPLO 374F

4-((4-(metoximetil)ciclohexil)metilamino)-3-nitrobenzenosulfonamida

Se agitó EJEMPLO 374E (450 mg) y 4-fluoro-3-nitrobenzenosulfonamida (693 mg) en tetrahidrofurano (10 mL) durante la noche. La mezcla de la reacción se concentró y el residuo se suspendió en una mezcla de CH₃CN, metanol y agua. Los precipitados se recogieron, se lavó con agua y se secó para dar el compuesto del título.

EJEMPLO 374G

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-4,4-dimetilciclohex-1-enil)metil)piperazin-1-il)-N-(4-((4-(metoximetil)ciclohexil)metilamino)-3-nitrofenilsulfonil)benzamida

El compuesto del título se preparó como se describe en el EJEMPLO 11D usando EJEMPLO 374F en lugar de EJEMPLO 11B. ¹H NMR (400 MHz, sulfóxido de dimetilo-d₆) □ 11,69 (s, 1H), 11,40 (s, 1H), 8,53 - 8,61 (m, 2H), 8,04 (d, 1H), 7,77 - 7,82 (m, 1H), 7,47 - 7,55 (m, 3H), 7,34 (d, 2H), 7,02 - 7,09 (m, 3H), 6,68 (dd, 1H), 6,39 (dd, 1H), 6,19 (d, 1H), 3,18 - 3,27 (m, 5H), 3,04 - 3,14 (m, 5H), 2,75 (s, 2H), 2,11 - 2,24 (m, 6H), 1,95 (s, 2H), 1,69 - 1,84 (m, 3H), 1,33 - 1,63 (m, 7H), 0,84 - 1,05 (m, 9H).

EJEMPLO 375

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 375A

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 Cs₂CO₃ (5,86 g) en dimetilformamida (15 mL) se calentó a 100 °C durante la noche. Luego de enfriarse 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.

5 EJEMPLO 375B

(1-(tiazol-2-il)piperidin-4-il)metanol

Este ejemplo se preparó utilizando el EJEMPLO 375A en lugar del EJEMPLO 339A en el EJEMPLO 339B.

10 EJEMPLO 375C

5-cloro-6-((1-(tiazol-2-il)piperidin-4-il)metoxi)piridin-3-sulfonamida

Este ejemplo se preparó utilizando el EJEMPLO 375B en lugar de (tetrahidro-2H-piran-4-il)metanol y EJEMPLO 40A en lugar del EJEMPLO 36A en el EJEMPLO 36B.

15 EJEMPLO 375D

2-(1H-pirrol[2,3-b]piridin-5-iloxi)-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)benzamida

Este ejemplo se preparó utilizando el EJEMPLO 375C en lugar del EJEMPLO 11B en el EJEMPLO 11D. ^1H NMR (500MHz, sulfóxido de dimetilo- d_6) δ 11,65 (s, 1H), 8,49 (s, 1H), 8,17 (s, 1H), 8,01 (d, 1H), 7,54 (d, 1H), 7,48-7,49 (m, 2H), 7,35 (d, 2H), 7,14 (d, 1H), 7,05 (d, 2H), 6,80 (d, 1H), 6,67 (dd, 1H), 6,38 (dd, 1H), 6,21 (d, 1H), 4,28 (d, 2H), 3,92 (d, 2H), 2,98-3,10 (m, 6H), 2,86 (s, 2H), 2,30 (m, 4H), 2,03-2,15 (m, 3H), 1,96 (s, 2H), 1,96 (s, 2H), 1,82-1,86 (m, 2H), 1,33-1,44 (m, 4H), 0,93 (s, 6H).

25 EJEMPLO 376

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-pirrol[2,3-b]piridin-5-iloxi)benzamida

30 EJEMPLO 376A

(4-hidroxi-4-metilciclohexil)metilcarbamato de tert-butilo

Se disolvió una solución de (4-oxociclohexil)metilcarbamato de tert-butilo (1,00 g) 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), se lavó con cloruro de amonio (25 mL), se lavó con 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.

5

EJEMPLO 376B**4-(aminometil)-1-metilciclohexanol**

A una solución de EJEMPLO 376A (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 2h se agregó ácido trifluoroacético adicional (0,5 mL). Luego de otras 4 h la reacción se concentró y se secó bajo alto vacío. El sólido oleoso resultante se trituró con éter dietílico con sonicación. El filtrado y lavado con éter dietílico dio el compuesto del título como una sal de ácido trifluoroacético y una mezcla de isómeros cis y trans.

15

EJEMPLO 376C**6-((cis-4-hidroxi-4-metilciclohexil)metilamino)-5-nitropiridin-3-sulfonamida**

Este ejemplo se preparó utilizando el EJEMPLO 364D en lugar de 4-fluoro-3-nitrobencenosulfonamida y EJEMPLO 376B en lugar de (4-fluorotetrahidro-2H-piran-4-il)metanamina en el EJEMPLO 138D. El compuesto del título se aisló 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 0,1% TFA.

20

EJEMPLO 376D

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-pirrolol[2,3-b]piridin-5-iloxi)benzamida

25

Este ejemplo se preparó utilizando el EJEMPLO 376C en lugar del EJEMPLO 11B en el EJEMPLO 11D. ^1H NMR (500MHz, sulfóxido de dimetilo- d_6) δ 11,64 (s, 1H), 8,91 (s, 1H), 8,72 (d, 1H), 8,70 (d, 1H), 8,01 (d, 1H), 7,47-7,54 (m, 3H), 7,35 (d, 2H), 7,04 (d, 2H), 6,68 (dd, 1H), 6,36 (dd, 1H), 6,21 (d, 1H), 3,93 (s, 1H), 3,48 (t, 2H), 3,10 (s, 4H), 2,83 (s, 2H), 2,15-2,33 (m, 6H), 1,96 (s, 1H), 1,34-1,59 (m, 9H), 1,17-1,24 (m, 2H), 1,07 (s, 2H), 0,92 (s, 6H).

30

EJEMPLO 377

4-(4-([2-(4-clorofenil)-5-metoxi-5-metilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([(trans-4-hidroxi-4-metilciclohexil)metil]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

El compuesto del título se preparó utilizando el EJEMPLO 378D en lugar del EJEMPLO 1E y EJEMPLO 337M en lugar del EJEMPLO 1F en el EJEMPLO 1G. ¹H NMR (500 MHz, piridina-d₅) δ 13,07 (s, 1H), 9,31 (d, 1H), 8,68 (t, 1H), 8,44 (d, 1H), 8,37 (dd, 1H), 8,10 (d, 1H), 7,68 (m, 1H), 7,66 (d, 1H), 7,41 (m, 2H), 7,09 (m, 2H), 6,92 (d, 1H), 6,74 (dd, 1H), 6,52 (d, 1H), 6,50 (dd, 1H), 3,20 (m, 5H), 3,06 (t, 4H), 2,77 (m, 2H), 2,57 (d, 1H), 2,49 (m, 1H), 2,17 (m, 6H), 1,86 (m, 5H), 1,69 (m, 4H), 1,40 (s, 3H), 1,23 (m, 5H).

EJEMPLO 378

4-(4-([2-(4-clorofenil)-5-metoxi-5-metilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([3-nitro-4-[(tetrahydro-2H-piran-4-ilmetil)amino]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida

EJEMPLO 378A

2-cloro-5-metoxi-5-metilciclohex-1-encarbaldehido

Se trató dimetilformamida (1,298 mL) en diclorometano (2,0 mL) a -10 °C por goteo con POCl₃ (1,426 mL) para dar una solución incolora. La mezcla se agitó 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 acuosa al 25% de acetato de sodio. Luego de fusionarse el hielo, 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 de NaHCO₃ y salmuera, se secó (MgSO₄), se filtró y se concentró. El material concentrado se cromatografió sobre gel de sílice con acetato de etilo entre 0 y 5% en hexanos como eluyente.

EJEMPLO 378B

2-(4-clorofenil)-5-metoxi-5-metilciclohex-1-encarbaldehido

Se combinó EJEMPLO 378A (1,55 g), ácido 4-clorofenilborónico (1,542 g), PdOAc₂ (0,055 g), K₂CO₃ (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 (MgSO₄), se filtró a través de un tapón de celite, se

concentró y se cromatografió sobre gel de sílice con acetato de etilo entre 5 y 20% en hexanos como eluyente.

EJEMPLO 378C

- 5 2-(1H-pirrol[2,3-b]piridin-5-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 el EJEMPLO 378B en lugar de 4'-clorobifenil-2-carboxaldehído y EJEMPLO 15F en lugar de piperazin-1-carboxilato de tert-butilo en el EJEMPLO 1A excepto que una pequeña cantidad de DMSO se agregó a la
10 mezcla de la reacción.

EJEMPLO 378D

ácido 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-5-metoxi-5-metilciclohex-1-enil)metil)piperazin-1-il)benzoico

- 15 El compuesto del título se preparó utilizando el EJEMPLO 378C en lugar del EJEMPLO 15G en el EJEMPLO 15H.

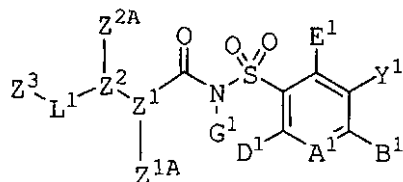
EJEMPLO 378E

- 20 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-((2-(4-clorofenil)-5-metoxi-5-metilciclohex-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 el EJEMPLO 378D en lugar del EJEMPLO 1E en el EJEMPLO 1G. ¹H NMR (500 MHz, piridina-d₅) □ 13,07 (s, 1H), 9,31 (d, 1H), 8,68 (t, 1H), 8,43 (d, 1H), 8,37 (dd, 1H), 8,09 (d, 1H), 7,68 (m, 1H), 7,66 (d, 1H), 7,41 (m, 2H), 7,09 (m, 2H), 6,90 (d, 1H), 6,74 (dd, 1H), 6,52 (d, 1H), 6,50 (dd, 1H), 3,97 (dd, 2H), 3,30 (td, 2H), 3,21 (s, 3H), 3,15 (m, 2H), 3,06 (t, 4H), 2,77 (m, 2H), 2,57 (d, 1H), 2,50 (m, 1H), 2,16 (m, 6H), 1,81 (m, 2H), 1,63 (m, 1H), 1,57 (dd, 2H), 1,32 (m, 2H), 1,21 (s, 3H).

REIVINDICACIONES:

1. Un compuesto CARACTERIZADO PORQUE tiene la Fórmula (I)



5 (I),

o una sal terapéuticamente aceptable del mismo, en donde

A¹ es N o C(A²);

A² es H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ o C(O)OR¹A;

15 B¹ es H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ o C(O)OR¹A;

20 D¹ es H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ o C(O)OR¹A;

25 E¹ es H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ o C(O)OR¹A;

30

$C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, 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} , SO_2R^{17} , NH_2 , NHR^{17} , $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$,
5 $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ o $NHSO_2R^{17}$; o

E^1 y Y^1 , junto con los átomos a los cuales están unidos, son benceno, naftileno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; y

A^2 , B^1 , y D^1 se seleccionan en forma independiente entre H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$,
10 $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$, $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 ,
15 $C(O)OH$, $C(O)NH_2$ o $C(O)OR^{1A}$; o

Y^1 y B^1 , junto con los átomos a los cuales están unidos, son benceno, naftileno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; y

A^2 , D^1 , y E^1 se seleccionan en forma independiente entre H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$,
20 $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$, $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 ,
25 $C(O)OH$, $C(O)NH_2$ o $C(O)OR^{1A}$; o

A^2 y B^1 , junto con los átomos a los cuales están unidos, son benceno, naftileno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; y

D^1 , E^1 , y Y^1 se seleccionan en forma independiente entre H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$,
30 $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$, $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 ,
35 $C(O)OH$, $C(O)NH_2$ o $C(O)OR^{1A}$; o

A² y D¹, junto con los átomos a los cuales están unidos, son benceno, naftaleno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; y

B¹, E¹, y Y¹ se seleccionan en forma independiente entre H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹,
 5 NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃,
 10 C(O)OH, C(O)NH₂ o C(O)OR^{1A};

G¹ es H, o C(O)O;

R es alquilo;

R¹ es R², R³, R⁴ o R⁵;

R^{1A} es cicloalquilo, cicloalquenilo o cicloalquinilo;

15 R² es fenilo, que no está fusionado o está fusionado con R^{2A}; R^{2A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R³ es heteroarilo, que no está fusionado o está fusionado con R^{3A}; R^{3A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R⁴ es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{4A}; R^{4A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R⁵ 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 R⁶, NC(R^{6A})(R^{6B}), R⁷, OR⁷, SR⁷, S(O)R⁷, SO₂R⁷, NHR⁷, N(R⁷)₂, C(O)R⁷, C(O)NH₂, C(O)NHR⁷,
 25 C(O)N(R⁷)₂, NHC(O)R⁷, NR⁷C(O)R⁷, NHSO₂R⁷, NHC(O)OR⁷, SO₂NH₂, SO₂NHR⁷, SO₂N(R⁷)₂, NHC(O)NH₂, NHC(O)NHR⁷, NHC(O)CH(CH₃)NHC(O)CH(CH₃)NH₂, NHC(O)CH(CH₃)NHC(O)CH(CH₃)NHR⁷, OH, (O), C(O)OH, N₃, CN, NH₂, CF₃, CF₂CF₃, F, Cl, Br o I;

R⁶ es C₂-C₅-espiroalquilo, cada uno de los cuales no está sustituido o está sustituido con OH, (O), N₃, CN, CF₃, CF₂CF₃, F, Cl, Br, I, NH₂, NH(CH₃) o N(CH₃)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, donde cada uno tiene una unidad CH₂ no reemplazada o reemplazada con O, C(O), CNOH, CNOCH₃, S, S(O), SO₂ o NH;

35 R⁷ es R⁸, R⁹, R¹⁰ o R¹¹;

R^8 es fenilo, que no está fusionado o está fusionado con R^{8A} ; R^{8A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^9 es heteroarilo, que no está fusionado o está fusionado con R^{9A} ; R^{9A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

5 R^{10} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{10A} ; R^{10A} es benceno, heteroareno, 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 en forma independiente entre
 10 R^{12} , OR^{12} , SR^{12} , $S(O)R^{12}$, SO_2R^{12} , $C(O)R^{12}$, $CO(O)R^{12}$, $OC(O)R^{12}$, $OC(O)OR^{12}$, NH_2 , NHR^{12} , $N(R^{12})_2$, $NHC(O)R^{12}$, $NR^{12}C(O)R^{12}$, $NHS(O)_2R^{12}$, $NR^{12}S(O)_2R^{12}$, $NHC(O)OR^{12}$, $NR^{12}C(O)OR^{12}$, $NHC(O)NH_2$, $NHC(O)NHR^{12}$, $NHC(O)N(R^{12})_2$, $NR^{12}C(O)NHR^{12}$, $NR^{12}C(O)N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, $C(O)NHOH$, $C(O)NHOR^{12}$, $C(O)NHSO_2R^{12}$, $C(O)NR^{12}SO_2R^{12}$, SO_2NH_2 , SO_2NHR^{12} , $SO_2N(R^{12})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{12}$, $C(N)N(R^{12})_2$,
 15 $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_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 R^{13A} ; R^{13A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{14} es heteroarilo, que no está fusionado o está fusionado con R^{14A} ; R^{14A} es benceno, heteroareno, 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 R^{15A} ; R^{15A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{16} es alquilo, alquenilo o alquinilo;

25 R^{17} es R^{18} , R^{19} , R^{20} o R^{21} ;

R^{18} es fenilo, que no está fusionado o está fusionado con R^{18A} ; R^{18A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{19} es heteroarilo, que no está fusionado o está fusionado con R^{19A} ; R^{19A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

30 R^{20} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo cada uno de los cuales no está fusionado o está fusionado con R^{20A} ; R^{20A} es benceno, heteroareno, 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 en forma independiente entre
 35 R^{22} , OR^{22} , SR^{22} , $S(O)R^{22}$, SO_2R^{22} , $C(O)R^{22}$, $CO(O)R^{22}$, $OC(O)R^{22}$, $OC(O)OR^{22}$, NH_2 , NHR^{22} , $N(R^{22})_2$, $NHC(O)R^{22}$, $NR^{22}C(O)R^{22}$, $NHS(O)_2R^{22}$, $NR^{22}S(O)_2R^{22}$, $NHC(O)OR^{22}$, $NR^{22}C(O)OR^{22}$,

NHC(O)NH₂, NHC(O)NHR²², NHC(O)N(R²²)₂, NR²²C(O)NHR²², NR²²C(O)N(R²²)₂, C(O)NH₂, C(O)NHR²², C(O)N(R²²)₂, C(O)NHOH, C(O)NHOR²², C(O)NHSO₂R²², C(O)NR²²SO₂R²², SO₂NH₂, SO₂NHR²², SO₂N(R²²)₂, C(O)H, C(O)OH, C(N)NH₂, C(N)NHR²², C(N)N(R²²)₂, CNOH, CNOCH₃, OH, (O), CN, N₃, NO₂, CF₃, CF₂CF₃, OCF₃, OCF₂CF₃, F, Cl, Br o I;

5 R²² es R²³, R²⁴ o R²⁵;

R²³ es fenilo, que no está fusionado o está fusionado con R^{23A}; R^{23A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R²⁴ es heteroareno, que no está fusionado o está fusionado con R^{24A}; R^{24A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

10 R²⁵ es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{25A}; R^{25A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

Z¹ es R²⁶ o R²⁷;

Z² es R²⁸, R²⁹ o R³⁰;

15 Z^{1A} y Z^{2A} están ambos ausentes o se toman juntos para formar CH₂, CH₂CH₂ o Z^{12A};

Z^{12A} es C₂-C₆-alquileo que tienen una o dos unidades CH₂ reemplazadas por NH, N(CH₃), S, S(O) o SO₂;

L¹ es un R³⁷, OR³⁷, SR³⁷, S(O)R³⁷, SO₂R³⁷, C(O)R³⁷, CO(O)R³⁷, OC(O)R³⁷, OC(O)OR³⁷, NHR³⁷, C(O)NH, C(O)NR³⁷, C(O)NHOR³⁷, C(O)NHSO₂R³⁷, SO₂NH, SO₂NHR³⁷,
20 C(N)NH, C(N)NHR³⁷;

R²⁶ es fenileno, que no está fusionado o está fusionado con R^{26A}; R^{26A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R²⁷ es heteroarileno, que no está fusionado o está fusionado con R^{27A}; R^{27A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

25 R²⁸ es fenileno, que no está fusionado o está fusionado con R^{28A}; R^{28A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R²⁹ es heteroarileno, que no está fusionado o está fusionado con R^{29A}; R^{29A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

30 R³⁰ es cicloalquileno, cicloalquenileno, heterocicloalquileno o heterocicloalquenileno, cada uno de los cuales no está fusionado o está fusionado con R^{30A}; R^{30A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R³⁷ es una unión o R^{37A};

R^{37A} es alquileo, alquenileno, o alquinileno, cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente
35 entre R^{37B}, OR^{37B}, SR^{37B}, S(O)R^{37B}, SO₂R^{37B}, C(O)R^{37B}, CO(O)R^{37B}, OC(O)R^{37B}, OC(O)OR^{37B}, NH₂, NHR^{37B}, N(R^{37B})₂, NHC(O)R^{37B}, NR^{37B}C(O)R^{37B}, NHS(O)₂R^{37B}, NR^{37B}S(O)₂R^{37B},

- $\text{NHC(O)OR}^{37\text{B}}$, $\text{NR}^{37\text{B}}\text{C(O)OR}^{37\text{B}}$, NHC(O)NH_2 , $\text{NHC(O)NHR}^{37\text{B}}$, $\text{NHC(O)N(R}^{37\text{B}})_2$,
 $\text{NR}^{37\text{B}}\text{C(O)NHR}^{37\text{B}}$, $\text{NR}^{37\text{B}}\text{C(O)N(R}^{37\text{B}})_2$, C(O)NH_2 , $\text{C(O)NHR}^{37\text{B}}$, $\text{C(O)N(R}^{37\text{B}})_2$, C(O)NHOH ,
 $\text{C(O)NHOR}^{37\text{B}}$, $\text{C(O)NHSO}_2\text{R}^{37\text{B}}$, $\text{C(O)NR}^{37\text{B}}\text{SO}_2\text{R}^{37\text{B}}$, SO_2NH_2 , $\text{SO}_2\text{NHR}^{37\text{B}}$, $\text{SO}_2\text{N(R}^{37\text{B}})_2$,
 C(O)H , C(O)OH , C(N)NH_2 , $\text{C(N)NHR}^{37\text{B}}$, $\text{C(N)N(R}^{37\text{B}})_2$, CNOH , CNOCH_3 , OH , (O) , CN , N_3 ,
5 NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br y I ;
 $\text{R}^{37\text{B}}$ es alquilo, alquenilo, alquinilo, o $\text{R}^{37\text{C}}$;
 $\text{R}^{37\text{C}}$ es fenilo, heteroarilo, cicloalquilo, cicloalquenilo, heterocicloalquilo, o
heterocicloalquenilo;
 Z^3 es R^{38} , R^{39} o R^{40} ;
10 R^{38} es fenilo, que no está fusionado o está fusionado con $\text{R}^{38\text{A}}$; $\text{R}^{38\text{A}}$ es benceno,
heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;
 R^{39} es heteroarilo, que no está fusionado o está fusionado con $\text{R}^{39\text{A}}$; $\text{R}^{39\text{A}}$ es benceno,
heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;
 R^{40} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno
15 de los cuales no está fusionado o está fusionado con $\text{R}^{40\text{A}}$; $\text{R}^{40\text{A}}$ es benceno, heteroareno,
cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;
en donde las unidades representadas por R^{26} y R^{27} están sustituidas (es decir, si $\text{Z}^{1\text{A}}$ y
 $\text{Z}^{2\text{A}}$ están ausentes) o adicionalmente sustituidas (es decir, si $\text{Z}^{1\text{A}}$ y $\text{Z}^{2\text{A}}$ están presentes) con
 R^{41} , OR^{41} , SR^{41} , S(O)R^{41} , SO_2R^{41} , C(O)R^{41} , CO(O)R^{41} , OC(O)R^{41} , OC(O)OR^{41} , NHR^{41} ,
20 $\text{N(R}^{41})_2$, NHC(O)R^{41} , $\text{NR}^{41}\text{C(O)R}^{41}$, $\text{NHS(O)}_2\text{R}^{41}$, $\text{NR}^{41}\text{S(O)}_2\text{R}^{41}$, NHC(O)OR^{41} , $\text{NR}^{41}\text{C(O)OR}^{41}$,
 NHC(O)NHR^{41} , $\text{NHC(O)N(R}^{41})_2$, $\text{NR}^{41}\text{C(O)NHR}^{41}$, $\text{NR}^{41}\text{C(O)N(R}^{41})_2$, C(O)NHR^{41} , $\text{C(O)N(R}^{41})_2$,
 C(O)NHOR^{41} , $\text{C(O)NHSO}_2\text{R}^{41}$, $\text{C(O)NR}^{41}\text{SO}_2\text{R}^{41}$, $\text{SO}_2\text{NHR}^{41}$, $\text{SO}_2\text{N(R}^{41})_2$, C(N)NHR^{41} , o
 $\text{C(N)N(R}^{41})_2$;
 R^{41} es heteroarilo, que está fusionado con $\text{R}^{43\text{A}}$; $\text{R}^{43\text{A}}$ es benceno, heteroareno,
25 cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; que no está fusionado o
está fusionado con benceno, heteroareno o $\text{R}^{43\text{B}}$; $\text{R}^{43\text{B}}$ es cicloalcano, cicloalqueno,
heterocicloalcano o heterocicloalqueno;
en donde las porciones cíclicas representadas por E^1 y Y^1 juntos, Y^1 y B^1 juntos, A^2 y
 B^1 juntos, A^2 y D^1 juntos, $\text{R}^{1\text{A}}$, R^2 , $\text{R}^{2\text{A}}$, R^3 , $\text{R}^{3\text{A}}$, R^4 , $\text{R}^{4\text{A}}$, R^6 , $\text{R}^{6\text{C}}$, R^8 , $\text{R}^{8\text{A}}$, R^9 , $\text{R}^{9\text{A}}$, R^{10} , $\text{R}^{10\text{A}}$, R^{13} ,
30 $\text{R}^{13\text{A}}$, R^{14} , $\text{R}^{14\text{A}}$, R^{15} , $\text{R}^{15\text{A}}$, R^{18} , $\text{R}^{18\text{A}}$, R^{19} , $\text{R}^{19\text{A}}$, R^{20} , $\text{R}^{20\text{A}}$, R^{23} , $\text{R}^{23\text{A}}$, R^{24} , $\text{R}^{24\text{A}}$, R^{25} , $\text{R}^{25\text{A}}$, R^{26} ,
 $\text{R}^{26\text{A}}$, R^{27} , $\text{R}^{27\text{A}}$, R^{28} , $\text{R}^{28\text{A}}$, R^{29} , $\text{R}^{29\text{A}}$, R^{30} , $\text{R}^{30\text{A}}$, $\text{R}^{37\text{B}}$, R^{38} , $\text{R}^{38\text{A}}$, R^{39} , $\text{R}^{39\text{A}}$, R^{40} , y $\text{R}^{40\text{A}}$ están no
sustituidas, no sustituidas adicionalmente, sustituidas o sustituidas adicionalmente en forma
independiente con uno o dos o tres o cuatro o cinco sustituyentes seleccionados en forma
independiente entre $\text{R}^{57\text{A}}$, R^{57} , OR^{57} , SR^{57} , S(O)R^{57} , SO_2R^{57} , C(O)R^{57} , CO(O)R^{57} , OC(O)R^{57} ,
35 OC(O)OR^{57} , NH_2 , NHR^{57} , $\text{N(R}^{57})_2$, NHC(O)R^{57} , $\text{NR}^{57}\text{C(O)R}^{57}$, $\text{NHS(O)}_2\text{R}^{57}$, $\text{NR}^{57}\text{S(O)}_2\text{R}^{57}$,
 NHC(O)OR^{57} , $\text{NR}^{57}\text{C(O)OR}^{57}$, NHC(O)NH_2 , NHC(O)NHR^{57} , $\text{NHC(O)N(R}^{57})_2$, $\text{NR}^{57}\text{C(O)NHR}^{57}$,

$\text{NR}^{57}\text{C}(\text{O})\text{N}(\text{R}^{57})_2$, $\text{C}(\text{O})\text{NH}_2$, $\text{C}(\text{O})\text{NHR}^{57}$, $\text{C}(\text{O})\text{N}(\text{R}^{57})_2$, $\text{C}(\text{O})\text{NHOH}$, $\text{C}(\text{O})\text{NHOR}^{57}$, $\text{C}(\text{O})\text{NHSO}_2\text{R}^{57}$, $\text{C}(\text{O})\text{NR}^{57}\text{SO}_2\text{R}^{57}$, SO_2NH_2 , $\text{SO}_2\text{NHR}^{57}$, $\text{SO}_2\text{N}(\text{R}^{57})_2$, $\text{C}(\text{O})\text{H}$, $\text{C}(\text{O})\text{OH}$, $\text{C}(\text{N})\text{NH}_2$, $\text{C}(\text{N})\text{NHR}^{57}$, $\text{C}(\text{N})\text{N}(\text{R}^{57})_2$, CNOH , CNOCH_3 , OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I ;

5 $\text{R}^{57\text{A}}$ es eespiroalquilo, o eespiroheteroalquilo;

R^{57} es R^{58} , R^{59} , R^{60} o R^{61} ;

R^{58} es fenilo, que no está fusionado o está fusionado con $\text{R}^{58\text{A}}$; $\text{R}^{58\text{A}}$ es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{59} es heteroarilo, que no está fusionado o está fusionado con $\text{R}^{59\text{A}}$; $\text{R}^{59\text{A}}$ es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{60} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con $\text{R}^{60\text{A}}$; $\text{R}^{60\text{A}}$ es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{61} 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^{62} , OR^{62} , SR^{62} , $\text{S}(\text{O})\text{R}^{62}$, SO_2R^{62} , $\text{C}(\text{O})\text{R}^{62}$, $\text{CO}(\text{O})\text{R}^{62}$, $\text{OC}(\text{O})\text{R}^{62}$, $\text{OC}(\text{O})\text{OR}^{62}$, NH_2 , NHR^{62} , $\text{N}(\text{R}^{62})_2$, $\text{NHC}(\text{O})\text{R}^{62}$, $\text{NR}^{62}\text{C}(\text{O})\text{R}^{62}$, $\text{NHS}(\text{O})_2\text{R}^{62}$, $\text{NR}^{62}\text{S}(\text{O})_2\text{R}^{62}$, $\text{NHC}(\text{O})\text{OR}^{62}$, $\text{NR}^{62}\text{C}(\text{O})\text{OR}^{62}$, $\text{NHC}(\text{O})\text{NH}_2$, $\text{NHC}(\text{O})\text{NHR}^{62}$, $\text{NHC}(\text{O})\text{N}(\text{R}^{62})_2$, $\text{NR}^{62}\text{C}(\text{O})\text{NHR}^{62}$, $\text{NR}^{62}\text{C}(\text{O})\text{N}(\text{R}^{62})_2$, $\text{C}(\text{O})\text{NH}_2$, $\text{C}(\text{O})\text{NHR}^{62}$, $\text{C}(\text{O})\text{N}(\text{R}^{62})_2$, $\text{C}(\text{O})\text{NHOH}$, $\text{C}(\text{O})\text{NHOR}^{62}$, $\text{C}(\text{O})\text{NHSO}_2\text{R}^{62}$, $\text{C}(\text{O})\text{NR}^{62}\text{SO}_2\text{R}^{62}$, SO_2NH_2 , $\text{SO}_2\text{NHR}^{62}$, $\text{SO}_2\text{N}(\text{R}^{62})_2$, $\text{C}(\text{O})\text{H}$, $\text{C}(\text{O})\text{OH}$, $\text{C}(\text{N})\text{NH}_2$, $\text{C}(\text{N})\text{NHR}^{62}$, $\text{C}(\text{N})\text{N}(\text{R}^{62})_2$, CNOH , CNOCH_3 , OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I ;

R^{62} es R^{63} , R^{64} , R^{65} o R^{66} ;

R^{63} es fenilo, que no está fusionado o está fusionado con $\text{R}^{63\text{A}}$; $\text{R}^{63\text{A}}$ es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{64} es heteroarilo, que no está fusionado o está fusionado con $\text{R}^{64\text{A}}$; $\text{R}^{64\text{A}}$ es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{65} es cicloalquilo, cicloalquenilo, heterocicloalquilo, o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con $\text{R}^{65\text{A}}$; $\text{R}^{65\text{A}}$ es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{66} 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^{67} , OR^{67} , SR^{67} , $\text{S}(\text{O})\text{R}^{67}$, SO_2R^{67} , $\text{C}(\text{O})\text{R}^{67}$, $\text{CO}(\text{O})\text{R}^{67}$, $\text{OC}(\text{O})\text{R}^{67}$, $\text{OC}(\text{O})\text{OR}^{67}$, NH_2 , NHR^{67} , $\text{N}(\text{R}^{67})_2$, $\text{NHC}(\text{O})\text{R}^{67}$, $\text{NR}^{67}\text{C}(\text{O})\text{R}^{67}$, $\text{NHS}(\text{O})_2\text{R}^{67}$, $\text{NR}^{67}\text{S}(\text{O})_2\text{R}^{67}$, $\text{NHC}(\text{O})\text{OR}^{67}$, $\text{NR}^{67}\text{C}(\text{O})\text{OR}^{67}$, $\text{NHC}(\text{O})\text{NH}_2$, $\text{NHC}(\text{O})\text{NHR}^{67}$, $\text{NHC}(\text{O})\text{N}(\text{R}^{67})_2$, $\text{NR}^{67}\text{C}(\text{O})\text{NHR}^{67}$, $\text{NR}^{67}\text{C}(\text{O})\text{N}(\text{R}^{67})_2$, $\text{C}(\text{O})\text{NH}_2$, $\text{C}(\text{O})\text{NHR}^{67}$, $\text{C}(\text{O})\text{N}(\text{R}^{67})_2$, $\text{C}(\text{O})\text{NHOH}$, $\text{C}(\text{O})\text{NHOR}^{67}$, $\text{C}(\text{O})\text{NHSO}_2\text{R}^{67}$, $\text{C}(\text{O})\text{NR}^{67}\text{SO}_2\text{R}^{67}$,

SO_2NH_2 , $\text{SO}_2\text{NHR}^{67}$, $\text{SO}_2\text{N(R}^{67})_2$, C(O)H , C(O)OH , C(N)NH_2 , C(N)NHR^{67} , $\text{C(N)N(R}^{67})_2$, CNOH , CNOCH_3 , OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I ;

R^{67} es alquilo, alquenilo, alquinilo, fenilo, heteroarilo, cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo;

- 5 en donde las porciones cíclicas representadas por $\text{R}^{57\text{A}}$, R^{58} , R^{59} , R^{60} , R^{63} , R^{64} , R^{65} , y R^{67} no están sustituidas o están sustituidas con uno o dos o tres o cuatro sustituyentes seleccionados en forma independiente entre R^{68} , OR^{68} , SR^{68} , S(O)R^{68} , SO_2R^{68} , C(O)R^{68} , CO(O)R^{68} , OC(O)R^{68} , OC(O)OR^{68} , NH_2 , NHR^{68} , $\text{N(R}^{68})_2$, NHC(O)R^{68} , $\text{NR}^{68}\text{C(O)R}^{68}$, $\text{NHS(O)}_2\text{R}^{68}$, $\text{NR}^{68}\text{S(O)}_2\text{R}^{68}$, NHC(O)OR^{68} , $\text{NR}^{68}\text{C(O)OR}^{68}$, NHC(O)NH_2 , NHC(O)NHR^{68} , $\text{NHC(O)N(R}^{68})_2$, $\text{NR}^{68}\text{C(O)NHR}^{68}$, $\text{NR}^{68}\text{C(O)N(R}^{68})_2$, C(O)NH_2 , C(O)NHR^{68} , $\text{C(O)N(R}^{68})_2$, C(O)NHOH , C(O)NHOR^{68} , $\text{C(O)NHSO}_2\text{R}^{68}$, $\text{C(O)NR}^{68}\text{SO}_2\text{R}^{68}$, SO_2NH_2 , $\text{SO}_2\text{NHR}^{68}$, $\text{SO}_2\text{N(R}^{68})_2$, C(O)H , C(O)OH , C(N)NH_2 , C(N)NHR^{68} , $\text{C(N)N(R}^{68})_2$, CNOH , CNOCH_3 , OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I ;

R^{68} es R^{69} , R^{70} , R^{71} o R^{72} ;

- 15 R^{69} es fenilo, que no está fusionado o está fusionado con $\text{R}^{69\text{A}}$; $\text{R}^{69\text{A}}$ es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{70} es heteroarilo, que no está fusionado o está fusionado con $\text{R}^{70\text{A}}$; $\text{R}^{70\text{A}}$ es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

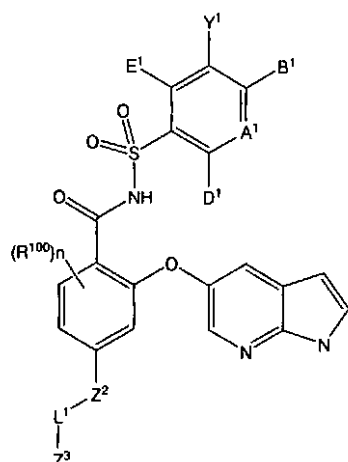
- 20 R^{71} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con $\text{R}^{71\text{A}}$; $\text{R}^{71\text{A}}$ es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

- R^{72} 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^{73} , OR^{73} , SR^{73} , S(O)R^{73} , SO_2R^{73} , C(O)R^{73} , CO(O)R^{73} , OC(O)R^{73} , OC(O)OR^{73} , NH_2 , NHR^{73} , $\text{N(R}^{73})_2$, NHC(O)R^{73} , $\text{NR}^{73}\text{C(O)R}^{73}$, $\text{NHS(O)}_2\text{R}^{73}$, $\text{NR}^{73}\text{S(O)}_2\text{R}^{73}$, NHC(O)OR^{73} , $\text{NR}^{73}\text{C(O)OR}^{73}$, NHC(O)NH_2 , NHC(O)NHR^{73} , $\text{NHC(O)N(R}^{73})_2$, $\text{NR}^{73}\text{C(O)NHR}^{73}$, $\text{NR}^{73}\text{C(O)N(R}^{73})_2$, C(O)NH_2 , C(O)NHR^{73} , $\text{C(O)N(R}^{73})_2$, C(O)NHOH , C(O)NHOR^{73} , $\text{C(O)NHSO}_2\text{R}^{73}$, $\text{C(O)NR}^{73}\text{SO}_2\text{R}^{73}$, SO_2NH_2 , $\text{SO}_2\text{NHR}^{73}$, $\text{SO}_2\text{N(R}^{73})_2$, C(O)H , C(O)OH , C(N)NH_2 , C(N)NHR^{73} , $\text{C(N)N(R}^{73})_2$, CNOH , CNOCH_3 , OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I ;

- 30 R^{73} es alquilo, alquenilo, alquinilo, fenilo, heteroarilo, cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo; y

- en donde las unidades representadas por R^{69} , R^{70} , y R^{71} no están sustituidas o están sustituidas con uno o dos o tres o cuatro sustituyentes seleccionados en forma independiente entre NH_2 , C(O)NH_2 , C(O)NHOH , SO_2NH_2 , CF_3 , CF_2CF_3 , C(O)H , C(O)OH , C(N)NH_2 , OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I .

2. Un compuesto CARACTERIZADO PORQUE tiene la Fórmula (II)



(II),

o una sal terapéuticamente aceptable del mismo, en donde

5 R^{100} tiene los valores que se describen para los sustituyentes de R^{26} ;

n es 0, 1, 2, o 3;

A^1 es N o $C(A^2)$;

A^2 es H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$,
 10 $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$, $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 , $C(O)OH$, $C(O)NH_2$ o $C(O)OR^{1A}$;

15 B^1 es H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$, $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$,
 20 $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 , $C(O)OH$, $C(O)NH_2$ o $C(O)OR^{1A}$;

D^1 es H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 ,
 25 $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$, $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$,

$C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 , $C(O)OH$, $C(O)NH_2$ o $C(O)OR^{1A}$;

E^1 es H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$,
 5 $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$, $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 , $C(O)OH$, $C(O)NH_2$ o $C(O)OR^{1A}$; y

10 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} , SO_2R^{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

E^1 y Y^1 , junto con los átomos a los cuales están unidos, son benceno, naftileno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; y

15 A^2 , B^1 , y D^1 se seleccionan en forma independiente entre H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$,
 20 $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 , $C(O)OH$, $C(O)NH_2$ o $C(O)OR^{1A}$; o

Y^1 y B^1 , junto con los átomos a los cuales están unidos, son benceno, naftileno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; y

25 A^2 , D^1 , y E^1 se seleccionan en forma independiente entre H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHSO_2NHR^1$, $NHSO_2N(R^1)_2$, $NR^1SO_2NHR^1$, $NR^1SO_2N(R^1)_2$, $C(O)NHNOH$, $C(O)NHNOR^1$,
 30 $C(O)NHSO_2R^1$, $C(NH)NH_2$, $C(NH)NHR^1$, $C(NH)N(R^1)_2$, $NHSO_2NHR^1$, $NHSO_2N(CH_3)R^1$, $N(CH_3)SO_2N(CH_3)R^1$, F, Cl, Br, I, CN, NO_2 , N_3 , OH, $C(O)H$, $CHNOH$, $CH(NOCH_3)$, CF_3 , $C(O)OH$, $C(O)NH_2$ o $C(O)OR^{1A}$; o

A^2 y B^1 , junto con los átomos a los cuales están unidos, son benceno, naftileno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; y

35 D^1 , E^1 , y Y^1 se seleccionan en forma independiente entre H, 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 , $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$,

NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂,
 NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹,
 NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹,
 C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹,
 5 N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃,
 C(O)OH, C(O)NH₂ o C(O)OR^{1A}; o

A² y D¹, junto con los átomos a los cuales están unidos, son benceno, naftaleno,
 heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; y

B¹, E¹, y Y¹ se seleccionan en forma independiente entre H, R¹, OR¹, SR¹, S(O)R¹,
 10 SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹,
 NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂,
 NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹,
 NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNOH, C(O)NHNOR¹,
 C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹,
 15 N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃,
 C(O)OH, C(O)NH₂ o C(O)OR^{1A};

R¹ es R², R³, R⁴ o R⁵;

R^{1A} es cicloalquilo, cicloalquenilo o cicloalquinilo;

R² es fenilo, que no está fusionado o está fusionado con R^{2A}; R^{2A} es benceno,
 20 heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R³ es heteroarilo, que no está fusionado o está fusionado con R^{3A}; R^{3A} es benceno,
 heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R⁴ es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno
 de los cuales no está fusionado o está fusionado con R^{4A}; R^{4A} es benceno, heteroareno,
 25 cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R⁵ 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 R⁶,
 NC(R^{6A})(R^{6B}), R⁷, OR⁷, SR⁷, S(O)R⁷, SO₂R⁷, NHR⁷, N(R⁷)₂, C(O)R⁷, C(O)NH₂, C(O)NHR⁷,
 C(O)N(R⁷)₂, NHC(O)R⁷, NR⁷C(O)R⁷, NHSO₂R⁷, NHC(O)OR⁷, SO₂NH₂, SO₂NHR⁷, SO₂N(R⁷)₂,
 30 NHC(O)NH₂, NHC(O)NHR⁷, NHC(O)CH(CH₃)NHC(O)CH(CH₃)NH₂,
 NHC(O)CH(CH₃)NHC(O)CH(CH₃)NHR⁷, OH, (O), C(O)OH, N₃, CN, NH₂, CF₃, CF₂CF₃, F, Cl,
 Br o I;

R⁶ es C₂-C₅-eespiroalquilo, cada uno de los cuales no está sustituido o está
 sustituido con OH, (O), N₃, CN, CF₃, CF₂CF₃, F, Cl, Br, I, NH₂, NH(CH₃) o N(CH₃)₂;

R^{6A} y R^{6B} se seleccionan en forma independiente entre alquilo o, junto con el N al cual
 35 están unidos, R^{6C};

R^{6C} es aziridin-1-ilo, azetidin-1-ilo, pirrolidin-1-ilo o piperidin-1-ilo, donde cada uno tiene una unidad CH_2 no reemplazada o reemplazada con O, C(O), CNOH, CNOCH₃, S, S(O), SO₂ o NH;

R^7 es R^8 , R^9 , R^{10} o R^{11} ;

5 R^8 es fenilo, que no está fusionado o está fusionado con R^{8A} ; R^{8A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^9 es heteroarilo, que no está fusionado o está fusionado con R^{9A} ; R^{9A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

10 R^{10} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{10A} ; R^{10A} es benceno, heteroareno, 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 en forma independiente entre R^{12} , OR^{12} , SR^{12} , $S(O)R^{12}$, SO_2R^{12} , $C(O)R^{12}$, $CO(O)R^{12}$, $OC(O)R^{12}$, $OC(O)OR^{12}$, NH_2 , NHR^{12} , $N(R^{12})_2$, $NHC(O)R^{12}$, $NR^{12}C(O)R^{12}$, $NHS(O)_2R^{12}$, $NR^{12}S(O)_2R^{12}$, $NHC(O)OR^{12}$, $NR^{12}C(O)OR^{12}$, $NHC(O)NH_2$, $NHC(O)NHR^{12}$, $NHC(O)N(R^{12})_2$, $NR^{12}C(O)NHR^{12}$, $NR^{12}C(O)N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, $C(O)NHOH$, $C(O)NHOR^{12}$, $C(O)NHSO_2R^{12}$, $C(O)NR^{12}SO_2R^{12}$, SO_2NH_2 , SO_2NHR^{12} , $SO_2N(R^{12})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{12}$, $C(N)N(R^{12})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I ;

20 R^{12} es R^{13} , R^{14} , R^{15} o R^{16} ;

R^{13} es fenilo, que no está fusionado o está fusionado con R^{13A} ; R^{13A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{14} es heteroarilo, que no está fusionado o está fusionado con R^{14A} ; R^{14A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

25 R^{15} es cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno, cada uno de los cuales no está fusionado o está fusionado con R^{15A} ; R^{15A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{16} es alquilo, alquenilo o alquinilo;

R^{17} es R^{18} , R^{19} , R^{20} o R^{21} ;

30 R^{18} es fenilo, que no está fusionado o está fusionado con R^{18A} ; R^{18A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{19} es heteroarilo, que no está fusionado o está fusionado con R^{19A} ; R^{19A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

35 R^{20} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo cada uno de los cuales no está fusionado o está fusionado con R^{20A} ; R^{20A} es benceno, heteroareno, 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 en forma independiente entre R^{22} , OR^{22} , SR^{22} , $S(O)R^{22}$, SO_2R^{22} , $C(O)R^{22}$, $CO(O)R^{22}$, $OC(O)R^{22}$, $OC(O)OR^{22}$, NH_2 , NHR^{22} , $N(R^{22})_2$, $NHC(O)R^{22}$, $NR^{22}C(O)R^{22}$, $NHS(O)_2R^{22}$, $NR^{22}S(O)_2R^{22}$, $NHC(O)OR^{22}$, $NR^{22}C(O)OR^{22}$, $NHC(O)NH_2$, $NHC(O)NHR^{22}$, $NHC(O)N(R^{22})_2$, $NR^{22}C(O)NHR^{22}$, $NR^{22}C(O)N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, $C(O)NHOH$, $C(O)NHOR^{22}$, $C(O)NHSO_2R^{22}$, $C(O)NR^{22}SO_2R^{22}$, SO_2NH_2 , SO_2NHR^{22} , $SO_2N(R^{22})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{22}$, $C(N)N(R^{22})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I ;

R^{22} es R^{23} , R^{24} o R^{25} ;

10 R^{23} es fenilo, que no está fusionado o está fusionado con R^{23A} ; R^{23A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{24} es heteroareno, que no está fusionado o está fusionado con R^{24A} ; R^{24A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

15 R^{25} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{25A} ; R^{25A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

Z^2 es R^{28} , R^{29} o R^{30} ;

20 L^1 es un R^{37} , OR^{37} , SR^{37} , $S(O)R^{37}$, SO_2R^{37} , $C(O)R^{37}$, $CO(O)R^{37}$, $OC(O)R^{37}$, $OC(O)OR^{37}$, NHR^{37} , $C(O)NH$, $C(O)NR^{37}$, $C(O)NHOR^{37}$, $C(O)NHSO_2R^{37}$, SO_2NH , SO_2NHR^{37} , $C(N)NH$, $C(N)NHR^{37}$;

R^{28} es fenileno, que no está fusionado o está fusionado con R^{28A} ; R^{28A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{29} es heteroarileno, que no está fusionado o está fusionado con R^{29A} ; R^{29A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

25 R^{30} es cicloalquilenilo, cicloalquenilenilo, heterocicloalquilenilo o heterocicloalquenilenilo, cada uno de los cuales no está fusionado o está fusionado con R^{30A} ; R^{30A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{37} es una unión o R^{37A} ;

30 R^{37A} es alquilenilo, alquenilenilo, o alquinilenilo, cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre R^{37B} , OR^{37B} , SR^{37B} , $S(O)R^{37B}$, SO_2R^{37B} , $C(O)R^{37B}$, $CO(O)R^{37B}$, $OC(O)R^{37B}$, $OC(O)OR^{37B}$, NH_2 , NHR^{37B} , $N(R^{37B})_2$, $NHC(O)R^{37B}$, $NR^{37B}C(O)R^{37B}$, $NHS(O)_2R^{37B}$, $NR^{37B}S(O)_2R^{37B}$, $NHC(O)OR^{37B}$, $NR^{37B}C(O)OR^{37B}$, $NHC(O)NH_2$, $NHC(O)NHR^{37B}$, $NHC(O)N(R^{37B})_2$, $NR^{37B}C(O)NHR^{37B}$, $NR^{37B}C(O)N(R^{37B})_2$, $C(O)NH_2$, $C(O)NHR^{37B}$, $C(O)N(R^{37B})_2$, $C(O)NHOH$, $C(O)NHOR^{37B}$, $C(O)NHSO_2R^{37B}$, $C(O)NR^{37B}SO_2R^{37B}$, SO_2NH_2 , SO_2NHR^{37B} , $SO_2N(R^{37B})_2$,

C(O)H, C(O)OH, C(N)NH₂, C(N)NHR^{37B}, C(N)N(R^{37B})₂, CNOH, CNOCH₃, OH, (O), CN, N₃, NO₂, CF₃, CF₂CF₃, OCF₃, OCF₂CF₃, F, Cl, Br y I ;

R^{37B} es alquilo, alquenilo, alquinilo, o R^{37C};

R^{37C} es fenilo, heteroarilo, cicloalquilo, cicloalquenilo, heterocicloalquilo, o
5 heterocicloalquenilo;

Z³ es R³⁸, R³⁹ o R⁴⁰;

R³⁸ es fenilo, que no está fusionado o está fusionado con R^{38A}; R^{38A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R³⁹ es heteroarilo, que no está fusionado o está fusionado con R^{39A}; R^{39A} es benceno,
10 heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R⁴⁰ es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{40A}; R^{40A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

en donde las porciones cíclicas representadas por E¹ y Y¹ juntos, Y¹ y B¹ juntos, A² y
15 B¹ juntos, A² y D¹ juntos, R^{1A}, R², R^{2A}, R³, R^{3A}, R⁴, R^{4A}, R⁶, R^{6C}, R⁸, R^{8A}, R⁹, R^{9A}, R¹⁰, R^{10A}, R¹³, R^{13A}, R¹⁴, R^{14A}, R¹⁵, R^{15A}, R¹⁸, R^{18A}, R¹⁹, R^{19A}, R²⁰, R^{20A}, R²³, R^{23A}, R²⁴, R^{24A}, R²⁵, R^{25A}, R²⁶, R^{26A}, R²⁷, R^{27A}, R²⁸, R^{28A}, R²⁹, R^{29A}, R³⁰, R^{30A}, R^{37B}, R³⁸, R^{38A}, R³⁹, R^{39A}, R⁴⁰, y R^{40A} están no
sustituidas, no sustituidas adicionalmente, sustituidas o sustituidas adicionalmente en forma
independiente con uno o dos o tres o cuatro o cinco sustituyentes seleccionados en forma
20 independiente entre R^{57A}, R⁵⁷, OR⁵⁷, SR⁵⁷, S(O)R⁵⁷, SO₂R⁵⁷, C(O)R⁵⁷, CO(O)R⁵⁷, OC(O)R⁵⁷, OC(O)OR⁵⁷, NH₂, NHR⁵⁷, N(R⁵⁷)₂, NHC(O)R⁵⁷, NR⁵⁷C(O)R⁵⁷, NHS(O)₂R⁵⁷, NR⁵⁷S(O)₂R⁵⁷, NHC(O)OR⁵⁷, NR⁵⁷C(O)OR⁵⁷, NHC(O)NH₂, NHC(O)NHR⁵⁷, NHC(O)N(R⁵⁷)₂, NR⁵⁷C(O)NHR⁵⁷, NR⁵⁷C(O)N(R⁵⁷)₂, C(O)NH₂, C(O)NHR⁵⁷, C(O)N(R⁵⁷)₂, C(O)NHOH, C(O)NHOR⁵⁷, C(O)NHOSO₂R⁵⁷, C(O)NR⁵⁷SO₂R⁵⁷, SO₂NH₂, SO₂NHR⁵⁷, SO₂N(R⁵⁷)₂, C(O)H, C(O)OH,
25 C(N)NH₂, C(N)NHR⁵⁷, C(N)N(R⁵⁷)₂, CNOH, CNOCH₃, OH, (O), CN, N₃, NO₂, CF₃, CF₂CF₃, OCF₃, OCF₂CF₃, F, Cl, Br o I;

R^{57A} es eespiroalquilo o heteroeespiroalquilo;

R⁵⁷ es R⁵⁸, R⁵⁹, R⁶⁰ o R⁶¹;

R⁵⁸ es fenilo, que no está fusionado o está fusionado con R^{58A}; R^{58A} es benceno,
30 heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R⁵⁹ es heteroarilo, que no está fusionado o está fusionado con R^{59A}; R^{59A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R⁶⁰ es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{60A}; R^{60A} es benceno, heteroareno,
35 cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{61} 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^{62} , OR^{62} , SR^{62} , $S(O)R^{62}$, SO_2R^{62} , $C(O)R^{62}$, $CO(O)R^{62}$, $OC(O)R^{62}$, $OC(O)OR^{62}$, NH_2 , NHR^{62} , $N(R^{62})_2$, $NHC(O)R^{62}$, $NR^{62}C(O)R^{62}$, $NHS(O)_2R^{62}$, $NR^{62}S(O)_2R^{62}$, $NHC(O)OR^{62}$, $NR^{62}C(O)OR^{62}$,
 5 $NHC(O)NH_2$, $NHC(O)NHR^{62}$, $NHC(O)N(R^{62})_2$, $NR^{62}C(O)NHR^{62}$, $NR^{62}C(O)N(R^{62})_2$, $C(O)NH_2$, $C(O)NHR^{62}$, $C(O)N(R^{62})_2$, $C(O)NHOH$, $C(O)NHOR^{62}$, $C(O)NHSO_2R^{62}$, $C(O)NR^{62}SO_2R^{62}$, SO_2NH_2 , SO_2NHR^{62} , $SO_2N(R^{62})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{62}$, $C(N)N(R^{62})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I ;

R^{62} es R^{63} , R^{64} , R^{65} o R^{66} ;

10 R^{63} es fenilo, que no está fusionado o está fusionado con R^{63A} ; R^{63A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{64} es heteroarilo, que no está fusionado o está fusionado con R^{64A} ; R^{64A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{65} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{65A} ; R^{65A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{66} 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^{67} , OR^{67} , SR^{67} , $S(O)R^{67}$, SO_2R^{67} , $C(O)R^{67}$, $CO(O)R^{67}$, $OC(O)R^{67}$, $OC(O)OR^{67}$, NH_2 , NHR^{67} ,
 20 $N(R^{67})_2$, $NHC(O)R^{67}$, $NR^{67}C(O)R^{67}$, $NHS(O)_2R^{67}$, $NR^{67}S(O)_2R^{67}$, $NHC(O)OR^{67}$, $NR^{67}C(O)OR^{67}$, $NHC(O)NH_2$, $NHC(O)NHR^{67}$, $NHC(O)N(R^{67})_2$, $NR^{67}C(O)NHR^{67}$, $NR^{67}C(O)N(R^{67})_2$, $C(O)NH_2$, $C(O)NHR^{67}$, $C(O)N(R^{67})_2$, $C(O)NHOH$, $C(O)NHOR^{67}$, $C(O)NHSO_2R^{67}$, $C(O)NR^{67}SO_2R^{67}$, SO_2NH_2 , SO_2NHR^{67} , $SO_2N(R^{67})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{67}$, $C(N)N(R^{67})_2$, $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I ;

25 R^{67} es alquilo, alquenilo, alquinilo, fenilo, heteroarilo, cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo;

en donde las porciones cíclicas representadas por R^{57A} , R^{58} , R^{59} , R^{60} , R^{63} , R^{64} , R^{65} , y R^{67} no están sustituidas o están sustituidas con uno o dos o tres o cuatro sustituyentes seleccionados en forma independiente entre R^{68} , OR^{68} , SR^{68} , $S(O)R^{68}$, SO_2R^{68} , $C(O)R^{68}$,
 30 $CO(O)R^{68}$, $OC(O)R^{68}$, $OC(O)OR^{68}$, NH_2 , NHR^{68} , $N(R^{68})_2$, $NHC(O)R^{68}$, $NR^{68}C(O)R^{68}$, $NHS(O)_2R^{68}$, $NR^{68}S(O)_2R^{68}$, $NHC(O)OR^{68}$, $NR^{68}C(O)OR^{68}$, $NHC(O)NH_2$, $NHC(O)NHR^{68}$, $NHC(O)N(R^{68})_2$, $NR^{68}C(O)NHR^{68}$, $NR^{68}C(O)N(R^{68})_2$, $C(O)NH_2$, $C(O)NHR^{68}$, $C(O)N(R^{68})_2$, $C(O)NHOH$, $C(O)NHOR^{68}$, $C(O)NHSO_2R^{68}$, $C(O)NR^{68}SO_2R^{68}$, SO_2NH_2 , SO_2NHR^{68} , $SO_2N(R^{68})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{68}$, $C(N)N(R^{68})_2$, $CNOH$, $CNOCH_3$, OH , (O) ,
 35 CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I ;

R^{68} es R^{69} , R^{70} , R^{71} o R^{72} ;

R^{69} es fenilo, que no está fusionado o está fusionado con R^{69A} ; R^{69A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{70} es heteroarilo, que no está fusionado o está fusionado con R^{70A} ; R^{70A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

5 R^{71} es cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, cada uno de los cuales no está fusionado o está fusionado con R^{71A} ; R^{71A} es benceno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno;

R^{72} es alquilo, alquenilo o alquenilo, cada uno de los cuales no está sustituido o está sustituido con uno o dos o tres sustituyentes seleccionados en forma independiente entre
 10 R^{73} , OR^{73} , SR^{73} , $S(O)R^{73}$, SO_2R^{73} , $C(O)R^{73}$, $CO(O)R^{73}$, $OC(O)R^{73}$, $OC(O)OR^{73}$, NH_2 , NHR^{73} , $N(R^{73})_2$, $NHC(O)R^{73}$, $NR^{73}C(O)R^{73}$, $NHS(O)_2R^{73}$, $NR^{73}S(O)_2R^{73}$, $NHC(O)OR^{73}$, $NR^{73}C(O)OR^{73}$, $NHC(O)NH_2$, $NHC(O)NHR^{73}$, $NHC(O)N(R^{73})_2$, $NR^{73}C(O)NHR^{73}$, $NR^{73}C(O)N(R^{73})_2$, $C(O)NH_2$, $C(O)NHR^{73}$, $C(O)N(R^{73})_2$, $C(O)NHOH$, $C(O)NHOR^{73}$, $C(O)NHSO_2R^{73}$, $C(O)NR^{73}SO_2R^{73}$, SO_2NH_2 , SO_2NHR^{73} , $SO_2N(R^{73})_2$, $C(O)H$, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{73}$, $C(N)N(R^{73})_2$,
 15 $CNOH$, $CNOCH_3$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I ;

R^{73} es alquilo, alquenilo, alquenilo, fenilo, heteroarilo, cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo; y

en donde las unidades representadas por R^{69} , R^{70} , y R^{71} no están sustituidas o están sustituidas con uno o dos o tres o cuatro sustituyentes seleccionados en forma
 20 independiente entre NH_2 , $C(O)NH_2$, $C(O)NHOH$, SO_2NH_2 , CF_3 , CF_2CF_3 , $C(O)H$, $C(O)OH$, $C(N)NH_2$, OH , (O) , CN , N_3 , NO_2 , CF_3 , CF_2CF_3 , OCF_3 , OCF_2CF_3 , F , Cl , Br o I .

3. El compuesto de la reivindicación 1, CARACTERIZADO PORQUE

G^1 es H;

25 A^1 es N o $C(A^2)$; y

A^2 es H.

4. El compuesto de la reivindicación 1, CARACTERIZADO PORQUE

G^1 es H;

30 A^1 es N o $C(A^2)$;

A^2 es H; y

B^1 es NHR^1 .

5. El compuesto de la reivindicación 1, CARACTERIZADO PORQUE

35 G^1 es H;

A^1 es N o $C(A^2)$;

A² es H;
 B¹ es NHR¹; y
 D¹ es H.

5 6. El compuesto de la reivindicación 1, CARACTERIZADO PORQUE
 G¹ es H;
 A¹ es N o C(A²);
 A² es H;
 B¹ es NHR¹;
 10 D¹ es H; y
 E¹ es H.

 7. El compuesto de la reivindicación 1, CARACTERIZADO PORQUE
 G¹ es H;
 15 A¹ es N o C(A²);
 A² es H;
 B¹ es NHR¹;
 D¹ es H;
 E¹ es H; y
 20 Y¹ es NO₂.

 8. Un compuesto de la reivindicación 1 o la reivindicación 2, 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-
 25 ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-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-(1H-pirrol[2,3-b]piridin-5-iloxi)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-(1H-pirrol[2,3-b]piridin-5-
 30 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-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-{4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il}-N-({3-nitro-4-
 35 [(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-
 iloxi)benzamida;

- 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)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- Trans-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)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({4-{{2-metoxietil}amino}-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-{{(3S)-tetrahidro-2H-piran-3-ilmetil}amino}fenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-{{(3R)-tetrahidro-2H-piran-3-ilmetil}amino}fenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-(2-naftilsulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 4-(4-{{4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il}metil}piperazin-1-il)-N-{{3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-({4-{{2-metoxietil}amino}-3-[(trifluorometil)sulfonil]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-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-{{3-nitro-4-(tetrahidro-2H-piran-4-ilmetoxi)fenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-[(2,2,2-trifluoroetil)amino]fenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-[(3,3,3-trifluoropropil)amino]fenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- Cis-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}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 35

- 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil)piperazin-1-il)-N-([4-((1,4-dioxan-2-ilmetil)amino]-3-nitrofenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5 4-(4-([4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil)piperazin-1-il)-N-([4-((1,4-dioxan-2-ilmetoxi)-3-nitrofenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- Trans-4-(4-([4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil)piperazin-1-il)-N-([4-((4-morfolin-4-ilciclohexil)amino]-3-nitrofenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- Trans-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)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 4-(4-([4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil)piperazin-1-il)-N-([5-ciano-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([5-ciano-6-
- 15 (tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- Cis-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)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([5-cloro-6-
- 25 (tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil)piperazin-1-il)-N-([5-cloro-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-([4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil)piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)-N-([4-((tetrahidro-2H-piran-4-ilmetil)amino]-3-(trifluorometil)fenil]sulfonil)benzamida;
- 4-(4-([4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil)piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)-N-([4-((tetrahidro-2H-piran-4-ilmetil)amino]-3-
- 35 [(trifluorometil)sulfonil]fenil]sulfonil)benzamida;

- Trans-4-(4-([4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil)piperazin-1-il)-N-([4-([4-morfolin-4-ilciclohexil)amino]-3-[(trifluorometil)sulfonil]fenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil)piperazin-1-il)-N-([4-([1-metilpiperidin-4-il)amino]-3-[(trifluorometil)sulfonil]fenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5 5-([4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzoil]amino)sulfonil)-2-(tetrahidro-2H-piran-4-ilmetoxi)nicotinamida;
- N-([5-bromo-6-([1-metilpiperidin-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([1-metilpiperidin-4-il)metoxi]-3-nitrofenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([5-ciano-6-(1,4-dioxan-2-ilmetoxi)piridin-3-il)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 N-([5-bromo-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-pirrolo[2,3-b]piridin-5-iloxi)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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 N-([3-cloro-5-ciano-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-pirrolo[2,3-b]piridin-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-pirrolo[2,3-b]piridin-5-iloxi)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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 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-(1H-pirrolo[2,3-b]piridin-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-([3-cloro-4-([2-(2-metoxietoxi)etil]sulfonil)fenil)sulfonil)-4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 35 4-(4-([2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil)piperazin-1-il)-N-([4-([2-(2-metoxietoxi)etil]sulfonil)-3-nitrofenil)sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

- Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-morfolin-4-ilciclohexil)oxi]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
N-({5-bromo-6-[(1-tetrahidro-2H-piran-4-il)piperidin-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 5 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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
Cis-4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-N-({4-[(4-morfolin-4-ilciclohexil)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 10 Trans-N-({4-[(4-bis(ciclopropilmetil)amino)ciclohexil]amino)-3-nitrofenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
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)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 15 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(morfolin-3-ilmetil)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-N-({4-[(4-metilpiperazin-1-il)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-morfolin-4-ilbut-2-inil)oxi]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 20 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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-oxo-3,4-dihidroquinazolin-6-il}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 25 Trans-4-(4-{[8-(4-clorofenilo) eespiro[4,5]dec-7-en-7-il]metil}piperazin-1-il)-N-({4-[(4-morfolin-4-ilciclohexil)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
Cis-4-(4-{[4-(4-clorofenil)-6,6-dimetil-5,6-dihidro-2H-piran-3-il]metil}piperazin-1-il)-N-({4-[(4-metoxiciclohexil)metil]amino)-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-{[8-(4-clorofenilo) eespiro[4,5]dec-7-en-7-il]metil}piperazin-1-il)-N-({4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
Trans-4-(4-{[8-(4-clorofenilo) eespiro[4,5]dec-7-en-7-il]metil}piperazin-1-il)-N-({4-[(4-metoxiciclohexil)metil]amino)-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 35 4-(4-{[2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-{[2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[5-ciano-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 3-{[4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]amino}sulfonil]-2-nitrofenoxi]metil}morfoline-4-carboxilato de tert-butilo ;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-(morfolin-3-ilmetoxi)-3-nitrofenil]sulfonil}-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[8-(4-clorofenilo)eespiro[4,5]dec-7-en-7-il]metil}piperazin-1-il)-N-{[3-nitro-4-{(tetrahidro-2H-piran-4-ilmetil)amino}fenil}sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[1-(metilsulfonil)piperidin-4-il]amino}-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-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]amino}-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-{[4-cloro-3-nitrofenil]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-nitro-4-{[1-(2,2,2-trifluoroetil)piperidin-4-il]amino}fenil}sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[5-ciano-6-{[1-(tetrahidro-2H-piran-4-ilpiperidin-4-il)oxi]piridin-3-il}sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[5-isopropil-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-{[3-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- y sus sales terapéuticamente aceptables y sus metabolitos..
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[1-[2-fluoro-1-(fluorometil)etil]piperidin-4-il]amino}-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[1-(2,2-difluoroetil)piperidin-4-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[1-morfolin-4-ilciclohexil]metil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[4-(dicropropilamino)ciclohexil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-6,6-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-({5-bromo-6-[(4-etilmorfolin-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-{[4-etilmorfolin-3-il]metoxi}-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(4-tetrahidro-2H-piran-4-ilmorfolin-3-il)metoxi]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-[(3S)-1-tetrahidro-2H-piran-4-ilpiperidin-3-il]amino]fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-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-ilmetil)amino]piridin-3-il}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)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-pirrolo[2,3-b]piridin-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({5-ciano-6-[(4-morfolin-4-ilciclohexil)amino]piridin-3-il}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-
iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(1S,3R)-3-
5 morfolin-4-ilciclopentil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-
iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(1R,3S)-3-
morfolin-4-ilciclopentil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-
iloxi)benzamida;
- 10 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-{[morfolin-2-
ilmetil]amino}-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-
[(tetrahidrofurano-3-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-{[1-[cis-3-
15 fluorotetrahidro-2H-piran-4-il]piperidin-4-il]amino}-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-
b]piridin-5-iloxi)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-ilazetid-3-il]amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-
iloxi)benzamida;
- 20 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-{[1-
tetrahidrofurano-3-ilazetid-3-il]amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-
iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-{[(3R)-1-
tetrahidro-2H-piran-4-ilpirrolidin-3-il]metil]amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-
25 iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-5,5-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-{[4-
fluorotetrahidro-2H-piran-4-il]metoxi}-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-
iloxi)benzamida;
- 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-
30 enil]metil}piperazin-1-il)-N-(4-{[(trans-4-hidroxiciclohexil)metoxi]-3-nitrofenil}sulfonil)benzamida;
- 2-(1H-pirrol[2,3-b]piridin-5-iloxi)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-
enil]metil}piperazin-1-il)-N-(4-{[(cis-4-metoxiciclohexil)metoxi]-3-nitrofenil}sulfonil)benzamida;
- Cis-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[4-
(ciclopropilamino)ciclohexil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-
35 iloxi)benzamida;

- Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{[4-(tetrahidro-2H-piran-4-ilamino)ciclohexil]amino}fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- Trans-N-({5-bromo-6-[4-morfolin-4-ilciclohexil]oxi}piridin-3-il)sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-metoxiciclohexil)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-{[4-({[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]amino}sulfonil)-2-nitrofenoxi]metil}-4-fluoropiperidin-1-carboxilato de tert-butilo ;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-fluoropiperidin-4-il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{[4-(4-tetrahidro-2H-piran-4-ilpiperazin-1-il)ciclohexil]amino}fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-([4-({1-[2-fluoro-1-(fluorometil)etil]piperidin-4-il}metoxi)-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-[(3R)-1-tetrahidro-2H-piran-4-ilpirrolidin-3-il]amino}fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-([4-[(3R)-1-(2,2-dimetiltetrahidro-2H-piran-4-il)pirrolidin-3-il]amino]-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-[(3S)-1-tetrahidro-2H-piran-4-ilpirrolidin-3-il]amino}fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-([4-[(3S)-1-(2,2-dimetiltetrahidro-2H-piran-4-il)pirrolidin-3-il]amino]-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-([4-[(4-metilmorfolin-2-il)metil]amino]-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-([4-({2-metoxietil}morfolin-2-il)metil]amino)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

- N-[(4-{[(4-acetilmorfolin-2-il)metil]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[trans-4-(fluorometil)-1-oxetan-3-ilpirrolidin-3-il]metoxi}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 5 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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-[(1-oxetan-3-ilpiperidin-4-il)amino]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 10 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[1-ciclobutilpiperidin-4-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[1-(2,2-dimetiltetrahidro-2H-piran-4-il)piperidin-4-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 15 b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3S)-1-ciclopropilpirrolidin-3-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-[(1-tetrahidrofurano-3-ilpiperidin-4-il)amino]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 20 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3R)-1-ciclopropilpirrolidin-3-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-[(3S)-1-tetrahidro-2H-piran-4-ilpirrolidin-3-il]metil]amino)fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 25 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3-hidroxi-2,2-dimetilpropil)amino]-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[1-(metilsulfonil)piperidin-3-il]metil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 30 N-[(4-{[(1-acetilpiperidin-3-il)metil]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3R)-1-(metilsulfonil)pirrolidin-3-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-3,3-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-
5 [(tetrahidro-2H-piran-4-ilmetil)amino]fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[1-[2-fluoro-1-(fluorometil)etil]azetidin-3-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[1-(metilsulfonil)pirrolidin-3-il]metil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-[(4-{[(1-acetilpirrolidin-3-il)metil]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 N-[(4-{[(3R)-1-acetilpirrolidin-3-il]amino}-3-nitrofenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[3-metoxi-2,2-dimetilpropil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(1R,3R)-3-
20 hidroxiciclopentil]metil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(1S,3S)-3-hidroxiciclopentil]metil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(1S,3R)-3-hidroxiciclopentil]metil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(1R,3S)-3-hidroxiciclopentil]metil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{[(3S)-2-oxopiperidin-3-il]amino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[1-[2-fluoro-1-(fluorometil)etil]azetidin-3-il]metil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
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- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(3-nitro-4-{{(1-oxetan-3-ilazetid-3-il)metil}amino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(3-nitro-4-{{(1-oxetan-3-ilpiperidin-4-il)metil}amino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{(1-ciclopropilpiperidin-4-il)metil}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(4-(2-fluoroetil)morfolin-2-il}metil}amino)-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 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]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(4-fluoro-1-oxetan-3-ilpiperidin-4-il)metoxi}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(2S)-4,4-difluoro-1-oxetan-3-ilpirrolidin-2-il}metoxi}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(3-nitro-4-{{(4-tetraidro-2H-piran-4-ilmorfolin-3-il)metil}amino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(4-{{(4-ciclobutilmorfolin-3-il)metil}amino}-3-nitrofenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-[(3-nitro-4-{{(4-tetraidrofurano-3-ilmorfolin-3-il)metil}amino}fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(1-[2-fluoro-1-(fluorometil)etil]piperidin-4-il)metil}amino}-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(1-ciclopropil-4-fluoropiperidin-4-il)metoxi}-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(4-metoxibencil)amino}-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
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- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-{{3-(trifluorometoxi)bencil}amino}fenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{3-metoxibencil}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{4-(difluorometoxi)bencil}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-(1,4-dioxaeespiro[4,5]dec-8-ilamino)-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 Trans-N-{{4-{{4-(acetilamino)ciclohexil}amino}-3-nitrofenil}sulfonil}-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 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}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(3S)-1-(2-fluoroetil)pirrolidin-3-il}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(3S)-1-(2,2-difluoroetil)pirrolidin-3-il}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(3R)-1-(2-fluoroetil)pirrolidin-3-il}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{3-nitro-4-{{(3S)-1-oxetan-3-ilpirrolidin-3-il}metoxi}fenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{4-hidroxibencil}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{3-hidroxibencil}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{3-(difluorometoxi)bencil}amino}-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{(cis-3-morfolin-4-ilciclopentil}metil}amino)-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- Trans-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{4-((metilsulfonil)amino)ciclohexil}amino)-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
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- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(1-ciclopropilpiperidin-4-il)amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(1-oxetan-3-ilpiperidin-4-il)metoxi]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-fluoro-1-tetrahidro-2H-piran-4-ilpiperidin-4-il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-fluoro-1-tetrahidrofurano-3-ilpiperidin-4-il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-([4-[(4-fluoro-1-(metilsulfonil)piperidin-4-il)metoxi]-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(3R)-1-oxetan-3-ilpirrolidin-3-il]metil}amino)fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-hidroxiciclohexil)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-([4-[(4-[3-(dimetilamino)propoxi]bencil}amino)-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-([4-[(4-(2-morfolin-4-iletoxi)bencil}amino)-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-([4-[(E)-4-hidroxi-1-adamantil]metil}amino)-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-([4-[(Z)-4-hidroxi-1-adamantil]metil}amino)-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-({4-[(1S,4S)-biciclo[2,2,1]hept-5-en-2-ilmetoxi]-3-nitrofenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(1-metil-5-oxopirrolidin-3-il)amino]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-([4-[(1R,4R,5R,6S)-5,6-dihidroxibiciclo[2,2,1]hept-2-il]metoxi]-3-nitrofenil}sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(1R,4R,5S,6R)-5,6-dihidroxiciclo[2,2,1]hept-2-il]metoxi}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-[(3-oxociclohexil)metoxi]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-5,5-dimetilciclohexa-1,3-dien-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-[(3S)-1-oxetan-3-ilpirrolidin-3-il]metil]amino)fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- Cis-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-[(3S)-1-oxetan-3-ilpirrolidin-3-il]amino)fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[4-[2-(2-metoxietoxi)etil]morfolin-2-il]metil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 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]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[4-(N,N-dimetilglicil)morfolin-2-il]metil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- ácido (2-{[(4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]sulfamoil]-2-nitrofenil)amino]metil}morfolin-4-il)acético;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-[(4-(oxetan-3-il)morfolin-2-il]metil]amino)fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[5-(metilsulfonil)-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il]sulfonil]-2-(1H-pirrol[2,3-b]piridin-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-[(trifluorometil)sulfonil]fenil}sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[4-metiltetrahidro-2H-piran-4-il]metoxi]-3-nitrofenil}sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]sulfamoi]-2-nitrofenil}piperazin-1-carboxilato de etilo ;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-[4-(morfolin-4-il)piperidin-1-il]-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{[(3R)-1-(oxetan-3-il)pirrolidin-3-il]amino}fenil}sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3R)-1-(1,3-difluoropropan-2-il)pirrolidin-3-il]amino]-3-[(trifluorometil)sulfonil]fenil}sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[1-isopropilpiperidin-4-il]amino]-3-nitrofenil}sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-[(4-{[1-tert-butilpiperidin-4-il]amino]-3-nitrofenil}sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[1-(2-metoxietil)piperidin-3-il]metil}amino)-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[1-(cianometil)piperidin-3-il]metil}amino)-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[4-fluoro-1-metilpiperidin-4-il]metoxi]-3-[(trifluorometil)sulfonil]fenil}sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

- N-[(5-cloro-6-[(3R)-1-(1,3-difluoropropan-2-il)pirrolidin-3-il]amino}piridin-3-il)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-[(4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil}sulfamoil]-2-nitrofenil)amino]piperazin-1-carboxilato de tert-butilo ;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-(pentafluoro- $\square^6$ -sulfanil)-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[4-metoxitetrahidro-2H-piran-4-il]metoxil}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-[(3R)-1-(1,3-difluoropropan-2-il)pirrolidin-3-il]oxi)-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{[4-(oxetan-3-il)piperazin-1-il]amino}fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{[4-(tetrahidro-2H-piran-4-il)piperazin-1-il]amino}fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{(3R)-tetrahidrofurano-3-ilamino}fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-[(4-{[1-tert-butilpiperidin-4-il]amino}-3-[(trifluorometil)sulfonil]fenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[4-(oxetan-3-il)morfolin-2-il]metil]amino}-3-[(trifluorometil)sulfonil]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;

- N-[(5-cloro-6-[[[(2S)-4-(cianometil)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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5 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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-[(5-cloro-6-[[[(2R)-4-(cianometil)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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 N-({5-cloro-6-[3-hidroxi-2-(hidroximetil)-2-metilpropoxi]piridin-3-il}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-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]piridin-3-il}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-({[4-(1,3-difluoropropan-2-il)morfolin-2-il]metil}amino)-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 N-[(5-cloro-6-[[1-(cianometil)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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 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)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 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)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[[1-(oxetan-3-il)azetidín-3-il]amino}fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 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]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 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]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 N-[(5-cloro-6-[[1-(N,N-dimetilglicil)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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 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]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-{4-[[4'-(clorobifenil-2-il)metil]-4-metoxipiperidin-1-il]-N-[(5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 4-{4-[[4'-(clorobifenil-2-il)metil]-4-metoxipiperidin-1-il]-N-[(3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[9-(4-clorofenil)-3-(1,3-difluoropropan-2-il)-3-azaeespiro[5,5]undec-8-en-8-il]metil]piperazin-1-il)-N-[(3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 4-(4-[[9-(4-clorofenil)-3-isopropil-3-azaeespiro[5,5]undec-8-en-8-il]metil]piperazin-1-il)-N-[(3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[9-(4-clorofenil)-3-(1,3-difluoropropan-2-il)-3-azaeespiro[5,5]undec-8-en-8-il]metil]piperazin-1-il)-N-[(5-cloro-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-[[9-(4-clorofenil)-3-isopropil-3-azaeespiro[5,5]undec-8-en-8-il]metil]piperazin-1-il)-N-[(5-cloro-6-(tetrahidro-2H-piran-4-ilmetoxi)piridin-3-il)sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 35 N-[(5-cloro-6-[(4-fluoro-1-metilpiperidin-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

- N-[(5-cloro-6-[[1-(N,N-dimetilglicil)-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-{4-[(4'-clorobifenil-2-il)metil]-4-fluoropiperidin-1-il}-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-{4-[(4'-clorobifenil-2-il)metil]-4-fluoropiperidin-1-il}-N-({5-cloro-6-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]piridin-3-il}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[9-(4-clorofenil)-3-isopropil-3-azaeespiro[5,5]undec-8-en-8-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)-N-({4-[(tetrahidro-2H-piran-4-ilmetil)amino]-3-(trifluorometil)fenil}sulfonil)benzamida;
- N-[(5-cloro-6-[(3R)-1-(1,3-difluoropropan-2-il)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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[2-(tetrahidrofurano-3-iloxi)etoxi]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({5-ciano-6-[2-(tetrahidro-2H-piran-4-il)etoxi]piridin-3-il}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-(3-furilmetoxi)-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-[(5-cloro-6-[(3R)-1-(1,3-difluoropropan-2-il)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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-[(5-cloro-6-[[1-(1,3-difluoropropan-2-il)-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-({3-cloro-4-[(4-fluoro-1-metilpiperidin-4-il)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-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-ilmetoxi)fenil]sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
N-[(5-cloro-6-{[1-(2,2-difluoroetil)-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5 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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[6-{[1-(1,3-difluoropropan-2-il)-4-fluoropiperidin-4-il]metoxi}-5-(trifluorometil)piridin-3-il]sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[5-cloro-6-[2-(tetrahydrofurano-2-il)etoxi]piridin-3-il]sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}-3-metilpiperazin-1-il)-N-{[3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil]sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[3-(ciclopropilamino)propil]amino}-3-nitrofenil]sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 N-{[5-cloro-6-(2-metoxietoxi)piridin-3-il]sulfonil}-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 N-[(3-cloro-4-{[1-(metoxiacetil)piperidin-4-il]metoxi}fenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
N-[(3-cloro-4-{[1-(N,N-dimetilglicil)piperidin-4-il]metoxi}fenil)sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 Trans-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohexil]metil}piperidin-1-il)-N-{[3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil]sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)-N-{[6-(tetrahidro-2H-piran-4-ilmetoxi)-5-(trifluorometil)piridin-3-il]sulfonil}benzamida;
- 35 N-[(5-cloro-6-[(trans-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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-((6-{{(trans-4-metoxiciclohexil)metoxi}-5-(trifluorometil)piridin-3-il}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-((6-{{(cis-4-metoxiciclohexil)metoxi}-5-(trifluorometil)piridin-3-il}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 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}piperidin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-((3-cloro-4-{{(trans-4-(morfolin-4-il)ciclohexil)metoxi}fenil}sulfonil)-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{3-
- 15 [ciclopropil(1,3-tiazol-5-ilmetil)amino]propil}amino)-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-((3-cloro-4-{{(trans-4-hidroxiciclohexil)metoxi}fenil}sulfonil)-4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-((3-cloro-4-
- 20 [(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-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-(trifluorometil)fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{3-[ciclopropil(2,2,2-trifluoroetil)amino]propil}amino)-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-((3-cloro-4-{{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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-((3,5-difluoro-4-{{4-fluorotetrahidro-2H-piran-4-il}metoxi}fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{{2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il}metil}piperazin-1-il)-N-{{4-{{3-[ciclopropil(oxetan-3-il)amino]propil}amino)-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-
- 35 iloxi)benzamida;

- N-[(3-cloro-4-[[1-(1-metil-L-prolil)piperidin-4-il]metoxi]fenil)sulfonil]-4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-({3,4-difluoro-5-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 5 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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperidin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 10 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperidin-1-il)-N-[[3-cloro-4-(tetrahidro-2H-piran-4-ilmetoxi)fenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
2-[[4-[[4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]sulfamoil]-2-nitrofenil)amino]metil]morfoline-4-carboxilato de metilo ;
- 15 2-[[4-[[4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]sulfamoil]-2-nitrofenil)amino]metil]-N-etil-N-metilmorfoline-4-carboxamida;
- 20 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]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[4-[[3-[ciclobutil(ciclopropil)amino]propil]amino]-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 25 4-(4-[[2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil]piperazin-1-il)-N-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[3-cloro-4-(tetrahidrofurano-3-ilmetoxi)fenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-[[2-(4-clorofenil)-5,5-difluorociclohex-1-en-1-il]metil]piperazin-1-il)-N-[[4-[[4-(trans-4-hidroxiciclohexil)metil]amino]-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-({3-cloro-4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]fenil}sulfonil)-4-(4-[[9-(4-clorofenil)-3-(oxetan-3-il)-3-azaeespiro[5,5]undec-8-en-8-il]metil]piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 35

- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-(((2R)-4-ciclopropilmorfolin-2-il]metil)amino)-3-nitrofenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[5-(4-clorofenilo) eespiro[2,5]oct-5-en-6-il]metil}piperazin-1-il)-N-{[3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-{[5-cloro-6-({4-[ciclopropil(oxetan-3-il)amino]ciclohexil}metoxi)piridin-3-il]sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[5-(4-clorofenilo) eespiro[2,5]oct-5-en-6-il]metil}piperazin-1-il)-N-{[4-({[4-ciclopropilmorfolin-2-il]metil]amino)-3-nitrofenil]sulfonil]-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-{[3-cloro-4-({4-ciclopropilmorfolin-2-il]metoxi)fenil]sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- N-{[3-cloro-4-({[4-ciclopropilmorfolin-2-il]metil]amino)fenil]sulfonil]-4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 2-{[2-cloro-4-({4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzoil]sulfamoil]fenil]amino]metil}-N-etil-N-metilmorfoline-4-carboxamida;
- (2S)-2-{[3-cloro-5-({4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzoil]sulfamoil]piridin-2-il)oxi]metil}-N-etil-N-metilmorfoline-4-carboxamida;
- N-{[5-cloro-6-({[4-ciclopropilmorfolin-2-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 2-{[3-cloro-5-({4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzoil]sulfamoil]piridin-2-il)amino]metil}-N-etil-N-metilmorfoline-4-carboxamida;
- 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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[2-cianoetil](ciclopropil)amino]ciclohexil}amino]-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 5 N-({5-cloro-6-[(trans-4-hidroxi-4-metilciclohexil)metoxi]piridin-3-il}sulfonil)-4-(4-{[5-(4-clorofenilo) eespiro[2,5]oct-5-en-6-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 10 N-[(5-cloro-6-[(1R,2S,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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 15 N-[(5-cloro-6-{[4-fluoro-1-(oxetan-3-il)piperidin-4-il]metoxi]piridin-3-il}sulfonil)-4-(4-{[5-(4-clorofenilo) eespiro[2,5]oct-5-en-6-il]metil}piperazin-1-il)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-([4-{[4-(3,3-difluoropirrolidin-1-il)ciclohexil]amino]-3-nitrofenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 20 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-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 25 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[4-[(2,2-difluorociclopropil)amino]ciclohexil]amino]-3-nitrofenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;
- 30 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-nitro-4-(2-oxaespiro[3,5]non-7-ilmetoxi)fenil}sulfonil}-2-(1H-pirrolo[2,3-b]piridin-5-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-pirrolo[2,3-b]piridin-5-iloxi)benzamida;

- 4-(4-{[2-(4-clorofenil)-5,5-bis(fluorometil)ciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-
[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-
iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-[(4-
5 ciclopropilmorfolin-2-il)metoxi]-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-
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-pirrol[2,3-b]piridin-5-
iloxi)benzamida;
- 10 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-pirrol[2,3-b]piridin-5-
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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 15 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(trans-4-etil-4-
hidroxiciclohexil)metil]amino}-3-nitrofenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(cis-4-etil-4-
hidroxiciclohexil)metil]amino}-3-nitrofenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-5-(metoximetil)-5-metilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-
20 4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-
iloxi)benzamida;
- 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)-2-(1H-pirrol[2,3-b]piridin-5-
iloxi)benzamida;
- 25 N-({3-cloro-4-[(trans-4-hidroxi-4-metilciclohexil)metoxi]fenil}sulfonil)-4-(4-{[2-(4-clorofenil)-4,4-
dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({4-({[2-
cianoetil)(ciclopropil)amino]-1-fluorociclohexil}metoxi)-3-nitrofenil}sulfonil)-2-(1H-pirrol[2,3-
b]piridin-5-iloxi)benzamida;
- 30 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({5-nitro-6-
[(tetrahidro-2H-piran-4-ilmetil)amino]piridin-3-il}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-
iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(2-
oxaespiro[3,5]non-7-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 35 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4-ciano-4-
metilciclohexil)metil]amino}-3-nitrofenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;

- pivalato de{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]}{4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]-3-nitrofenil}sulfonil}amino}metilo;
- butirato de {-[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil]}{4-[(4-fluorotetrahidro-2H-piran-4-il)metoxi]-3-nitrofenil}sulfonil}amino}metilo ;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)-N-{[3-(tetrahidro-2H-piran-4-ilmetil)-3H-[1,2,3]triazolo[4,5-b]piridin-6-il}sulfonil}benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(6-{[(trans-4-hidroxi-4-metilciclohexil)metil]amino}-5-nitropiridin-3-il)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-(4-{[4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzoil}sulfamoi]-2-nitrofenil)morfoline-4-carboxamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[4-{[4-(metoximetil)ciclohexil]metil}amino]-3-nitrofenil}sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-5-metoxi-5-metilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(trans-4-hidroxi-4-metilciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-5-metoxi-5-metilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- y sus sales terapéuticamente aceptables y sus metabolitos..

9. Un compuesto CARACTERIZADO PORQUE es 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-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida o una sal sal farmacéuticamente aceptable del mismo.

10. Un compuesto CARACTERIZADO PORQUE es Trans-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]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida o una sal sal farmacéuticamente aceptable del mismo.

11. Un compuesto CARACTERIZADO PORQUE es Cis-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]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida o una sal sal farmacéuticamente aceptable del mismo.

12. Un compuesto CARACTERIZADO PORQUE es Trans-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]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida o una sal sal farmacéuticamente aceptable del mismo.

13. Un compuesto CARACTERIZADO PORQUE es 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-pirrol[2,3-b]piridin-5-iloxi)benzamida o una sal sal farmacéuticamente aceptable del mismo.

14. Un compuesto CARACTERIZADO PORQUE es 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-pirrol[2,3-b]piridin-5-iloxi)benzamida o una sal sal farmacéuticamente aceptable del mismo.

15. Un compuesto CARACTERIZADO PORQUE es 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-pirrol[2,3-b]piridin-5-iloxi)benzamida o una sal sal farmacéuticamente aceptable del mismo.

16. Un compuesto CARACTERIZADO PORQUE es 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-pirrol[2,3-b]piridin-5-iloxi)benzamida o una sal farmacéuticamente aceptable del mismo.

17. Un compuesto CARACTERIZADO PORQUE es N-({5-bromo-6-[(1-tetrahydro-2H-piran-4-il)piperidin-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-pirrol[2,3-b]piridin-5-iloxi)benzamida; o una sal farmacéuticamente aceptable del mismo.

18. Un compuesto CARACTERIZADO PORQUE es 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3R)-1-(metilsulfonil)pirrolidin-3-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida; o una sal farmacéuticamente aceptable del mismo.

19. Un compuesto CARACTERIZADO PORQUE es 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[3-(ciclopropil(oxetan-3-il)amino]propil)amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida; o una sal farmacéuticamente aceptable del mismo.

20. Un compuesto CARACTERIZADO PORQUE es 4-(4-{[2-(4-clorofenil)-5-metoxi-5-metilciclohex-1-en-1-il]metil}piperazin-1-il)-N-({3-nitro-4-[(tetrahydro-2H-piran-4-ilmetil)amino]fenil)sulfonil)-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida; o una sal farmacéuticamente aceptable del mismo.

21. Un compuesto de la reivindicación 1 o la reivindicación 2, CARACTERIZADO PORQUE el compuesto se selecciona entre:
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(trans-4-hidroxil-4-metilciclohexil)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3R)-1-(metilsulfonil)pirrolidin-3-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[3-(ciclopropil(oxetan-3-il)amino]propil)amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida; o una sal farmacéuticamente aceptable del mismo.

22. Un compuesto de la reivindicación 1 o la reivindicación 2, CARACTERIZADO PORQUE el compuesto se selecciona entre:

N-[(5-cloro-6-[[1-(cianometil)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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[4-([3-
 [ciclopropil(oxetan-3-il)amino]propil)amino]-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-
 5 iloxi)benzamida; o una sal farmacéuticamente aceptable del mismo.

23. Un compuesto de la reivindicación 1 o la reivindicación 2, CARACTERIZADO PORQUE el compuesto se selecciona entre:
 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[4-([(trans-4-hidroxi-
 10 4-metilciclohexil)metil]amino)-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida o
 una sal farmacéuticamente aceptable del mismo.

15 24. Un compuesto CARACTERIZADO PORQUE es 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[4-([3-[ciclopropil(oxetan-3-
 il)amino]propil)amino]-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 o una sal farmacéuticamente aceptable del mismo.

20 25. Un compuesto de la reivindicación 1 o la reivindicación 2, CARACTERIZADO PORQUE el compuesto se selecciona entre:
 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[3-nitro-4-([(3R)-1-
 tetrahidro-2H-piran-4-ilpirrolidin-3-il]metil]amino)fenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-
 iloxi)benzamida; 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[4-
 25 [[(4-metilmorfolin-2-il)metil]amino]-3-nitrofenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-
 iloxi)benzamida; o una sal farmacéuticamente aceptable del mismo.

26. Un compuesto de la reivindicación 1 o la reivindicación 2, CARACTERIZADO PORQUE el compuesto se selecciona entre:
 30 4-(4-[[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-N-[[3-nitro-4-([(3S)-
 tetrahidro-2H-piran-3-ilmetil]amino)fenil]sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
 N-[(5-bromo-6-[(1-tetrahidro-2H-piran-4-il)piperidin-4-il]amino]piridin-3-il)sulfonil]-4-(4-[[2-(4-
 35 clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil]piperazin-1-il)-2-(1H-pirrol[2,3-b]piridin-5-
 iloxi)benzamida;

- N-[(4-{[(4-aminotetrahydro-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-{[3-nitro-4-{[(3R)-1-tetrahydro-2H-piran-4-ilpirrolidin-3-il]metil]amino}fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4-metilmorfolin-2-il)metil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(3R)-1-(metilsulfonil)pirrolidin-3-il]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[4-metoxitetrahydro-2H-piran-4-il]metoxi}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-[(5-cloro-6-{[1-(cianometil)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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[3-(ciclopropil(oxetan-3-il)amino]propil]amino}-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- N-[(5-cloro-6-{[(1R,2S,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-pirrol[2,3-b]piridin-5-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-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- 4-(4-{[2-(4-clorofenil)-5-metoxi-5-metilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(3-nitro-4-{[tetrahydro-2H-piran-4-ilmetil]amino}fenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida;
- o una sal farmacéuticamente aceptable del mismo.

30

27. Un compuesto CARACTERIZADO PORQUE es N-[(5-cloro-6-{[1-(cianometil)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-pirrol[2,3-b]piridin-5-iloxi)benzamida;

o una sal farmacéuticamente aceptable del mismo.

35

28. Un compuesto de la reivindicación 1 o la reivindicación 2, CARACTERIZADO PORQUE el compuesto se selecciona entre:

5 N-[(4-{[(4-aminotetrahydro-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-pirrol[2,3-b]piridin-5-iloxi)benzamida; 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4-metoxitetrahydro-2H-piran-4-il)metoxi]-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida; o una sal farmacéuticamente aceptable del mismo.

10 29. Un compuesto CARACTERIZADO PORQUE es 4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-N-[(4-{[(4-metoxitetrahydro-2H-piran-4-il)metoxi]-3-nitrofenil)sulfonil]-2-(1H-pirrol[2,3-b]piridin-5-iloxi)benzamida o una sal farmacéuticamente aceptable del mismo.

15 30. Una composición para el tratamiento de cáncer de vejiga, cáncer de cerebro, cáncer de mama, cáncer de médula ósea, cáncer de cuello uterino, leucemia linfocítica crónica, cáncer colorrectal, cáncer de esófago, cáncer hepatocelular, leucemia linfoblástica, linfoma folicular, formas malignas linfoides originadas de células T o de células B, melanoma, leucemia mielogénica, mieloma, cáncer oral, cáncer de ovario, cáncer de pulmón de células no pequeñas, leucemia linfocítica crónica, mieloma, cáncer de próstata, cáncer de pulmón de células pequeñas o cáncer de bazo, CARACTERIZADA PORQUE dicha composición comprende un excipiente y una cantidad terapéuticamente eficaz de un compuesto de la reivindicación 1 o de la reivindicación 2.

25 31. Un método de tratamiento de cáncer de vejiga, cáncer de cerebro, cáncer de mama, cáncer de médula ósea, cáncer de cuello uterino, leucemia linfocítica crónica, cáncer colorrectal, cáncer de esófago, cáncer hepatocelular, leucemia linfoblástica, linfoma folicular, formas malignas linfoides originadas de células T o de células B, melanoma, leucemia mielogénica, mieloma, cáncer oral, cáncer de ovario, cáncer de pulmón de células no pequeñas, leucemia linfocítica crónica, mieloma, cáncer de próstata, cáncer de pulmón de células pequeñas o cáncer de bazo en un paciente, CARACTERIZADO PORQUE dicho método comprende administrarle al paciente una cantidad terapéuticamente eficaz de un compuesto de la reivindicación 1 o de la reivindicación 2.

35 32. Un método de tratamiento de cáncer de vejiga, cáncer de cerebro, cáncer de mama, cáncer de médula ósea, cáncer de cuello uterino, leucemia linfocítica crónica, cáncer colorrectal, cáncer de esófago, cáncer hepatocelular, leucemia linfoblástica, linfoma folicular,

- formas malignas linfoides originadas de células T o de células B, melanoma, leucemia mielogénica, mieloma, cáncer oral, cáncer de ovario, cáncer de pulmón de células no pequeñas, leucemia linfocítica crónica, mieloma, cáncer de próstata, cáncer de pulmón de células pequeñas o cáncer de bazo en un paciente, CARACTERIZADO PORQUE dicho
- 5 método comprende administrarle al paciente una cantidad terapéuticamente eficaz del compuesto de la reivindicación 1 o de la reivindicación 2 y una cantidad terapéuticamente eficaz de un agente terapéutico adicional o más de un agente terapéutico adicional.

AGENTES INDUCTORES DE APOPTOSIS PARA EL TRATAMIENTO DE CÁNCER Y
ENFERMEDADES INMUNES Y AUTOINMUNES

RESUMEN

Compuestos que inhiben la actividad de proteínas anti-apoptóticas Bcl-2,
5 composiciones que contienen a dichos compuestos y métodos de tratamiento de
enfermedades durante cuyo transcurso hay expresión de la proteína anti-apoptótica Bcl-2.

21667

COLOMBIA

PODER**POWER OF ATTORNEY**

El (los)

I (we) the undersigned

ABBOTT LABORATORIES

ABBOTT LABORATORIES

Domiciliados en

Of

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

100 Abbott Park Road
Abbott Park
Illinois 60064
USA

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

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

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:

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:

- Obtención de patentes de invención, modelos y dibujos industriales; registro de marcas de fábrica, 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;
- Para la obtención de registros sanitarios;
- 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.

- 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;
- For the obtainment of Sanitary registrations;
- 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;

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.

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.

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

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.

Dado y firmado hoy 19 de Noviembre de 2008

Given and signed this 19 day of November, 2008

en Abbott Park, Illinois,
ESTADOS UNIDOS DE AMERICA

in Abbott Park, Illinois, USA 60064

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

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

(Se requiere legalización consular o mediante apostilla)

(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@castellanosyca.com

* Abbott at its sole discretion

Como Notario Veintiseis del Circulo de Bogotá, hago constar que esta copia coincide con original que se ha presentado Bogotá D.C., Colombia.

26 DIC 2011

GUSTAVO SAMPER RODRIGUEZ
NOTARIO VEINTISEIS

COLOMBIA

CERTIFICADO NOTARIAL (Sociedad)

Hoy 19 de 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 19 del **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



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

Como Notario Veintiseis del Circuito de
Bogotá, hago constar que este copia
coincide con original que se ha presentado.
Bogotá D.C. Colombia.

26 DIC 2011

GUSTAVO SAMPER RODRIGUEZ
NOTARIO VEINTISEIS



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

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Bogotá, hago constar que esta copia
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Bogotá D.C. Colombia.

26 DIC 2011

GUSTAVO SAMPER RODRIGUEZ
NOTARIO VEINTISEIS



-----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)

Como Notario Verificador del Circulo de Bogotá, hago constar que esta copia coincide con original que se ha presentado Bogotá D.C. - Colombia.

26 DIC 2011

GUSTAVO SAMPER RODRIGUEZ
NOTARIO VENTISEIS

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

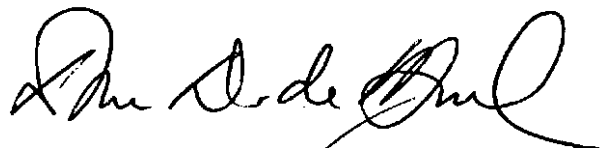
Secretario de Estado

Estado de Illinois

(Sello en oblea dorada)

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

Bogotá, D. C., Diciembre 17, 2008



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Bogotá, hago constar que esta copia
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Bogotá D.C. - Colombia.

26 DIC 2011

GUSTAVO SAMPER RODRIGUEZ
NOTARIO VEINTISEIS

NO SE ASUME
RESPONSABILIDAD
DEL TEXTO

MINISTERIO DE
RELACIONES EXTERIORES

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Don Rogue
NOTARIO VEINTISEIS
AS FUNCIONES INDICADAS

MR
CITE BZELBACUCLOR
BOGOTA D.C.

12644354

114

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Bogotá, hago constar que esta copia
coincide con original que se ha presentado
Bogotá D.C. Colombia.

26 DIC 2011

GUSTAVO SAMPER RODRIGUEZ
NOTARIO VEINTISEIS

EN BLANCO
NOTARIA VEINTISEIS

EN BLANCO
NOTARIA VEINTISEIS

EN BLANCO
NOTARIA VEINTISEIS



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) N° de solicitud:

(22) Fecha de solicitud:

(51) Clasificación Internacional:

(71) Solicitante(s) **ABBOTT LABORATORIES**

(72) Inventor(es) **MILAN BRUNCKO, HONG DING, GEORGE DOHERTY, STEVEN ELMORE, LISA HASVOLD, LAURA HEXAMER, AARON R. KUNZER, XIAOHONG SONG, ANDREW J. SOUERS, GERARD SULLIVAN, ZHI-FU TAO, GARY T. WANG, LE WANG, XILU WANG, MICHAEL WENDT, ROBERT MANTEI, TODD M. HANSEN**

(74) Apoderado: **DRA. MARGARITA CASTELLANOS ABONDANO**

(30) Prioridad	(31) No. Prioridad	(32) Fecha	(33) País
	61/181.203	26/05/2009	US

(85) Fecha inicio fase nacional:

(86) Datos relativos a la presentación de la solicitud PCT

Fecha de presentación de la solicitud: **26/05/2010**

No. de solicitud **PCT/US2010/036198**

(87) Publicación internacional

Fecha: **02/12/2010**

N° publicación: **WO 2010/138588 A2**

(54) Título: **AGENTES INDUCTORES DE APOPTOSIS PARA EL TRATAMIENTO DE CANCER Y ENFERMEDADES INMUNES Y AUTOINMUNES**



Industria y Comercio

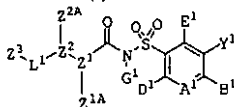
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCION PCT

(21) N° de solicitud:		(51) Int. Cl.:	
22) Fecha de solicitud:		(71) Solicitante(s) ABBOTT LABORATORIES	
(30) Prioridad	(31) N° Prioridad	32) Fecha	(33) Pais
	61/181.203	26/05/2009	US
		(72) Inventor(es) MILAN BRUNCKO HONG DING GEORGE DOHERTY Y OTROS	
		(74) Apoderado: MARGARITA CASTELLANOS ABONDANO	
(85)	Fecha limite inicio fase nacional:		
(86)	Datos relativos a la presentación de la solicitud PCT		
	Fecha de presentación de la solicitud: 26/05/2010		
	N° de solicitud PCT/US2010/036198		
(87)	Publicación internacional		
	Fecha: 02/12/2010		
	N° publicación: WO 2010/138588 A2		
(54) Titulo: AGENTES INDUCTORES DE APOPTOSIS PARA EL TRATAMIENTO DE CANCER Y ENFERMEDADES INMUNES Y AUTOINMUNES			

Reivindicación(es):

1. Un compuesto CARACTERIZADO PORQUE tiene la Fórmula (I)



(I),

o una sal terapéuticamente aceptable del mismo, en donde A¹ es N o C(A²);

A² es H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNH₂, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ o C(O)OR^{1A}; B¹ es H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNH₂, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ o C(O)OR^{1A}; D¹ es H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNH₂, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ o C(O)OR^{1A}; E¹ es H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNH₂, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ o C(O)OR^{1A}; o A² y B¹, junto con los átomos a los cuales están unidos, son benceno, naftileno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; y

NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNH₂, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ o C(O)OR^{1A}; y Y¹ es H, CN, NO₂, C(O)OH, F, Cl, Br, I, CF₃, OCF₃, CF₂CF₃, OCF₂CF₃, R¹⁷, OR¹⁷, C(O)R¹⁷, C(O)OR¹⁷, SR¹⁷, SO₂R¹⁷, NH₂, NHR¹⁷, N(R¹⁷)₂, NHC(O)R¹⁷, C(O)NH₂, C(O)NHR¹⁷, C(O)N(R¹⁷)₂, NHS(O)R¹⁷ o NHSO₂R¹⁷; o

E¹ y Y¹, junto con los átomos a los cuales están unidos, son benceno, naftileno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; y

A², B¹, y D¹ se seleccionan en forma independiente entre H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNH₂, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ o C(O)OR^{1A}; o Y¹ y B¹, junto con los átomos a los cuales están unidos, son benceno, naftileno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; y

A², D¹, y E¹ se seleccionan en forma independiente entre H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNH₂, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂, NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ o C(O)OR^{1A}; o A² y B¹, junto con los átomos a los cuales están unidos, son benceno, naftileno, heteroareno, cicloalcano, cicloalqueno, heterocicloalcano o heterocicloalqueno; y

...



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LISTA DE CHEQUEO
ADMISION A TRAMITE - NUEVAS CREACIONES

PATENTE DE INVENCION ☐ 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 INVENCION PCT ☒ MODELO DE UTILIDAD PCT ☐ Art. 33 Decisión 486/00
Circular Única

- ☒ Indicación que se solicita una PCT
☒ Datos de identificación del solicitante o de la persona que presenta la solicitud
☒ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
☐ Dibujos de ser estos pertinentes
☒ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)
- Completa ☒ 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 ☐