

Industria y Comercio

SUPERINTENDENCIA

Organización CSA Ltda

Delegatura de Propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCION

DVN
NOV

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

07-81882

21. EXPEDIENTE No.

54. TÍTULO

COMPUESTOS DE HETEROARILLO Y MIS ARILLO

SUSTITUIDOS COMO ANTAGONISTAS 5HT2A SELECTIVOS

51. CLASIFICACIÓN INTERNACIONAL

A61K31/16

74. SOLICITANTE

AVENTIS PHARMACEUTICALS INC.

DOMICILIO

NEW JERSEY, ESTADOS UNIDOS DE AMERICA

74. APODERADO

EMILIO FERRERO

C.C. 438.019 de Usaquén

22. BOGOTÁ, D. C.,

307099

(FORMA P-10)

SS.



Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-081882- -00000-0000

Fecha: 2007-08-10 16:40:51 Dep. 2020 NUECREACION
Tra. 11 PATENTE IYII Eve: 379 FASENACIONAL II
Act. 411 PRESENTACION Folios: 415

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

10/sep/2007

1

☒ Patente de Invención.
☐ Capítulo I.

☐ Patente de Modelo de Utilidad.
☒ Capítulo II.

2

SOLICITANTE
(71)

Nombre: **AVENTIS PHARMACEUTICALS INC.**
sociedad constituida y existente bajo las leyes del Estado de Delaware, Estados Unidos de América.

Dirección: 300 Somerset Corporate Blvd, Bridgewater, New Jersey 08807-2854, Estados Unidos de América

Domicilio: Bridgewater, New Jersey, Estados Unidos de América

IDENTIFICACIÓN

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

3

REPRESENTANTE O APODERADO

Nombre: **EMILIO FERRERO**
Dirección: **Carrera 4ª. No. 72-35**
Teléfono: **347 36 11**
Fax: **211 86 50**
E-mail: clientes@camyp.com.
Domicilio: **Bogotá, Colombia.**

IDENTIFICACIÓN

C.C. ☒ NIT ☐
C.E. ☐ Otro ☐
Cual _____
Número 438.019 T.P 31.929

4

INVENTOR (ES)
(72)

1. David Mark FINK
1 Kensington Court,
Lebanon,
New Jersey 08833,
Estados Unidos de América

3. Richard Simon TODD
33 Gore Road,
Burnham Slough SL1 8AB UK,
Reino Unido

5. Hazel HUNT
8/9 Spire Green Centre,
Harlow Essex CM19 5TR,
Reino Unido

2. Helen Katherine SMITH
8/9 Spire Green Centre,
Harlow Essex CB19 5TR,
Reino Unido

4. Paul Robert EASTWOOD
Calle Alcalde De Mostoles 7, 41,
80825 Barcelona,
España

5

PCT (86)
Solicitud Internacional No. PCT/US2006/004879 Fecha: 10 de febrero de 2006
Publicación Internacional No. WO 2006/086705 A1 Fecha: 17 de agosto de 2006

6

Título (54)
COMPUESTOS DE HETEROARILLO Y BIS ARILLO SUSTITUIDOS COMO ANTAGONISTAS 5HT_{2A} SELECTIVOS

7

Clasificación Internacional (51) C07D 209/008

2

8	Prioridad	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	SI ☒ NO ☐	<u>US</u>	<u>10 de febrero de 2005</u>	<u>60/651,911</u>

9

Comprobante de pago No.: 07-61,641 **Fecha:** 31 de julio de 2007

10

Anexos:

☒

Comprobante de pago de la tasa de presentación de la solicitud por \$ 482.000.oo.

☐

Comprobante de pago por reivindicación de prioridad.

☒

Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.

☒

Poderes, si fuere el caso.

☒

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 efectuado por la IPEA.

☐

Traducción del examen preliminar 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

☐

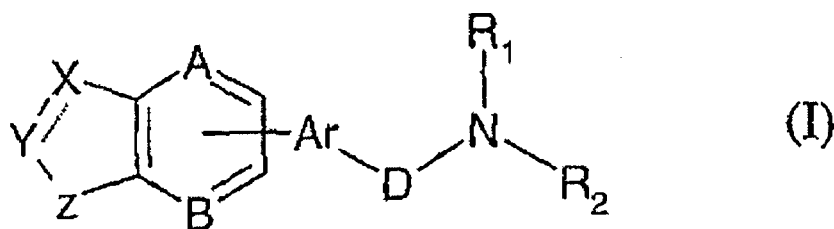
De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.

☒

Otros: VER HOJA DE DOCUMENTOS ANEXOS

11

FIGURA CARACTERÍSTICA



12

Solicito la concesión de la patente,

NOMBRE:

EMILIO FERRERO

FIRMA :

C.C. 438.019 de Usaquén T.P. 31.929

FBH

DOCUMENTOS ANEXOS

1. ☒ Publicación Internacional WO 2006/086705 A1

Descripción:

Páginas 122 en el idioma original

Páginas 164 en español

Reivindicaciones: Número (s) 31

Figuras: Número (s)

2. ☒ **Forma PCT/ISA/210.** Informe de Búsqueda Internacional.

3. ☒ Extracto de publicación.

**SE REALIZARON MODIFICACIONES EN LA FASE
INTERNACIONAL**

5

Xo

APOSTILLE

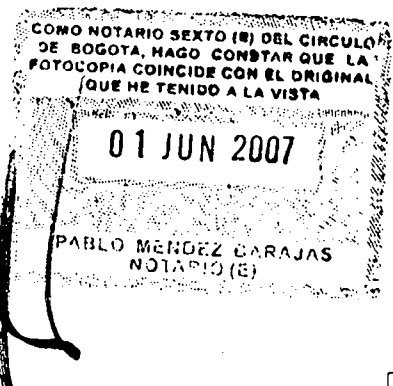
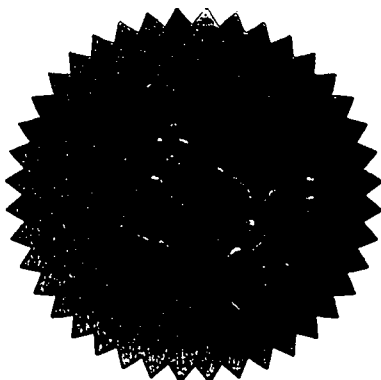
(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
TINA M WISBESKI
3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY
4. BEARS THE SEAL/STAMP OF:
TINA M WISBESKI, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 5TH DAY OF MARCH 2007
7. BY: Bradley Abelow, NEW JERSEY TREASURER
8. NO. A284990
9. SEAL/STAMP:
10. SIGNATURE

Bradley Abelow



Representación y Poder con autenticación notarial y Apostille para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales, enseñas, nombres de dominio, lemas comerciales, licencias.

Representation and Power-of-Attorney with notarial authentication and Apostille for patents, utility models, industrial designs, trademarks, commercial names, trade emblems, domain names, slogans, licenses.

REPRESENTACION Y PODER

REPRESENTATION AND POWER-OF-ATTORNEY

Yo (nosotros), abajo firmado (s)/I (we), the undersigned

AVENTIS PHARMACEUTICALS INC

domiciliado (s) en/of 300 Somerset Corporate Boulevard

Bridgewater, New Jersey 08807

United States of America

el presente nombramos a EMILIO FERRERO, tpa. 31929; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y DANIEL PEÑA, tpa. 65.620, domiciliados en la Carrera 4a N° 72-35, Bogotá, Colombia, en obediencia a lo dispuesto en el parágrafo 1o del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si ratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primero o segundo suplentes, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, nombres de dominio, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protección del

in due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint EMILIO FERRERO, tpa. 31929; LUZ CLEMENCIA DE PAEZ, tpa. 23555 and DANIEL PEÑA, tpa. 65620, domiciled at Carrera 4a N° 72-35, Bogotá, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second alternate depending on case, and the mere fact or its exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time. In addition, we grant a power of attorney to the above-named attorneys-at-law so that they may obtain the protection of my (our) industrial property and against unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative-contencioso and judicial, as well as before Arbitration Courts in all matters concerning the following: a) Obtainment of patents, utility models and industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, domain names, vegetal varieties and denominations of origin; its renewal, assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b) Actions of unfair competition,

consumidor, oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la protección de secretos industriales, y en general los juicios civiles, penales, administrativos o contencioso-administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

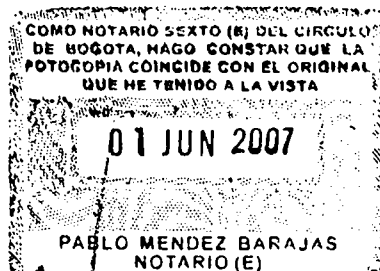
protection to the consumer, oppositions or observations, administrative or Court cancellation, nullity, infringement, granting of licenses, the action for writ mandamus, the protection of trade secrets, and in general the civil, penal, and administrative suits relating to those rights; actions and suits instituted by me (us) or against me (us). And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

Dado y firmado hoy/Given and signed this 27 Day of February 2007
en/in Bridgewater, New Jersey United States of America

por/by Andrea Q. Ryan, Assistant Secretary

Firma/Signature

Andrea Q. Ryan



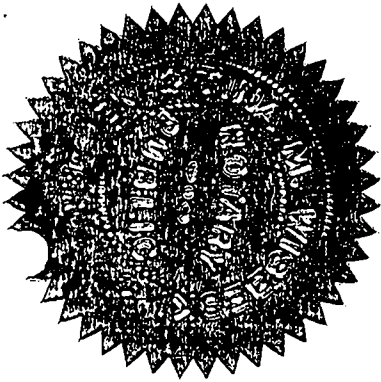
NOTARIAL CERTIFICATE
(Corporation)

UNITED STATES OF AMERICA)
STATE OF NEW JERSEY) ss.
COUNTY OF SOMERSET)

On this 27th day of February, 2007, personally appeared before me, **Andrea Q. Ryan**, Assistant Secretary, known or identified to me to be the individual described in and who executed the foregoing document, **Power of Attorney**, and acknowledged the same as a free act and deed for uses and purposes therein expressed by authority of the said Corporation incorporated under the laws of the State of Delaware, United States of America.

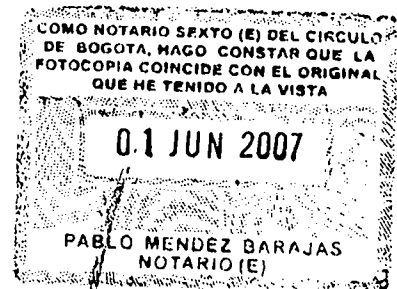
I further certify that said authority, dated **December 19, 2003**, is based on a **Resolution of the Board of Directors of said Corporation**, which I have seen, appointing the said individual Assistant Secretary with full power to sign the foregoing document on behalf of the said Corporation and that the purposes for which said document is granted are within the scope of the objects or activities of said Corporation,

SEAL



Tina M. Wisbeski
Notary Public

Tina M. Wisbeski
Notary Public, State of New Jersey
My Commission Expires August 5, 2009



9

1

TRADUCCIÓN OFICIAL 115/2007 DE UN DOCUMENTO ESCRITO EN INGLÉS Y EN ESPAÑOL DE ACUERDO CON EL CUAL **AVENTIS PHARMACEUTICALS INC**, EMPRESA DOMICILIADA EN 300 SOMERSET CORPORATE BOULEVARD, BRIDGEWATER, NEW JERSEY 08807, ESTADOS UNIDOS DE AMÉRICA OTORGA PODER A EMILIO FERRERO, TPA 31929; LUZ CLEMENCIA DE PAEZ, TPA 23555 Y A DANIEL PEÑA, TPA 65620.

EXPEDIDO Y FIRMADO HOY 27 DE FEBRERO DE 2007 EN BRIDGEWATER, NEW JERSEY, ESTADOS UNIDOS DE AMÉRICA, POR ANDREA Q. RYAN, APODERADO

FIRMADO: (ILEGIBLE)

CERTIFICACIÓN NOTARIAL
(SOCIEDAD)

ESTADOS UNIDOS DE AMÉRICA

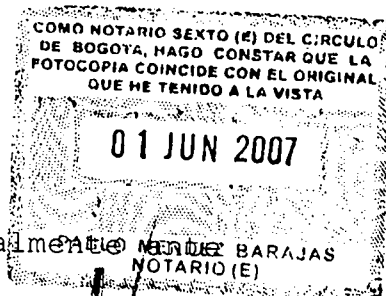
ESTADO DE NUEVA JERSEY

CONDADO DE SOMERSET

DECLARACIÓN JURADA

Hoy 27 de febrero de 2007, compareció personalmente ante mí, ANDREA Q. RYAN, apoderado, conocido o quien se identificó ante mí como la persona descrita y quien firmó el documento precedente, poder, y reconoció el mismo como un acto de su libre albedrío para los usos y objetivos allí expresados, mediante autorización de dicha sociedad, constituida de acuerdo con las leyes del estado de Delaware, Estados Unidos de América.

Además certifico que dicha autorización, de fecha 19 de diciembre de 2003, se basa en la resolución de la junta directiva de dicha resolución, que he visto, y designó a dicho secretario asistente con plenos poderes para firmar el documento precedente a nombre de dicha empresa y que los objetivos para los cuales se otorga dicho documento



están dentro del alcance del objeto social o actividades de dicha sociedad.

FIRMADO: TINA M. WISBESKI.

SELLO: NOTARIO PÚBLICO, ESTADO DE NUEVA JERSEY, MI CARGO VENCE EL DE AGOSTO DE 2009.

APOSTILLA

(CONVENCIÓN DE LA HAYA DEL 5 DE OCTUBRE DE 1961)

1. PAIS: ESTADOS UNIDOS DE AMÉRICA

Este documento público

2. ha sido firmado por TINA M WISBESKI

3. quien actúa en su calidad de NOTARIO PÚBLICO DE NUEVA JERSEY

4. y lleva el sello/estampilla de TINA M. WISBESKI, NOTARIO

CERTIFICADO

5. en Trenton, Nueva Jersey de 2007

6. el 5 de marzo

7. por: Bradley Abelow, tesorero de Nueva Jersey

8. Certificado número A284990

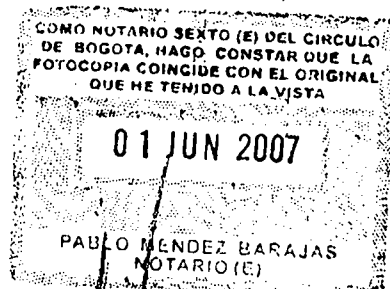
9. Sello: (ILEGIBLE)

10. Firma: BRADLEY ABELAI

COLO- 15896-841-006-4

WPCL002G ID 8837

Bogotá, 16 de mayo de 2007.



Edgar Calado
 Edgardo Calado Rogosa
 'TRADUCTOR OFICIAL'
 INGLES - ESPAÑOL - INGLES
 Res. 541 Febrero de 1976

MINISTERIO DE
RELACIONES
EXTERIORES

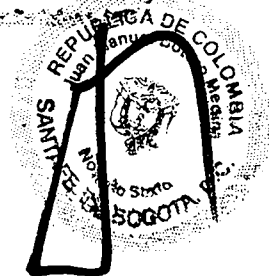
NO ASUME
RESPONSABILIDAD
DEL TEXTO

852919
eduardo cordero
CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPENA
LAS FUNCIONES INDICADAS

2007 MAY 17 P 12:15
Bam
JEFE DE LEGALIZACIONES
, BOGOTA D.C.

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FIRMA
Eduardo Cordero
COINCIDE (N) CON LA FIRMA REGISTRADA POR
EL (ELLOS) EN ESTA NOTARIA
SANTAFE DE BOGOTA, 17 MAY 2007





COMO NOTARIO SEXTO (E) DEL CIRCULO
DE BOGOTA, HAGO CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA

01 JUN 2007

PABLO MENDEZ SARAJAS
NOTARIO (E)

P

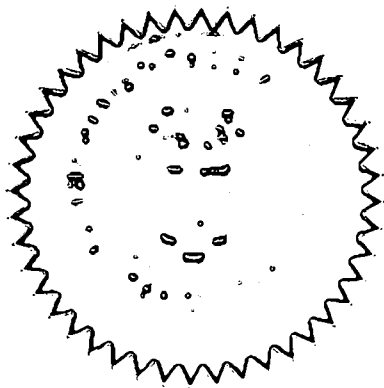
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
TINA M WISBESKI
3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY
4. BEARS THE SEAL/STAMP OF:
TINA M WISBESKI, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 27TH DAY OF JUNE 2007
7. BY: Bradley Abelow, NEW JERSEY TREASURER
8. NO. A295657
9. SEAL/STAMP:
10. SIGNATURE



Bradley Abelow

12

NOTARIAL TRUE COPY

UNITED STATES OF AMERICA)
STATE OF NEW JERSEY) ss.
COUNTY OF SOMERSET)

TO ALL TO WHOM THESE PRESENTS SHALL COME,

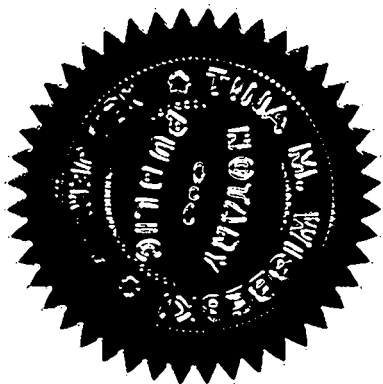
I Do Hereby Certify under the Oath of my Office and Seal that the annexed document(s) are TRUE COPIES of the original document(s) which I have compared.

IN TESTIMONY WHEREOF, I have hereunto set my hand and affixed the Seal under the Oath of my Office

At Bridgewater, New Jersey, United States of America

this 21st day of June, 2007.

SEAL:



Notary Public
Tina M. Wisbeski
Notary Public, State of New Jersey
My Commission Expires August 5, 2009

ASSIGNMENT AND AGREEMENT

For value received and intending to be legally bound, I/we, the undersigned joint inventor(s) (Assignor(s)), sell, assign and transfer to **Aventis Pharmaceuticals Inc.** (Assignee), 300 Somerset Corporate Boulevard, Bridgewater, New Jersey 08807-2854, United States of America, and its successors, assigns and legal representatives, the entire right, title and interest in and to my/our invention and any improvements thereon for all countries of the world, relating in and to the application for United States Letters Patent therefor, assigned Attorney Docket No. USAV2001/0107 US PSP and (if filed prior to the execution hereof) filed on February 10, 2005, as Serial No. 60/651,911, entitled

SUBSTITUTED BIS ARYL AND HETEROARYL COMPOUNDS AS
SELECTIVE 5HT_{2A} ANTAGONISTS

and all the rights and privileges, including any and all benefits under the International Convention for the Protection of Industrial Property, including the right to claim priority based on said United States application, and under any and all Letters Patent which may be granted therefor, and all right, title and interest in and to every patent application filed or to be filed on said invention in any other country or patent organization, including continuations, divisions, renewals, revivals, and any substitute applications of said United States application, and any and all patents which may issue thereon, and any reissues, pipelines and extensions, and governmental exclusivity rights of the same.

I/we authorize and request competent authorities to grant and issue any and all patents on said invention to said assignee or its successor, assigns and legal representatives, or to such nominees as said assignee may designate.

I/we agree that, when requested, I/we will, without charge to said assignee but at its expense, sign all papers, take all rightful oaths, and do all acts which may be necessary, desirable or convenient for securing and maintaining patents for said invention in any and all countries and for vesting title thereto in said assignee, its successors, assigns, legal representatives or nominees.

I/we covenant with said assignee, its successors, assigns and legal representatives, that the rights and property herein conveyed are free and clear of any encumbrance, and that I/we have full right to convey the same as herein expressed.

Signed at Bridgewater, NJ USA on this 11th day of April, 2005.
(City, State and Nation)

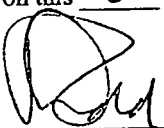
Signature: _____

Inventor's Name: **David Marc FINK**Residential Address: **1 Kensington Ct.
Lebanon, NJ 08833**

Signed at _____ on this _____ day of _____, 2005.
(City, State and Nation)

Signature: _____
Inventor's Name: **Helen Katherine SMITH**
Residential Address: **8/9 Spire Green Centre**
CM19 5TR Harlow (United Kingdom)

Signed at READING, BERKSHIRE, UK on this 25th day of August, 2005.
(City, State and Nation)

Signature:  _____
Inventor's Name: **Richard Simon TODD**
Residential Address: **33 Gore Road**
Burnham, Slough, SL1 8AB UK

Signed at _____ on this _____ day of _____, 2005.
(City, State and Nation)

Signature: _____
Inventor's Name: **Paul Robert EASTWOOD**
Residential Address: **Calle Alcade de Mostoles 7, 4 1**
08025 Barcelona (Spain)

Signed at _____ on this _____ day of _____, 2005.
(City, State and Nation)

Signature: _____
Inventor's Name: **Hazel Dyke**
Residential Address: **8/9 Spire Green Centre**
CM19 5TR Harlow (United Kingdom)

Signed at LA PAZ, BOLIVIA on this 13TH day of SEPTEMBER, 2005.
(City, State and Nation)

Signature: 
Inventor's Name: **Helen Katherine SMITH**
Residential Address: **8/9 Spire Green Centre**
CM19 5TR Harlow (United Kingdom)

Signed at _____ on this _____ day of _____, 2005.
(City, State and Nation)

Signature: _____
Inventor's Name: **Richard Simon TODD**
Residential Address: **33 Gore Road**
Burnham, Slough, SL1 8AB UK

Signed at _____ on this _____ day of _____, 2005.
(City, State and Nation)

Signature: _____
Inventor's Name: **Paul Robert EASTWOOD**
Residential Address: **Calle Alcade de Mostoles 7, 4 1**
08025 Barcelona (Spain)

Signed at _____ on this _____ day of _____, 2005.
(City, State and Nation)

Signature: _____
Inventor's Name: **Hazel Hunt**
Residential Address: **8/9 Spire Green Centre**
CM19 5TR Harlow (United Kingdom)

Signed at _____ on this _____ day of _____, 2005.
(City, State and Nation)

Signature: _____
Inventor's Name: **Helen Katherine SMITH**
Residential Address: **8/9 Spire Green Centre**
CM19 5TR Harlow (United Kingdom)

Signed at _____ on this _____ day of _____, 2005.
(City, State and Nation)

Signature: _____
Inventor's Name: **Richard Simon TODD**
Residential Address: **8/9 Spire Green Centre**
CM19 5TR Harlow (United Kingdom)

Signed at Barcelona, Spain on this 7 day of April, 2005.
(City, State and Nation)

Signature: Paul Robert Eastwood
Inventor's Name: **Paul Robert EASTWOOD**
Residential Address: **Calle Alcade de Mostoles 7, 4 1**
08025 Barcelona (Spain)

Signed at _____ on this _____ day of _____, 2005.
(City, State and Nation)

Signature: _____
Inventor's Name: **Hazel HUNT**
Residential Address: **8/9 Spire Green Centre**
CM19 5TR Harlow (United Kingdom)

17

USAV2001/0107 US PSP

Signed at _____ on this _____ day of _____, 2005.
(City, State and Nation)

Signature: _____
Inventor's Name: **Helen Katherine SMITH**
Residential Address: **8/9 Spire Green Centre**
CM19 5TR Harlow (United Kingdom)

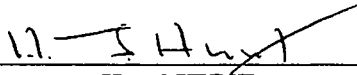
Signed at _____ on this _____ day of _____, 2005.
(City, State and Nation)

Signature: _____
Inventor's Name: **Richard Simon TODD**
Residential Address: **8/9 Spire Green Centre**
CM19 5TR Harlow (United Kingdom)

Signed at _____ on this _____ day of _____, 2005.
(City, State and Nation)

Signature: _____
Inventor's Name: **Paul Robert EASTWOOD**
Residential Address: **Calle Alcade de Mostoles 7, 4 1**
08025 Barcelona (Spain)

Signed at Harlow, UK on this 12th day of April, 2005.
(City, State and Nation)

Signature: 
Inventor's Name: **Hazel HUNT**
Residential Address: **8/9 Spire Green Centre**
CM19 5TR Harlow (United Kingdom)



UNITED STATES PATENT AND TRADEMARK OFFICE

UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

NOVEMBER 08, 2005

PTAS

500059244A

BALARAM GUPTA
ROUTE #202-206/P.O. BOX 6800
MAIL CODE: D303-A
BRIDGEWATER, NJ 08807

500059244A

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 571-272-3350. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, MAIL STOP: ASSIGNMENT SERVICES DIVISION, P.O. BOX 1450, ALEXANDRIA, VA 22313.

RECORDATION DATE: 11/08/2005

REEL/FRAME: 016747/0272
NUMBER OF PAGES: 10

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).
DOCKET NUMBER: USAV2001/0107USPSP

ASSIGNOR:

FINK, DAVID MARC

DOC DATE: 04/11/2005

ASSIGNOR:

TODD, RICHARD SIMON

DOC DATE: 08/25/2005

ASSIGNOR:

SMITH, HELEN KATHERINE

DOC DATE: 09/13/2005

ASSIGNOR:

EASTWOOD, PAUL ROBERT

DOC DATE: 04/07/2005

ASSIGNOR:

FUNT, HAZEL

DOC DATE: 04/12/2005

19

016747/0272 PAGE 2

ASSIGNEE:

AVENTIS PHARMACEUTICALS INC.
300 SOMERSET CORPORATE BLVD.
BRIDGEWATER, NEW JERSEY 08807-2854

SERIAL NUMBER: 60651911

FILING DATE: 02/10/2005

PATENT NUMBER:

ISSUE DATE:

TITLE: SUBSTITUTED BIS ARYL AND HETEROARYL COMPOUNDS AS SELECTIVE 5HT2A
ANTAGONISTS

ANTHONY ROYALL, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

PATENT ASSIGNMENT

Electronic Version v1.1
Stylesheet Version v1.1

11/08/2005
500059244

SUBMISSION TYPE:

NEW ASSIGNMENT

NATURE OF CONVEYANCE:

ASSIGNMENT

CONVEYING PARTY DATA

Name	Execution Date
David Marc Fink	04/11/2005
Richard Simon Todd	08/25/2005
Helen Katherine Smith	09/13/2005
Paul Robert Eastwood	04/07/2005
Hazel Hunt	04/12/2005

RECEIVING PARTY DATA

Name:	Aventis Pharmaceuticals Inc.
Street/Address:	300 Somerset Corporate Blvd.
City:	Bridgewater
State/Country:	NEW JERSEY
Postal Code:	07007-2854

PROPERTY NUMBERS Total: 1

Property Type	Number
Application Number:	50651911

CORRESPONDENCE DATA

Fax Number: (908)231-2626
Correspondence will be sent via US Mail when the fax attempt is unsuccessful.
Phone: 908-231-3364
Email: robin.inman@aventis.com
Correspondent Name: Balaram Gupta
Address Line 1: Route #202-206/P.O. Box 6800
Address Line 2: Mail Code: D303-A
Address Line 4: Bridgewater, NEW JERSEY 08807

ATTORNEY DOCKET NUMBER:

USAV2001/0107USPSP

NAME OF SUBMITTER:

Robin J. Inman

CH \$40.00 50651911

21

Total Attachments: 8

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source=USAV2001-0107 US PSP ASSIGNMENT#page8.tif

TRADUCCIÓN OFICIAL No. 08.08/07a realizada por Diego Vargas, Traductor Oficial, Resolución No. 0001 de 1999 del Ministerio de Justicia, registrado ante el Ministerio de Relaciones Exteriores de Colombia.

USAV2001/0107 USP

CESIÓN Y ACUERDO

Por valor recibido y con la intención de quedar legalmente obligados, yo/nosotros, el(los) suscrito(s) inventor(es) (Cedente(s)), vendemos, cedemos y transferimos a **Aventis Pharmaceuticals Inc.** (Cesionario), 300 Somerset Corporate Boulevard, Bridgewater, Nueva Jersey 08807-2854, Estados Unidos de América y a sus sucesores, cesionarios y representantes legales, todo el derecho, título e interés en y a mí/nuestra invención y a cualquier perfeccionamiento para la misma en todos los países del mundo, con relación a y en la solicitud de patente de invención de los Estados Unidos para la misma, asignada la Referencia de Asunto No. USAV2001/0107 US PSP y (en caso de haber sido presentada con anterioridad a la suscripción del presente) presentada el 10 de febrero de 2005, con el Expediente No. de Serie 60/651,911, titulada:

y todos los derechos y privilegios, incluyendo cualquier y todos los beneficios de conformidad con la Convención Internacional para la Protección de Propiedad Industrial, incluyendo el derecho de reivindicar prioridad con fundamento en la mencionada solicitud de patente de los Estados Unidos y en cualquier otra y todas las patentes de invención que le puedan ser otorgadas a la misma y todo el derecho, título e interés en y cada solicitud de patente presentada o que se llegue a presentar para dicha invención en

cualquier otro país u organización de patentes, incluyendo continuaciones, divisiones, renovaciones y reestablecimientos así como cualquier solicitud sustituta de dicha solicitud de los Estados Unidos, y cualquier y todas las patentes de invención que se lleguen a expedir para la misma, y cualquier nuevo examen, trámite y extensión y derechos gubernamentales exclusivos de la misma.

Yo/nosotros autorizamos y le solicitamos a las autoridades competentes otorgar y expedir cualquier y todas las patentes para dicha invención a nombre del mencionado cesionario o su sucesor, cesionarios y representantes legales o al de aquellos nominatarios que dicho cesionario designe.

Yo/nosotros nos comprometemos a que, por petición, yo/nosotros, sin cobro a dicho cesionario pero por su cuenta, firmaremos todos los documentos, tomaremos todo los juramentos legales y realizaremos todas los actos que sean necesarios, apropiados o convenientes para obtener y mantener las patentes para dicha invención en cualquier y todos los países y para invertir el título de las mismas en dicho cesionario, sus sucesores, cesionarios, representantes legales o nominatarios.

Yo/nosotros garantizamos a dicho cesionario y a sus sucesores, cesionarios y representantes legales que los derechos y la propiedad traspasada por el presente está libre y exenta de todo gravamen y que yo/nosotros tenemos el pleno derecho de enajenar la misma de la forma expresada en el presente.

Firmado en Bridgewater, NJ, EE.UU. hoy 11 de abril de 2005.
(Ciudad, Estado y Nación)

Firma: Firma Ilegible
Nombre del inventor: David Marc FINK
Dirección residencial: 1 Kensington Ct.
Líbano, NJ 08833

24

Firmado en Reading, Berkshire, Reino Unido hoy 25 de agosto de 2005.
(Ciudad, Estado y Nación)

Firma: Firma Ilegible
Nombre del inventor: Richard Simon TODD
Dirección residencial: 3 Gore Road
Burnham, Slough SL 1 8AB UK

Firmado en La Paz, Bolivia hoy 13 de septiembre de 2005.
(Ciudad, Estado y Nación)

Firma: Firma Ilegible
Nombre del inventor: Helen Katherine SMITH
Dirección residencial: 8/9 Spire Green Centre
CM19 5TR Harlow (Reino Unido)

Firmado en Barcelona, España hoy 7 de abril de 2005.
(Ciudad, Estado y Nación)

Firma: Firma Ilegible
Nombre del inventor: Paul Robert EASTWOOD
Dirección residencial: Calle Alcade de Mostoles 7, 4 1
08025 Barcelona (España)

Firmado en Harlow, Reino Unido hoy 12 de abril de 2005.
(Ciudad, Estado y Nación)

Firma: Firma Ilegible
Nombre del inventor: Hazel HUNT
Dirección residencial: 8/9 Spire Green Centre
CM19 5TR Harlow (Reino Unido)

ESCUDO DE ARMAS DE LA OFICINA DE PATENTES

OFICINA DE MARCAS Y PATENTES DE LOS ESTADOS UNIDOS

SUBSECRETARIO DE COMERCIO PARA LA PROPIEDAD INTELECTUAL Y
DIRECTOR DE LA OFICINA DE MARCAS Y PATENTES DE LOS ESTADOS UNIDOS

08 DE NOVIEMBRE DE 2005

CÓDIGO DE BARRAS

PTAS

500059244A

BALARAM GUPTA
ROUTE #202-206/P.O.BOX 6800
MAIL CODE: D303-A
BRIDGEWATER, NJ 08807

OFICINA DE MARCAS Y PATENTES DE LOS ESTADOS UNIDOS
NOTIFICACIÓN DE REGISTRO DE DOCUMENTO DE CESIÓN

EL DOCUMENTO ADJUNTO HA SIDO REGISTRADO POR LA DIVISIÓN DE CESIONES
DE LA OFICINA DE MARCAS Y PATENTES DE LOS ESTADOS UNIDOS. UNA COPIA

25
COMPLETA EN MICROFILME ESTÁ DISPONIBLE EN LA SALA DE BÚSQUEDAS CON EL ROLLO Y CUADRO QUE SE MENCIONA A CONTINUACIÓN.

POR FAVOR REVISE TODA LA INFORMACIÓN QUE CONTIENE ESTA NOTIFICACIÓN. LA INFORMACIÓN QUE CONTIENEN ESTA NOTIFICACIÓN DE INSCRIPCIÓN REFLEJA LOS DATOS EXISTENTES EN EL SISTEMA DE CESIÓN DE MARCAS Y PATENTES. EN CASO DE QUE USTED ENCUENTRE ERRORES O TENGA PREGUNTAS EN RELACIÓN CON ESTA NOTIFICACIÓN, PUEDE CONTACTAR AL FUNCIONARIO CUYO NOMBRE APARECE EN ESTA NOTIFICACIÓN AL 571-272-3350. POR FAVOR ENVÍE SU SOLICITUD DE CORRECCIÓN AL: U.S. PATENT AND TRADEMARK OFFICE, MAIL STOP: ASSIGNMENT SERVICES DIVISION, P.O. BOX 1450, ALEXANDRIA, VA 2313.

FECHA DE REGISTRO: 11/08/2005

ROLLO/CUADRO: 016747/0272

NÚMERO DE PÁGINAS: 10

ABSTRACTO: CESIÓN DEL INTERÉS DEL CEDENTE (VER DOCUMENTO PARA INFORMACIÓN).

NUMERO ASUNTO: USAV2007/0107USPSP

CEDENTE:

FINK, DAVID MARC

FECHA DEL DOCUMENTO: 04/11/2005

CEDENTE:

TODD, RICHARD SIMON

FECHA DEL DOCUMENTO: 08/25/2005

CEDENTE:

SMITH, HELEN KATHERINE

FECHA DEL DOCUMENTO: 09/13/2005

CEDENTE:

EASTWOOD, PAUL ROBERT

FECHA DEL DOCUMENTO: 04/07/2005

CEDENTE:

HUNT, HAZEL

FECHA DEL DOCUMENTO: 04/12/2005

CESIONARIO:

AVENTIS PHARMACEUTICALS INC.

300 SOMERSET CORPORATE BLVD.

BRIDGEWATER, NUEVA JERSEY 08807-2854

NÚMERO DE SERIE: 60651911

FECHA DE PRESENTACIÓN: 02/10/2005

NÚMERO DE PATENTE:

FECHA DE EXPEDICIÓN:

26

TÍTULO: COMPUESTOS SUSTITUIDOS DE BIS ARILO Y HETEROARILO COMO ANTAGONISTAS SELECTIVOS DE 5HT_{2A}

ANTIONE ROYALL, EXAMINADOR
 DIVISIÓN DE CESIONES
 OFICINA DE REGISTROS PÚBLICOS

CESIÓN DE PATENTE

Versión Electrónica v1.1 11/08/2005
 Versión Formulario v1.1 500059244

CLASE DE PRESENTACIÓN:	NUEVA CESIÓN
CLASE DE TRANSFERENCIA:	CESIÓN

INFORMACIÓN DE LA PARTE TRANSFERENTE:

Nombre	Fecha de Firma
David Marc Fink	04/11/2005
Richard Simmon Todd	08/25/2005
Helen Katherine Smith	09/13/2005
Paul Robert Eastwood	04/07/2005
Hazel Hunt	04/12/2005

INFORMACIÓN DE LA PARTE RECEPTORA

Nombre:	Aventis Pharmaceuticals Inc.
Dirección:	300 Sommerset Corporate Blvd.
Ciudad:	Bridgewater
Estado/País:	NUEVA YORK
Código Postal:	05807-2854

NÚMERO DE BIENES Total: 1

Clase de Propiedad	Número
Solicitud Número:	60651911

INFORMACIÓN DE CORRESPONDENCIA

Número de Fax: (908)231-2626

Correspondencia será enviada por correo aéreo de los Estados Unidos si la transmisión por fax es infructuosa.

Teléfono: 908-231-3364
 Dirección electrónica: robin.inman@aventis.com
 Nombre del Corresponsal: Balaram Gupta
 Línea de Dirección 1: Route #202-206/P.O.Box 6800
 Línea de Dirección 2: Mail Code: D303-A
 Línea de Dirección 4: Bridgewater, NUEVA JERSEY, 08807

25

NÚMERO ASUNTO APODERADO:	USAV2001/0107USPSP
NOMBRE DEL REMITENTE:	Robin J. Inman
Total Anexos: 8 fuente=USAV2001-0107USPSP ASSIGNMENT#page1.tif fuente=USAV2001-0107USPSP ASSIGNMENT#page2.tif fuente=USAV2001-0107USPSP ASSIGNMENT#page3.tif fuente=USAV2001-0107USPSP ASSIGNMENT#page4.tif fuente=USAV2001-0107USPSP ASSIGNMENT#page5.tif fuente=USAV2001-0107USPSP ASSIGNMENT#page6.tif fuente=USAV2001-0107USPSP ASSIGNMENT#page7.tif fuente=USAV2001-0107USPSP ASSIGNMENT#page8.tif	

COPIA FIEL NOTARIZADA

ESTADOS UNIDOS DE AMÉRICA)
ESTADO DE NUEVA JERSEY) Declaración Juramentada
CONDADO DE SOMERSET)

A TODOS AQUELLOS A QUIENES LOS PRESENTES LLEGASEN:

Por el presente certifico de conformidad con el juramento de posesión de mí cargo y sello que el anexo documento(s) son COPIAS FIELES del original del documento(s) con el cual las he comparado.

EN TESTIMONIO DE LO CUAL, al presente firmo y fijo el Sello bajo de conformidad con el juramento de posesión de mi cargo

En Bridgewater, Nueva Jersey, Estados Unidos de América

Hoy 21 de Junio de 2007.

SELLO

Firma Ilegible
Notario Público
Tina M. Wisbeski
Notario Público, Estado de Nueva Jersey
Mí Comisión Vence 5 de Agosto de 2009

Nuestra Referencia: USAV2001/0107 CO PCT

APOSTILLA

(CONVENTION DE LA HAYE DU 5 OCTUBRE 1961)

1. PAÍS: ESTADOS UNIDOS DE AMÉRICA
2. ESTE DOCUMENTO PÚBLICO HA SIDO FIRMADO POR:
TINA M. WISBESKI
3. ACTUANDO EN CALIDAD DE:
NOTARIO PÚBLICO DE NUEVA JERSEY
4. LLEVA EL SELLO/ESTAMPILLA DEL:
TINA M. WISBESKI, NOTARIO

CERTIFICADO

5. En TRENTON, NUEVA JERSEY
6. EL 27 DE JUNIO DE 2007
7. POR: Bradley Abelow, TESORERO DE NUEVA JERSEY
8. NO. **A295657**
9. SELLO/ESTAMPILLA
10. FIRMA



Firma ilegible

Es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

DVZ/ID-9074/WPCL002G/COLO 15896-841-018-9

Diego F. Vargas
DIEGO F. VARGAS Z.
TRADUCTOR E INTERPRETE OFICIAL
ESPAÑOL - INGLÉS - INGLÉS - ESPAÑOL
RES. 0001 DE ENERO 4 DE 1999
MINISTERIO DE JUSTICIA

COINCIDE CON LA FIRMA REGISTRADA POR EL (ELLOS) EN ESTA NOTARIA

MINISTERIO DE
RELACIONES EXTERIORES

640623

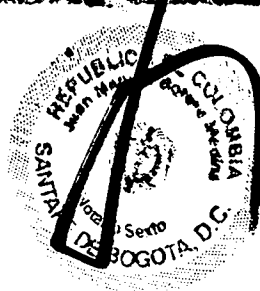
2007 AGO -8 P 12:00

Bam

Diego Vargas
CUBA
COLOMBIA
BOGOTA D.C.

JEFE DE LEGALIZACION
BOGOTA D.C.

COMO NOTARIO SEXTO DEL CIRCUITO DE SANTAFE
BOGOTA, HAGO CONSTAR QUE LA(S) Diego Vargas
Diego Vargas
COINCIDE CON LA FIRMA REGISTRADA POR
EL (ELLOS) EN ESTA NOTARIA
SANTAFE DE BOGOTA. 08 AGO 2007



VIII-3-1	Declaration: Entitlement to claim priority Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)) Name	in relation to this international application AVENTIS PHARMACEUTICALS INC. is entitled to claim priority of earlier application No. 60/651,911 by virtue of the following:
VIII-3-1(i v)		an assignment from FINK, David Mark to AVENTIS PHARMACEUTICALS INC., dated 11 April 2005 (11.04.2005)
VIII-3-1(i v)		an assignment from SMITH, Helen Katherine to AVENTIS PHARMACEUTICALS INC., dated 13 September 2005 (13.09.2005)
VIII-3-1(i v)		an assignment from TODD, Richard Simon to AVENTIS PHARMACEUTICALS INC., dated 25 August 2005 (25.08.2005)
VIII-3-1(i v)		an assignment from EASTWOOD, Paul Robert to AVENTIS PHARMACEUTICALS INC., dated 07 April 2005 (07.04.2005)
VIII-3-1(i v)		an assignment from HUNT, Hazel to AVENTIS PHARMACEUTICALS INC., dated 12 April 2005 (12.04.2005)
VIII-3-1(i x)	This declaration is made for the purposes of:	all designations

VIII-4-1	Declaration: Inventorship (only for the purposes of the designation of the United States of America) Declaration of Inventorship (Rules 4.17(iv) and 51bis.1(a)(iv)) for the purposes of the designation of the United States of America:	I hereby declare that I believe I am the original, first and sole (if only one inventor is listed below) or joint (if more than one inventor is listed below) inventor of the subject matter which is claimed and for which a patent is sought. This declaration is directed to the international application of which it forms a part (if filing declaration with application). This declaration is directed to international application No. PCT/ (if furnishing declaration pursuant to Rule 26ter). I hereby declare that my residence, mailing address, and citizenship are as stated next to my name. I hereby state that I have reviewed and understand the contents of the above-identified international application, including the claims of said application. I have identified in the request of said application, in compliance with PCT Rule 4.10, any claim to foreign priority, and I have identified below, under the heading "Prior Applications", by application number, country or Member of the World Trade Organization, day, month, and year of filing, any application for a patent or inventor's certificate filed in a country other than the United States of America, including any PCT international application designating at least one country other than the United States of America, having a filing date before that of the application on which foreign priority is claimed.
VIII-4-1-1	Prior applications:	

		I hereby acknowledge the duty to disclose information that is known by me to be material to patentability as defined by 37 C.F.R. § 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the PCT international filing date of the continuation-in-part application. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.
VIII-4-1-1-1	Name (LAST, First)	EASTWOOD, Paul Robert
VIII-4-1-1-2	Residence: (city and either US State, if applicable, or country)	Barcelona, Spain
VIII-4-1-1-3	Mailing address:	Calle Alcade de Mostoles 7, 41 80825 Barcelona Spain
VIII-4-1-1-4	Citizenship:	GB
VIII-4-1-1-5	Inventor's Signature: (The signature must be that of the inventor, not that of the agent)	
VIII-4-1-1-6	Date:	

PCT REQUEST

Original (for SUBMISSION)

VIII-4-1-2-1	Name (LAST, First)	HUNT, Hazel
VIII-4-1-2-2	Residence: (city and either US State, if applicable, or country)	Harlow, United Kingdom
VIII-4-1-2-3	Mailing address:	8/9 Spire Green Centre Harlow, Essex CM19 5TR United Kingdom
VIII-4-1-2-4	Citizenship:	GB
VIII-4-1-2-5	Inventor's Signature: (The signature must be that of the inventor, not that of the agent)	
VIII-4-1-2-6	Date	
VIII-4-1-3-1	Name (LAST, First)	FINK, David Mark
VIII-4-1-3-2	Residence: (city and either US State, if applicable, or country)	Lebanon, New Jersey
VIII-4-1-3-3	Mailing address:	1 Kensington Court Lebanon, NJ 08833 United States of America
VIII-4-1-3-4	Citizenship:	US
VIII-4-1-3-5	Inventor's Signature: (The signature must be that of the inventor, not that of the agent)	
VIII-4-1-3-6	Date	
VIII-4-1-4-1	Name (LAST, First)	SMITH, Helen Katherine
VIII-4-1-4-2	Residence: (city and either US State, if applicable, or country)	Harlow, United Kingdom
VIII-4-1-4-3	Mailing address:	8/9 Spire Green Centre Harlow, Essex CB19 5TR United Kingdom
VIII-4-1-4-4	Citizenship:	GB
VIII-4-1-4-5	Inventor's Signature: (The signature must be that of the inventor, not that of the agent)	
VIII-4-1-4-6	Date	

US20010107WO

9/10

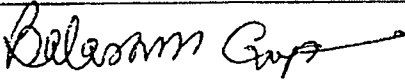
PCT REQUEST

Original (for SUBMISSION)

VIII-4-1-5-1	Name (LAST, First)	TODD, Richard Simon
VIII-4-1-5-2	Residence: (city and either US State, if applicable, or country)	Harlow, United Kingdom
VIII-4-1-5-3	Mailing address:	8/9 Spire Green Centre Harlow, Essex CM19 5TR United Kingdom
VIII-4-1-5-4	Citizenship:	GB
VIII-4-1-5-5	Inventor's Signature: (The signature must be that of the inventor, not that of the agent)	
VIII-4-1-5-6	Date	

PCT REQUEST

Original (for SUBMISSION)

IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	10	✓
IX-2	Description	122	-
IX-3	Claims	35	-
IX-4	Abstract	1	✓
IX-5	Drawings	0	-
IX-7	TOTAL	168	
	Accompanying Items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-9	Original separate power of attorney	✓	-
IX-17	PCT-SAFE physical media	-	✓
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Name (LAST, First)	GUPTA, Balaram	
X-1-2	Name of signatory		
X-1-3	Capacity		

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
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PCT REQUEST

Original (for SUBMISSION)

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form PCT/RO/101 PCT Request	
0-4-1	Prepared Using	PCT-SAFE [EASY model] Version 3.50 (Build 0002.175)
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0-7	Applicant's or agent's file reference	US20010107WO
I	Title of Invention	SUBSTITUTED BIS ARYL AND HETEROARYL COMPOUNDS AS SELECTIVE 5HT2A ANTAGONISTS
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V	DESIGNATIONS	
V-1	The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.	
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	10 February 2005 (10.02.2005)
VI-1-2	Number	60/651,911
VI-1-3	Country	US
VI-2	Priority document request	
	The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)
VIII	Declarations	Number of declarations
VIII-1	Declaration as to the identity of the inventor	-
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	1
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	1
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-

39

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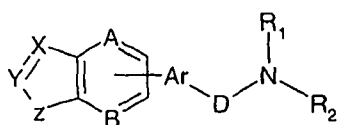
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(54) Title: SUBSTITUTED BIS ARYL AND HETEROARYL COMPOUNDS AS SELECTIVE 5HT_{2A} ANTAGONISTS



(I)

(57) Abstract: The present invention relates to a series of substituted bis aryl and heteroaryl compounds of formula (I): Wherein X, Y, Z, A, B, D, Ar, R₁ and R₂ are as defined herein. The compounds of this invention are selective 5HT_{2A} antagonists, and are therefore, useful in treating a variety of diseases including but not limited to a wide variety of sleep disorders as disclosed and claimed herein.

WO 2006/086705 A1

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**SUBSTITUTED BIS ARYL AND HETEROARYL COMPOUNDS AS SELECTIVE
5HT_{2A} ANTAGONISTS**

15

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to a series of substituted bis aryl and heteroaryl compounds as described herein. More specifically, the present invention relates to a series of dialkylamino, piperidiny1 or piperazinyl substituted bis aryl and heteroaryl derivatives. This invention also relates to methods of making these compounds. The compounds of this invention are selective serotonin, 5HT_{2A}, antagonists and are, therefore, useful as pharmaceutical agents, especially in the treatment and/or prevention of a variety of diseases including diseases associated with the central nervous system. More specifically, the compounds of this invention are useful in the treatment of a variety of sleep disorders.

25 Description of the Art

Chronic insomnia among adults in the United States has been estimated to be present in ten per cent of the adult population, and the annual cost for its treatment is estimated at \$10.9 billion. *JAMA* 1997; 278: 2170-2177 at 2170. Chronic insomniacs report elevated levels of stress, anxiety, depression and medical illnesses. The most common class of medications for treating insomnia are the benzodiazepines, but the adverse effect profile of benzodiazepines include daytime sedation, diminished motor coordination, and cognitive impairments. Furthermore, the National Institutes of Health Consensus conference on

41

Sleeping Pills and Insomnia in 1984 have developed guidelines discouraging the use of such sedative-hypnotics beyond 4-6 weeks because of concerns raised over drug misuse, dependency, withdrawal and rebound insomnia. *JAMA* 1997; 278: 2170-2177 at 2170. Therefore, it is desirable to have a pharmacological agent for the treatment of insomnia which

5 is more effective and/or has fewer side effects than those currently used.

The prevalence of obstructive sleep apnea is estimated to be approximately 1-10% in the adult population, but may be higher in elderly individuals; Diagnostic and Statistical Manual of Mental Disorders 4th ed., American Psychiatric Association, Washington D.C. (1994). Preliminary evidence suggests that having obstructive sleep apnea may contribute to

10 increased susceptibility to cardiovascular complications such as hypertension, cardiac arrhythmias, stroke, and myocardial infarction. Excessive daytime sleepiness is also a major complication.

Currently, the therapies used to treat obstructive sleep apnea include weight loss for the obese patient, Nasal-continuous positive Airway Pressure (a facemask used at night which

15 produces a positive pressure within the upper airway), pharyngeal surgery and the administration of a variety of pharmacologic agents which have not been proven to be entirely successful. *Chest* 109 (5):1346-1358 (May 1996) entitled Treatment of Obstructive Sleep Apnea, a Review, hereby incorporated by reference. These agents include Acetazolamide, Medroxyprogesterone, Opioid Antagonists, Nicotine, Angiotensin-Converting Enzyme

20 Inhibitors and Psychotropic Agents (including those that prevent the reuptake of biogenic amines such as norepinephrine, dopamine and serotonin). *Id.* At 1353. Many of these pharmacological agents used also have a ventilatory depressant action (such as benzodiazepines) or other side effects such as urinary hesitancy and/or impotence in men (Protriptyline) so that a new agent with fewer side effects is needed for the treatment of

25 obstructive sleep apnea. Even though serotonin is a sleep-inducing agent and may be a ventilatory stimulant (*Id.* At 1354), 5HT_{2A} receptor antagonists have been found useful in treating obstructive sleep apnea. See also *Am. J. Respir Crit Care Med* (153) pp 776-786 (1996) where serotonin antagonists exacerbated sleep apnea produced in English bulldogs. But compare, *Journal of Physiology* (466) pp 367-382 (1993), where it is postulated that an

30 excess of serotonin due to dysfunction of the serotonin biosynthesis mechanisms might set up conditions which favor obstructive apneas; *European Journal of Pharmacology* (259):71-74 (1994) further work on rat model with 5HT₂ antagonist.

EP 1 262 197 discloses a method of treating sleep disorders including sleep apnea by administering to a patient in need of such a treatment a 5HT_{1A} antagonist or an alpha-2-adrenergic antagonist in combination with an antidepressant such as serotonin reuptake inhibitor (SRI). Such a combination exhibits an improvement in efficacy.

5 US Patent 6,143,792 discloses that a specific 5HT_{2A} receptor antagonist is useful in the treatment of the sleep apnea syndrome. Similarly, US Patent 6,576,670 discloses that a specific 5HT_{2A} and 5HT_{2AC} receptor antagonist is useful in the treatment of snoring and upper airway high resistance syndrome.

10 US Patent 6,277,864 discloses that a specific 5HT_{2A} receptor antagonist is useful in the treatment of a variety of sleep disorders.

All of the references described herein are incorporated herein by reference in their entirety.

15 However, there is still a need for developing a compound that not only exhibits selective 5HT_{2A} antagonistic activity but also exhibits improved safety properties with no or minimal side-effects.

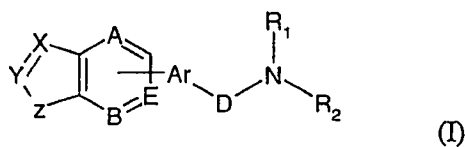
Accordingly, it is an object of this invention to provide a series of dialkylamino, piperidinyl or piperazinyl substituted bis aryl and heteroaryl derivatives which are potent, selective serotonin, 5HT_{2A}, antagonists.

20 It is also an object of this invention to provide processes for the preparation of the dialkylamino, piperidinyl or piperazinyl substituted bis aryl and heteroaryl derivatives as disclosed herein.

Other objects and further scope of the applicability of the present invention will become apparent from the detailed description that follows.

SUMMARY OF THE INVENTION

25 Thus in accordance with this invention there is provided a compound, including enantiomers, stereoisomers, and tautomers of said compound and pharmaceutically acceptable salts, solvates or derivatives thereof, with said compound having the general structure shown in formula I:



30 wherein:

$X \equiv Y$ denotes either a single or double bond between X and Y;

X is CR, CHR, CO, N, O or S;

Y is CR, CHR, CO, S(O)₂, N or NR;

Z is NR, CO-NR, S(O)₂-NR;

5 A, B and E are the same or different and independently from each other are CR or N;

D is either CH₂ or CO;

Ar is substituted or unsubstituted aryl or heteroaryl;

each R is independently chosen from hydrogen, halogen, CN, C(O)NR₃R₄, C₁₋₄alkyl,

C₁₋₄alkoxy, C₁₋₄alkenyl, aryl, heteroaryl, arylC₁₋₄alkyl, heteroarylC₁₋₄alkyl,

10 fluoroalkyl or fluoroalkoxy of the formula C_nH_xF_y or OC_nH_xF_y wherein n is an integer from 1 to 4, x is an integer from 0 to 8, y is an integer from 1 to 9 and sum of x and y is 2n+1; wherein

R₃ and R₄ are hydrogen or C₁₋₄alkyl; or

R₃ and R₄ taken together with the nitrogen atom to which they are attached

15 form an unsubstituted or at least monosubstituted heterocycle;

R₁ and R₂ are the same or different and selected independently of each other from

substituted or unsubstituted aryl, heteroaryl, aryloyl, heteroaryloyl, arylsulfonyl,

heteroarylsulfonyl, arylC₁₋₄alkyl, heteroarylC₁₋₄alkyl, aminoC₁₋₄alkyl,

C₁₋₄alkylaminoC₁₋₄alkyl, C₃₋₈cycloalkylaminoC₁₋₄alkyl,

20 diC₃₋₈cycloalkylaminoC₁₋₄alkyl, C₃₋₈cycloalkylC₁₋₄alkylaminoC₁₋₄alkyl,

diC₁₋₄alkylaminoalkyl, heterocycle, heterocycleC₁₋₄alkyl,

C₁₋₄alkylheterocycleC₁₋₄alkyl; or

R₁ and R₂ taken together with the nitrogen atom to which they are attached form an

unsubstituted or at least monosubstituted heterocycle; and wherein

25 the substituents are selected from the group consisting of substituted or unsubstituted

aryl, heteroaryl, arylC₁₋₄alkyl, heteroarylC₁₋₄alkyl, heterocycle, C₃₋₈cycloalkyl, C₁₋

4alkyl, C₁₋₄alkoxy, C₁₋₄alkenyl, fluoroalkyl or fluoroalkoxy of the formula C_nH_xF_y or

OC_nH_xF_y wherein n is an integer from 1 to 4, x is an integer from 0 to 8, y is an integer

from 1 to 9 and sum of x and y is 2n+1, -NO₂, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂,

30 -CN, -C(O)R₅, -NHC(O)(C₁₋₄alkyl), -SO₂Cl, -SO₂(C₁₋₄alkyl), halogen and hydroxy;

wherein

R₅ is hydroxy, C₁₋₃alkoxy, -O-phenyl, -NH₂, -NH(C₁₋₃alkyl), -N(C₁₋₃alkyl)₂ or phenyl;

24

heteroaryl is a 5 to 10-membered, aromatic, mono- or bicyclic heterocycle containing one or more heteroatoms selected from the group consisting of N, O and S;

aryl is a 6 to 10-membered, aromatic mono- or bicyclic ring; and

heterocycle is a 3 to 10-membered, non-aromatic, mono- or bicyclic heterocycle

5 containing one or more heteroatoms selected from the group consisting of N, O and S.

The compounds of this invention can be formulated into pharmaceutical compositions and are useful in treating a variety of disease states. Especially, the compounds of this invention are selective serotonin, 5HT_{2A}, antagonists and are, therefore, useful in the treatment of a wide variety of diseases associated with the central nervous system. More particularly, the compounds of this invention are useful in the treatment of a wide variety of sleep disorders including but not limited to insomnia and obstructive sleep apnea.

DETAILED DESCRIPTION OF THE INVENTION

The terms as used herein have the following meanings:

As used herein, the expression "C₁₋₆alkyl" includes methyl and ethyl groups, and straight-chained or branched propyl, butyl, pentyl and hexyl groups. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl and tert-butyl. Derived expressions such as "C₁₋₄alkoxy", "C₁₋₄thioalkyl", "C₁₋₄alkoxyC₁₋₄alkyl", "hydroxyC₁₋₄alkyl", "C₁₋₄alkylcarbonyl", "C₁₋₄alkoxycarbonylC₁₋₄alkyl", "C₁₋₄alkoxycarbonyl", "aminoC₁₋₄alkyl", "C₁₋₄alkylamino", "C₁₋₄alkylcarbamoylC₁₋₆alkyl", "C₁₋₄dialkylcarbamoylC₁₋₄alkyl", "mono- or di-C₁₋₄alkylaminoC₁₋₄alkyl", "aminoC₁₋₄alkylcarbonyl", "diphenylC₁₋₄alkyl", "phenylC₁₋₄alkyl", "phenylcarboylC₁₋₄alkyl" and "phenoxyC₁₋₄alkyl" are to be construed accordingly.

As used herein, the expression "C₂₋₆alkenyl" includes ethenyl and straight-chained or branched propenyl, butenyl, pentenyl and hexenyl groups. Similarly, the expression "C₂₋₆alkynyl" includes ethynyl and propynyl, and straight-chained or branched butynyl, pentynyl and hexynyl groups.

As used herein the expression "C₁₋₄acyl" shall have the same meaning as "C₁₋₆alkanoyl", which can also be represented structurally as "R-CO-", where R is a C₁₋₃alkyl as defined herein. Additionally, "C₁₋₃alkylcarbonyl" shall mean same as C₁₋₄acyl. Specifically, "C₁₋₄acyl" shall mean formyl, acetyl or ethanoyl, propanoyl, n-butanoyl, etc. Derived expressions such as "C₁₋₄acyloxy" and "C₁₋₄acyloxyalkyl" are to be construed accordingly.

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As used herein, the expression "C₁₋₆ perfluoroalkyl" means that all of the hydrogen atoms in said alkyl group are replaced with fluorine atoms. Illustrative examples include trifluoromethyl and pentafluoroethyl, and straight-chained or branched heptafluoropropyl, nonafluorobutyl, undecafluoropentyl and tridecafluorohexyl groups. Derived expression, "C₁₋₆ perfluoroalkoxy", is to be construed accordingly.

As used herein, the expression "aryl" means substituted or unsubstituted phenyl or naphthyl. Specific examples of substituted phenyl or naphthyl include o-, p-, m-tolyl, 1,2-, 1,3-, 1,4-xylyl, 1-methylnaphthyl, 2-methylnaphthyl, etc. "Substituted phenyl" or "substituted naphthyl" also include any of the possible substituents as further defined herein or one known in the art. Derived expression, "arylsulfonyl," is to be construed accordingly. Specific examples of arylsulfonyl include benzenesulfonyl, p-toluenesulfonyl, and the like.

As used herein, the expression "C₆₋₁₂arylC₁₋₄alkyl" means that the C₆₋₁₂aryl as defined herein is further attached to C₁₋₄alkyl as defined herein. Representative examples include benzyl, phenylethyl, 2-phenylpropyl, 1-naphthylmethyl, 2-naphthylmethyl and the like.

As used herein, the expression "heteroaryl" includes all of the known heteroatom containing aromatic radicals. Representative 5-membered heteroaryl radicals include furanyl, thienyl or thiophenyl, pyrrolyl, isopyrrolyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, isothiazolyl, and the like. Representative 6-membered heteroaryl radicals include pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, and the like radicals. Representative examples of bicyclic heteroaryl radicals include, benzofuranyl, benzothiophenyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, indazolyl, pyridofuranyl, pyridothienyl, and the like radicals.

Similarly, the expression "heteroarylC₁₋₄alkyl" means that the heteroaryl as defined herein is further attached to C₁₋₄alkyl as defined herein. Representative examples include furanylmethyl, thienylethyl, 2-(thiophenyl)propyl, pyrrolylmethyl, isopyrrolylethyl, pyrazolylmethyl, imidazolylmethyl, and the like.

As used herein, the expression "heterocycle" includes all of the known reduced heteroatom containing cyclic radicals. Representative 5-membered heterocycle radicals include tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, 2-thiazolinyl, tetrahydrothiazolyl, tetrahydrooxazolyl, and the like. Representative 6-membered heterocycle radicals include piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, and the like. Various other heterocycle radicals include, without limitation, aziridinyl, azepanyl, diazepanyl, diazabicyclo[2.2.1]hept-2-yl, and triazocanyl, and the like. Derived expression

46

"heterocycleC₁₋₄alkyl" is to be construed accordingly. Specific examples of heterocycleC₁₋₄alkyl include without any limitation the following: N-pyrrolidinylmethyl, N-pyrrolidinyethyl, pyrrolidinyl-2-methyl, 2-pyrrolidinyl-2-ethyl, and the like. Similarly, the expression "C₁₋₄alkylheterocycleC₁₋₄alkyl" should be construed accordingly. Representative examples include without any limitation the following: N-ethylpyrrolidinyl-N'-methyl, 2-ethyl-N-pyrrolidinyethyl, N-ethyl-pyrrolidinyl-2-methyl, 2-pyrrolidinyethyl-2-ethyl, and the like.

"Halogen" or "halo" means chloro, fluoro, bromo, and iodo.

As used herein, "patient" means a warm blooded animal, such as for example rat, mice, dogs, cats, guinea pigs, and primates such as humans.

As used herein, the expression "pharmaceutically acceptable carrier" means a non-toxic solvent, dispersant, excipient, adjuvant, or other material which is mixed with the compound of the present invention in order to permit the formation of a pharmaceutical composition, i.e., a dosage form capable of administration to the patient. One example of such a carrier is pharmaceutically acceptable oil typically used for parenteral administration.

The term "pharmaceutically acceptable salts" as used herein means that the salts of the compounds of the present invention can be used in medicinal preparations. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, methanesulfonic acid, 2-hydroxyethanesulfonic acid, p-toluenesulfonic acid, fumaric acid, maleic acid, hydroxymaleic acid, malic acid, ascorbic acid, succinic acid, glutaric acid, acetic acid, salicylic acid, cinnamic acid, 2-phenoxybenzoic acid, hydroxybenzoic acid, phenylacetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, glycolic acid, lactic acid, pyruvic acid, malonic acid, carbonic acid or phosphoric acid. The acid metal salts such as sodium monohydrogen orthophosphate and potassium hydrogen sulfate can also be formed. Also, the salts so formed may present either as mono- or di- acid salts and can exist substantially anhydrous or can be hydrated. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal

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salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts, and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The expression "stereoisomers" is a general term used for all isomers of the individual molecules that differ only in the orientation of their atoms in space. Typically it includes mirror image isomers that are usually formed due to at least one asymmetric center, (enantiomers). Where the compounds according to the invention possess two or more asymmetric centers, they may additionally exist as diastereoisomers, also certain individual molecules may exist as geometric isomers (cis/trans). Similarly, certain compounds of this invention may exist in a mixture of two or more structurally distinct forms that are in rapid equilibrium, commonly known as tautomers. Representative examples of tautomers include keto-enol tautomers, phenol-keto tautomers, nitroso-oxime tautomers, imine-enamine tautomers, etc. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

The term "solvate" as used herein means that an aggregate that consists of a solute ion or molecule with one or more solvent molecules. Similarly, a "hydrate" means that a solute ion or molecule with one or more water molecules.

In a broad sense, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a few of the specific embodiments as disclosed herein, the term "substituted" means substituted with one or more substituents independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆perfluoroalkyl, phenyl, hydroxy, -CO₂H, an ester, an amide, C₁-C₆alkoxy, C₁-C₆thioalkyl, C₁-C₆perfluoroalkoxy, -NH₂, Cl, Br, I, F, -NH-lower alkyl, and -N(lower alkyl)₂. However, any of the other suitable substituents known to one skilled in the art can also be used in these embodiments.

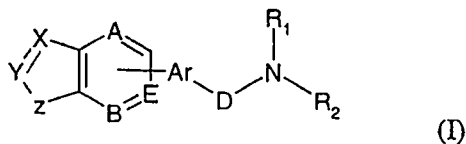
"Therapeutically effective amount" means an amount of the compound which is effective in treating the named disease, disorder or condition.

The term "treating" refers to:

- (i) preventing a disease, disorder or condition from occurring in a patient that may be predisposed to the disease, disorder and/or condition, but has not yet been diagnosed as having it;
- (ii) inhibiting the disease, disorder or condition, i.e., arresting its development; and
- (iii) relieving the disease, disorder or condition, i.e., causing regression of the disease, disorder and/or condition.

48

Thus, in accordance with the practice of this invention there is provided a compound including enantiomers, stereoisomers, and tautomers of said compound and pharmaceutically acceptable salts, solvates or derivatives thereof, with said compound having the general structure shown in formula I:



wherein:

$X \equiv Y$ denotes either a single or double bond between X and Y;

X is CR, CHR, CO, N, O or S;

Y is CR, CHR, CO, S(O)₂, N or NR;

Z is NR, CO-NR, S(O)₂-NR;

A, B and E are the same or different and independently from each other are CR or N;

D is either CH₂ or CO;

Ar is substituted or unsubstituted aryl or heteroaryl;

each R is independently chosen from hydrogen, halogen, CN, C(O)NR₃R₄, C₁₋₄alkyl,

C₁₋₄alkoxy, C₁₋₄alkenyl, aryl, heteroaryl, arylC₁₋₄alkyl, heteroarylC₁₋₄alkyl,

fluoroalkyl or fluoroalkoxy of the formula C_nH_xF_y or OC_nH_xF_y wherein n is an

integer from 1 to 4, x is an integer from 0 to 8, y is an integer from 1 to 9 and sum of x and y is 2n+1; wherein

R₃ and R₄ are hydrogen or C₁₋₄alkyl; or

R₃ and R₄ taken together with the nitrogen atom to which they are attached form an unsubstituted or at least monosubstituted heterocycle;

R₁ and R₂ are the same or different and selected independently of each other from substituted or unsubstituted aryl, heteroaryl, aryloyl, heteroaryloyl, arylsulfonyl, heteroarylsulfonyl, arylC₁₋₄alkyl, heteroarylC₁₋₄alkyl, aminoC₁₋₄alkyl,

C₁₋₄alkylaminoC₁₋₄alkyl, C₃₋₈cycloalkylaminoC₁₋₄alkyl,

diC₃₋₈cycloalkylaminoC₁₋₄alkyl, C₃₋₈cycloalkylC₁₋₄alkylaminoC₁₋₄alkyl,

diC₁₋₄alkylaminoalkyl, heterocycle, heterocycleC₁₋₄alkyl,

C₁₋₄alkylheterocycleC₁₋₄alkyl; or

R₁ and R₂ taken together with the nitrogen atom to which they are attached form an unsubstituted or at least monosubstituted heterocycle; and wherein

the substituents are selected from the group consisting of substituted or unsubstituted aryl, heteroaryl, arylC₁₋₄alkyl, heteroarylC₁₋₄alkyl, heterocycle, C₃₋₈cycloalkyl, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkenyl, fluoroalkyl or fluoroalkoxy of the formula C_nH_xF_y or OC_nH_xF_y wherein n is an integer from 1 to 4, x is an integer from 0 to 8, y is an integer from 1 to 9 and sum of x and y is 2n+1, -NO₂, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, -CN, -C(O)R₅, -NHC(O)(C₁₋₄alkyl), -SO₂Cl, -SO₂(C₁₋₄alkyl), halogen and hydroxy; wherein

R₅ is hydroxy, C₁₋₃alkoxy, -O-phenyl, -NH₂, -NH(C₁₋₃alkyl), -N(C₁₋₃alkyl)₂ or phenyl; heteroaryl is a 5 to 10-membered, aromatic, mono- or bicyclic heterocycle containing one or more heteroatoms selected from the group consisting of N, O and S; aryl is a 6 to 10-membered, aromatic mono- or bicyclic ring; and heterocycle is a 3 to 10-membered, non-aromatic, mono- or bicyclic heterocycle containing one or more heteroatoms selected from the group consisting of N, O and S.

In one aspect of this invention, the compounds of formula (I) having the following substituents are preferred:

D is CH₂;

Ar is substituted or unsubstituted phenyl, pyridinyl, pyrazinyl, furanyl or thiophenyl; wherein the substituents are selected from the group consisting of fluorine, chlorine, C₁₋₄alkyl, C₁₋₄alkoxy and -CF₃;

each R is independently chosen from hydrogen, CN or C₁₋₄alkyl;

R₁ and R₂ are the same or different and selected independently of each other from substituted or unsubstituted benzoyl, thiophenylcarbonyl, pyridinylcarbonyl, pyrazinylcarbonyl, pyrimidinylcarbonyl, pyridazinylcarbonyl, dihydrobenzo[1,4]dioxinylcarbonyl, benzo[1,3]dioxolylcarbonyl, phenylC₀₋₄alkyl, thiophenylC₁₋₄alkyl, aza-bicyclo[2.2.2]octylC₀₋₄alkyl, aza-bicyclo[3.2.1]octylC₀₋₄alkyl, piperidinylC₀₋₄alkyl, pyrrolidinylC₀₋₄alkyl, C₁₋₄alkylaminoC₁₋₄alkyl and diC₁₋₄alkylaminoC₁₋₄alkyl; wherein the substituted moieties may be substituted with one or more substituents selected from the group consisting of fluorine, chlorine, C₁₋₄alkyl, C₃₋₈cycloalkyl, C₁₋₄alkoxy, OCF₃ and CF₃; or

R₁ and R₂ taken together with the nitrogen atom to which they are attached form a unsubstituted or at least monosubstituted heterocycle selected from the group

50

consisting of piperazine and diazepane; wherein the substituents are selected from the group consisting of phenyl, fluorophenyl, trifluoromethylphenyl, pyridinyl, thiophenyl, furanyl and C₁₋₄alkyl.

In a further aspect of this invention, the compounds of formula (I) with the following
5 substituents are preferred:

X --- Y denotes a double bond between X and Y;

X is CR;

Y is CR;

Z is NR;

10 A, B and E are the same or different and independently from each other are CH or N;
Ar is phenyl, fluorophenyl, chlorophenyl, pyridinyl, pyrazinyl, furanyl or thiophenyl;
each R is independently chosen from hydrogen, CN, methyl, ethyl, methoxy, fluorine, CF₃ or OCF₃;

15 R₁ and R₂ are the same or different and selected independently of each other from
benzyl, fluorobenzyl, fluorobenzoyl, chlorobenzoyl, isopropoxybenzoyl, trifluoromethylbenzoyl, fluoro-trifluoromethylbenzoyl, trifluoromethoxybenzoyl, thiophenylcarbonyl, pyridinylcarbonyl, pyrazinylcarbonyl, pyrimidinylcarbonyl, pyridazinylcarbonyl, dihydro-benzo[1,4]dioxinylcarbonyl, benzo[1,3]dioxolylcarbonyl, aza-bicyclo[2.2.2]octyl, aza-bicyclo[2.2.2]octylmethyl, N-methyl-piperidinyl,
20 pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolidinylpropyl and dimethylaminoethyl;

or

25 R₁ and R₂ taken together with the nitrogen atom to which they are attached form a unsubstituted or at least monosubstituted heterocycle selected from the group consisting of piperazine and diazepane; wherein the substituents are selected from the group consisting of phenyl, fluorophenyl, trifluoromethylphenyl, pyridinyl, thiophenyl, furanyl and methyl.

30 Examples of compounds encompassed within the above noted embodiment without any limitations include the following:

N-benzyl-N-[3-(1H-indol-5-yl)-benzyl]-N',N'-dimethyl-ethane-1,2-diamine;

4-fluoro-N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

- N-(2-dimethylamino-ethyl)-4-fluoro-N-[2-fluoro-5-(2-methyl-1H-indol-5-yl)-benzyl]-benzamide;
- N-(2-dimethylamino-ethyl)-4-fluoro-N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-benzamide;
- 5 4-fluoro-N-[3-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-benzamide;
- thiophene-2-carboxylic acid [3-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide;
- thiophene-2-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide;
- 10 thiophene-2-carboxylic acid (2-dimethylamino-ethyl)-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-amide;
- 4-fluoro-N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-benzamide;
- N-(1-aza-bicyclo[2.2.2]oct-4-ylmethyl)-4-fluoro-N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-benzamide trifluoro-acetate;
- 15 4-fluoro-N-[5-(1H-indol-5-yl)-pyridin-3-ylmethyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;
- 4-fluoro-N-[4-fluoro-3-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-benzamide;
- 20 4-fluoro-N-[4-(1H-indol-5-yl)-thiophen-2-ylmethyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide acetate;
- (4-fluoro-benzyl)-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amine;
- N-(4-fluoro-benzyl)-N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N',N'-dimethyl-ethane-1,2-diamine;
- 25 (1-aza-bicyclo[2.2.2]oct-4-ylmethyl)-(4-fluoro-benzyl)-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-amine acetate;
- N-(2-dimethylamino-ethyl)-4-fluoro-N-[5-(1H-indol-5-yl)-pyridin-3-ylmethyl]-benzamide trifluoroacetate;
- 30 4-fluoro-N-[5-(1H-indol-5-yl)-thiophen-2-ylmethyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

- 4-fluoro-N-[4-(1H-indol-5-yl)-furan-2-ylmethyl]-N-(1-methyl-piperidin-4-yl)-benzamide;
- N-(1-aza-bicyclo[2.2.2]oct-3R-yl)-4-fluoro-N-[2-fluoro-5-(1H-indol-6-yl)-benzyl]-benzamide;
- 5 pyrimidine-4-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide;
- pyrimidine-2-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide;
- pyridazine-3-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide;
- 10 pyridazine-4-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide;
- 2,3-dihydro-benzo[1,4]dioxine-6-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide;
- 15 N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-4-isopropoxy-N-(1-methyl-piperidin-4-yl)-benzamide;
- N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-3-isopropoxy-N-(1-methyl-piperidin-4-yl)-benzamide;
- N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-4-
- 20 trifluoromethoxy-benzamide;
- 4-chloro-N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-benzamide;
- benzo[1,3]dioxole-5-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide;
- 25 N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-4-trifluoromethyl-benzamide;
- 4-fluoro-N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-3-trifluoromethyl-benzamide;
- N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-isonicotinamide;
- 30 N-[3-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-4-trifluoromethyl-benzamide;
- 4-fluoro-N-[4-fluoro-3-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

- N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-4-trifluoromethyl-benzamide;
- 4-fluoro-N-[3-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;
- N-[3-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-4-trifluoromethyl-
- 5 benzamide;
- N-[3-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-isonicotinamide;
- N-[4-fluoro-3-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-4-trifluoromethyl-benzamide;
- N-[3-(1H-indol-5-yl)-benzyl]-N-(3-pyrrolidin-1-yl-propyl)-isonicotinamide;
- 10 N-[4-fluoro-3-(1H-indol-5-yl)-benzyl]-N-(3-pyrrolidin-1-yl-propyl)-isonicotinamide;
- pyridine-2-carboxylic acid [3-(1H-indol-5-yl)-benzyl]-(3-pyrrolidin-1-yl-propyl)-amide;
- N-[3-(1H-indol-5-yl)-benzyl]-N-(3-pyrrolidin-1-yl-propyl)-4-trifluoromethyl-benzamide;
- 15 pyridine-2-carboxylic acid [4-fluoro-3-(1H-indol-5-yl)-benzyl]-(3-pyrrolidin-1-yl-propyl)-amide;
- pyridine-2-carboxylic acid [4-(1H-indol-5-yl)-thiophen-2-ylmethyl]-(3-pyrrolidin-1-yl-propyl)-amide;
- N-[4-(1H-indol-5-yl)-thiophen-2-ylmethyl]-N-(3-pyrrolidin-1-yl-propyl)-4-
- 20 trifluoromethyl-benzamide;
- N-[4-(1H-indol-5-yl)-thiophen-2-ylmethyl]-N-(2-pyrrolidin-1-yl-ethyl)-isonicotinamide;
- pyridine-2-carboxylic acid [4-(1H-indol-5-yl)-thiophen-2-ylmethyl]-(2-pyrrolidin-1-yl-ethyl)-amide;
- 25 N-[4-(1H-indol-5-yl)-thiophen-2-ylmethyl]-N-(2-pyrrolidin-1-yl-ethyl)-4-trifluoromethyl-benzamide;
- pyridine-2-carboxylic acid [4-(1H-indol-5-yl)-furan-2-ylmethyl]-(3-pyrrolidin-1-yl-propyl)-amide;
- N-[4-(1H-indol-5-yl)-furan-2-ylmethyl]-N-(3-pyrrolidin-1-yl-propyl)-4-
- 30 trifluoromethyl-benzamide;
- N-[4-(1H-indol-5-yl)-furan-2-ylmethyl]-N-(2-pyrrolidin-1-yl-ethyl)-isonicotinamide;

54

- pyridine-2-carboxylic acid [4-(1H-indol-5-yl)-furan-2-ylmethyl]-(2-pyrrolidin-1-yl-ethyl)-amide;
- N-[4-(1H-indol-5-yl)-furan-2-ylmethyl]-N-(2-pyrrolidin-1-yl-ethyl)-4-trifluoromethyl-benzamide;
- 5 N-[4-(1H-indol-5-yl)-thiophen-2-ylmethyl]-N-(3-pyrrolidin-1-yl-propyl)-isonicotinamide;
- N-[4-(1H-indol-5-yl)-furan-2-ylmethyl]-N-(3-pyrrolidin-1-yl-propyl)-isonicotinamide;
- N-[2-chloro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-isonicotinamide;
- pyridine-2-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide;
- 10 N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-nicotinamide;
- N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-3-trifluoromethoxy-benzamide;
- N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-isonicotinamide;
- 15 N-[4-fluoro-3-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-isonicotinamide;
- N-[4-fluoro-3-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-4-trifluoromethoxy-benzamide acetate;
- N-[3-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-isonicotinamide;
- pyrazine-2-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide;
- 20 5-[4-fluoro-3-(4-methyl-2-pyridin-3-yl-piperazin-1-ylmethyl)-phenyl]-1H-indole acetate;
- 5-{4-fluoro-3-[4-methyl-2-(4-trifluoromethyl-phenyl)-piperazin-1-ylmethyl]-phenyl}-1H-indole;
- 25 5-[4-fluoro-3-(4-methyl-2-pyridin-2-yl-piperazin-1-ylmethyl)-phenyl]-1H-indole acetate;
- 5-{5-[2S-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-pyridin-3-yl}-1H-indole acetate;
- 5-{4-fluoro-3-[2S-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-phenyl}-1H-indole;
- 30 5-[4-fluoro-3-(2-furan-2-yl-4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-indole;

55

- 5- $\{5-[2S-(4\text{-fluoro-phenyl})-4\text{-methyl-piperazin-1-ylmethyl}]\text{-furan-3-yl}\}$ -1H-indole trifluoro-acetate;
- 5- $\{5-[2S-(4\text{-fluoro-phenyl})-4\text{-methyl-piperazin-1-ylmethyl}]\text{-pyridin-3-yl}\}$ -1H-indole acetate;
- 5- $\{5-[2S-(4\text{-fluoro-phenyl})-4\text{-methyl-piperazin-1-ylmethyl}]\text{-furan-3-yl}\}$ -1H-indole;
- 5- $\{3-(4\text{-methyl-piperazin-1-ylmethyl})\text{-phenyl}\}$ -1H-indole;
- 5- $\{4\text{-fluoro-3-}(4\text{-methyl-2-pyridin-4-yl-piperazin-1-ylmethyl})\text{-phenyl}\}$ -1H-indole;
- 5- $\{3-[2S-(4\text{-fluoro-phenyl})-4\text{-methyl-piperazin-1-ylmethyl}]\text{-phenyl}\}$ -1H-indole;
- 5- $\{6-[2S-(4\text{-fluoro-phenyl})-4\text{-methyl-piperazin-1-ylmethyl}]\text{-pyrazin-2-yl}\}$ -1H-indole acetate;
- 5- $\{4\text{-fluoro-3-}[2S-(4\text{-fluoro-phenyl})-4\text{-methyl-piperazin-1-ylmethyl}]\text{-phenyl}\}$ -1H-indole acetate;
- 5- $\{4\text{-fluoro-3-}[2S-(4\text{-fluoro-phenyl})-4\text{-methyl-piperazin-1-ylmethyl}]\text{-phenyl}\}$ -1H-indole-3-carbonitrile;
- 5- $\{3-(4\text{-methyl-[1,4]diazepan-1-ylmethyl})\text{-phenyl}\}$ -1H-indole;
- 5- $\{4\text{-fluoro-3-}[2S-(4\text{-fluoro-phenyl})-4\text{-methyl-piperazin-1-ylmethyl}]\text{-phenyl}\}$ -3-methyl-1H-indole;
- N- $\{5-(3\text{-cyano-1H-indol-5-yl})-2\text{-fluoro-benzyl}\}$ -N-(2-dimethylamino-ethyl)-4-fluoro-benzamide;
- 5- $\{4\text{-fluoro-3-}[2S-(4\text{-fluoro-phenyl})-4\text{-methyl-piperazin-1-ylmethyl}]\text{-phenyl}\}$ -1H-indole-3-carbonitrile;
- 5- $\{3-[(2\text{-dimethylamino-ethyl})-(4\text{-fluoro-benzyl})\text{-amino}]\text{-methyl}\}$ -4-fluoro-phenyl)-1H-indole-3-carbonitrile trifluoro-acetate;
- 4-fluoro-N- $\{2\text{-fluoro-5-(1H-pyrrolo[3,2-b]pyridin-5-yl)-benzyl}\}$ -N-(2-pyrrolidin-1-yl-ethyl)-benzamide;
- 5- $\{4\text{-fluoro-3-}[2-(4\text{-fluoro-phenyl})-4\text{-methyl-piperazin-1-ylmethyl}]\text{-phenyl}\}$ -1H-pyrrolo[3,2-b]pyridine; and
- 4-fluoro-N- $\{2\text{-fluoro-5-(1H-pyrrolo[2,3-c]pyridin-5-yl)-benzyl}\}$ -N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

or a pharmaceutically acceptable salt thereof or an optical or stereoisomer thereof.

- In yet another embodiment of this invention, the compounds of formula (I) having the following substituents are also preferred:

$X=Y$ denotes a double bond between X and Y;

X is CR;

Y is N;

Z is NR;

A, B and E are CH;

5 Ar is phenyl, fluorophenyl, chlorophenyl, pyridinyl, pyrazinyl, furanyl or thiophenyl;
each R is independently chosen from hydrogen, methyl, ethyl, methoxy, fluorine, CF₃
or OCF₃;

R₁ and R₂ are the same or different and selected independently of each other from
benzyl, fluorobenzyl, fluorobenzoyl, chlorobenzoyl, isopropoxybenzoyl,
10 trifluoromethylbenzoyl, fluoro-trifluoromethylbenzoyl,
trifluoromethoxybenzoyl, thiophenylcarbonyl, pyridinylcarbonyl,
pyrazinylcarbonyl, pyrimidinylcarbonyl, pyridazinylcarbonyl, dihydro-
benzo[1,4]dioxinylcarbonyl, benzo[1,3]dioxolylcarbonyl, N-methyl-aza-
bicyclo[2.2.2]octyl, aza-bicyclo[2.2.2]octyl, aza-bicyclo[2.2.2]octylmethyl, N-
15 methyl-piperidinyl, piperidinyl, N-methyl-pyrrolidinyl, pyrrolidinylmethyl,
pyrrolidinylethyl, pyrrolidinylpropyl, methylaminoethyl, and
dimethylaminoethyl;

or

R₁ and R₂ taken together with the nitrogen atom to which they are attached form a
20 unsubstituted or at least monosubstituted heterocycle selected from the group
consisting of piperazine and diazepane; wherein the substituents are selected
from the group consisting of phenyl, fluorophenyl, trifluoromethylphenyl,
pyridinyl, thiophenyl, furanyl and methyl.

25 Examples of compounds within the scope of this embodiment without any limitations
may be enumerated as follows:

N-benzyl-N-[3-(1H-indazol-5-yl)-benzyl]-N',N'-dimethyl-ethane-1,2-diamine
hydrochloride;

N-(4-fluoro-benzyl)-N-[5-(1H-indazol-5-yl)-pyridin-3-ylmethyl]-N',N'-dimethyl-
ethane-1,2-diamine acetate;

30 (4-fluoro-benzyl)-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-pyrrolidin-2S-ylmethyl-amine;
(4-fluoro-benzyl)-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-piperidin-4-yl-amine;

57

- N-(4-fluoro-benzyl)-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N'-methyl-ethane-1,2-diamine;
- (4-fluoro-benzyl)-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amine;
- 5 (4-fluoro-benzyl)-[4-(1H-indazol-5-yl)-furan-2-ylmethyl]-(1-methyl-piperidin-4-yl)-amine;
- 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;
- 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(exo-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-benzamide;
- 10 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(endo-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-benzamide;
- 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(1-methyl-piperidin-3-yl)-benzamide;
- 15 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(1-methyl-piperidin-3S-yl)-benzamide trifluoro-acetate;
- 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(1-methyl-pyrrolidin-3R-yl)-benzamide trifluoro-acetate;
- 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(1-methyl-pyrrolidin-3S-yl)-benzamide trifluoro-acetate;
- 20 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(3-pyrrolidin-1-yl-propyl)-benzamide;
- 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-benzamide;
- 25 N-(1-aza-bicyclo[2.2.2]oct-3R-yl)-4-fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-benzamide;
- chiral N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(1-methyl-pyrrolidin-3R-yl)-4-trifluoromethyl-benzamide;
- 4-fluoro-N-[4-(1H-indazol-5-yl)-furan-2-ylmethyl]-N-(1-methyl-piperidin-4-yl)-benzamide;
- 30 5-{4-fluoro-3-[2-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-phenyl}-1H-indazole;
- 5-[4-fluoro-3-(2S-thiophen-2-yl-piperazin-1-ylmethyl)-phenyl]-1H-indazole acetate;

5-[4-fluoro-3-(2-thiophen-2-yl-piperazin-1-ylmethyl)-phenyl]-1H-indazole;
chiral 5-[4-fluoro-3-(2-thiophen-2-yl-piperazin-1-ylmethyl)-phenyl]-1H-indazole
acetate;

5-{4-fluoro-3-[2*S*-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-phenyl}-1H-
indazole;

5-{5-[2*S*-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-pyridin-3-yl}-1H-indazole;

5-{5-[2*S*-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-pyridin-3-yl}-1H-indazole;

5-{5-[2*S*-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-furan-3-yl}-1H-indazole;

5-[4-fluoro-3-(4-methyl-2*R*-thiophen-2-yl-piperazin-1-ylmethyl)-phenyl]-1H-indazole
acetate;

5-[4-fluoro-3-(4-methyl-2*S*-thiophen-2-yl-piperazin-1-ylmethyl)-phenyl]-1H-indazole
acetate; and

5-{5-[2*S*-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-furan-3-yl}-1H-indazole;

or a pharmaceutically acceptable salt thereof or an optical or stereoisomer thereof.

In another embodiment of this invention, compounds of formula (I) having the
following substituents are preferred:

$X \equiv Y$ denotes a double bond between X and Y;

X is N;

Y is CR;

Z is NR;

A, B and E are CH;

Ar is phenyl, fluorophenyl, chlorophenyl, pyridinyl, pyrazinyl, furanyl or thiophenyl;

each R is independently chosen from hydrogen, methyl, ethyl, methoxy, CF₃ or OCF₃;

R₁ and R₂ are the same or different and selected independently of each other from

benzyl, fluorobenzyl, fluorobenzoyl, chlorobenzoyl, isopropoxybenzoyl,

trifluoromethylbenzoyl, fluoro-trifluoromethylbenzoyl,

trifluoromethoxybenzoyl, thiophenylcarbonyl, pyridinylcarbonyl,

pyrazinylcarbonyl, pyrimidinylcarbonyl, pyridazinylcarbonyl, dihydro-

benzo[1,4]dioxinylcarbonyl, benzo[1,3]dioxolylcarbonyl, N-methyl-aza-

bicyclo[2.2.2]octyl, aza-bicyclo[2.2.2]octyl, aza-bicyclo[2.2.2]octylmethyl, N-

methyl-piperidinyl, piperidinyl, N-methyl-pyrrolidinyl, pyrrolidinylmethyl,

59

pyrrolidinylethyl, pyrrolidinylpropyl, methylaminoethyl, dimethylaminoethyl and dimethylaminopropyl;

or

5 R₁ and R₂ taken together with the nitrogen atom to which they are attached form a unsubstituted or at least monosubstituted heterocycle selected from the group consisting of piperazine and diazepane; wherein the substituents are selected from the group consisting of phenyl, fluorophenyl, trifluoromethylphenyl, pyridinyl, thiophenyl, furanyl and methyl.

Specific examples of compounds within the scope of this embodiment without any
~10 limitations are listed as follows:

N-[3-(1H-benzimidazol-5-yl)-benzyl]-N-benzyl-N',N'-dimethyl-ethane-1,2-diamine hydrochloride; and

N-[3-(1H-benzimidazol-5-yl)-benzyl]-N-benzyl-N',N'-dimethyl-propane-1,3-diamine hydrochloride;

15 or a pharmaceutically acceptable salt thereof or an optical or stereoisomer thereof.

In another embodiment of this invention the compound of formula (I) is having the following substituents:

X --- Y denotes a double bond between X and Y;

X is N;

20 Y is N;

Z is NR;

A, B and E are CH;

Ar is phenyl, fluorophenyl, chlorophenyl, pyridinyl, pyrazinyl, furanyl or thiophenyl;

R is hydrogen, methyl or ethyl;

25 R₁ and R₂ are the same or different and selected independently of each other from benzyl, fluorobenzyl, fluorobenzoyl, difluorobenzoyl, chlorobenzoyl, isopropoxybenzoyl, trifluoromethylbenzoyl, fluoro-trifluoromethylbenzoyl, trifluoromethoxybenzoyl, thiophenylcarbonyl, pyridinylcarbonyl, pyrazinylcarbonyl, pyrimidinylcarbonyl, pyridazinylcarbonyl, dihydro-
30 benzo[1,4]dioxinylcarbonyl, benzo[1,3]dioxolylcarbonyl, thiophenylmethyl, N-methyl-aza-bicyclo[2.2.2]octyl, aza-bicyclo[2.2.2]octyl, aza-bicyclo[2.2.2]octylmethyl, N-methyl-piperidinyl, N-isopropyl-piperidinyl, N-

cyclopropyl-piperidinyl, piperidinyl, N-methyl-pyrrolidinyl, N-ethyl-pyrrolidinylmethyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolidinylpropyl, methylaminoethyl, dimethylaminoethyl and dimethylaminopropyl;

or

- 5 R₁ and R₂ taken together with the nitrogen atom to which they are attached form a unsubstituted or at least monosubstituted heterocycle selected from the group consisting of piperazine and diazepane; wherein the substituents are selected from the group consisting of phenyl, fluorophenyl, trifluoromethylphenyl, pyridinyl, thiophenyl, furanyl and methyl.

- 10 Examples of compounds of formula (I) falling within the scope of the above noted embodiment include without any limitations the following:

- N-[3-(1H-benzotriazol-5-yl)-benzyl]-N-benzyl-N',N'-dimethyl-propane-1,3-diamine;
[5-(1H-benzotriazol-5-yl)-2-fluoro-benzyl]-(4-fluoro-benzyl)-pyrrolidin-2R-ylmethyl-amine trihydrochloride;
- 15 [5-(1H-benzotriazol-5-yl)-2-fluoro-benzyl]-piperidin-4-yl-thiophen-2-ylmethyl-amine;
[5-(1H-benzotriazol-5-yl)-2-fluoro-benzyl]-(4-fluoro-benzyl)-piperidin-4-yl-amine;
N-[5-(1H-benzotriazol-5-yl)-2-fluoro-benzyl]-N-(4-fluoro-benzyl)-N'-methyl-ethane-1,2-diamine;
- 20 [5-(1H-benzotriazol-5-yl)-2-fluoro-benzyl]-(1-ethyl-pyrrolidin-2S-ylmethyl)-(4-fluoro-benzyl)-amine hydrochloride;
[5-(1H-benzotriazol-5-yl)-2-fluoro-benzyl]-(4-fluoro-benzyl)-(1-methyl-piperidin-4-yl)-amine hydrochloride;
- N-[3-(1H-benzotriazol-5-yl)-benzyl]-N-benzyl-N',N'-dimethyl-ethane-1,2-diamine hydrochloride;
- 25 N-[5-(1H-benzotriazol-5-yl)-2-fluoro-benzyl]-N-(1-ethyl-pyrrolidin-2S-ylmethyl)-4-fluoro-benzamide;
- N-[3-(1H-benzotriazol-5-yl)-benzyl]-4-fluoro-N-(2-pyrrolidin-1-yl-ethyl)-benzamide hydrochloride;
- thiophene-2-carboxylic acid [5-(1H-benzotriazol-5-yl)-2-fluoro-benzyl]-(2-pyrrolidin-1-yl-ethyl)-amide hydrochloride;
- 30 N-[5-(1H-benzotriazol-5-yl)-2-fluoro-benzyl]-2,4-difluoro-N-(2-pyrrolidin-1-yl-ethyl)-benzamide hydrochloride;

N-[5-(1H-benzotriazol-5-yl)-2-fluoro-benzyl]-4-fluoro-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

N-[5-(1H-benzotriazol-5-yl)-2-fluoro-benzyl]-4-fluoro-N-piperidin-4-yl-benzamide;

N-[5-(1H-benzotriazol-5-yl)-2-fluoro-benzyl]-4-fluoro-N-(1-isopropyl-piperidin-4-yl)-benzamide;

N-[5-(1H-benzotriazol-5-yl)-2-fluoro-benzyl]-N-(1-cyclopropyl-piperidin-4-yl)-4-fluoro-benzamide;

N-[5-(1H-benzotriazol-5-yl)-2-fluoro-benzyl]-N-(1-methyl-piperidin-4-yl)-4-fluoro-benzamide;

5-[3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-benzotriazole;

5-[4-fluoro-3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-benzotriazole; and

5-[4-fluoro-3-[2S-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-phenyl]-1H-benzotriazole;

or a pharmaceutically acceptable salt thereof or an optical or stereoisomer thereof.

In yet another embodiment of this invention the compound of formula (I) is having the following substituents:

$X \text{---} Y$ denotes a single bond between X and Y;

X is CHR;

Y is CHR;

Z is NR;

A, B and E are CH;

Ar is phenyl, fluorophenyl, chlorophenyl, pyridinyl, pyrazinyl, furanyl or thiophenyl;

each R is independently chosen from hydrogen, methyl, ethyl or CF₃;

R₁ and R₂ are the same or different and selected independently of each other from

benzyl, fluorobenzyl, fluorobenzoyl, difluorobenzoyl, chlorobenzoyl,

isopropoxybenzoyl, trifluoromethylbenzoyl, fluoro-trifluoromethylbenzoyl,

trifluoromethoxybenzoyl, thiophenylcarbonyl, pyridinylcarbonyl,

pyrazinylcarbonyl, pyrimidinylcarbonyl, pyridazinylcarbonyl, dihydro-

benzo[1,4]dioxinylcarbonyl, benzo[1,3]dioxolylcarbonyl, thiophenylmethyl, N-

methyl-aza-bicyclo[2.2.2]octyl, aza-bicyclo[2.2.2]octyl, aza-

bicyclo[2.2.2]octylmethyl, N-methyl-piperidinyl, N-isopropyl-piperidinyl, N-

cyclopropyl-piperidinyl, piperidinyl, N-methyl-pyrrolidinyl, N-ethyl-

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pyrrolidinylmethyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolidinylpropyl, methylaminoethyl, dimethylaminoethyl and dimethylaminopropyl;

or

5 R₁ and R₂ taken together with the nitrogen atom to which they are attached form a unsubstituted or at least monosubstituted heterocycle selected from the group consisting of piperazine and diazepane; wherein the substituents are selected from the group consisting of phenyl, fluorophenyl, trifluoromethylphenyl, pyridinyl, thiophenyl, furanyl and methyl.

10 An example of a compound of formula (I) falling within the scope of the above noted embodiment includes without any limitations the following:

N-[5-(2,3-dihydro-1H-indol-5-yl)-2-fluoro-benzyl]-N-(2-dimethylamino-ethyl)-4-fluoro-benzamide;

or a pharmaceutically acceptable salt thereof or an optical or stereoisomer thereof.

15 In yet another embodiment of this invention the compound of formula (I) is having the following substituents:

$X \text{---} Y$ denotes a single bond between X and Y;

X is O, S or NR;

Y is CO;

Z is NR;

20 A, B and E are CH;

Ar is phenyl, fluorophenyl, chlorophenyl, pyridinyl, pyrazinyl, furanyl or thiophenyl; each R is independently chosen from hydrogen, methyl or ethyl;

R₁ and R₂ are the same or different and selected independently of each other from benzyl, fluorobenzyl, benzoyl, fluorobenzoyl, difluorobenzoyl, chlorobenzoyl, 25 isopropoxybenzoyl, trifluoromethylbenzoyl, fluoro-trifluoromethylbenzoyl, trifluoromethoxybenzoyl, thiophenylcarbonyl, pyridinylcarbonyl, pyrazinylcarbonyl, pyrimidinylcarbonyl, pyridazinylcarbonyl, dihydro-benzo[1,4]dioxinylcarbonyl, benzo[1,3]dioxolylcarbonyl, thiophenylmethyl, N-methyl-aza-bicyclo[2.2.2]octyl, aza-bicyclo[2.2.2]octyl, aza- 30 bicyclo[2.2.2]octylmethyl, N-methyl-piperidinyl, N-isopropyl-piperidinyl, N-cyclopropyl-piperidinyl, piperidinyl, N-methyl-pyrrolidinyl, N-ethyl-

pyrrolidinylmethyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolidinylpropyl, methylaminoethyl, dimethylaminoethyl and dimethylaminopropyl;

or

R₁ and R₂ taken together with the nitrogen atom to which they are attached form a
5 unsubstituted or at least monosubstituted heterocycle selected from the group consisting of piperazine and diazepane; wherein the substituents are selected from the group consisting of phenyl, fluorophenyl, trifluoromethylphenyl, pyridinyl, thiophenyl, furanyl and methyl.

10 Examples of compounds of formula (I) falling within the scope of the above noted embodiment include without any limitations the following:

6-(3-{[benzyl-(2-dimethylamino-ethyl)-amino]-methyl}-phenyl)-3H-benzothiazol-2-one hydrochloride;

N-(2-dimethylamino-ethyl)-N-[3-(2-oxo-2,3-dihydro-benzothiazol-6-yl)-benzyl]-benzamide hydrochloride;

15 4-chloro-N-(2-dimethylamino-ethyl)-N-[3-(2-oxo-2,3-dihydro-benzothiazol-6-yl)-benzyl]-benzamide hydrochloride;

N-(3-dimethylamino-propyl)-N-[3-(2-oxo-2,3-dihydro-benzothiazol-6-yl)-benzyl]-benzamide; hydrochloride;

20 6-(3-{[benzyl-(2-dimethylamino-ethyl)-amino]-methyl}-phenyl)-3H-benzooxazol-2-one hydrochloride;

6-(5-{[(2-dimethylamino-ethyl)-(4-fluoro-benzyl)-amino]-methyl}-pyridin-3-yl)-3H-benzooxazol-2-one;

6-(5-{[(2-dimethylamino-ethyl)-(4-fluoro-benzyl)-amino]-methyl}-furan-3-yl)-3H-benzooxazol-2-one;

25 6-(3-{[(1-ethyl-pyrrolidin-2R-ylmethyl)-(4-fluoro-benzyl)-amino]-methyl}-4-fluorophenyl)-3H-benzooxazol-2-one trifluoro-acetate;

6-(4-fluoro-3-{[(4-fluoro-benzyl)-(1-methyl-piperidin-4-yl)-amino]-methyl}-phenyl)-3H-benzooxazol-2-one;

30 6-(5-{[(4-fluoro-benzyl)-(1-methyl-piperidin-4-yl)-amino]-methyl}-furan-3-yl)-3H-benzooxazol-2-one;

4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

64

- N-(2-dimethylamino-ethyl)-N-[3-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-benzamide hydrochloride;
- N-(1-ethyl-pyrrolidin-2-ylmethyl)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-benzamide;
- 5 4-chloro-N-(2-dimethylamino-ethyl)-N-[3-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-benzamide hydrochloride;
- N-(1-ethyl-pyrrolidin-2*R*-ylmethyl)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-benzamide trifluoro-acetate;
- 4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-benzamide;
- 10 N-(1-aza-bicyclo[2.2.2]oct-3*S*-yl)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-benzamide hydrochloride;
- N-(1-aza-bicyclo[2.2.2]oct-3*R*-yl)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-benzamide hydrochloride;
- 15 N-(2-dimethylamino-ethyl)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-benzamide;
- 6-[3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-3*H*-benzooxazol-2-one;
- 6-{5-[2*R*-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-furan-3-yl}-3*H*-benzooxazol-2-one;
- 20 6-{5-[2*S*-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-furan-2-yl}-3*H*-benzooxazol-2-one;
- 6-{5-[2*S*-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-thiophen-3-yl}-3*H*-benzooxazol-2-one;
- 6-[4-fluoro-3-(2-thiophen-2-yl-piperazin-1-ylmethyl)-phenyl]-3*H*-benzooxazol-2-one;
- 25 6-{5-[2*S*-(4-fluorophenyl)-4-methylpiperazine-1-ylmethyl]-furan-3-yl}-3*H*-benzooxazol-2-one;
- 6-{5-[2*S*-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-furan-3-yl}-3*H*-benzooxazol-2-one acetate;
- 6-{4-fluoro-3-[2*S*-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-phenyl}-3*H*-benzooxazol-2-one;
- 30 6-{5-[2*S*-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-pyridin-3-yl}-3*H*-benzooxazol-2-one acetate; and

5-(3-{{benzyl-(2-dimethylamino-ethyl)-amino}-methyl}-phenyl)-1,3-dihydro-benzimidazol-2-one hydrochloride;

or a pharmaceutically acceptable salt thereof or an optical or stereoisomer thereof.

In yet another embodiment of this invention the compound of formula (I) is having the
5 following substituents:

$X \text{---} Y$ denotes a single bond between X and Y;

X is O or CO;

Y is CHR or NR;

Z is CONR;

10 A, B and E are the same or different and independently from each other are CH or N;

Ar is phenyl, fluorophenyl, chlorophenyl, pyridinyl, pyrazinyl, furanyl or thiophenyl;

each R is independently chosen from hydrogen, methyl or ethyl;

R₁ and R₂ are the same or different and selected independently of each other from

benzyl, fluorobenzyl, benzoyl, fluorobenzoyl, difluorobenzoyl, chlorobenzoyl,
15 isopropoxybenzoyl, trifluoromethylbenzoyl, fluoro-trifluoromethylbenzoyl,
trifluoromethoxybenzoyl, thiophenylcarbonyl, pyridinylcarbonyl,
pyrazinylcarbonyl, pyrimidinylcarbonyl, pyridazinylcarbonyl, dihydro-
benzo[1,4]dioxinylcarbonyl, benzo[1,3]dioxolylcarbonyl, thiophenylmethyl, N-
methyl-aza-bicyclo[2.2.2]octyl, aza-bicyclo[2.2.2]octyl, aza-
20 bicyclo[2.2.2]octylmethyl, N-methyl-piperidinyl, N-isopropyl-piperidinyl, N-
cyclopropyl-piperidinyl, piperidinyl, N-methyl-pyrrolidinyl, N-ethyl-
pyrrolidinylmethyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolidinylpropyl,
methylaminoethyl, dimethylaminoethyl and dimethylaminopropyl;

or

25 R₁ and R₂ taken together with the nitrogen atom to which they are attached form a
unsubstituted or at least monosubstituted heterocycle selected from the group
consisting of piperazine and diazepane; wherein the substituents are selected
from the group consisting of phenyl, fluorophenyl, trifluoromethylphenyl,
pyridinyl, thiophenyl, furanyl and methyl.

30 Examples of compounds of formula (I) falling within the scope of the above noted
embodiment include without any limitations the following:

66

6-(3-{[benzyl-(2-dimethylamino-ethyl)-amino]-methyl}-phenyl)-3-methyl-1H-quinazoline-2,4-dione hydrochloride; and

7-(3-{[benzyl-(2-dimethylamino-ethyl)-amino]-methyl}-phenyl)-4H-pyrido[3,2-b][1,4]oxazin-3-one hydrochloride;

5 or a pharmaceutically acceptable salt thereof or an optical or stereoisomer thereof.

In yet another embodiment of this invention the compound of formula (I) is having the following substituents:

$X=Y$ denotes a double bond between X and Y;

X is CR;

10 Y is CR;

Z is NR;

A, B and E are the same or different and independently from each other are CH or N;

D is CO;

Ar is phenyl, fluorophenyl, chlorophenyl, pyridinyl, pyrazinyl, furanyl or thiophenyl;

15 each R is independently chosen from hydrogen, methyl, ethyl, methoxy, fluorine, CF_3 or OCF_3 ;

R_1 and R_2 are the same or different and selected independently of each other from

benzyl, fluorobenzyl, benzoyl, fluorobenzoyl, difluorobenzoyl, chlorobenzoyl,

isopropoxybenzoyl, trifluoromethylbenzoyl, fluoro-trifluoromethylbenzoyl,

20 trifluoromethoxybenzoyl, thiophenylcarbonyl, pyridinylcarbonyl,

pyrazinylcarbonyl, pyrimidinylcarbonyl, pyridazinylcarbonyl, dihydro-

benzo[1,4]dioxinylcarbonyl, benzo[1,3]dioxolylcarbonyl, thiophenylmethyl, N-

methyl-aza-bicyclo[2.2.2]octyl, aza-bicyclo[2.2.2]octyl, aza-

bicyclo[2.2.2]octylmethyl, N-methyl-piperidinyl, N-isopropyl-piperidinyl, N-

25 cyclopropyl-piperidinyl, piperidinyl, N-methyl-pyrrolidinyl, N-ethyl-

pyrrolidinylmethyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolidinylpropyl,

methylaminoethyl, dimethylaminoethyl and dimethylaminopropyl;

or

30 R_1 and R_2 taken together with the nitrogen atom to which they are attached form a unsubstituted or at least monosubstituted heterocycle selected from the group consisting of piperazine and diazepane; wherein the substituents are selected

from the group consisting of phenyl, fluorophenyl, trifluoromethylphenyl, pyridinyl, thiophenyl, furanyl and methyl.

An example of a compound of formula (I) falling within the scope of the above noted embodiment includes without any limitations the following:

5 [2-fluoro-5-(1H-indol-5-yl)-phenyl]-[2S-(4-fluoro-phenyl)-4-methyl-piperazin-1-yl]-methanone;

or a pharmaceutically acceptable salt thereof or an optical or stereoisomer thereof.

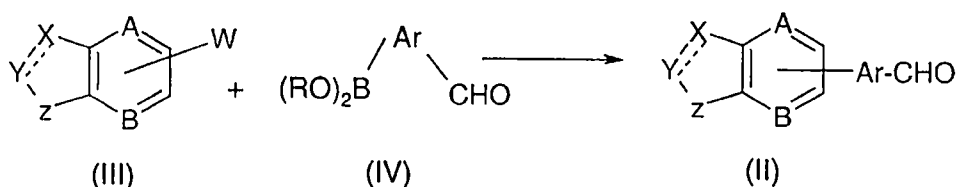
The compounds of this invention can be synthesized by any of the procedures known to one skilled in the art. Specifically, several of the starting materials used in the preparation
10 of the compounds of this invention are known or are themselves commercially available. The compounds of this invention and several of the precursor compounds may also be prepared by methods used to prepare similar compounds as reported in the literature and as further described herein.

More specifically, the compounds disclosed herein can be synthesized according to the
15 following procedures of Schemes 1 - 10, wherein the X, Y, Z, A, B, D, E, Ar, R₁ and R₂ are as defined for Formula I unless otherwise indicated.

Schemes 1 and 2 illustrate synthesis of a key intermediate II used in the preparation of compounds of formula I. However, the intermediate aldehyde II can be synthesized by any of the methods known in the art.

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Scheme 1



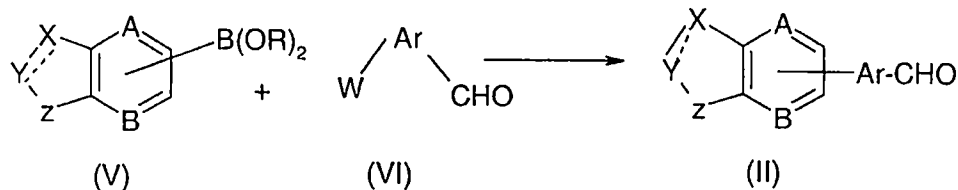
As shown in Scheme 1, the aldehyde II is prepared starting from a compound of the formula III, wherein W is halogen or trifluoromethanesulfonate (triflate). As illustrated, III is reacted with boronic acid or ester of the formula IV (wherein R is hydrogen, C₁₋₄alkyl or the
25 two R's taken together with the oxygen atoms to which they are attached form a five or six membered ring) to obtain aldehyde intermediate II. This reaction can be carried out by any of the methods known in the art. For example, such addition reactions are carried out in the presence of a suitable catalyst such as palladium compounds. Examples of palladium compounds suitable for such coupling reactions include tetrakis(triphenylphosphine)palladium

chloride or $\text{PdCl}_2(\text{dppf})$ ($\text{dppf} = 1,1'$ bis(diphenylphosphino)ferrocene), and the like. The reaction is also generally carried out in the presence of a suitable base, such as for example, cesium carbonate and the like. Further, any groups that may interfere with this addition reaction may need to be protected. For instance, when $Z = \text{NH}$, the nitrogen may be suitably protected before carrying out this coupling reaction. Any of the known nitrogen protecting groups can be employed as long as such protecting groups do not interfere with this reaction. Such protecting groups are described in T. W. Greene, *Protective Groups in Organic Synthesis*, J. Wiley-Interscience Publication (1999). The reaction can further be carried out in a suitable solvent preferably an organic solvent such as dioxane, dimethylsulfoxide, dimethylformamide, or the like, or in the presence of water as a co-solvent, and at subambient to superambient temperature conditions. Normally, the reaction is carried out at elevated temperatures, for example, at the reflux temperature of the solvent and preferably in an inert atmosphere. The reaction mixture can be heated using conventional methods or alternatively using microwave irradiation. However, as noted above, any of the other known methods can also be used to bring about this coupling reaction to form the aldehyde II.

Alternatively, the aldehyde II can also be prepared using a boronic acid or ester of formula V and an aromatic aldehyde of formula VI as illustrated in Scheme 2. This coupling reaction can essentially be carried out under similar conditions as described above in order to obtain the aldehyde II.

20

Scheme 2



Scheme 3 illustrates preparation of a series of compounds of formula I wherein D is CH_2 and R_2 is either $\text{Ar}'\text{CH}_2$ or $\text{Ar}'\text{CO}$ and wherein Ar' is aryl or heteroaryl as described herein.

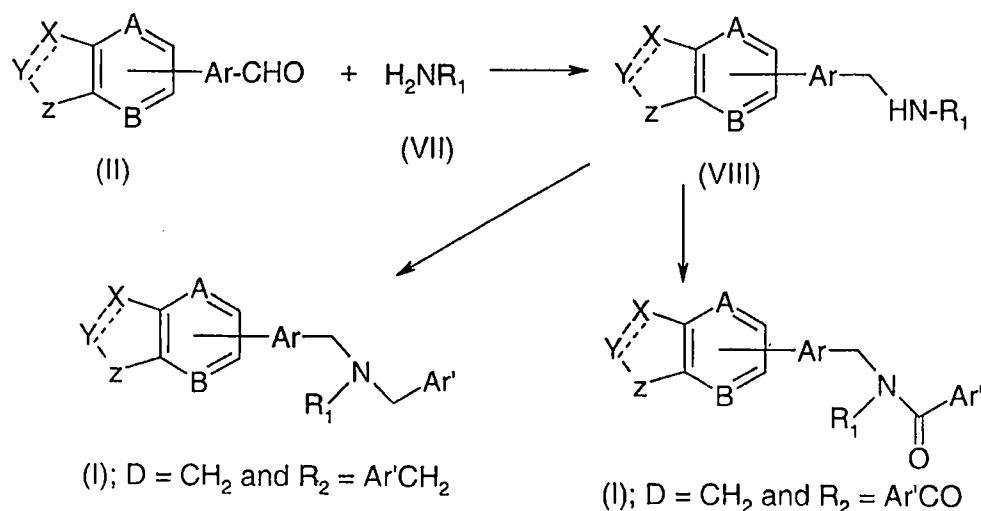
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In Scheme 3, the intermediate aldehyde II is reacted with a desirable amine under reductive alkylation conditions to form compound of formula VIII. This amine coupling reaction can be carried out using any of the known methods in the art. Generally such reductive amination can be carried out using a reducing agent such as sodiumcyanoborohydride, or sodium triacetoxyborohydride, ($\text{NaB}(\text{O}_2\text{CCH}_3)_3\text{H}$), and the like

in a suitable reaction medium, such as tetrahydrofuran or dichloroethane. Alternatively, the reaction of the aldehyde and amine can be carried out in the presence of a dehydrating agent, such as, for example, molecular sieves, in an organic solvent such as methanol, followed by addition of a reducing agent such as sodium borohydride.

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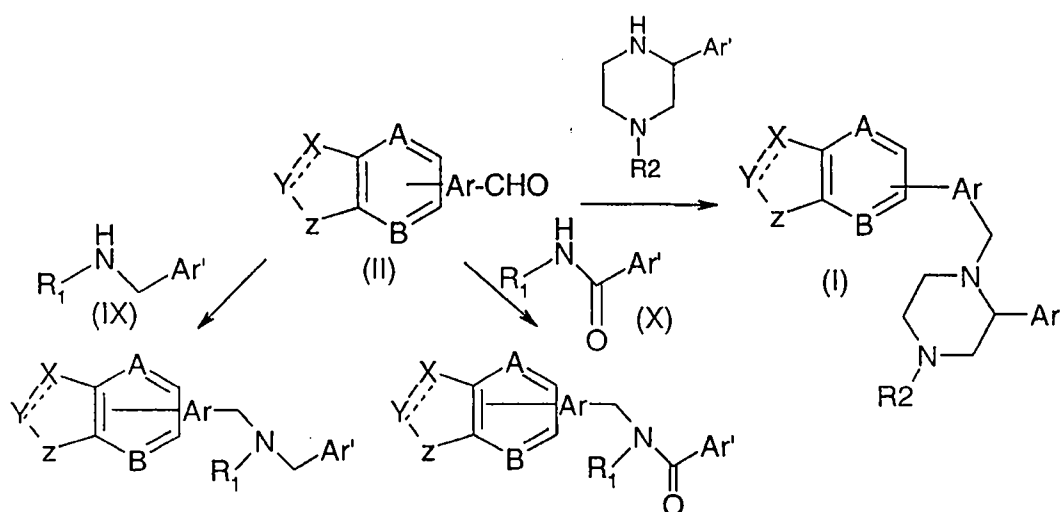
Scheme 3



The intermediate amino compound VIII thus formed is then subjected to another reductive alkylation reaction using a suitable aromatic aldehyde to form compounds of formula I wherein D = CH₂ and R₂ = Ar'CH₂. This alkylation reaction can also be carried out under essentially similar conditions as described above. That is, compound of formula VIII is reacted with Ar'CHO in the presence of a suitable reducing agent such as sodium triacetoxyborohydride (NaB(O₂CCH₃)₃H) to form the corresponding compound of formula I. The compound of formula VIII can be reacted with a suitable aromatic carboxylic acid of formula Ar'CO₂H or carboxylic acid chloride to form compound of formula I wherein D = CH₂ and R₂ = Ar'CO. This reaction can again be carried out using any of the methods known in the art. For instance such acylation reactions with carboxylic acid chlorides are carried out in the presence of a suitable base such as triethylamine or diisopropylethylamine in an organic solvent such as dichloromethane. Alternatively reaction of the compound of formula VIII with a carboxylic acid and an amine coupling reagent such as, for example, *O*-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) in the presence of a base such as diisopropylethylamine also affords compounds of formula I.

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Scheme 4

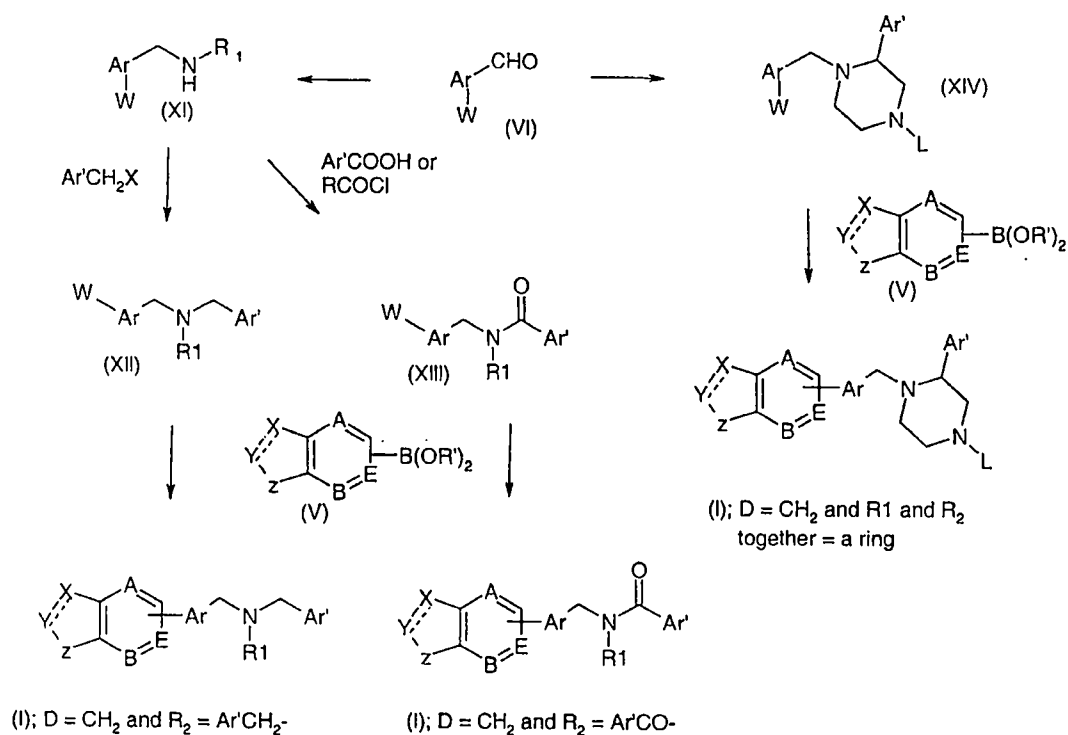


(I); D = CH₂ and R₂ = Ar'CH₂ (I); D = CH₂ and R₂ = Ar'CO

Alternatively, compounds of formula I of the types shown in Scheme 3 can also be prepared starting from the aldehyde II and a suitable amino compound IX or X as illustrated in Scheme 4. The compound of formula II can also be reacted with cyclic amines such as piperidine derivatives shown to form the corresponding compounds of formula I. Again this amination reaction can be carried out under similar conditions as described above. That is, the aldehyde II is reacted with suitable amine IX or piperidine derivative or suitable amide X in the presence of a suitable reducing agent such as sodium triacetoxyborohydride (NaB(O₂CCH₃)₃H) to form the corresponding compounds of formula I.

Scheme 5 illustrates further variation of a synthetic method for the preparation of compounds of formula I. In this approach, halo-aromatic aldehyde of formula VI is first reacted with an amine to form compound of formula XI, which is reacted either with aralkyl halide or aromatic carboxylic acid to form corresponding compounds of formula XII and XIII. The latter compounds are finally reacted with boronic acids or esters of formula V to form the corresponding compounds of formula I wherein D = CH₂ and R₂ is either Ar'CH₂ or Ar'CO.

Scheme 5



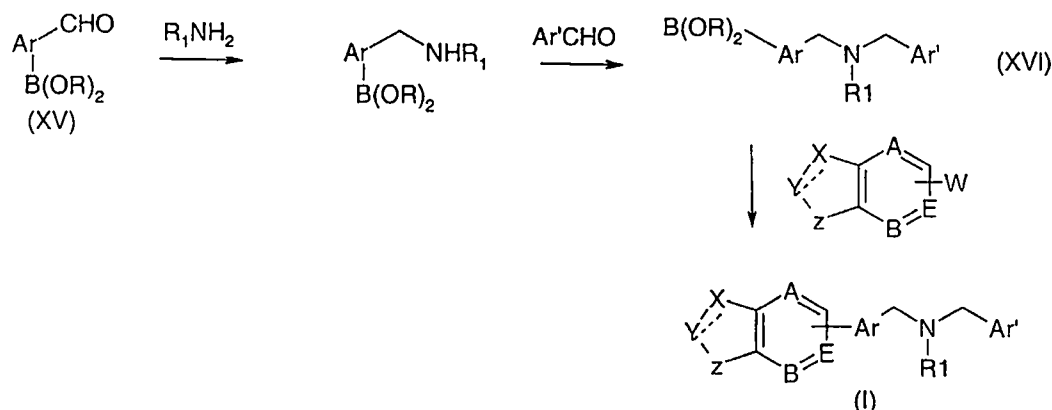
Similar reaction conditions can be employed for various steps set forth in Scheme 5 as described above. For instance, the reductive amination reaction of the halo-aromatic aldehyde VI with the amine is affected under reductive conditions in the presence of a reducing agent such as sodium triacetoxyborohydride as discussed above for similar reductive amination reactions. The amino compound XI so formed is then subjected to arylation or aroylation by reacting respectively with aralkyl halide such as arylmethylhalide of formula Ar'CH₂-halo or an aromatic carboxylic acid such as Ar'CO₂H under conditions as described in scheme 4 to obtain the corresponding compounds of formula XII and XIII. Finally, each of which is reacted with the boron compound V to form the corresponding compound of formula I.

The compounds of formula I may also be prepared as outlined in Scheme 6, using the methods described above. For example, the reductive alkylation reaction of the boranyl-aromatic aldehyde XV with an amine is affected under reductive conditions in the presence of a reducing agent such as sodium triacetoxyborohydride as discussed above for similar reductive alkylation reactions. Further treatment of the amine obtained with an aldehyde under similar conditions then provides the boranyl-amine XVI. This boronic acid or ester can then be coupled to an aryl or heteroaryl halide or trifluoromethanesulfonate, in the presence of

72

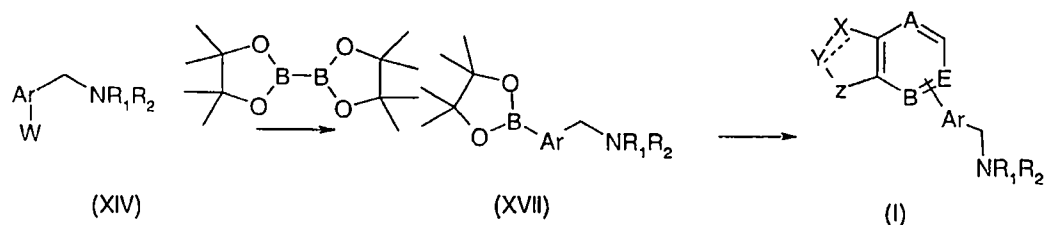
a suitable organometallic coupling agent as described earlier to afford compounds of formula I.

Scheme 6



In a similar fashion, as shown in Scheme 7, the boranyl-amine XVII may be prepared by treatment of an amino substituted aryl halide or triflate with a borylating agent such as bis(pinacolato)diboron in the presence of an organometallic coupling agent such as $\text{Pd}(\text{dppf})\cdot\text{DCM}$ in an organic solvent such as dioxane, dimethylsulfoxide or dimethylformamide at elevated temperature. This boronic acid or ester can then be coupled with an aryl halide or trifluoromethanesulfonate under the conditions described above, or for example using fibreCat 1001 in the presence of a phase transfer catalyst such as tetrabutylammonium bromide, a base such as cesium carbonate in a mixture of an organic solvent such as dioxane and water at elevated temperatures.

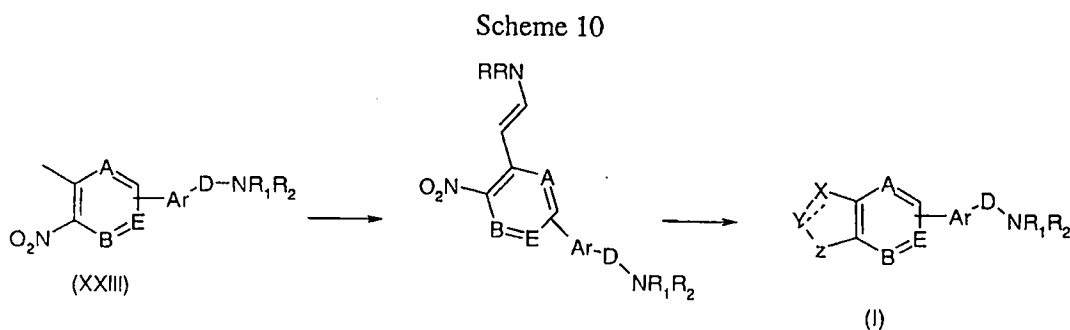
Scheme 7



Compounds of formula I may also be prepared as outlined in Scheme 8. Carboxylic acids or esters may be prepared as described for aldehydes in Schemes 1 and 2. Reduction of the acids or esters to the alcohols XIX may be carried out by any number of methods known in the art, including the use of, for example, hydride reducing agents such as lithium aluminum hydride in an appropriate solvent such as diethyl ether or THF. The alcohols so prepared can be activated by transformation into a halide, a mesylate, triflate or nosylate. For example mesylates may be prepared by treating the alcohols with methanesulfonyl chloride or

73

known in the art. For example, as shown in Scheme 10, an indole may be prepared from a suitably substituted biaryl or heteroaryl (prepared by the methods described above). Treatment of the nitro compound XXIII with dimethylformamide dimethylacetal in a suitable solvent, such as dimethylformamide, followed by hydrogenation using a Pd or Pt catalyst (for example 10% Pd supported on carbon) provides a compound of formula I where X, Y, and Z are C=C-N and are part of an indole.



As noted above, various modifications can be made to the above described schemes in order to prepare various other compounds of formula I employing suitable starting materials and using other methods known in the art. A wide variety of such specific synthetic examples are further provided below.

In another aspect of this invention, a specific disease, a disorder or a condition that can be treated with the compound of this invention include, without any limitation a wide variety of sleep disorders. In addition, the compounds of this invention are selective serotonin antagonists particularly the compounds of this invention are selective antagonists at the 5HT_{2A} receptor.

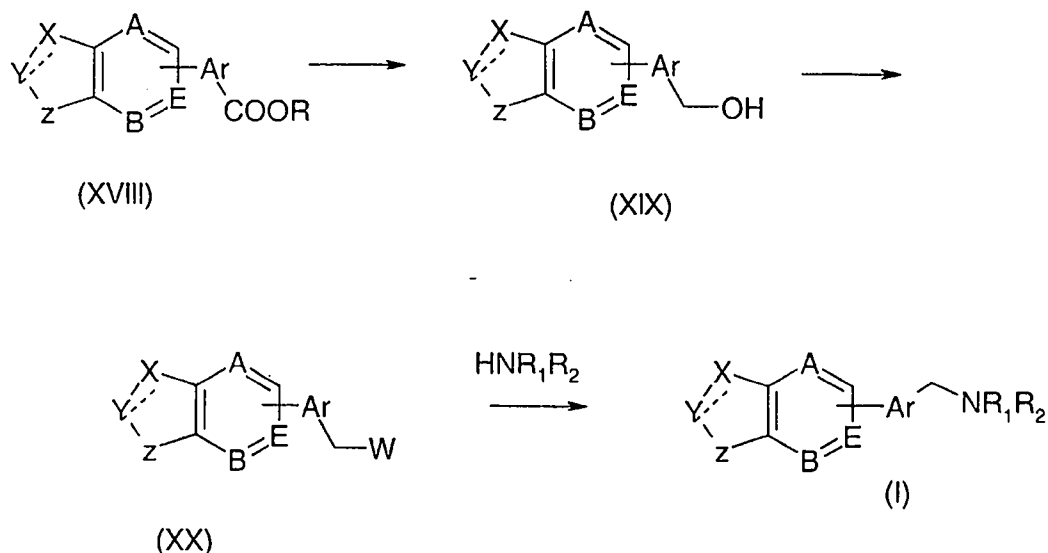
One of skill in the art readily appreciates that the pathologies and disease states expressly stated herein are not intended to be limiting rather to illustrate the efficacy of the compounds of the present invention. Thus it is to be understood that the compounds of this invention may be used to treat any disease caused by the effects of 5HT_{2A} receptor. That is, as noted above, the compounds of the present invention are selective 5HT_{2A} antagonists and thus may be effectively administered to ameliorate any disease state which is mediated all or in part by 5HT_{2A} receptor.

All of the various embodiments of the compounds used in the methods of this invention as disclosed herein can be used in the method of treating various disease states as described herein. As stated herein, the compounds used in the method of this invention are

74

methanesulfonyl anhydride in the presence of a base such as triethyl amine or diisopropylethylamine in an appropriate solvent such as DCM or DCE. Compounds XX can then be transformed to the targets of formula I by treatment with an appropriate amine.

Scheme 8

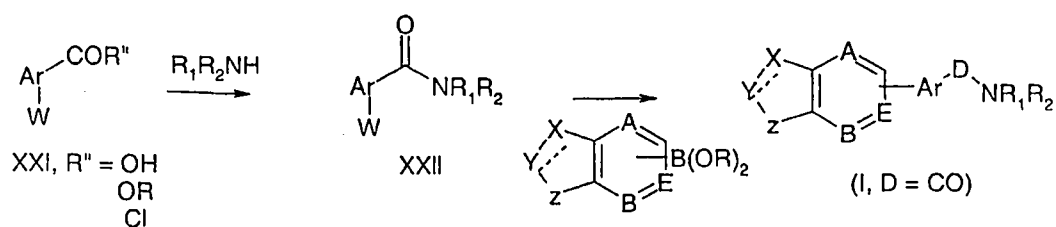


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Compounds of formula I in which D = CO may be prepared by methods similar to those described above, replacing a reductive alkylation with an amide forming reaction. For example (Scheme 9), in a method related to the one described in Scheme 5, amidation of a carboxylic acid or carboxylic acid derivative can be accomplished by many known methods. For example amides XXII may be obtained by treatment of carboxylic acids XXI ($R'' = \text{H}$) upon treatment with an amine in the presence of a coupling agent, such as HOBT, HOAT or HATU, with a base such as triethylamine or diisopropylamine in an appropriate solvent, for example dimethylformamide or dichloromethane. Subsequent organometallic coupling as described above provides compounds of formula I (D = CO).

15

Scheme 9



In an alternative approach to the preparation of the compounds of this invention, the heterocyclic ring formed by X, Y, and Z may be prepared by any of a variety of methods

75

capable of antagonizing the effects of 5HT_{2A} receptor and thereby alleviating the effects and/or conditions caused due to the activity of 5HT_{2A} receptor.

In a specific embodiment of this invention the compounds of this invention are particularly suitable for the treatment of a variety of sleep disorders. The term "sleep disorder" as used herein shall mean all of the description as delineated in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (1994), hereafter referred to as DSM-IV, published by the American Psychiatric Association. Specific sleep disorders that can be treated in accordance with this invention include without any limitation insomnia, primary insomnia, sleep disorder related to another mental disorder substance induced sleep disorder and obstructive sleep apnea. Further description and discussion of sleep disorders are found in the International Classification of Sleep Disorders: Diagnostic and Coding Manual (1990), published by the American Sleep Disorders Association.

The term "insomnia" as used herein includes all sleep disorders, which are not caused due to other factors such as mental disorders, other medical conditions and substance induced sleep disorders. Insomnia as used herein shall also mean primary sleep disorders as defined in DSM-IV, which includes two sub-categories, namely, dyssomnias and parasomnias.

The term "primary insomnia" shall mean all of the definitions provided in DSM-IV. In addition, "primary insomnia" as used herein also includes "sleep maintenance insomnia." The DSM-IV lists the diagnostic criteria for primary insomnia as follows:

- A. The predominant complaint is difficulty initiating or maintaining sleep, or nonrestorative sleep, for at least one month.
- B. The sleep disturbance (or associated day time fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- C. The sleep disturbance does not occur exclusively during the course of narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorder, or a parasomnia.
- D. The disturbance does not occur exclusively during the course of another mental disorder (e.g., major depressive disorder, generalized anxiety disorder, a delirium).
- E. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

70

The term "sleep disorder related to another mental disorder" as used herein includes both insomnia and hypersomnia related to another mental disorder. The DSM-IV lists the diagnostic criteria for insomnia related to another mental disorder as follows:

- 5 A. The predominant complaint is difficulty initiating or maintaining sleep, or nonrestorative sleep, for at least one month that is associated with daytime fatigue or impaired daytime functioning.
- B. The sleep disturbance (or daytime sequelae) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- 10 C. The insomnia is judged to be related to another axis I or axis II disorder (e.g., major depressive disorder, generalized anxiety disorder, adjustment disorder with anxiety, schizophrenia, etc.), but is sufficiently severe to warrant independent clinical attention.
- D. The disturbance is not better accounted for by another sleep disorder (e.g., narcolepsy, breathing-related sleep disorder, a parasomnia).
- 15 E. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

Similarly, the DSM-IV lists the diagnostic criteria for hypersomnia related to another mental disorder as follows:

- 20 A. The predominant complaint is excessive sleepiness for at least one month as evidenced by either prolonged sleep episodes or daytime sleep episodes that occur almost daily.
- B. The excessive sleepiness causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- 25 C. The hypersomnia is judged to be related to another axis I or axis II disorder (e.g., major depressive disorder, dysthymic disorder, schizophrenia, etc.), but is sufficiently severe to warrant independent clinical attention.
- D. The disturbance is not better accounted for by another sleep disorder (e.g., narcolepsy, breathing-related sleep disorder, a parasomnia) or by an inadequate amount of sleep.
- 30 E. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

77

The term "substance induced sleep disorder" as used herein means a prominent disturbance in sleep that is sufficiently severe to warrant independent clinical attention and is judged to be due to the direct physiological effects of a substance (i.e., a drug of abuse, a medication, or toxin exposure). Specific examples of drug of abuse, a medication or toxin exposure as referred to herein include without any limitations caffeine, alcohol, amphetamine, opioids, sedatives, hypnotics, anxiolytics, and the like. The DSM-IV lists the diagnostic criteria for substance induced sleep disorder as follows:

- A. A prominent disturbance in sleep that is sufficiently severe to warrant independent clinical attention.
- 10 B. There is evidence from the history, physical examination, or laboratory findings of either (1) or (2): (1) the symptoms in criterion A developed during, or within a month of, substance intoxication or withdrawal; (2) medication use is etiologically related to the sleep disturbance.
- 15 C. The disturbance is not better accounted for by a sleep disorder that is not substance induced. Evidence that the symptoms are better accounted for by a sleep disorder that is not substance induced might include the following: the symptoms precede the onset of the substance use (or medication use); the symptoms persist for a substantial period of time (e.g., about a month) after the cessation of acute withdrawal or severe intoxication, or are substantially in
20 excess of what would be expected given the type or amount of the substance used or the duration of use; or there is evidence that suggests the existence of an independent non-substance-induced sleep disorder (e.g., a history of recurrent non-substance-related episodes).
- D. The disturbance does not occur exclusively during the course of a delirium.
- 25 E. The sleep disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

As used herein "withdrawal" refers to a syndrome characterized by untoward physical changes that occur following cessation of or reduction in substance use, or administration of a pharmacologic antagonist (or medication).

- 30 The term "obstructive sleep apnea" as used herein is breathing related sleep disorder as defined in DSM-IV. It is also referred to as upper airway resistance syndrome and generally involves repeated episodes of upper-airway obstruction during sleep and is normally

characterized by loud snores or brief gasps that alternate with episodes of silence. The DSM-IV lists the diagnostic criteria for breathing related sleep disorder as follows:

- A. Sleep disruption, leading to excessive sleepiness or insomnia, that is judged to be due to a sleep-related breathing condition (e.g., obstructive sleep or central sleep apnea syndrome or central alveolar hypoventilation syndrome).
- B. The disturbance is not better accounted for by another mental disorder and is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or another general medical condition (other than a breathing related disorder).

Subjective and Objective Determinations of Sleep Disorders: There are a number of ways to determine whether the onset, duration or quality of sleep (e.g. non-restorative or restorative sleep) is impaired or improved. One method is a subjective determination of the patient, e.g., do they feel drowsy or rested upon waking. Other methods involve the observation of the patient by another during sleep, e.g., how long it takes the patient to fall asleep, how many times does the patient wake up during the night, how restless is the patient during sleep, etc. Another method is to objectively measure the stages of sleep.

Polysomnography is the monitoring of multiple electrophysiological parameters during sleep and generally includes measurement of electro-encephalogram (EEG) activity, electroculographic activity and electromyographic activity (EMG), as well as other measurements. These results, along with observations, can measure not only sleep latency (the amount of time required to fall asleep), but also sleep continuity (overall balance of sleep and wakefulness) which may be an indication of the quality of sleep.

There are five distinct sleep stages which can be measured by polysomnography: rapid eye movement (REM) sleep and four stages of no-rapid eye movement (NREM) sleep (stages 1, 2, 3 and 4). Stage 1 NREM sleep is a transition from wakefulness to sleep and occupies about 5% of time spent asleep in healthy adults. Stage 2 NREM sleep, which is characterized by specific EEG waveforms (sleep spindles and K complexes), occupies about 50% of time spent asleep. Stages 3 and 4 NREM sleep (also known collectively as slow-wave sleep) are the deepest levels of sleep and occupy about 10-20% of sleep time. REM sleep, during which the majority of typical story like dreams occur, occupies about 20-25% of total sleep.

These sleep stages have a characteristic temporal organization across the night. NREM stages 3 and 4 tend to occur in the first one-third to one-half of the night and increase

in duration in response to sleep deprivation. REM sleep occurs cyclically through the night, alternating with NREM sleep about every 80-100 minutes. REM sleep periods increase in duration toward the morning. Human sleep also varies characteristically across the life span. After relative stability with large amounts of slow-wave sleep in childhood and early adolescence, sleep continuity and depth deteriorate across the adult age range. This deterioration is reflected by increased wakefulness and stage 1 sleep and decreased stages 3 and 4 sleep.

In general, the compounds of this invention improve quality of sleep through serotonergic mechanisms (acting at the 5HT_{2A} receptor site) when administered to a patient suffering from any of the sleep disorders as described hereinabove. That is, in general, it has been found that the administration of compounds of this invention increases the duration of stages 3 and 4 of slow wave sleep (SWS, measured as NREM sleep). This is also measured by decrease in wake after sleep onset (WASO), the primary efficacy measure in the clinical trial. In addition, enhancement of SWS in older adults may also yield increases in cognition and enhanced quality of life. SWS could play an important role in the regulation of cognitive processes in older adults. It has been shown that there is a direct relationship between the SWS amount and performance on daily cognitive testing. Thus, it has now been found that compounds of this invention are useful in increasing cognition and thereby enhancing quality of life in a patient, preferably in older adults.

The improvement in sleep quality is measured by polysomnography. The results of polysomnographic and sleep EEG studies in small numbers of young and aged healthy volunteers, and in patients with primary insomnia have shown an increase of SWS, and a decrease in WASO.

In another embodiment of the method of this invention, the compounds of this invention can be administered by any of the methods known in the art. Specifically, the compounds of this invention can be administered by oral, intramuscular, subcutaneous, rectal, intratracheal, intranasal, intraperitoneal or topical route.

Finally, in yet another embodiment of this invention, there is also provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound, including enantiomers, stereoisomers, and tautomers of said compound and pharmaceutically acceptable salts, solvates or derivatives thereof, with said compound having the general structure shown in formula I as described herein.

80

As described herein, the pharmaceutical compositions of this invention feature 5HT_{2A} antagonistic activity and thus are useful in treating any disease, condition or a disorder caused due to the effects of 5HT_{2A} in a patient. Again, as described above, all of the preferred embodiments of the compounds of this invention as disclosed herein can be used in preparing the pharmaceutical compositions as described herein.

Preferably the pharmaceutical compositions of this invention are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. Alternatively, the compositions may be presented in a form suitable for once-weekly or once-monthly administration; for example, an insoluble salt of the active compound, such as the fatty acid salt, for example stearate, etc. may be adapted to provide a depot preparation for intramuscular injection. An erodible polymer containing the active ingredient may be envisaged. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof.

Similarly, the pharmaceutical compositions of this invention can also be mixed with a wide variety of pharmaceutically acceptable excipients. Examples of pharmaceutically acceptable excipients include without any limitation acacia, acesulfame potassium, albumin, aliphatic polyesters, aspartame, bentonite, butylparaben, calcium stearate, canola oil, carbomer, carboxymethylcellulose, cellulose acetate, dextrin, guar gum, hydroxyethyl cellulose, maltodextrin, starch, and the like.

When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Flavored unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets or pills of the novel composition

can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

The pharmaceutical compositions of this invention can be administered by any of the methods known in the art. In general, the pharmaceutical compositions of this invention can be administered by oral, intramuscular, subcutaneous, rectal, intratracheal, intranasal, intraperitoneal or topical route. The preferred administrations of the pharmaceutical composition of this invention are by oral and intranasal routes. Any of the known methods to administer pharmaceutical compositions by an oral or an intranasal route can be used to administer the composition of this invention.

In the treatment of various disease states as described herein, a suitable dosage level is about 0.001 to 250 mg/kg per day, preferably about 0.005 to 100 mg/kg per day, and especially about 0.05 to 20 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

More specifically, the dosage range at which the compounds of this invention exhibit its ability to treat sleep disorders, including each specific type of sleep disorder, can vary depending upon the specific disorder, its severity, the patient, any underlying disease states that the patient is suffering from, and other medications that may be concurrently administered to the patient. Generally though, as noted above, the compounds of this invention will exhibit

its ability to treat sleep disorders at a range of from about 0.001mg/kg/day to about 100mg/kg/day.

This invention is further illustrated by the following examples which are provided for illustration purposes and in no way limit the scope of the present invention.

5

Examples (General)

Reactions generally are run under an inert atmosphere. All commercial chemicals and solvents are reagent grade and were used without further purification unless otherwise specified. All reactions except those in aqueous solution or otherwise noted were carried out with the use of standard techniques for the exclusion of moisture. Flash chromatography was carried out using silica gel 60 (35–70 μ m) according to the literature procedure (Still, W.C.; Kahn, M; Mitra, A. *J. Org. Chem.* 1978 43, 2923) or a variation of this method using commercially available silica gel cartridges (for example Isco Redi Sep) Reactions using focused or single mode microwave irradiation were performed on instruments from CEM Corporation or Personal Chemistry. The ^1H NMR spectra are run at 300 MHz or 400 MHz on a Gemini 300, Varian VXR 300 or Varian Inova-400 spectrometer and are determined in a deuterated solvent, such as DMSO- D_6 or CDCl_3 unless otherwise noted. Chemical shifts values are indicated in parts per million (ppm) with reference to tetramethylsilane (TMS) as the internal standard. Liquid chromatography with mass spectral analysis (LC/MS) is recorded on a Platform LC Mass Spectrometer with electrospray source operating in positive and negative ion mode and an HP1100 with inline HP1100 DAD detection and SEDEX ELS detection using a Waters XTerra MS C18 3.5 μ m 4.6 x 30 mm or a Phenomenex Luna C18(2) 30 x 4.6mm column eluting with 0.1% formic acid in water/acetonitrile (short LC/MS), or a Finnigan TSQ700 Mass Spectrometer with electrospray source operating in positive ion mode and an HP1050 system with inline HP1050 Single Wavelength UV detector at 254 nm using a Higgins Clipseus C18 5 μ m 100 x 3.0mm column eluting with 0.1% formic acid in water/acetonitrile (long LC/MS), or a Micromass LCTAPI LC-TOF (time of flight) Mass Spectrometer and Masslynx Data System. Ionization mode = electrospray (esi), values are determined for the protonated molecular ions ($\text{M}^+ + 1$) using a Synergi 2U HYDRO-RP 20 x 4 mm column, eluting with 0.1% trifluoroacetic acid (TFA) in water/acetonitrile (method 3)

As used in the examples and preparations that follow, the terms used therein shall have the meanings indicated: "kg" refers to kilograms, "g" refers to grams, "mg" refers to

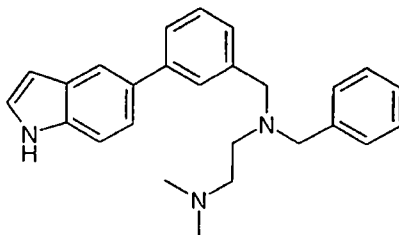
milligrams, "μg" refers to micrograms, "pg" refers to picograms, "lb" refers to pounds, "oz" refers to ounces, "mol" refers to moles, "mmol" refers to millimoles, "μmole" refers to micromoles, "nmole" refers to nanomoles, "L" refers to liters, "mL" or "ml" refers to milliliters, "μL" refers to microliters, "gal" refers to gallons, "°C" refers to degrees Celsius, "R_f" refers to retention factor, "mp" or "m.p." refers to melting point, "dec" refers to decomposition, "bp" or "b.p." refers to boiling point, "mm of Hg" refers to pressure in millimeters of mercury, "cm" refers to centimeters, "nm" refers to nanometers, "abs." refers to absolute, "conc." refers to concentrated, "c" refers to concentration in g/mL, "dppf" refers to 1,1' bis(diphenylphosphino)ferrocene, "THF" refers to tetrahydrofuran, "DMF" refers to dimethylformamide, "DMAP" refers to dimethylaminopyridine; "DMSO" refers to dimethylsulfoxide; "NMP" refers to 1-methyl-2-pyrrolidinone, "DCM" refers to dichloromethane, "DCE" refers to dichloroethane, "EtOAc" refers to ethyl acetate, "MeOH" refers to methanol, "HOAc" or "AcOH" refers to acetic acid, "H₂O" refers to water; "NaOH" refers to sodium hydroxide, "HCl" refers to hydrochloric acid, "Cs₂CO₃" refers to cesium carbonate, "MgSO₄" refers to magnesium sulfate, "Na₂SO₄" refers to sodium sulfate, "brine" refers to a saturated aqueous sodium chloride solution, "HATU" refers to O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, "M" refers to molar, "mM" refers to millimolar, "μM" refers to micromolar, "nM" refers to nanomolar, "N" refers to normal, "TLC" refers to thin layer chromatography, "HPLC" refers to high performance liquid chromatography, "HRMS" refers to high resolution mass spectrum, "L.O.D." refers to loss on drying, "μCi" refers to microcuries, "i.p." refers to intraperitoneally, "i.v." refers to intravenously, anhyd = anhydrous; aq = aqueous; min = minute; hr = hour; d = day; sat. = saturated; s = singlet, d = doublet; t = triplet; q = quartet; m = multiplet; dd = doublet of doublets; br = broad; LC = liquid chromatograph; MS = mass spectrograph; ESI/MS = electrospray ionization/mass spectrograph; RT = retention time; M = molecular ion.

The following examples describe the procedures used in the preparation of the compounds of this invention.

Example 1

N-Benzyl-N-[3-(1H-indol-5-yl)-benzyl]-N',N'-dimethyl-ethane-1,2-diamine

84



Step 1: 3-(1H-Indol-5-yl)-benzaldehyde: A mixture of 5-bromo-indole (8.7 g, 44.4 mmol), 3-formylbenzeneboronic acid (10 g, 66.7 mmol), cesium carbonate in water (2M, 88.8 mL, 178 mmol) in 450 mL of dioxane was degassed (evacuate in vacuo and pressurize with nitrogen, 3 times) PdCl₂(dppf).DCM (1.1 g, 1.3 mmol) was added and the mixture degassed one more time as described above. The resulting mixture was heated at 100°C for 3h, then it was allowed to cool to room temperature and partitioned between diethyl ether and water. The aqueous phase was extracted with diethyl ether and the combined organic phases were washed with water, brine, dried over MgSO₄, filtered and evaporated to give the crude product.

10 Chromatography on silica gel (elution with ethyl acetate/heptane) afforded 5.6 g of the desired product.

Step 2: N-Benzyl-N-[3-(1H-indol-5-yl)-benzyl]-N',N'-dimethyl-ethane-1,2-diamine: Sodium triacetoxyborohydride (480 mg, 2.3 mmol) was added to a solution of 3-(1H-indol-5-yl)-benzaldehyde (250 mg, 1.1 mmol) and N'-benzyl-N,N-dimethyl-ethane-1,2-diamine (600 mg, 3.4 mmol) and acetic acid (204 mg, 3.4 mmol) in 8 mL of tetrahydrofuran. The mixture was stirred at ambient temperature overnight, and then it was diluted with ethyl acetate, and neutralized with the careful addition of saturated sodium bicarbonate solution. The layers were separated and the organic phase was treated with polystyrene supported isocyanate resin (1.49 mmol/g, 1.7 g) for 2 h. The mixture was filtered and the filtrate was washed with 1M sodium carbonate solution. The aqueous phase was extracted into ethyl acetate, and the combined organic phases were dried over magnesium sulfate, filtered and concentrated to leave 290 mg of the title compound. LC/MS (short method): retention time, 2.61 min; (M+H) = 384.

20

¹H NMR (400 MHz, chloroform-D) δ ppm: 2.20 (s, 6 H) 2.49-2.55 (m, 2 H), 2.65- 2.68 (m, 2 H) 3.66 (s, 2 H) 3.69 (s, 2 H) 6.61 (br s, 1 H) 7.21-7.26 (m, 3 H) 7.28 - 7.34 (m, 3 H) 7.35 - 7.41 (m, 3 H) 7.45 (s, 2 H) 7.52 (d, 1 H, J= 7.6 Hz), 7.64 (s, 1 H) 7.85 (s, 1 H) 8.26 (s, 1 H).

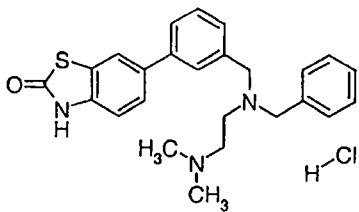
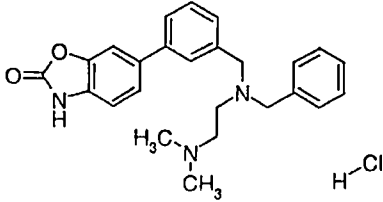
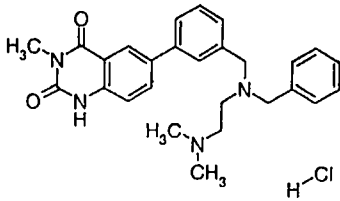
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85

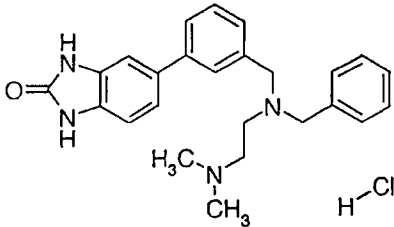
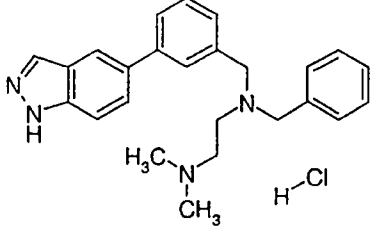
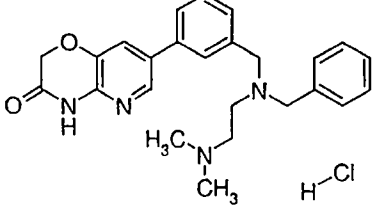
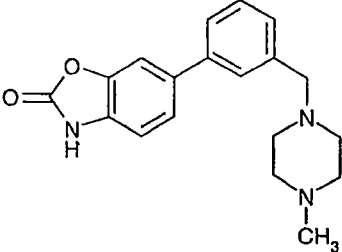
Examples 2 to 16

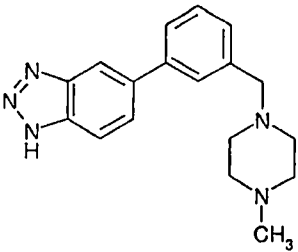
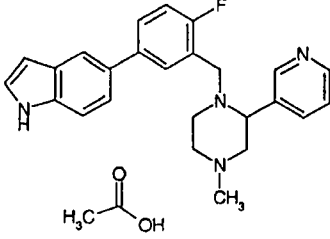
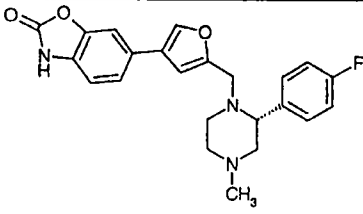
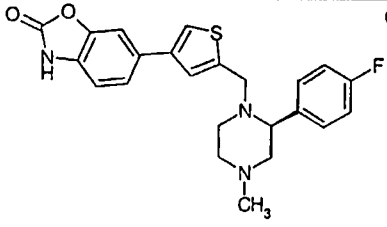
Example 1 was substantially repeated in Examples 2 to 16 with the exception of utilizing the respective starting materials and reagents in appropriate quantities in order to prepare the Examples 2 to 16 as tabulated in Table 1. Also summarized in Table 1 are the observed LC/MS data for Examples 2 to 16.

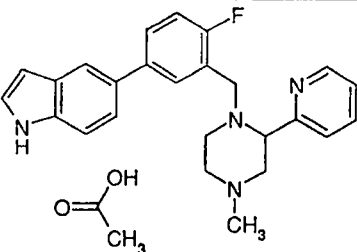
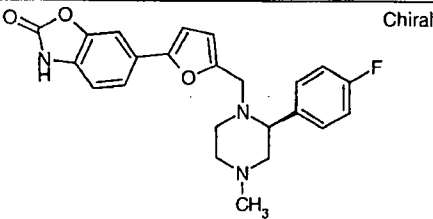
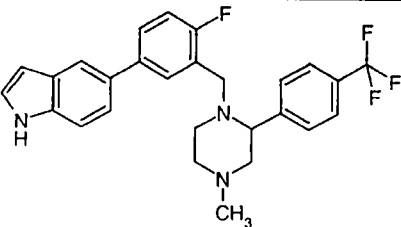
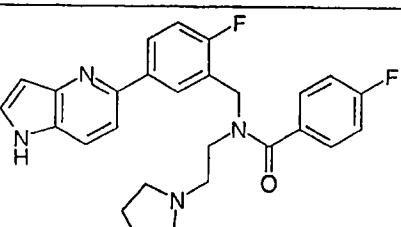
Table 1

Example No.	Chemical Structure and Chemical Name	LC/MS Data	
		RT (mins.)	M + H
2	 6-(3-([Benzyl-(2-dimethylamino-ethyl)-amino]-methyl)-phenyl)-3H-benzothiazol-2-one hydrochloride.	2.5 ^a	418
3	 6-(3-([Benzyl-(2-dimethylamino-ethyl)-amino]-methyl)-phenyl)-3H-benzooxazol-2-one hydrochloride.	2.41 ^a	402
4	 6-(3-([Benzyl-(2-dimethylamino-ethyl)-amino]-methyl)-phenyl)-3-methyl-1H-quinazoline-2,4-dione hydrochloride.	2.38 ^a	443

86

5	 5-(3-([Benzyl-(2-dimethylamino-ethyl)-amino]-methyl)-phenyl)-1,3-dihydro-benzoimidazol-2-one hydrochloride.	2.23 ^a	401
6	 N-Benzyl-N-[3-(1H-indazol-5-yl)-benzyl]-N',N'-dimethyl-ethane-1,2-diamine hydrochloride.	1.53 ^a	385
7	 7-(3-([Benzyl-(2-dimethylamino-ethyl)-amino]-methyl)-phenyl)-4H-pyrido[3,2-b][1,4]oxazin-3-one hydrochloride.	1.47 ^a	417
8	 6-[3-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3H-benzooxazol-2-one	1.75 ^a	324

9 ^c	 5-[3-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-1H-benzotriazole	1.64 ^a	308
10	 5-[4-Fluoro-3-(4-methyl-2-pyridin-3-yl-piperazin-1-ylmethyl)-phenyl]-1H-indole acetate	2.17 ^a 5.07 ^b	401
11	 6-{5-[2<i>R</i>-(4-Fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-furan-3-yl}-3H-benzooxazol-2-one. Chiral	5.69 ^b	408
12	 6-{5-[2<i>S</i>-(4-Fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-thiophen-3-yl}-3H-benzooxazol-2-one. Chiral	6.03 ^b	424

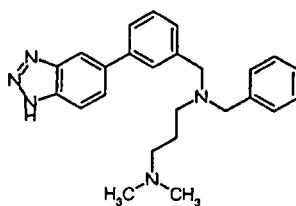
13	 5-[4-Fluoro-3-(4-methyl-2-pyridin-2-yl-piperazin-1-ylmethyl)-phenyl]-1H-indole acetate.	6.18 ^b	401
14	 6-{5-[2S-(4-Fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-furan-2-yl}-3H-benzooxazol-2-one	5.98 ^b	408
15	 5-{4-Fluoro-3-[4-methyl-2-(4-trifluoromethyl-phenyl)-piperazin-1-ylmethyl]-phenyl}-1H-indole	7.87 ^b	468
16 ^d	 4-Fluoro-N-[2-fluoro-5-(1H-pyrrolo[3,2-b]pyridin-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	1.88 ^b	419

^a short LC/MS method; ^b long LC/MS method; ^c this Example 9 was synthesized following the procedures of Example 42; ^d this Example 16 was synthesized following the procedures of Example 20; n.a. – not available

Example 17

89

N-[3-(1H-Benzotriazol-5-yl)-benzyl]-N-benzyl-N',N'-dimethyl-propane-1,3-diamine



Step 1: N-Benzyl-N-(3-boranyl-benzyl)-N',N'-dimethyl-propane-1,2-diamine: Sodium triacetoxymethylborohydride (8.84 g, 14.0 mmol) and then 4.5 mL of acetic acid were added to a solution of 3-boranylbenzenecarboxaldehyde (2.0 g, 13.34 mmol) and N'-benzyl-N,N-dimethyl-ethane-1,2-diamine (2.5 g, 40.0 mmol) in 100 mL of 1,2-dichloroethane. The mixture was stirred at ambient temperature overnight, and then it was neutralized with the careful addition of saturated sodium bicarbonate solution. The layers were separated and the aqueous phase extracted into dichloromethane. The combined organic phases were dried over magnesium sulfate, filtered and concentrated to leave the crude product. Trituration with a mixture of diethyl ether and hexane gave 2.9 g of product. LC/MS: Retention time, 1.26 min; (M+H) = 313.

Following the procedures as set forth above, N-benzyl-N-(3-boranyl-benzyl)-N',N'-dimethyl-propane-1,3-diamine was prepared starting from N'-benzyl-N,N-dimethyl-propane-1,3-diamine.

Step 2: N-Benzyl-N',N'-dimethyl-N-[3-(1-trityl-1H-benzotriazol-5-yl)-benzyl]-propane-1,3-diamine: A mixture of 5-bromo-1-trityl-1H-benzotriazole (220 mg, 0.5 mmol), N-benzyl-N-(3-boranyl-benzyl)-N',N'-dimethyl-propane-1,3-diamine (180 g, 0.55 mmol), and cesium carbonate solution in water (2M, 1 mL, 2 mmol) taken altogether in 10 mL of dioxane was degassed (evacuate in vacuo and pressurize with argon, two times) and PdCl₂(dppf).DCM (21 mg, 0.025 mmol) was added and the mixture was degassed two more times as described above. The resulting mixture was heated at 90°C for 3 h, then it was allowed to cool to room temperature and the volatiles were removed in vacuo. The residue was partitioned between dichloromethane and water. The aqueous phase was extracted with dichloromethane and the combined organic phases were dried over MgSO₄, filtered and evaporated to give the crude product. Chromatography on silica gel (elution with methanol/dichloromethane) followed by trituration of the material obtained with diethyl ether gave 68 mg of the title compound.

Step 3: N-[3-(1H-Benzotriazol-5-yl)-benzyl]-N-benzyl-N',N'-dimethyl-propane-1,3-diamine: N-Benzyl-N',N'-dimethyl-N-[3-(1-trityl-1H-benzotriazol-5-yl)-benzyl]-propane-1,3-diamine

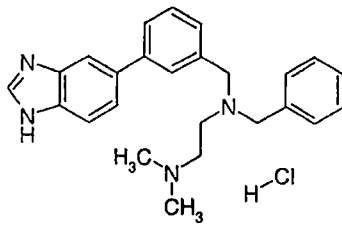
(60 mg, 0.093 mmol) was dissolved in a mixture of 5 mL of ethanol, 5 mL of dioxane and 8 mL of 2M aqueous hydrochloric acid solution, and the resulting mixture was stirred at room temperature for 6 h. The volatiles were removed in vacuo and the residue partitioned between diethyl ether and 1M HCl solution. The aqueous phase was washed with diethyl ether and the combined organic phases were concentrated in vacuo to obtain the crude product, which was dissolved in small amount of 1M HCl solution and freeze dried. Purification by HPLC (elution with) afforded 30 mg of the title compound. LC/MS (short method): Retention time 1.19 min; (M+H) = 400.

¹H NMR (400 MHz, methanol-D₄) δ ppm: 2.28 - 2.43 (m, 2 H) 2.89 (s, 6 H) 3.10 - 3.20 (m, 2 H) 3.24 - 3.30 (m, 2 H) 4.47 - 4.60 (m, 4 H) 7.47 - 7.54 (m, 3 H) 7.57 - 7.68 (m, 4 H) 7.83 - 7.91 (m, 2 H) 7.94 - 8.02 (m, 2 H) 8.18 (s, 1 H).

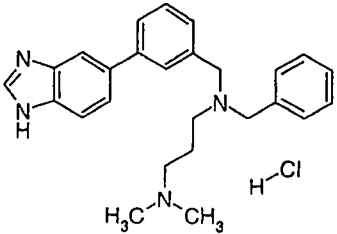
Examples 18 and 19

Example 17 was substantially repeated in Examples 18 and 19 with the exception of utilizing the respective starting materials and reagents in appropriate quantities in order to prepare the Examples 18 and 19 as tabulated in Table 2. Also summarized in Table 2 are the observed LC/MS data for Examples 18 and 19.

Table 2

Example No.	Chemical Structure and Chemical Name	LC/MS Data	
		RT (mins.)	M + H
18	 N-[3-(1H-Benzoimidazol-5-yl)-benzyl]-N-benzyl-N',N'-dimethyl-ethane-1,2-diamine hydrochloride.	1.26 ^a	385

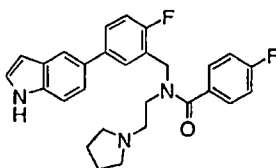
91

19	 N-[3-(1H-Benzimidazol-5-yl)-benzyl]-N-benzyl-N',N'-dimethyl-propane-1,3-diamine hydrochloride.	1.01 ^a	399
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^a = short LC/MS method

Example 20

4-Fluoro-N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide



- 5 Step 1: [2-Fluoro-5-(1H-indol-5-yl)-benzyl]-(2-pyrrolidin-1-yl-ethyl)-amine. Sodium triacetoxyborohydride (530 g, 2.51 mmol) and then enough acetic acid to bring the pH to 5 were added to a solution of 5-(4-fluoro-3-formylphenyl)-1H-indole (200 mg, 0.84 mmol) and 1-(2-aminoethyl)pyrrolidine (191 mg, 1.67 mmol) in 15 mL of 1,2-dichloroethane. The mixture was stirred at ambient temperature overnight, and then it was diluted with
- 10 dichloromethane, and neutralized with the careful addition of saturated sodium bicarbonate solution. The layers were separated and the aqueous phase extracted into dichloromethane. The combined organic phases were dried over magnesium sulfate, filtered and concentrated to leave the crude product. Chromatography (elution with methanol/dichloromethane) provided 90 mg of the title compound. LC/MS: Retention time, 0.34 min.
- 15 Step 2: 4-Fluoro-N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide: 4-Fluorobenzoyl chloride (93 mg, 0.59 mmol) was added to a solution of [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(2-pyrrolidin-1-yl-ethyl)-amine (90 mg, 0.27 mmol) and triethyl amine (81 mg, 0.8 mmol) in 10 ml of dichloromethane at room temperature. The resulting mixture was stirred at ambient temperature for 2 h, and then the volatiles were
- 20 removed in vacuo and the residue was dissolved in ethyl acetate and washed with 1 M HCl solution and water. The aqueous phase was extracted with ethyl acetate, and the combined organic phases were dried over magnesium sulfate, filtered and concentrated to leave the crude

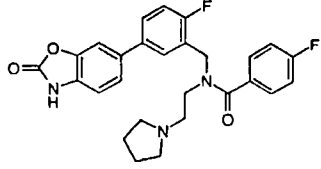
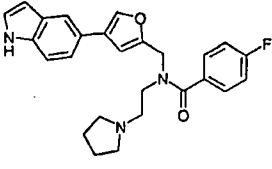
product. Chromatography (elution with methanol/dichloromethane) provided 181 mg of product. This was dissolved in dichloromethane and washed with saturated sodium bicarbonate solution. The organic phase was dried over magnesium sulfate, filtered and concentrated to afford 92 mg of the title compound. LC/MS: Retention time, 2.55 min; (M+H) = 460.

¹H NMR (400 MHz, chloroform-D) δ ppm: 1.72 (br s, 1 H) 2.16 (br s, 3 H) 2.38 (br s, 1 H) 2.63 (br s, 1 H) 2.90 - 3.34 (m, 4 H) 3.44 (br s, 1 H) 3.86 (br s, 1 H) 4.81 (br s, 2 H) 6.56 - 6.67 (s, 1 H) 7.11 (t, J=9.40 Hz, 3 H) 7.30 - 7.43 (m, 3 H) 7.46 (d, J=9.40 Hz, 1 H) 7.49 - 7.69 (m, 3 H) 7.77 (s, 1 H) 8.37 (s, 1 H).

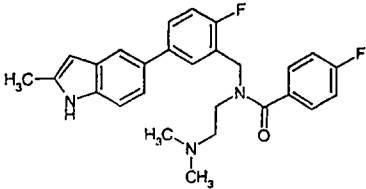
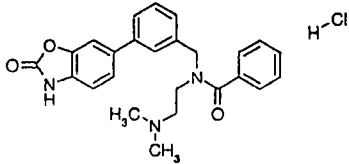
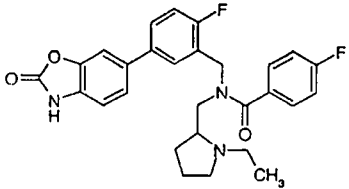
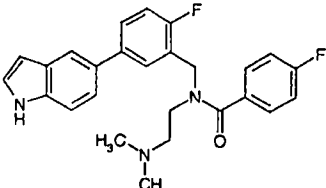
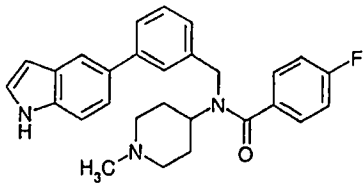
Examples 21 to 41

Example 20 was substantially repeated in Examples 21 to 41 with the exception of utilizing the respective starting materials and reagents in appropriate quantities in order to prepare the Examples 21 to 41 as tabulated in Table 3. Also summarized in Table 3 are the observed LC/MS data for Examples 21 to 41.

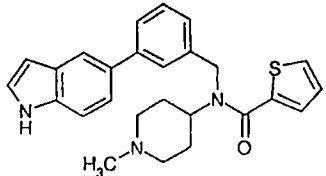
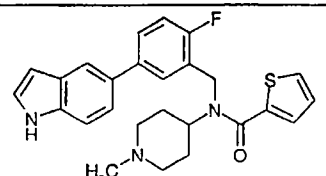
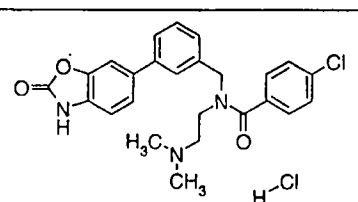
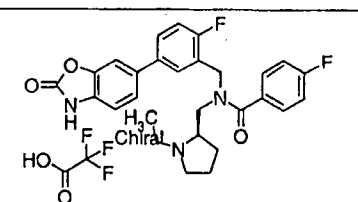
Table 3

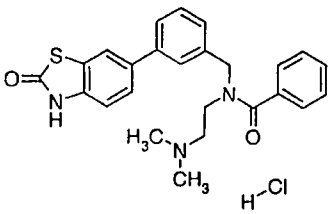
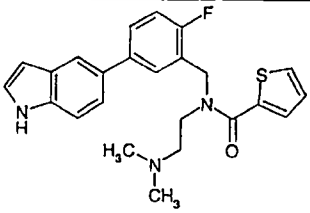
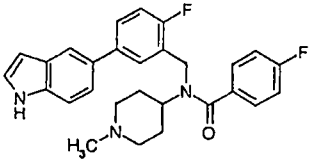
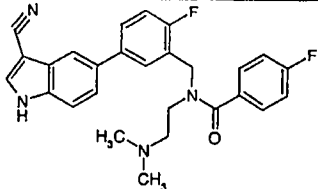
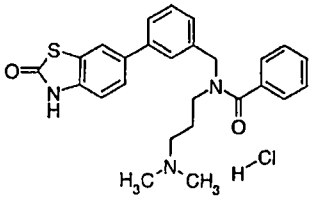
Example No.	Chemical Structure and Chemical Name	LC/MS Data	
		RT (mins.)	M + H
21	 4-Fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihydrobenzooxazol-6-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	2.43 ^a	478
22 ^c	 4-Fluoro-N-[4-(1H-indol-5-yl)-furan-2-ylmethyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	5.45 ^b	432

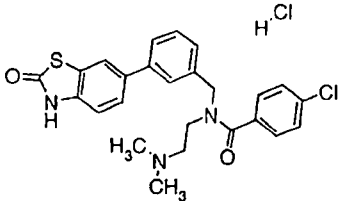
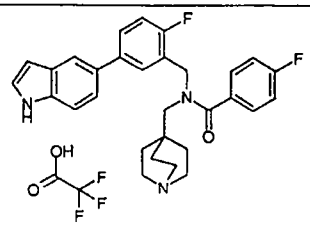
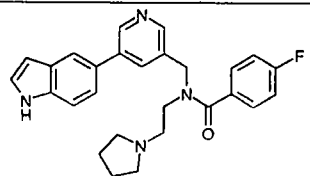
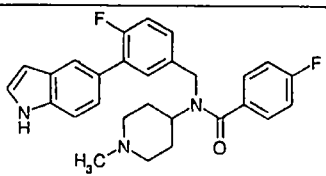
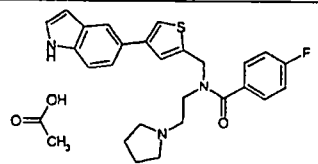
43

23	 N-(2-Dimethylamino-ethyl)-4-fluoro-N-[2-fluoro-5-(2-methyl-1H-indol-5-yl)-benzyl]-benzamide	6.69 ^b	448
24	 N-(2-Dimethylamino-ethyl)-N-[3-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-benzamide hydrochloride.	2.18 ^a	416
25	 N-(1-Ethyl-pyrrolidin-2-ylmethyl)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-benzamide.	2.47 ^a	492
26	 N-(2-Dimethylamino-ethyl)-4-fluoro-N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-benzamide.	6.5 ^b	434
27	 4-Fluoro-N-[3-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-benzamide.	2.5 ^a	442

94

28	 Thiophene-2-carboxylic acid [3-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide.	2.46 ^a	430
29	 Thiophene-2-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide.	5.17 ^b	448
30	 4-Chloro-N-(2-dimethylamino-ethyl)-N-[3-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-benzamide hydrochloride.	2.37 ^a	450
31 ^c	 N-(1-Ethyl-pyrrolidin-2<i>R</i>-ylmethyl)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-benzamide trifluoro-acetate.	2.29 ^a	492

32	 N-(2-Dimethylamino-ethyl)-N-[3-(2-oxo-2,3-dihydro-benzothiazol-6-yl)-benzyl]-benzamide hydrochloride.	2.27 ^a	432
33	 Thiophene-2-carboxylic acid (2-dimethylamino-ethyl)-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-amide	5.29 ^b	422
34	 4-Fluoro-N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-benzamide	6.23 ^b	460
35	 N-[5-(3-Cyano-1H-indol-5-yl)-2-fluoro-benzyl]-N-(2-dimethylamino-ethyl)-4-fluoro-benzamide	5.4 ^b	459
36	 N-(3-Dimethylamino-propyl)-N-[3-(2-oxo-2,3-dihydro-benzothiazol-6-yl)-benzyl]-benzamide; hydrochloride	1.48 ^a	446

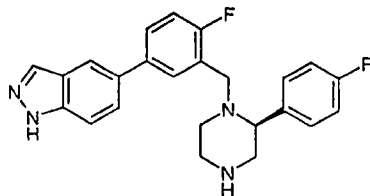
37	 4-Chloro-N-(2-dimethylamino-ethyl)-N-[3-(2-oxo-2,3-dihydro-benzothiazol-6-yl)-benzyl]-benzamide hydrochloride.	2.43 ^a	466
38	 N-(1-Aza-bicyclo[2.2.2]oct-4-ylmethyl)-4-fluoro-N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-benzamide trifluoroacetate	5.75 ^b	486
39	 4-Fluoro-N-[5-(1H-indol-5-yl)-pyridin-3-ylmethyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide.	4.28 ^b	443
40	 4-Fluoro-N-[4-fluoro-3-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-benzamide	6.29 ^b	460
41	 4-Fluoro-N-[4-(1H-indol-5-yl)-thiophen-2-ylmethyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide acetate.	6.53 ^b	448

67

^a = short LC/MS method; ^b = long LC/MS method; ^c this Example was synthesized following the procedures of Example 104.

Example 42

5-{4-Fluoro-3-[2S-(4-fluorophenyl)-piperazin-1-ylmethyl]-phenyl}-1H-indazole



5

Step 1: 2S-(4-Fluorophenyl)-piperazine: A solution of ethylene diamine (7.4 g, 123.5 mmol) in ethanol (100 mL) was added dropwise over 15 minutes to a stirring solution of 4-fluoroglyoxal (21.0 g, 123.5 mmol) in ethanol (300 mL) and the reaction was left for 4 hours. Sodium borohydride (23.5 g, 622 mmol) was added and the mixture was stirred overnight at room temperature. Water (200 mL) was added and the mixture was stirred for 1 hour after which the majority of the ethanol was removed *in vacuo*. The concentrated solution was extracted with DCM (4 x 100 mL) and the combined extracts were combined, washed with brine and dried over Na₂SO₄. The solvent was removed *in vacuo* to yield a pale yellow solid (19.0 g, 86%). 8.8 g of this material was dissolved in methanol (60 mL) and added to a solution of *N*-acetyl-L-leucine (16.5 g, 95.2 mmol) in methanol (100 mL). Ethyl acetate (550 mL) was added and the mixture was left at room temperature overnight. The precipitate was filtered and dried to give a solid (9.0 g) which was taken up in 4M NaOH aq. (100 mL) and extracted with DCM (4 x 100 mL). The combined extracts were combined, washed with brine and the solvent was removed *in vacuo* to yield a solid (3.1 g). This solid was re-crystallized from EtOAc to yield 2.23 g of the S enantiomer (the title compound). The enantiomeric excess was determined by chiral chromatography employing the following chiral chromatographic conditions: Column: Phenomenex Chirex (S)-ICR 250 x 4.6 mm; solvent: n-heptane:ethanol [80:20] + 0.3% TFA; L = 254 nm, flow rate = 1 mL/min, UV sensitivity = 0.1 AUF; ~1 mg of compound in 1 mL of n-heptane:ethanol [75:25] using authentic chiral compounds and racemate as reference.

25

Step 2: 3S-(4-Fluorophenyl)-piperazine-1-carboxylic acid *tert*-butyl ester: 2S-(4-Fluorophenyl)-piperazine (3.75 g, 20.83 mmol) was dissolved in dichloromethane and cooled to 0°C. A solution of di-*tert*-butyl-dicarbonate (4.77 g, 21.87 mmol) in 10 mL of

94

dichloromethane was added and the reaction was left at 0°C for one hour. The solvent was removed *in vacuo* to yield a crystalline white solid (5.85g).

Step 3: 5-Bromo-indazole-1-carboxylic acid *tert*-butyl ester: Di-*tert*-butyldicarbonate (11.4 g, 52.21 mmol), triethylamine (6.27 g, 62.16 mmol) and 4-(*N,N*-dimethylaminopyridine (304 mg, 2.49 mmol) were added sequentially to a solution of 5-bromoindazole (9.8 g, 49.73 mmol) in tetrahydrofuran at room temperature. The mixture was stirred at room temperature for 71.5 h and then it was heated at reflux for 16 h. The volatiles were removed in *vacuo* and the residue was dissolved in dichloromethane and washed with brine, dried over magnesium sulfate, filtered and concentrated to leave the crude product. Chromatography (elution with diethyl ether/heptane) gave 13.98 g of the title compound. LC: Retention time, 3.93 min.

Step 4: 5-(4-Fluoro-3-formylphenyl)-indazole-1-carboxylic acid *tert*-butyl ester: A mixture of 5-bromo-indazole-1-carboxylic acid *tert*-butyl ester (3.37 mmol), 2-fluoro-4-(4,4,5,5-tetramethyl-[1, 3] dioxoboran-2-yl)-benzaldehyde (1.01 g, 4.04 mmol)) PdCl₂(dppf).DCM (27 mg, 0.03 mmol) in 16 mL of dioxane was degassed (evacuate in *vacuo* and pressurize with argon, three times); cesium carbonate in water (2M, 6.73 mL, 13.46 mmol) was added and the mixture degassed three more times as described above. The resulting mixture was heated at 85°C for 6 h, then it was allowed to cool to room temperature and left overnight. The mixture was diluted with dichloromethane and washed with brine. The aqueous phase was extracted with dichloromethane and the combined organic phases were washed with brine, dried over MgSO₄, filtered and evaporated to give crude product. Chromatography on silica gel (elution with diethyl ether/heptane) gave 820 mg of the title compound.

Step 5: 5-{4-Fluoro-3-[2*S*-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-phenyl}-1*H*-indazole: 3*S*-(4-Fluorophenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (150 mg, 0.54 mmol) and 5-(4-fluoro-3-formylphenyl)-indazole-1-carboxylic acid *tert*-butyl ester (210 mg, 0.62 mmol) was dissolved in DCE (5 mL) and glacial acetic acid was added (32 mg, 0.54 mmol) followed by sodium *tris*-acetoxyborohydride (341 mg, 1.6 mmol). The reaction was stirred overnight at room temperature. Dichloromethane was added and the mixture was washed with water and brine and dried over Na₂SO₄. The solvent was removed *in vacuo* to give the crude product. Chromatography (elution with methanol/dichloromethane) provided 200 mg of product. This was treated with 15 mL of 95% aqueous TFA for 1.5 h. The volatiles were removed in *vacuo* and residue triturated with diethyl ether (3x) leaving 70 mg of product. LC/MS (long run): Retention time, 6.14 min; (M+H) = 405.

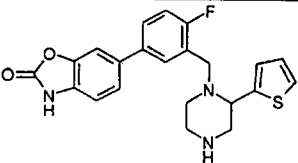
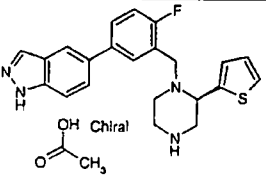
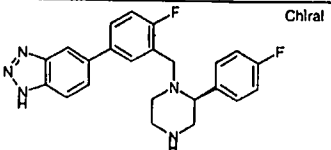
99

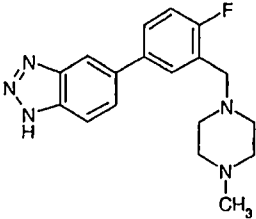
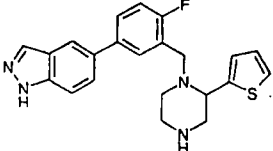
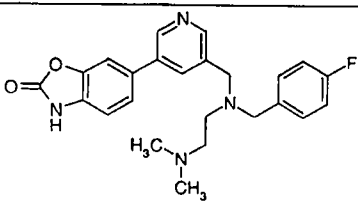
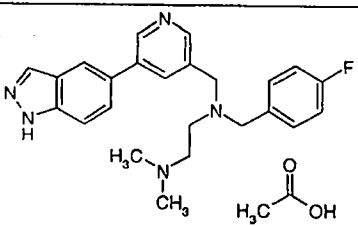
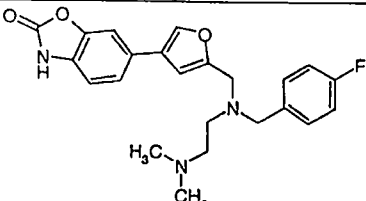
¹H NMR (400 MHz, methanol-D₄) δ ppm: 2.57 (td, J=12.64, 2.64 Hz, 1 H) 3.09 - 3.36 (m, 5 H) 3.41 (d, J = 13.6 Hz, 1 H) 3.67 (dd, J=11.43, 3.08 Hz, 1 H) 3.77 (d, J=13.6 Hz, 1 H) 7.10 - 7.21 (m, 3 H) 7.53 - 7.62 (m, 6 H) 7.94 (t, J=1.32 Hz, 1 H) 8.11 (s, 1 H).

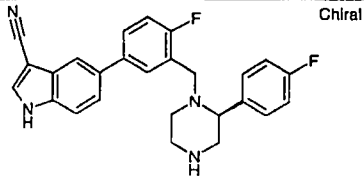
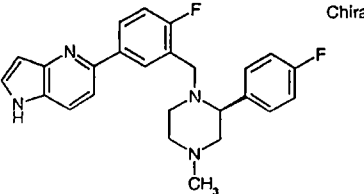
Examples 43 to 52

- 5 Example 42 was substantially repeated in Examples 43 to 52 with the exception of utilizing the respective starting materials and reagents in appropriate quantities in order to prepare the Examples 43 to 52 as tabulated in Table 4. Also summarized in Table 4 are the observed LC/MS data for Examples 43 to 52.

Table 4

Example No.	Chemical Structure and Chemical Name	LC/MS Data	
		RT (mins.)	M + H
43	 6-[4-Fluoro-3-(2-thiophen-2-yl-piperazin-1-ylmethyl)-phenyl]-3H-benzooxazol-2-one	5.04 ^b	410
44	 5-[4-Fluoro-3-(2S-thiophen-2-yl-piperazin-1-ylmethyl)-phenyl]-1H-indazole acetate	5.19 ^b	393
45	 5-{4-Fluoro-3-[2S-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-phenyl}-1H-benzotriazole	5.05 ^b	406

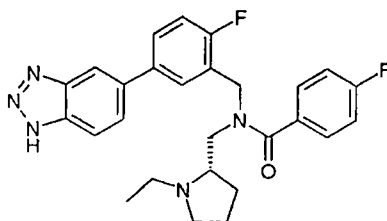
46	 5-[4-Fluoro-3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-benzotriazole	1.88 ^a	326
47	 5-[4-Fluoro-3-(2-thiophen-2-yl-piperazin-1-ylmethyl)-phenyl]-1H-indazole	5.86 ^b	393
48 ^c	 6-(5-[[2-Dimethylamino-ethyl)-(4-fluoro-benzyl)-amino]-methyl}-pyridin-3-yl)-3H-benzooxazol-2-one	4.02 ^b	421
49 ^c	 N-(4-Fluoro-benzyl)-N-[5-(1H-indazol-5-yl)-pyridin-3-ylmethyl]-N',N'-dimethyl-ethane-1,2-diamine acetate	3.72 ^b	404.2
50 ^c	 6-(5-[[2-Dimethylamino-ethyl)-(4-fluoro-benzyl)-amino]-methyl}-furan-3-yl)-3H-benzooxazol-2-one	5.16 ^b	410

51	 5-{4-Fluoro-3-[2S-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-phenyl}-1H-indole-3-carbonitrile	6.03 ^b	429
52	 5-{4-Fluoro-3-[2-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-phenyl}-1H-pyrrolo[3,2-b]pyridine	4.49 ^b	419

^a = short LC/MS method; ^b = long LC/MS method; ^c = prepared as in Example 113, Step 1.

Example 53

N-[5-(1H-Benzotriazol-5-yl)-2-fluoro-benzyl]-N-(1-ethyl-pyrrolidin-2S-ylmethyl)-4-fluoro-benzamide



5

Step 1: (1-Ethyl-pyrrolidin-2S-ylmethyl)-[2-fluoro-5-(1-trityl-1H-benzotriazol-5-yl)-benzyl]-amine: A mixture of 2-fluoro-5-(1-trityl-1H-benzotriazol-5-yl)-benzaldehyde (368 mg, 0.76 mmol), (S)-(+)-1-ethyl-2-aminomethylpyrrolidine (120 mg, 0.83 mmol) and molecular sieves in 10 mL of methanol was stirred at ambient temperature for 3h. The mixture was cooled to -78°C, and sodium borohydride (72 mg, 1.9 mmol) was added and the mixture was allowed to warm to room temperature and stirred overnight. The volatiles were removed in vacuo and the residue was diluted with dichloromethane and washed with water. The aqueous phase extracted with dichloromethane, and the combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated to leave the crude product. Chromatography (elution with methanol/dichloromethane) gave 255 mg of product.

15

102

Step 2: N-(1-Ethyl-pyrrolidin-2S-ylmethyl)-4-fluoro-N-[2-fluoro-5-(1-trityl-1H-benzotriazol-5-yl)-benzyl]-benzamide. HATU (122mg, 0.32 mmol) was added to a solution of (1-ethyl-pyrrolidin-2-ylmethyl)-[2-fluoro-5-(1-trityl-1H-benzotriazol-5-yl)-benzyl]-amine (127 mg, 0.21 mmol), 4-fluorobenzoic acid (45 mg, 0.32 mmol) and diisopropylethylamine (82 mg, 0.64 mmol) in 1 mL of dimethylformamide, and the resulting mixture stirred at ambient temperature overnight. The mixture was diluted with dichloromethane, and washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, filtered and concentrated to leave the crude product. Chromatography (elution with methanol/dichloromethane) provided 98 mg of product. LC/MS: Retention time, 3.39 min; (M+H) = 718.

Step 3: N-[5-(1H-Benzotriazol-5-yl)-2-fluoro-benzyl]-N-(1-ethyl-pyrrolidin-2S-ylmethyl)-4-fluoro-benzamide: N-(1-Ethyl-pyrrolidin-2-ylmethyl)-4-fluoro-N-[2-fluoro-5-(1-trityl-1H-benzotriazol-5-yl)-benzyl]-benzamide (143 mg, 0.2 mmol) in 4 mL of methanol and 2 mL of 4M HCl in dioxane was stirred at room temperature for 24 h. The solvent was removed in vacuo and the residue purified by HPLC. The material obtained was treated with hydrochloric acid to leave 100 mg of the title compound. LC/MS (long run): Retention time, 5.64 min; (M+H) = 476.

¹H NMR (400 MHz, methanol-D₄) δ ppm: 1.29 - 1.46 (m, 3 H) 1.86 - 1.99 (m, 1 H) 2.04 - 2.19 (m, 2 H) 2.31 (ddd, J=13.19, 7.03 Hz, 1 H) 3.08 - 3.28 (m, 2 H) 3.48 (br s, 1 H) 3.68 - 3.78 (m, 2 H) 3.85 (dd, J=14.73, 5.49 Hz, 1 H) 4.02 (dd, J=14.73, 5.49 Hz 1 H) 4.76 - 4.95 (m, 2 H) 7.18 - 7.32 (m, 3 H) 7.51 - 7.64 (m, 3 H) 7.71 - 7.79 (m, 2 H) 7.98 (d, J=8.57 Hz, 1 H) 8.06 (s, 1 H).

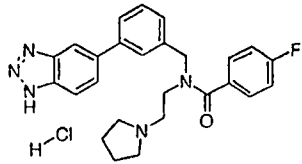
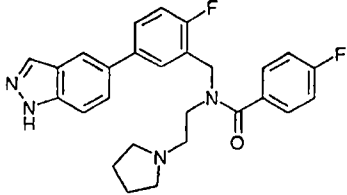
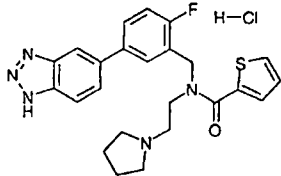
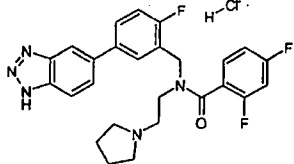
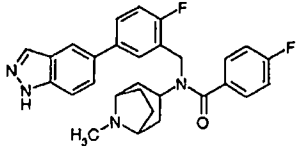
Examples 54 to 65

Example 53 was substantially repeated in Examples 54 to 65 with the exception of utilizing the respective starting materials and reagents in appropriate quantities in order to prepare the Examples 54 to 65 as tabulated in Table 5. Also summarized in Table 5 are the observed LC/MS data for Examples 54 to 65.

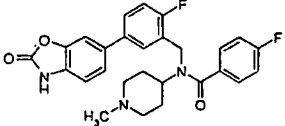
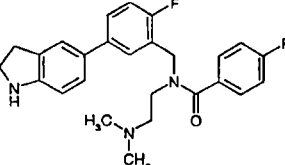
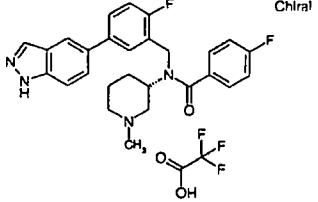
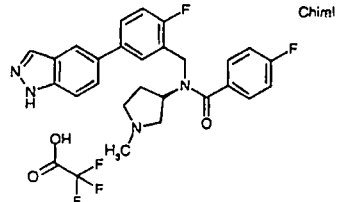
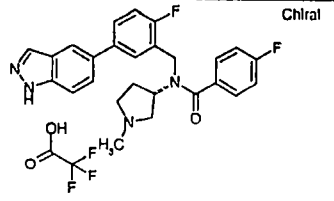
Table 5

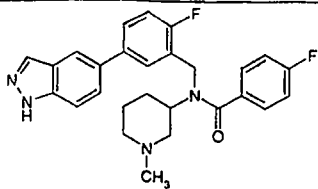
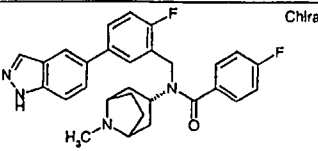
Example No.	Chemical Structure and Chemical Name	LC/MS Data	
		RT (mins.)	M + H

b03

54	 N-[3-(1H-Benzotriazol-5-yl)-benzyl]-4-fluoro-N-(2-pyrrolidin-1-yl-ethyl)-benzamide hydrochloride	5.26 ^b	444
55	 4-Fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	4.82 ^b	461
56	 Thiophene-2-carboxylic acid [5-(1H-benzotriazol-5-yl)-2-fluoro-benzyl]-(2-pyrrolidin-1-yl-ethyl)-amide hydrochloride	5.22 ^b	450
57	 N-[5-(1H-Benzotriazol-5-yl)-2-fluoro-benzyl]-2,4-difluoro-N-(2-pyrrolidin-1-yl-ethyl)-benzamide hydrochloride	5.53 ^b	480
58	 4-Fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(endo-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-benzamide	5.09 ^b	487

104

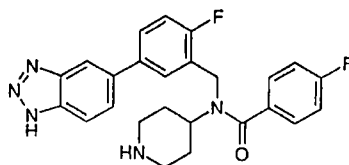
59	 4-Fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-benzamide	4.79 ^b	478
60	 N-[5-(2,3-Dihydro-1H-indol-5-yl)-2-fluoro-benzyl]-N-(2-dimethylamino-ethyl)-4-fluoro-benzamide	3.91 ^b	436
61	 4-Fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(1-methyl-piperidin-3S-yl)-benzamide trifluoro-acetate	4.99 ^b	461
62	 4-Fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(1-methyl-pyrrolidin-3R-yl)-benzamide trifluoro-acetate	4.42 ^b	447
63	 4-Fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(1-methyl-pyrrolidin-3S-yl)-benzamide trifluoro-acetate	4.35 ^b	447

64	 4-Fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(1-methyl-piperidin-3-yl)-benzamide	4.91 ^b	461
65	 4-Fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(exo-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-benzamide	5.22 ^b	487

^b = long LC/MS method

Example 66

N-[5-(1H-Benzotriazol-5-yl)-2-fluoro-benzyl]-4-fluoro-N-piperidin-4-yl-benzamide



- 5 Step 1: 4-Oxo-piperidine-1-carboxylic acid-2-trimethylsilanyl-ethyl ester: Carbonic acid 4-nitro-phenyl ester-2-trimethylsilanyl-ethyl ester (8.33 g, 29.3 mmol), triethylamine (12.3 g, 122 mmol) and DMAP (3.6 g, 29.5 mmol) were added to a room temperature solution of 4-piperidone hydrochloride (4.52 g, 33.4 mmol) in 100 mL of acetonitrile. The resulting mixture was heated at reflux for 2 h, then cooled and the volatiles were removed in vacuo.
- 10 The residue was dissolved in dichloromethane, washed with water and 1M NaOH solution, and concentrated in vacuo to leave 6.3 g of product.
- Step 2: 4-Amino-piperidine-1-carboxylic acid 2-trimethylsilanyl-ethyl ester: A slurry of 10% palladium on carbon (200 mg) in water was added to 4-oxo-piperidine-1-carboxylic acid-2-trimethylsilanyl-ethyl ester (2.42 g, 10 mmol) in 100 mL of methanol. Ammonium formate
- 15 (6.0 g, 95 mmol) in water was added dropwise, and the mixture stirred vigorously overnight. The mixture was filtered and the filtrate concentrated in vacuo to leave the crude product. Chromatography (elution with methanol-dichloromethane) provided 0.98 g of product.
- Step 3: 4-[2-Fluoro-5-(1-trityl-1H-benzotriazol-5-yl)-benzylamino]-piperidine-1-carboxylic acid 2-trimethylsilanyl-1-ethyl ester: Sodium triacetoxyborohydride (890 mg, 4.2 mmol) and

19b

acetic acid (126 mg, 4.2 mmol) were added to a solution of 5-(4-fluoro-3-formylphenyl)-1-trityl-1H-benzotriazole (1.0 mg, 2.1 mmol) and 4-amino-piperidine-1-carboxylic acid 2-trimethylsilanyl-ethyl ester (760 mg, 3.1 mmol) in dichloroethane. The mixture was stirred at ambient temperature overnight, and then it was diluted with dichloromethane, and neutralized with careful addition of 1 M sodium carbonate solution. The layers were separated and the aqueous phase extracted with dichloromethane. The combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated to leave the crude product. Chromatography provided 980 mg of product. LC/MS: Retention time, 3.27 and 3.34 min; (M+H) = 712.

Step 4: 4-((4-Fluoro-benzoyl)-[2-fluoro-5-(1-trityl-1H-benzotriazol-5-yl)-benzyl]-amino)-piperidine-1-carboxylic acid 2-trimethylsilanyl-ethyl ester: HATU was added to a solution of 4-[2-fluoro-5-(1-trityl-1H-benzotriazol-5-yl)-benzylamino]-piperidine-1-carboxylic acid 2-trimethylsilanyl-ethyl ester, 4-fluorobenzoic acid and diisopropylethylamine and the resulting mixture stirred at ambient temperature overnight. The mixture was diluted with ethyl acetate washed with 1 M sodium carbonate solution. The layers were separated and the aqueous phase extracted with ethyl acetate. The combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated to leave the crude product. Chromatography (elution with diethyl ether/hexane, followed by ethyl acetate/hexane) provided 740 mg of product.

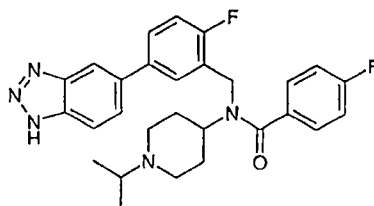
Step 5: N-[5-(1H-Benzotriazol-5-yl)-2-fluoro-benzyl]-4-fluoro-N-piperidin-4-yl-benzamide and 4-Fluoro-N-[2-fluoro-5-(1-trityl-1H-benzotriazol-5-yl)-benzyl]-N-piperidin-4-yl-benzamide: Tetrabutylammonium fluoride (1M in THF, 2.6 mL, 2.6 mmol) was added to a mixture of 4-((4-fluoro-benzoyl)-[2-fluoro-5-(1-trityl-1H-benzotriazol-5-yl)-benzyl]-amino)-piperidine-1-carboxylic acid 2-trimethylsilanyl-ethyl ester (730 mg, 0.88 mmol) and 4 angstrom molecular sieves in 5 mL of THF. After 3 h the mixture was filtered and the solvent was removed *in vacuo*. The residue was eluted through an SCX cation exchange column (elution with dichloromethane, followed by 1-2% ammonia in methanol) to give a mixture of products. Chromatography (elution with methanol/dichloromethane, followed by methanol/dichloromethane with a small amount of 1-2% ammonia in methanol) gave 110 mg of 4-fluoro-N-[2-fluoro-5-(1-trityl-1H-benzotriazol-5-yl)-benzyl]-N-piperidin-4-yl-benzamide (LC/MS: Retention time, 3.03 min; (M+H) = 690) and 170 mg of N-[5-(1H-benzotriazol-5-

yl)-2-fluoro-benzyl]-4-fluoro-N-piperidin-4-yl-benzamide (LCMS: Retention time, 2.22 min; (M+H) = 448).

¹H NMR (400 MHz, methanol-D₄) δ ppm: 1.72 - 2.11 (m, 5 H) 2.36 - 2.73 (m, 2 H) 3.03 - 3.24 (m, 2 H) 3.82 - 4.17 (m, 1 H) 4.74 - 4.84 (m, 1 H) 7.12 - 7.29 (m, 3 H) 7.47 - 7.56 (m, 2 H) 7.58 - 7.69 (m, 8 H) 7.93 (d, 1 H, J = 8.6 Hz) 7.98 (s, 1 H).

Example 67

N-[5-(1H-Benzotriazol-5-yl)-2-fluoro-benzyl]-4-fluoro-N-(1-isopropyl-piperidin-4-yl)-benzamide



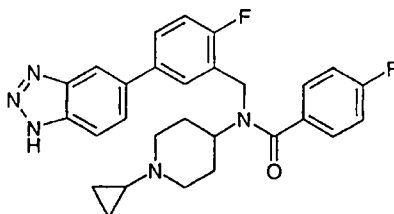
Step 1: 4-Fluoro-N-[2-fluoro-5-(1-trityl-1H-benzotriazol-5-yl)-benzyl]-N-(1-isopropyl-piperidin-4-yl)-benzamide: A mixture of 4-Fluoro-N-[2-fluoro-5-(1-trityl-1H-benzotriazol-5-yl)-benzyl]-N-piperidin-4-yl-benzamide (25 mg, 0.04 mmol), isopropyl iodide (34 mg, 0.2 mmol) and potassium carbonate (28 mg, 0.2 mmol) in 2 mL of DMF was heated at 40°C for 3 h when additional isopropyl iodide (34 mg, 0.2 mmol) was added. The mixture was heated for an additional 2 h and then left at ambient temperature for 10 days. The mixture was diluted with water and the product extracted into ethyl acetate. The combined organic phases were dried over magnesium sulfate, filtered and concentrated to leave the crude product. Chromatography (elution with methanol/dichloromethane) provided 18 mg of product.

Step 2: N-[5-(1H-Benzotriazol-5-yl)-2-fluoro-benzyl]-4-fluoro-N-(1-isopropyl-piperidin-4-yl)-benzamide: Trifluoroacetic acid (TFA, 0.25 mL) was added to a solution of 4-fluoro-N-[2-fluoro-5-(1-trityl-1H-benzotriazol-5-yl)-benzyl]-N-(1-isopropyl-piperidin-4-yl)-benzamide (18 mg, 0.024 mmol) in 1 mL of dichloromethane and the resulting mixture stirred at ambient temperature for 3 h, when an additional 0.5 mL of TFA was added. This was stirred overnight and then the mixture was neutralized by the careful addition of 1M sodium carbonate. The layers were separated, the aqueous phase was extracted with dichloromethane, and the combined organic phases were dried over magnesium sulfate, filtered, and the volatiles were removed in vacuo to leave the crude product. Chromatography (elution with methanol/dichloromethane) provided 6.5 mg of product. LC/MS: Retention time, 2.25 min; (M+H) = 490.

108

Example 68

N-[5-(1H-Benzotriazol-5-yl)-2-fluoro-benzyl]-N-(1-cyclopropyl-piperidin-4-yl)-4-fluoro-benzamide



5 Step 1: N-(1-Cyclopropyl-piperidin-4-yl)-4-fluoro-N-[2-fluoro-5-(1-trityl-1H-benzotriazol-5-yl)-benzyl]-benzamide. Solid supported cyanoborohydride (2.5 mmol/g, 46 mg) was added to a solution of 4-fluoro-N-[2-fluoro-5-(1-trityl-1H-benzotriazol-5-yl)-benzyl]-N-piperidin-4-yl-benzamide (20 mg, 0.029 mmol), (1-ethoxy-cyclopropoxy)-trimethylsilane (25 mg, 0.145 mmol) and acetic acid (1.74 mg, 0.029 mmol) in 1 mL of methanol. The mixture was stirred
10 at 45°C for 2 h and then at 75°C overnight. The mixture was cooled and filtered and the filtrate concentrated in vacuo to provide the crude product. Chromatography provided 14 mg of product. LC/MS: Retention time, 3.20 min; (M+H) = 730.

Step 2: N-[5-(1H-Benzotriazol-5-yl)-2-fluoro-benzyl]-N-(1-cyclopropyl-piperidin-4-yl)-4-fluoro-benzamide. Trifluoroacetic acid (TFA, 1 mL) was added to a solution of N-(1-cyclopropyl-piperidin-4-yl)-4-fluoro-N-[2-fluoro-5-(1-trityl-1H-benzotriazol-5-yl)-benzyl]-benzamide (14 mg, 0.019 mmol) in 1 mL of dichloromethane and the resulting mixture stirred
15 at ambient temperature overnight and then the mixture was neutralized by careful addition of 1M sodium carbonate. The layers were separated, the aqueous phase was extracted with dichloromethane, and the combined organic phases were dried over magnesium sulfate,
20 filtered, and the volatiles were removed in vacuo to leave the crude product. Chromatography (elution with methanol/dichloromethane) provided 9 mg of the title compound. LC/MS: Retention time, 2.22 min; (M+H) = 488.

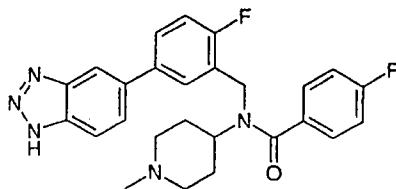
¹H NMR (400 MHz, chloroform-D) δ ppm: 0.17 - 0.48 (m, 4 H) 1.31 - 2.10 (m, 8 H) 2.97 (br s, 2 H) 4.74 (br s, 2 H) 7.01 (br s, 3 H) 7.31 - 7.60 (m, 5 H) 7.71 - 8.03 (m, 2 H).

25

Example 69

N-[5-(1H-Benzotriazol-5-yl)-2-fluoro-benzyl]-N-(1-methyl-piperidin-4-yl)-4-fluoro-benzamide

209

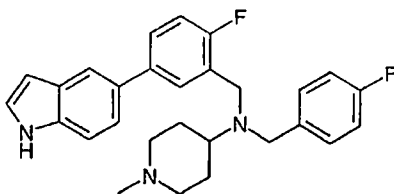


Sodium triacetoxyborohydride (8.5 mg, 0.04 mmol) was added to a mixture of 4-fluoro-N-[2-fluoro-5-(1-trityl-1H-benzotriazol-5-yl)-benzyl]-N-piperidin-4-yl-benzamide (25 mg, 0.04 mmol), formaldehyde (37% aqueous solution, 15 μ L, 0.18 mmol) and acetic acid (2.4 mg, 0.04 mmol) in 1 mL of methanol. The mixture was stirred at ambient temperature overnight, and then it was diluted with dichloromethane, and neutralized with the careful addition of 1 M sodium carbonate solution. The layers were separated and the aqueous phase was extracted with dichloromethane. The combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated to leave the crude product. Chromatography provided 15 mg of product. Trifluoroacetic acid (TFA, 0.5 mL) was added to a solution of the material obtained above in 1 mL of dichloromethane and the resulting mixture stirred at ambient temperature for 5 h, and then the mixture was neutralized by the careful addition of 1M sodium carbonate. The layers were separated, the aqueous phase was extracted with dichloromethane, and the combined organic phases were dried over magnesium sulfate, filtered, and the volatiles were removed in vacuo to leave the crude product. Chromatography provided 6.5 mg of product. LC/MS: Retention time, 2.20 min; (M+H) = 462.

^1H NMR (400 MHz, chloroform- D) δ ppm: 1.54 - 2.09 (m, 7 H) 2.26 (s, 3 H) 2.93 (br s, 2 H) 4.82 (br s, 2 H) 7.00 (br s, 3 H) 7.38 - 7.54 (m, 4 H) 7.59 (br s, 1 H) 7.86 (d, $J=8.57$ Hz, 2 H) 7.92 (s, 1 H).

Example 70

(4-Fluoro-benzyl)-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amine



Step 1: [2-Fluoro-5-(1H-indol-5-yl)-benzyl] -(1-methyl-piperidin-4-yl)-amine. Sodium triacetoxyborohydride (400 mg, 1.88 mmol) and then enough acetic acid to bring the pH to 5 were added to a solution of 5-(4-fluoro-3-formylphenyl)-1H-indole (150 mg, 0.63 mmol) and

110

1-methyl-piperidin-4-ylamine (144 mg, 1.23 mmol) in 15 mL of 1,2-dichloroethane. The mixture was stirred at ambient temperature overnight, and then it was diluted with dichloromethane and washed with water. The aqueous phase extracted with dichloromethane, and the combined organic phases were dried over magnesium sulfate, filtered and concentrated to leave the crude product, which was eluted through an SCX cation exchange column (elution with methanol, followed by 2M ammonia in methanol) to give 250 mg of product.

Step 2: (4-Fluoro-benzyl)-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amine: Sodium triacetoxyborohydride (470 mg, 2.23 mmol) and then enough acetic acid to bring the pH to 5 were added to a solution of [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amine (250 mg, 0.74 mmol) and 4-fluorobenzaldehyde (183 mg, 1.48 mmol) in 15 mL of 1,2-dichloroethane. The mixture was stirred at ambient temperature overnight, and then it was diluted with dichloromethane, and neutralized with the careful addition of saturated sodium bicarbonate solution. The organic phase was separated and dried over magnesium sulfate, filtered and concentrated to leave the crude product. Chromatography (elution with methanol/ethyl acetate) provided 232 mg of product. LC/MS (long run): Retention time, 6.12 min; (M+H) = 446.

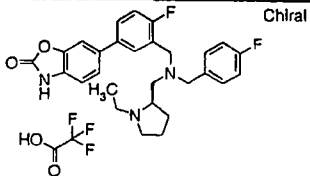
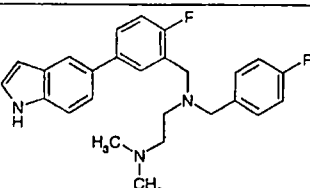
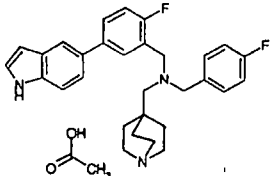
¹H NMR (400 MHz, chloroform-D) δ ppm: 1.73 - 1.84 (m, 4 H) 1.90 (t, J = 11.2 Hz, 2 H) 2.23 (s, 3 H) 2.46 - 2.60 (m, 1 H) 2.92 (d, 2 H) 3.66 (s, 2 H) 3.72 (s, 2 H) 6.59 (s, 1 H) 6.93 (t, J=8.74 Hz, 2 H) 7.00 (dd, J=9.78, 8.46 Hz, 1 H) 7.22 - 7.26 (m, 1 H) 7.27 - 7.34 (m, 3 H) 7.37 - 7.46 (m, 2 H) 7.66 (dd, J=7.14, 2.31 Hz, 1 H) 7.72 (s, 1 H) 8.22 (s, 1 H).

Examples 71 to 73

Example 70 was substantially repeated in Examples 71 to 73 with the exception of utilizing the respective starting materials and reagents in appropriate quantities in order to prepare the Examples 71 to 73 as tabulated in Table 6. Also summarized in Table 6 are the observed LC/MS data for Examples 71 to 73.

Table 6

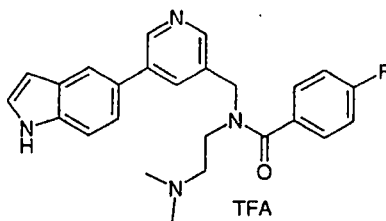
Example No.	Chemical Structure and Chemical Name	LC/MS Data	
		RT (mins.)	M + H

71	 6-(3-([(1-Ethyl-pyrrolidin-2R-ylmethyl)-(4-fluorobenzyl)-amino]-methyl)-4-fluorophenyl)-3H-benzooxazol-2-one trifluoro-acetate	2.62 ^a	478
72	 N-(4-Fluorobenzyl)-N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N',N'-dimethylethane-1,2-diamine	7.12 ^b	420
73	 (1-Aza-bicyclo[2.2.2]oct-4-ylmethyl)-(4-fluorobenzyl)-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-amine acetate	6.53 ^b	472

^a = short LC/MS method; ^b = long LC/MS method

Example 74

N-(2-Dimethylamino-ethyl)-4-fluoro-N-[5-(1H-indol-5-yl)-pyridin-3-ylmethyl]-benzamide trifluoroacetate



5

Step 1: 5-(1H-Indol-5-yl)-pyridine-3-carbaldehyde: Indole-5-boronic acid (1 g, 6.25 mmol), 5-bromopyridine-3-carboxaldehyde (1.3 g, 6.9 mmol) and PdCl₂(dppf).DCM (2.2g, 2.7 mmol) and 15 ml of dioxane were evenly distributed amongst five 5mL microwave vessels (Smith Personal Chemistry). The mixtures were degassed (evacuate in vacuo and pressurize with

112

nitrogen). Sodium carbonate in water (2M, 9.38 mL, 18.7 mmol) was evenly distributed amongst the reaction vessels and the mixtures degassed two more times as described above. The mixture was heated to 100°C for 12 min in a Smith synthesizer. The samples were cooled, combined and washed with water. The aqueous phase was extracted with dichloromethane and the combined organic phases were dried over MgSO₄, filtered and evaporated to give crude product. Chromatography (elution with ethyl acetate/cyclohexane) provided 870 mg of product.

Step 2: N'-[5-(1H-Indol-5-yl)-pyridin-3-ylmethyl]-N,N-dimethyl-ethane-1,2-diamine: Sodium triacetoxyborohydride (855 mg, 4.05 mmol) and then enough acetic acid to bring the pH to 5 were added to a solution of 5-(1H-indol-5-yl)-pyridine-3-carbaldehyde (300 mg, 1.35 mmol) and N,N-dimethylethylene diamine (237 mg, 2.7 mmol) in 15 mL of 1,2-dichloroethane. The mixture was stirred at ambient temperature for 48h, and then the volatiles were removed in the presence of celite. The product was eluted from the celite through silica gel (elution with methanol/dichloromethane) to give 328 mg of product. LC/MS: Retention time, 0.43 min; (M+H) = 295.19.

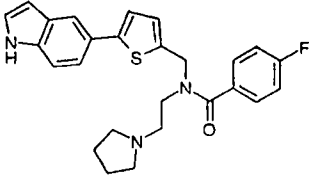
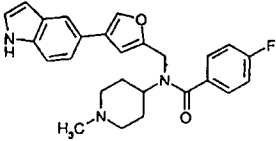
Step 3: N-(2-Dimethylamino-ethyl)-4-fluoro-N-[5-(1H-indol-5-yl)-pyridin-3-ylmethyl]-benzamide: 4-Fluorobenzoyl chloride (111 mg, 0.7 mmol) was added to a solution of N'-[5-(1H-indol-5-yl)-pyridin-3-ylmethyl]-N,N-dimethyl-ethane-1,2-diamine (160 mg, 0.54 mmol) and triethyl amine (109 mg, 1.08 mmol) in 15 mL of dichloromethane at room temperature. The resulting mixture was stirred at ambient temperature overnight, and then a further 111 mg of 4-fluorobenzoyl chloride was added and the mixture stirred for an additional 2 h. The volatiles were removed in vacuo to leave the crude product. Chromatography (elution with methanol/dichloromethane) provided 231 mg of material. This was dissolved in dichloromethane and washed with 1M sodium hydroxide solution. The organic phase was dried over magnesium sulfate, filtered and concentrated to leave material which was further purified by HPLC (elution with acetonitrile/water/TFA) to give 21 mg of product. LC/MS (long run): Retention time, 3.85 min; (M+H) = 417.

Example 75 and 76

Example 74 was substantially repeated in Examples 75 and 76 with the exception of utilizing the respective starting materials and reagents in appropriate quantities in order to prepare the Examples 75 and 76 as tabulated in Table 7. Also summarized in Table 7 are the observed LC/MS data for Examples 75 and 76.

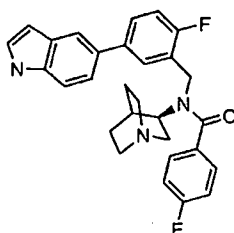
113

Table 7

Example No.	Chemical Structure and Chemical Name	LC/MS Data	
		RT (mins.)	M + H
75	 4-Fluoro-N-[5-(1H-indol-5-yl)-thiophen-2-ylmethyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	5.06 ^b	448
76	 4-Fluoro-N-[4-(1H-indol-5-yl)-furan-2-ylmethyl]-N-(1-methyl-piperidin-4-yl)-benzamide	5.33 ^b	432

^b = long LC/MS method

Example 77

N-(1-Aza-bicyclo[2.2.2]oct-3*R*-yl)-4-fluoro-N-[2-fluoro-5-(1H-indol-6-yl)-benzyl]-benzamide

5

Step 1: (R)-N-(1-Aza-bicyclo[2.2.2]oct-3*R*-yl)-N-(5-bromo-2-fluoro-benzyl)amine: Sodium triacetoxyborohydride (1.6 g, 7.53 mmol) and enough acetic acid to bring the pH to 5 were added to a solution of 5-bromo-2-fluorobenzaldehyde (510 mg, 2.51 mmol), (R)-(-)-1-aza-bicyclo[2.2.2]oct-3*R*-ylamine (1.0 g, 5.02 mmol) and triethylamine (508 mg, 5.02 mmol) in 8 mL of 1,2-dichloroethane. The mixture was stirred at ambient temperature for 4.5 h, and then it was quenched by the careful addition of 1 M sodium hydroxide solution. The aqueous phase was extracted with ethyl acetate, and the combined organic phases were dried over magnesium sulfate, filtered and concentrated to leave 816 mg of product.

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114

Step 2: (R)-N-(1-Aza-bicyclo[2.2.2]oct-3R-yl)-N-(5-bromo-2-fluoro-benzyl)-4-fluoro-benzamide: 4-Fluorobenzoyl chloride (597 mg, 3.77 mmol) was added to a solution of the material obtained above in 10 mL of pyridine at ambient temperature. The mixture was stirred at room temperature and then 1 M sodium hydroxide solution was added, and the product
5 extracted into ethyl acetate, and the volatiles were removed in vacuo to leave a mixture of starting material and product. This was treated again with 4-fluorobenzoyl chloride (597 mg, 3.77 mmol) in 10 mL of pyridine at ambient temperature. 1 M sodium hydroxide solution was added, and the product extracted into ethyl acetate, and the volatiles were removed in vacuo to leave the crude product. Chromatography (elution with triethylamine/ methanol/ethyl acetate)
10 gave 508 mg of product. LC/MS (short run): Retention time, 2.26 min; (M+H) = 435/437.

Step 3: N-(1-Aza-bicyclo[2.2.2]oct-3R-yl)-4-fluoro-N-[2-fluoro-5-(1H-indol-6-yl)-benzyl]-benzamide: A mixture of (R)-N-(1-Aza-bicyclo[2.2.2]oct-3R-yl)-N-(5-bromo-2-fluoro-benzyl)-4-fluoro-benzamide (150 mg, 0.345 mmol), 5-indoleboronic acid (83 mg, 0.517 mmol), sodium carbonate in water (2M, 0.69 mL, 1.38 mmol) in 2 mL of dioxane was
15 degassed (evacuate in vacuo and pressurize with nitrogen, four times) PdCl₂(dppf).DCM (12 mg, 0.0017 mmol) was added and the mixture degassed four times as described above. The resulting mixture was heated at 80°C overnight, then it was allowed to cool to room temperature, filtered and the filtrate diluted with dichloromethane and washed with water. The aqueous phases were extracted with dichloromethane and the combined organic phases
20 were dried over MgSO₄, filtered and evaporated to give crude product. Chromatography on silica gel (elution with methanol/dichloromethane) afforded 20 mg of the product. LC/MS (short run): Retention time, 2.63 min; (M+H) = 472.

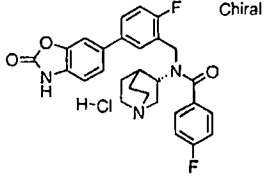
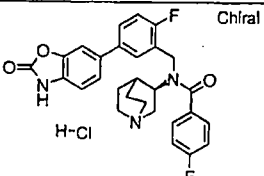
¹H NMR (400 MHz, chloroform-D) δ ppm: 1.50 - 1.76 (m, 2 H) 1.98 (br s, 1 H) 2.13 (br s, 1 H) 2.71 - 3.00 (m, 4 H) 3.02 - 3.24 (m, 2 H) 3.38 (br s, 1 H) 4.21 (br s, 1 H) 4.76 - 4.93 (m, 1 H) 6.62 (br s, 1 H) 7.01 - 7.12 (m, 3 H) 7.26 - 7.29 (m, 1 H) 7.33 (d, 1 H, J = 8.4 Hz) 7.36 - 7.54 (m, 5 H) 7.75 (br s, 1 H).

Examples 78 and 79

Example 77 was substantially repeated in Examples 78 and 79 with the exception of utilizing the respective starting materials and reagents in appropriate quantities in order to
30 prepare the Examples 78 and 79 as tabulated in Table 8. Also summarized in Table 8 are the observed LC/MS data for Examples 78 and 79.

115

Table 8

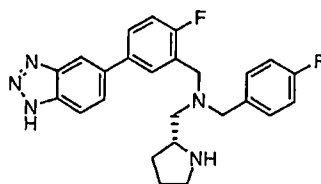
Example No.	Chemical Structure and Chemical Name	LC/MS Data	
		RT (mins.)	M + H
78	 N-(1-Aza-bicyclo[2.2.2]oct-3<i>S</i>-yl)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-benzamide hydrochloride	2.35 ^a	490
79	 N-(1-Aza-bicyclo[2.2.2]oct-3<i>R</i>-yl)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-benzamide hydrochloride	2.37 ^a	490

^a = short LC/MS method

Example 80

[5-(1*H*-Benzotriazol-5-yl)-2-fluoro-benzyl]-(4-fluoro-benzyl)-pyrrolidin-2*R*-ylmethyl-amine trihydrochloride

5



3 HCl

Step 1: (*R*)-2-[(4-Fluoro-benzylamino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester: Sodium triacetoxyborohydride (15.9 g, 75.4 mmol) and enough acetic acid to bring the pH to 5 were added to a solution of *N*-tert-butoxycarbonyl-L-prolinal (5 g, 25 mmol) and 4-fluorobenzylamine (6.28 g, 50.3 mmol) in 200 mL of 1,2-dichloroethane. The mixture was stirred at ambient temperature overnight, and then it was diluted with dichloromethane, and washed with saturated sodium bicarbonate solution. The organic phase was dried over

10

magnesium sulfate, filtered and concentrated to leave the crude product. Chromatography (elution with methanol/ethyl acetate) afforded 6.0 g of product.

Step 2: (R)-2-((4-Fluoro-benzyl)-[2-fluoro-5-(1-trityl-1H-benzotriazol-5-yl)-benzyl]-amino)-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester: Sodium triacetoxyborohydride (159 mg, 0.75 mmol) and acetic acid (36 mg, 0.6 mmol) were added to a mixture of 5-(4-fluoro-3-formylphenyl)-1-trityl-1H-benzotriazole (145 mg, 0.3 mmol) and (R)-2-[(4-fluoro-benzylamino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester (111mg, 0.36 mmol) and 4 angstrom molecular sieves in 5 mL of dichloroethane. The mixture was stirred at ambient temperature overnight, and then it was diluted with dichloromethane, and washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, filtered and concentrated to leave the crude product. Chromatography (elution with ethyl acetate/cyclohexane) provided 119 mg of product. LC/MS: Retention time, 4.02, 4.21 min; (M+H) = 776.

Step 3: (R)-[5-(1H-Benzotriazol-5-yl)-2-fluoro-benzyl]-(4-fluoro-benzyl)-pyrrolidin-2-ylmethyl-amine: A solution of hydrochloric acid in dioxane (4M, 2 mL) was added to a solution of (R)-2-((4-fluoro-benzyl)-[2-fluoro-5-(1-trityl-1H-benzotriazol-5-yl)-benzyl]-amino)-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (119 mg, 0.15 mmol) in 5 mL of methanol and the resulting solution stirred at ambient temperature for 24 h. The volatiles were removed in vacuo and purified by HPLC. The product obtained was treated with hydrochloric acid to give 40 mg of product. LC/MS (long run): Retention time, 6.20 min; (M+H) = 433. ¹H NMR (400 MHz, methanol-D₄) δ ppm: 1.68 - 1.85 (m, 1 H) 1.97 - 2.16 (m, 2 H) 2.31 - 2.45 (m, 1 H) 3.38 (t, J=7.47 Hz, 2 H) 3.60 - 3.84 (m, 2 H) 4.26 (br s, 1 H) 4.75 (d, J = 13.18 Hz, 1H) 4.53 - 4.72 (m, 3 H) 7.20 (t, J=8.57 Hz, 2 H) 7.38 (t, J=9.23 Hz, 1 H) 7.76 (br s, 2 H) 7.86 - 7.96 (m, 2 H) 8.00 (d, 1 H) 8.10 - 8.22 (m, 1 H) 8.24 (s, 1 H).

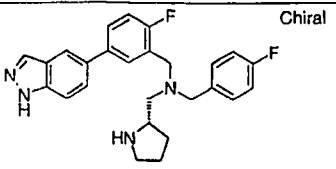
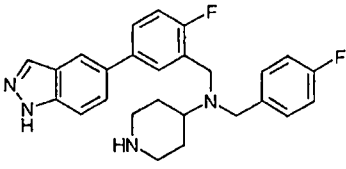
Examples 81 and 82

Example 80 was substantially repeated in Examples 81 and 82 with the exception of utilizing the respective starting materials and reagents in appropriate quantities in order to prepare the Examples 81 and 82 as tabulated in Table 9. Also summarized in Table 9 are the observed LC/MS data for Examples 81 and 82.

Table 9

Example	LC/MS Data
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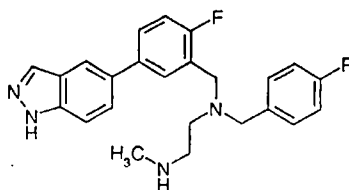
182

No.	Chemical Structure and Chemical Name	RT (mins.)	M + H
81	 (4-Fluoro-benzyl)-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-pyrrolidin-2<i>S</i>-ylmethyl-amine	6.51 ^b	433
82	 (4-Fluoro-benzyl)-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-piperidin-4-yl-amine	4.9 ^b	433

^b = long LC/MS method

Example 83

N-(4-Fluoro-benzyl)-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N'-methyl-ethane-1,2-diamine



- 5 Step 1: 5-(3-{[2-(tert-Butoxycarbonyl-methyl-amino)-ethylamino]-methyl}-4-fluoro-phenyl)-indazole-1-carboxylic acid tert-butyl ester: Sodium triacetoxyborohydride (250 mg, 1.2 mmol) and acetic acid (42 mg, 1.2 mmol) were added to a mixture of 5-(4-fluoro-3-formylphenyl)-indazole-1-carboxylic acid tert-butyl ester (270 mg, 0.8 mmol) and (2-amino-ethyl)-methyl-carbamic acid tert-butyl ester (210mg, 1.2 mmol) in 8 mL of dichloroethane.
- 10 The mixture was stirred at ambient temperature overnight, and then it was diluted with water, the layers were separated and the aqueous phase was extracted with dichloromethane. The combined organic layers were washed with sequentially with water, saturated sodium bicarbonate solution and water, dried over magnesium sulfate, filtered and concentrated to leave the crude product. Chromatography (elution with methanol/dichloromethane) provided
- 15 400 mg of product. LC/MS: Retention time, 2.66 min; (M+H) = 499.

Step 2: 5-(3-([2-(tert-butoxycarbonyl-methyl-amino)-ethyl]-(3-fluoro-benzyl)- amino]-methyl)-4-fluoro-phenyl)-indazole-1-carboxylic acid tert-butyl ester: Sodium triacetoxyborohydride (254 mg, 1.2 mmol) and acetic acid (48 mg, 0.8 mmol) were added to a mixture of 5-(3-([2-(tert-butoxycarbonyl-methyl-amino)-ethylamino]-methyl)-4-fluoro-phenyl)-indazole-1-carboxylic acid tert-butyl ester (400 mg, 0.8 mmol) and 4-fluorobenzaldehyde (99 mg, 0.8 mmol) in 15 mL of dichloroethane. The mixture was stirred at ambient temperature for 80h, and then it was diluted with water, the layers were separated and the aqueous phase was extracted with dichloromethane. The combined organic layers were washed with sequentially with water, saturated sodium bicarbonate solution and water, dried over magnesium sulfate, filtered and concentrated to leave the crude product. Chromatography (elution with ethyl acetate/pentane) provided 360 mg of product. LC/MS: Retention time, 4.10 min; (M+H) = 607.

Step 3: N-(3-Fluoro-benzyl)-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N'-methyl-ethane-1,2-diamine: A solution of 2-((4-fluoro-benzyl)-[2-fluoro-5-(1-trityl-1H-benzotriazol-5-yl)-benzyl]-amino)-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (360 mg, 0.59 mmol) in 2 mL of diethyl ether was treated with a solution of hydrochloric acid in dioxane (4M, 12 mL) and the resulting solution stirred at ambient temperature for 4 h. The volatiles were removed in vacuo and the residue was dissolved in water and neutralized with saturated sodium bicarbonate solution. The product was extracted into ethyl acetate and the combined organic layers were washed with sequentially with water, dried over magnesium sulfate, filtered and concentrated to leave the crude product. The residue was dissolved in hot ethyl acetate and the solid obtained upon cooling was collected to give 65 mg of product. LC/MS (long run): Retention time, 6.02 min; (M+H) = 407.

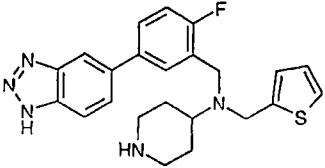
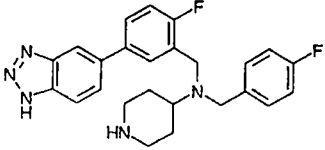
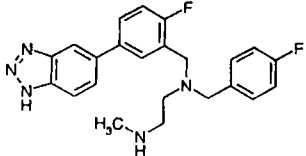
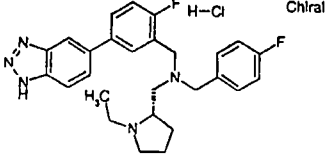
¹H NMR (400 MHz, chloroform-D) δ ppm: 2.29 (s, 3 H) 2.64 - 2.73 (m, 4 H) 3.60 (s, 2 H) 3.70 (s, 2 H) 6.95 (t, J=8.7 Hz, 2 H) 7.08 (t, J=8.7 Hz 1 H) 7.27 (dd, J=8.35, 5.49 Hz, 2 H) 7.39 - 7.46 (m, 1 H) 7.48 - 7.52 (m, 2 H) 7.53 - 7.57 (m, 1 H) 7.81 (s, 1 H) 8.07 (s, 1 H).

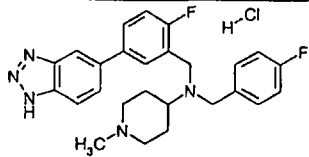
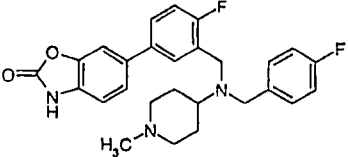
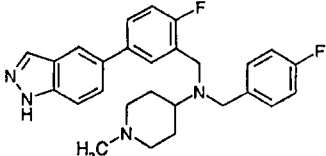
Examples 84 to 90

Example 83 was substantially repeated in Examples 84 to 90 with the exception of utilizing the respective starting materials and reagents in appropriate quantities in order to prepare the Examples 84 to 90 as tabulated in Table 10. Also summarized in Table 10 are the observed LC/MS data for Examples 84 to 90.

119

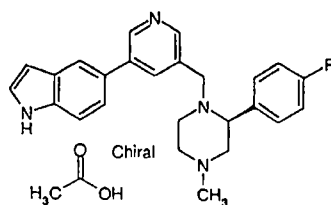
Table 10

Example No.	Chemical Structure and Chemical Name	LC/MS Data	
		RT (mins.)	M + H
84	 [5-(1H-Benzotriazol-5-yl)-2-fluoro-benzyl]-piperidin-4-yl-thiophen-2-ylmethyl-amine	4.73 ^b	422
85	 [5-(1H-Benzotriazol-5-yl)-2-fluoro-benzyl]-(4-fluoro-benzyl)-piperidin-4-yl-amine	4.74 ^b	434
86	 N-[5-(1H-Benzotriazol-5-yl)-2-fluoro-benzyl]-N-(4-fluoro-benzyl)-N'-methyl-ethane-1,2-diamine	5.71 ^b	408
87	 [5-(1H-Benzotriazol-5-yl)-2-fluoro-benzyl]-(1-ethyl-pyrrolidin-2S-ylmethyl)-(4-fluoro-benzyl)-amine hydrochloride	6.46 ^b	462

88	 [5-(1H-Benzotriazol-5-yl)-2-fluoro-benzyl]-(4-fluoro-benzyl)-(1-methyl-piperidin-4-yl)-amine hydrochloride	4.95 ^b	448
89	 6-(4-Fluoro-3-[(4-fluoro-benzyl)-(1-methyl-piperidin-4-yl)-amino]-methyl)-phenyl-3H-benzooxazol-2-one	5.07 ^b	464
90	 (4-Fluoro-benzyl)-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amine	4.71 ^b	447

^b = long LC/MS method

Example 91

5-5-[2*S*-(4-Fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-pyridin-3-yl}-1H-indole acetate

- 5 Step 1: (*S*)-4-(5-Bromo-pyridin-3-ylmethyl)-3-(4-fluoro-phenyl)-piperazine-1-carboxylic acid tert-butyl ester: Sodium triacetoxyborohydride (1.27 g, 6 mmol) and acetic acid (120 mg, 2 mmol) were added to a mixture of 5-bromo-pyridine-3-carboxaldehyde (372 mg, 2 mmol) and 3*S*-(4-fluorophenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (560 mg, 2 mmol) in 10 mL of dichloroethane. The mixture was stirred at ambient temperature overnight, and then it was
- 10 diluted with dichloromethane and water, the layers were separated and organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated to leave the crude

121

product. Chromatography (elution with ethyl acetate/pentane) provided 625 mg of product. LC/MS: Retention time, 4.2 min; (M+H) = 452.

Step 2: (S)-1-(5-Bromo-pyridin-3-ylmethyl)-2-(4-fluoro-phenyl)-piperazine: A mixture of trifluoroacetic acid and water (TFA:water = 19:1, 10 mL) was added to a solution of (S)-4-(5-bromo-pyridin-3-ylmethyl)-3-(4-fluoro-phenyl)-piperazine-1-carboxylic acid tert-butyl ester (300 mg, 0.67 mmol) in 3 mL of dichloromethane and the resulting mixture stirred at ambient temperature for 1.5 h, and then the volatiles were removed in vacuo to leave 470 mg of product. LC/MS: Retention time, 2.13 min; (M+H) = 351.

Step 3: (S)-1-(5-Bromo-pyridin-3-ylmethyl)-2-(4-fluoro-phenyl)-4-methyl-piperazine: Sodium triacetoxyborohydride (1.5 g, 7 mmol) was added to a mixture of (S)-1-(5-bromo-pyridin-3-ylmethyl)-2-(4-fluoro-phenyl)-piperazine (as tris(trifluoroacetate) salt) (820 mg, 1.2 mmol) and formaldehyde (37% aqueous solution, 3 mL, 36.9 mmol) in 20 mL of methanol. The mixture was stirred at ambient temperature overnight, and then the volatiles were removed in vacuo and the residue dissolved in water and the pH was adjusted to 11 by the addition of 10 M sodium hydroxide solution. The product was extracted into dichloromethane and the combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated to leave 431 mg of product. LC/MS: Retention time, 2.15 min; (M+H) = 366.

Step 4: 5-{5-[2S-(4-Fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-pyridin-3-yl}-1H-indole: A mixture of (S)-1-(5-bromo-pyridin-3-ylmethyl)-2-(4-fluoro-phenyl)-4-methyl-piperazine (181 mg, 0.5 mmol), 5-indoleboronic acid (100 mg, 0.62 mmol), cesium carbonate in water (2M, 1 mL, 2 mmol) in 8 mL of dioxane was degassed (evacuate in vacuo and pressurize with nitrogen, three times) PdCl₂(dppf).DCM (40 mg, 0.05 mmol) was added and the mixture degassed two more times as described above. The resulting mixture was heated at 90°C for 6 h, then it was allowed to cool to room temperature and the volatiles were removed in vacuo. The residue was triturated with water, the water was decanted and the residue dissolved in methanol. This was filtered and the filtrate evaporated to give crude product. Chromatography on silica gel (elution with DCE:MeOH:AcOH:H₂O = 240:15:3:2) afforded 110 mg of the product. LC/MS (long run): Retention time, 3.97 min; (M+H) = 401.

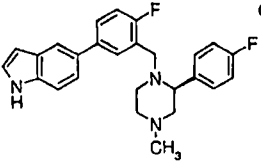
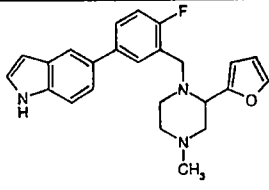
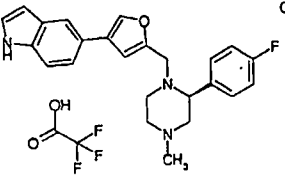
Examples 92 to 94

Example 91 was substantially repeated in Examples 92 to 94 with the exception of utilizing the respective starting materials and reagents in appropriate quantities in order to

122

prepare the Examples 92 to 94 as tabulated in Table 11. Also summarized in Table 11 are the observed LC/MS data for Examples 92 to 94.

Table 11

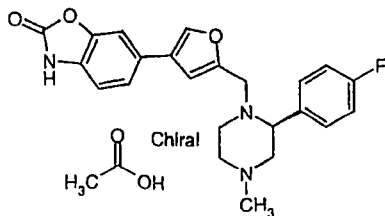
Example No.	Chemical Structure and Chemical Name	LC/MS Data	
		RT (mins.)	M + H
92	 5-{4-Fluoro-3-[2S-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-phenyl}-1H-indole	7.02 ^b	418
93	 5-[4-Fluoro-3-(2-furan-2-yl-4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-indole	5.43 ^b	390
94	 5-{5-[2S-(4-Fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-furan-3-yl}-1H-indole; compound with trifluoro-acetate	5.6 ^b	390

^b = long LC/MS method

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Example 95

6-{5-[2S-(4-Fluorophenyl)-4-methylpiperazine-1-ylmethyl]-furan-3-yl}-3H-benzoxazol-2-one



123

Step 1: 6-Bromo-3H-benzoxazol-2-one: To a mixture of 3H-benzoxazol-2-one (20 g, 0.15 mol) in DCM (500 mL) was added bromine (8.34 mL, 0.16 mol). After stirring at room temperature for 19.5 h, the orange precipitate that had formed was filtered off and washed with DCM until the orange color was washed out. The filtrate was concentrated to approximately 33% of its original volume and filtered and washed as before. The combined solids weighed 28.36 g and contained *ca.* 8-9% starting material.

Step 2: 6-Bromo-3-trityl-benzoxazol-2-one: To a solution of 6-bromo-3H-benzoxazol-2-one (15 g; *ca.* 0.07 mol, containing 8-9% 3H-benzoxazol-2-one) and triethylamine (11.1 mL, 0.08 mol) in DCM (250 mL) was added trityl chloride (21.5 g, 0.08 mol). The solution was stirred at room temperature for 18 h and was then washed with distilled water (3 x 250 mL), brine (250 mL) and dried (MgSO₄), filtered and evaporated to give an off-white colored solid. The product was dissolved in refluxing EtOAc then allowed to cool to room temperature with constant stirring for several hours. The solids were collected (21.16 g) and the filtrate was concentrated until precipitation occurred, re-heated (reflux) for several hours and allowed to cool with stirring to encourage a second crystallization (7.88 g).

Step 3: 6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-3-trityl-3H-benzoxazol-2-one: A mixture of 6-bromo-3-trityl-benzoxazol-2-one (2.5 g, 5.48 mmol), bis(pinacolato)diboron (1.53 g, 6.03 mmol), potassium acetate (2.15 g, 21.91 mmol) and PdCl₂(dppf).DCM (447 mg, 0.55 mmol) in degassed, anhydrous DMSO was evacuated and then repressurized with nitrogen. This process was repeated several times to minimize the amount of oxygen in the reaction mixture. The mixture was heated at 85°C (oil bath temperature) under a nitrogen atmosphere for 2.5 h. The reaction was diluted with DCM (700 mL) and washed twice with distilled water (300 mL each), brine (300 mL), dried (MgSO₄), filtered and evaporated to give a dark brown syrup.

The reaction was repeated and the product was combined with that prepared above and chromatographed on a column of silica gel, eluting with 20% Et₂O in heptane giving the desired product as a white powder (3.76 g, 68%).

Step 4: 4-(4-Bromofuran-2-ylmethyl)-3S-(4-fluorophenyl)-piperazine-1-carboxylic acid *tert*-butyl ester: 3S-(4-Fluorophenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (1.0 g, 3.57 mmol) and 4-bromo-2-furaldehyde (0.63 g, 3.6 mmol) was dissolved in DCE (15 mL) and glacial acetic acid was added (0.23 mL, 3.55 mmol) followed by sodium triacetoxymethylborohydride (2.30 g, 10.85 mmol). The reaction was stirred overnight at room

124

temperature. DCM (50 mL) was added and the mixture was washed with water (1 x 50 mL) and brine (1 x 50 mL) and dried over Na₂SO₄. The solvent was removed *in vacuo* to give an oil, which solidified on standing to provide 1.6 g of product. LC/MS: Retention time, 4.32 min; (M+H) = 439.

- 5 Step 5: 1-(4-bromofuran-2-ylmethyl)-2*S*-(4-fluorophenyl)-piperazine-trifluoroacetate: 4-(4-Bromofuran-2-ylmethyl)-3*S*-(4-fluorophenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (0.68 g, 1.55 mmol) was taken up in a mixture of 95% TFA aq. and DCM [70:30] and was stirred for 30 mins. The solvent was removed *in vacuo* to yield a gum (0.90 g, quantitative crude yield). LCMS: Retention time, 2.33 min; (M+H) = 339.23.
- 10 Step 6: 1-(4-Bromofuran-2-ylmethyl)-2*S*-(4-fluorophenyl)-4-methylpiperazine: A solution of 1-(4-bromofuran-2-ylmethyl)-2*S*-(4-fluorophenyl)-piperazine di-trifluoroacetate (0.60 g, 1.06 mmol) in methanol (15 mL) was treated with 37% aqueous formaldehyde (2.5 mL, ~30 mmol) followed by sodium triacetoxyborohydride (1.25 g, 5.5 mmol). The reaction was stirred at room temperature overnight after which the solvent was removed *in vacuo* to give a gum.
- 15 Water (20 mL) was added and adjusted to pH 11 with 10M NaOH aq. The mixture was extracted with DCM and the combined DCM layers were washed with brine and dried over Na₂SO₄. Solvent removal *in vacuo* afforded an oil (0.35 g, 94%). This compound was purified *via* flash silica gel chromatography using DCM:MeOH:AcOH:water (240:15:3:2) as eluent. LC/MS: Retention time, 2.28 min; (M+H) = 353.
- 20 Step 7: 6-{5-[2*S*-(4-Fluorophenyl)-4-methylpiperazine-1-ylmethyl]-furan-3-yl}-3-trityl-3H-benzoxazol-2-one: 1-(4-Bromofuran-2-ylmethyl)-2*S*-(4-fluorophenyl)-4-methylpiperazine (0.164 g, 0.33 mmol) and 6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3-trityl-3H-benzoxazol-2-one (0.105 g, 0.30 mmol) were dissolved in dioxane (8 mL) and 2M Cs₂CO₃ aq. (0.65 mL, 1.3 mmol) was added. The mixture was de-gassed and nitrogen was introduced
- 25 (three times) when PdCl₂(dppf).DCM (0.027 g, 0.03 mmol) was added. After a further de-gassing, the reaction was heated at 100°C for 4 hours. DCM (20 mL) was added to the mixture and was washed with water and brine. The organic layer was dried over MgSO₄ and the solvent removed *in vacuo*. Chromatography using DCM:MeOH:AcOH:water (240:15:3:2) as eluent gave 0.11 g of the product (68%). LC/MS: Retention time, 3.13 min; (M+H) = 650
- 30 Step 8: 6-{5-[2*S*-(4-Fluorophenyl)-4-methylpiperazine-1-ylmethyl]-furan-3-yl}-3H-benzoxazol-2-one: 6-{5-[2*S*-(4-Fluorophenyl)-4-methylpiperazine-1-ylmethyl]-furan-3-yl}-3-trityl-3H-benzoxazol-2-one (0.33 g, 0.51 mmol) was taken up in 90% TFA aq. (20 mL) and

125

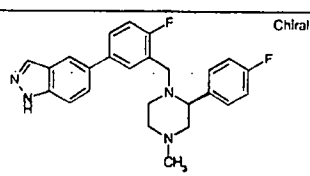
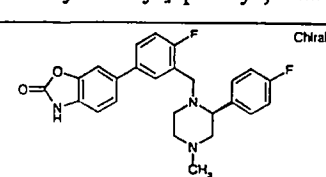
stirred at room temperature for 2 hours. The solvent was removed *in vacuo* and co-evaporation of residual TFA was achieved using water (3 x ~2 mL) to afford a brown solid. Chromatography using DCM:MeOH:AcOH:water (180:20:3:2) as eluent provided 0.15 g of the product (73%). LC/MS (long run): Retention time, 4.39 min; (M+H) = 408.

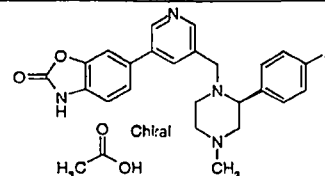
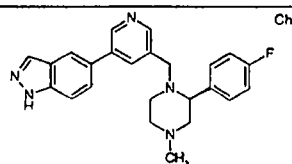
¹H NMR (400 MHz, methanol-D₄) δ ppm: 2.73 (td, J=12.58, 2.75 Hz, 1 H) 2.83 (s, 3 H) 3.04 (t, J=11.76 Hz, 1 H) 3.16 - 3.26 (m, 2 H) 3.33 - 3.42 (m, 2 H) 3.50 (dd, J=12.09, 1.98 Hz, 1 H) 3.65 - 3.71 (m, 2 H) 6.54 (s, 1 H) 7.07 (d, J=8.13 Hz, 1 H) 7.20 (t, J=8.79 Hz, 2 H) 7.33 (dd, J=8.13, 1.54 Hz, 1 H) 7.39 (d, J=1.54 Hz, 1 H) 7.56 (dd, J=8.46, 5.39 Hz, 2 H) 7.83 (d, J=0.88 Hz, 1 H).

Examples 96 to 99

Example 95 was substantially repeated in Examples 96 to 99 with the exception of utilizing the respective starting materials and reagents in appropriate quantities in order to prepare the Examples 96 to 99 as tabulated in Table 12. Also summarized in Table 12 are the observed LC/MS data for Examples 96 to 99.

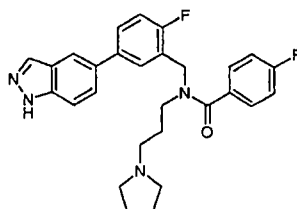
Table 12

Example No.	Chemical Structure and Chemical Name	LC/MS Data	
		RT ^a (mins.)	M + H
96	 5-{4-Fluoro-3-[2S-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-phenyl}-1H-indazole	6.22 ^b	419
97	 6-{4-Fluoro-3-[2S-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-phenyl}-3H-benzooxazol-2-one	6.19 ^b	436

98	 6-{5-[2<i>S</i>-(4-Fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-pyridin-3-yl}-3<i>H</i>-benzooxazol-2-one acetate	3.85 ^b	419
99	 5-{5-[2<i>S</i>-(4-Fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-pyridin-3-yl}-1<i>H</i>-indazole	3.55 ^b	402

^b = long LC/MS method

Example 100

4-Fluoro-N-[2-fluoro-5-(1*H*-indazol-5-yl)-benzyl]-N-(3-pyrrolidin-1-yl-propyl)-benzamide

- 5 Step 1: 5-{4-Fluoro-3-[(3-pyrrolidin-1-yl-propylamino)-methyl]-phenyl}-indazole-1-carboxylic acid tert-butyl ester: Sodium triacetoxyborohydride (190 mg, 0.88 mmol) was added to a mixture of 5-(4-fluoro-3-formylphenyl)-indazole-1-carboxylic acid tert-butyl ester (100 mg, 0.29 mmol) and N-(3-aminopropyl)pyrrolidine (74 mg, 0.59 mmol) and acetic acid (105 mg, 1.8 mmol) in dichloroethane. The mixture was stirred at ambient temperature
- 10 overnight, and then it was diluted with dichloromethane and washed with 1 M sodium carbonate solution. The layers were separated and the aqueous phase extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered and concentrated to leave the crude product. Chromatography (elution with methanol/dichloromethane) provided 130 mg of product. LC/MS: Retention time, 1.98 min;
- 15 (M+H) = 453.

Step 2: 4-Fluoro-N-[2-fluoro-5-(1*H*-indazol-5-yl)-benzyl]-N-(3-pyrrolidin-1-yl-propyl)-benzamide: HATU (100 mg, 0.28 mmol) was added to a solution of 5-{4-fluoro-3-[(3-

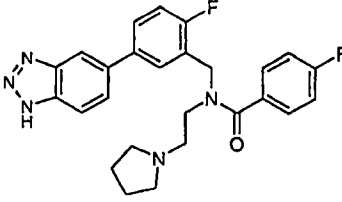
pyrrolidin-1-yl-propylamino)-methyl]-phenyl}-indazole-1-carboxylic acid tert-butyl ester (125 mg, 0.28 mmol), 4-fluorobenzoic acid (39 mg, 0.28 mmol) and diisopropylethylamine (89 mg, 0.69 mmol) in 3 mL of dimethylformamide, and the resulting mixture stirred at ambient temperature for 5 h. The mixture was diluted with ethyl acetate washed with 1 M sodium carbonate solution. The layers were separated and the aqueous phase extracted with ethyl acetate. The combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated to leave the crude product. Chromatography (elution with methanol/dichloromethane) provided 100 mg of product. 2 mL of TFA was added to 98 mg of this material in 2 mL of dichloromethane and the mixture stirred at room temperature for 5 h, and the volatiles were removed in vacuo. Chromatography (elution with methanol/dichloromethane) provided 64 mg of product. LC/MS: Retention time, 2.65 min; (M+H) = 475.

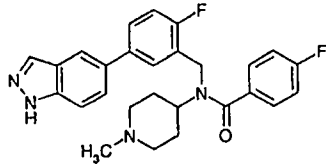
¹H NMR (400 MHz, chloroform-D) δ ppm: 1.98-2.21 (m, 6 H) 2.76 (br s, 2 H) 3.17 (br s, 2 H) 3.59 (br s, 2 H) 3.80 (br s, 2 H) 4.67 (br s, 2 H) 7.07-7.16 (m, 3 H) 7.34 (br s, 1 H) 7.41 - 7.72 (m, 5 H) 7.84 (br s, 1 H) 8.11 (br s, 1 H) 12.98 (br s, 1 H).

Examples 101 and 102

Example 100 was substantially repeated in Examples 101 and 102 with the exception of utilizing the respective starting materials and reagents in appropriate quantities in order to prepare the Examples 101 and 102 as tabulated in Table 13. Also summarized in Table 13 are the observed LC/MS data for Examples 101 and 102.

Table 13

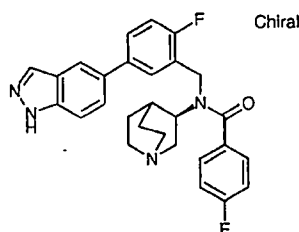
Example No.	Chemical Structure and Chemical Name	LC/MS Data	
		RT (mins.)	M + H
101	 N-[5-(1H-Benzotriazol-5-yl)-2-fluoro-benzyl]-4-fluoro-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	4.87 ^b	462

102	 4-Fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-benzamide	5 ^b	461
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^b = long LC/MS method

Example 103

N-(1-Aza-bicyclo[2.2.2]oct-3R-yl)-4-fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-benzamide



5

- Step 1: 5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-indazole-1-carboxylic acid *tert*-butyl ester: A mixture of 5-bromo-indazole-1-carboxylic acid *tert*-butyl ester (1.8 g, 6.19 mmol), bis(pinacolato)diboron (1.73 g, 6.80 mmol), potassium acetate (2.43 g, 24.7 mmol) and PdCl₂(dppf).DCM (505 mg, 0.62 mmol) in degassed, anhydrous DMSO was evacuated and then repressurized with nitrogen. This process was repeated several times to minimize the amount of oxygen in the reaction mixture. The mixture was heated at 85°C for 4.5 h. The reaction was diluted with DCM and washed with water and brine, dried over MgSO₄, filtered and evaporated to give a dark brown syrup. Chromatography on silica gel, eluting with 75% diethyl ether/heptane gave 1.47 g of the product.
- Step 2: N-(1-Aza-bicyclo[2.2.2]oct-3R-yl)-4-fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-benzamide: A mixture of (R)-N-(1-aza-bicyclo[2.2.2]oct-3-yl)-N-(5-bromo-2-fluoro-benzyl)-4-fluoro-benzamide (180 mg, 0.41 mmol), 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indazole-1-carboxylic acid *tert*-butyl ester (170 mg, 0.50 mmol), cesium carbonate in water (2M, 0.82 mL, 1.65 mmol) in 2 mL of dioxane was degassed (evacuate in vacuo and pressurize with nitrogen) PdCl₂(dppf).DCM (34 mg, 0.04 mmol) was added and the mixture degassed as above. The resulting mixture was heated at 85°C for 4 h, then it was allowed to cool to room temperature diluted with chloroform and water. The layers were separated and the organic phase was washed with brine, dried over MgSO₄, filtered and evaporated to give

20

129

crude product. Chromatography on silica gel (elution with methanol/dichloromethane) afforded 100 mg of the product. This material was dissolved in 95% aqueous TFA and stirred at room temperature for 4 h. The volatiles were removed in vacuo to leave the crude product. Chromatography (elution with methanol/dichloromethane) afforded 38 mg of product.

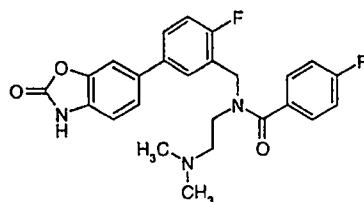
5 LC/MS (long run): Retention time, 5.88 min; (M+H) = 473.

¹H NMR (400 MHz, methanol-D₄) δ ppm: 1.82 - 1.93 (m, 1 H) 1.94 - 2.06 (m, 2 H) 2.30 - 2.53 (m, 2 H) 3.22 - 3.40 (m, 1 H) 3.58 - 3.68 (m, 1 H) 3.72 (ddd, J=13.24, 6.65, 2.09 Hz, 1 H) 3.82 - 3.91 (m, 1 H) 4.25 - 4.33 (m, 1 H) 4.80 (d, J=16.93, 1 H) 4.91 (d, J=16.93, 1 H) 7.14 - 7.25 (m, 3 H) 7.37 (dd, J=7.25, 2.20 Hz, 1 H) 7.54 - 7.67 (m, 5 H) 7.93 (s, 1 H) 8.11 (s, 1 H).

10

Example 104

N-(2-Dimethylamino-ethyl)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-benzamide



Sodium triacetoxyborohydride (440 mg, 2.1 mmol) was added to a mixture of 2-fluoro-5-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzaldehyde (180 mg, 0.7 mmol) and N',N'-dimethylaminoethylenediamine (184 mg, 2.1 mmol) and acetic acid (84 mg, 1.4 mmol) in 5 mL of dichloroethane. The mixture was stirred at ambient temperature overnight, and then it was diluted with dichloromethane and washed with 1 M sodium carbonate solution. The layers were separated and the aqueous phase extracted with dichloromethane. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to leave the crude product. Chromatography (elution with methanol/dichloromethane) provided 130 mg of product. HATU (76 mg, 0.2 mmol) was added to a solution of the above material (65 mg, 0.2 mmol), 4-fluorobenzoic acid (28 mg, 0.2 mmol) and diisopropylethylamine (65 mg, 0.5 mmol) in 3 mL of dimethylformamide, and the resulting mixture stirred at ambient temperature for 4 h. The mixture was diluted with ethyl acetate washed with 1 M sodium carbonate solution. The layers were separated and the aqueous phase extracted with ethyl acetate. The combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated to leave the crude product. Chromatography (two times, elution with methanol/dichloromethane) provided 36 mg of

130

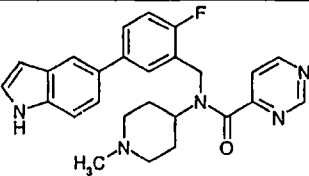
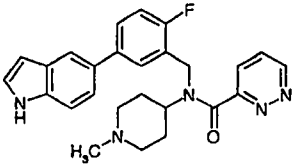
product. The product was dissolved in ethyl acetate and washed with 1 M sodium carbonate solution. The aqueous phase was extracted with ethyl acetate, and the combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated to leave 26 mg of product. LC/MS (long run): Retention time: 5.64 min; (M+H) = 452.

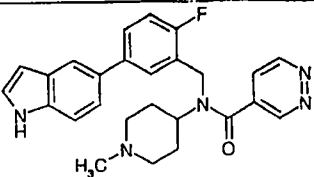
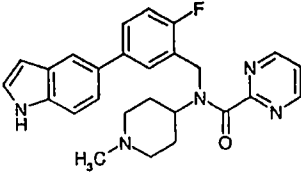
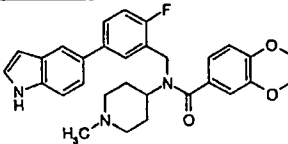
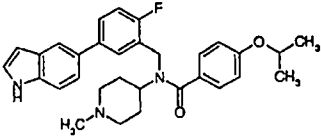
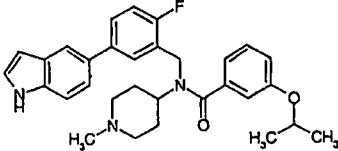
5 ¹H NMR (400 MHz, methanol-D₄) δ ppm: 2.03 (br s, 3 H) 2.27 (br s, 3 H) 2.38 - 2.68 (m, 2 H) 3.44 (br s, 1 H) 3.64 (br s, 1 H) 4.70 (br s, 1 H) 4.89 (br s, 1 H) 7.15 (d, J=8.13 Hz, 2 H) 7.17 - 7.27 (m, 2 H) 7.34 - 7.43 (m, 2 H) 7.46 (s, 1 H) 7.48 - 7.54 (m, 2 H) 7.54 - 7.61 (m, 1 H).

Examples 105 to 112

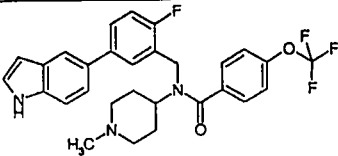
10 Example 104 was substantially repeated in Examples 105 to 112 with the exception of utilizing the respective starting materials and reagents in appropriate quantities in order to prepare the Examples 105 to 112 as tabulated in Table 14. Also summarized in Table 14 are the observed LC/MS data for Examples 105 to 112.

Table 14

Example No.	Chemical Structure and Chemical Name	LC/MS Data	
		RT (mins.)	M + H
105	 Pyrimidine-4-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide	5.24 ^b	444
106	 Pyridazine-3-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide	5.18 ^b	444

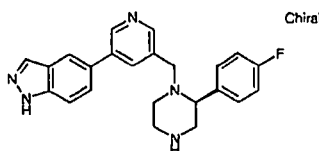
107	 Pyridazine-4-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide	5.05 ^b	444
108	 Pyrimidine-2-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide	5 ^b	444
109	 2,3-Dihydro-benzo[1,4]dioxine-6-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide	6.38 ^b	500
110	 N-[2-Fluoro-5-(1H-indol-5-yl)-benzyl]-4-isopropoxy-N-(1-methyl-piperidin-4-yl)-benzamide	7.14 ^b	500
111	 N-[2-Fluoro-5-(1H-indol-5-yl)-benzyl]-3-isopropoxy-N-(1-methyl-piperidin-4-yl)-benzamide	7.1 ^b	500

132

112	 N-[2-Fluoro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-4-trifluoromethoxy-benzamide	7.37 ^b	526
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^b = long LC/MS method

Example 113

5-{5-[2*S*-(4-Fluoro-phenyl)-piperazin-1-ylmethyl]-pyridin-3-yl}-1H-indazole

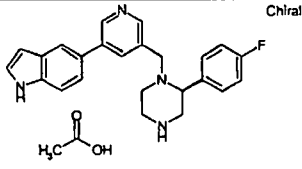
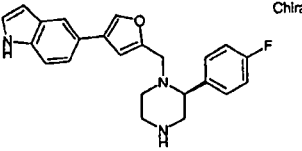
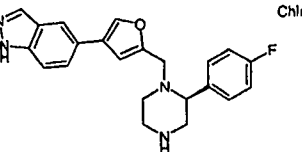
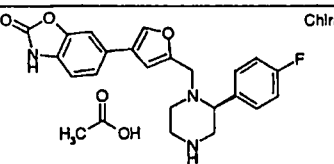
5 Step 1: 5-{5-[4-tert-Butoxycarbonyl-2*S*-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-pyridin-3-yl}-indazole-1-carboxylic acid tert-butyl ester: 4-(5-Bromo-pyridin-3-ylmethyl)-3-(4-fluoro-phenyl)-piperazine-1-carboxylic acid tert-butyl ester (225 mg, 0.5 mmol) and 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indazole-1-carboxylic acid tert-butyl ester (172 mg, 0.5 mmol) were dissolved in dioxane (8 mL) and 2M Cs₂CO₃ aq. (1 mL, 2 mmol) was added. The mixture was de-gassed and nitrogen was introduced (three times) when PdCl₂(dppf).DCM (30 mg, 0.036 mmol) was added. The reaction was heated at 90°C for 4 hours. The volatiles were removed in *vacuo* and the residue was dissolved in dichloromethane. The organic phase was washed with water and brine. The organic layer was dried over Na₂SO₄ and the solvent removed *in vacuo*. Purification was achieved *via* flash silica gel chromatography (elution with ethyl acetate/pentane) to give 175 mg of product. LC/MS: Retention time, 4.05 min; (M+H) = 587.

Step 2: 5-{5-[2*S*-(4-Fluoro-phenyl)-piperazin-1-ylmethyl]-pyridin-3-yl}-1H-indazole: 7 mL of 95% aqueous TFA was added to a solution of 5-{5-[4-tert-butoxycarbonyl-2*S*-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-pyridin-3-yl}-indazole-1-carboxylic acid tert-butyl ester (170 mg, 0.29 mmol) in 3 mL of dichloromethane, and the resulting mixture was stirred at room temperature for 1 h. The solvent was removed to afford the crude product. Purification was achieved *via* flash silica gel chromatography using DCM:MeOH:AcOH:water as eluent. The pooled fractions were combined and the solvent was removed *in vacuo* with co-evaporation of residual AcOH using water (3 x ~2 mL) and MeOH:DCM (1:1, 10 mL) to give 125 mg of product. LCMS (long run): Retention time, 3.6 min; (M+H) = 388.

Examples 114 to 117

Example 113 was substantially repeated in Examples 114 to 117 with the exception of utilizing the respective starting materials and reagents in appropriate quantities in order to prepare the Examples 114 to 117 as tabulated in Table 15. Also summarized in Table 15 are the observed LC/MS data for Examples 114 to 117.

Table 15

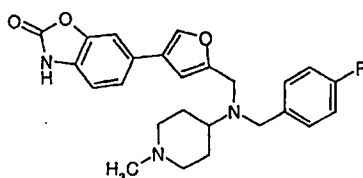
Example No.	Chemical Structure and Chemical Name	LC/MS Data	
		RT (mins.)	M + H
114	 5-{5-[2<i>S</i>-(4-Fluoro-phenyl)-piperazin-1-ylmethyl]-pyridin-3-yl}-1H-indole acetate	3.72 ^b	387
115	 5-{5-[2<i>S</i>-(4-Fluoro-phenyl)-piperazin-1-ylmethyl]-furan-3-yl}-1H-indole	5.52 ^b	376
116	 5-{5-[2<i>S</i>-(4-Fluoro-phenyl)-piperazin-1-ylmethyl]-furan-3-yl}-1H-indazole	4.86 ^b	377
117	 6-{5-[2<i>S</i>-(4-Fluoro-phenyl)-piperazin-1-ylmethyl]-furan-3-yl}-3H-benzooxazol-2-one acetate	4.27 ^b	394

^b = long LC/MS method

134

Example 118

6-(5-{[(4-Fluoro-benzyl)-(1-methyl-piperidin-4-yl)-amino]-methyl}-furan-3-yl)-3H-benzooxazol-2-one



- 5 Step 1: 6-{5-[(1-Methyl)-piperidin-4-ylamino]-methyl}-furan-3-yl}-3-trityl-3H-benzooxazol-2-one: Sodium triacetoxyborohydride (339 mg, 1.6 mmol) was added to a solution of 4-(2-oxo-3-trityl-2,3-dihydro-benzooxazol-6-yl)-furan-2-carbaldehyde (377 mg, 0.8 mmol) and 1-methyl-piperidin-4-ylamine (219 mg, 1.92 mmol) and acetic acid (192 mg, 3.2 mmol) in 10 mL of 1,2-dichloroethane. The mixture was stirred at ambient temperature for 21h, and then it was diluted with dichloromethane and washed with saturated sodium carbonate solution. The aqueous phase was extracted with dichloromethane, and the combined organic phases were washed with water and brine, dried over magnesium sulfate, filtered and concentrated to leave the crude product. Chromatography (elution with dichloromethane/methanol/acetic acid/water) gave 189 mg of product. LC/MS: Retention time, 2.38 min; (M+H) = 570.
- 10 Step 2: 6-(5-{[(4-Fluoro-benzyl)-(1-methyl-piperidin-4-yl)-amino]-methyl}-furan-3-yl)-3-trityl-3H-benzooxazol-2-one: Sodium triacetoxyborohydride (71 mg, 0.33 mmol) was added to a solution of 6-{5-[(1-methyl-piperidin-4-ylamino)-methyl]-furan-3-yl}-3-trityl-3H-benzooxazol-2-one (95 mg, 0.17 mmol) and 4-fluorobenzaldehyde (21 mg, 0.2 mmol) and acetic acid (20 mg, 0.33 mmol) in 1.5 mL of 1,2-dichloroethane. The mixture was stirred at ambient temperature for 20 h, and then it was diluted with chloroform and washed with saturated sodium carbonate solution. The aqueous phase was extracted with chloroform, and the combined organic phases were washed with water and brine, dried over magnesium sulfate, filtered and concentrated to leave the crude product. Chromatography (elution with dichloromethane/methanol) gave 64 mg of product. LC/MS: Retention time, 2.99 min; (M+H) = 678.
- 20 Step 3: 6-(5-{[(4-Fluoro-benzyl)-(1-methyl-piperidin-4-yl)-amino]-methyl}-furan-3-yl)-3H-benzooxazol-2-one: 1 mL of 95% aqueous TFA was added to a solution of 6-(5-{[(4-fluoro-benzyl)-(1-methyl-piperidin-4-yl)-amino]-methyl}-furan-3-yl)-3-trityl-3H-benzooxazol-2-one (64 mg, 0.09 mmol) in 2 mL of dichloromethane, and the resulting mixture was stirred at
- 25

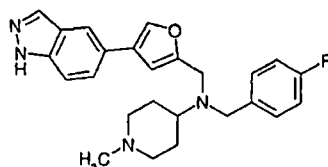
135

room temperature for 1 h. The solvent was removed to afford the crude product. Purification was achieved *via* flash silica gel chromatography (elution with DCM:MeOH:AcOH:water). The pooled fractions were combined and the solvent was removed *in vacuo* with co-evaporation of residual AcOH using toluene to give 16 mg of product. LC/MS (long run): Retention time, 3.83 min; (M+H) = 436.

¹H NMR (400 MHz, methanol-D₄) δ ppm: 1.86 (q, J = 13.14 Hz, 2 H) 2.14 (d, J = 13.8 Hz, 2 H) 2.84 (s, 3 H) 2.92 - 3.08 (m, 3 H) 3.55 (d, J = 13.14 Hz, 2 H) 3.75 (s, 2 H) 3.79 (s, 2 H) 6.62 (s, 1 H) 6.68-7.11 (m, 3H), 7.34 (d, J = 8.06 Hz, 1 H) 7.38-7.44 (m, 3 H) 7.82 (s, 1 H).

Example 119

(4-Fluoro-benzyl)-[4-(1H-indazol-5-yl)-furan-2-ylmethyl]-(1-methyl-piperidin-4-yl)-amine



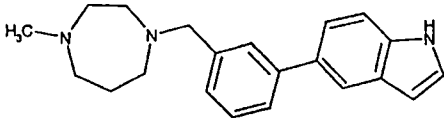
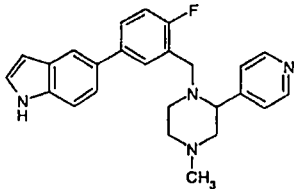
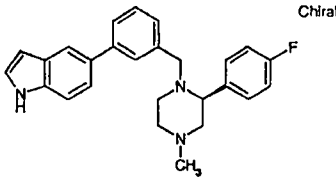
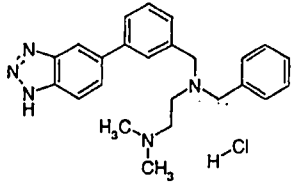
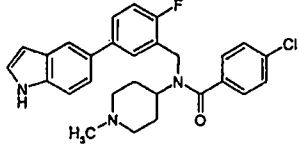
Example 118 was substantially repeated in Example 119 with the exception of utilizing the respective starting materials and reagents in appropriate quantities in order to prepare the Example 119. LC/MS (long run): Retention time, 4.07 min; (M+H) = 419.

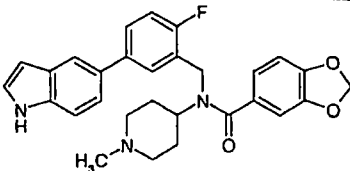
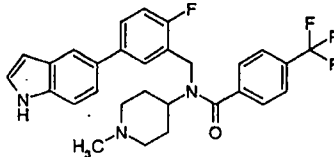
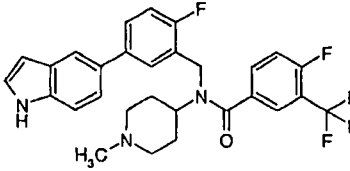
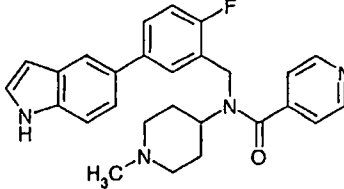
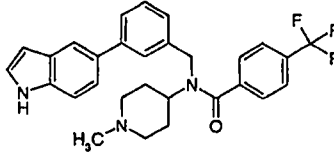
Examples 120 to 169

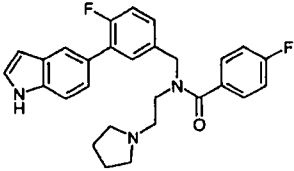
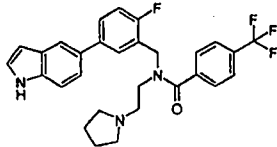
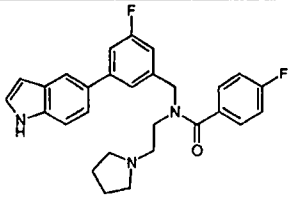
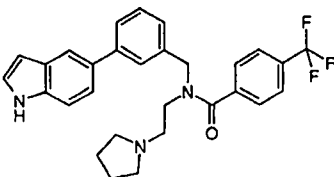
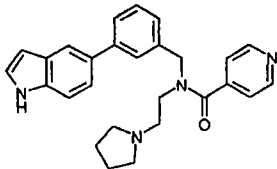
The following Examples 120 to 169 were prepared following various procedures as described herein with the exception of utilizing the respective starting materials and reagents in appropriate quantities in order to prepare the Examples 120 to 169 as tabulated in Table 16. Also summarized in Table 16 are the synthetic method used for the preparation of respective Example and the observed LC/MS data.

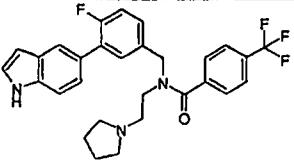
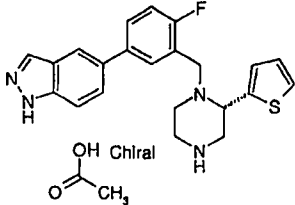
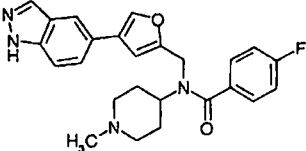
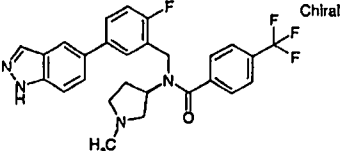
Table 16

Example No.	Synthetic Method Used	Chemical Structure and Chemical Name	LC/MS Data	
			RT (mins.)	M + H
120	Example 1	5-[3-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-1H-indole	n.a.	n.a.

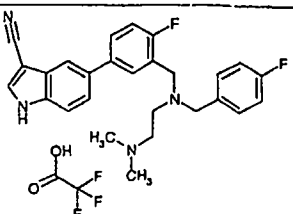
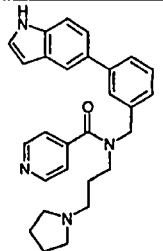
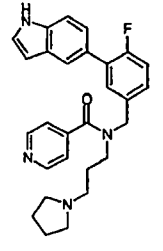
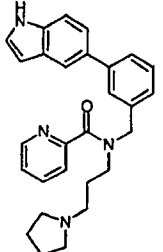
121	Example 1	 5-[3-(4-Methyl-[1,4]diazepan-1-ylmethyl)-phenyl]-1H-indole	n.a.	n.a.
122	Example 1	 5-[4-Fluoro-3-(4-methyl-2-pyridin-4-yl-piperazin-1-ylmethyl)-phenyl]-1H-indole	4.91 ^b	401
123	Example 1	 5-{3-[2S-(4-Fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-phenyl}-1H-indole	7.02 ^b	400
124	Example 17	 N-[3-(1H-Benzotriazol-5-yl)-benzyl]-N-benzyl-N',N'-dimethyl-ethane-1,2-diamine hydrochloride	n.a.	n.a.
125	Example 20	 4-Chloro-N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-benzamide	6.72 ^b	476

126	Example 20	 Benzo[1,3]dioxole-5-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide	6.15 ^b	486
127	Example 20	 N-[2-Fluoro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-4-trifluoromethyl-benzamide	7.06 ^b	510
128	Example 20	 4-Fluoro-N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-3-trifluoromethyl-benzamide	7.11 ^b	528
129	Example 20	 N-[2-Fluoro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-isonicotinamide	4.99 ^b	443
130	Example 20	 N-[3-(1H-Indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-4-trifluoromethyl-benzamide	6.92 ^b	492

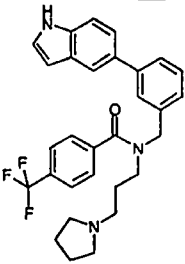
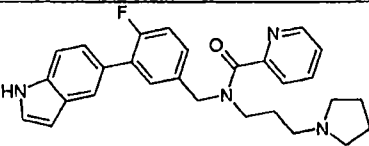
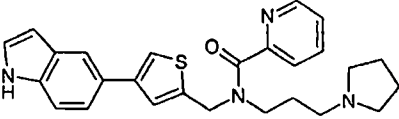
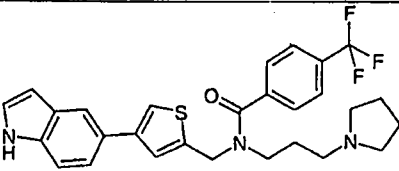
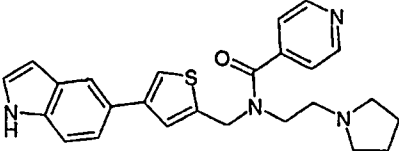
131	Example 20	 4-Fluoro-N-[4-fluoro-3-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	6.73 ^b	460
132	Example 20	 N-[2-Fluoro-5-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-4-trifluoromethyl-benzamide	6.85 ^b	510
133	Example 20	 4-Fluoro-N-[3-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	6.75 ^b	460
134	Example 20	 N-[3-(1H-Indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-4-trifluoromethyl-benzamide	7.07 ^b	492
135	Example 20	 N-[3-(1H-Indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-isonicotinamide	5.05 ^b	425

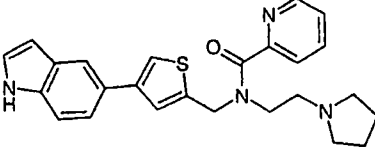
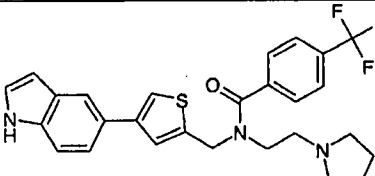
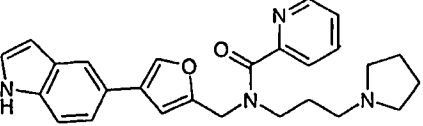
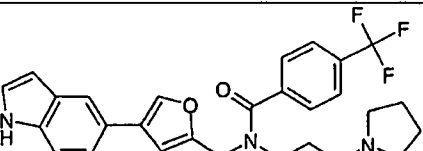
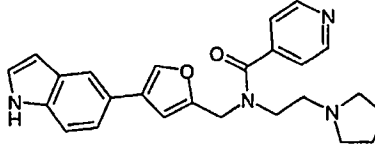
136	Example 20	 N-[4-Fluoro-3-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-4-trifluoromethyl-benzamide	7.16 ^b	510
137	Example 42	 5-[4-Fluoro-3-(2<i>R</i>-thiophen-2-yl-piperazin-1-ylmethyl)-phenyl]-1H-indazole acetate	5.16 ^b	393
138	Example 53	 4-Fluoro-N-[4-(1H-indazol-5-yl)-furan-2-ylmethyl]-N-(1-methyl-piperidin-4-yl)-benzamide	4.61 ^b	433
139	Example 53	 N-[2-Fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(1-methyl-pyrrolidin-3<i>R</i>-yl)-4-trifluoromethyl-benzamide	6.64 ^b	497

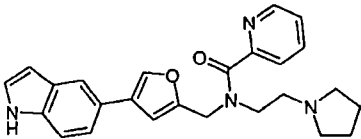
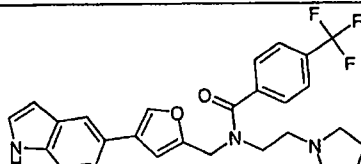
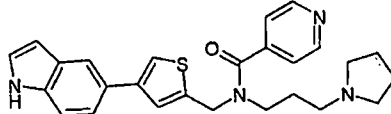
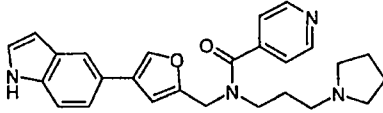
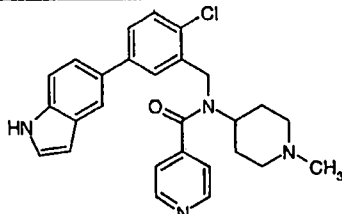
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140	Example 70	 5-(3-([(2-Dimethylamino-ethyl)-(4-fluoro-benzyl)-amino]-methyl)-4-fluoro-phenyl)-1H-indole-3-carbonitrile trifluoro-acetate	5.78 ^b	445
141	Example 77	 N-[3-(1H-Indol-5-yl)-benzyl]-N-(3-pyrrolidin-1-yl-propyl)-isonicotinamide	2.12 ^c	439
142	Example 77	 N-[4-Fluoro-3-(1H-indol-5-yl)-benzyl]-N-(3-pyrrolidin-1-yl-propyl)-isonicotinamide	2.15 ^c	457
143	Example 77	 Pyridine-2-carboxylic acid [3-(1H-indol-5-yl)-benzyl]-(3-pyrrolidin-1-yl-propyl)-amide	2.3 ^c	439

141

144	Example 77	 N-[3-(1H-Indol-5-yl)-benzyl]-N-(3-pyrrolidin-1-yl-propyl)-4-trifluoromethyl-benzamide	2.73°	506
145	Example 77	 Pyridine-2-carboxylic acid [4-fluoro-3-(1H-indol-5-yl)-benzyl]-(3-pyrrolidin-1-yl-propyl)-amide	2.35°	457
146	Example 77	 Pyridine-2-carboxylic acid [4-(1H-indol-5-yl)-thiophen-2-ylmethyl]-(3-pyrrolidin-1-yl-propyl)-amide	2.64°	445
147	Example 77	 N-[4-(1H-Indol-5-yl)-thiophen-2-ylmethyl]-N-(3-pyrrolidin-1-yl-propyl)-4-trifluoromethyl-benzamide	3.0°	512
148	Example 77	 N-[4-(1H-Indol-5-yl)-thiophen-2-ylmethyl]-N-(2-pyrrolidin-1-yl-ethyl)-isonicotinamide	2.47°	431

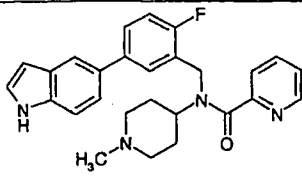
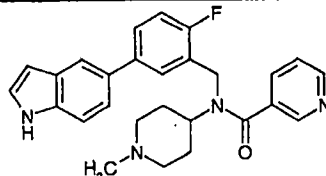
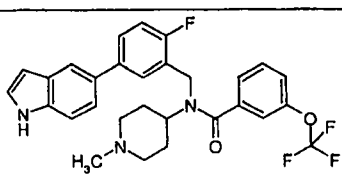
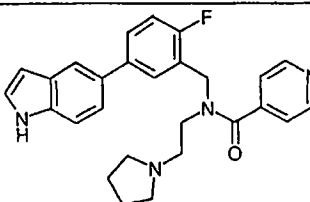
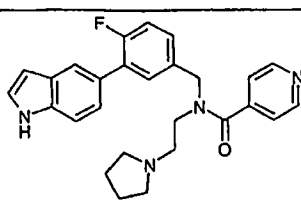
149	Example 77	 Pyridine-2-carboxylic acid [4-(1H-indol-5-yl)-thiophen-2-ylmethyl]-(2-pyrrolidin-1-yl-ethyl)-amide	2.67 ^c	431
150	Example 77	 N-[4-(1H-Indol-5-yl)-thiophen-2-ylmethyl]-N-(2-pyrrolidin-1-yl-ethyl)-4-trifluoromethyl-benzamide	3.01 ^c	498
151	Example 77	 Pyridine-2-carboxylic acid [4-(1H-indol-5-yl)-furan-2-ylmethyl]-(3-pyrrolidin-1-yl-propyl)-amide	2.55 ^c	429
152	Example 77	 N-[4-(1H-Indol-5-yl)-furan-2-ylmethyl]-N-(3-pyrrolidin-1-yl-propyl)-4-trifluoromethyl-benzamide	2.95 ^c	496
153	Example 77	 N-[4-(1H-Indol-5-yl)-furan-2-ylmethyl]-N-(2-pyrrolidin-1-yl-ethyl)-isonicotinamide	2.37 ^c	415

154	Example 77	 Pyridine-2-carboxylic acid [4-(1H-indol-5-yl)-furan-2-ylmethyl]-(2-pyrrolidin-1-yl-ethyl)-amide	2.55 ^c	415
155	Example 77	 N-[4-(1H-Indol-5-yl)-furan-2-ylmethyl]-N-(2-pyrrolidin-1-yl-ethyl)-4-trifluoromethyl-benzamide	2.94 ^c	482
156	Example 77	 N-[4-(1H-Indol-5-yl)-thiophen-2-ylmethyl]-N-(3-pyrrolidin-1-yl-propyl)-isonicotinamide	2.44 ^c	445
157	Example 77	 N-[4-(1H-Indol-5-yl)-furan-2-ylmethyl]-N-(3-pyrrolidin-1-yl-propyl)-isonicotinamide	2.39 ^c	429
158	Example 77	 N-[2-Chloro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-isonicotinamide	2.54 ^c	459

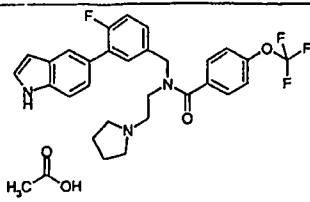
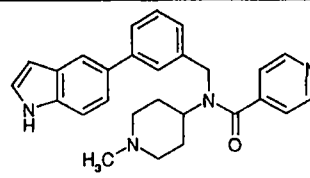
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159	Example 95	Chiral 5-[4-Fluoro-3-(4-methyl-2R-thiophen-2-yl)-piperazin-1-ylmethyl]-phenyl]-1H-indazole acetate	6.11 ^b	407
160	Example 95	Chiral 5-[4-Fluoro-3-(4-methyl-2R-thiophen-2-yl)-piperazin-1-ylmethyl]-phenyl]-1H-indazole acetate	6.04 ^b	407
161	Example 103	Chiral 5-{5-[2S-(4-Fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-furan-3-yl}-1H-indazole	4.91 ^b	391
162	Example 104	Pyrazine-2-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide	5.63 ^b	444

145

163	Example 104	 Pyridine-2-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide	5.55 ^b	443
164	Example 104	 N-[2-Fluoro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-nicotinamide	5.15 ^b	443
165	Example 104	 N-[2-Fluoro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-3-trifluoromethoxy-benzamide	7.06 ^b	526
166	Example 104	 N-[2-Fluoro-5-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-isonicotinamide	5.19 ^b	443
167	Example 104	 N-[4-Fluoro-3-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-isonicotinamide	5.22 ^b	443

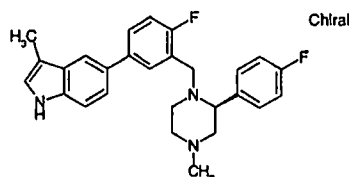
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168	Example 104	 N-[4-Fluoro-3-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-4-trifluoromethoxy-benzamide acetate	7.34 ^b	460
169	Example 104	 N-[3-(1H-Indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-isonicotinamide	4.69 ^b	425

^a = short LC/MS method; ^b = long LC/MS method; ^c = method 3; n.a. = not available.

Example 170

5-{4-Fluoro-3-[2*S*-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-phenyl}-3-methyl-1H-indole



5

- Step 1: (*S*)-2-(4-Fluoro-phenyl)-1-[2-fluoro-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-4-methyl-piperazine: A mixture of (*S*)-1-(5-bromo-2-fluoro-benzyl)-2-(4-fluoro-phenyl)-4-methyl-piperazine (0.87 g, 2.28 mmol), bis(pinacolato)diboron (0.61 g, 2.39 mmol), potassium acetate (0.89 g, 9.11 mmol) and PdCl₂(dppf).DCM (186 mg, 0.23 mmol) in degassed, anhydrous DMSO was evacuated and then repressurized with nitrogen. This process was repeated several times to minimize the amount of oxygen in the reaction mixture. The mixture was heated at 85°C for 4 h. The reaction was diluted with DCM and washed with water and brine, dried over MgSO₄, filtered and evaporated to give a dark brown syrup. Chromatography on silica gel, eluting with 2% isopropanol/DCM gave 709 mg of the product.
- Step 2: 5-{4-Fluoro-3-[2*S*-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-phenyl}-3-methyl-1H-indole. FibreCat 1001 (4 mg, 0.0006mmol) was added to a mixture of 5-bromo-3-

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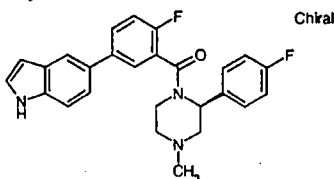
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methyldole (30 mg, 0.14mmol, (S)-2-(4-fluoro-phenyl)-1-[2-fluoro-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-4-methyl-piperazine (60 mg, 0.14 mmol), tetrabutylammonium bromide (45 mg, 0.14 mmol), and cesium carbonate (2M, 280 μ L, 0.56 mmol) in 4mL of 50% aqueous dioxane. The mixture was heated at 150°C for 5 min. with
 5 microwave irradiation. The mixture was filtered and the volatiles were removed *in vacuo*. The residue was partitioned between ethyl acetate and water, the phases were separated and the organics were dried over magnesium sulfate, filtered and concentrated. The residue was chromatographed (silica gel, elution with methanol/DCM) to give 32 mg of product. LC/MS (long run): Retention time, 6.54 min; (M+H) = 432.2

10

Example 171

[2-Fluoro-5-(1H-indol-5-yl)-phenyl]-[2S-(4-fluoro-phenyl)-4-methyl-piperazin-1-yl]-methanone



Step 1: (5-Bromo-2-fluoro-phenyl)-[(S)-2-(4-fluoro-phenyl)-piperazin-1-yl]-methanone:
 15 Diisopropylamine (0.47 g, 3.7mmol) and HATU (0.69 g, 1.8 mmol) were added to a mixture of 5-bromo-2-fluorophenylcarboxylic acid 90.4 g, 1.8 mmol) and (S)-3-(4-fluoro-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (0.34 g, 1.8 mmol) in 50mL of dimethylformamide. The mixture was stirred at ambient temperature for 15 h. The volatiles were removed *in vacuo*, and the residue was partitioned between ethyl acetate and 1M sodium
 20 bicarbonate solution. The organic phase was washed with water, dried over magnesium sulfate, filtered and concentrated to leave 0.46 g of product. This material was dissolved in 4.5 mL of dichloromethane and added to 10 mL of 95% trifluoroacetic acid/water. This mixture was stirred at room temperature for 1.5 h and then the volatiles were removed *in vacuo*. The residue was purified by chromatography on silica gel (elution with 3%
 25 ethanol/dichloromethane) to give 0.32 g of product. LC/MS: Retention time, 2.08 min; (M+H) = 381/383

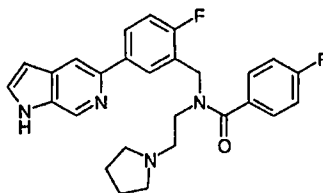
Step 2: (5-Bromo-2-fluoro-phenyl)-[(S)-2-(4-fluoro-phenyl)-4-methyl-piperazin-1-yl]-methanone: Formaldehyde (1.47 mL, 19.4 mmol of 37% aqueous solution) was added to (5-Bromo-2-fluoro-phenyl)-[(S)-2-(4-fluoro-phenyl)-piperazin-1-yl]-methanone (0.32 g, 0.65

mmol) in 10 mL of methanol. The mixture was stirred at ambient temperature for 1 h and then sodium triacetoxyborohydride (0.82 g, 3.9 mmol) was added and the resulting mixture was stirred overnight. The volatiles were removed *in vacuo*, and the residue was portioned between ethyl acetate and 1M sodium bicarbonate solution. The organic phase was washed with 1M sodium bicarbonate solution and brine, dried over magnesium sulfate, filtered and concentrated to leave 0.21 g of product. LC/MS: Retention time, 2.14 min; (M+H) = 395/397.

Step 3 [2-Fluoro-5-(1H-indol-5-yl)-phenyl]-[2S-(4-fluoro-phenyl)-4-methyl-piperazin-1-yl]-methanone: A mixture of (5-bromo-2-fluoro-phenyl)-[(S)-2-(4-fluoro-phenyl)-4-methyl-piperazin-1-yl]-methanone (0.2 g, 0.51 mmol) indole-5-boronic acid (0.086 g, 0.53 mmol), cesium carbonate in water (2M, 1.01 mL, 2.0 mmol) in 10 mL of dioxane was degassed (evacuate *in vacuo* and pressurize with nitrogen, 3 times). PdCl₂(dppf).DCM (0.037 g, 0.0513 mmol) was added and the mixture was heated at 110 - 110°C for 1.5 h. The volatiles were removed *in vacuo*, and the residue was partitioned between ethyl acetate and water. The organic phase was washed with water, dried over MgSO₄, filtered and evaporated to give a dark brown syrup. Chromatography on silica gel, eluting with 2% ethanol/DCM gave 74 mg of the product. LC/MS (long run): Retention time, 5.24 min; (M+H)=432

Example 172

4-Fluoro-N-[2-fluoro-5-(1H-pyrrolo[2,3-c]pyridin-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide

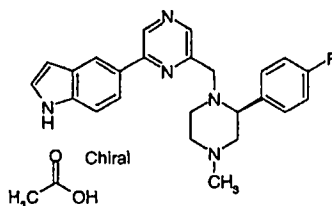


Step 1: N-{5-[4-((E)-2-Dimethylamino-vinyl)-5-nitro-pyridin-2-yl]-2-fluoro-benzyl}-4-fluoro-N-(2-pyrrolidin-1-yl-ethyl)-benzamide: 4-Fluoro-N-[2-fluoro-5-(4-methyl-5-nitro-pyridin-2-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide (prepared according to example 20, 600 mg, 1.25 mmol) in 15 mL of dimethylformamide was treated with dimethylformamide dimethyl acetal (0.23 mL, 1.68 mmol), and the resulting mixture was heated at 80°C for 5 h. The mixture was allowed to cool and the volatiles were removed. The residue was partitioned between ethyl acetate and water. The organic phase was washed with water, dried over MgSO₄, filtered and evaporated to give an oil. The above process was repeated to give 485 mg of product.

Step 2: 4-Fluoro-N-[2-fluoro-5-(1H-pyrrolo[2,3-c]pyridin-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide: *N*-{5-[4-((*E*)-2-Dimethylamino-vinyl)-5-nitro-pyridin-2-yl]-2-fluoro-benzyl}-4-fluoro-*N*-(2-pyrrolidin-1-yl-ethyl)-benzamide (485 mg, 0.9 mmol) in 30 mL of ethyl acetate was treated with 100 mg of 10% Pd/C under 3 bar of hydrogen for 18 h. The mixture was filtered through celite and the filtrate was concentrated *in vacuo*. The residue was chromatographed (alumina, elution with 2% methanol/dichloromethane) to afford 230 mg of product. LC/MS: Retention time, 1.79 min; (M+H)=461. ¹H NMR (400 MHz, DMSO-D₆) δ ppm: 1.61 (br s, 4 H) 2.37 (br ss, 2 H) 2.56 - 2.71 (br s, 2 H) 3.45 (t, J=6.26 Hz, 2 H) 4.75 (s, 2 H) 6.55 (s, 1 H) 7.17 - 7.28 (m, 3 H) 7.45 - 7.52 (m, 2 H) 7.56 (t, J=2.64 Hz, 1 H) 8.00 (ddd, J=8.30, 5.44, 2.31 Hz, 2 H) 8.07 (d, J=7.47 Hz, 1 H) 8.82 (s, 1 H) 11.40 (s, 1 H).

Example 173

5-{6-[2*S*-(4-Fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-pyrazin-2-yl}-1H-indole acetate



150

Step 1: 6-Chloro-pyrazine-2-carboxylic acid ethyl ester: Ethyl pyrazine carboxylate (4.0 g, 13.14 mmol) in 200 mL of DCM was treated at 0°C with meta-chloroperbenzoic acid (57-80%, 5.67 g). The mixture was allowed to warm to ambient temperature and stirred for 72 h, when an additional 4.28 g of meta-chloroperbenzoic acid was added. After an additional 4 d, 5 6 mL of acetone was added and stored for 2.5 d. Then 2.2 g of sodium metabisulfite in 5 mL of water was added and stirred for 2 h. Ethyl acetate was added and the mixture was washed with brine, dried over sodium sulfate, filtered and concentrated to leave a solid which was purified by chromatography (silica gel, elution with ethyl acetate/pentane), affording 3.35 g of the N-oxide. The N-oxide thus prepared (2.0 g, 11.89 mmol) in 10.53 mL of phosphorous 10 oxychloride and 18 mL of toluene was heated at 100°C for 1.5 h. The mixture was carefully treated with ice and then with saturated aqueous sodium carbonate solution. The product was extracted into ethyl acetate, and the combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography (elution with ethyl acetate/pentane) to give 1.27 g of 6-chloro-pyrazine-2-carboxylic acid ethyl ester. 15

Step 2: 6-(1*H*-Indol-5-yl)-pyrazine-2-carboxylic acid ethyl ester: 6-Chloro-pyrazine-2-carboxylic acid ethyl ester (1.35 g, 7.23 mmol) was added to indole-5-boronic acid (1.16 g, 7.23 mmol), cesium carbonate (9.43 g, 28.9 mmol) and PdCl₂(dppf).DCM (591 mg, 0.72 mmol) in 30 mL of dioxane. The mixture was degassed (evacuate *in vacuo* and pressurize 20 with nitrogen), 14.5 mL of water was added and the mixture degassed. The mixture was heated at 85°C for 2.5 h. and the mixture was allowed to cool and the layers were separated. The aqueous phase was extracted with chloroform and the combined organic layers were washed with brine, dried over sodium sulfate, filtered and evaporated. Chromatography of the residue on silica gel, eluting with ethyl acetate/pentane afforded 1.07 g of product. LC/MS: 25 Retention time, 3.21 min; (M+H)=268.1.

Step 3: 6-(1*H*-Indol-5-yl)-pyrazin-2-yl methanol: A chilled solution of 6-(1*H*-indol-5-yl)-pyrazine-2-carboxylic acid ethyl ester (1.07 g, 4.0 mmol) in 20 mL of THF was added to a solution of lithium aluminum hydride (243 mg, 6.4 mmol) in 20 mL of THF at -78°C. The mixture was stirred at -78°C for 45 min, and then it was warmed to 0°C and stirred for a 30 further 45 min, and finally it was stirred at room temperature for 1.5 h. 0.25 mL of water and 0.25 mL of 15% sodium hydroxide solution followed by an additional 0.75 mL of water was added, the mixture was filtered through celite and the filter cake was washed with DCM. The

151

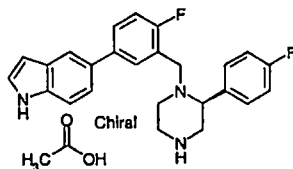
filtrate was concentrated and the residue dissolved in chloroform, washed with water and brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was recrystallized from hot ethyl acetate to give 486 mg of a solid. Chromatography (silica gel, elution with methanol/DCM) afforded 308 mg of 6-(1*H*-indol-5-yl)-pyrazin-2-yl methanol.

- 5 Step 4: 5-{6-[2*S*-(4-Fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-pyrazin-2-yl}-1*H*-indole acetate: Methanesulfonic anhydride (226 mg, 1.3 mmol) was added to 6-(1*H*-indol-5-yl)-pyrazin-2-yl methanol (146 mg, 0.65 mmol) in THF. Triethylamine (0.27 mL, 1.94 mmol) was added and the mixture allowed to stir at ambient temperature for 45 min. at which time (S)-3-(4-fluoro-phenyl)-1-methyl-piperazine (315 mg, 1.62 mmol) was added and the mixture
10 was stirred for an additional 18 h, when the volatiles were removed *in vacuo* and combined with the product from an additional reaction performed with 140 mg of the alcohol. This was diluted with DCM, and the organic phase was washed with water and brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (elution with DCM/methanol/acetic acid/water) to provide 110 mg of the title
15 compound. LC/MS (long run): Retention time, 2.34 min; (M+H)=402.

¹H NMR (400 MHz, methanol-D₄) δ ppm: 1.97 (s, 3 H) 2.51 (s, 3 H) 2.57 (t, J = 11.7 Hz, 1 H) 2.66-2.74 (m, 2 H) 3.04 (dd, J=11.65, 2.42 Hz, 1 H) 3.10 - 3.17 (m, 2 H) 3.43 (d, J=14.6 Hz, 1 H) 3.69 (dd, J=10.88, 2.97 Hz, 1 H) 3.88 (d, J=14.6 Hz, 1 H) 6.57 (m, 1H) 7.12 (t, J=8.79 Hz, 2 H) 7.31 (d, J=3.08 Hz, 1 H) 7.50 (d, J=8.57 Hz, 1 H) 7.55 (dd, J=8.46, 5.39 Hz, 2
20 H) 7.82 (dd, J=8.57, 1.76 Hz, 1 H) 8.28 (d, J=1.32 Hz, 1 H) 8.34 (s, 1 H) 8.93 (s, 1 H).

Example 174

5-{4-Fluoro-3-[2*S*-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-phenyl}-1*H*-indole acetate

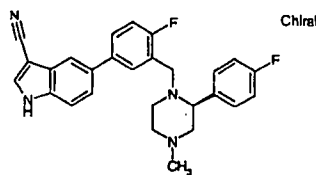


- The title compound was prepared by the methods of example 91, without the
25 methylation in step 3. LC/MS (long run): Retention time, 5.76 min; (M+H)=404.

Example 175

5-{4-Fluoro-3-[2*S*-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-phenyl}-1*H*-indole-3-carbonitrile

152



A mixture of 5-{4-fluoro-3-[2*S*-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-phenyl}-1*H*-indole-3-carbonitrile (prepared according to the methods in example 113, 79 mg, 0.18 mmol), formaldehyde (37% aq. solution, 0.13 mL), acetic acid (0.011 mL, 0.18 mmol) in 2.5 mL of methanol was treated with sodium triacetoxyborohydride (214 mg, 1.01 mmol) overnight. The volatiles were removed *in vacuo* and saturated sodium bicarbonate solution was added. The product was extracted into DCM and the combined organics were washed with water, dried over sodium sulfate, filtered and concentrated. Chromatography (reverse phase preparative HPLC, elution with acetonitrile/water provided 52 mg of product. LC/MS (long run): Retention time, 5.96 min; (M+H)=443.

Biological Examples

Example 176

Receptor Binding Assay

Cell Culture: BHK cells stably expressing the human 5HT_{2A} receptor were maintained in Dulbecco's Modified Eagle's Medium supplemented with 0.4 /ml Geneticin, 1% Sodium Pyruvate, 1% Pen-Strep and 10% Fetal Calf Serum, and treated with 5 mM sodium butyrate for 24 h to increase receptor expression before harvesting. Cells were harvested by mechanical scraping, washed with Phosphate Buffered Saline, and stored at -80°C in 10% DMSO in 1 mg/ml aliquots until used. Protein determination was made according to Lowry.

Membranes from cell lines expressing the human dopamine D_{2L}, and α -adrenergic_{1A} (α 1A) receptors were prepared as previously described (Kongsamut et al., 1996 and Brooks et al., 1999). Membranes from cell lines expressing the human 5HT_{2C} receptor were obtained from Packard Bioscience.

Receptor Binding Assays: The 5HT_{2A} and D_{2L} assays were conducted at 37°C in a Tris buffer containing salts (50 mM Tris Buffer, pH 7.7; 120 mM NaCl; 5 mM KCl; 2 mM CaCl₂; 1 mM MgCl₂). Cell membranes (previously prepared and frozen) were rapidly thawed. Membranes were diluted to an appropriate concentration (to produce 100 μ g protein/assay point for 5HT_{2A}, and 58 μ g protein/assay point for D_{2L}) in Tris buffer and homogenized. Assays were conducted on 96-well plates, using 2.5 and 1 nM [³H]N-methyl spiperone as radioligand for

W3

5HT_{2A} and D_{2L} assays, respectively. Plates were incubated at 37°C in a shaking water bath for 30 and 60 min, for 5HT_{2A} and D_{2L}, respectively. Nonspecific binding was defined using 100 µM methylsergide and eticlopride, for 5HT_{2A} and D_{2L}, respectively.

5 The 5HT_{2C} assay was conducted at 37°C in a Tris buffer (50 mM Tris, 4 mM CaCl₂ and 1% ascorbate, pH 7.4). Cell membranes (purchased from Packard Bioscience) were rapidly thawed. Membranes were diluted to an appropriate concentration (to produce 1 unit protein/assay point) in Tris buffer and homogenized. Assays were conducted on 96-well plates, using 5 nM [³H]mesulergine as radioligand. Plates were incubated at 37°C in a shaking water bath for 60 min. Nonspecific binding was defined using 100 µM mianserin.

10 The α_{1A} assay was conducted at 37°C in a Tris buffer (50 mM Tris HCL, pH 7.7 containing 0.1% Ascorbic acid). Cell membranes (previously prepared and frozen) were rapidly thawed. Membranes were diluted to an appropriate concentration (to produce 130 µg protein/assay point) in Tris buffer and homogenized. Assays were conducted on 96-well plates, using 1 nM [³H]prazosin as radioligand. Plates were incubated at 37°C in a shaking
15 water bath for 60 min. Nonspecific binding was defined using 100 µM phentolamine.

Assays were terminated by rapid filtration through Millipore MAFB or MAFC (5HT_{2C}) filter plates (presoaked in 50 mM Tris HCl, pH 7.7, with 0.1% Brij) using a Millipore Cell Harvester. The filter plates were then washed with ice-cold 50 mM Tris buffer, pH 7.7, and allowed to dry overnight. 50 µl of Microscint scintillation cocktail were added and the plates
20 were counted in a Packard Topcount scintillation counter.

IC₅₀ and K_i calculations were performed using nonlinear regression one-site competition analysis (GraphPad, Prism), with top and bottom limits held constant at 0% and 100% inhibition, respectively. The percent inhibition at each drug concentration was the average of duplicate determinations. Except where indicated, each determination was
25 performed 2 to 5 times.

5-HT_{2A} Functional Assay: BHK cells were maintained as described above, and seeded overnight in 96 well collagen coated plates (black-wall, clear bottom) at a density of 45000/75µl of medium in 0.5% serum. The following day, the calcium dye kit (Molecular Probes) was prepared in Hank's Balanced Salt Solution with the addition of 5mM probenecid
30 (pH 7.4), and cells were incubated with this solution for 1 hour at 37°C. Compounds were prepared as a 10 mM DMSO stock and diluted from there; the agonist (serotonin) were prepared fresh daily.

154

Dye loaded cells were excited at 488nm and the emission detected at 525nm using a 515nm cut-off filter and a high photomultiplier setting on a Molecular Devices FLEXstation™. Wells were read (1 column at a time) at 2 second intervals for a total period of 375 seconds. Compound or vehicle were added at 15 seconds followed by the addition of 5-HT (1μM final) at 315 seconds (5 min pretreatment), or compound was added during dye loading (60 min pretreatment).

The signal was calculated by subtracting the peak response from the mean of the baseline fluorescence. The percentage of the maximum response to 1μM 5-HT was then calculated in order to generate IC₅₀ curves.

References:

Brooks K. M., Cai J., Sandrasagra A., Roehr J. E., Errazo R., Vargas H. M.; Interaction of clozapine and other antipsychotic drugs with human alpha 1-adrenergic receptor subtypes, Proc. West Pharmacol. Soc. 1999; 42:67-69.

Kongsamut S., Roehr J. E., Cai J., Hartman H. B., Weissensee P., Kerman L. L., Tang L., Sandrasagra A.; Iloperidone binding to human and rat dopamine and 5-HT receptors, Eur. J. Pharmacol. 1996; 317(2-3):417-423.

The observed K_i values (expressed in nanomolar concentration, nM) at the receptor site 5HT_{2A} for the compounds of this invention are tabulated in Table 17.

Table 17

Example No.	5-HT _{2A} K _i (nM)
1	10.8
2	2.4
3	0.9
4	33.5
5	217.6
6	2.7
7	210.0
8	35.4
9	227.0
10	13.8
11	16.2
13	3.3

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14	1,4
15	13.8
16	4.9
17	7.2
18	74.8
19	76.5
20	0.32
21	0.26
23	0.37
24	0.56
25	0.6
26	0.68
27	0.7
28	0.7
29	0.7
30	0.77
31	0.92
32	1.1
33	1.19
34	1.25
35	2.8
36	4.1
37	4.1
38	14.4
39	1.1
40	0.58
42	0.61
43	0.6
45	0.99
47	1.24
48	0.6

156

49	0.4
50	2.5
51	9.2
52	3.1
53	2.13
54	0.9
55	0.31
56	6.51
57	0.71
58	1.23
59	0.89
60	1.13
61	0.7
62	0.75
63	0.58
64	0.6
65	0.9
66	0.67
67	2.16
68	3.14
69	1.35
70	0.72
71	0.49
72	2.37
74	1.05
75	2.14
76	4.74
77	0.49
78	0.76
79	0.61
80	14.9

81	2.0
82	0.51
83	0.82
84	0.37
85	0.42
86	1.68
87	14.2
88	1.16
89	1.0
90	0.42
91	0.6
93	0.6
95	1.9
96	0.89
97	0.77
98	1.2
99	0.29
100	0.6
101	0.39
102	0.88
103	1.01
104	0.31
105	3.8
106	9.0
107	85.0
108	16.0
110	85.0
111	85.0
112	6.0
113	0.4
114	0.48

115	2.88
116	1.79
117	4.79
118	1.1
119	0.78
120	65.0
121	82.0
140	22.6
171	85.0
174	0.9
175	3.2

Example 177

Head Twitch Assay

This Example 177 illustrates the study of efficacy of the compounds of this invention at the 5HT_{2A} receptor site in animal models. In this Example 177, the inhibition of dimethyltryptamine (DMT) induced head twitch in the mouse was measured using the compounds of this invention as set forth below.

5-MeODMT (5-Methoxy-N,N-dimethyltryptamine) Inhibition: Groups of male mice are administered test compounds at selected doses. At an appropriate interval thereafter, 5-MeODMT (dissolved in 0.5% ascorbic acid) is administered at a dose of 30 mg/kg i.p. Immediately after administration of 5-MeODMT, and continuing for the following 6 min, the number of head twitches for each animal is counted. For inhibitory effects, animals exhibiting no head twitches during this 6 min period are considered blocked. The ED₅₀ is calculated as the dose necessary to block head twitch in 50% of the test animals. All experiments are performed with at least 10 animals per condition.

The observed ED₅₀ values (expressed as mg/kg) for the compounds of this invention are tabulated in Table 18.

Table 18

Example No.	ED ₅₀ mg/kg, sc
3	< 1 (100% effect @ 1mg/kg)
20	0.27

159

21	<3 (60% effect @ 3mg/kg)
23	0.16
26	0.82
27	0.59
34	1.09
42	1.73
44	0.54
47	~3 (50% effect @ 3 mg/kg)
91	0.41
92	0.53
94	~ 3 (50% effect @ 3 mg/kg)
95	0.5
98	0.49
104	6.36
133	0.92
159	0.04
161	0.16

Example 178

Sleep Maintenance Insomnia Studies

5 This Example 178 illustrates the study of efficacy of the compounds of this invention in improving the sleep quality in animal models.

To record cortical electro-encephalogram (EEG), male Sprague-Dawley rats are fitted with four miniature screw electrodes placed through the skull (1.5 mm either side of the central suture, 1.5, 3.0, 4.5 and 6.0 mm anterior to lambda) and allowed to recover for 7 days. Freely moving animals are then placed (in their own home cage) in a soundproof, temperature and humidity-controlled recording room. For each rat, recordings are made from the two leads providing the largest theta rhythm amplitude. Theta rhythm (5 - 9Hz) and slower electrical activities (0 - 4Hz) are recorded in waking animals (W). Only slow waves (0 - 4Hz) and sleep spindles (12-14Hz) are observed during slow wave sleep (SWS). Theta rhythm alone is recorded during paradoxical sleep (PS). For each rat and each vigilance level (W, SWS, PS), a

10

160

minimum of 90 averaged power spectra, corresponding to visually identified episodes, are summed in order to obtain an averaged reference spectrum. The effects of the compounds of this invention on each of these rhythms are measured.

The compounds of this invention are administered either 5 hours after lights on or 18 hours after lights-on. Six animals are included in each treatment group. All of the compounds of this invention are administered intraperitoneally. A vehicle control and positive reference compound are included in each study. A satellite group of animals are dosed to examine pharmacokinetics; blood, from which, plasma fractions are obtained, and brain samples are collected from these animals.

10

Example 179

Obstructive Sleep Apnea Studies

Intraperitoneal application of L-tryptophan (10mg/kg) and pargyline (50mg/kg) to anaesthetized newborn rats depresses the amplitude of the inspiratory discharges of the genioglossal muscle and induces obstructive apneas (OA). The following procedure describes how to determine the efficacy of the compounds of this invention when compared with the efficacy of theophylline.

15

Experiments are carried out on newborn Sprague Dawley rats. The animals are anaesthetized by intraperitoneal injection of low doses of sodium pentobarbitone (7-10mg/kg), kept lying (dorsal cubitus) on a warming blanket and are spontaneously ventilating.

20

The electromyogram (EMG) activity of the genioglossal muscles and the diaphragm are recorded with fine insulated wires (bipolar recordings) inserted within the muscles, filtered (100-3,000 Hz), amplified (x 5-10,000) and integrated (time constant 50 ms). The rib cage movements are recorded via a captor gently touching the lower ribs and/or the abdominal wall. The air flow changes resulting from the respiratory chest movements are recorded via a facial mask and a highly sensitive pressure recorder.

25

Effects of a compound of this invention on depression of genioglossal EMG induced by L-tryptophan and pargyline can be measured as follows: Ten to fifteen minutes after induction of anesthesia, the animals receive first an intraperitoneal injection of a compound of this invention, and a control recording is taken to define the mean amplitude of the integrated EMGs. Then, the animal receives an intraperitoneal injection of L-tryptophan plus pargyline ("L-Trp+Parg") 10mg/kg and 50mg/kg, respectively, and the changes in EMG amplitudes are checked every 10 minutes and are expressed as percent (%) of control values.

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161

In general, the pre-treatment with a compound of this invention at dosage levels of about 0.1 mg/kg to about 1.0 mg/kg can prevent the depression of genioglossal (GG) discharge induced by injection of L-Trp+Parg.

Effects of the compound pretreatment on the occurrence of obstructive apnea (OAs) induced by l-tryptophan and pargyline injection can be measured as follows: The respiratory movements and resulting air flow changes are measured in 30 newborn rats which receive first a pre-treatment with a compound of this invention at either 0.1, 1 or 3mg/kg and 10 min later L-Trp+Parg injection. Generally, L-Trp+Parg injection induces OAs in newborn rats. The rats which receives the compound of this invention are expected to display short lasting OAs to no OAs depending on the dosage administered. For instance, the rats receiving 0.1 mg/kg to 1 mg/kg of the compound of this invention may exhibit short lasting OAs. Whereas the rats receiving higher dosages of about 3 mg/kg are expected show no OAs.

Effects of theophylline pre-treatment on the occurrence of obstructive apneas induced by l-tryptophan and pargyline injection are measured as follows: Five newborn rats receive theophylline at 10mg/kg and 5 other animals receive theophylline at 30mg/kg. In both cases, L-Trp+Prg injection depresses the amplitude of GG inspiratory discharges and this effect is not prevented by either dose of theophylline. In a second set of experiments, induction of OAs after L-Trp+Prg injection also is not prevented by theophylline at 10 or 30 mg/kg.

Although the invention has been illustrated by certain of the preceding examples, it is not to be construed as being limited thereby; but rather, the invention encompasses the generic area as hereinbefore disclosed. Various modifications and embodiments can be made without departing from the spirit and scope thereof.

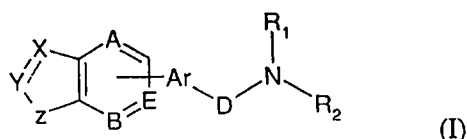
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162

CLAIMS

What is claimed is:

1. A compound, including enantiomers, stereoisomers, and tautomers of said compound
 5 and pharmaceutically acceptable salts, solvates or derivatives thereof, with said
 compound having the general structure shown in formula I:



wherein:

$X \equiv Y$ denotes either a single or double bond between X and Y;

10 X is CR, CHR, CO, N, O or S;

Y is CR, CHR, CO, S(O)₂, N or NR;

Z is NR, CO-NR, S(O)₂-NR;

A, B and E are the same or different and independently from each other are CR or N;

D is either CH₂ or CO;

15 Ar is substituted or unsubstituted aryl or heteroaryl;

each R is independently chosen from hydrogen, halogen, CN, C(O)NR₃R₄, C₁₋₄alkyl,
 C₁₋₄alkoxy, C₁₋₄alkenyl, aryl, heteroaryl, arylC₁₋₄alkyl, heteroarylC₁₋₄alkyl,
 fluoroalkyl or fluoroalkoxy of the formula C_nH_xF_y or OC_nH_xF_y wherein n is an
 integer from 1 to 4, x is an integer from 0 to 8, y is an integer from 1 to 9 and
 20 sum of x and y is 2n+1; wherein

R₃ and R₄ are hydrogen or C₁₋₄alkyl; or

R₃ and R₄ taken together with the nitrogen atom to which they are attached
 form an unsubstituted or at least monosubstituted heterocycle;

R₁ and R₂ are the same or different and selected independently of each other from
 25 substituted or unsubstituted aryl, heteroaryl, aryloyl, heteroaryloyl, arylsulfonyl,
 heteroarylsulfonyl, arylC₁₋₄alkyl, heteroarylC₁₋₄alkyl, aminoC₁₋₄alkyl,
 C₁₋₄alkylaminoC₁₋₄alkyl, C₃₋₈cycloalkylaminoC₁₋₄alkyl,
 diC₃₋₈cycloalkylaminoC₁₋₄alkyl, C₃₋₈cycloalkylC₁₋₄alkylaminoC₁₋₄alkyl,
 diC₁₋₄alkylaminoalkyl, heterocycle, heterocycleC₁₋₄alkyl,
 30 C₁₋₄alkylheterocycleC₁₋₄alkyl; or

R₁ and R₂ taken together with the nitrogen atom to which they are attached form an
 unsubstituted or at least monosubstituted heterocycle; and wherein
 the substituents are selected from the group consisting of substituted or unsubstituted
 aryl, heteroaryl, arylC₁₋₄alkyl, heteroarylC₁₋₄alkyl, heterocycle, C₃₋₈cycloalkyl, C₁₋₄
 5 alkyl, C₁₋₄alkoxy, C₁₋₄alkenyl, fluoroalkyl or fluoroalkoxy of the formula C_nH_xF_y or
 OC_nH_xF_y wherein n is an integer from 1 to 4, x is an integer from 0 to 8, y is an integer
 from 1 to 9 and sum of x and y is 2n+1, -NO₂, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂,
 -CN, -C(O)R₅, -NHC(O)(C₁₋₄alkyl), -SO₂Cl, -SO₂(C₁₋₄alkyl), halogen and hydroxy;
 wherein
 10 R₅ is hydroxy, C₁₋₃alkoxy, -O-phenyl, -NH₂, -NH(C₁₋₃alkyl), -N(C₁₋₃alkyl)₂ or phenyl;
 heteroaryl is a 5 to 10-membered, aromatic, mono- or bicyclic heterocycle containing
 one or more heteroatoms selected from the group consisting of N, O and S;
 aryl is a 6 to 10-membered, aromatic mono- or bicyclic ring; and
 heterocycle is a 3 to 10-membered, non-aromatic, mono- or bicyclic heterocycle
 15 containing one or more heteroatoms selected from the group consisting of N, O
 and S.

2. The compound as set forth in claim 1, wherein:
 D is CH₂;
 20 Ar is substituted or unsubstituted phenyl, pyridinyl, pyrazinyl, furanyl or thiophenyl;
 wherein the substituents are selected from the group consisting of fluorine,
 chlorine, C₁₋₄alkyl, C₁₋₄alkoxy and -CF₃;
 each R is independently chosen from hydrogen, CN or C₁₋₄alkyl;
 R₁ and R₂ are the same or different and selected independently of each other from
 25 substituted or unsubstituted benzoyl, thiophenylcarbonyl, pyridinylcarbonyl,
 pyrazinylcarbonyl, pyrimidinylcarbonyl, pyridazinylcarbonyl, dihydro-
 benzo[1,4]dioxinylcarbonyl, benzo[1,3]dioxolylcarbonyl, phenylC₀₋₄alkyl,
 thiophenylC₁₋₄alkyl, aza-bicyclo[2.2.2]octylC₀₋₄alkyl, aza-
 bicyclo[3.2.1]octylC₀₋₄alkyl, piperidinylC₀₋₄alkyl, pyrrolidinylC₀₋₄alkyl,
 30 C₁₋₄alkylaminoC₁₋₄alkyl and diC₁₋₄alkylaminoC₁₋₄alkyl; wherein the substituted
 moieties may be substituted with one or more substituents selected from the

164

group consisting of fluorine, chlorine, C₁₋₄alkyl, C₃₋₈cycloalkyl, C₁₋₄alkoxy, OCF₃ and CF₃; or

R₁ and R₂ taken together with the nitrogen atom to which they are attached form a unsubstituted or at least monosubstituted heterocycle selected from the group consisting of piperazine and diazepane; wherein the substituents are selected from the group consisting of phenyl, fluorophenyl, trifluoromethylphenyl, pyridinyl, thiophenyl, furanyl and C₁₋₄alkyl.

3. The compound as set forth in claim 2, wherein:

10 $X \equiv Y$ denotes a double bond between X and Y;

X is CR;

Y is CR;

Z is NR;

A, B and E are the same or different and independently from each other are CH or N;

15 Ar is phenyl, fluorophenyl, chlorophenyl, pyridinyl, pyrazinyl, furanyl or thiophenyl; each R is independently chosen from hydrogen, CN, methyl, ethyl, methoxy, fluorine, CF₃ or OCF₃;

R₁ and R₂ are the same or different and selected independently of each other from benzyl, fluorobenzyl, fluorobenzoyl, chlorobenzoyl, isopropoxybenzoyl, trifluoromethylbenzoyl, fluoro-trifluoromethylbenzoyl, trifluoromethoxybenzoyl, thiophenylcarbonyl, pyridinylcarbonyl, pyrazinylcarbonyl, pyrimidinylcarbonyl, pyridazinylcarbonyl, dihydrobenzo[1,4]dioxinylcarbonyl, benzo[1,3]dioxolylcarbonyl, aza-bicyclo[2.2.2]octyl, aza-bicyclo[2.2.2]octylmethyl, N-methyl-piperidinyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolidinylpropyl and dimethylaminoethyl;

or

R₁ and R₂ taken together with the nitrogen atom to which they are attached form a unsubstituted or at least monosubstituted heterocycle selected from the group consisting of piperazine and diazepane; wherein the substituents are selected from the group consisting of phenyl, fluorophenyl, trifluoromethylphenyl, pyridinyl, thiophenyl, furanyl and methyl.

165

4. The compound as set forth in claim 3 selected from the group consisting of:
N-benzyl-N-[3-(1H-indol-5-yl)-benzyl]-N',N'-dimethyl-ethane-1,2-diamine;
4-fluoro-N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;
5 N-(2-dimethylamino-ethyl)-4-fluoro-N-[2-fluoro-5-(2-methyl-1H-indol-5-yl)-benzyl]-
benzamide;
N-(2-dimethylamino-ethyl)-4-fluoro-N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-
benzamide;
4-fluoro-N-[3-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-benzamide;
10 thiophene-2-carboxylic acid [3-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-
amide;
thiophene-2-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-
4-yl)-amide;
thiophene-2-carboxylic acid (2-dimethylamino-ethyl)-[2-fluoro-5-(1H-indol-5-yl)-
15 benzyl]-amide;
4-fluoro-N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-
benzamide;
N-(1-aza-bicyclo[2.2.2]oct-4-ylmethyl)-4-fluoro-N-[2-fluoro-5-(1H-indol-5-yl)-
benzyl]-benzamide trifluoro-acetate;
20 4-fluoro-N-[5-(1H-indol-5-yl)-pyridin-3-ylmethyl]-N-(2-pyrrolidin-1-yl-ethyl)-
benzamide;
4-fluoro-N-[4-fluoro-3-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-
benzamide;
4-fluoro-N-[4-(1H-indol-5-yl)-thiophen-2-ylmethyl]-N-(2-pyrrolidin-1-yl-ethyl)-
25 benzamide acetate;
(4-fluoro-benzyl)-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-
amine;
N-(4-fluoro-benzyl)-N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N',N'-dimethyl-ethane-1,2-
diamine;
30 (1-aza-bicyclo[2.2.2]oct-4-ylmethyl)-(4-fluoro-benzyl)-[2-fluoro-5-(1H-indol-5-yl)-
benzyl]-amine acetate;

- N-(2-dimethylamino-ethyl)-4-fluoro-N-[5-(1H-indol-5-yl)-pyridin-3-ylmethyl]-benzamide trifluoroacetate;
4-fluoro-N-[5-(1H-indol-5-yl)-thiophen-2-ylmethyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;
5 4-fluoro-N-[4-(1H-indol-5-yl)-furan-2-ylmethyl]-N-(1-methyl-piperidin-4-yl)-benzamide;
N-(1-aza-bicyclo[2.2.2]oct-3*R*-yl)-4-fluoro-N-[2-fluoro-5-(1H-indol-6-yl)-benzyl]-benzamide;
pyrimidine-4-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-10 4-yl)-amide;
pyrimidine-2-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide;
pyridazine-3-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide;
15 pyridazine-4-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide;
2,3-dihydro-benzo[1,4]dioxine-6-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide;
N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-4-isopropoxy-N-(1-methyl-piperidin-4-yl)-20 benzamide;
N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-3-isopropoxy-N-(1-methyl-piperidin-4-yl)-benzamide;
N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-4-trifluoromethoxy-benzamide;
25 4-chloro-N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-benzamide;
benzo[1,3]dioxole-5-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide;
N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-4-trifluoromethyl-30 benzamide;
4-fluoro-N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-3-trifluoromethyl-benzamide;

167

- N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-isonicotinamide;
N-[3-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-4-trifluoromethyl-
benzamide;
4-fluoro-N-[4-fluoro-3-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;
5 N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-4-trifluoromethyl-
benzamide;
4-fluoro-N-[3-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;
N-[3-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-4-trifluoromethyl-
benzamide;
10 N-[3-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-isonicotinamide;
N-[4-fluoro-3-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-4-trifluoromethyl-
benzamide;
N-[3-(1H-indol-5-yl)-benzyl]-N-(3-pyrrolidin-1-yl-propyl)-isonicotinamide;
N-[4-fluoro-3-(1H-indol-5-yl)-benzyl]-N-(3-pyrrolidin-1-yl-propyl)-isonicotinamide;
15 pyridine-2-carboxylic acid [3-(1H-indol-5-yl)-benzyl]-(3-pyrrolidin-1-yl-propyl)-
amide;
N-[3-(1H-indol-5-yl)-benzyl]-N-(3-pyrrolidin-1-yl-propyl)-4-trifluoromethyl-
benzamide;
pyridine-2-carboxylic acid [4-fluoro-3-(1H-indol-5-yl)-benzyl]-(3-pyrrolidin-1-yl-
20 propyl)-amide;
pyridine-2-carboxylic acid [4-(1H-indol-5-yl)-thiophen-2-ylmethyl]-(3-pyrrolidin-1-yl-
propyl)-amide;
N-[4-(1H-indol-5-yl)-thiophen-2-ylmethyl]-N-(3-pyrrolidin-1-yl-propyl)-4-
trifluoromethyl-benzamide;
25 N-[4-(1H-indol-5-yl)-thiophen-2-ylmethyl]-N-(2-pyrrolidin-1-yl-ethyl)-
isonicotinamide;
pyridine-2-carboxylic acid [4-(1H-indol-5-yl)-thiophen-2-ylmethyl]-(2-pyrrolidin-1-yl-
ethyl)-amide;
N-[4-(1H-indol-5-yl)-thiophen-2-ylmethyl]-N-(2-pyrrolidin-1-yl-ethyl)-4-
30 trifluoromethyl-benzamide;
pyridine-2-carboxylic acid [4-(1H-indol-5-yl)-furan-2-ylmethyl]-(3-pyrrolidin-1-yl-
propyl)-amide;

168

- N-[4-(1H-indol-5-yl)-furan-2-ylmethyl]-N-(3-pyrrolidin-1-yl-propyl)-4-trifluoromethyl-benzamide;
- N-[4-(1H-indol-5-yl)-furan-2-ylmethyl]-N-(2-pyrrolidin-1-yl-ethyl)-isonicotinamide;
- pyridine-2-carboxylic acid [4-(1H-indol-5-yl)-furan-2-ylmethyl]-(2-pyrrolidin-1-yl-ethyl)-amide;
- N-[4-(1H-indol-5-yl)-furan-2-ylmethyl]-N-(2-pyrrolidin-1-yl-ethyl)-4-trifluoromethyl-benzamide;
- N-[4-(1H-indol-5-yl)-thiophen-2-ylmethyl]-N-(3-pyrrolidin-1-yl-propyl)-isonicotinamide;
- N-[4-(1H-indol-5-yl)-furan-2-ylmethyl]-N-(3-pyrrolidin-1-yl-propyl)-isonicotinamide;
- N-[2-chloro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-isonicotinamide;
- pyridine-2-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide;
- N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-nicotinamide;
- N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-3-trifluoromethoxy-benzamide;
- N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-isonicotinamide;
- N-[4-fluoro-3-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-isonicotinamide;
- N-[4-fluoro-3-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-4-trifluoromethoxy-benzamide acetate;
- N-[3-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-isonicotinamide;
- pyrazine-2-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide;
- 5-[4-fluoro-3-(4-methyl-2-pyridin-3-yl-piperazin-1-ylmethyl)-phenyl]-1H-indole acetate;
- 5-{4-fluoro-3-[4-methyl-2-(4-trifluoromethyl-phenyl)-piperazin-1-ylmethyl]-phenyl}-1H-indole;
- 5-[4-fluoro-3-(4-methyl-2-pyridin-2-yl-piperazin-1-ylmethyl)-phenyl]-1H-indole acetate;
- 5-{5-[2S-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-pyridin-3-yl}-1H-indole acetate;

- 5-{4-fluoro-3-[2*S*-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-phenyl}-1H-indole;
5-{4-fluoro-3-(2-furan-2-yl-4-methyl-piperazin-1-ylmethyl)-phenyl}-1H-indole;
5-{5-[2*S*-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-furan-3-yl}-1H-indole
5 trifluoro-acetate;
5-{5-[2*S*-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-pyridin-3-yl}-1H-indole acetate;
5-{5-[2*S*-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-furan-3-yl}-1H-indole;
5-[3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-indole;
5-[4-fluoro-3-(4-methyl-2-pyridin-4-yl-piperazin-1-ylmethyl)-phenyl]-1H-indole;
10 5-{3-[2*S*-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-phenyl}-1H-indole;
5-{6-[2*S*-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-pyrazin-2-yl}-1H-indole
acetate;
5-{4-fluoro-3-[2*S*-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-phenyl}-1H-indole acetate;
5-{4-fluoro-3-[2*S*-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-phenyl}-1H-
15 indole-3-carbonitrile;
5-[3-(4-methyl-[1,4]diazepan-1-ylmethyl)-phenyl]-1H-indole;
5-{4-fluoro-3-[2*S*-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-phenyl}-3-
methyl-1H-indole;
N-[5-(3-cyano-1H-indol-5-yl)-2-fluoro-benzyl]-N-(2-dimethylamino-ethyl)-4-fluoro-
20 benzamide;
5-{4-fluoro-3-[2*S*-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-phenyl}-1H-indole-3-
carbonitrile;
5-(3-[(2-dimethylamino-ethyl)-(4-fluoro-benzyl)-amino]-methyl)-4-fluoro-phenyl)-
1H-indole-3-carbonitrile trifluoro-acetate;
25 4-fluoro-N-[2-fluoro-5-(1H-pyrrolo[3,2-*b*]pyridin-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-
ethyl)-benzamide;
5-{4-fluoro-3-[2-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-phenyl}-1H-
pyrrolo[3,2-*b*]pyridine; and
4-fluoro-N-[2-fluoro-5-(1H-pyrrolo[2,3-*c*]pyridin-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-
30 ethyl)-benzamide;
or a pharmaceutically acceptable salt thereof or an optical or stereoisomer thereof.

770

5. The compound as set forth in claim 2, wherein:

$X=Y$ denotes a double bond between X and Y;

X is CR;

Y is N;

5 Z is NR;

both A, B and E are CH;

Ar is phenyl, fluorophenyl, chlorophenyl, pyridinyl, pyrazinyl, furanyl or thiophenyl;

each R is independently chosen from hydrogen, methyl, ethyl, methoxy, fluorine, CF₃ or OCF₃;

10 R₁ and R₂ are the same or different and selected independently of each other from benzyl, fluorobenzyl, fluorobenzoyl, chlorobenzoyl, isopropoxybenzoyl, trifluoromethylbenzoyl, fluoro-trifluoromethylbenzoyl, trifluoromethoxybenzoyl, thiophenylcarbonyl, pyridinylcarbonyl, pyrazinylcarbonyl, pyrimidinylcarbonyl, pyridazinylcarbonyl, dihydro-
15 benzo[1,4]dioxinylcarbonyl, benzo[1,3]dioxolylcarbonyl, N-methyl-aza-bicyclo[2.2.2]octyl, aza-bicyclo[2.2.2]octyl, aza-bicyclo[2.2.2]octylmethyl, N-methyl-piperidinyl, piperidinyl, N-methyl-pyrrolidinyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolidinylpropyl, methylaminoethyl, and dimethylaminoethyl;

20 or

R₁ and R₂ taken together with the nitrogen atom to which they are attached form a unsubstituted or at least monosubstituted heterocycle selected from the group consisting of piperazine and diazepane; wherein the substituents are selected from the group consisting of phenyl, fluorophenyl, trifluoromethylphenyl,
25 pyridinyl, thiophenyl, furanyl and methyl.

6. The compound as set forth in claim 5 selected from the group consisting of:

N-benzyl-N-[3-(1H-indazol-5-yl)-benzyl]-N',N'-dimethyl-ethane-1,2-diamine hydrochloride;

30 N-(4-fluoro-benzyl)-N-[5-(1H-indazol-5-yl)-pyridin-3-ylmethyl]-N',N'-dimethyl-ethane-1,2-diamine acetate;

(4-fluoro-benzyl)-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-pyrrolidin-2S-ylmethyl-amine;

- (4-fluoro-benzyl)-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-piperidin-4-yl-amine;
N-(4-fluoro-benzyl)-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N'-methyl-ethane-1,2-diamine;
(4-fluoro-benzyl)-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amine;
5 (4-fluoro-benzyl)-[4-(1H-indazol-5-yl)-furan-2-ylmethyl]-(1-methyl-piperidin-4-yl)-amine;
4-fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;
10 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-benzamide;
4-fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-benzamide;
4-fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(1-methyl-piperidin-3-yl)-benzamide;
15 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(1-methyl-piperidin-3*S*-yl)-benzamide trifluoro-acetate;
4-fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(1-methyl-pyrrolidin-3*R*-yl)-benzamide trifluoro-acetate;
20 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(1-methyl-pyrrolidin-3*S*-yl)-benzamide trifluoro-acetate;
4-fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(3-pyrrolidin-1-yl-propyl)-benzamide;
4-fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-benzamide;
25 N-(1-aza-bicyclo[2.2.2]oct-3*R*-yl)-4-fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-benzamide;
chiral N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(1-methyl-pyrrolidin-3*R*-yl)-4-trifluoromethyl-benzamide;
30 4-fluoro-N-[4-(1H-indazol-5-yl)-furan-2-ylmethyl]-N-(1-methyl-piperidin-4-yl)-benzamide;
5-{4-fluoro-3-[2-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-phenyl}-1H-indazole;

- 5-[4-fluoro-3-(2*S*-thiophen-2-yl-piperazin-1-ylmethyl)-phenyl]-1*H*-indazole acetate;
 5-[4-fluoro-3-(2-thiophen-2-yl-piperazin-1-ylmethyl)-phenyl]-1*H*-indazole;
 chiral 5-[4-fluoro-3-(2-thiophen-2-yl-piperazin-1-ylmethyl)-phenyl]-1*H*-indazole
 acetate;
 5 5-{4-fluoro-3-[2*S*-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-phenyl}-1*H*-
 indazole;
 5-{5-[2*S*-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-pyridin-3-yl}-1*H*-indazole;
 5-{5-[2*S*-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-pyridin-3-yl}-1*H*-indazole;
 5-{5-[2*S*-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-furan-3-yl}-1*H*-indazole;
 10 5-[4-fluoro-3-(4-methyl-2*R*-thiophen-2-yl-piperazin-1-ylmethyl)-phenyl]-1*H*-indazole
 acetate;
 5-[4-fluoro-3-(4-methyl-2*S*-thiophen-2-yl-piperazin-1-ylmethyl)-phenyl]-1*H*-indazole
 acetate; and
 5-{5-[2*S*-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-furan-3-yl}-1*H*-indazole;
 15 or a pharmaceutically acceptable salt thereof or an optical or stereoisomer thereof.

7. The compound as set forth in claim 2, wherein:

$X \equiv Y$ denotes a double bond between X and Y;

X is N;

20 Y is CR;

Z is NR;

both A, B and E are CH;

Ar is phenyl, fluorophenyl, chlorophenyl, pyridinyl, pyrazinyl, furanyl or thiophenyl;

each R is independently chosen from hydrogen, methyl, ethyl, methoxy, CF₃ or OCF₃;

25 R₁ and R₂ are the same or different and selected independently of each other from

benzyl, fluorobenzyl, fluorobenzoyl, chlorobenzoyl, isopropoxybenzoyl,

trifluoromethylbenzoyl, fluoro-trifluoromethylbenzoyl,

trifluoromethoxybenzoyl, thiophenylcarbonyl, pyridinylcarbonyl,

pyrazinylcarbonyl, pyrimidinylcarbonyl, pyridazinylcarbonyl, dihydro-

30 benzo[1,4]dioxinylcarbonyl, benzo[1,3]dioxolylcarbonyl, N-methyl-aza-

bicyclo[2.2.2]octyl, aza-bicyclo[2.2.2]octyl, aza-bicyclo[2.2.2]octylmethyl, N-

methyl-piperidinyl, piperidinyl, N-methyl-pyrrolidinyl, pyrrolidinylmethyl,

pyrrolidinylethyl, pyrrolidinylpropyl, methylaminoethyl, dimethylaminoethyl and dimethylaminopropyl;

or

- 5 R_1 and R_2 taken together with the nitrogen atom to which they are attached form a unsubstituted or at least monosubstituted heterocycle selected from the group consisting of piperazine and diazepane; wherein the substituents are selected from the group consisting of phenyl, fluorophenyl, trifluoromethylphenyl, pyridinyl, thiophenyl, furanyl and methyl.
- 10 8. The compound as set forth in claim 7 selected from the group consisting of:
N-[3-(1H-benzoimidazol-5-yl)-benzyl]-N-benzyl-N',N'-dimethyl-ethane-1,2-diamine hydrochloride; and
N-[3-(1H-benzoimidazol-5-yl)-benzyl]-N-benzyl-N',N'-dimethyl-propane-1,3-diamine hydrochloride;
15 or a pharmaceutically acceptable salt thereof or an optical or stereoisomer thereof.

9. The compound as set forth in claim 2, wherein:
 $X=Y$ denotes a double bond between X and Y;
 X is N;
 20 Y is N;
 Z is NR;
 A, B and E are CH;
 Ar is phenyl, fluorophenyl, chlorophenyl, pyridinyl, pyrazinyl, furanyl or thiophenyl;
 R is hydrogen, methyl or ethyl;
 25 R_1 and R_2 are the same or different and selected independently of each other from
 benzyl, fluorobenzyl, fluorobenzoyl, difluorobenzoyl, chlorobenzoyl,
 isopropoxybenzoyl, trifluoromethylbenzoyl, fluoro-trifluoromethylbenzoyl,
 trifluoromethoxybenzoyl, thiophenylcarbonyl, pyridinylcarbonyl,
 pyrazinylcarbonyl, pyrimidinylcarbonyl, pyridazinylcarbonyl, dihydro-
 30 benzo[1,4]dioxinylcarbonyl, benzo[1,3]dioxolylcarbonyl, thiophenylmethyl, N-
 methyl-aza-bicyclo[2.2.2]octyl, aza-bicyclo[2.2.2]octyl, aza-
 bicyclo[2.2.2]octylmethyl, N-methyl-piperidinyl, N-isopropyl-piperidinyl, N-

cyclopropyl-piperidinyl, piperidinyl, N-methyl-pyrrolidinyl, N-ethyl-pyrrolidinylmethyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolidinylpropyl, methylaminoethyl, dimethylaminoethyl and dimethylaminopropyl;

or

- 5 R₁ and R₂ taken together with the nitrogen atom to which they are attached form a unsubstituted or at least monosubstituted heterocycle selected from the group consisting of piperazine and diazepane; wherein the substituents are selected from the group consisting of phenyl, fluorophenyl, trifluoromethylphenyl, pyridinyl, thiophenyl, furanyl and methyl.

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10. The compound as set forth in claim 9 selected from the group consisting of:

N-[3-(1H-benzotriazol-5-yl)-benzyl]-N-benzyl-N',N'-dimethyl-propane-1,3-diamine;
[5-(1H-benzotriazol-5-yl)-2-fluoro-benzyl]-(4-fluoro-benzyl)-pyrrolidin-2R-ylmethyl-amine trihydrochloride;

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[5-(1H-benzotriazol-5-yl)-2-fluoro-benzyl]-piperidin-4-yl-thiophen-2-ylmethyl-amine;
[5-(1H-benzotriazol-5-yl)-2-fluoro-benzyl]-(4-fluoro-benzyl)-piperidin-4-yl-amine;
N-[5-(1H-benzotriazol-5-yl)-2-fluoro-benzyl]-N-(4-fluoro-benzyl)-N'-methyl-ethane-1,2-diamine;

20

[5-(1H-benzotriazol-5-yl)-2-fluoro-benzyl]-(1-ethyl-pyrrolidin-2S-ylmethyl)-(4-fluoro-benzyl)-amine hydrochloride;
[5-(1H-benzotriazol-5-yl)-2-fluoro-benzyl]-(4-fluoro-benzyl)-(1-methyl-piperidin-4-yl)-amine hydrochloride;

N-[3-(1H-benzotriazol-5-yl)-benzyl]-N-benzyl-N',N'-dimethyl-ethane-1,2-diamine hydrochloride;

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N-[5-(1H-benzotriazol-5-yl)-2-fluoro-benzyl]-N-(1-ethyl-pyrrolidin-2S-ylmethyl)-4-fluoro-benzamide;

N-[3-(1H-benzotriazol-5-yl)-benzyl]-4-fluoro-N-(2-pyrrolidin-1-yl-ethyl)-benzamide hydrochloride;

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thiophene-2-carboxylic acid [5-(1H-benzotriazol-5-yl)-2-fluoro-benzyl]-(2-pyrrolidin-1-yl-ethyl)-amide hydrochloride;

N-[5-(1H-benzotriazol-5-yl)-2-fluoro-benzyl]-2,4-difluoro-N-(2-pyrrolidin-1-yl-ethyl)-benzamide hydrochloride;

175

N-[5-(1H-benzotriazol-5-yl)-2-fluoro-benzyl]-4-fluoro-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;
 N-[5-(1H-benzotriazol-5-yl)-2-fluoro-benzyl]-4-fluoro-N-piperidin-4-yl-benzamide;
 N-[5-(1H-benzotriazol-5-yl)-2-fluoro-benzyl]-4-fluoro-N-(1-isopropyl-piperidin-4-yl)-benzamide;
 N-[5-(1H-benzotriazol-5-yl)-2-fluoro-benzyl]-N-(1-cyclopropyl-piperidin-4-yl)-4-fluoro-benzamide;
 N-[5-(1H-benzotriazol-5-yl)-2-fluoro-benzyl]-N-(1-methyl-piperidin-4-yl)-4-fluoro-benzamide;
 5-[3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-benzotriazole;
 5-[4-fluoro-3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-benzotriazole; and
 5-[4-fluoro-3-[2S-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-phenyl]-1H-benzotriazole;
 or a pharmaceutically acceptable salt thereof or an optical or stereoisomer thereof.

11. The compound as set forth in claim 2, wherein:

$X \text{---} Y$ denotes a single bond between X and Y;

X is CHR;

Y is CHR;

Z is NR;

A, B and E are CH;

Ar is phenyl, fluorophenyl, chlorophenyl, pyridinyl, pyrazinyl, furanyl or thiophenyl;
 each R is independently chosen from hydrogen, methyl or ethyl;

R₁ and R₂ are the same or different and selected independently of each other from
 benzyl, fluorobenzyl, fluorobenzoyl, difluorobenzoyl, chlorobenzoyl,
 isopropoxybenzoyl, trifluoromethylbenzoyl, fluoro-trifluoromethylbenzoyl,
 trifluoromethoxybenzoyl, thiophenylcarbonyl, pyridinylcarbonyl,
 pyrazinylcarbonyl, pyrimidinylcarbonyl, pyridazinylcarbonyl, dihydro-
 benzo[1,4]dioxinylcarbonyl, benzo[1,3]dioxolylcarbonyl, thiophenylmethyl, N-
 methyl-aza-bicyclo[2.2.2]octyl, aza-bicyclo[2.2.2]octyl, aza-
 bicyclo[2.2.2]octylmethyl, N-methyl-piperidinyl, N-isopropyl-piperidinyl, N-
 cyclopropyl-piperidinyl, piperidinyl, N-methyl-pyrrolidinyl, N-ethyl-

178

pyrrolidinylmethyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolidinylpropyl, methylaminoethyl, dimethylaminoethyl and dimethylaminopropyl;

or

R₁ and R₂ taken together with the nitrogen atom to which they are attached form a
 5 unsubstituted or at least monosubstituted heterocycle selected from the group consisting of piperazine and diazepane; wherein the substituents are selected from the group consisting of phenyl, fluorophenyl, trifluoromethylphenyl, pyridinyl, thiophenyl, furanyl and methyl.

- 10 12. The compound as set forth in claim 11 which is:
 N-[5-(2,3-dihydro-1H-indol-5-yl)-2-fluoro-benzyl]-N-(2-dimethylamino-ethyl)-4-fluoro-benzamide;
 or a pharmaceutically acceptable salt thereof or an optical or stereoisomer thereof.

- 15 13. The compound as set forth in claim 2, wherein:

$X \text{---} Y$ denotes a single bond between X and Y;

X is O, S or NR;

Y is CO;

Z is NR;

- 20 A, B and E are CH;

Ar is phenyl, fluorophenyl, chlorophenyl, pyridinyl, pyrazinyl, furanyl or thiophenyl;
 each R is independently chosen from hydrogen, methyl or ethyl;

R₁ and R₂ are the same or different and selected independently of each other from
 benzyl, fluorobenzyl, benzoyl, fluorobenzoyl, difluorobenzoyl, chlorobenzoyl,
 25 isopropoxybenzoyl, trifluoromethylbenzoyl, fluoro-trifluoromethylbenzoyl, trifluoromethoxybenzoyl, thiophenylcarbonyl, pyridinylcarbonyl, pyrazinylcarbonyl, pyrimidinylcarbonyl, pyridazinylcarbonyl, dihydro-benzo[1,4]dioxinylcarbonyl, benzo[1,3]dioxolylcarbonyl, thiophenylmethyl, N-methyl-aza-bicyclo[2.2.2]octyl, aza-bicyclo[2.2.2]octyl, aza-bicyclo[2.2.2]octylmethyl, N-methyl-piperidinyl, N-isopropyl-piperidinyl, N-cyclopropyl-piperidinyl, piperidinyl, N-methyl-pyrrolidinyl, N-ethyl-

30

177

pyrrolidinylmethyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolidinylpropyl, methylaminoethyl, dimethylaminoethyl and dimethylaminopropyl;

or

R₁ and R₂ taken together with the nitrogen atom to which they are attached form a
 5 unsubstituted or at least monosubstituted heterocycle selected from the group consisting of piperazine and diazepane; wherein the substituents are selected from the group consisting of phenyl, fluorophenyl, trifluoromethylphenyl, pyridinyl, thiophenyl, furanyl and methyl.

- 10 14. The compound as set forth in claim 13 selected from the group consisting of:
- 6-(3-{[benzyl-(2-dimethylamino-ethyl)-amino]-methyl}-phenyl)-3H-benzothiazol-2-one hydrochloride;
- N-(2-dimethylamino-ethyl)-N-[3-(2-oxo-2,3-dihydro-benzothiazol-6-yl)-benzyl]-benzamide hydrochloride;
- 15 4-chloro-N-(2-dimethylamino-ethyl)-N-[3-(2-oxo-2,3-dihydro-benzothiazol-6-yl)-benzyl]-benzamide hydrochloride;
- N-(3-dimethylamino-propyl)-N-[3-(2-oxo-2,3-dihydro-benzothiazol-6-yl)-benzyl]-benzamide; hydrochloride;
- 20 6-(3-{[benzyl-(2-dimethylamino-ethyl)-amino]-methyl}-phenyl)-3H-benzooxazol-2-one hydrochloride;
- 6-(5-{[(2-dimethylamino-ethyl)-(4-fluoro-benzyl)-amino]-methyl}-pyridin-3-yl)-3H-benzooxazol-2-one;
- 6-(5-{[(2-dimethylamino-ethyl)-(4-fluoro-benzyl)-amino]-methyl}-furan-3-yl)-3H-benzooxazol-2-one;
- 25 6-(3-{[(1-ethyl-pyrrolidin-2R-ylmethyl)-(4-fluoro-benzyl)-amino]-methyl}-4-fluoro-phenyl)-3H-benzooxazol-2-one trifluoro-acetate;
- 6-(4-fluoro-3-{[(4-fluoro-benzyl)-(1-methyl-piperidin-4-yl)-amino]-methyl}-phenyl)-3H-benzooxazol-2-one;
- 6-(5-{[(4-fluoro-benzyl)-(1-methyl-piperidin-4-yl)-amino]-methyl}-furan-3-yl)-3H-benzooxazol-2-one;
- 30 4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

- N-(2-dimethylamino-ethyl)-N-[3-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-benzamide hydrochloride;
- N-(1-ethyl-pyrrolidin-2-ylmethyl)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-benzamide;
- 5 4-chloro-N-(2-dimethylamino-ethyl)-N-[3-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-benzamide hydrochloride;
- N-(1-ethyl-pyrrolidin-2*R*-ylmethyl)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-benzamide trifluoro-acetate;
- 4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-N-(1-methyl-10 piperidin-4-yl)-benzamide;
- N-(1-aza-bicyclo[2.2.2]oct-3*S*-yl)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-benzamide hydrochloride;
- N-(1-aza-bicyclo[2.2.2]oct-3*R*-yl)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-benzamide hydrochloride;
- 15 N-(2-dimethylamino-ethyl)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-benzamide;
- 6-[3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-3*H*-benzooxazol-2-one;
- 6-{5-[2*R*-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-furan-3-yl}-3*H*-benzooxazol-2-one;
- 20 6-{5-[2*S*-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-furan-2-yl}-3*H*-benzooxazol-2-one;
- 6-{5-[2*S*-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-thiophen-3-yl}-3*H*-benzooxazol-2-one;
- 6-[4-fluoro-3-(2-thiophen-2-yl-piperazin-1-ylmethyl)-phenyl]-3*H*-benzooxazol-2-one;
- 25 6-{5-[2*S*-(4-fluorophenyl)-4-methylpiperazine-1-ylmethyl]-furan-3-yl}-3*H*-benzooxazol-2-one;
- 6-{5-[2*S*-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-furan-3-yl}-3*H*-benzooxazol-2-one acetate;
- 6-{4-fluoro-3-[2*S*-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-phenyl}-3*H*-benzooxazol-2-one;
- 30 6-{5-[2*S*-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-pyridin-3-yl}-3*H*-benzooxazol-2-one acetate; and

179

5-(3-([benzyl-(2-dimethylamino-ethyl)-amino]-methyl)-phenyl)-1,3-dihydro-benzoimidazol-2-one hydrochloride;
or a pharmaceutically acceptable salt thereof or an optical or stereoisomer thereof.

5 15. The compound as set forth in claim 2, wherein:

$X\text{---}Y$ denotes a single bond between X and Y;

X is O or CO;

Y is CHR or NR;

Z is CONR;

10 A, B and E are the same or different and independently from each other are CH or N;

Ar is phenyl, fluorophenyl, chlorophenyl, pyridinyl, pyrazinyl, furanyl or thiophenyl;

each R is independently chosen from hydrogen, methyl or ethyl;

R₁ and R₂ are the same or different and selected independently of each other from

15 benzyl, fluorobenzyl, benzoyl, fluorobenzoyl, difluorobenzoyl, chlorobenzoyl, isopropoxybenzoyl, trifluoromethylbenzoyl, fluoro-trifluoromethylbenzoyl, trifluoromethoxybenzoyl, thiophenylcarbonyl, pyridinylcarbonyl, pyrazinylcarbonyl, pyrimidinylcarbonyl, pyridazinylcarbonyl, dihydro-benzo[1,4]dioxinylcarbonyl, benzo[1,3]dioxolylcarbonyl, thiophenylmethyl, N-methyl-aza-bicyclo[2.2.2]octyl, aza-bicyclo[2.2.2]octyl, aza-bicyclo[2.2.2]octylmethyl, N-methyl-piperidinyl, N-isopropyl-piperidinyl, N-cyclopropyl-piperidinyl, piperidinyl, N-methyl-pyrrolidinyl, N-ethyl-pyrrolidinylmethyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolidinylpropyl, methylaminoethyl, dimethylaminoethyl and dimethylaminopropyl;

or

25 R₁ and R₂ taken together with the nitrogen atom to which they are attached form a unsubstituted or at least monosubstituted heterocycle selected from the group consisting of piperazine and diazepane; wherein the substituents are selected from the group consisting of phenyl, fluorophenyl, trifluoromethylphenyl, pyridinyl, thiophenyl, furanyl and methyl.

30

16. The compound as set forth in claim 15 selected from the group consisting of:

6-(3-([benzyl-(2-dimethylamino-ethyl)-amino]-methyl)-phenyl)-3-methyl-1H-quinazoline-2,4-dione hydrochloride; and
 7-(3-([benzyl-(2-dimethylamino-ethyl)-amino]-methyl)-phenyl)-4H-pyrido[3,2-b][1,4]oxazin-3-one hydrochloride;
 5 or a pharmaceutically acceptable salt thereof or an optical or stereoisomer thereof.

17. The compound as set forth in claim 1, wherein:

$X \equiv Y$ denotes a double bond between X and Y;

X is CR;

10 Y is CR;

Z is NR;

A, B and E are the same or different and independently from each other are CH or N;

D is CO;

Ar is phenyl, fluorophenyl, chlorophenyl, pyridinyl, pyrazinyl, furanyl or thiophenyl;

15 each R is independently chosen from hydrogen, methyl, ethyl, methoxy, fluorine, CF₃ or OCF₃;

R₁ and R₂ are the same or different and selected independently of each other from

benzyl, fluorobenzyl, benzoyl, fluorobenzoyl, difluorobenzoyl, chlorobenzoyl,

isopropoxybenzoyl, trifluoromethylbenzoyl, fluoro-trifluoromethylbenzoyl,

20 trifluoromethoxybenzoyl, thiophenylcarbonyl, pyridinylcarbonyl,

pyrazinylcarbonyl, pyrimidinylcarbonyl, pyridazinylcarbonyl, dihydro-

benzo[1,4]dioxinylcarbonyl, benzo[1,3]dioxolylcarbonyl, thiophenylmethyl, N-

methyl-aza-bicyclo[2.2.2]octyl, aza-bicyclo[2.2.2]octyl, aza-

bicyclo[2.2.2]octylmethyl, N-methyl-piperidinyl, N-isopropyl-piperidinyl, N-

25 cyclopropyl-piperidinyl, piperidinyl, N-methyl-pyrrolidinyl, N-ethyl-

pyrrolidinylmethyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolidinylpropyl,

methylaminoethyl, dimethylaminoethyl and dimethylaminopropyl;

or

R₁ and R₂ taken together with the nitrogen atom to which they are attached form a

30 unsubstituted or at least monosubstituted heterocycle selected from the group consisting of piperazine and diazepane; wherein the substituents are selected

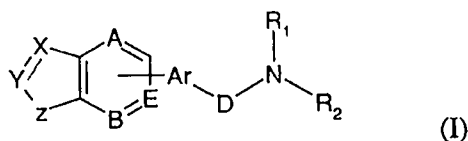
18)

from the group consisting of phenyl, fluorophenyl, trifluoromethylphenyl, pyridinyl, thiophenyl, furanyl and methyl.

18. The compound as set forth in claim 17 which is:

[2-fluoro-5-(1H-indol-5-yl)-phenyl]-[2S-(4-fluoro-phenyl)-4-methyl-piperazin-1-yl]-methanone;
or a pharmaceutically acceptable salt thereof or an optical or stereoisomer thereof.

19. A pharmaceutical composition comprising one or more compounds of formula I, including enantiomers, stereoisomers, and tautomers of said compound and pharmaceutically acceptable salts, solvates or derivatives thereof, in combination with one or more pharmaceutically acceptable carriers, diluents or excipients:



wherein:

$X \equiv Y$ denotes either a single or double bond between X and Y;

X is CR, CHR, CO, N, O or S;

Y is CR, CHR, CO, S(O)₂, N or NR;

Z is NR, CO-NR, S(O)₂-NR;

A, B and E are the same or different and independently from each other are CR or N;

D is either CH₂ or CO;

Ar is substituted or unsubstituted aryl or heteroaryl;

each R is independently chosen from hydrogen, halogen, CN, C(O)NR₃R₄, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkenyl, aryl, heteroaryl, arylC₁₋₄alkyl, heteroarylC₁₋₄alkyl, fluoroalkyl or fluoroalkoxy of the formula C_nH_xF_y or OC_nH_xF_y wherein n is an integer from 1 to 4, x is an integer from 0 to 8, y is an integer from 1 to 9 and sum of x and y is 2n+1; wherein

R₃ and R₄ are hydrogen or C₁₋₄alkyl; or

R₃ and R₄ taken together with the nitrogen atom to which they are attached form an unsubstituted or at least monosubstituted heterocycle;

182

R₁ and R₂ are the same or different and selected independently of each other from substituted or unsubstituted aryl, heteroaryl, aryloyl, heteroaryloyl, arylsulfonyl, heteroarylsulfonyl, arylC₁₋₄alkyl, heteroarylC₁₋₄alkyl, aminoC₁₋₄alkyl, C₁₋₄alkylaminoC₁₋₄alkyl, C₃₋₈cycloalkylaminoC₁₋₄alkyl, diC₃₋₈cycloalkylaminoC₁₋₄alkyl, C₃₋₈cycloalkylC₁₋₄alkylaminoC₁₋₄alkyl, diC₁₋₄alkylaminoalkyl, heterocycle, heterocycleC₁₋₄alkyl, C₁₋₄alkylheterocycleC₁₋₄alkyl; or

R₁ and R₂ taken together with the nitrogen atom to which they are attached form an unsubstituted or at least monosubstituted heterocycle; and wherein

the substituents are selected from the group consisting of substituted or unsubstituted aryl, heteroaryl, arylC₁₋₄alkyl, heteroarylC₁₋₄alkyl, heterocycle, C₃₋₈cycloalkyl, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkenyl, fluoroalkyl or fluoroalkoxy of the formula C_nH_xF_y or OC_nH_xF_y wherein n is an integer from 1 to 4, x is an integer from 0 to 8, y is an integer from 1 to 9 and sum of x and y is 2n+1, -NO₂, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, -CN, -C(O)R₅, -NHC(O)(C₁₋₄alkyl), -SO₂Cl, -SO₂(C₁₋₄alkyl), halogen and hydroxy; wherein

R₅ is hydroxy, C₁₋₃alkoxy, -O-phenyl, -NH₂, -NH(C₁₋₃alkyl), -N(C₁₋₃alkyl)₂ or phenyl; heteroaryl is a 5 to 10-membered, aromatic, mono- or bicyclic heterocycle containing

one or more heteroatoms selected from the group consisting of N, O and S;

aryl is a 6 to 10-membered, aromatic mono- or bicyclic ring; and

heterocycle is a 3 to 10-membered, non-aromatic, mono- or bicyclic heterocycle

containing one or more heteroatoms selected from the group consisting of N, O and S.

20. The composition as set forth in claim 19, wherein the compound of formula (I) is having:

D is CH₂;

Ar is substituted or unsubstituted phenyl, pyridinyl, pyrazinyl, furanyl or thiophenyl;

wherein the substituents are selected from the group consisting of fluorine,

chlorine, C₁₋₄alkyl, C₁₋₄alkoxy and -CF₃;

each R is independently chosen from hydrogen, CN or C₁₋₄alkyl;

R₁ and R₂ are the same or different and selected independently of each other from substituted or unsubstituted benzoyl, thiophenylcarbonyl, pyridinylcarbonyl, pyrazinylcarbonyl, pyrimidinylcarbonyl, pyridazinylcarbonyl, dihydro-benzo[1,4]dioxinylcarbonyl, benzo[1,3]dioxolylcarbonyl, phenylC_{0.4}alkyl, thiophenylC_{1.4}alkyl, aza-bicyclo[2.2.2]octylC_{0.4}alkyl, aza-bicyclo[3.2.1]octylC_{0.4}alkyl, piperidinylC_{0.4}alkyl, pyrrolidinylC_{0.4}alkyl, C_{1.4}alkylaminoC_{1.4}alkyl and diC_{1.4}alkylaminoC_{1.4}alkyl; wherein the substituted moieties may be substituted with one or more substituents selected from the group consisting of fluorine, chlorine, C_{1.4}alkyl, C₃₋₈cycloalkyl, C_{1.4}alkoxy, OCF₃ and CF₃; or

R₁ and R₂ taken together with the nitrogen atom to which they are attached form a unsubstituted or at least monosubstituted heterocycle selected from the group consisting of piperazine and diazepane; wherein the substituents are selected from the group consisting of phenyl, fluorophenyl, trifluoromethylphenyl, pyridinyl, thiophenyl, furanyl and C_{1.4}alkyl.

21. The composition as set forth in claim 19, wherein the compound of formula (I) is selected from the group consisting of:
- N-benzyl-N-[3-(1H-indol-5-yl)-benzyl]-N',N'-dimethyl-ethane-1,2-diamine;
- 4-fluoro-N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;
- N-(2-dimethylamino-ethyl)-4-fluoro-N-[2-fluoro-5-(2-methyl-1H-indol-5-yl)-benzyl]-benzamide;
- N-(2-dimethylamino-ethyl)-4-fluoro-N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-benzamide;
- 4-fluoro-N-[3-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-benzamide;
- thiophene-2-carboxylic acid [3-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide;
- thiophene-2-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide;
- thiophene-2-carboxylic acid (2-dimethylamino-ethyl)-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-amide;

- 4-fluoro-N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-benzamide;
- N-(1-aza-bicyclo[2.2.2]oct-4-ylmethyl)-4-fluoro-N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-benzamide trifluoro-acetate;
- 5 4-fluoro-N-[5-(1H-indol-5-yl)-pyridin-3-ylmethyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;
- 4-fluoro-N-[4-fluoro-3-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-benzamide;
- 4-fluoro-N-[4-(1H-indol-5-yl)-thiophen-2-ylmethyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide acetate;
- 10 (4-fluoro-benzyl)-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amine;
- N-(4-fluoro-benzyl)-N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N',N'-dimethyl-ethane-1,2-diamine;
- 15 (1-aza-bicyclo[2.2.2]oct-4-ylmethyl)-(4-fluoro-benzyl)-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-amine acetate;
- N-(2-dimethylamino-ethyl)-4-fluoro-N-[5-(1H-indol-5-yl)-pyridin-3-ylmethyl]-benzamide trifluoroacetate;
- 4-fluoro-N-[5-(1H-indol-5-yl)-thiophen-2-ylmethyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;
- 20 4-fluoro-N-[4-(1H-indol-5-yl)-furan-2-ylmethyl]-N-(1-methyl-piperidin-4-yl)-benzamide;
- N-(1-aza-bicyclo[2.2.2]oct-3*R*-yl)-4-fluoro-N-[2-fluoro-5-(1H-indol-6-yl)-benzyl]-benzamide;
- 25 pyrimidine-4-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide;
- pyrimidine-2-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide;
- pyridazine-3-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide;
- 30 pyridazine-4-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide;

185

- 2,3-dihydro-benzo[1,4]dioxine-6-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-
(1-methyl-piperidin-4-yl)-amide;
N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-4-isopropoxy-N-(1-methyl-piperidin-4-yl)-
benzamide;
5 N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-3-isopropoxy-N-(1-methyl-piperidin-4-yl)-
benzamide;
N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-4-
trifluoromethoxy-benzamide;
4-chloro-N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-
10 benzamide;
benzo[1,3]dioxole-5-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-
piperidin-4-yl)-amide;
N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-4-trifluoromethyl-
benzamide;
15 4-fluoro-N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-3-
trifluoromethyl-benzamide;
N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-isonicotinamide;
N-[3-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-4-trifluoromethyl-
benzamide;
20 4-fluoro-N-[4-fluoro-3-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;
N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-4-trifluoromethyl-
benzamide;
4-fluoro-N-[3-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;
N-[3-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-4-trifluoromethyl-
25 benzamide;
N-[3-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-isonicotinamide;
N-[4-fluoro-3-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-4-trifluoromethyl-
benzamide;
N-[3-(1H-indol-5-yl)-benzyl]-N-(3-pyrrolidin-1-yl-propyl)-isonicotinamide;
30 N-[4-fluoro-3-(1H-indol-5-yl)-benzyl]-N-(3-pyrrolidin-1-yl-propyl)-isonicotinamide;
pyridine-2-carboxylic acid [3-(1H-indol-5-yl)-benzyl]-(3-pyrrolidin-1-yl-propyl)-
amide;

- N-[3-(1H-indol-5-yl)-benzyl]-N-(3-pyrrolidin-1-yl-propyl)-4-trifluoromethyl-benzamide;
- pyridine-2-carboxylic acid [4-fluoro-3-(1H-indol-5-yl)-benzyl]-(3-pyrrolidin-1-yl-propyl)-amide;
- 5 pyridine-2-carboxylic acid [4-(1H-indol-5-yl)-thiophen-2-ylmethyl]-(3-pyrrolidin-1-yl-propyl)-amide;
- N-[4-(1H-indol-5-yl)-thiophen-2-ylmethyl]-N-(3-pyrrolidin-1-yl-propyl)-4-trifluoromethyl-benzamide;
- N-[4-(1H-indol-5-yl)-thiophen-2-ylmethyl]-N-(2-pyrrolidin-1-yl-ethyl)-
- 10 isonicotinamide;
- pyridine-2-carboxylic acid [4-(1H-indol-5-yl)-thiophen-2-ylmethyl]-(2-pyrrolidin-1-yl-ethyl)-amide;
- N-[4-(1H-indol-5-yl)-thiophen-2-ylmethyl]-N-(2-pyrrolidin-1-yl-ethyl)-4-trifluoromethyl-benzamide;
- 15 pyridine-2-carboxylic acid [4-(1H-indol-5-yl)-furan-2-ylmethyl]-(3-pyrrolidin-1-yl-propyl)-amide;
- N-[4-(1H-indol-5-yl)-furan-2-ylmethyl]-N-(3-pyrrolidin-1-yl-propyl)-4-trifluoromethyl-benzamide;
- N-[4-(1H-indol-5-yl)-furan-2-ylmethyl]-N-(2-pyrrolidin-1-yl-ethyl)-isonicotinamide;
- 20 pyridine-2-carboxylic acid [4-(1H-indol-5-yl)-furan-2-ylmethyl]-(2-pyrrolidin-1-yl-ethyl)-amide;
- N-[4-(1H-indol-5-yl)-furan-2-ylmethyl]-N-(2-pyrrolidin-1-yl-ethyl)-4-trifluoromethyl-benzamide;
- N-[4-(1H-indol-5-yl)-thiophen-2-ylmethyl]-N-(3-pyrrolidin-1-yl-propyl)-
- 25 isonicotinamide;
- N-[4-(1H-indol-5-yl)-furan-2-ylmethyl]-N-(3-pyrrolidin-1-yl-propyl)-isonicotinamide;
- N-[2-chloro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-isonicotinamide;
- pyridine-2-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amide;
- 30 N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-nicotinamide;
- N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-3-trifluoromethoxy-benzamide;

187

- N-[2-fluoro-5-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-isonicotinamide;
N-[4-fluoro-3-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-isonicotinamide;
N-[4-fluoro-3-(1H-indol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-4-trifluoromethoxy-
benzamide acetate;
5 N-[3-(1H-indol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-isonicotinamide;
pyrazine-2-carboxylic acid [2-fluoro-5-(1H-indol-5-yl)-benzyl]-(1-methyl-piperidin-4-
yl)-amide;
5-[4-fluoro-3-(4-methyl-2-pyridin-3-yl-piperazin-1-ylmethyl)-phenyl]-1H-indole
acetate;
10 5-{4-fluoro-3-[4-methyl-2-(4-trifluoromethyl-phenyl)-piperazin-1-ylmethyl]-phenyl}-
1H-indole;
5-[4-fluoro-3-(4-methyl-2-pyridin-2-yl-piperazin-1-ylmethyl)-phenyl]-1H-indole
acetate;
5-{5-[2S-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-pyridin-3-yl}-1H-indole
15 acetate;
5-{4-fluoro-3-[2S-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-phenyl}-1H-
indole;
5-[4-fluoro-3-(2-furan-2-yl-4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-indole;
5-{5-[2S-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-furan-3-yl}-1H-indole
20 trifluoro-acetate;
5-{5-[2S-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-pyridin-3-yl}-1H-indole acetate;
5-{5-[2S-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-furan-3-yl}-1H-indole;
5-[3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-indole;
5-[4-fluoro-3-(4-methyl-2-pyridin-4-yl-piperazin-1-ylmethyl)-phenyl]-1H-indole;
25 5-{3-[2S-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-phenyl}-1H-indole;
5-{6-[2S-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-pyrazin-2-yl}-1H-indole
acetate;
5-{4-fluoro-3-[2S-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-phenyl}-1H-indole acetate;
5-{4-fluoro-3-[2S-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-phenyl}-1H-
30 indole-3-carbonitrile;
5-[3-(4-methyl-[1,4]diazepan-1-ylmethyl)-phenyl]-1H-indole;

- 5- {4-fluoro-3-[2*S*-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-phenyl}-3-methyl-1*H*-indole;
 N-[5-(3-cyano-1*H*-indol-5-yl)-2-fluoro-benzyl]-N-(2-dimethylamino-ethyl)-4-fluoro-benzamide;
 5- {4-fluoro-3-[2*S*-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-phenyl}-1*H*-indole-3-carbonitrile;
 5-(3- {[(2-dimethylamino-ethyl)-(4-fluoro-benzyl)-amino]-methyl}-4-fluoro-phenyl)-1*H*-indole-3-carbonitrile trifluoro-acetate;
 4-fluoro-N-[2-fluoro-5-(1*H*-pyrrolo[3,2-*b*]pyridin-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;
 5- {4-fluoro-3-[2-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-phenyl}-1*H*-pyrrolo[3,2-*b*]pyridine; and
 4-fluoro-N-[2-fluoro-5-(1*H*-pyrrolo[2,3-*c*]pyridin-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;
 or a pharmaceutically acceptable salt thereof or an optical or stereoisomer thereof.
22. The composition as set forth in claim 19, wherein the compound of formula (I) is selected from the group consisting of:
 N-benzyl-N-[3-(1*H*-indazol-5-yl)-benzyl]-N',N'-dimethyl-ethane-1,2-diamine hydrochloride;
 N-(4-fluoro-benzyl)-N-[5-(1*H*-indazol-5-yl)-pyridin-3-ylmethyl]-N',N'-dimethyl-ethane-1,2-diamine acetate;
 (4-fluoro-benzyl)-[2-fluoro-5-(1*H*-indazol-5-yl)-benzyl]-pyrrolidin-2*S*-ylmethyl-amine;
 (4-fluoro-benzyl)-[2-fluoro-5-(1*H*-indazol-5-yl)-benzyl]-piperidin-4-yl-amine;
 N-(4-fluoro-benzyl)-N-[2-fluoro-5-(1*H*-indazol-5-yl)-benzyl]-N'-methyl-ethane-1,2-diamine;
 (4-fluoro-benzyl)-[2-fluoro-5-(1*H*-indazol-5-yl)-benzyl]-(1-methyl-piperidin-4-yl)-amine;
 (4-fluoro-benzyl)-[4-(1*H*-indazol-5-yl)-furan-2-ylmethyl]-(1-methyl-piperidin-4-yl)-amine;
 4-fluoro-N-[2-fluoro-5-(1*H*-indazol-5-yl)-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

789

- 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(exo-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-benzamide;
4-fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(endo-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-benzamide;
5 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(1-methyl-piperidin-3-yl)-benzamide;
4-fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(1-methyl-piperidin-3S-yl)-benzamide trifluoro-acetate;
4-fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(1-methyl-pyrrolidin-3R-yl)-benzamide trifluoro-acetate;
10 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(1-methyl-pyrrolidin-3S-yl)-benzamide trifluoro-acetate;
4-fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(3-pyrrolidin-1-yl-propyl)-benzamide;
15 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(1-methyl-piperidin-4-yl)-benzamide;
N-(1-aza-bicyclo[2.2.2]oct-3R-yl)-4-fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-benzamide;
chiral N-[2-fluoro-5-(1H-indazol-5-yl)-benzyl]-N-(1-methyl-pyrrolidin-3R-yl)-4-trifluoromethyl-benzamide;
20 4-fluoro-N-[4-(1H-indazol-5-yl)-furan-2-ylmethyl]-N-(1-methyl-piperidin-4-yl)-benzamide;
5-{4-fluoro-3-[2-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-phenyl}-1H-indazole;
5-[4-fluoro-3-(2S-thiophen-2-yl-piperazin-1-ylmethyl)-phenyl]-1H-indazole acetate;
25 5-[4-fluoro-3-(2-thiophen-2-yl-piperazin-1-ylmethyl)-phenyl]-1H-indazole;
chiral 5-[4-fluoro-3-(2-thiophen-2-yl-piperazin-1-ylmethyl)-phenyl]-1H-indazole acetate;
5-{4-fluoro-3-[2S-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-phenyl}-1H-indazole;
30 5-{5-[2S-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-pyridin-3-yl}-1H-indazole;
5-{5-[2S-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-pyridin-3-yl}-1H-indazole;
5-{5-[2S-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-furan-3-yl}-1H-indazole;

- 5-[4-fluoro-3-(4-methyl-2*R*-thiophen-2-yl-piperazin-1-ylmethyl)-phenyl]-1*H*-indazole acetate;
- 5-[4-fluoro-3-(4-methyl-2*S*-thiophen-2-yl-piperazin-1-ylmethyl)-phenyl]-1*H*-indazole acetate;
- 5-{5-[2*S*-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-furan-3-yl}-1*H*-indazole;
- N-[3-(1*H*-benzoimidazol-5-yl)-benzyl]-*N*-benzyl-*N*',*N*'-dimethyl-ethane-1,2-diamine hydrochloride;
- N-[3-(1*H*-benzoimidazol-5-yl)-benzyl]-*N*-benzyl-*N*',*N*'-dimethyl-propane-1,3-diamine hydrochloride;
- 10 N-[3-(1*H*-benzotriazol-5-yl)-benzyl]-*N*-benzyl-*N*',*N*'-dimethyl-propane-1,3-diamine;
- [5-(1*H*-benzotriazol-5-yl)-2-fluoro-benzyl]-(4-fluoro-benzyl)-pyrrolidin-2*R*-ylmethyl-amine trihydrochloride;
- [5-(1*H*-benzotriazol-5-yl)-2-fluoro-benzyl]-piperidin-4-yl-thiophen-2-ylmethyl-amine;
- [5-(1*H*-benzotriazol-5-yl)-2-fluoro-benzyl]-(4-fluoro-benzyl)-piperidin-4-yl-amine;
- 15 N-[5-(1*H*-benzotriazol-5-yl)-2-fluoro-benzyl]-*N*-(4-fluoro-benzyl)-*N*'-methyl-ethane-1,2-diamine;
- [5-(1*H*-benzotriazol-5-yl)-2-fluoro-benzyl]-(1-ethyl-pyrrolidin-2*S*-ylmethyl)-(4-fluoro-benzyl)-amine hydrochloride;
- [5-(1*H*-benzotriazol-5-yl)-2-fluoro-benzyl]-(4-fluoro-benzyl)-(1-methyl-piperidin-4-yl)-amine hydrochloride;
- 20 N-[3-(1*H*-benzotriazol-5-yl)-benzyl]-*N*-benzyl-*N*',*N*'-dimethyl-ethane-1,2-diamine hydrochloride;
- N-[5-(1*H*-benzotriazol-5-yl)-2-fluoro-benzyl]-*N*-(1-ethyl-pyrrolidin-2*S*-ylmethyl)-4-fluoro-benzamide;
- 25 N-[3-(1*H*-benzotriazol-5-yl)-benzyl]-4-fluoro-*N*-(2-pyrrolidin-1-yl-ethyl)-benzamide hydrochloride;
- thiophene-2-carboxylic acid [5-(1*H*-benzotriazol-5-yl)-2-fluoro-benzyl]-(2-pyrrolidin-1-yl-ethyl)-amide hydrochloride;
- N-[5-(1*H*-benzotriazol-5-yl)-2-fluoro-benzyl]-2,4-difluoro-*N*-(2-pyrrolidin-1-yl-ethyl)-benzamide hydrochloride;
- 30 N-[5-(1*H*-benzotriazol-5-yl)-2-fluoro-benzyl]-4-fluoro-*N*-(2-pyrrolidin-1-yl-ethyl)-benzamide;

191

N-[5-(1H-benzotriazol-5-yl)-2-fluoro-benzyl]-4-fluoro-N-piperidin-4-yl-benzamide;
 N-[5-(1H-benzotriazol-5-yl)-2-fluoro-benzyl]-4-fluoro-N-(1-isopropyl-piperidin-4-yl)-
 benzamide;
 N-[5-(1H-benzotriazol-5-yl)-2-fluoro-benzyl]-N-(1-cyclopropyl-piperidin-4-yl)-4-
 5 fluoro-benzamide;
 N-[5-(1H-benzotriazol-5-yl)-2-fluoro-benzyl]-N-(1-methyl-piperidin-4-yl)-4-fluoro-
 benzamide;
 5-[3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-benzotriazole;
 5-[4-fluoro-3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-benzotriazole;
 10 5-[4-fluoro-3-[2S-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-phenyl]-1H-benzotriazole;
 and
 N-[5-(2,3-dihydro-1H-indol-5-yl)-2-fluoro-benzyl]-N-(2-dimethylamino-ethyl)-4-
 fluoro-benzamide;
 or a pharmaceutically acceptable salt thereof or an optical or stereoisomer thereof.

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23. The composition as set forth in claim 19, wherein the compound of formula (I) is selected from the group consisting of:

6-(3-{[benzyl-(2-dimethylamino-ethyl)-amino]-methyl}-phenyl)-3H-benzothiazol-2-
 one hydrochloride;
 20 N-(2-dimethylamino-ethyl)-N-[3-(2-oxo-2,3-dihydro-benzothiazol-6-yl)-benzyl]-
 benzamide hydrochloride;
 4-chloro-N-(2-dimethylamino-ethyl)-N-[3-(2-oxo-2,3-dihydro-benzothiazol-6-yl)-
 benzyl]-benzamide hydrochloride;
 N-(3-dimethylamino-propyl)-N-[3-(2-oxo-2,3-dihydro-benzothiazol-6-yl)-benzyl]-
 25 benzamide; hydrochloride;
 6-(3-{[benzyl-(2-dimethylamino-ethyl)-amino]-methyl}-phenyl)-3H-benzooxazol-2-
 one hydrochloride;
 6-(5-{[(2-dimethylamino-ethyl)-(4-fluoro-benzyl)-amino]-methyl}-pyridin-3-yl)-3H-
 benzooxazol-2-one;
 30 6-(5-{[(2-dimethylamino-ethyl)-(4-fluoro-benzyl)-amino]-methyl}-furan-3-yl)-3H-
 benzooxazol-2-one;

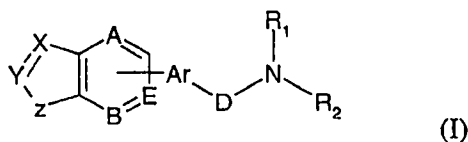
- 6-(3-([(1-ethyl-pyrrolidin-2*R*-ylmethyl)-(4-fluoro-benzyl)-amino]-methyl]-4-fluoro-phenyl)-3*H*-benzooxazol-2-one trifluoro-acetate;
- 6-(4-fluoro-3-([(4-fluoro-benzyl)-(1-methyl-piperidin-4-yl)-amino]-methyl]-phenyl)-3*H*-benzooxazol-2-one;
- 5 6-(5-([(4-fluoro-benzyl)-(1-methyl-piperidin-4-yl)-amino]-methyl]-furan-3-yl)-3*H*-benzooxazol-2-one;
- 4-fluoro-*N*-[2-fluoro-5-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-*N*-(2-pyrrolidin-1-yl-ethyl)-benzamide;
- N*-(2-dimethylamino-ethyl)-*N*-[3-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-benzamide hydrochloride;
- 10 *N*-(1-ethyl-pyrrolidin-2-ylmethyl)-4-fluoro-*N*-[2-fluoro-5-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-benzamide;
- 4-chloro-*N*-(2-dimethylamino-ethyl)-*N*-[3-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-benzamide hydrochloride;
- 15 *N*-(1-ethyl-pyrrolidin-2*R*-ylmethyl)-4-fluoro-*N*-[2-fluoro-5-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-benzamide trifluoro-acetate;
- 4-fluoro-*N*-[2-fluoro-5-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-*N*-(1-methyl-piperidin-4-yl)-benzamide;
- N*-(1-aza-bicyclo[2.2.2]oct-3*S*-yl)-4-fluoro-*N*-[2-fluoro-5-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-benzamide hydrochloride;
- 20 *N*-(1-aza-bicyclo[2.2.2]oct-3*R*-yl)-4-fluoro-*N*-[2-fluoro-5-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-benzamide hydrochloride;
- N*-(2-dimethylamino-ethyl)-4-fluoro-*N*-[2-fluoro-5-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-benzyl]-benzamide;
- 25 6-[3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-3*H*-benzooxazol-2-one;
- 6-{5-[2*R*-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-furan-3-yl}-3*H*-benzooxazol-2-one;
- 6-{5-[2*S*-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-furan-2-yl}-3*H*-benzooxazol-2-one;
- 30 6-{5-[2*S*-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-thiophen-3-yl}-3*H*-benzooxazol-2-one;
- 6-[4-fluoro-3-(2-thiophen-2-yl-piperazin-1-ylmethyl)-phenyl]-3*H*-benzooxazol-2-one;

193

- 6-{5-[2*S*-(4-fluorophenyl)-4-methylpiperazine-1-ylmethyl]-furan-3-yl}-3H-benzoxazol-2-one;
 6-{5-[2*S*-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-furan-3-yl}-3H-benzooxazol-2-one acetate;
 5 6-{4-fluoro-3-[2*S*-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-phenyl}-3H-benzooxazol-2-one;
 6-{5-[2*S*-(4-fluoro-phenyl)-4-methyl-piperazin-1-ylmethyl]-pyridin-3-yl}-3H-benzooxazol-2-one acetate; and
 5-(3-{[benzyl-(2-dimethylamino-ethyl)-amino]-methyl}-phenyl)-1,3-dihydro-
 10 benzoimidazol-2-one hydrochloride;
 or a pharmaceutically acceptable salt thereof or an optical or stereoisomer thereof.

24. The composition as set forth in claim 19, wherein the compound of formula (I) is selected from the group consisting of:
 15 6-(3-{[benzyl-(2-dimethylamino-ethyl)-amino]-methyl}-phenyl)-3-methyl-1*H*-quinazoline-2,4-dione hydrochloride;
 7-(3-{[benzyl-(2-dimethylamino-ethyl)-amino]-methyl}-phenyl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one hydrochloride; and
 [2-fluoro-5-(1*H*-indol-5-yl)-phenyl]-[2*S*-(4-fluoro-phenyl)-4-methyl-piperazin-1-yl]-
 20 methanone;
 or a pharmaceutically acceptable salt thereof or an optical or stereoisomer thereof.

25. A method of treating a sleep disorder in a patient comprising administering to said patient a therapeutically effective amount of a compound of formula I, including
 25 enantiomers, stereoisomers, and tautomers of said compound and pharmaceutically acceptable salts, solvates or derivatives thereof, optionally in combination with one or more pharmaceutically acceptable carriers, diluents or excipients:



wherein:

- 30 $X \equiv Y$ denotes either a single or double bond between X and Y;

X is CR, CHR, CO, N, O or S;

Y is CR, CHR, CO, S(O)₂, N or NR;

Z is NR, CO-NR, S(O)₂-NR;

A, B and E are the same or different and independently from each other are CR or N;

5 D is either CH₂ or CO;

Ar is substituted or unsubstituted aryl or heteroaryl;

each R is independently chosen from hydrogen, halogen, CN, C(O)NR₃R₄, C₁₋₄alkyl,

C₁₋₄alkoxy, C₁₋₄alkenyl, aryl, heteroaryl, arylC₁₋₄alkyl, heteroarylC₁₋₄alkyl,

fluoroalkyl or fluoroalkoxy of the formula C_nH_xF_y or OC_nH_xF_y wherein n is an

10 integer from 1 to 4, x is an integer from 0 to 8, y is an integer from 1 to 9 and

sum of x and y is 2n+1; wherein

R₃ and R₄ are hydrogen or C₁₋₄alkyl; or

R₃ and R₄ taken together with the nitrogen atom to which they are attached

form an unsubstituted or at least monosubstituted heterocycle;

15 R₁ and R₂ are the same or different and selected independently of each other from

substituted or unsubstituted aryl, heteroaryl, aryloyl, heteroaryloyl, arylsulfonyl,

heteroarylsulfonyl, arylC₁₋₄alkyl, heteroarylC₁₋₄alkyl, aminoC₁₋₄alkyl,

C₁₋₄alkylaminoC₁₋₄alkyl, C₃₋₈cycloalkylaminoC₁₋₄alkyl,

diC₃₋₈cycloalkylaminoC₁₋₄alkyl, C₃₋₈cycloalkylC₁₋₄alkylaminoC₁₋₄alkyl,

20 diC₁₋₄alkylaminoalkyl, heterocycle, heterocycleC₁₋₄alkyl,

C₁₋₄alkylheterocycleC₁₋₄alkyl; or

R₁ and R₂ taken together with the nitrogen atom to which they are attached form an

unsubstituted or at least monosubstituted heterocycle; and wherein

the substituents are selected from the group consisting of substituted or unsubstituted

25 aryl, heteroaryl, arylC₁₋₄alkyl, heteroarylC₁₋₄alkyl, heterocycle, C₃₋₈cycloalkyl, C₁₋

4alkyl, C₁₋₄alkoxy, C₁₋₄alkenyl, fluoroalkyl or fluoroalkoxy of the formula C_nH_xF_y or

OC_nH_xF_y wherein n is an integer from 1 to 4, x is an integer from 0 to 8, y is an integer

from 1 to 9 and sum of x and y is 2n+1, -NO₂, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂,

-CN, -C(O)R₅, -NHC(O)(C₁₋₄alkyl), -SO₂Cl, -SO₂(C₁₋₄alkyl), halogen and hydroxy;

30 wherein

R₅ is hydroxy, C₁₋₃alkoxy, -O-phenyl, -NH₂, -NH(C₁₋₃alkyl), -N(C₁₋₃alkyl)₂ or phenyl;

- heteroaryl is a 5 to 10-membered, aromatic, mono- or bicyclic heterocycle containing one or more heteroatoms selected from the group consisting of N, O and S; aryl is a 6 to 10-membered, aromatic mono- or bicyclic ring; and heterocycle is a 3 to 10-membered, non-aromatic, mono- or bicyclic heterocycle
- 5 containing one or more heteroatoms selected from the group consisting of N, O and S.
26. The method as set forth in claim 25, wherein the compound of formula (I) is having: D is CH₂;
- 10 Ar is substituted or unsubstituted phenyl, pyridinyl, pyrazinyl, furanyl or thiophenyl; wherein the substituents are selected from the group consisting of fluorine, chlorine, C₁₋₄alkyl, C₁₋₄alkoxy and -CF₃;
- each R is independently chosen from hydrogen, CN or C₁₋₄alkyl;
- R₁ and R₂ are the same or different and selected independently of each other from
- 15 substituted or unsubstituted benzoyl, thiophenylcarbonyl, pyridinylcarbonyl, pyrazinylcarbonyl, pyrimidinylcarbonyl, pyridazinylcarbonyl, dihydrobenzo[1,4]dioxinylcarbonyl, benzo[1,3]dioxolylcarbonyl, phenylC₀₋₄alkyl, thiophenylC₁₋₄alkyl, aza-bicyclo[2.2.2]octylC₀₋₄alkyl, aza-bicyclo[3.2.1]octylC₀₋₄alkyl, piperidinylC₀₋₄alkyl, pyrrolidinylC₀₋₄alkyl,
- 20 C₁₋₄alkylaminoC₁₋₄alkyl and diC₁₋₄alkylaminoC₁₋₄alkyl; wherein the substituted moieties may be substituted with one or more substituents selected from the group consisting of fluorine, chlorine, C₁₋₄alkyl, C₃₋₈cycloalkyl, C₁₋₄alkoxy, OCF₃ and CF₃; or
- R₁ and R₂ taken together with the nitrogen atom to which they are attached form a
- 25 unsubstituted or at least monosubstituted heterocycle selected from the group consisting of piperazine and diazepane; wherein the substituents are selected from the group consisting of phenyl, fluorophenyl, trifluoromethylphenyl, pyridinyl, thiophenyl, furanyl and C₁₋₄alkyl.
- 30 27. The method as set forth in claim 25, wherein the sleep disorder is insomnia.
28. The method as set forth in claim 25, wherein the sleep disorder is primary insomnia.

29. The method as set forth in claim 25, wherein the sleep disorder is a sleep disorder related to another mental disorder.
- 5 30. The method as set forth in claim 25, wherein the sleep disorder is a substance induced sleep disorder.
31. The method as set forth in claim 25, wherein the sleep disorder is an obstructive sleep apnea.

10

COMPUESTOS DE HETEROARILO Y BIS ARILO SUSTITUIDOS COMO
ANTAGONISTAS 5HT_{2A} SELECTIVOS

ANTECEDENTES DE LA INVENCION

5

Campo de la Invención

La presente invención se relaciona con una serie de compuestos de heteroarilo y bis arilo sustituidos como se describe aquí. Más específicamente, la presente invención se relaciona con una serie de derivados de heteroarilo y bis arilo sustituidos de dialquilamino, piperidinilo o piperazinilo. Esta invención también se relaciona con métodos para elaborar estos compuestos. Los compuestos de esta invención son antagonistas 5HT_{2A}, de serotonina selectivos y son, por lo tanto, útiles como agentes farmacéuticos, especialmente en el tratamiento y/o prevención de una variedad de enfermedades que incluyen enfermedades asociadas con el sistema nervioso central. Más específicamente, los compuestos de esta invención son útiles en el tratamiento de una variedad de trastornos del sueño.

20 **Descripción de la Técnica**

El insomnio crónico entre adultos en los Estados Unidos se ha estimado que está presente en el diez por ciento de la población adulta, y el costo anual para este tratamiento se estima en \$10.9 billones. *JAMA* 1997; 278: 2170-2177 a 2170. Los insomnes crónicos reportan niveles elevados de estrés, ansiedad, depresión y enfermedades. La clase más común de medicamentos para tratar el insomnio son las benzodiazepinas, pero el perfil de efecto adverso de las

benzodiazepinas incluye sedación diurna, coordinación motriz disminuida, y deterioros cognitivos. Adicionalmente, la conferencia "National Institutes of Health Consensus" sobre Pastillas para Dormir e Insomnio en 1984 han desarrollado directrices que se desalientan el uso de tales hipnóticos-sedantes más allá de 4-6
5 semanas debido a preocupaciones surgidas por el mal uso de la droga, dependencia, retiro y regreso de insomnio. *JAMA* 1997; 278: 2170-2177 en 2170. Por lo tanto, es deseable tener un agente farmacológico para el tratamiento del insomnio que sea más efectivo y/o tenga menos efectos colaterales que aquellos actualmente utilizados.

10

La prevalencia de la apnea obstructiva del sueño se estima que es aproximadamente 1-10% en la población adulta, pero puede ser mayor en individuos ancianos; *Diagnostic and Statistical Manual of Mental Disorders 4th ed.*, American Psychiatric Association, Washington D. C. (1994). La evidencia
15 preliminar sugiere que tener apnea obstructiva del sueño puede contribuir a incrementar la susceptibilidad a complicaciones cardiovasculares tales como hipertensión, arritmias cardíacas, apoplejía e infarto del miocardio. El excesivo sueño durante el día también es una complicación mayor.

20

Actualmente, las terapias suelen tratar la apnea obstructiva del sueño que incluye pérdida de peso para pacientes obesos, Presión de las Vías Aéreas positivas Nasales-continuas (una máscara utilizada en la noche que produce una presión positiva dentro de la vía aérea superior), cirugía faríngea y la administración de una variedad de agentes farmacológicos que no se han probado
25 que sean completamente exitosos. *Chest* 109 (5): 1346-1358 (Mayo 1996) titulado *Treatment of Obstructive Sleep Apnea, a Review*, incorporada aquí como referencia. Estos agentes incluyen Acetazolamida, Medroxiprogesterona,

Antagonistas Opioides, Nicotina, Agentes Psicotrópicos e Inhibidores de Enzima de Conversión de Angiotensina (que incluyen aquellas que evitan la retoma de aminas biogénicas tal como norepinefrina, dopamina y serotonina). *Id.* At 1353. Muchos de estos agentes farmacológicos utilizados también tienen acción

5 depresora ventilatoria (tal como las benzodiazepinas) u otros efectos colaterales tal como disuria inicial y/o impotencia en hombres (Protriptilina) de tal forma que un nuevo agente con menores efectos colaterales se necesita para el tratamiento del apnea obstructiva del sueño. Aunque la serotonina es un agente que induce el

10 sueño y puede ser un estimulador ventilatorio (*Id.* At 1354), los antagonistas del receptor 5HT_{2A} se han encontrado que son útiles en el tratamiento del apnea obstructiva del sueño. Ver también *Am. J. Respir Crit Care Med* (153) pp 776-786 (1996) en donde los antagonistas de serotonina exacerban el apnea del sueño producida en bulldogs Ingleses. Pero comparar, *Journal of Physiology* (466) pp 367-382 (1993), en donde se postula que un exceso de serotonina se debe a la

15 disfunción de los mecanismos de biosíntesis de la serotonina que puede establecer condiciones que favorecen las apneas obstructivas; *European Journal of Pharmacology* (259):71-74 (1994) trabajo adicional en modelo de ratones con antagonistas 5HT₂.

20 La EP 1 262 197 describe un método para tratar trastornos del sueño que incluyen apnea del sueño al administrar a un paciente en necesidad de tal tratamiento un antagonista 5HT_{1A} o un antagonista alfa-2-adrenérgico en combinación con un antidepresivo tal como inhibidor de retoma de serotonina (SRI). Tal una combinación exhibe una mejora en la eficacia.

25 La Patente Estadounidense 6,143,792 describe que un antagonista del receptor 5HT_{2A} específico es útil en el tratamiento del síndrome de apnea del

sueño. De forma similar, la Patente Estadounidense 6,576,670 describe que un antagonista del receptor $5HT_{2A/C}$ y $5HT_{2A}$ específico son útiles en el tratamiento de ronquido y síndrome de alta resistencia de las vías aéreas superiores.

5 La Patente Estadounidense 6,277,864 describe que un antagonista del receptor $5HT_{2A}$ específico es útil en el tratamiento de una variedad de trastornos del sueño.

Todas las referencias descritas aquí se incorporan aquí como referencia en
10 su totalidad.

Sin embargo, subsiste la necesidad para desarrollar un compuesto que no solo exhiba la actividad antagonista $5HT_{2A}$ selectiva sino que también exhiba propiedades seguras mejoradas con ninguno o mínimos efectos colaterales.

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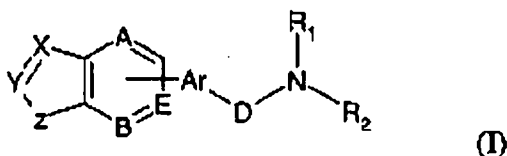
De acuerdo con esto, es un objeto de esta invención suministrar una serie de derivados de heteroarilo y bis arilo sustituidos de dialquilamino, piperidinilo o piperazinilo que son potentes, antagonistas $5HT_{2A}$ selectivos de serotonina,

20 Es también un objeto de esta invención suministrar procesos para la preparación de los derivados heteroarilo y bis arilo sustituidos de dialquilamino, piperidinilo o piperazinilo de como se describe aquí.

Otros objetos y alcances adicionales de la aplicabilidad de la presente
25 invención serán evidentes a partir de la descripción detallada que sigue.

RESUMEN DE LA INVENCION

Así de acuerdo con esta invención se suministra aquí un compuesto, que incluye enantiómeros, estereoisómeros, y tautómeros de dicho compuesto y sales farmacéuticamente aceptables, solvatos o derivados de este, con dicho compuesto que tiene la estructura general mostrada en la fórmula I:



en donde:

10 $X \text{ --- } Y$ denota un enlace doble o sencillo entre X y Y;

X es CR, CHR, CO, N, O o S;

Y es CR, CHR, CO, S(O)₂, N o NR;

Z es NR, CO-NR, S(O)₂-NR;

15 A, B y E son los mismos o diferentes e independientemente uno del otro son CR o N;

D es CH₂ o CO;

Ar es arilo o heteroarilo sustituido o no sustituido;

20 cada R se escoge independientemente de hidrógeno, halógeno, CN, C(O)NR₃R₄, alquilo C₁₋₄, alcoxi C₁₋₄, alquenilo C₁₋₄, arilo, heteroarilo, arilalquilo C₁₋₄, heteroarilalquilo C₁₋₄, fluoroalquilo o fluoroalcoxi de la fórmula C_nH_xF_y o OC_nH_xF_y en donde n es un entero entre 1 a 4, x es un entero entre 0 a 8, y es un entero entre 1 a 9 y la suma de x y y es 2n+1; en donde

R₃ y R₄ son hidrógeno o alquilo C₁₋₄; o

25 R₃ y R₄ tomados junto con el átomo de nitrógeno al cual ellos están adheridos forman un heterociclo no sustituido o al menos monosustituido;

R_1 y R_2 son los mismos o diferentes y se seleccionan independientemente uno del otro de arilo sustituido o no sustituido, heteroarilo, ariloilo, heteroariloilo, arilsulfonilo, heteroarilsulfonilo, arilalquilo C_{1-4} , heteroarilalquilo C_{1-4} , aminoalquilo C_{1-4} , alquilo C_{1-4} aminoalquilo C_{1-4} , cicloalquilo C_{3-8} aminoalquilo C_{1-4} , dicicloalquilo C_{3-8} aminoalquilo C_{1-4} , cicloalquilo C_{3-8} alquilo C_{1-4} aminoalquilo C_{1-4} , dialquilamino C_{1-4} alquilo, heterociclo, heterocicloalquilo C_{1-4} , alquilo C_{1-4} heterociclo C_{1-4} ; o

R_1 y R_2 tomados junto con el átomo de nitrógeno al cual ellos están adheridos forman un heterociclo no sustituido o al menos monosustituido; y en donde los sustituyentes se seleccionan del grupo que consiste de arilo sustituido o no sustituido, heteroarilo, arilalquilo C_{1-4} , heteroarilalquilo C_{1-4} , heterociclo, cicloalquilo C_{3-8} , alquilo C_{1-4} , alcoxi C_{1-4} , alquenilo C_{1-4} , fluoroalquilo o fluoroalcoxi de la fórmula $C_nH_xF_y$ o $OC_nH_xF_y$ en donde n es un entero entre 1 a 4, x es un entero entre 0 a 8, y es un entero entre 1 a 9 y la suma de x y y es $2n+1$, $-NO_2$, $-NH_2$, $-NH$ (alquilo C_{1-4}), $-N$ (alquilo C_{1-4}) $_2$, $-CN$, $-C(O)R_5$, $-NHC(O)$ (alquilo C_{1-4}), $-SO_2Cl$, $-SO_2$ (alquilo C_{1-4}), halógeno y hidroxí; en donde

R_5 es hidroxí, alcoxi C_{1-3} , $-O$ -fenilo, $-NH_2$, $-NH$ (alquilo C_{1-3}), $-N$ (alquilo C_{1-3}) $_2$ o fenilo; heteroarilo es un heterociclo aromático, mono- o bicíclico de 5 a 10 miembros que contiene uno o más heteroátomos seleccionados del grupo que consiste de N, O y S;

arilo es un anillo aromático, mono- o bicíclico de 6 a 10 miembros; y

heterociclo es un heterociclo no aromático, mono- o bicíclico de 3 a 10 miembros que contiene uno o más heteroátomos seleccionados del grupo que consiste de N, O y S.

Los compuestos de esta invención se pueden formular dentro de composiciones farmacéuticas y son útiles en el tratamiento de una variedad de estados de enfermedad. Especialmente, los compuestos de esta invención son antagonistas 5HT_{2A} de serotonina selectivos y son, por lo tanto, útiles en el

5 tratamiento de una amplia variedad de enfermedades asociadas con el sistema nervioso central. Más particularmente, los compuestos de esta invención son útiles en el tratamiento de una amplia variedad de trastornos del sueño que incluyen pero no se limitan a insomnio y apnea del sueño obstructiva.

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DESCRIPCIÓN DETALLADA DE LA INVENCION

Los términos como se utilizan aquí tienen los siguientes significados:

Como se utiliza aquí, la expresión "alquilo C₁₋₆" incluye grupos metilo y etilo,

15 y grupos propilo, butilo, pentilo y hexilo de cadena lineal o ramificada. Grupos alquilo particulares son metilo, etilo, n-propilo, isopropilo y terc-butilo. Expresiones derivadas tales como "alcoxi C₁₋₄", "tioalquilo C₁₋₄" "alcoxi alquilo C₁₋₄ 1-4", "hidroxialquilo C₁₋₄", "alquilo C₁₋₄carbonilo", "alcoxi C₁₋₄carbonilalquilo C₁₋₄", "alcoxi C₁₋₄carbonilo", "aminoalquilo C₁₋₄", "alquilamino C₁₋₄", "alquilo C₁₋₄carbamoilalquilo

20 C₁₋₆", "dialquilo C₁₋₄carbamoilalquilo C₁₋₄" "mono- o di-alquilamino alquilo C₁₋₄ C₁₋₄", "aminoalquilo C₁₋₄carbonilo" "difenilalquilo C₁₋₄", "fenilalquilo C₁₋₄", "fenilcarboilalquilo C₁₋₄" y "fenoxialquilo C₁₋₄" se constituyen de acuerdo con esto.

Como se utiliza aquí, la expresión "alquenilo C₂₋₆" incluye etenilo y grupos

25 propenilo, butenilo, pentenilo y hexenilo de cadena lineal o ramificada. En forma similar, la expresión "alquinilo C₂₋₆" incluye etinilo y propinilo, y grupos butinilo, pentinilo y hexinilo de cadena lineal o ramificada.

Como se utiliza aquí la expresión acilo C₁₋₄" tendrán el mismo significado como "alcanoilo C₁₋₆", que también se puede representar estructuralmente como "R-CO-", en donde R es un alquilo C₁₋₃ como se define aquí. Adicionalmente,
5 "alquilcarbonilo C₁₋₃" tendrán el mismo significado como acilo C₁₋₂. Específicamente, "aciloC₁₋₄" significará formilo, acetilo o etanoilo, propanoilo, n-butanoilo, etc. Expresiones derivadas tales como "aciloxiC₁₋₄" y "aciloxialquiloC₁₋₄" se constituyen de acuerdo con esto.

10 Como se utiliza aquí, la expresión "perfluoroalquilo C₁₋₆" significa que todos los átomos de hidrógeno en dicho grupo alquilo se reemplazan con átomos de flúor. Ejemplos ilustrativos incluyen trifluorometilo y pentafluoroetilo, y grupos heptafluoropropilo, nonafluorobutilo, undecafluoropentilo y tridecafluorohexilo de cadena lineal o ramificada. La expresión derivada, "perfluoroalcoxi C₁₋₆", se
15 constituye de acuerdo con esto.

Como se utiliza aquí, la expresión "arilo" significa fenilo o naftilo sustituido o no sustituido. Ejemplos específicos de fenilo o naftilo sustituido incluyen o-, p-, m-tolilo, 1,2-, 1,3-, 1,4-xililo, 1-metilnaftilo, 2-metilnaftilo, etc. "Fenilo sustituido" o
20 "naftilo sustituido" también incluye cualquiera de los posibles sustituyentes como adicionalmente se define aquí o uno conocido en la técnica. La expresión derivada, "arilsulfonilo," se constituye de acuerdo con esto. Ejemplos específicos de arilsulfonilo incluyen bencenosulfonilo, p-toluenosulfonilo, y similares.

25 Como se utiliza aquí, la expresión "arilC₆₋₁₂alquilo C₁₋₄" significa que el arilo C₆₋₁₂ como se define aquí se adhiere adicionalmente a alquilo C₁₋₄ como se define

aquí. Ejemplos representativos incluyen bencilo, feniletilo, 2-fenilpropilo, 1-naftilmetilo, 2-naftilmetilo y similares.

Como se utiliza aquí, la expresión "heteroarilo" incluye todos los
5 heteroátomos conocidos que contienen radicales aromáticos. Radicales
heteroarilo de 5 miembros representativos incluyen furanilo, tienilo o tiofenilo,
pirrolilo, isopirrolilo, pirazolilo, imidazolilo, oxazolilo, tiazolilo, isotiazolilo, y
similares. Radicales heteroarilo de 6 miembros representativos incluyen piridinilo,
piridazinilo, pirimidinilo, pirazinilo, triazinilo, y radicales similares. Ejemplos
10 representativos de radicales heteroarilo bicíclicos incluyen, benzofuranilo,
benzotiofenilo, indolilo, quinolinilo, isoquinolinilo, bencimidazolilo, indazolilo,
piridofuranilo, piridotienilo, y radicales similares.

En forma similar, la expresión "heteroarilalquilo C₁₋₄" significa que el
15 heteroarilo como se define aquí se adhiere adicionalmente a alquilo C₁₋₄ como se
define aquí. Ejemplos representativos incluyen furanilmetilo, tieniletilo, 2-
(tiofenil)propilo, pirrolilmetilo, isopirroliletilo, pirazolilmetilo, imidazolilmetilo, y
similares.

20 Como se utiliza aquí, la expresión "heterociclo" incluye todos los radicales
cíclicos que contienen heteroátomos reducidos conocidos. Los radicales
heterociclo de 5 miembros representativos incluyen tetrahydrofuranilo,
tetrahydrotiofenilo, pirrolidinilo, 2-tiazolinilo, tetrahydrotiazolilo, tetrahydrooxazolilo, y
similares. Radicales heterociclo de 6 miembros representativos incluyen
25 piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, y similares. Otros varios
radicales heterociclo incluyen, sin limitación, aziridinilo, azepanilo, diazepanilo,
diazabicyclo[2.2.1]hept-2-ilo, y triazocanilo, y similares. La expresión derivada

206

"heterocicloalquilo C₁₋₄" se constituye de acuerdo con esto. Ejemplos específicos de heterocicloalquilo C₁₋₄ incluyen sin ninguna limitación los siguientes: N-pirrolidinilmetilo, N-pirrolidiniletilo, pirrolidinil-2-metilo, 2-pirrolidinil-2-etilo, y similares. En forma similar, la expresión "alquilo C₁₋₄heterocicloalquilo C₁₋₄" debe
5 ser constituida de acuerdo con esto. Ejemplos representativos incluyen sin ninguna limitación los siguientes: N-etilpirrolidinil-N'-metilo, 2-etil-N-pirrolidiniletilo, N-etil-pirrolidinil-2-metilo, 2-pirrolidiniletil-2-etilo, y similares.

"Halógeno" o "halo" significa cloro, flúor, bromo, y yodo.

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Como se utiliza aquí, "paciente" significa un animal de sangre caliente, tal como, por ejemplo ratas, ratones, perros, gatos, conejillos de indias, y primates tal como humanos.

15 Como se utiliza aquí, la expresión "portador farmacéuticamente aceptable" significa un disolvente no tóxico, dispersante, excipiente, adyuvante, u otro material que se mezcle con el compuesto de la presente invención con el fin de permitir la formación de una composición farmacéutica, es decir, una forma de dosis capaz de administración al paciente. Un ejemplo de tal un portador es aceite
20 aceptable farmacéuticamente típicamente utilizado para administración parenteral.

El término "sales farmacéuticamente aceptables" como se utiliza aquí significa que las sales de los compuestos de la presente invención se pueden utilizar en preparaciones medicinales. Otras sales pueden, sin embargo, ser útiles
25 en la preparación de los compuestos de acuerdo con la invención o de sus sales farmacéuticamente aceptables. Sales farmacéuticamente aceptables adecuadas de los compuestos de esta invención incluyen sales de adición de ácido que

207

pueden, por ejemplo, ser formadas al mezclar una solución del compuesto de acuerdo con la invención con una solución de un ácido farmacéuticamente aceptable tal como ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido metanosulfónico, ácido 2-hidroxietanosulfónico, ácido p-toluenosulfónico, ácido 5 fumárico, ácido maleico, ácido hidroximaleico, ácido málico, ácido ascórbico, ácido succínico, ácido glutárico, ácido acético, ácido salicílico, ácido cinámico, ácido 2-fenoxibenzoico, ácido hidroxibenzoico, ácido fenilacético, ácido benzoico, ácido oxálico, ácido cítrico, ácido tartárico, ácido glicólico, ácido láctico, ácido pirúvico, ácido malónico, ácido carbónico o ácido fosfórico. También se pueden formar las 10 sales de metal ácido tales como ortofosfato monohidrogen de sodio e hidrogen sulfato de potasio. También, las sales formadas se pueden presentar como sales mono- o di- ácidas y pueden existir sustancialmente anhidras o pueden ser hidratadas. Adicionalmente, cuando los compuestos de la invención llevan una porción ácida, las sales farmacéuticamente aceptables adecuadas de estas 15 pueden incluir sales de metal álcali, por ejemplo sales de sodio y potasio; sales de metal alcalinotérreo, por ejemplo sales de calcio y magnesio, y sales formadas con ligandos orgánicos, por ejemplo sales de amonio cuaternario.

La expresión "estereoisómeros" es un término general utilizado para todos 20 los isómeros de las moléculas individuales que difieren solo en la orientación de sus átomos en el espacio. Típicamente esto incluye isómeros de reflejo de espejo que usualmente se forman debido al menos a un centro asimétrico, (enantiómeros). En donde los compuestos de acuerdo con la invención poseen dos o más centros asimétricos, ellos pueden adicionalmente existir como 25 diaestereoisómeros, también ciertas moléculas individuales pueden existir como isómeros geométricos (cis/trans). En forma similar, ciertos compuestos de esta invención pueden existir en una mezcla de dos o más formas distintas

208

estructuralmente que están en equilibrio rápido, comúnmente conocidos como tautómeros. Ejemplos representativos de tautómeros incluyen tautómeros ceto-enol, tautómeros fenol-ceto, tautómeros nitroso-oxima, tautómeros imina-enamina, etc. Se entiende que todos los tales isómeros y mezclas de estos en cualquier
5 proporción se abarcan dentro del alcance de la presente invención.

El término "solvato" como se utiliza aquí significa que un agregado que consiste de una molécula o ión soluto con una o más moléculas disolventes. En forma similar, un "hidrato" significa un ión soluto o molécula con una o más
10 moléculas de agua.

En un sentido más amplio, el término "sustituido" se contempla que incluyen todos los sustituyentes permisibles de compuestos orgánicos. En algunas de las modalidades específicas como se describe aquí, el término "sustituido" significa
15 sustituido con uno o más sustituyentes independientemente seleccionados del grupo que consiste de alquilo C₁₋₆, alquenilo C₂₋₆, perfluoroalquilo C₁₋₆, fenilo, hidroxilo, -CO₂H, un éster, una amida, alcoxi C₁₋₆, tioalquilo C₁₋₆, perfluoroalcoxi C₁₋₆, -NH₂, Cl, Br, I, F, -NH-alquilo inferior, y -N(alquilo inferior)₂. Sin embargo, también se puede utilizar cualquiera de los otros sustituyentes
20 conocidos por un experto en la técnica en estas modalidades.

"Cantidad terapéuticamente efectiva" significa una cantidad del compuesto que es efectiva en tratar la enfermedad, trastorno o condición mencionada. El término "tratar se refiere a:

(i) prevenir una enfermedad, trastorno o condición que ocurre en un paciente que puede estar predispuesto a la enfermedad, trastorno y/o condición, pero que todavía no le ha sido diagnosticada;

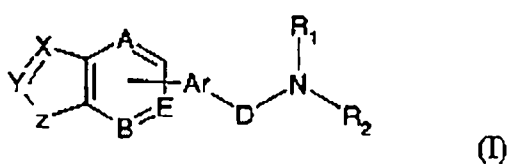
5 (ii) inhibir la enfermedad, trastorno o condición, es decir, detener su desarrollo; y

(iii) aliviar la enfermedad, trastorno o condición, es decir, provocar la regresión de la enfermedad, trastorno y/o condición.

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Así, de acuerdo con la práctica de esta invención se suministra aquí un compuesto que incluye enantiómeros, estereoisómeros, y tautómeros de dicho compuesto y sales farmacéuticamente aceptables, solvatos o derivados de este, a dicho compuesto que tiene la estructura general mostrada en la fórmula I:

15



en donde:

20 $X \text{ --- } Y$ denota un enlace doble o sencillo entre X y Y;

X es CR, CHR, CO, N, O o S;

Y es CR, CHR, CO, S(O)₂, N o NR;

Z es NR, CO-NR, S(O)₂-NR;

A, B y E son los mismos o diferentes e independientemente uno del otro son CR o

25 N;

D es CH₂ o CO;

Ar es arilo o heteroarilo sustituido o no sustituido;

cada R se escoge independientemente de hidrógeno, halógeno, CN, C(O)NR₃R₄,
alquilo C₁₋₄, alcoxi C₁₋₄, alquenilo C₁₋₄, arilo, heteroarilo, arilalquilo C₁₋₄,
heteroarilalquilo C₁₋₄, fluoroalquilo o fluoroalcoxi de la fórmula C_nH_xF_y o
5 OC_nH_xF_y en donde n es un entero entre 1 a 4, x es un entero entre 0 a 8, y
es un entero entre 1 a 9 y la suma de x y y es 2n+1; en donde

R₃ y R₄ son hidrógeno o alquilo C₁₋₄; o

10 R₃ y R₄ tomados junto con el átomo de nitrógeno al cual ellos están adheridos
forman un heterociclo no sustituido o al menos monosustituido;

R₁ y R₂ son los mismos o diferentes y se seleccionan independientemente uno del
otro de arilo sustituido o no sustituido, heteroarilo, ariloilo, heteroariloilo,
15 arilsulfonilo, heteroarilsulfonilo, arilalquilo C₁₋₄, heteroarilalquilo C₁₋₄,
aminoalquilo C₁₋₄, alquilamino C₁₋₄alquilo C₁₋₄, cicloalquilo C₃₋₈aminoalquilo
C₁₋₄, dicicloalquilo C₃₋₈aminoalquilo C₁₋₄, cicloalquilo C₃₋₈alquilamino C₁₋₄,
4alquilo C₁₋₄, dialquilamino alquilo C₁₋₄, heterociclo, heterociclo alquilo C₁₋₄,
heterocicloalquilo C₁₋₄alquilo C₁₋₄; o

20

R₁ y R₂ tomados junto con el átomo de nitrógeno al cual ellos están adheridos
forman un heterociclo no sustituido o al menos monosustituido; y en donde
los sustituyentes se seleccionan del grupo que consiste de arilo sustituido o
no sustituido, heteroarilo, arilalquilo C₁₋₄, heteroariloalquilo C₁₋₄, heterociclo,
25 cicloalquilo C₃₋₈, alquilo C₁₋₄, alcoxi C₁₋₄, alquenilo C₁₋₄, fluoroalquilo o
fluoroalcoxi de la fórmula C_nH_xF_y o OC_nH_xF_y en donde n es un entero entre 1
a 4, x es un entero entre 0 a 8, y es un entero entre 1 a 9 y la suma de x y y

es $2n+1$, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{NH}(\text{alquilo } \text{C}_{1-4})$, $-\text{N}(\text{alquilo } \text{C}_{1-4})_2$, $-\text{CN}$, $-\text{C}(\text{O})\text{R}_5$, $-\text{NHC}(\text{O})(\text{alquilo } \text{C}_{1-4})$, $-\text{SO}_2\text{Cl}$, $-\text{SO}_2(\text{alquilo } \text{C}_{1-4})$, halógeno y hidroxí; en donde

- 5 R_5 es hidroxí, alcoxi C_{1-3} , $-\text{O}$ -fenilo, $-\text{NH}_2$, $-\text{NH}(\text{alquilo } \text{C}_{1-3})$, $-\text{N}(\text{alquilo } \text{C}_{1-3})_2$ o fenilo; heteroarilo es un heterociclo aromático, mono- o bicíclico de 5 a 10 miembros que contiene uno o más heteroátomos seleccionados del grupo que consiste de N, O y S; arilo es un anillo aromático, mono- o bicíclico de 6 a 10 miembros; y heterociclo es un heterociclo no aromático, mono- o
10 bicíclico de 3 a 10 miembros que contiene uno o más heteroátomos seleccionados del grupo que consiste de N, O y S.

En un aspecto de esta invención, los compuestos de fórmula (I) que tienen los siguientes sustituyentes se prefieren:

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D es CH_2 ;

Ar es fenilo sustituido o no sustituido, piridinilo, pirazinilo, furanilo o tiofenilo; en donde los sustituyentes se seleccionan del grupo que consiste de flúor,

20

cloro, alquilo C_{1-4} , alcoxi C_{1-4} y $-\text{CF}_3$;

cada R se escoge independientemente de hidrógeno, CN o alquilo C_{1-4} ;

R_1 y R_2 son los mismos o diferentes y se seleccionan independientemente uno del
25 otro de benzoilo sustituido o no sustituido, tiofenilcarbonilo, piridinilcarbonilo, pirazinilcarbonilo, pirimidinilcarbonilo, piridazinilcarbonilo, dihidro-benzo[1,4]dioxinilcarbonilo, benzo[1,3]dioxolilcarbonilo, fenil C_0 .

alquilo, tiofenilalquilo C₁₋₄, aza-biciclo[2.2.2]octilalquilo C₀₋₄, aza-biciclo[3.2.1]octilalquilo C₀₋₄, piperidinilalquilo C₀₋₄, pirrolidinilalquilo C₀₋₄, aminoalquilo C₁₋₄alquilo C₁₋₄ y diaminoalquilo C₁₋₄alquilo C₁₋₄; en donde las porciones sustituidas se pueden sustituir con uno o más sustituyentes seleccionados del grupo que consiste de flúor, cloro, alquilo C₁₋₄, cicloalquilo C₃₋₈, alcoxi C₁₋₄, OCF₃ y CF₃; o

R₁ y R₂ tomados junto con el átomo de nitrógeno al cual ellos están adheridos forman un heterociclo no sustituido o al menos monosustituido seleccionado del grupo que consiste de piperazina y diazepam; en donde los sustituyentes se seleccionan del grupo que consiste de fenilo, fluorofenilo, trifluorometilfenilo, piridinilo, tiofenilo, furanilo y alquilo C₁₋₄.

En un aspecto adicional de esta invención, se prefieren los compuestos de fórmula (I) que tienen los siguientes sustituyentes:

X = Y denota un enlace doble entre X y Y;

X es CR;

Y es CR;

20 Z es NR;

A, B y E son los mismos o diferentes e independientemente uno del otro son CH o N;

Ar es fenilo, fluorofenilo, clorofenilo, piridinilo, pirazinilo, furanilo o tiofenilo;

cada R se escoge independientemente de hidrógeno, CN, metilo, etilo, metoxi, flúor, CF₃ o OCF₃;

R₁ y R₂ son los mismos o diferentes y se seleccionan independientemente uno del otro de bencilo, fluorobencilo, fluorobenzoilo, clorobenzoilo, isopropoxibenzoilo, trifluorometilbenzoilo, fluoro-trifluorometilbenzoilo, trifluorometoxibenzoilo, tiofenilcarbonilo, piridinilcarbonilo, pirazinilcarbonilo, 5 pirimidinilcarbonilo, piridazinilcarbonilo, dihidro-benzo[1,4]dioxinilcarbonilo, benzo[1,3]dioxolilcarbonilo, aza-biciclo[2.2.2]octilo, aza-biciclo[2.2.2]octilmetilo, N-metil-piperidinilo, pirrolidinilmetilo, pirrolidiniletilo, pirrolidinilpropilo y dimetilaminoetilo; o

- 10 R₁ y R₂ tomados junto con el átomo de nitrógeno al cual ellos están adheridos forman un heterociclo no sustituido o al menos monosustituido seleccionado del grupo que consiste de piperazina y diazepan; en donde los sustituyentes se seleccionan del grupo que consiste de fenilo, fluorofenilo, trifluorometilfenilo, piridinilo, tiofenilo, furanilo y metilo.

15

Ejemplos de los compuestos abarcados dentro de la modalidad anteriormente anotada sin ninguna limitación incluyen los siguientes:

- N-bencil-N-[3-(1H-indol-5-il)-bencil]-N',N'-dimetil-etano-1,2-diamina;
- 20 4-fluoro-N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-benzamida;
- N-(2-dimetilamino-etil)-4-fluoro-N-[2-fluoro-5-(2-metil-1H-indol-5-il)-bencil]-benzamida;
- N-(2-dimetilamino-étil)-4-fluoro-N-[2-fluoro-5-(1H-indol-5-il)-bencil]-
- 25 benzamida;
- 4-fluoro-N-[3-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-benzamida;

[3-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido tiofen-2-carboxílico;

[2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido tiofen-2-carboxílico;

5 (2-dimetilamino-etil)-[2-fluoro-5-(1H-indol-5-il)-bencil]-amida de ácido tiofen-2-carboxílico;

4-fluoro-N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-benzamida;

10 Trifluoro-acetato de N-(1-aza-biciclo[2.2.2]oct-4-ilmetil)-4-fluoro-N-[2-fluoro-5-(1H-indol-5-il)-bencil]-benzamida;

4-fluoro-N-[5-(1H-indol-5-il)-piridin-3-ilmetil]-N-(2-pirrolidin-1-il-etil)-benzamida;

4-fluoro-N-[4-fluoro-3-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-benzamida;

15 Acetato de 4-fluoro-N-[4-(1H-indol-5-il)-tiofen-2-ilmetil]-N-(2-pirrolidin-1-il-etil)-benzamida;

(4-fluoro-bencil)-[2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amina;

20 N-(4-fluoro-bencil)-N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N',N'-dimetil-etano-1,2-diamina;

Acetato de (1-aza-biciclo[2.2.2]oct-4-ilmetil)-(4-fluoro-bencil)-[2-fluoro-5-(1H-indol-5-il)-bencil]-amina;

Trifluoroacetato de N-(2-dimetilamino-etil)-4-fluoro-N-[5-(1H-indol-5-il)-piridin-3-ilmetil]-benzamida;

25 4-fluoro-N-[5-(1H-indol-5-il)-tiofen-2-ilmetil]-N-(2-pirrolidin-1-il-etil)-benzamida;

4-fluoro-N-[4-(1H-indol-5-il)-furan-2-ilmetil]-N-(1-metil-piperidin-4-il)-benzamida;

N-(1-aza-biciclo[2.2.2]oct-3*R*-il)-4-fluoro-N-[2-fluoro-5-(1H-indol-6-il)-bencil]-benzamida;

5 [2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido pirimidina-4-carboxílico;

[2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido pirimidina-2-carboxílico;

10 [2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido piridazina-3-carboxílico;

[2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido piridazina-4-carboxílico;

[2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido 2,3-dihidro-benzo[1,4]dioxina-6-carboxílico;

15 N-[2-fluoro-5-(1H-indol-5-il)-bencil]-4-isopropoxi-N-(1-metil-piperidin-4-il)-benzamida;

N-[2-fluoro-5-(1H-indol-5-il)-bencil]-3-isopropoxi-N-(1-metil-piperidin-4-il)-benzamida;

20 N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-4-trifluorometoxi-benzamida;

4-cloro-N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-benzamida;

[2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido benzo[1,3]dioxol-5-carboxílico;

25 N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-4-trifluorometil-benzamida;

4-fluoro-N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-3-trifluorometil-benzamida;

N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-isonicotinamida;

N-[3-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-4-trifluorometil-benzamida;

4-fluoro-N-[4-fluoro-3-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-benzamida;

N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-4-trifluorometil-benzamida;

4-fluoro-N-[3-fluoro-5-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-benzamida;

N-[3-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-4-trifluorometil-benzamida;

N-[3-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-isonicotinamida;

N-[4-fluoro-3-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-4-trifluorometil-benzamida;

N-[3-(1H-indol-5-il)-bencil]-N-(3-pirrolidin-1-il-propil)-isonicotinamida;

N-[4-fluoro-3-(1H-indol-5-il)-bencil]-N-(3-pirrolidin-1-il-propil)-isonicotinamida;

[3-(1H-indol-5-il)-bencil]-(3-pirrolidin-1-il-propil)-amida de ácido piridin-2-carboxílico;

N-[3-(1H-indol-5-il)-bencil]-N-(3-pirrolidin-1-il-propil)-4-trifluorometil-benzamida;

[4-fluoro-3-(1H-indol-5-il)-bencil]-(3-pirrolidin-1-il-propil)-amida de ácido piridin-2-carboxílico;

[4-(1H-indol-5-il)-tiofen-2-ilmetil]-(3-pirrolidin-1-il-propil)-amida de ácido piridin-2-carboxílico;

N-[4-(1H-indol-5-il)-tiofen-2-ilmetil]-N-(3-pirrolidin-1-il-propil)-4-trifluorometil-benzamida;

N-[4-(1H-indol-5-il)-tiofen-2-ilmetil]-N-(2-pirrolidin-1-il-etil)-isonicotinamida;
[4-(1H-indol-5-il)-tiofen-2-ilmetil]-(2-pirrolidin-1-il-etil)-amida de ácido piridin-2-carboxílico;

N-[4-(1H-indol-5-il)-tiofen-2-ilmetil]-N-(2-pirrolidin-1-il-etil)-4-trifluorometil-benzamida;

[4-(1H-indol-5-il)-furan-2-ilmetil]-(3-pirrolidin-1-il-propil)-amida de ácido piridin-2-carboxílico;

N-[4-(1H-indol-5-il)-furan-2-ilmetil]-N-(3-pirrolidin-1-il-propil)-4-trifluorometil-benzamida;

N-[4-(1H-indol-5-il)-furan-2-ilmetil]-N-(2-pirrolidin-1-il-etil)-isonicotinamida;
[4-(1H-indol-5-il)-furan-2-ilmetil]-(2-pirrolidin-1-il-etil)-amida de ácido piridin-2-carboxílico;

N-[4-(1H-indol-5-il)-furan-2-ilmetil]-N-(2-pirrolidin-1-il-etil)-4-trifluorometil-benzamida;

N-[4-(1H-indol-5-il)-tiofen-2-ilmetil]-N-(3-pirrolidin-1-il-propil)-isonicotinamida;

N-[4-(1H-indol-5-il)-furan-2-ilmetil]-N-(3-pirrolidin-1-il-propil)-isonicotinamida;

N-[2-cloro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-isonicotinamida;

[2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido piridin-2-carboxílico;

N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-nicotinamida;

N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-3-trifluorometoxi-benzamida;

N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-isonicotinamida;

N-[4-fluoro-3-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-isonicotinamida;

Acetato de N-[4-fluoro-3-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-4-trifluorometoxi-benzamida;

N-[3-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-isonicotinamida;

5 [2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido pirazina-2-carboxílico;

Acetato de 5-[4-fluoro-3-(4-metil-2-piridin-3-il-piperazin-1-ilmetil)-fenil]-1H-indol;

5-{4-fluoro-3-[4-metil-2-(4-trifluorometil-fenil)-piperazin-1-ilmetil]-fenil}-1H-indol;

10 Acetato de 5-[4-fluoro-3-(4-metil-2-piridin-2-il-piperazin-1-ilmetil)-fenil]-1H-indol;

Acetato de 5-{5-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-piridin-3-il}-1H-indol;

5-{4-fluoro-3-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-fenil}-1H-indol;

15 5-[4-fluoro-3-(2-furan-2-il-4-metil-piperazin-1-ilmetil)-fenil]-1H-indol;

Trifluoro-acetato de 5-{5-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-furan-3-il}-1H-indol;

Acetato de 5-{5-[2S-(4-fluoro-fenil)-piperazin-1-ilmetil]-piridin-3-il}-1H-indol;

5-{5-[2S-(4-fluoro-fenil)-piperazin-1-ilmetil]-furan-3-il}-1H-indol;

20 5-[3-(4-metil-piperazin-1-ilmetil)-fenil]-1H-indol;

5-[4-fluoro-3-(4-metil-2-piridin-4-il-piperazin-1-ilmetil)-fenil]-1H-indol;

5-{3-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-fenil}-1H-indol;

Acetato de 5-{6-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-pirazin-2-il}-1H-indol;

25 Acetato de 5-{4-fluoro-3-[2S-(4-fluoro-fenil)-piperazin-1-ilmetil]-fenil}-1H-indol;

5-{4-fluoro-3-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-fenil}-1H-indol-3-carbonitrilo;

5-[3-(4-metil-[1,4]diazepan-1-ilmetil)-fenil]-1H-indol;

5-{4-fluoro-3-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-fenil}-3-metil-1H-indol;

N-[5-(3-ciano-1H-indol-5-il)-2-fluoro-bencil]-N-(2-dimetilamino-etil)-4-fluoro-benzamida;

5-{4-fluoro-3-[2S-(4-fluoro-fenil)-piperazin-1-ilmetil]-fenil}-1H-indol-3-carbonitrilo;

10 Trifluoro-acetato de 5-{6-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-pirazin-2-il}-1H-indol;

4-fluoro-N-[2-fluoro-5-(1H-pirrolo[3,2-b]piridin-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-benzamida;

15 5-{4-fluoro-3-[2-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-fenil}-1H-pirrolo[3,2-b]piridina; y

4-fluoro-N-[2-fluoro-5-(1H-pirrolo[2,3-c]piridin-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-benzamida;

o una sal farmacéuticamente aceptable de estos o un óptico o estereoisómero de estos.

20

En aún otra modalidad de esta invención, también se prefieren los compuestos de fórmula (I) que tienen los siguientes sustituyentes:

X — Y denota un enlace doble entre X y Y;

25 X es CR;

Y es N;

Z es NR;

220

A, B y E son CH;

Ar es fenilo, fluorofenilo, clorofenilo, piridinilo, pirazinilo, furanilo o tiofenilo;

cada R se escoge independientemente de hidrógeno, metilo, etilo, metoxi, flúor,

5 CF₃ o OCF₃;

R₁ y R₂ son los mismos o diferentes y se seleccionan independientemente uno del

otro de bencilo, fluorobencilo, fluorobenzoilo, clorobenzoilo,

isopropoxibenzoilo, trifluorometilbenzoilo, fluoro-trifluorometilbenzoilo,

10 trifluorometoxibenzoilo, tiofenilcarbonilo, piridinilcarbonilo, pirazinilcarbonilo,

pirimidinilcarbonilo, piridazinilcarbonilo, dihidro-benzo[1,4]dioxinilcarbonilo,

benzo[1,3]dioxolilcarbonilo, N-metil-aza-biciclo[2.2.2]octilo, aza-

biciclo[2.2.2]octilo, aza-biciclo[2.2.2]octilmetilo, N-metil-piperidinilo,

piperidinilo, N-metil-pirrolidinilo, pirrolidinilmetilo, pirrolidiniletilo,

15 pirrolidinilpropilo, metilaminoetilo, y dimetilaminoetilo; o

R₁ y R₂ tomados junto con el átomo de nitrógeno al cual ellos están adheridos

forman un heterociclo no sustituido o al menos monosustituido seleccionado

del grupo que consiste de piperazina y diazepam; en donde los

20 sustituyentes se seleccionan del grupo que consiste de fenilo, fluorofenilo,

trifluorornetilfenilo, piridinilo, tiofenilo, furanilo y metilo.

Se puede enumerar ejemplos de compuestos dentro del alcance de esta
modalidad sin ninguna limitación como sigue:

25

Clorhidrato de N-bencil-N-[3-(1H-indazol-5-il)-bencil]-N',N'-dimetil-etano-1,2-
diamina;

Acetato de N-(4-fluoro-bencil)-N-[5-(1H-indazol-5-il)-piridin-3-ilmetil]-N',N'-dimetil-etano-1,2-diamina;

(4-fluoro-bencil)-[2-fluoro-5-(1H-indazol-5-il)-bencil]-pirrolidin-2S-ilmetil-amina;

5 (4-fluoro-bencil)-[2-fluoro-5-(1H-indazol-5-il)-bencil]-piperidin-4-il-amina;
N-(4-fluoro-bencil)-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N'-metil-etano-1,2-diamina;

(4-fluoro-bencil)-[2-fluoro-5-(1H-indazol-5-il)-bencil]-(1-metil-piperidin-4-il)-amina;

10 (4-fluoro-bencil)-[4-(1H-indazol-5-il)-furan-2-ilmetil]-(1-metil-piperidin-4-il)-amina;

4-fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-benzamida;

4-fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(exo-8-metil-8-aza-
15 biciclo[3.2.1]oct-3-il)-benzamida;

4-fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(endo-8-metil-8-aza-biciclo[3.2.1] oct-3-il)-benzamida;

4-fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(1-metil-piperidin-3-il)-benzamida;

20 Trifluoro-acetato de 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(1-metil-piperidin-3S-il)-benzamida;

Trifluoro-acetato de 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(1-metil-pirrolidin-3R-il)-benzamida;

Trifluoro-acetato de 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(1-
25 metil-pirrolidin-3S-il)-benzamida;

4-fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(3-pirrolidin-1-il-propil)-benzamida;

4-fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-benzamida;

N-(1-aza-biciclo[2.2.2]oct-3*R*-il)-4-fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-benzamida;

5 N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(1-metil-pirrolidin-3*R*-il)-4-trifluorometil-benzamida quiral;

4-fluoro-N-[4-(1H-indazol-5-il)-furan-2-ilmetil]-N-(1-metil-piperidin-4-il)-benzamida;

5-{4-fluoro-3-[2-(4-fluoro-fenil)-piperazin-1-ilmetil]-fenil}-1H-indazol;

10 Acetato de 5-[4-fluoro-3-(2*S*-tiofen-2-il-piperazin-1-ilmetil)-fenil]-1H-indazol;

5-[4-fluoro-3-(2-tiofen-2-il-piperazin-1-ilmetil)-fenil]-1H-indazol;

Acetato de 5-[4-fluoro-3-(2-tiofen-2-il-piperazin-1-ilmetil)-fenil]-1H-indazol quiral;

5-{4-fluoro-3-[2*S*-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-fenil}-1H-indazol;

15 5-{5-[2*S*-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-piridin-3-il}-1H-indazol;

5-{5-[2*S*-(4-fluoro-fenil)-piperazin-1-ilmetil]-piridin-3-il}-1H-indazol;

5-{5-[2*S*-(4-fluoro-fenil)-piperazin-1-ilmetil]-furan-3-il}-1H-indazol;

Acetato de 5-[4-fluoro-3-(4-metil-2*R*-tiofen-2-il-piperazin-1-ilmetil)-fenil]-1H-indazol;

20 Acetato de 5-[4-fluoro-3-(4-metil-2*S*-tiofen-2-il-piperazin-1-ilmetil)-fenil]-1H-indazol; y

5-{5-[2*S*-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-furan-3-il}-1H-indazol;

o una sal farmacéuticamente aceptable de estos o un óptico o estereoisómero de estos.

25

En otra modalidad de esta invención, los compuestos de fórmula (I) que tienen los siguientes sustituyentes se prefieren:

X = Y denota un enlace doble entre X y Y;

X es N;

Y es CR;

5 Z es NR;

A, B y E son CH;

Ar es fenilo, fluorofenilo, clorofenilo, piridinilo, pirazinilo, furanilo o tiofenilo;

cada R se escoge independientemente de hidrógeno, metilo, etilo, metoxi, CF₃ o

10 OCF₃;

R₁ y R₂ son los mismos o diferentes y se seleccionan independientemente uno del

otro de bencilo, fluorobencilo, fluorobenzoilo, clorobenzoilo,

isopropoxibenzoilo, trifluorometilbenzoilo, fluoro-trifluorometilbenzoilo,

15 trifluorometoxibenzoilo, tiofenilcarbonilo, piridinilcarbonilo, pirazinilcarbonilo,

pirimidinilcarbonilo, piridazinilcarbonilo, dihidro-benzo[1,4]dioxinilcarbonilo,

benzo[1,3]dioxolilcarbonilo, N-metil-aza-biciclo[2.2.2]octilo, aza-

biciclo[2.2.2]octilo, aza-biciclo[2.2.2]octilmetilo, N-metil-piperidinilo,

piperidinilo, N-metil-pirrolidinilo, pirrolidinilmetilo, pirrolidiniletilo,

20 pirrolidinilpropilo, metilaminoetilo, dimetilaminoetilo y dimetilaminopropilo; o

R₁ y R₂ tomados junto con el átomo de nitrógeno al cual ellos están adheridos

forman un heterociclo no sustituido o al menos monosustituido seleccionado

del grupo que consiste de piperazina y diazepan; en donde los

25 sustituyentes se seleccionan del grupo que consiste de fenilo, fluorofenilo,

trifluorometilfenilo, piridinilo, tiofenilo, furanilo y metilo.

Ejemplos específicos de compuestos dentro del alcance de esta modalidad sin ninguna limitación se listan como sigue:

5 Clorhidrato de N-[3-(1H-benzoimidazol-5-il)-bencil]-N-bencil-N',N'-dimetil-etano-1,2-diamina; y

Clorhidrato de N-[3-(1H-benzoimidazol-5-il)-bencil]-N-bencil-N',N'-dimetil-propano-1,3-diamina;

o una sal farmacéuticamente aceptable de estos o un óptico o estereoisómero de estos.

10

En otra modalidad de esta invención el compuesto de fórmula (I) tiene los siguientes sustituyentes:

$X \equiv Y$ denota un enlace doble entre X y Y;

15 X es N;

Y es N;

Z es NR;

A, B y E son CH;

Ar es fenilo, fluorofenilo, clorofenilo, piridinilo, pirazinilo, furanilo o tiofenilo;

20

R es hidrógeno, metilo o etilo;

R₁ y R₂ son los mismos o diferentes y se seleccionan independientemente uno del otro de bencilo, fluorobencilo, fluorobenzoilo, difluorobenzoilo, 25 clorobenzoilo, isopropoxibenzoilo, trifluorometilbenzoilo, fluoro-trifluorometilbenzoilo, trifluorometoxibenzoilo, tiofenilcarbonilo, piridinilcarbonilo, pirazinilcarbonilo, pirimidinilcarbonilo, piridazinilcarbonilo,

225

dihidro-benzo[1,4]dioxinilcarbonilo, benzo[1,3]dioxolilcarbonilo,
tiofenilmetilo, N-metil-aza-biciclo[2.2.2]octilo, aza-biciclo[2.2.2]octilo, aza-
biciclo[2.2.2]octilmetilo, N-metil-piperidinilo, N-isopropil-piperidinilo, N-
ciclopropil-piperidinilo, piperidinilo, N-metil-pirrolidinilo, N-etil-
5 pirrolidinilmetilo, pirrolidinilmetilo, pirrolidiniletilo, pirrolidinilpropilo,
metilaminoetilo, dimetilaminoetilo y dimetilaminopropilo; o

R₁ y R₂ tomados junto con el átomo de nitrógeno al cual ellos están adheridos
forman un heterociclo no sustituido o al menos monosustituido seleccionado
10 del grupo que consiste de piperazina y diazepan; en donde los
sustituyentes se seleccionan del grupo que consiste de fenilo, fluorofenilo,
trifluorometilfenilo, piridinilo, tiofenilo, furanilo y metilo.

Ejemplos de compuestos de fórmula (I) que caen dentro del alcance de la
15 modalidad anteriormente anotada incluyen sin ninguna limitación los siguientes:

N-[3-(1H-benzotriazol-5-il)-bencil]-N-bencil-N',N'-dimetil-propano-1,3-
diamina;

Triclorhidrato de [5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-(4-fluoro-bencil)-
20 pirrolidin-2R-ilmetil-amina;

[5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-piperidin-4-il-tiofen-2-ilmetil-amina;

[5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-(4-fluoro-bencil)-piperidin-4-il-
amina;

N-[5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-N-(4-fluoro-bencil)-N'-metil-etano-
25 1,2-diamina;

Clorhidrato de [5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-(1-etil-pirrolidin-2S-
ilmetil)-(4-fluoro-bencil)-amina;

Clorhidrato de [5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-(4-fluoro-bencil)-(1-metil-piperidin-4-il)-amina;

Clorhidrato de N-[3-(1H-benzotriazol-5-il)-bencil]-N-bencil-N',N'-dimetil-etano-1,2-diamina;

5 N-[5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-N-(1-etil-pirrolidin-2S-ilmetil)-4-fluoro-benzamida;

Clorhidrato de N-[3-(1H-benzotriazol-5-il)-bencil]-4-fluoro-N-(2-pirrolidin-1-il-etil)-benzamida;

10 Clorhidrato de [5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-(2-pirrolidin-1-il-etil)-amida de ácido tiofen-2-carboxílico;

Clorhidrato de N-[5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-2,4-difluoro-N-(2-pirrolidin-1-il-etil)-benzamida;

N-[5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-4-fluoro-N-(2-pirrolidin-1-il-etil)-benzamida;

15 N-[5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-4-fluoro-N-piperidin-4-il-benzamida;

N-[5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-4-fluoro-N-(1-isopropil-piperidin-4-il)-benzamida;

20 N-[5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-N-(1-ciclopropil-piperidin-4-il)-4-fluoro-benzamida;

N-[5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-N-(1-metil-piperidin-4-il)-4-fluoro-benzamida;

5-[3-(4-metil-piperazin-1-ilmetil)-fenil]-1H-benzotriazol;

5-[4-fluoro-3-(4-metil-piperazin-1-ilmetil)-fenil]-1H-benzotriazol; y

25 5-{4-fluoro-3-[2S-(4-fluoro-fenil)-piperazin-1-ilmetil]-fenil}-1H-benzotriazol;

o una sal farmacéuticamente aceptable de estos o un óptico o estereoisómero de estos.

227

En aún otra modalidad de esta invención el compuesto de fórmula (I) tiene los siguientes sustituyentes:

5 X — Y denota un enlace sencillo entre X y Y;

X es CHR;

Y es CHR;

Z es NR;

A, B y E son CH;

10 Ar es fenilo, fluorofenilo, clorofenilo, piridinilo, pirazinilo, furanilo o tiofenilo;

cada R se escoge independientemente de hidrógeno, metilo, etilo o CF₃;

R₁ y R₂ son los mismos o diferentes y se seleccionan independientemente uno del

15 otro de bencilo, fluorobencilo, fluorobenzoilo, difluorobenzoilo, clorobenzoilo, isopropoxibenzoilo, trifluorometilbenzoilo, fluoro-trifluorometilbenzoilo, trifluorometoxibenzoilo, tiofenilcarbonilo, piridinilcarbonilo, pirazinilcarbonilo, pirimidinilcarbonilo, piridazinilcarbonilo, dihidro-benzo[1,4]dioxinilcarbonilo, benzo[1,3]dioxolilcarbonilo, 20 tiofenilmetilo, N-metil-aza-biciclo[2.2.2]octilo, aza-biciclo[2.2.2]octilo, aza-biciclo[2.2.2]octilmetilo, N-metil-piperidinilo, N-isopropil-piperidinilo, N-ciclopropil-piperidinilo, piperidinilo, N-metil-pirrolidinilo, N-etil-pirrolidinilmetilo, pirrolidinilmetilo, pirrolidiniletilo, pirrolidinilpropilo, metilaminoetilo, dimetilaminoetilo y dimetilaminopropilo; o

25

R₁ y R₂ tomados junto con el átomo de nitrógeno al cual ellos están adheridos forman un heterociclo no sustituido o al menos monosustituido seleccionado

del grupo que consiste de piperazina y diazepam; en donde los sustituyentes se seleccionan del grupo que consiste de fenilo, fluorofenilo, trifluorometilfenilo, piridinilo, tiofenilo, furanilo y metilo.

- 5 Un ejemplo de un compuesto de fórmula (I) que cae dentro del alcance de la modalidad anteriormente anotada incluye sin ninguna limitación los siguientes:

N-[5-(2,3-dihidro-1H-indol-5-il)-2-fluoro-bencil]-N-(2-dimetilamino-etil)-4-fluoro-benzamida;

- 10 o una sal farmacéuticamente aceptable de estos o un óptico o estereoisómero de estos.

En aún otra modalidad de esta invención el compuesto de fórmula (I) tiene los siguientes sustituyentes:

15

X — Y denota un enlace sencillo entre X y Y;

X es O, S o NR;

Y es CO;

Z es NR;

- 20 A, B y E son CH;

Ar es fenilo, fluorofenilo, clorofenilo, piridinilo, pirazinilo, furanilo o tiofenilo;

cada R se escoge independientemente de hidrógeno, metilo o etilo;

- 25 R₁ y R₂ son los mismos o diferentes y se seleccionan independientemente uno del otro de bencilo, fluorobencilo, benzoilo, fluorobenzoilo, difluorobenzoilo, clorobenzoilo, isopropoxibenzoilo, trifluorometilbenzoilo, fluoro-

trifluorometilbenzoilo, trifluorometoxibenzoilo, tiofenilcarbonilo,
piridinilcarbonilo, pirazinilcarbonilo, pirimidinilcarbonilo, piridazinilcarbonilo,
dihidro-benzo[1,4]dioxinilcarbonilo, benzo[1,3]dioxolilcarbonilo,
tiofenilmetilo, N-metil-aza-biciclo[2.2.2]octilo, aza-biciclo[2.2.2]octilo, aza-
5 biciclo[2.2.2]octilmetilo, N-metil-piperidinilo, N-isopropil-piperidinilo, N-
ciclopropil-piperidinilo, piperidinilo, N-metil-pirrolidinilo, N-etil-
pirrolidinilmetilo, pirrolidinilmetilo, pirrolidiniletilo, pirrolidinilpropilo,
metilaminoetilo, dimetilaminoetilo y dimetilaminopropilo; o

- 10 R₁ y R₂ tomados junto con el átomo de nitrógeno al cual ellos están adheridos
forman un heterociclo no sustituido o al menos monosustituido seleccionado
del grupo que consiste de piperazina y diazepan; en donde los
sustituyentes se seleccionan del grupo que consiste de fenilo, fluorofenilo,
trifluorometilfenilo, piridinilo, tiofenilo, furanilo y metilo.

15

Ejemplos de compuestos de fórmula (I) que caen dentro del alcance de la
modalidad anteriormente anotada incluyen sin ninguna limitación los siguientes:

20 Clorhidrato de 6-(3-[[bencil-(2-dimetilamino-etil)-amino]-metil]-fenil)-3H-
benzotiazol-2-ona;

Clorhidrato de N-(2-dimetilamino-etil)-N-[3-(2-oxo-2,3-dihidro-benzotiazol-6-
il)-bencil]-benzamida;

Clorhidrato de 4-cloro-N-(2-dimetilamino-etil)-N-[3-(2-oxo-2,3-dihidro-
benzotiazol-6-il)-bencil]-benzamida;

25 N-(3-dimetilamino-propil)-N-[3-(2-oxo-2,3-dihidro-benzotiazol-6-il)-bencil]-
benzamida; clorhidrato;

Clorhidrato de 6-(3-[[bencil-(2-dimetilamino-etil)-amino]-metil]-fenil)-3H-benzooxazol-2-ona;

6-(5-[[2-dimetilamino-etil)-(4-fluoro-bencil)-amino]-metil]-piridin-3-il)-3H-benzooxazol-2-ona;

5 6-(5-[[2-dimetilamino-etil)-(4-fluoro-bencil)-amino]-metil]-furan-3-il)-3H-benzooxazol-2-ona;

Trifluoro-acetato de 6-(3-[[1-etil-pirrolidin-2R-ilmetil)-(4-fluoro-bencil)-amino]-metil]-4-fluoro-fenil)-3H-benzooxazol-2-ona;

10 6-(4-fluoro-3-[[4-fluoro-bencil)-(1-metil-piperidin-4-il)-amino]-metil]-fenil)-3H-benzooxazol-2-ona;

6-(5-[[4-fluoro-bencil)-(1-metil-piperidin-4-il)-amino]-metil]-furan-3-il)-3H-benzooxazol-2-ona;

4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-N-(2-pirrolidin-1-il-etil)-benzamida;

15 Clorhidrato de N-(2-dimetilamino-etil)-N-[3-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-benzamida;

N-(1-etil-pirrolidin-2-ilmetil)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-benzamida;

20 Clorhidrato de 4-cloro-N-(2-dimetilamino-etil)-N-[3-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-benzamida;

Trifluoro-cetato de N-(1-etil-pirrolidin-2R-ilmetil)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-benzamida;

4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-N-(1-metil-piperidin-4-il)-benzamida;

25 Clorhidrato de N-(1-aza-biciclo[2.2.2]oct-3S-il)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-benzamida;

Clorhidrato de N-(1-aza-biciclo[2.2.2]oct-3*R*-il)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-benzamida;

N-(2-dimetilamino-etil)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-benzamida;

5 6-[3-(4-metil-piperazin-1-ilmetil)-fenil]-3H-benzooxazol-2-ona;

6-{5-[2*R*-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-furan-3-il}-3H-benzooxazol-2-ona;

6-{5-[2*S*-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-furan-2-il}-3H-benzooxazol-2-ona;

10 6-{5-[2*S*-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-tiofen-3-il}-3H-benzooxazol-2-ona;

6-[4-fluoro-3-(2-tiofen-2-il-piperazin-1-ilmetil)-fenil]-3H-benzooxazol-2-ona;

6-{5-[2*S*-(4-fluorofenil)-4-metilpiperazina-1-ilmetil]-furan-3-il}-3H-benzoxazol-2-ona;

15 Acetato de 6-{5-[2*S*-(4-fluoro-fenil)-piperazin-1-ilmetil]-furan-3-il}-3H-benzooxazol-2-ona;

6-{4-fluoro-3-[2*S*-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-fenil}-3H-benzooxazol-2-ona;

20 Acetato de 6-{5-[2*S*-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-piridin-3-il}-3H-benzooxazol-2-ona; y

Clorhidrato de 5-(3-[[bencil-(2-dimetilamino-etil)-amino]-metil]-fenil)-1,3-dihidro-benzoimidazol-2-ona;

o una sal farmacéuticamente aceptable de estos o un óptico o estereoisómero de estos.

25

En aún otra modalidad de esta invención el compuesto de fórmula (I) tiene los siguientes sustituyentes:

$X \text{ --- } Y$ denota un enlace sencillo entre X y Y;

X es O o CO;

Y es CHR o NR;

5 Z es CONR;

A, B y E son los mismos o diferentes e independientemente uno del otro son CH o N;

Ar es fenilo, fluorofenilo, clorofenilo, piridinilo, pirazinilo, furanilo o tiofenilo;

10

cada R se escoge independientemente de hidrógeno, metilo o etilo;

R₁ y R₂ son los mismos o diferentes y se seleccionan independientemente uno del otro de bencilo, fluorobencilo, benzoilo, fluorobenzoilo, difluorobenzoilo, clorobenzoilo, isopropoxibenzoilo, trifluorometilbenzoilo, fluoro-
15 trifluorometilbenzoilo, trifluorometoxibenzoilo, tiofenilcarbonilo, piridinilcarbonilo, pirazinilcarbonilo, pirimidinilcarbonilo, piridazinilcarbonilo, dihidro-benzo[1,4]dioxinilcarbonilo, benzo[1,3]dioxolilcarbonilo, tiofenilmetilo, N-metil-aza-biciclo[2.2.2]octilo, aza-biciclo[2.2.2]octilo, aza-
20 biciclo[2.2.2]octilmetilo, N-metil-piperidinilo, N-isopropil-piperidinilo, N-ciclopropil-piperidinilo, piperidinilo, N-metil-pirrolidinilo, N-etil-pirrolidinilmetilo, pirrolidinilmetilo, pirrolidiniletilo, pirrolidinilpropilo, metilaminoetilo, dimetilaminoetilo y dimetilaminopropilo; o

25 R₁ y R₂ tomados junto con el átomo de nitrógeno al cual ellos están adheridos forman un heterociclo no sustituido o al menos monosustituido seleccionado del grupo que consiste de piperazina y diazepam; en donde los

sustituyentes se seleccionan del grupo que consiste de fenilo, fluorofenilo, trifluorometilfenilo, piridinilo, tiofenilo, furanilo y metilo.

Ejemplos de compuestos de fórmula (I) que caen dentro del alcance de la
5 modalidad anteriormente anotada incluyen sin ninguna limitación los siguientes:

Clorhidrato de 6-(3-{{bencil-(2-dimetilamino-etil)-amino}-metil}-fenil)-3-metil-1H-quinazolina-2,4-diona; y

Clorhidrato de 7-(3-{{bencil-(2-dimetilamino-etil)-amino}-metil}-fenil)-4H-
10 pirido[3,2-b][1,4]oxazin-3-ona;

o una sal farmacéuticamente aceptable de estos o un óptico o estereoisómero de estos.

En aún otra modalidad de esta invención el compuesto de fórmula (I) tiene
15 los siguientes sustituyentes:

$X \equiv Y$ denota un enlace doble entre X y Y;

X es CR;

Y es CR;

20 Z es NR;

A, B y E son los mismos o diferentes e independientemente uno del otro son CH o N;

D es CO;

25 Ar es fenilo, fluorofenilo, clorofenilo, piridinilo, pirazinilo, furanilo o tiofenilo;

cada R se escoge independientemente de hidrógeno, metilo, etilo, metoxi, flúor, CF₃ o OCF₃;

R₁ y R₂ son los mismos o diferentes y se seleccionan independientemente uno del

5 otro de bencilo, fluorobencilo, benzoilo, fluorobenzoilo, difluorobenzoilo, clorobenzoilo, isopropoxibenzoilo, trifluorometilbenzoilo, fluoro-trifluorometilbenzoilo, trifluorometoxibenzoilo, tiofenilcarbonilo, piridinilcarbonilo, pirazinilcarbonilo, pirimidinilcarbonilo, piridazinilcarbonilo, dihidro-benzo[1,4]dioxinilcarbonilo, benzo[1,3]dioxolilcarbonilo, 10 tiofenilmetilo, N-metil-aza-biciclo[2.2.2]octilo, aza-biciclo[2.2.2]octilo, aza-biciclo[2.2.2]octilmetilo, N-metil-piperidinilo, N-isopropil-piperidinilo, N-ciclopropil-piperidinilo, piperidinilo, N-metil-pirrolidinilo, N-etil-pirrolidinilmetilo, pirrolidinilmetilo, pirrolidiniletilo, pirrolidinilpropilo, metilaminoetilo, dimetilaminoetilo y dimetilaminopropilo; o

15

R₁ y R₂ tomados junto con el átomo de nitrógeno al cual ellos están adheridos forman un heterociclo no sustituido o al menos monosustituido seleccionado del grupo que consiste de piperazina y diazepan; en donde los sustituyentes se seleccionan del grupo que consiste de fenilo, fluorofenilo, 20 trifluorometilfenilo, piridinilo, tiofenilo, furanilo y metilo.

Un ejemplo de un compuesto de fórmula (I) que cae dentro del alcance de la modalidad anteriormente anotada incluye sin ninguna limitación los siguientes:

25

[2-fluoro-5-(1H-indol-5-il)-fenil]-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-il]-metanona;

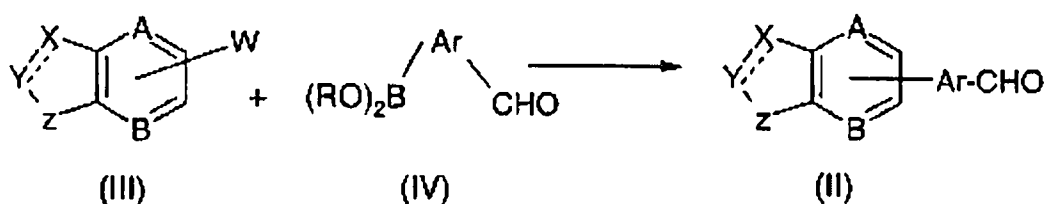
o una sal farmacéuticamente aceptable de estos o un óptico o estereoisómero de estos.

Los compuestos de esta invención se pueden sintetizar por cualquiera de los procedimientos conocidos por un experto en la técnica. Específicamente, varios de los materiales de partida utilizados en la preparación de los compuestos de esta invención se conocen o están disponibles comercialmente. Los compuestos de esta invención y varios de los compuestos precursores pueden también ser preparados por métodos utilizados para preparar compuestos similares como se reporta en la literatura y como adicionalmente se describe aquí.

Más específicamente, los compuestos descritos aquí se pueden sintetizar de acuerdo con los siguientes procedimientos de los Esquemas 1- 10, en donde X, Y, Z, A, B, D, E, Ar, R₁ y R₂ son como se define para la Fórmula I a menos que se indique de otra manera.

Los esquemas 1 y 2 ilustran la síntesis de un intermediario clave II utilizado en la preparación de compuestos de fórmula I. Sin embargo, el aldehído intermediario II se puede sintetizar por cualquiera de los métodos conocidos en la técnica.

Esquema 1



Como se muestra en el Esquema 1, el aldehído II se prepara partiendo de un compuesto de la fórmula III, en donde W es halógeno o trifluorometanosulfonato (triflato). Como se ilustra, III se hace reaccionar con ácido borónico o éster de la fórmula IV (en donde R es hidrógeno, alquilo C₁₋₄ o los dos R tomados junto con los átomos de oxígeno a los cuales ellos están adheridos forman un anillo de cinco o seis miembros) para obtener el intermediario aldehído II. Esta reacción se puede llevar a cabo por cualquiera de los métodos conocidos en la técnica. Por ejemplo, tales reacciones de adición se llevan a cabo en la presencia de un catalizador adecuado tal como compuestos de paladio. Ejemplos de compuestos de paladio adecuados para tales reacciones de acoplamiento incluyen cloruro de tetrakis(trifenilfosfina)paladio o PdCl₂(dppf) (dppf = 1,1'-bis(difenilfosfino)ferroceno), y similares. La reacción también se lleva a cabo en la presencia de una base adecuada, tal como por ejemplo, carbonato de cesio y similares. Adicionalmente, cualquiera de los grupos que pueden interferir con esta reacción de adición pueden necesitar ser protegidos. Por ejemplo, cuando Z = NH, el nitrógeno puede ser adecuadamente protegido antes de llevar a cabo esta reacción de acoplamiento. Cualquiera de los grupos protectores de nitrógeno conocidos pueden ser empleados siempre y cuando tales grupos protectores no interfieran con esta reacción. Tales grupos protectores se describen en T. W. Greene, Protective Groups in Organic Synthesis, J. Wiley-Interscience Publication (1999). La reacción se puede llevar a cabo adicionalmente en un disolvente adecuado preferiblemente un disolvente orgánico tal como dioxano, dimetilsulfóxido, dimetilformamida, o similares, o en la presencia de agua como un codisolvente, y en condiciones de temperatura de subambiente a superambiente. Normalmente, la reacción se lleva a cabo a temperaturas elevadas, por ejemplo, a la temperatura de reflujo del disolvente y preferiblemente en una atmósfera inerte. La mezcla de reacción se puede calentar utilizando métodos convencionales o

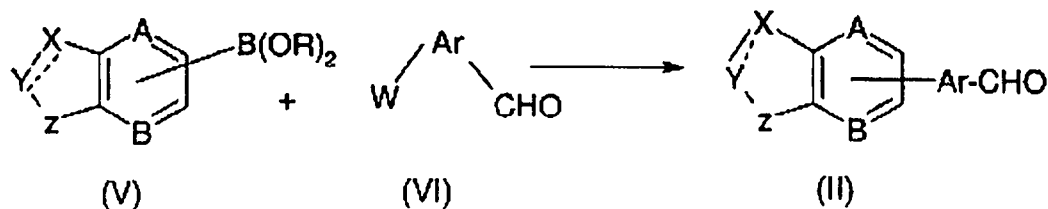
alternativamente utilizando irradiación de microondas. Sin embargo, como se anotó anteriormente, cualquiera de los otros métodos conocidos pueden también ser utilizados para producir esta reacción de acoplamiento para formar el aldehído II.

5

Alternativamente, el aldehído II puede también ser preparado utilizando un ácido borónico o éster de fórmula V y un aldehído aromático de fórmula VI como se ilustra en el Esquema 2. Esta reacción de acoplamiento se puede llevar a cabo esencialmente bajo condiciones similares como se describió anteriormente con el fin de obtener el aldehído II.

10

Esquema 2



15

El esquema 3 ilustra la preparación de una serie de compuestos de fórmula I en donde D es CH_2 y R_2 es Ar^5CH_2 o $Ar'CO$ y en donde Ar' es arilo o heteroarilo como se describe aquí.

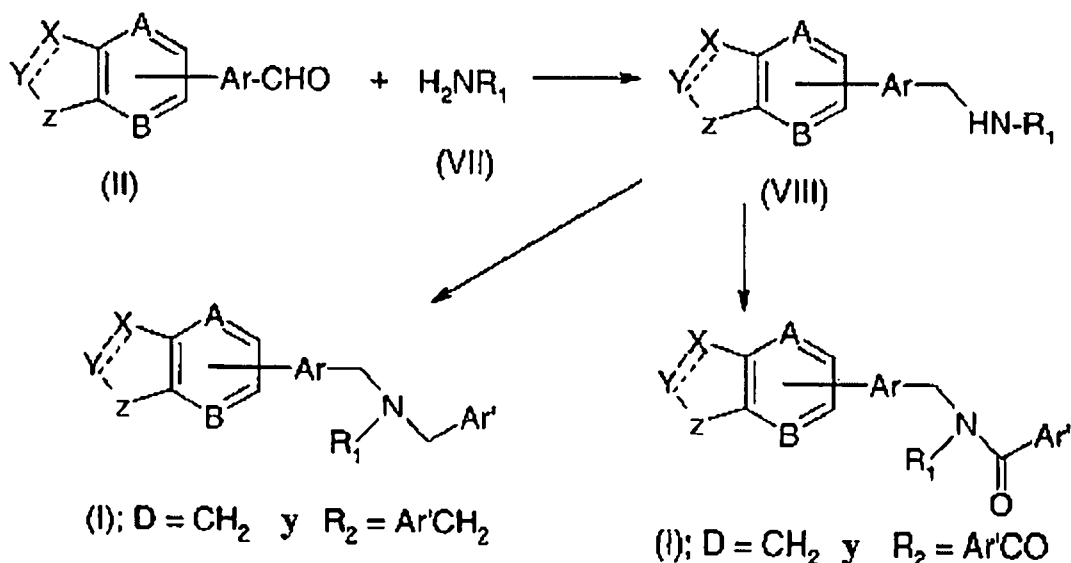
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En el Esquema 3, el aldehído intermediario II se hace reaccionar con una amina deseable bajo condiciones de alquilación reductora para formar el compuesto de fórmula VIII. Esta reacción de acoplamiento de amina se puede llevar a cabo utilizando cualquiera de los métodos conocidos en la técnica. Generalmente tal aminación reductora se puede llevar a cabo utilizando un agente de reducción tal como sodiocianoborohidruro, o triacetoxiborohidruro de sodio,

25

($\text{NaB}(\text{O}_2\text{CCH}_3)_3\text{H}$), y similares en un medio de reacción adecuado, tal como tetrahidrofurano o dicloroetano. Alternativamente, la reacción del aldehído y la amina se puede llevar a cabo en la presencia de un agente de deshidratación, tal como, por ejemplo, tamices moleculares, en un disolvente orgánico tal como metanol, seguido por la adición de un agente de reducción tal como borohidruro sódico.

Esquema 3



10

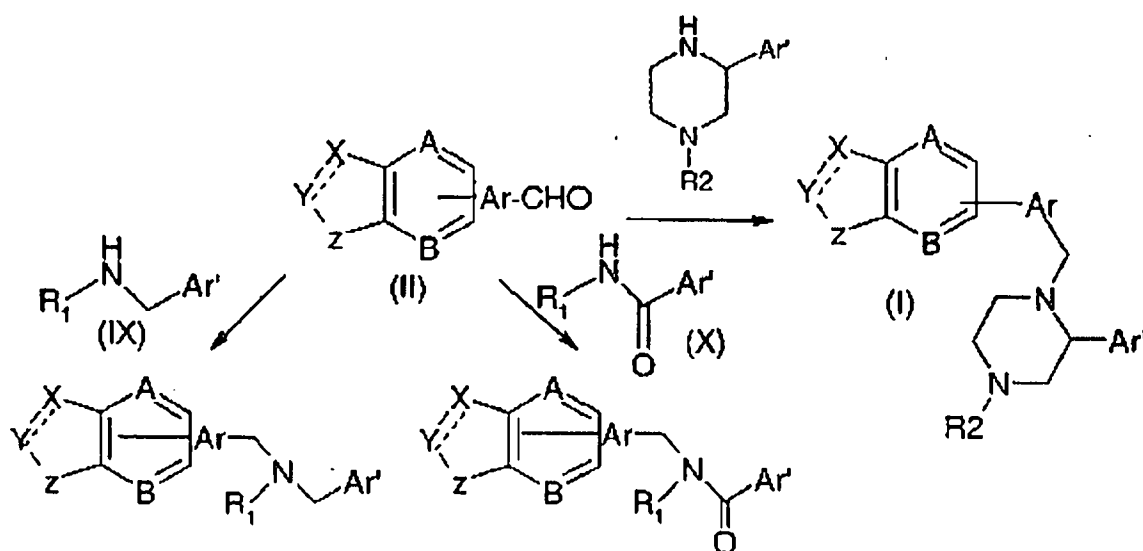
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El compuesto intermediario amino VIII así formado luego se somete a otra reacción de alquilación reductora utilizando un aldehído aromático adecuado para formar los compuestos de fórmula I en donde $\text{D} = \text{CH}_2$ y $\text{R}_2 = \text{Ar}'\text{CH}_2$. Esta reacción de alquilación también se puede llevar a cabo bajo condiciones esencialmente similares como se describió anteriormente. Esto es, el compuesto de fórmula VIII se hace reaccionar con $\text{Ar}'\text{CHO}$ en la presencia de un agente de reducción adecuado tal como triacetoxiborohidruro de sodio ($\text{NaB}(\text{O}_2\text{CCH}_3)_3\text{H}$) para formar el correspondiente compuesto de fórmula I. El compuesto de fórmula VIII se puede hacer reaccionar con un ácido carboxílico adecuado de fórmula

Ar⁵CO₂H o cloruro de ácido carboxílico para formar el compuesto de fórmula I en donde D = CH₂ y R₂ = Ar'CO. Esta reacción otra vez se puede llevar a cabo utilizando cualquiera de los métodos conocidos en la técnica. Por ejemplo tales reacciones de acilación con cloruros de ácidos carboxílicos se llevan a cabo en la presencia de una base adecuada tal como trietilamina o diisopropiletilamina en un disolvente orgánico tal como diclorometano. Alternativamente la reacción del compuesto de fórmula VIII con un ácido carboxílico y un reactivo de acoplamiento amina tal como, por ejemplo, hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (HATU) en la presencia de una base tal como diisopropiletilamina también proporciona compuestos de fórmula 1.

Esquema 4



(I); D = CH₂ y R₂ = Ar¹CH₂ (I); D = CH₂ y R₂ = Ar¹CO

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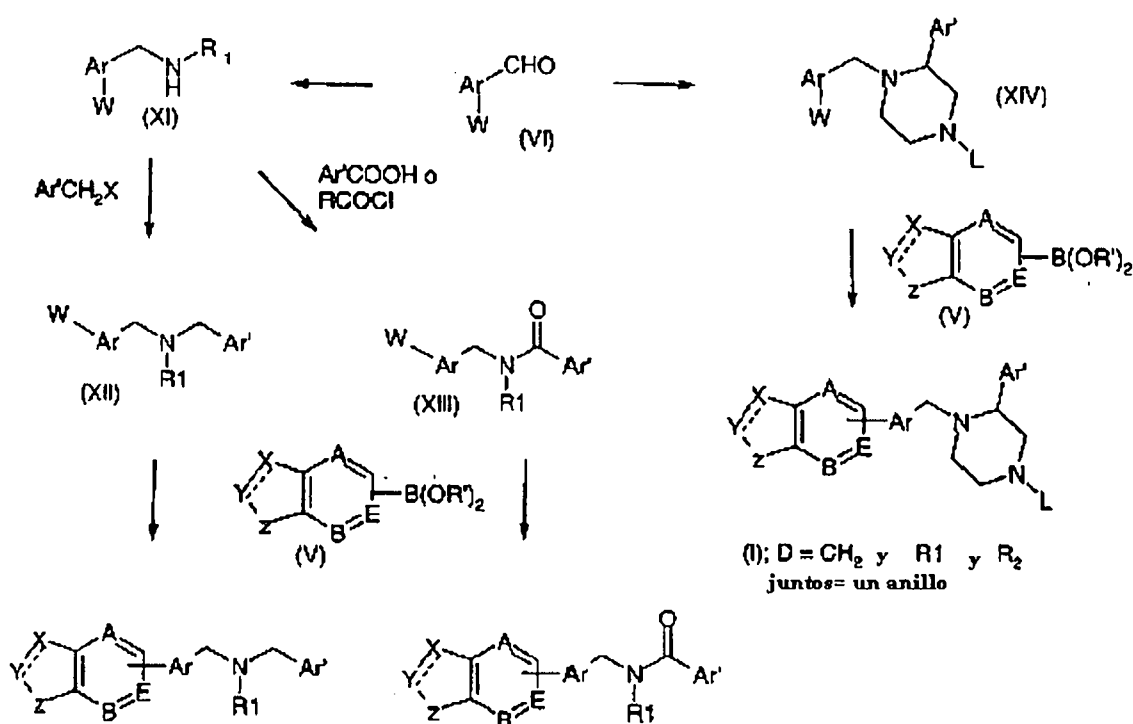
Alternativamente, los compuestos de fórmula I de los tipos mostrados en el Esquema 3 pueden también ser preparados partiendo del aldehído II y un compuesto amino IX o X adecuado como se ilustra en el Esquema 4. El compuesto de fórmula II también se puede hacer reaccionar con aminas cíclicas tal como derivados de piperidina mostrados para formar los compuestos

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correspondientes de fórmula I. Otra vez esta reacción de aminación se puede llevar a cabo bajo condiciones similares como se describió anteriormente. Esto es, el aldehído II se hace reaccionar con amina IX adecuada o derivado de piperidina o amida X adecuada en la presencia de un agente de reducción adecuado tal como triacetoxiborohidruro de sodio ($\text{NaB}(\text{O}_2\text{CCH}_3)_3\text{H}$) para formar los compuestos correspondientes de fórmula I.

El esquema 5 ilustra adicionalmente la variación de un método sintético para la preparación de compuestos de fórmula I. En este enfoque, el aldehído halo-aromático de fórmula VI se hace reaccionar primero con una amina para formar el compuesto de fórmula XI, que se hace reaccionar con haluro de aralquilo o ácido carboxílico aromático para formar los compuestos correspondientes de fórmula XII y XIII. Los últimos compuestos se hacen reaccionar finalmente con ácido borónicos o ésteres de fórmula V para formar los compuestos correspondientes de fórmula I en donde $\text{D} = \text{CH}_2$ y R_2 es Ar^5CH_2 o $\text{Ar}'\text{CO}$.

Esquema 5



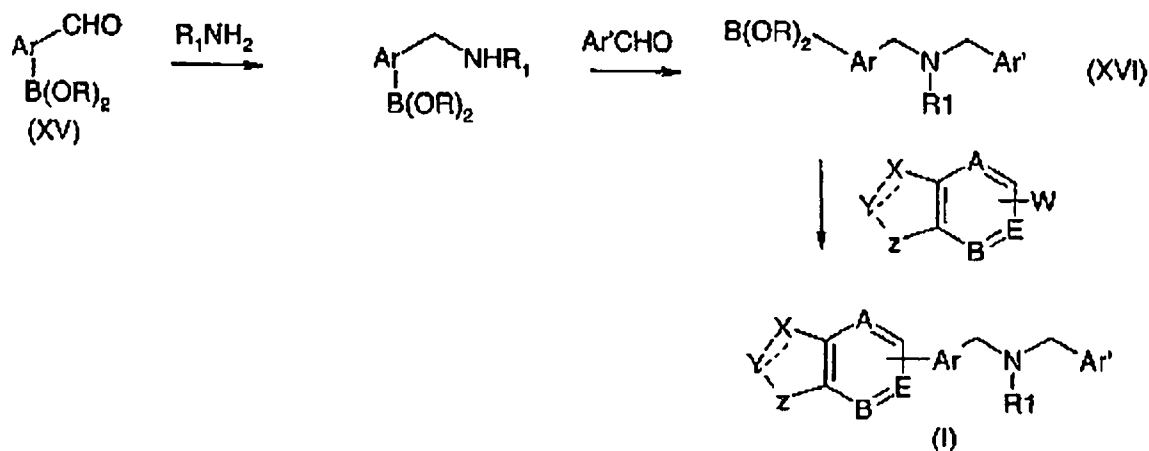
(I); $D = CH_2$ y $R_2 = Ar^1CH_2-$ (I); $D = CH_2$ y $R_2 = Ar^1CO-$

Condiciones de reacción similares se pueden emplear para varias etapas establecidas en el Esquema 5 como se describió anteriormente. Por ejemplo, la
5 reacción de aminación reductora del aldehído halo-aromático VI con la amina se afecta bajo condiciones de reducción en la presencia de un agente de reducción tal como triacetoxiborohidruro de sodio como se discutió anteriormente para reacciones de aminación reductoras similares. El compuesto amino XI así formado luego se somete a arilación o aroilación al hacerlo reaccionar respectivamente con
10 haluro de aralquilo tal como arilmetilhaluro de fórmula Ar^1CH_2 -halo o un ácido carboxílico aromático tal como Ar^5CO_2H bajo condiciones como se describe en el Esquema 4 para obtener los compuestos correspondientes de fórmula XII y XIH. Finalmente, cada uno de los cuales se hace reaccionar con el compuesto de boro V para formar el correspondiente compuesto de fórmula I.

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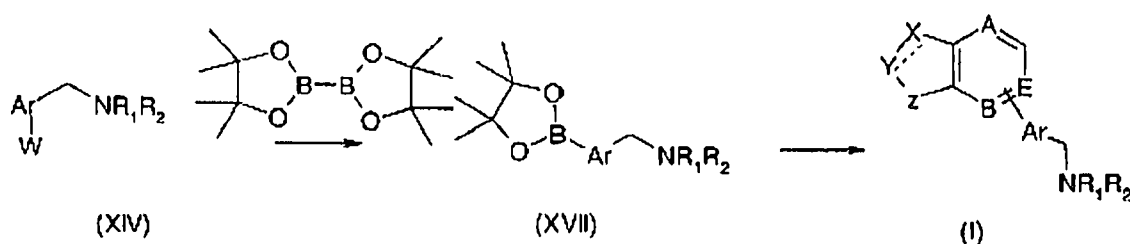
Los compuestos de fórmula I pueden también ser preparados como se destaca en el Esquema 6, utilizando los métodos descritos anteriormente. Por ejemplo, la reacción de alquilación reductora del aldehído aromático-boranilo XV con una amina se afecta bajo condiciones de reducción en la presencia de un
20 agente de reducción tal como triacetoxiborohidruro de sodio como se discutió anteriormente para reacciones de alquilación reductora similares. El tratamiento adicional de la amina obtenida con un aldehído bajo condiciones similares luego suministra la amina-boranilo XVI. Este ácido borónico o éster puede luego ser acoplado a un haluro de arilo o heteroarilo o trifluorometanosulfonato, en la
25 presencia de un agente de acoplamiento organometálico adecuado como se describió anteriormente para proporcionar compuestos de fórmula I.

Esquema 6



- 5 En una forma similar, como se muestra en el Esquema 7, la amina-boranilo XVII se puede preparar mediante el tratamiento de un haluro arilo amino sustituido o triflato con un agente de borilación tal como bis(pinacolato)diboro en la presencia de un agente de acoplamiento organometálico tal como $\text{Pd}(\text{dppf})\cdot\text{DCM}$ en un disolvente orgánico tal como dioxano, dimetilsulfóxido o dimetilformamida a
- 10 temperatura elevada. Este ácido borónico o éster luego puede ser acoplado con un haluro de arilo o trifluorometanosulfonato bajo las condiciones descritas anteriormente, o por ejemplo utilizando fibreCat 1001 en la presencia de un catalizador de fase de transferencia tal como bromuro de tetrabutilamonio, una base tal como carbonato de cesio en una mezcla de un disolvente orgánico tal
- 15 como dioxano y agua a temperaturas elevadas.

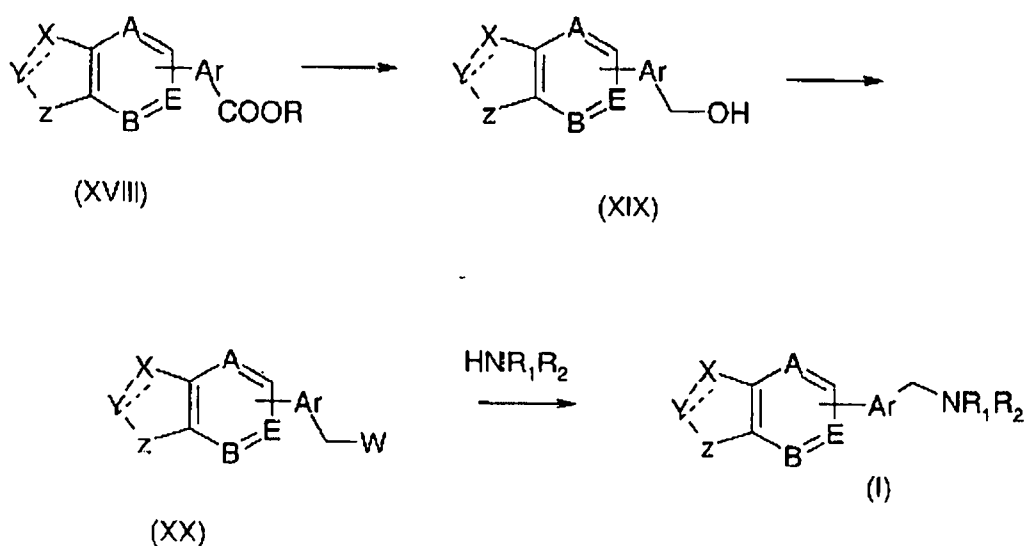
Esquema 7



Los compuestos de fórmula I pueden también ser preparados como se destaca en el Esquema 8. Los ácidos carboxílicos o ésteres se pueden preparar como se describe para los aldehídos en los Esquemas 1 y 2. La reducción de los ácidos o ésteres a los alcoholes XIX se puede llevar a cabo por cualquier número de métodos conocidos en la técnica, que incluyen el uso de, por ejemplo, agentes de reducción de hidruro tal como hidruro de aluminio litio en un disolvente apropiado tal como dietil éter o THF. Los alcoholes así preparados se pueden activar por la transformación en un haluro, un mesilato, triflato o nosilato. Por ejemplo mesilatos se puede preparar al tratar los alcoholes con cloruro de metanosulfonilo o anhídrido de metanosulfonilo en la presencia de una base tal como trietil amina o diisopropiletilamina en un disolvente apropiado tal como DCM o DCE. Los compuestos XX pueden luego ser transformados en los objetivos de fórmula I mediante el tratamiento con una amina apropiada.

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Esquema 8



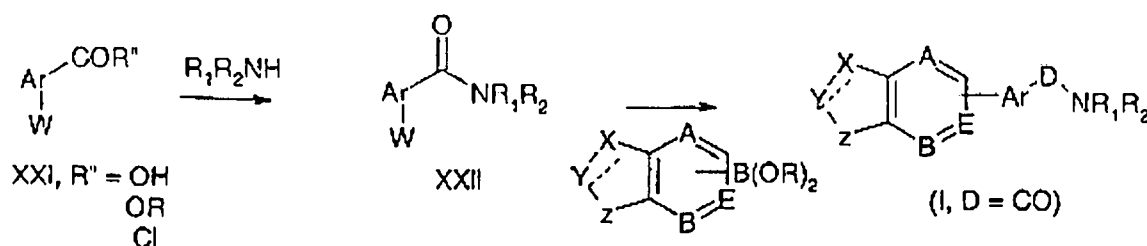
Los compuestos de fórmula I en los que D = CO se pueden preparar mediante métodos similares a aquellos descritos anteriormente, al reemplazar un alquilación reductora con una reacción formadora de amida. Por ejemplo (Esquema 9), en un método relacionado con el uno descrito en el Esquema 5, la

5 amidación de un ácido carboxílico o derivado de ácido carboxílico se puede alcanzar por muchos métodos conocidos. Por ejemplo amidas XXII se pueden obtener mediante el tratamiento de ácidos carboxílicos XXI ($R'' = H$) luego de tratamiento con una amina en la presencia de un agente de acoplamiento, tal como HOBT, HOAT o HATU, con una base tal como trietilamina o diisopropilamina

10 en un disolvente apropiado, por ejemplo dimetilformamida o diclorometano. El acoplamiento organometálico posterior como se describió anteriormente suministra compuestos de fórmula I (D = CO).

Esquema 9

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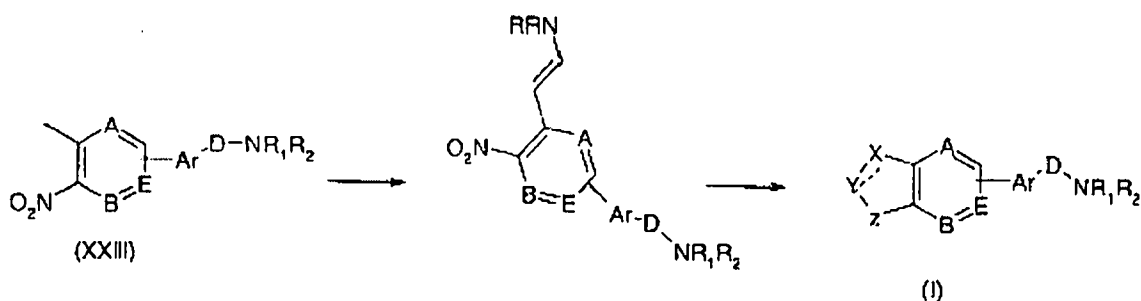
En un enfoque alternativo para la preparación de los compuestos de esta invención, el anillo heterocíclico formado por X, Y, y Z se puede preparar por cualquiera de una variedad de métodos conocidos en la técnica. Por ejemplo, como se muestra en el Esquema 10, un indol se puede preparar a partir de un heteroarilo o biarilo sustituido adecuado (preparado por los métodos descritos anteriormente). El tratamiento del compuesto nitro XXIII con dimetilformamida dimetilacetal en un disolvente adecuado, tal como dimetilformamida, seguido por

245

hidrogenación utilizando un catalizador Pd o Pt (por ejemplo 10% de Pd sostenido en carbono) suministra un compuesto de fórmula 1 en donde X, Y, y Z son C=C- N y son parte de un indol.

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Esquema 10



Como se anotó anteriormente, varias modificaciones pueden ser hechas a los esquemas descritos anteriormente con el fin de preparar varios otros compuestos de fórmula I empleando materiales de partida adecuados y utilizando otros métodos conocidos en la técnica. Una amplia variedad de tales ejemplos sintéticos específicos se suministran adicionalmente adelante.

En otro aspecto de esta invención, una enfermedad específica, un trastorno o una condición que se puede tratar con el compuesto de esta invención incluye, sin ninguna limitación una amplia variedad de trastornos del sueño. En adición, los compuestos de esta invención son antagonistas de serotonina selectivos particularmente los compuestos de esta invención son antagonistas selectivos del receptor 5HT_{2A}.

Un experto en la técnica fácilmente apreciará que las patologías y estados de enfermedad establecidos expresamente aquí no se destinan como limitantes más bien se destinan para ilustrar la eficacia de los compuestos de la presente

2 yb

invención. Así se entiende que los compuestos de esta invención pueden ser utilizados para tratar cualquier enfermedad originada por los efectos del receptor de 5HT_{2A}. Esto es, como se anotó anteriormente, los compuestos de la presente invención son antagonistas 5HT_{2A} selectivos y así se pueden administrar

5 efectivamente para mejorar cualquier estado de enfermedad media todo o en parte por el receptor 5HT_{2A}. Todas las varias modalidades de los compuestos utilizados en los métodos de esta invención como se describe aquí se pueden utilizar en el método para tratamiento de varios estados de enfermedad como se describe aquí. Como se indica aquí, los compuestos utilizados en el método de esta invención

10 son capaces de antagonizar los efectos del receptor de 5HT_{2A} y por lo tanto aliviar los efectos y/o condiciones originadas debido a la actividad del receptor 5HT_{2A}.

En una modalidad específica de esta invención los compuestos de esta invención son particularmente adecuados para el tratamiento de una variedad de

15 trastornos del sueño. El término "trastorno del sueño" como se utiliza aquí debe significar toda la descripción como se delinea en el Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (1994), referido de aquí en adelante como DSM-IV, publicada por the American Psychiatric Association. Los trastornos específicos del sueño que se pueden tratar de acuerdo con esta invención

20 incluyen sin ninguna limitación insomnio, insomnio primario, trastorno del sueño relacionado con otro trastorno mental, apnea obstructiva del sueño y trastorno del sueño inducido por sustancia. La descripción adicional y discusión de los trastornos del sueño se encuentran en the International Classification of Sleep Disorders: Diagnostic y Coding Manual (1990), publicado por the American Sleep

25 Disorders Association.

247

El término "insomnio" como se utiliza aquí incluye todos los trastornos del sueño, que no se originan debido a otros factores debido tales como trastornos mentales, otras condiciones médicas y trastornos del sueño inducidos por sustancias. El insomnio como se utiliza aquí también debe significar trastornos
5 primarios del sueño como se define en DSM-IV, que incluye dos subcategorías, a saber, disomnio y parasomnias.

El término "insomnio primario" debe significar todas las definiciones previstas en el DSM-IV. Adicionalmente, "insomnio primario" como se utiliza aquí
10 también incluye "insomnio de mantenimiento del sueño." El DSM-IV lista el criterio de diagnóstico para el insomnio primario como sigue:

A. La queja predominante es la dificultad de iniciar o mantener el sueño, o sueño no restaurativo, durante al menos un mes.

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B. La interrupción del sueño (o asociado por la fatiga del día) origina distensión clínicamente significativa o deterioro en lo social, ocupacional, u otras áreas importantes de funcionalización.

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C. La interrupción del sueño no ocurre exclusivamente durante el curso de la narcolepsia, trastorno del sueño relacionado con la respiración, trastorno del sueño de ritmo circadiano, o una parasomnia.

D. La interrupción no ocurre exclusivamente durante el curso de otro
25 trastorno mental (por ejemplo, trastorno depresivo mayor, trastorno de ansiedad generalizada, un delirio).

E. La interrupción no se debe a efectos fisiológicos directos de una sustancia (por ejemplo, un abuso de droga, una medicación) o una condición médica general.

5 El término "trastorno del sueño relacionado con otro trastorno mental" como se utiliza aquí incluye insomnio e hipersomnio relacionado con otro trastorno mental. El DSM-IV lista el criterio de diagnóstico para insomnio relacionado con otro trastorno mental como sigue:

10 A. La queja predominante es la dificultad de iniciar o mantener el sueño, o sueño no restaurativo, durante al menos un mes que se asocia con fatiga diaria o funcionamiento diario debilitado.

B. La interrupción del sueño (o secuela del día) origina distensión
15 clínicamente significativa o deterioro en lo social, ocupacional, u otras áreas importantes de la funcionalización.

C. El insomnio se juzga que se relaciona con otro trastorno de eje I o eje II (por ejemplo, trastorno depresivo mayor, trastorno de ansiedad generalizada,
20 trastorno de ajuste con ansiedad, esquizofrenia, etc.), pero es suficientemente severo para llamar la atención clínica independiente.

D. La interrupción no cuenta mejor por otro trastorno del sueño (por ejemplo, la narcolepsia, trastorno del sueño relacionado con la respiración, una
25 parasomnia).

249

E. La interrupción no se debe a efectos fisiológicos directos de una sustancia (por ejemplo, un abuso de droga, una medicación) o una condición médica general.

5 De forma similar, el DSM-IV lista el criterio de diagnóstico para hipersomnio relacionado con otros trastornos mentales como sigue:

A. La queja predominante es el sueño excesivo durante al menos un mes como se evidencia por los episodios de sueño prolongados o episodios de
10 sueño en el día que ocurre casi diariamente.

B. El sueño excesivo origina distensión clínicamente significativa o deterioro en lo social, ocupacional, u otras áreas importantes de funcionalización.

15 C. El hipersomnio se juzga que se relaciona con otro trastorno eje I o eje II (por ejemplo, trastorno mayor depresivo, trastorno distímico, esquizofrenia, etc.), pero es suficientemente severo para llamar la atención clínica independiente.

D. La interrupción no se cuenta mejor para cualquier otro trastorno del
20 sueño (por ejemplo, la narcolepsia, trastorno del sueño relacionado con la respiración, una parasomnia) o mediante cualquier cantidad inadecuada de sueño.

E. La interrupción no se debe a los efectos fisiológicos directos de una sustancia (por ejemplo, un abuso de droga, una medicación) o una condición médica general.

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El término "trastorno del sueño inducido por sustancia" como se utiliza aquí significa un interrupción prominente en el sueño que es suficientemente severa

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para llamar la atención clínica independiente y se juzga que se debe a los efectos fisiológicos directos de una sustancia (es decir, un abuso de droga, una medicación, o una exposición a toxina). Ejemplos específicos de abuso de drogas, una medicación o exposición a toxina como se refiere aquí incluyen sin ninguna
5 limitación cafeína, alcohol, anfetamina, opioides, sedantes, hipnóticos, ansiolíticos, y similares. El DSM-IV lista el criterio de diagnóstico para trastorno del sueño inducidos por sustancias como sigue:

A. Una interrupción prominente en el sueño que es suficientemente
10 severa para llamar a atención clínica independiente.

B. Existe evidencia de la historia, examen físico, o hallazgos de laboratorio de (1) o (2): (1) los síntomas en el criterio durante el desarrollo de A o dentro de un mes de intoxicación por sustancia o retiro; (2) el uso de la medicación
15 se relaciona etiológicamente con la interrupción del sueño.

C. La interrupción no se cuenta mejor para un trastorno del sueño que no es inducido por sustancia. La evidencia de que los síntomas se cuentan mejor por un trastorno del sueño que no se induce por una sustancia puede incluir lo
20 siguiente: los síntomas preceden al inicio del uso de la sustancia (o uso de medicación); los síntomas persisten durante un periodo de tiempo sustancial (por ejemplo cerca de un mes) después de la cesación del retiro agudo o intoxicación severa, o está sustancialmente en exceso de lo que se pudiera esperar dado el tipo o cantidad de la sustancia utilizada o la duración del uso; o existe evidencia
25 que sugiere la existencias de un trastorno del sueño inducido sin sustancia independiente (por ejemplo, una historia de episodios relacionados sin sustancia recurrente).

D La interrupción no ocurre exclusivamente durante el curso de un delirio.

- 5 E. La interrupción del sueño origina distensión significativa clínicamente o deterioro en lo social, ocupacional, u otras áreas importantes de funcionalización.

Como se utiliza aquí "retiro" se refiere a un síndrome caracterizado por
10 cambios fisiológicos inconvenientes que ocurren luego de la cesación de o la reducción en el uso de sustancia, o la administración de un antagonista farmacológico (o medicación).

El término "apnea obstructiva del sueño" como se utiliza aquí es un
15 trastorno del sueño relacionado con la respiración como se define en el DSM-IV. También se refiere como síndrome de resistencia de las vías aéreas superiores e involucra generalmente episodios repetidos de obstrucción de las vías aéreas superiores durante el sueño y se caracterizan normalmente por ronquidos fuertes o espacios breves que alternan con episodios de silencio. El DSM-IV lista el
20 criterio de diagnóstico para trastornos del sueño relacionados con la respiración como sigue:

- A. Interrupción del sueño, que conduce a sueño excesivo o insomnio, que se juzga porque se debe a una condición de respiración relacionada con el
25 sueño (por ejemplo, síndrome de apnea del sueño central o sueño obstructivo o síndrome de hipoventilación alveolar central)

B. La interrupción no se cuenta mejor por otro trastorno mental y no se debe a efectos fisiológicos directos de una sustancia (por ejemplo, un abuso de droga, una medicación) u otra condición médica general (diferente de trastorno relacionado con la respiración).

5

Determinaciones Objetivas y Subjetivas de Trastornos del Sueño: existe un número de formas para determinar si el inicio, duración o calidad del sueño (por ejemplo sueño restaurador o no restaurador) se deteriora o mejora. Un método es una determinación subjetiva del paciente, por ejemplo, ellos se sienten somnolientos o cansados luego de despertar. Otros métodos involucran la observación del paciente por otro durante el sueño, por ejemplo, cuanto le toma al paciente en caer dormido, cuantas veces despierta el paciente durante la noche, como descansa el paciente durante el sueño, etc. Otro método es objetivamente las etapas del sueño.

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La polisomnografía es el monitoreo de múltiples parámetros electrofisiológicos durante el sueño e incluyen generalmente medición de la actividad de electroencefalograma (EEG), actividad electroculográfica y actividad electromiográfica (EMG), así como también otras mediciones. Estos resultados junto con observaciones, pueden medir no solo la latencia del sueño (la cantidad de tiempo requerido para caer dormido), sino también la continuidad del sueño (balance general del sueño y momento en que se despierta) que puede ser una indicación de la calidad del sueño.

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Existen cinco etapas distintas del sueño que se pueden medir por polisomnografía: movimiento rápido de los ojos en el sueño (REM) y cuatro etapas de no movimiento rápido de los ojos (NREM) en el sueño (etapas 1, 2, 3, y 4). La

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etapa 1 NREM de sueño es una transición de despierto a dormido y ocupa aproximadamente el 5% del tiempo que se gasta durmiendo en adultos saludables. La etapa 2 sueño NREM, que se caracteriza por formas onduladas EEG específicas (complejos K y husillos del sueño), ocupa aproximadamente 50% del tiempo de sueño gastado. Las etapas 3 y 4 de sueño NREM (también conocidas colectivamente como sueño de onda lenta) son los niveles más profundos de sueño y ocupan aproximadamente 10-20% del tiempo del sueño. El sueño REM, en donde ocurre la mayoría de sueños similares a historias típicas, ocupa aproximadamente 20-25% del sueño total.

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Estas etapas de sueño tienen una organización temporal característica a través de la noche. Las etapas 3 y 4 de NREM tienden a ocurrir en la primera tercera a una mitad de la noche e incrementan la duración en la respuesta para privación de sueño. El sueño REM ocurre cíclicamente a través de la noche, alternando con el sueño NREM durante aproximadamente 80-100 minutos. Los periodos de sueño REM incrementan la duración hacia la mañana. El sueño humano también varía característicamente a través de la duración de la vida. Después de la estabilidad relativa con grandes cantidades de sueño de onda lenta en la niñez y la preadolescencia, la continuidad y profundidad del sueño se deterioran a través del rango de la edad adulta. Este deterioro se refleja al incrementar la debilidad y la etapa 1 del sueño y la etapa 3 se reducen y la etapa 4.

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En general, los compuestos de esta invención suministran calidad de sueño a través de mecanismos serotoninérgicos (que actúan en el sitio del receptor 5HT_{2A}) cuando se administran a un paciente que sufre de cualquiera de los trastornos del sueño como se describió aquí anteriormente. Esto es, en general, se ha

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254

encontrado que la administración de compuestos de esta invención incrementan la duración de las etapas 3 y 4 del sueño de onda lenta (SWS, medido como sueño NREM). Esto también se mide al reducirse las veces que se despierta después del inicio del sueño (WASO), la medición de la eficacia primaria en el ensayo clínico.

5 Adicionalmente, la mejora del SWS en adultos mayores también puede incrementar la cognición y mejorar la calidad de vida. El SWS puede jugar un papel importante en la regulación de los procesos cognitivos en adultos viejos. Se ha mostrado que existe una relación directa entre la cantidad de SWS y el desempeño en pruebas cognitivas diarias. Así, se ha encontrado ahora que los
10 compuestos de esta invención son útiles en incrementar la cognición y por o tanto mejorar la calidad de vida de un paciente, preferiblemente en adultos viejos.

La mejora en la calidad del sueño se mide por polisomnografía. Los resultados de los estudios EEG del sueño y polisomnográficos en pequeños
15 números de voluntarios saludables jóvenes y mayores y en pacientes con insomnio primario han mostrado un incremento de SWS y una reducción en WASO.

En otra modalidad del método de esta invención, los compuestos de esta
20 invención se puede administrar por cualquiera de los métodos conocidos en la técnica. Específicamente, los compuestos de esta invención se puede administrar oralmente, intramuscular, subcutáneamente, rectalmente, intratraquealmente, intranasalmente, intraperitonealmente o por ruta tópica.

25 Finalmente, en aún otra modalidad de esta invención, también se suministra aquí una composición farmacéutica que comprende un portador farmacéuticamente aceptable y un compuesto, que incluye enantiómeros,

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estereoisómeros, y tautómeros de dicho compuesto y sales farmacéuticamente aceptables, solvatos o derivados de estos, con dicho compuesto que tiene la estructura general mostrada en la fórmula I como se describe aquí.

5 Como se describe aquí, las composiciones farmacéuticas de esta invención caracterizan la actividad antagonista del 5HT_{2A} y así son útiles en tratar cualquier enfermedad, condición o un trastorno originado debido a los efectos de 5HT_{2A} en un paciente. De nuevo, como se describió anteriormente, todas las modalidades preferidas de los compuestos de esta invención como se describen aquí se
10 pueden utilizar en la preparación de composiciones farmacéuticas como se describe aquí.

Preferiblemente las composiciones farmacéuticas de esta invención están en forma de dosis unitarias tales como comprimidos, píldoras, cápsulas, polvos,
15 gránulos, soluciones parenterales estériles o suspensiones, aerosoles medidos o aerosoles líquidos, gotas, ampollas, dispositivos autoinyectores o supositorios; para administración oral, parenteral, intranasal, sublingual o rectal, o para administración por inhalación o insuflación. Alternativamente, las composiciones se puede presentar en una forma adecuada durante una administración una vez a
20 la semana o una vez al mes, por ejemplo, una sal insoluble del compuesto activo, tal como la sal de ácido graso, por ejemplo estearato, etc. se puede adaptar para suministrar una preparación de depósito para inyección intramuscular. Un polímero erosionable que contiene el ingrediente activo también puede ser previsto. Para preparar composiciones sólidas tal como comprimidos, se mezcla el
25 principal ingrediente activo con un portador farmacéutico, por ejemplo ingredientes de formación de comprimido convencional tales como almidón de maíz, lactosa, sucrosa, sorbitol, talco, ácido esteárico, estearato de magnesio, fosfato de dicalcio

o gomas, y otros diluyentes farmacéuticos, por ejemplo agua, para formar una composición de preformulación sólida que contiene una mezcla homogénea de un compuesto de la presente invención, o una sal farmacéuticamente aceptable de esta.

5

De forma similar, las composiciones farmacéuticas de esta invención también se pueden mezclar con una amplia variedad de excipientes farmacéuticamente aceptables. Ejemplos de excipientes farmacéuticamente aceptables incluyen sin ninguna limitación acacia, acesulfamo potasio, albúmina, poliésteres alifáticos, aspartamo, bentonita, butilparabeno, estearato de calcio, 10 aceite de canola, carbomero, carboximetilcelulosa, acetato de celulosa, dextrina, goma guar, hidroxietilcelulosa, maltodextrina, almidón, y similares.

Cuando hacemos referencia a estas formulaciones de preformulación como 15 homogéneas, significa que el ingrediente activo se dispersa uniformemente a través de la composición de tal forma que la composición se puede subdividir fácilmente en formas de dosis unitaria igualmente efectiva tal como comprimidos, píldoras y cápsulas. Esta composición de preformulación sólida se subdivide luego en forma de dosis unitaria del tipo descrito anteriormente que contienen de 0.1 a 20 aproximadamente 500 mg del ingrediente activo de la presente invención. Formas de dosis unitarias saborizadas que contienen de 1 a 100 mg, por ejemplo 1, 2, 5, 10, 25, 50 o 100 mg, del ingrediente activo. Los comprimidos o píldoras de la composición novedosa se pueden cubrir o componer de otra forma para suministrar una forma de dosis que produce la ventaja de acción prolongada. Por 25 ejemplo, el comprimido o píldora puede comprender una dosis interna y un componente de dosis externo, el último está en la forma de una envoltura sobre el anterior. Los dos componentes se pueden separar mediante una capa entérica

que sirve para resistir la desintegración en el estómago y permite al componente interior pasar intacto dentro del duodeno o estar retrasado en la liberación. Una variedad de materiales también se pueden utilizar para tales capas entéricas o recubrimientos, tal como materiales que incluyen un número de ácidos poliméricos y mezclas de ácidos poliméricos con materiales tales como shellac, cetil alcohol y acetato de celulosa.

Las formas líquidas en las que las composiciones novedosas de la presente invención se pueden incorporar para administración oral o por inyección incluyen soluciones acuosas, jarabes saborizados adecuadamente, suspensiones acuosas o aceitosas, y emulsiones saborizadas con aceites comestibles tal como aceite de semilla de algodón, aceite de sésamo, aceite de coco o aceite de cacahuate, así como también elixires y vehículos farmacéuticos similares. Agentes de suspensión o dispersión adecuados para suspensiones acuosas incluyen gomas naturales y sintéticas tales como tragacanto, acacia, alginato, dextrano, carboximetilcelulosa de sodio, metilcelulosa, polivinil-pirrolidona o gelatina.

Las composiciones farmacéuticas de esta invención se pueden administrar por cualquiera de los métodos conocidos en la técnica. En general, las composiciones farmacéuticas de esta invención se pueden administrar por ruta oral, intramuscular, subcutánea, rectal, intratraqueal, intranasal, intraperitoneal o tópica. Las administraciones preferidas de las composiciones farmacéuticas de esta invención son la ruta oral e intranasal. Cualquiera de los métodos conocidos para administrar composiciones farmacéuticas mediante una ruta oral o intranasal se pueden utilizar para administrar la composición de esta invención.

En el tratamiento de varios estados de enfermedad como se describe aquí, un nivel de dosis adecuado es aproximadamente 0.001 a 250 mg/kg por día, preferiblemente aproximadamente 0.005 a 100 mg/kg por día, y especialmente aproximadamente 0.05 a 20 mg/kg por día. Los compuestos se pueden
5 administrar sobre un régimen de 1 a 4 veces por día.

Más específicamente, el rango de dosis en el que los compuestos de esta invención exhiben su capacidad para tratar trastornos del sueño, incluyen cada tipo específico de trastorno del sueño, que puede variar dependiendo del trastorno
10 específico, su severidad, el paciente, cualquier estado de enfermedad subyacente que el paciente está sufriendo, y otras medicaciones que se pueden administrar concurrentemente al paciente. Generalmente, como se anotó anteriormente, los compuestos de esta invención exhibirán su capacidad para tratar trastornos del sueño en un rango de aproximadamente 0.001 mg/kg/día a aproximadamente 100
15 mg/kg/día.

Esta invención se ilustra adicionalmente por los siguientes ejemplos que se suministran para propósito de ilustración y no limitan de ninguna forma el alcance de la presente invención.

20

Ejemplos (General)

Las reacciones se realizan generalmente bajo una atmósfera inerte. Todos los químicos comerciales y disolventes son de grado reactivo y se utilizan sin
25 purificación adicional a menos que se especifique otra cosa. Todas las reacciones excepto aquellas en las soluciones acuosas o establecidas de otra forma se llevan a cabo con el uso de técnicas estándar para la exclusión de humedad. La

cromatografía flash se lleva a cabo utilizando gel de sílice 60 (35-70 μm) de acuerdo con el procedimiento de la literatura (Still, W.C.; Kahn, M; Mitra, A. *J. Org. Chem.* 1978 43, 2923) o una variación de este método utilizando cartuchos de gel de sílice disponibles comercialmente (por ejemplo Isco Redi Sep). Se desarrollan reacciones utilizando irradiación de microondas de mod sencillo o enfocado en instrumentos de CEM Corporation o Personal Chemistry. El espectro RMN ^1H se corre a 300 MHz o 400 MHz en un espectrómetro Varian Inova-400, Varian VXR 300 o Gemini 300 y se determinan en un disolvente de deuterio, tal como DMSO- D_6 o CDCl_3 a menos que se especifique otra cosa. Los valores de cambios químicos se indican en partes por millón (ppm) con referencia al tetrametilsilano (TMS) como el estándar interno. Se registra la cromatografía líquida con análisis de espectro de masa (LC/MS) en un Espectrómetro de Masa LC de Plataforma con una fuente de electrorociado que opera en modo ión negativo y positivo un HP1100 con detección HP1100 DAD en línea y detección SEDEX ELS utilizando un Waters XTerra MS C18 3.5 μm 4.6 x 30 mm o una columna Phenomenex Luna C18(2) 30 x 4.6 mm que eluye con 0.1% de ácido fórmico en agua/acetonitrilo (LC/MS corto), o un Espectrómetro de Masa Finnigan TSQ700 con fuente de electrorociado que opera en modo ión positivo y un sistema HP1050 con detector UV de Longitud de onda único HP1050 en línea a 254 nm utilizando una columna Higgins Clipeus C18 5 μm 100 x 3.0 mm que eluye con 0.1% de ácido fórmico en agua/acetonitrilo (LC/MS largo), o un LCTAPI LC-TOF Micromasa (tiempo de vuelo) Sistema de Datos Masslynx y Espectrómetro de Masa. El modo de ionización=electrorociado (esi), los valores de determinan para iones moleculares protonados ($\text{M}^+ + 1$) utilizando una columna Synergi 2U HIDRO-RP 20 x 4 mm, que eluye con 0.1% de ácido Trifluoroacético (TFA) en agua/acetonitrilo (método 3).

Como se utiliza en los ejemplos y las preparaciones que siguen, los términos utilizados aquí deben tener el significado indicado: "kg" se refiere a kilogramos, "g" se refiere a gramos, "mg" se refiere a miligramos, "µg" se refiere a microgramos, "pg" se refiere a picogramos, "lb" se refiere a libras, "oz" se refiere a onzas, "mol" se refiere a moles, "mmol" se refiere a milimoles, "µmole" se refiere a micromoles, "nmole" se refiere a nanomoles, "L" se refiere a litros, "mL" o "ml" se refiere a mililitros, "µL" se refiere a microlitros, "gal" se refiere a galones, "°C" se refiere a grados Celsius, "R_f" se refiere a factor de retención, "pf" o "p.f." se refiere a punto de fusión, "dec" se refiere a descomposición, "pe" o "p.e." se refiere a punto de ebullición, "mm de Hg" se refiere a presión en milímetros de mercurio, "cm" se refiere a centímetros, "nm" se refiere a nanómetros, "abs." se refiere a absoluto, "conc." se refiere a concentrado, "c" se refiere a concentración en g/mL, "dppf" se refiere a 1,1' bis(difenilfosfino)ferroceno, "THF" se refiere a tetrahidrofurano, "DMF" se refiere a dimetilformamida, "DMAP" se refiere a dimetilaminopiridina; "DMSO" se refiere a dimetilsulfóxido; "NMP" se refiere a 1-metil-2-pirrolidinona, "DCM" se refiere a diclorometano, "DCE" se refiere a dicloroetano, "EtOAc" se refiere a acetato de etilo, "MeOH" se refiere a metanol, "HOAc" o "AcOH" se refiere a ácido acético, "H₂O" se refiere a agua; "NaOH" se refiere a hidróxido sodio, "HCl" se refiere a ácido clorhídrico, "Cs₂CO₃" se refiere a carbonato de cesio, "MgSO₄" se refiere a sulfato de magnesio, "Na₂SO₄" se refiere a sulfato de sodio, "solución salina" se refiere a una solución de cloruro de sodio acuosa saturada, "HATU" se refiere a hexafluorofosfato de O-(7-azabenzotriazol-1-il)-1,1,3,3-tetrametiluronio, "M" se refiere a molar, "mM" se refiere a milimolar, "µM" se refiere a micromolar, "nM" se refiere a nanomolar, "N" se refiere a normal, "TLC" se refiere a cromatografía de capa delgada, "HPLC" se refiere a cromatografía de líquido de alto desempeño, "HRMS" se refiere a espectro de masa de alta resolución, "L.O.D." se refiere a pérdida en el secado, "µCi" se refiere a

microcurios, "Lp." se refiere a intraperitonealmente, "Lv." se refiere a intravenosamente, anhid = anhidro; ac = acuoso; min = minuto; hr = hora; d = día; sat. = saturado; s = singlete, d = doblete; t = triplete; q = cuarteto; m = multiplete; dd = doblete de dobletes; br = amplio; LC = cromatografía líquida; MS = espectrografía de masa; ESI/MS = ionización por electrorociado/espectrografía de masa; RT = tiempo de retención; M = ión molecular.

Los siguientes ejemplos describen los procedimientos utilizados en la preparación de los compuestos de esta invención.

10

Ejemplo 1

N-Bencil-N-[3-(1H-indol-5-il)-bencil]-N',N'-dimetil-etano-1,2-diamina

Etapa 1: 3-(1H-Indol-5-il)-benzaldehído: Una mezcla de 5-bromo-indol (8.7 g, 44.4 mmol), ácido 3-formilbencenoborónico (10 g, 66.7 mmol), carbonato de cesio en agua (2M, 88.8 mL, 178 mmol) en 450 mL de dioxano se desgasifica (se evacua en vacío y se presuriza con nitrógeno, 3 veces) se agrega PdCl₂(dppf).DCM (1.1 g, 1.3 mmol) y la mezcla se desgasifica una vez más como se describió anteriormente. La mezcla resultante se calienta a 100° C durante 3h, luego se le permite enfriar a temperatura ambiente y se particiona entre dietil éter y agua. La fase acuosa se extrae con dietil éter y las fases orgánicas combinadas se lavan con agua, solución salina, se secan sobre MgSO₄, se filtran y se evaporan para dar el producto crudo. La cromatografía sobre gel de sílice (elusión con acetato de etilo/heptano) proporciona 5.6 g del producto deseado.

25

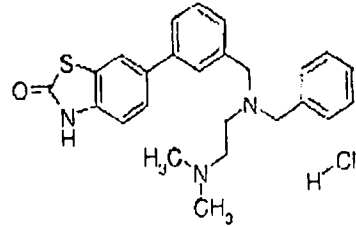
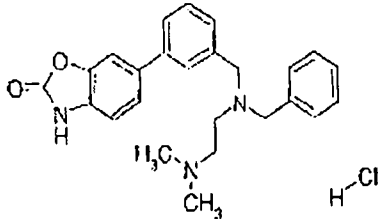
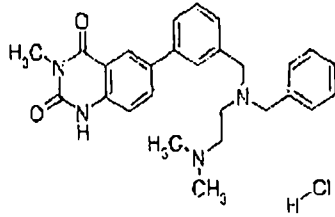
Etapa 2: N-Bencil-N-[3-(1H-indol-5-il)-bencil]-N',N'-dimetil-etano-1,2-diamina: Se agrega triacetoxiborohidruro de sodio (480 mg, 2.3 mmol) a una solución de 3-(1H-

indol-5-il)-benzaldehído (250 mg, 1.1 mmol) y N'-bencil-N,N-dimetil-etano-1,2-diamina (600 mg, 3.4 mmol) y ácido acético (204 mg, 3.4 mmol) en 8 mL de tetrahidrofurano. La mezcla se agita a temperatura ambiente durante la noche, y luego se diluye con acetato de etilo, y se neutraliza con la adición cuidadosa de solución de bicarbonato de sodio saturada. Las capas se separan y la fase orgánica se trata con resina de isocianato sostenida de poliestireno (1.49 mmol/g, 1.7 g) durante 2 h. La mezcla se filtra y el filtrado se lava con solución de carbonato de sodio 1M. La fase acuosa se extrae en acetato de etilo, y las fases orgánicas combinadas se secan sobre sulfato de magnesio, se filtran y se concentran para dar 290 mg del compuesto del título. LC/MS (método corto): tiempo de retención, 2.61 min; (M+H) = 384.

RMN ¹H (400 MHz, cloroformo-D) δ ppm: 2.20 (s, 6 H) 2.49-2.55 (m, 2 H), 2.65-2.68 (m, 2 H) 3.66 (s, 2 H) 3.69 (s, 2 H) 6.61 (br s, 1 H) 7.21-7.26 (m, 3 H) 7.28-7.34 (m, 3 H) 7.35 - 7.41 (m, 3 H) 7.45 (s, 2 H) 7.52 (d, 1 H, J= 7.6 Hz), 7.64 (s, 1 H) 7.85 (s, 1 H) 8.26 (s, 1 H).

Ejemplos 2 a 16

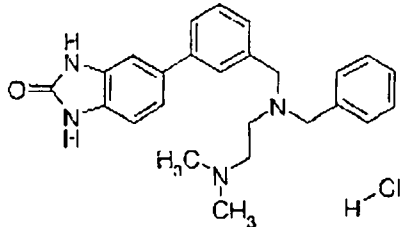
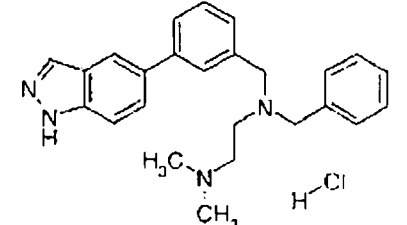
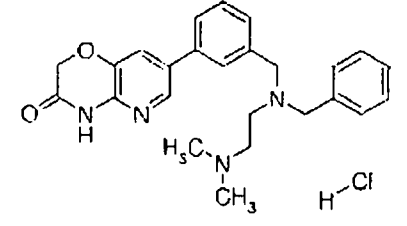
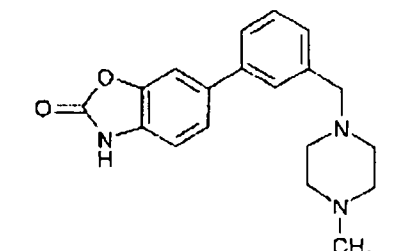
El ejemplo 1 se repite sustancialmente en los Ejemplos 2 a 16 con la excepción en la utilización de los materiales de partida y reactivos respectivos en cantidades apropiadas con el fin de preparar los Ejemplos 2 a 16 como se tabula en la Tabla 1. También resumidos en la Tabla 1 están los datos LC/MS observados para los ejemplos 2 a 16.

Ejemplo No.	Estructura Química y Nombre Químico	Datos LC/MS	
		RT (mins.)	M + H
2	 Clorhidrato de 6-(3-[[Bencil-(2-dimetilamino-etil)-amino]-metil]-fenil)-3H-benzotiazol-2-ona.	2.5 ^k	418
3	 Clorhidrato de 6-(3-[[Bencil-(2-dimetilamino-etil)-amino]-metil]-fenil)-3H-benzooxazol-2-ona.	2.41 ^a	402
4	 Clorhidrato de 6-(3-[[Bencil-(2-dimetilamino-etil)-amino]-metil]-fenil)-3-metil-1H-quinazolina-2,4-diona.	2.38 ⁿ	443

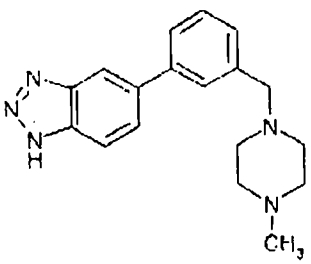
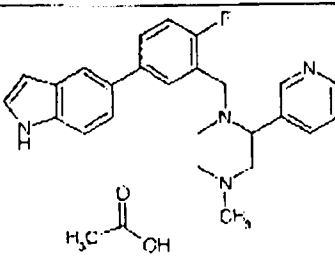
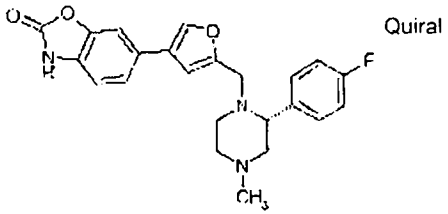
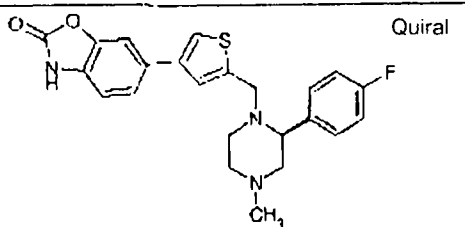
2.5^a

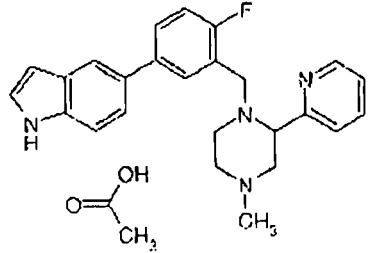
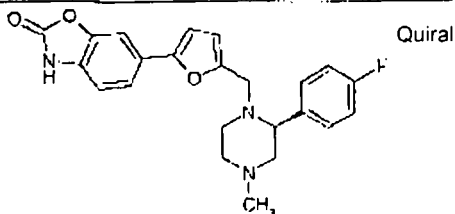
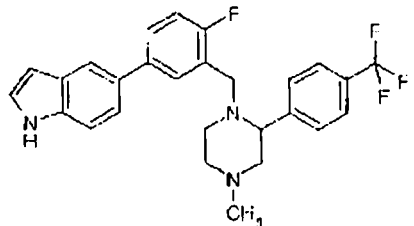
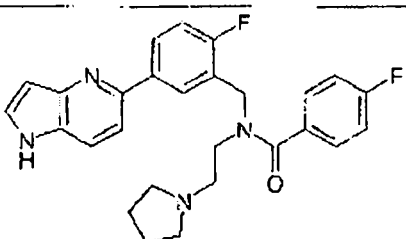
418

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5	 Clorhidrato de 5-(3-[[Bencil-(2-dimetilamino-etil)-amino]-metil]-fenil)-1,3-dihidro-benzoimidazol-2-ona.	2.23 ^a	401
6	 Clorhidrato de N-Bencil-N'-[3-(1H-indazol-5-il)-bencil]-N',N'-dimetil-etano-1,2-diamina.	1.53 ^a	385
7	 Clorhidrato de 7-(3-[[Bencil-(2-dimetilamino-etil)-amino]-metil]-fenil)-4H-pirido[3.2-b][1.4]oxazin-3-ona.	1.47 ^a	417
8	 6-[3-(4-Metil-piperazin-1-ilmetil)-fenil]-3H-benzooxazol-2-ona	1.75 ^a	324

265

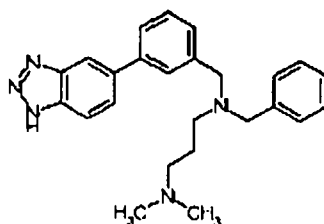
9 ^c	 5-[3-(4-Metil-piperazin-1-ilmetil)-fenil]1H-benzotriazol	1.64 ^a	308
10	 Acetato de 5-[4-Fluoro-3-(4-metil-2-piridin-3-il-piperazin-1-ilmetil)-fenil]-1H-indol	2.17 ^a 5.07 ^b	401
11	 6-{5-[2<i>R</i>-(4-Fluoro-fenil)-4-metil-piperazin-1-ilmetil]-furan-3-il}-3H-benzooxazol-2-ona. Quiral	5.69 ^b	408
12	 6-{5-[2<i>S</i>-(4-Fluoro-fenil)-4-metil-piperazin-1-ilmetil]-tiofen-3-il}-3H-benzooxazol-2-ona. Quiral	6.03 ^b	424

13	 Acetato de 5-[4-Fluoro-3-(4-metil-2-piridin-2-il-piperazin-1-ilmetil)-fenil]-1H-indol	6.18 ^b	401
14	 6-[5-[2S-(4-Fluoro-fenil)-4-metil-piperazin-1-ilmetil]-furan-2-il]-3H-benzooxazol-2-ona	5.98 ^b	408
15	 5-[4-Fluoro-3-[4-metil-2-(4-trifluorometil-fenil)-piperazin-1-ilmetil]-fenil]-1H-indol	7.87 ^b	468
16 ^u	 4-Fluoro-N-[2-fluoro-5-(1H-pirrol[3,2-b]piridin-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-benzamida	1.88 ^b	419

^a método LC/MS corto; ^b método LC/MS largo; ^c este Ejemplo 9 se sintetiza siguiendo los procedimientos del Ejemplo 42; ^d este Ejemplo 16 se sintetiza siguiendo los procedimientos del Ejemplo 20; n.a. - no disponible

Ejemplo 17

N-[3-(1H-Benzotriazol-5-il)-bencil]-N-bencil-N',N'-dimetil-propano-1,3-diamina



Etapa 1: N-Bencil-N-(3-boranil-bencil)-N',N'-dimetil-propano-1,2-diamina: Se agregan triacetoxiborohidruro de sodio (8.84 g, 14.0 mmol) y luego 4.5 mL de ácido acético a una solución de 3-boranilbencenocarboxaldehído (2.0 g, 13.34 mmol) y N'-bencil-N,N-dimetil-etano-1,2-diamina (2.5 g, 40.0 mmol) en 100 mL de 1,2-dicloroetano. La mezcla se agita a temperatura ambiente durante la noche, y luego esta se neutraliza con la adición cuidadosa de solución de bicarbonato de sodio saturada. Las capas se separan y la fase acuosa se extrae en diclorometano. Las fases orgánicas combinadas se secan sobre sulfato de magnesio, se filtran y se concentran para dar el producto crudo. La trituración con una mezcla de dietil éter y hexano da 2.9 g del producto. LC/MS: Tiempo de retención, 1.26 min; (M+H) = 313.

15 Siguiendo los procedimientos como se estableció anteriormente, N-bencil-N-(3-boranil-bencil)-N',N'-dimetil-propano-1,3-diamina se prepara partiendo de N'-bencil-N,N-dimetil-propano-1,3-diamina.

Etapa 2: N-Bencil-N',N'-dimetil-N-[3-(1-tritil-1H-benzotriazol-5-il)-bencil]-propano-1,3-diamina: Una mezcla de 5-bromo-1-tritil-1H-benzotriazol (220 mg, 0.5 mmol), N-bencil-N-(3-boranil-bencil)-N',N'-dimetil-propano-1,3-diamina (180 g, 0.55 mmol), y solución de carbonato de cesio en agua (2M, 1 mL, 2 mmol) se ponen juntas en 10 mL de dioxano se desgasifica (se evacua en vacío y se presuriza con argón, dos veces) y se agrega PdCl₂(dppf).DCM (21 mg, 0.025 mmol) y la mezcla se desgasifica dos o más veces como se describió anteriormente. La mezcla

resultante se calienta a 90° C durante 3 h, luego se le permite enfriar a temperatura ambiente y los volátiles se remueven en vacío. El residuo se particiona entre diclorometano y agua. La fase acuosa se extrae con diclorometano y las fases orgánicas combinadas se secan sobre MgSO₄, se filtran y se evaporan para dar el producto crudo. La cromatografía sobre gel de sílice (elusión con metanol/diclorometano) seguido por la trituración del material obtenido con dietil éter da 68 mg del compuesto del título.

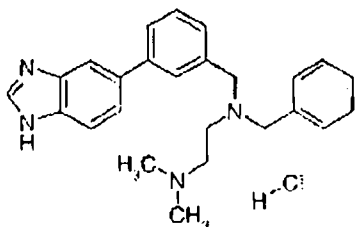
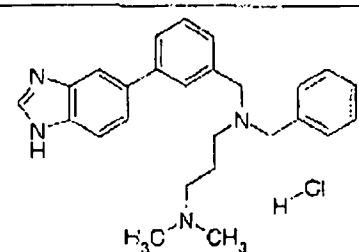
Etapa 3: N-[3-(1H-Benzotriazol-5-il)-bencil]-N-bencil-N',N'-dimetil-propano-1,3-diamina: Se disuelve N-Bencil-N',N'-dimetil-N-[3-(1-tritil-1H-benzotriazol-5-il)-bencil]-propano-1,3-diamina (60 mg, 0.093 mmol) en una mezcla de 5 mL de etanol, 5 mL de dioxano y 8 mL de solución de ácido clorhídrico acuosa 2M, y la mezcla resultante se agita a temperatura ambiente durante 6 h. Los volátiles se remueven en vacío y el residuo se particiona entre dietil éter y solución de HCl 1M. La fase acuosa se lava con dietil éter y las fases orgánicas combinadas se concentran en vacío para obtener el producto crudo, que se disuelve en una cantidad pequeña de solución de HCl 1M y secado por congelamiento. La purificación por HPLC (elusión con) proporciona 30 mg del compuesto del título. LC/MS (método corto): Tiempo de retención 1.19 min; (M+H) = 400.

RMN ¹H (400 MHz, metanol-D₄) δ ppm: 2.28 - 2.43 (m, 2 H) 2.89 (s, 6 H) 3.10 - 3.20 (m, 2 H) 3.24 - 3.30 (m, 2 H) 4.47 - 4.60 (m, 4 H) 7.47 - 7.54 (m, 3 H) 7.57 - 7.68 (m, 4 H) 7.83 - 7.91 (m, 2 H) 7.94 - 8.02 (m, 2 H) 8.18 (s, 1 H).

269

El Ejemplo 17 se repite sustancialmente en los Ejemplos 18 y 19 con la excepción en la utilización de los materiales de partida y reactivos respectivos en cantidades apropiadas con el fin de preparar los Ejemplos 18 y 19 como se tabula en la Tabla 2. También resumidos en la Tabla 2 están los datos LC/MS observados para los ejemplos 18 y 19.

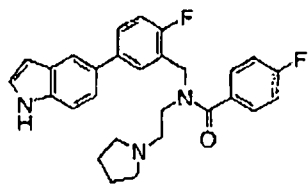
Tabla 2

Ejemplo No.	Estructura Química y Nombre Químico	Datos LC/MS	
		RT (mins.)	M + H
18	 Clorhidrato de N-[3-(1H-Benzoimidazol-5-il)-bencil]-N-bencil-N', N'-dimetil-etano-1,2-diamino.	1.26 ^a	385
19	 Clorhidrato de N-[3-(1H-Benzoimidazol-5-il)-bencil]-N-bencil-N',N'-dimetil-propano-1,3-diamina.	1.01 ^a	399

^a = método LC/MS corto

Ejemplo 20

4-Fluoro-N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-benzamida



Etapa 1: [2-Fluoro-5-(1H-indol-5-il)-bencil]-(2-pirrolidin-1-il-etil)-amina. Se agregan triacetoxiborohidruro de sodio (530 g, 2.51 mmol) y luego suficiente ácido acético para llevar el pH a 5 a una solución de 5-(4-fluoro-3-formilfenil)-1H-indol (200 mg, 0.84 mmol) y 1-(2-aminoetil)pirrolidina (191 mg, 1.67 mmol) en 15 mL de 1,2-dicloroetano. La mezcla se agita a temperatura ambiente durante la noche, y luego se diluye con diclorometano, y se neutraliza con la adición cuidadosa de solución de bicarbonato de sodio saturada. Las capas se separan y la fase acuosa se extrae en diclorometano. Las fases orgánicas combinadas se secan sobre sulfato de magnesio, se filtran y se concentran para dar el producto crudo. La cromatografía (elusión con metanol/diclorometano) suministra 90 mg del compuesto del título. LC/MS: Tiempo de retención, 0.34 min.

Etapa 2: 4-Fluoro-N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-benzamida: Se agrega cloruro de 4-fluorobenzilo (93 mg, 0.59 mmol) a una solución de [2-fluoro-5-(1H-indol-5-il)-bencil]-(2-pirrolidin-1-il-etil)-amina (90 mg, 0.27 mmol) y trietil amina (81 mg, 0.8 mmol) en 10 ml de diclorometano a temperatura ambiente. La mezcla resultante se agita a temperatura ambiente durante 2 h, y luego los volátiles se remueven en vacío y el residuo se disuelve en acetato de etilo y se lava con solución de HCl 1 M y agua. La fase acuosa se extrae con acetato de etilo, y las fases orgánicas combinadas se secan sobre sulfato de magnesio, se filtran y se concentran para dar el producto crudo. La cromatografía (elusión con metanol/diclorometano) suministra 181 mg del producto. Este se disuelve en diclorometano y se lava con solución de bicarbonato de sodio saturada. La fase orgánica se seca sobre sulfato de magnesio, se filtra y se concentra para proporcionar 92 mg del compuesto del título. LC/MS: Tiempo de retención, 2.55 min; (M+H) = 460.

271

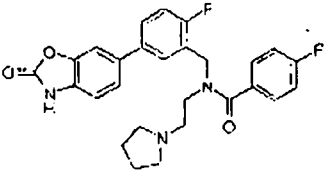
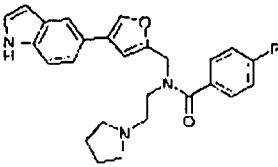
RMN ¹H (400 MHz, cloroformo-D) δ ppm: 1.72 (br s, 1 H) 2.16 (br s, 3 H) 2.38 (br s, 1 H) 2.63 (br s, 1 H) 2.90 - 3.34 (m, 4 H) 3.44 (br s, 1 H) 3.86 (br s, 1 H) 4.81 (br s, 2 H) 6.56 - 6.67 (s, 1 H) 7.11 (t, J=9.40 Hz, 3 H) 7.30 - 7.43 (m, 3 H) 7.46 (d, J=9.40 Hz, 1 H) 7.49 - 7.69 (m, 3 H) 7.77 (s, 1 H) 8.37 (s, 1 H).

5

Ejemplos 21 a 41

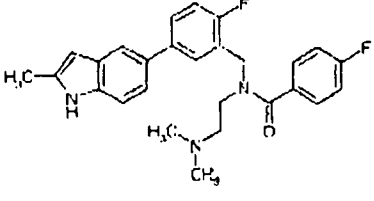
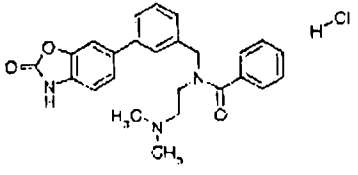
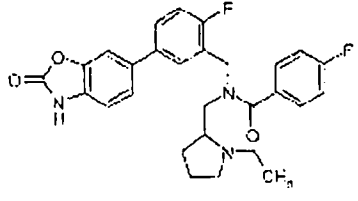
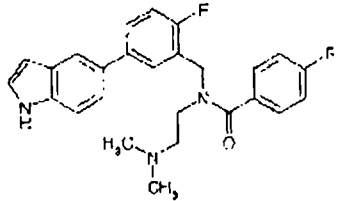
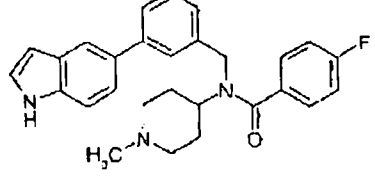
El Ejemplo 20 se repite sustancialmente en los Ejemplos 21 a 41 con la excepción en la utilización de los materiales de partida y reactivos respectivos en cantidades apropiadas con el fin de preparar, los Ejemplos 21 a 41 como se tabula en la Tabla 3. También resumidos en la Tabla 3 están los datos LC/MS observados para los ejemplos 21 a 41.

Tabla 3

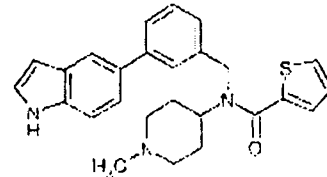
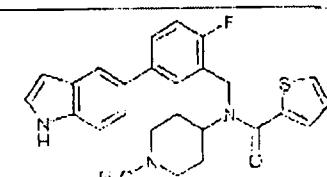
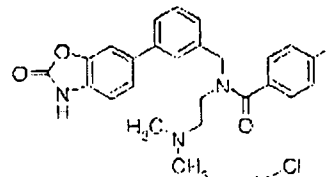
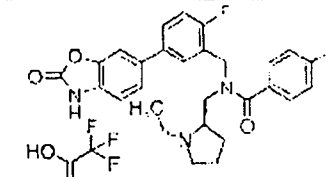
Ejemplo No.	Estructura Química y Nombre Químico	Datos LC/MS	
		RT (mins.)	M + H
21	 4-Fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihidro-benzooxazol-6-il5-bencil]-N-(2-pirrolidin-1-il-etil)-benzamida	2.43 ^a	478
22 ^c	 4-Fluoro-N-[4-(1h-indol-5-il)-furan-2-ilmetil]-N-(2-pirrolidin-1-il-etil)-benzamida	5.45 ^b	432

15

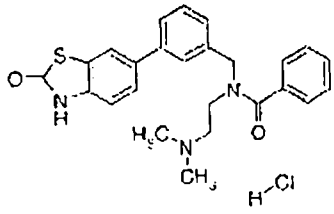
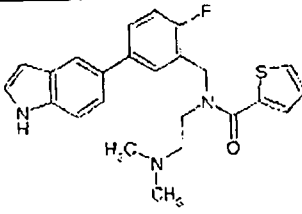
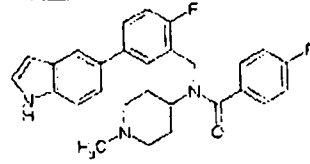
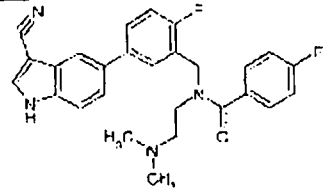
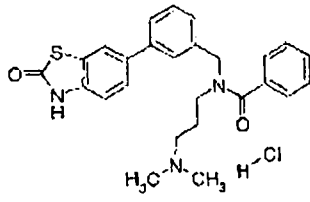
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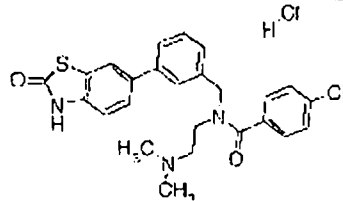
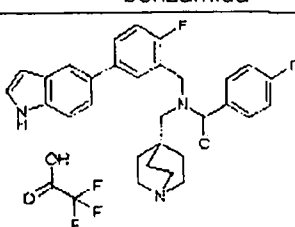
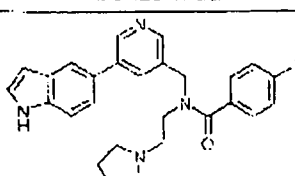
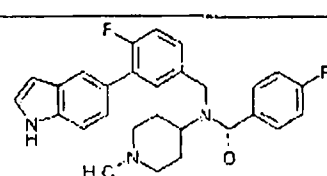
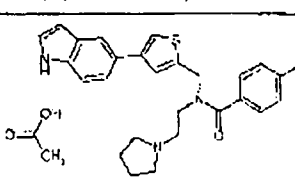
23	 N-(2-Dimetilamino-etil)-4-fluoro-N-[2-fluoro-5-(2-metil-1H-indol-5-il)-bencil]-benzamida	6.69 ^b	448
24	 Clorhidrato de N-(2-Dimetilamino-etil)-N-[3-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-benzamida.	2.18 ^a	416
25	 N-(1-Etil-pirrolidin-2-ilmetil)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-benzamida	2.47 ^a	492
26	 N-(2-Dimetilamino-etil)-4-fluoro-N-[2-fluoro-5-(1H-indol-5-il)-bencil]-benzamida	6.5 ^b	434
27	 4-Fluoro-N-[3-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-benzamida.	2.5 ^a	442

273

28	 Ácido Tiofeno-2-carboxílico [3-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida.	2.46 ^a	430
29	 Ácido tiofeno-2-carboxílico [2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida	5.17 ^b	448
30	 Clorhidrato de 4-Cloro-N-(2-dimetilamino-etil)-N-[3-(2,3-dihidro-benzooxazol-6-il)-bencil]-benzamida.	2.37 ^a	450
31 ^c	 Trifluoro-acetato de N-(1-Etil-pirrolidin-2R-ilmetil)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-benzamida	2.29 ^a	492

274

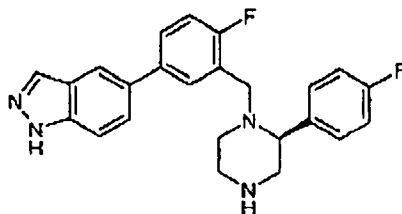
32	 Clorhidrato de N-(2-Dimetilamino-etil)-N-[3-(2-oxo-2,3-dihidro-benzotiazol-6-il)-bencil]-benzamida.	2.27 ^a	432
33	 Ácido tiofen-2-carboxílico (2-dimetilamino-etil)-[2-fluoro-5-(1H-indol-5-il)-bencil]-amida	5.29 ^b	422
34	 4-Fluoro-N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-benzamida	6.23 ^b	460
35	 N-[5-(3-Ciano-1H-indol-5-il)-2-fluoro-bencil]-N-(2-dimetilamino-etil)-4-fluoro-benzamida	5.4 ^b	459
36	 Clorhidrato de N-(3-Dimetilamino-propil)-N-[3-(2-oxo-2,3-dihidro-benzotiazol-6-il)-bencil]-benzamida;	1.48 ^a	446

37	 Clorhidrato de 4-Cloro-N-(2-dimetilamino-etil)-N-[3-(2-oxo-2,3-dihidro-benzotiazol-6-il)-bencil]-benzamida	2.43 ^a	466
38	 Trifluoro-acetato de N-(1-Aza-biciclo[2,2,2]oct-4-ilmetil)-4-fluoro-N-[2-fluoro-5-(1H-indol-5-il)-bencil]-benzamida	5.75 ^b	486
39	 4-Fluoro-N-[5-(1H-indol-5-il)-piridin-3-ilmetil]-N-(2-pirrolidin-1-il-etil)-benzamida	4.28 ^b	443
40	 4-Fluoro-N-[4-fluoro-3-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-benzamida	6.29 ^b	460
41	 Acetato de 4-Fluoro-N-[4-(1H-indol-5-il)-tiofen-2-ilmetil]-N-(2-pirrolidin-1-il-etil)-benzamida	6.53 ^b	448

^a = método LC/MS corto; ^b = método LC/MS largo; ^c este Ejemplo se sintetiza siguiendo los procedimientos del Ejemplo 104.

Ejemplo 42

5-{4-Fluoro-3-[2S-(4-fluoro-fenil)-piperazin-1-ilmetil]-fenil}-1H-indazol



- 5 Etapa 1: 2S-(4-Fluorofenil)-piperazina: Se agrega una solución de etilen diamina (7.4 g, 123.5 mmol) en etanol (100 mL) en forma de gota durante 15 minutos a una solución agitada de 4-fluoroglicoxal (21.0 g, 123.5 mmol) en etanol (300 mL) y la reacción se deja durante 4 horas. Se agrega borohidruro sodio (23.5 g, 622 mmol) y la mezcla se agita durante la noche a temperatura ambiente. Se agrega agua
- 10 (200 mL) y la mezcla se agita durante 1 hora después que la mayoría del etanol se remueve *in vacuo*. La solución concentrada se extrae con DCM (4 x 100 mL) y los extractos combinados se combinan, se lavan con solución salina y se secan sobre Na₂SO₄. El disolvente se remueve *in vacuo* para producir un sólido amarillo pálido (19.0 g, 86%). 8.8 g de este material se disuelve en metanol (60 mL) y se agrega a
- 15 una solución de N-acetil-1-leucina (16.5 g, 95.2 mmol) en metanol (100 mL). Se agrega acetato de etilo (550 mL) y la mezcla se deja a temperatura ambiente durante la noche. El precipitado se filtra y se seca para dar un sólido (9.0 g) que se toma en NaOH ac. 4M (100 mL) y se extrae con DCM (4 x 100 mL). Los extractos combinados se combinan, se lavan con solución salina y el disolvente se remueve
- 20 *in vacuo* para producir un sólido (3.1 g). Este sólido se recrystaliza a partir de EtOAc para producir 2.23 g del enantiómero S (el compuesto del título). El exceso enantiomérico se determina por cromatografía quiral empleando las siguientes condiciones cromatográficas quirales: Columna: Phenomenex Chirex (S)-ICR 250 x 4.6 mm; disolvente: n-heptano:etanol [80:20] + 0.3% de TFA; L = 254 nm, índice
- 25 de flujo = 1 mL/min, sensibilidad UV = 0.1 AUF; ~1 mg de compuesto en 1 mL de

n-heptano: etanol [75:25] utilizando racematos y compuestos quirales auténticos como referencia.

Etapa 2: éster de *terc*-butilo de ácido 3S-(4-Fluorofenil)-piperazina-1-carboxílico:

5 se disuelve 2S-(4-fluorofenil)-piperazina (3.75 g, 20.83 mmol) en diclorometano y se enfría a 0° C. Se agrega na solución de dicarbonato de di-*terc*-butilo (4.77 g, 21.87 mmol) en 10 mL de diclorometano y la reacción se deja a 0° C durante una hora. El disolvente se remueve *in vacuo* para producir un sólido blanco cristalino (5.85g).

10

Etapa 3: éster de *terc*-butilo de ácido 5-Bromo-indazol-1-carboxílico: Se agregan di-*terc*-butildicarbonato (11.4 g, 52.21 mmol), trietilamina (6.27 g, 62.16 mmol) y 4-(N,N-dimetilaminopiridina (304 mg, 2.49 mmol) secuencialmente a una solución de 5-bromoindazol (9.8 g, 49,73 mmol) en tetrahidrofuranoo a temperatura ambiente.

15 La mezcla se agita a temperatura ambiente durante 71.5 h y luego esta se calienta a reflujo durante 16 h. Los volátiles se remueven en vacío y el residuo se disuelve en diclorometano y se lava con solución salina, se seca sobre sulfato de magnesio, se filtra y se concentra para dar el producto crudo. La cromatografía (elusión con dietil éter/heptano) da 13.98 g del compuesto del título. LC: Tiempo
20 de retención, 3.93 min.

Etapa 4: éster de *terc*-butilo de ácido 5-(4-Fluoro-3-formilfenil)-indazol-1-carboxílico: Una mezcla de éster de *terc*-butilo de ácido 5-bromo-indazol-1-carboxílico (3.37 mmol), 2-fluoro-4-(4,4,5,5-tetrametil-[1,3]dioxoboran-2-il)-benzaldehído (1.01 g, 4.04 mmol)) PdCl₂(dppf).DCM (27 mg, 0.03 mmol) en 16
25 niL de dioxano se desgasifica (se evacua en vacío y se presuriza con argón, tres veces); se agrega carbonato de cesio en agua (2M, 6.73 mL, 13.46 mmol) y la

778

mezcla se desgasifica tres o más veces como se describió anteriormente. La mezcla resultante se calienta a 85° C durante 6 h, luego se le permite enfriar a temperatura ambiente y se deja durante la noche. La mezcla se diluye con diclorometano y se lava con solución salina. La fase acuosa se extrae con
5 diclorometano y las fases orgánicas combinadas se lavan con solución salina, se secan sobre MgSO₄, se filtran y se evaporan para dar el producto crudo. La cromatografía sobre gel de sílice (elusión con dietil éter/heptano) da 820 mg del compuesto del título.

- 10 Etapa 5: 5-{4-Fluoro-3-[2S-(4-fluoro-fenil)-piperazin-1-ilmetil]-fenil}-1H-indazol: éster de *terc*-butilo de ácido 3S-(4-Fluorofenil)-piperazina-1-carboxílico (150 mg, 0.54 mmol) y éster de *terc*-butilo de ácido 5-(4-fluoro-3-formilfenil)-indazol-1-carboxílico (210 mg, 0.62 mmol) se disuelve en DCE (5 mL) y se agrega ácido acético glacial (32 mg, 0.54 mmol) seguido por sodio *tris*-acetoxiborohidruro (341
15 mg, 1.6 mmol). La reacción se agita durante la noche a temperatura ambiente. Se agrega diclorometano y la mezcla se lava con agua y solución salina y se seca sobre Na₂SO₄. El disolvente se remueve *in vacuo* para dar el producto crudo. La cromatografía (elusión con metanol/diclorometano) suministra 200 mg del producto. Este se trata con 15 mL de TFA acuoso al 95% durante 1.5 h. Los
20 volátiles se remueven en vacío y el residuo se tritura con dietil éter (3x) dando 70 mg del producto. LC/MS (periodo largo): Tiempo de retención, 6.14 min; (M+H) = 405.

- RMN ¹H (400 MHz, metanol-D₄) δ ppm: 2.57 (td, J=12.64, 2.64 Hz, 1 H) 3.09 - 3.36
25 (m, 5 H) 3.41 (d, J = 13.6 Hz, 1 H) 3.67 (dd, J=1 1.43, 3.08 Hz, 1 H) 3.77 (d, J=13.6 Hz, 1 H) 7.10 - 7.21 (m, 3 H) 7.53 - 7.62 (m, 6 H) 7.94 (t, J=1.32 Hz, 1 H) 8.11 (s, 1 H).

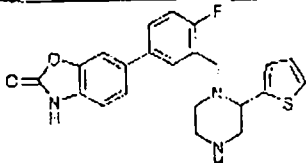
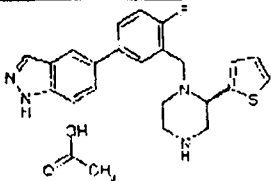
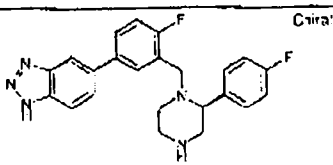
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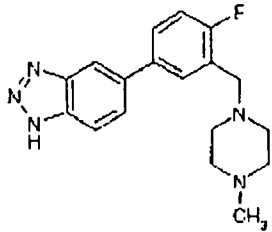
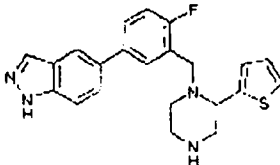
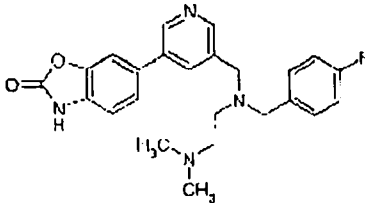
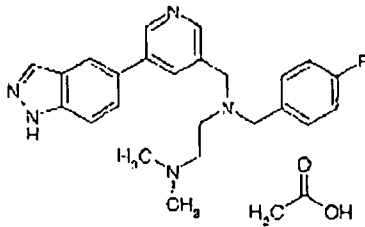
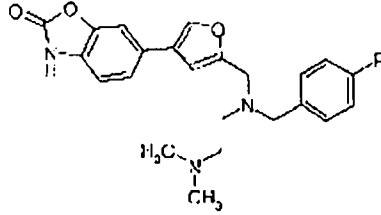
Ejemplos 43 a 52

Ejemplo 42 se repite sustancialmente en los Ejemplos 43 a 52 con la excepción en la utilización de los materiales de partida y reactivos respectivos en 5 cantidades apropiadas con el fin de preparar los Ejemplos 43 a 52 como se tabula en la Tabla 4. También resumidos en la Tabla 4 están los datos LC/MS observados para los ejemplos 43 a 52.

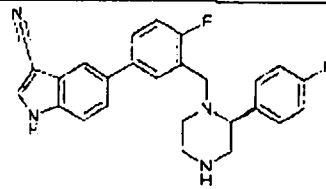
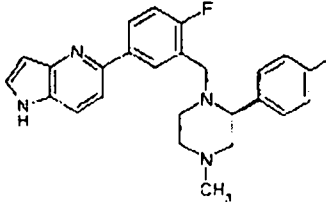
Tabla 4

10

Ejemplo No.	Estructura Química y Nombre Químico	Datos LC/MS	
		RT (mins.)	M + H
43	 6-[4-Fluoro-3-(2-tiofen-2-il-piperazin-1-ilmetil)-fenil]-3H-benzooxazol-2-ona	5.04 ^b	410
44	 Acetato de 5-[4-Fluoro-3-(2S-tiofen-2-il-piperazin-1-ilmetil)-fenil]-1H-indazol	5.19 ^h	393
45	 5-[4-Fluoro-3-[2S-(4-fluoro-fenil)-piperazin-1-ilmetil]-fenil]-1H-benzotriazol	5.05 ^b	406

46	 5-[4-Fluoro-3-(4-metil-piperazina-1-ilmetil)-fenil]-1H-benzotriazol	1.88 ^a	326
47	 5-[4-Fluoro-3-(2-tiofen-2-il-piperazin-1-ilmetil)-fenil]-1H-indazol	5.86 ^h	393
48 ^f	 6-(5-[[2-Dimetilamino-etil)-(4-fluoro-bencil)-amino]-metil]-piridin-3-il)-3H-benzooxazol-2-ona	4.02 ^h	421
49 ^c	 Acetato de N-(4-Fluoro-bencil)-N-[5-(1H-indazol-5-il)-piridin-3-ilmetil]-N',N'-dimetil-etano1,2-diamina	3.72 ^d	404.2
50 ^c	 6-(5-[[2-Dimetilamino-etil)-(4-fluoro-bencil)-amino]-metil]-furan-3-il)-3H-benzooxazol-2-ona	5.16 ^b	410

281

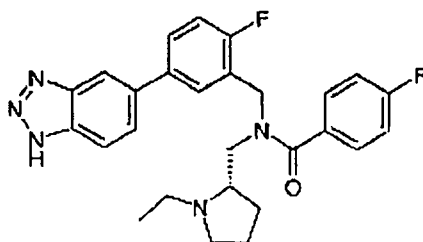
51	 Quiral 5-(4-Fluoro-3-[2S-(4-fluoro-fenil)-piperazin-1-ilmetil]-fenil)-1H-indol-3-carbonitrilo	6.03 ^c	429
52	 Quiral 5-(4-Fluoro-3-[2-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-fenil)-1H-pirrol[3,2-b]piridina	4.49 ^b	419

^a= método LC/MS corto; ^b= método LC/MS largo; ^c = preparado como en el Ejemplo 113, Etapa 1.

5

Ejemplo 53

N-[5-(1H-Benzotriazol-5-il)-2-fluoro-bencil]-N-(1-etil-pirrolidin-2S-ilmetil)-4-fluoro-benzamida



- 10 Etapa 1: (1-Etil-pirrolidin-2S-ilmetil)-[2-fluoro-5-(1-tritil-1H-benzotriazol-5-il)-bencil]-amina: Una mezcla de 2-fluoro-5-(1-tritil-1H-benzotriazol-5-il)-benzaldehído (368 mg, 0.76 mmol), (S)-(+)-1-etil-2-aminometilpirrolidina (120 mg, 0.83 mmol) y tamices moleculares en 10 mL de metanol se agita a temperatura ambiente durante 3h. La mezcla se enfría a - 78° C, y se agrega borohidruro sodio (72 mg,
- 15 1.9 mmol) y a la mezcla se le permite calentar a temperatura ambiente y se agita

282

durante la noche. Los volátiles se remueven en vacío y el residuo se diluye con diclorometano y se lava con agua. La fase acuosa se extrae con diclorometano, y las fases orgánicas combinadas se lavan con solución salina, se secan sobre sulfato de magnesio, se filtran y se concentran para dar el producto crudo. La cromatografía (elución con metanol/diclorometano) da 255 mg del producto.

Etapa 2: N-(1-Etil-pirrolidin-2S-ilmetil)-4-fluoro-N-[2-fluoro-5-(1-tritil-1H-benzotriazol-5-il)-bencil]-benzamida. Se agrega HATU (122mg, 0.32 mmol) a una solución de (1-etil-pirrolidin-2-ilnietil)-[2-fluoro-5-(1-tritil-1H-benzotriazol-5-il)-bencil]-amina (127 mg, 0.21 mmol), ácido 4-fluorobenzoico (45 mg, 0.32 mmol) y diisopropiletilamina (82 mg, 0.64 mmol) en 1 mL de dimetilformamida, y la mezcla resultante se agita a temperatura ambiente durante la noche. La mezcla se diluye con diclorometano, y se lava con solución de bicarbonato de sodio saturada y solución salina, se seca sobre sulfato de magnesio, se filtra y se concentra para dar el producto crudo. La cromatografía (elución con metanol/diclorometano) suministra 98 mg del producto. LC/MS: Tiempo de retención, 3.39 min; (M+H) = 718.

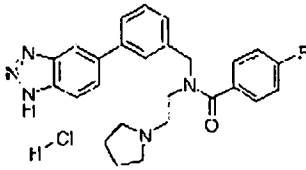
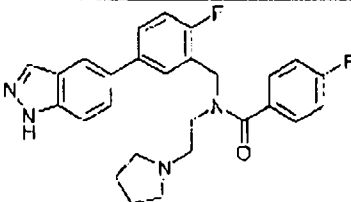
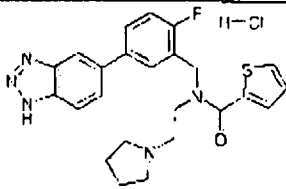
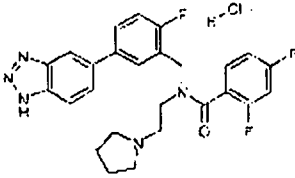
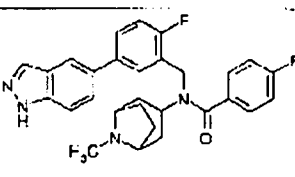
Etapa 3: N-[5-(1H-Benzotriazol-5-il)-2-fluoro-bencil]-N-(1-etil-pirrolidin-2S-ilmetil)-4-fluoro-benzamida: N-(1-Etil-pirrolidin-2-ilmetil)-4-fluoro-N-[2-fluoro-5-(1-tritil-1H-benzotriazol-5-il)-bencil]-benzamida (143 mg, 0.2 mmol) en 4 mL de metanol y 2 mL de 4M HCl en dioxano se agita a temperatura ambiente durante 24 h. El disolvente se remueve en vacío y el residuo purificado por HPLC. El material obtenido se trata con ácido clorhídrico para dar 100 mg del compuesto del título. LC/MS (periodo largo): Tiempo de retención, 5.64 min; (M+H) = 476.

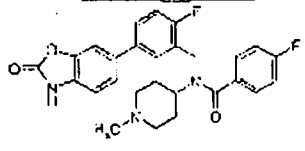
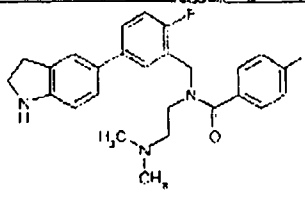
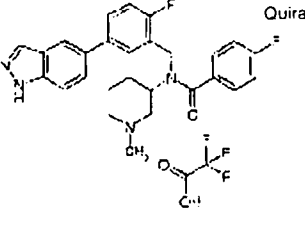
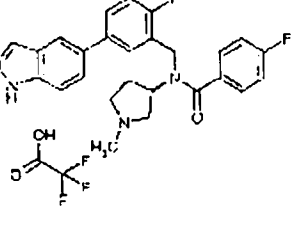
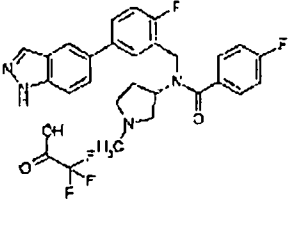
RMN ^1H (400 MHz, metanol- D_4) δ ppm: 1.29 - 1.46 (m, 3 H) 1.86 - 1.99 (m, 1 H)
2.04 - 2.19 (m, 2 H) 2.31 (ddd, $J=13.19, 7.03$ Hz, 1 H) 3.08 - 3.28 (m, 2 H) 3.48 (br
s, 1 H) 3.68 - 3.78 (m, 2 H) 3.85 (dd, $J=14.73, 5.49$ Hz, 1 H) 4.02 (dd, $J=14.73,$
5.49 Hz 1 H) 4.76 - 4.95 (m, 2 H) 7.18 - 7.32 (m, 3 H) 7.51- 7.64 (m, 3 H) 7.71-
5 7.79 (m, 2 H) 7.98 (d, $J=8.57$ Hz, 1 H) 8.06 (s, 1 H).

Ejemplos 54 a 65

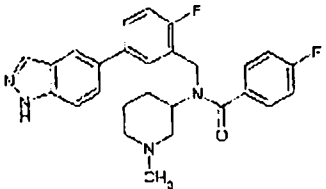
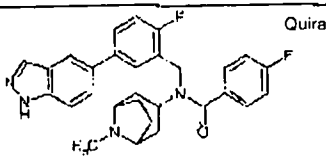
El Ejemplo 53 se repite sustancialmente en los Ejemplos 54 a 65 con la
10 excepción en la utilización de los materiales de partida y reactivos respectivos en
cantidades apropiadas con el fin de preparar los Ejemplos 54 a 65 como se tabula
en la Tabla 5. También resumidos en la Tabla 5 están los datos LC/MS
observados para los ejemplos 54 a 65.

Tabla 5

Ejemplo No.	Estructura Química y Nombre Químico	Datos LC/MS	
		RT (mins.)	M + H
54	 Clorhidrato de N-[3-(1H-benzotriazol-5-il)-bencil]-4-fluoro-N-(2-pirrolidin-1-il-etil)-benzamida	5.26 ^b	444
55	 4-Fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-benzamida	4.82 ^b	461
56	 Clorhidrato de [5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-(2-pirrolidin-1-il-etil)-amida de ácido tiofen-2-carboxílico	5.22 ^b	450
57	 Clorhidrato de N-[5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-2,4-difluoro-N-(2-pirrolidin-1-il-etil)-benzamida	5.53 ^b	480
58	 4-Fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(endo-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-benzamida	5.09 ^b	487

59	 4-Fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-N-(2-pirrolidin-1-il-etil)-benzamida	4.79 ^b	478
60	 N-[5-(2,3-Dihidro-1H-indol-5-il)-2-fluoro-bencil]-N-(2-dimetilamino-etil)-4-fluoro-benzamida	3.91 ^b	436
61	 Trifluoro-acetato de 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(1-metil-piperidin-3S-il)-benzamida	4.99 ^b	461
62	 Trifluoro-acetato de 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(1-metil-pirrolidin-3R-il)-benzamida	4.42 ^b	447
63	 Trifluoro-acetato de 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(1-metil-pirrolidin-3S-il)-benzamida	4.35 ^b	447

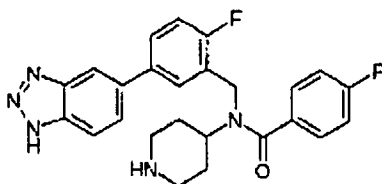
286

64	 4-Fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(1-metil-piperidin-3-il)-benzamida	4.91 ^b	461
65	 4-Fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(exo-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-benzamida	5.22 ^b	487

^b=método LC/MS largo;

Ejemplo 66

5 N-[5-(1H-Benzotriazol-5-il)-2-fluoro-bencil]-4-fluoro-N-piperidin-4-il-benzamida



Etapa 1: éster de 2-trimetilsilanil-etilo de ácido 4-Oxo-piperidina-1-carboxílico: se agregan éster de 2-trimetilsilanil-etilo- éster de 4-nitro-fenilo de ácido carbónico

10 (8.33 g, 29.3 mmol), trietilamina (12.3 g, 122 mmol) y DMAP (3.6 g, 29.5 mmol) a una solución a temperatura ambiente de clorhidrato de 4-piperidona (4.52 g, 33.4 mmol) en 100 mL de acetonitrilo. La mezcla resultante se calienta a reflujo durante 2 h, luego se enfría y los volátiles se remueven en vacío. El residuo se disuelve en diclorometano, se lava con agua y solución de NaOH 1M, y se concentra en vacío

15 para dar 6.3 g del producto.

283

Etapa 2: Éster de 2-trimetilsilanil-etilo de ácido 4-Amino-piperidina-1-carboxílico:

Se agrega una suspensión de 10% de paladio en carbono (200 mg) en agua a éster de 2-trimetilsilanil-etilo de ácido 4-oxo-piperidina-1-carboxílico (2.42 g, 10 mmol) en 100 mL de metanol. Se agrega en forma de gota formato de amonio (6.0 g, 95 mmol) en agua, y la mezcla se agita vigorosamente durante la noche. La mezcla se filtra y el filtrado se concentra en vacío para dar el producto crudo. La cromatografía (elusión con metanol-diclorometano) suministra 0.98 g del producto.

Etapa 3: Éster de 2-trimetilsilani-1-etilo de ácido 4-[2-Fluoro-5-(1-tritil-1H-

10 benzotriazol-5-il)-bencilamino]-piperidina-1-carboxílico: Se agregan triacetoxiborohidruro de sodio (890 mg, 4.2 mmol) y ácido acético (126 mg, 4.2 mmol) a una solución de 5-(4-fluoro-3-formilfenil)-1-tritil-1H-benzotriazol (1.0 mg, 2.1 mmol) y éster de 2-trimetilsilaniL-etilo de ácido 4-amino]-piperidina-1-carboxílico (760 mg, 3.1 mmol) en dicloroetano. La mezcla se agita a temperatura ambiente durante la noche, y luego se diluye con diclorometano, y se neutraliza con adición cuidadosa de solución de carbonato de sodio 1M. Las capas se separan y la fase acuosa se extrae con diclorometano. Las fases orgánicas combinadas se lavan con solución salina, se secan sobre sulfato de magnesio, se filtran y se concentran para dar el producto crudo. La cromatografía suministra 980 mg del producto. LC/MS: Tiempo de retención, 3.27 y 3.34 min; (M+H) = 712.

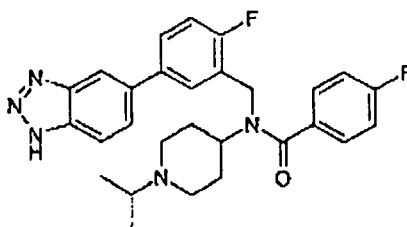
Etapa 4: Éster de 2-trimetilsilanil-etilo de ácido 4-{(4-Fluoro-benzoil)-[2-fluoro-5-(1-tritil-1H-benzotriazol-5-il)-bencil]-amino}-piperidina-1-carboxílico: se agrega HATU a una solución de éster de 2-trimetilsilani-1-etilo de ácido 4-[2-Fluoro-5-(1-tritil-1H-benzotriazol-5-il)-bencilamino]-piperidina-1-carboxílico, ácido 4-fluorobenzoico y diisopropiletilamina y la mezcla resultante se agita a temperatura ambiente durante la noche. La mezcla se diluye con acetato de etilo se lava con solución de

carbonato de sodio 1M. Las capas se separan y la fase acuosa se extrae con acetato de etilo. Las fases orgánicas combinadas se lavan con solución salina, se secan sobre sulfato de magnesio, se filtran y se concentran para dar el producto crudo. La cromatografía (elusión con dietil éter/hexano, seguido por acetato de etilo/hexano) suministra 740 mg del producto.

Etapa 5: N-[5-(1H-Benzotriazol-5-il)-2-fluoro-bencil]-4-fluoro-N-piperidiri-4-il-benzamida y 4-Fluoro-N-[2-fluoro-5-(1-tritil-1H-benzotriazol-5-il)-bencil]-N-piperidin-4-il-benzamida: Se agrega fluoruro de tetrabutilamonio (1M en THF, 2.6 mL, 2.6 mmol) a una mezcla de éster de 2-trimetilsilanil-etilo de ácido 4-((4-Fluorobenzoil)-[2-fluoro-5-(1-tritil-1H-benzotriazol-5-il)-bencil]-amino)-piperidina-1-carboxílico (730 mg, 0.88 mmol) y tamices moleculares de 4 Amstrongs en 5 mL de THF. Después de 3 h la mezcla se filtra y el disolvente se remueve *in vacuo*. El residuo se eluye a través de una columna de intercambio de catión SCX (elusión con diclorometano, seguido por 1-2% de amoniaco en metanol) para dar una mezcla del productos. La cromatografía (elusión con metanol/diclorometano, seguido por metanol/diclorometano con una cantidad pequeña de 1-2% de amoniaco en metanol) da 110 mg de 4-fluoro-N-[2-fluoro-5-(1-tritil-1H-benzotriazol-5-il)-bencil]-N-piperidin-4-il-benzamida (LC/MS: Tiempo de retención, 3.03 min; (M+H) = 690) y 170 mg de N-[5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-4-fluoro-N-piperidin-4-il-benzamida (LCMS: Tiempo de retención, 2.22 min; (M+H) = 448).

RMN ¹H (400 MHz, metanol-D₄) δ ppm: 1.72 - 2.11 (m, 5 H) 2.36 - 2.73 (m, 2 H) 3.03 - 3.24 (m, 2 H) 3.82 - 4.17 (m, 1 H) 4.74 - 4.84 (m, 1 H) 7.12 - 7.29 (m, 3 H) 7.47 - 7.56 (m, 2 H) 7.58 - 7.69 (m, 8 H) 7.93 (d, 1 H, J = 8.6 Hz) 7.98 (s, 1 H).

N-[5-(1H-Benzotriazol-5-il)-2-fluoro-bencil]-4-fluoro-N-(1-isopropil-piperidin-4-il)-benzamida



- 5 Etapa 1: 4-Fluoro-N-[2-fluoro-5-(1-tritil-1H-benzotriazol-5-il)-bencil]-N-(1-isopropil-piperidin-4-il)-benzamida: Una mezcla de 4-Fluoro-N-[2-fluoro-5-(1-tritil-1H-benzotriazol-5-il)-bencil]-N-piperidin-4-il-benzamida (25 mg, 0.04 mmol), yoduro de isopropilo (34 mg, 0.2 mmol) y carbonato de potasio (28 mg, 0.2 mmol) en 2 mL de DMF se calienta a 40° C durante 3 h cuando se agrega yoduro de isopropilo
- 10 adicional (34 mg, 0.2 mmol). La mezcla se calienta durante unas 2 horas adicionales y luego se deja a temperatura ambiente durante 10 días. La mezcla se diluye con agua y el producto se extrae en acetato de etilo. Las fases orgánicas combinadas se secan sobre sulfato de magnesio, se filtran y se concentran para dar el producto crudo. La cromatografía (elusión con metanol/diclorometano)
- 15 suministra 18 mg del producto.

- Etapa 2: N-[5-(1H-Benzotriazol-5-il)-2-fluoro-bencil]-4-fluoro-N-(1-isopropil-piperidin-4-il)-benzamida: Se agrega ácido trifluoroacético (TFA, 0.25 mL) a una solución de 4-fluoro-N-[2-fluoro-5-(1-tritil-1H-benzotriazol-5-il)-bencil]-N-(1-
- 20 isopropil-piperidin-4-il)-benzamida (18 mg, 0.024 mmol) en 1 mL de diclorometano y la mezcla resultante se agita a temperatura ambiente durante 3 h, cuando se agrega unos 0.5 mL adicionales de TFA. Esta se agita durante la noche y luego la mezcla se neutraliza por la adición cuidadosa de carbonato de sodio 1M. Las capas se separan, la fase acuosa se extrae con diclorometano, y las fases
- 25 orgánicas combinadas se secan sobre sulfato de magnesio, se filtran, y los

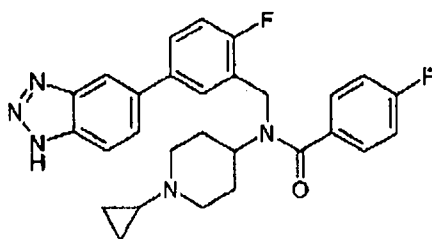
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volátiles se remueven en vacío para dar el producto crudo. La cromatografía (elusión con metanol/diclorometano) suministra 6.5 mg del producto. LC/MS: Tiempo de retención, 2.25 min; (M+H) = 490.

5

Ejemplo 68

N-[5-(1H-Benzotriazol-5-il)-2-fluoro-bencil]-N-(1-ciclopropil-piperidin-4-il)-4-fluoro-benzamida



10 Etapa 1: N-(1-Ciclopropil-piperidin-4-il)-4-fluoro-N-[2-fluoro-5-(1-tritil-1H-benzotriazol-5-il)-bencil]-benzamida. Se agrega cianoborohidruro sostenido en sólido (2.5 mmol/g, 46 mg) a una solución de 4-fluoro-N-[2-fluoro-5-(1-tritil-1H-benzotriazol-5-il)-bencil]-N-piperidin-4-il-benzamida (20 mg, 0.029 mmol), (1-etoxi-ciclopropoxi)-trimetilsilano (25 mg, 0.145 mmol) y ácido acético (1.74 mg, 0.029 mmol) en 1 mL de metanol. La mezcla se agita a 45° C durante 2 h y luego a 75° C durante la noche. La mezcla se enfría y se filtra y el filtrado se concentra en vacío para suministrar el producto crudo. La cromatografía suministra 14 mg del producto. LC/MS: Tiempo de retención, 3.20 min; (M+H) = 730.

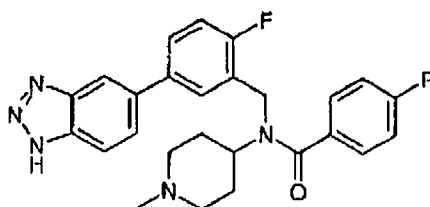
20 Etapa 2: N-[5-(1H-Benzotriazol-5-il)-2-fluoro-bencil]-N-(1-ciclopropil-piperidin-4-il)-4-fluoro-benzamida. Se agrega ácido trifluoroacético (TFA, 1 mL) a una solución de N-(1-ciclopropil-piperidin-4-il)-4-fluoro-N-[2-fluoro-5-(1-tritil-1H-benzotriazol-5-il)-bencil]-benzamida (14 mg, 0.019 mmol) en 1 mL de diclorometano y la mezcla resultante se agita a temperatura ambiente durante la noche y luego la mezcla se

neutraliza por adición cuidadosa de carbonato de sodio 1M. Las capas se separan, la fase acuosa se extrae con diclorometano, y las fases orgánicas combinadas se secan sobre sulfato de magnesio, se filtran, y los volátiles se remueven en vacío para dar el producto crudo. La cromatografía (elusión con metanol/diclorometano) suministra 9 mg del compuesto del título. LC/MS: Tiempo de retención, 2.22 min; (M+H) = 488.

RMN ¹H (400 MHz, cloroformo-D) δ ppm: 0.17 - 0.48 (m, 4 H) 1.31- 2.10 (m, 8 H) 2.97 (br s, 2 H) 4.74 (br s, 2 H) 7.01 (br s, 3 H) 7.31- 7.60 (m, 5 H) 7.71- 8.03 (m, 2 H).

Ejemplo 69

N-[5-(1H-Benzotriazol-5-il)-2-fluoro-bencil]-N-(1-metil-piperidin-4-il)-4-fluoro-benzamida



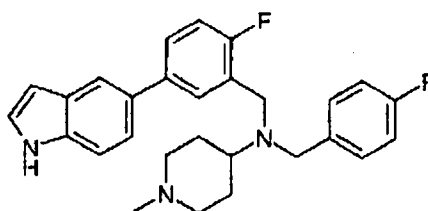
Se agrega triacetoxiborohidruro de sodio (8.5 mg, 0.04 mmol) a una mezcla de 4-fluoro-N-[2-fluoro-5-(1-tritil-1H-benzotriazol-5-il)-bencil]-N-piperidin-4-il-benzamida (25 mg, 0.04 mmol), formaldehído (37% de solución acuosa, 15 µL, 0.18 mmol) y ácido acético (2.4 mg, 0.04 mmol) en 1 mL de metanol. La mezcla se agita a temperatura ambiente durante la noche, y luego se diluye con diclorometano, y se neutraliza con la adición cuidadosa de solución de carbonato de sodio 1M. Las capas se separan y la fase acuosa se extrae con diclorometano. Las fases orgánicas combinadas se lavan con solución salina, se secan sobre

sulfato de magnesio, se filtran y se concentran para dar el producto crudo. La cromatografía suministra 15 mg del producto. Se agrega ácido trifluoroacético (TFA, 0.5 mL) a una solución del material obtenido anteriormente en 1 mL de diclorometano y la mezcla resultante se agita a temperatura ambiente durante 5 h, y luego la mezcla se neutraliza por la adición cuidadosa de carbonato de sodio 1M. Las capas se separan, la fase acuosa se extrae con diclorometano, y las fases orgánicas combinadas se secan sobre sulfato de magnesio, se filtran, y los volátiles se remueven en vacío para dar el producto crudo. La cromatografía suministra 6.5 mg del producto. LC/MS: Tiempo de retención, 2.20 min; (M+H) = 462.

RMN ^1H (400 MHz, cloroformo-D) δ ppm: 1.54 - 2.09 (m, 7 H) 2.26 (s, 3 H) 2.93 (br s, 2 H) 4.82 (br s, 2 H) 7.00 (br s, 3 H) 7.38 - 7.54 (m, 4 H) 7.59 (br s, 1 H) 7.86 (d, J=8.57 Hz, 2 H) 7.92 (s, 1 H).

Ejemplo 70

(4-Fluoro-bencil)-[2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amina



Etapa 1: [2-Fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amina. Se agregan triacetoxiborohidruro de sodio (400 mg, 1.88 mmol) y luego suficiente ácido acético para llevar el pH a 5 a una solución de 5-(4-fluoro-3-formilfenil)-1H-indol (150 mg, 0.63 mmol) y 1-metil-piperidin-4-ilamina (144 mg, 1.23 mmol) en 15 mL de 1,2-dicloroetano. La mezcla se agita a temperatura ambiente durante la noche, y luego se diluye con diclorometano y se lava con agua. La fase acuosa se

extrae con diclorometano, y las fases orgánicas combinadas se secan sobre sulfato de magnesio, se filtran y se concentran para dar el producto crudo, el cual se eluye a través de una columna de intercambio de catión SCX (elución con metanol, seguido por amoniaco 2M en metanol) para dar 250 mg del producto.

5

Etapas 2: (4-Fluoro-bencil)-[2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amina: Se agregan triacetoxiborohidruro de sodio (470 mg, 2.23 mmol) y luego suficiente ácido acético para llevar el pH a 5 a una solución de [2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amina (250 mg, 0.74 mmol) y 4-fluorobenzaldehído (183 mg, 1.48 mmol) en 15 mL de 1,2-dicloroetano. La mezcla se agita a temperatura ambiente durante la noche, y luego se diluye con diclorometano, y se neutraliza con la adición cuidadosa de solución de bicarbonato de sodio saturada. La fase orgánica se separa y se seca sobre sulfato de magnesio, se filtra y se concentra para dar el producto crudo. La cromatografía (elución con metanol/acetato de etilo) suministra 232 mg del producto. LC/MS (periodo largo): Tiempo de retención, 6.12 min; (M+H) = 446.

10

15

20

RMN ¹H (400 MHz, cloroformo-D) δ ppm: 1.73 - 1.84 (m, 4 H) 1.90 (t, J = 11.2 Hz, 2 H) 2.23 (s, 3 H) 2.46 - 2.60 (m, 1 H) 2.92 (d, 2 H) 3.66 (s, 2 H) 3.72 (s, 2 H) 6.59 (s, 1 H) 6.93 (t, J=8.74 Hz, 2 H) 7.00 (dd, J=9.78, 8.46 Hz, 1 H) 7.22 - 7.26 (m, 1 H) 7.27 - 7.34 (m, 3 H) 7.37 - 7.46 (m, 2 H) 7.66 (dd, J=7.14, 2.31 Hz, 1 H) 7.72 (s, 1 H) 8.22 (s, 1 H).

Ejemplos 71 a 73

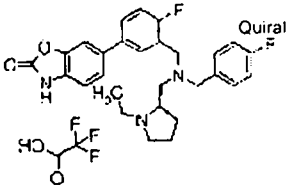
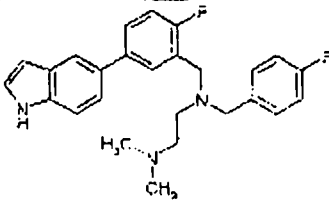
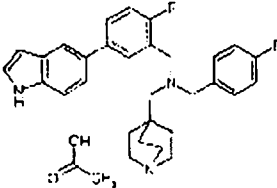
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El Ejemplo 70 se repite sustancialmente en los Ejemplos 71 a 73 con la excepción en la utilización de los materiales de partida y reactivos respectivos en

cantidades apropiadas con el fin de preparar los Ejemplos 71 a 73 como se tabula en la Tabla 6. También resumidos en la Tabla 6 están los datos LC/MS observados para los ejemplos 71 a 73.

5

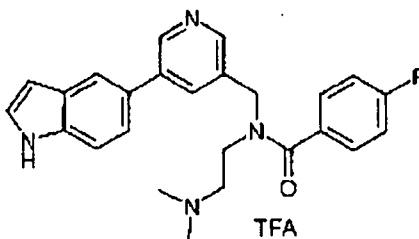
Tabla 6

Ejemplo No.	Estructura Química y Nombre Químico	Datos LC/MS	
		RT (mins.)	M + H
71	 Trifluoro-acetato de 6-(3-(((1-etil-pirrolidin-2<i>R</i>-ilmetil)-(4-fluoro-bencil)-amino)-metil)-4-fluoro-fenil)-3H-benzooxazol-2-ona	2.62 ^a	478
72	 N-(4-fluoro-bencil)-N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N',N'-dimetil-etano-1,2-diamina	7.12 ^b	420
73	 Acetato de (1-aza-biciclo[2.2.2]oct-4-ilmetil)-(4-fluoro-bencil)-[2-fluoro-5-(1H-indol-5-il)-bencil]-amina	6.53 ^b	472

^a= método LC/MS corto; ^b= método LC/MS largo

Ejemplo 74

Trifluoroacetato de N-(2-dimetilamino-etil)-4-fluoro-N-[5-(1H-indol-5-il)-piridin-3-ilmetil]-benzamida



5

Etapa 1: 5-(1H-Indol-5-il)-piridina-3-carbaldehído: ácido Indol-5-borónico (1 g, 6.25 mmol), 5-bromopiridina-3-carboxaldehído (1.3 g, 6.9 mmol) y $\text{PdCl}_2(\text{dppf})\cdot\text{DCM}$ (2.2 g, 2.7 mmol) y 15 ml de dioxano se distribuyen uniformemente entre cinco recipientes de microondas de 5 mL (Smith Personal Chemistry). Las mezclas se
10 desgasifican (se evacua en vacío y se presuriza con nitrógeno. Carbonato de sodio en agua (2M, 9.38 mL, 18.7 mmol) se distribuye uniformemente entre los recipientes de reacción y las mezclas desgasificadas dos o más veces como se describió anteriormente. La mezcla se calienta a 100° C durante 12 min en un sintetizador Smith. Las muestras se enfrían, se combinan y se lavan con agua. La
15 fase acuosa se extrae con diclorometano y las fases orgánicas combinadas se secan sobre MgSO_4 , se filtran y se evaporan para dar el producto crudo. La cromatografía (elusión con acetato de etilo/ciclohexano) suministra 870 mg del producto.

20 Etapa 2: N'-[5-(1H-Indol-5-il)-piridin-3-ilmetil]-N,N-dimetil-etano-1,2-diamina: Se agregan triacetoxiborohidruro de sodio (855 mg, 4.05 mmol) y luego suficiente ácido acético para llevar el pH a 5 a una solución de 5-(1H-indol-5-il)-piridina-3-carbaldehído (300 mg, 1.35 mmol) y N,N-dimetiletlen diamina (237 mg, 2.7 mmol) en 15 mL de 1,2-dicloroetano. La mezcla se agita a temperatura ambiente durante

48 h, y luego los volátiles se remueven en la presencia de celita. El producto se eluye a partir de la celita a través de gel de sílice (elusión con metanol/diclorometano) para dar 328 mg del producto. LC/MS: Tiempo de retención, 0.43 min; (M+H) = 295.19.

5

Etapa 3: N-(2-Dimetilamino-etil)-4-fluoro-N-[5-(1H-indol-5-il)-piridin-3-ilmetil]-benzamida: Se agrega cloruro de 4-fluorobenzoilo (111 mg, 0.7 mmol) a una solución de N'-[5-(1H-indol-5-il)-piridin-3-ilmetil]-N,N-dimetil-etano-1,2-diamina (160 mg, 0.54 mmol) y trietil amina (109 mg, 1.08 mmol) en 15 mL de diclorometano a temperatura ambiente. La mezcla resultante se agita a temperatura ambiente durante la noche, y luego se agrega 111 mg adicionales de cloruro de 4-fluorobenzoilo y la mezcla se agita durante 2 h adicionales. Los volátiles se remueven en vacío para dar el producto crudo. La cromatografía (elusión con metanol/diclorometano) suministra 231 mg del material. Este se disuelve en diclorometano y se lava con solución de hidróxido de sodio 1M. La fase orgánica se seca sobre sulfato de magnesio, se filtra y se concentra para dar el material que se purifica adicionalmente por HPLC (elusión con acetonitrilo/agua/TFA) para dar 21 mg del producto. LC/MS (periodo largo): Tiempo de retención, 3.85 min; (M+H) = 417.

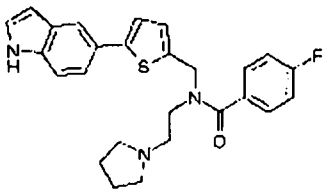
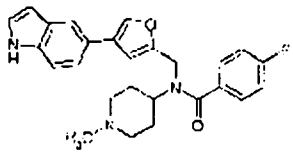
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Ejemplo 75 y 76

El Ejemplo 74 se repite sustancialmente en los Ejemplos 75 y 76 con la excepción en la utilización de los materiales de partida y reactivos respectivos en cantidades apropiadas con el fin de preparar los Ejemplos 75 y 76 como se tabula en la Tabla 7. También resumidos en la Tabla 7 están los datos LC/MS observados para los ejemplos 75 y 76.

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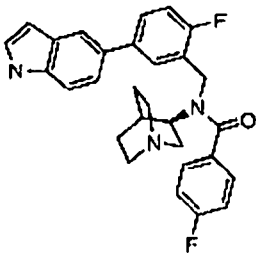
Tabla 7

Ejemplo No.	Estructura Química y Nombre Químico	Datos LC/MS	
		RT (mins.)	M + H
75	 4-Fluoro-N-[5-(1H-indol-5-il)-tiofen-2-ilmetil]-N-(2-pirrolidin-1-il-etil)-benzamida	5.06 ^b	448
76	 4-Fluoro-N-[4-(1H-indol-5-il)-furan-2-ilmetil]-N-(1-metil-piperidin-4-il)-benzamida	5.33 ^b	432

5 ^b= método LC/MS largo

Ejemplo 77

N-(1-Aza-biciclo[2.2.2]oct-3*R*-il)-4-fluoro-N-[2-fluoro-5-(1H-indol-6-il)-bencil]-benzamida



10

Etapa 1: (R)-N-(1-Aza-biciclo[2.2.2]oct-3*R*-il)-N-(5-bromo-2-fluoro-bencil)amina: Se agregan triacetoxiborohidruro de sodio (1.6 g, 7.53 mmol) y suficiente ácido acético para llevar el pH a 5 a una solución de 5-bromo-2-fluorobenzaldehído (510

mg, 2.51 mmol), (R)-(-)-1-aza-biciclo[2.2.2]oct-3*R*-ilamina (1.0 g, 5.02 mmol) y trietilamina (508 mg, 5.02 mmol) en 8 mL de 1,2-dicloroetano. La mezcla se agita a temperatura ambiente durante 4.5 h, y luego esta se apaga por la adición cuidadosa de solución de hidróxido de sodio 1M. La fase acuosa se extrae con acetato de etilo, y las fases orgánicas combinadas se secan sobre sulfato de magnesio, se filtran y se concentran para dar 816 mg del producto.

Etapa 2: (R)-N-(1-Aza-biciclo[2.2.2]oct-3*R*-il)-N-(5-bromo-2-fluoro-bencil)-4-fluoro-benzamida: Se agrega cloruro de 4-fluorobenzoilo (597 mg, 3.77 mmol) a una solución del material obtenido anteriormente en 10 mL de piridina a temperatura ambiente. La mezcla se agita a temperatura ambiente y luego se agrega una solución de hidróxido de sodio 1M, y el producto se extrae en acetato de etilo, y los volátiles se remueven en vacío para dar una mezcla de material de partida y producto. Esta se trata de nuevo con cloruro de 4-fluorobenzoilo (597 mg, 3.77 mmol) en 10 mL de piridina a temperatura ambiente. Se agrega una solución de hidróxido de sodio 1M, y el producto se extrae en acetato de etilo, y los volátiles se remueven en vacío para dar el producto crudo. La cromatografía (elución con trietilamina/metanol/acetato de etilo) da 508 mg del producto. LC/MS (periodo corto): Tiempo de retención, 2.26 min; (M+H) = 435/437.

20

Etapa 3: N-(1-Aza-biciclo[2.2.2]oct-3*R*-il)-4-fluoro-N-[2-fluoro-5<IH-indol-6-il)-bencil]-benzamida: Una mezcla de (R)-N-(1-Aza-biciclo[2.2.2]oct-3*R*-il)-N-(5-bromo-2-fluoro-bencil)-4-fluoro-benzamida (150 mg, 0.345 mmol), ácido 5-indolborónico (83 mg, 0.517 mmol), carbonato de sodio en agua (2M, 0.69 mL, 1.38 mmol) en 2 mL de dioxano se desgasifica (se evacua en vacío y se presuriza con nitrógeno, cuatro veces) se agrega PdCl₂(dppf).DCM (12 mg, 0.0017 mmol) y la mezcla se desgasifica cuatro veces como se describió anteriormente. La mezcla

25

299

resultante se calienta a 80° C durante la noche, luego se le permite enfriar a temperatura ambiente, se filtra y el filtrado se diluye con diclorometano y se lava con agua. Las fases acuosas se extraen con diclorometano y las fases orgánicas combinadas se secan sobre MgSO₄, se filtran y se evaporan para dar el producto
5 crudo. La cromatografía sobre gel de sílice (elusión con metanol/diclorometano) proporciona 20 mg del producto. LC/MS (periodo corto): Tiempo de retención, 2.63 min; (M+H) = 472.

RMN ¹H (400 MHz, cloroformo-D) δ ppm: 1.50 - 1.76 (m, 2 H) 1.98 (br s, 1 H) 2.13
10 (br s, 1 H) 2.71- 3.00 (m, 4 H) 3.02 - 3.24 (m, 2 H) 3.38 (br s, 1 H) 4.21 (br s, 1 H)
4.76 - 4.93 (m, 1 H) 6.62 (br s, 1 H) 7.01- 7.12 (m, 3 H) 7.26 - 7.29 (m, 1 H) 7.33
(d, 1 H, J = 8.4 Hz) 7.36 - 7.54 (m, 5 H) 7.75 (br s, 1 H).

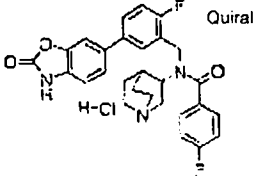
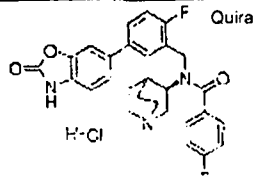
Ejemplos 78 y 79

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El Ejemplo 77 se repite sustancialmente en los Ejemplos 78 y 79 con la excepción en la utilización de los materiales de partida y reactivos respectivos en cantidades apropiadas con el fin de preparar los Ejemplos 78 y 79 como se tabula en la Tabla 8. También resumidos en la Tabla 8 están los datos LC/MS
20 observados para los ejemplos 78 y 79.

Tabla 8

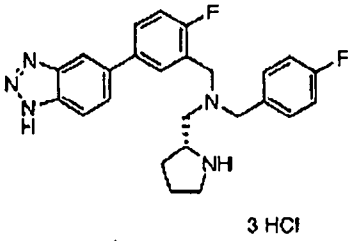
300

Ejemplo No.	Estructura Química y Nombre Químico	Datos LC/MS	
		RT (mins.)	M + H
78	 Clorhidrato de N-(1-aza-biciclo[2.2.2]oct-3<i>S</i>-il)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-benzamida	2.35 ^a	490
79	 Clorhidrato de N-(1-aza-biciclo[2.2.2]oct-3<i>R</i>-il)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-benzamida	2.37 ^a	490

^a = método LC/MS corto

Ejemplo 80

5 triclорhidrato de [5-(1H-Benzotriazol-5-il)-2-fluoro-bencil]-(4-fluoro-bencil)-pirrolidin-2*R*-ilmetil-amina



Etapa 1: Éster de terc-butilo de ácido (*R*)-2-[(4-Fluoro-bencilamino)-metil]-
10 pirrolidina-1-carboxílico: Se agregan triacetoxiborohidruro de sodio (15.9 g, 75.4 mmol) y suficiente ácido acético para llevar el pH a 5 a una solución de N-terc-butoxicarbonil-1-prolinal (5 g, 25 mmol) y 4-fluorobencilamina (6.28 g, 50.3 mmol)

301

en 200 mL de 1,2-dicloroetano. La mezcla se agita a temperatura ambiente durante la noche, y luego se diluye con diclorometano, y se lava con solución de bicarbonato de sodio saturada. La fase orgánica se seca sobre sulfato de magnesio, se filtra y se concentra para dar el producto crudo. La cromatografía
5 (elusión con metanol/acetato de etilo) proporciona 6.0 g del producto.

Etapa 2: Éster de terc-butilo de ácido (*R*)-2-((4-Fluoro-bencil)-[2-fluoro-5-(1-tritil-1H-benzotriazol-5-il)-bencil]-amino)-metil)-pirrolidina-1-carboxílico: Se agregan triacetoxiborohidruro de sodio (159 mg, 0.75 mmol) y ácido acético (36 mg, 0.6
10 mmol) a una mezcla de 5-(4-fluoro-3-formilfenil)-1-tritil-1H-benzotriazol (145 mg, 0.3 mmol) y éster de terc-butilo de ácido (*R*)-2-[(4-fluoro- bencilamino)-metil]-pirrolidina-1-carboxílico (111 mg, 0.36 mmol) y tamices moleculares de 4 Amstrongs en 5 mL de dicloroetano. La mezcla se agita a temperatura ambiente durante la noche, y luego se diluye con diclorometano, y se lava con solución de
15 bicarbonato de sodio saturada y solución salina, se seca sobre sulfato de magnesio, se filtra y se concentra para dar el producto crudo. La cromatografía (elusión con acetato de etilo/ciclohexano) suministra 119 mg del producto. LC/MS: Tiempo de retención, 4.02, 4.21 min; (M+H) = 776.

20 Etapa 3: (*R*)-[5-(1H-Benzotriazol-5-il)-2-fluoro-bencil]-(4-fluoro-bencil)-pirrolidin-2-ilmetil-amina: Se agrega una solución de ácido clorhídrico en dioxano (4M, 2 mL) a una solución de éster de terc-butilo de ácido (*R*)-2-((4-fluoro-bencil)-[2-fluoro-5-(1-tritil-1H-benzotriazol-5-il)-bencil]-amino)-metil)-pirrolidina-1-carboxílico (119 mg, 0.15 mmol) en 5 mL de metanol y la solución resultante se agita a temperatura
25 ambiente durante 24 h. Los volátiles se remueven en vacío y se purifican por HPLC. El producto obtenido se trata con ácido clorhídrico para dar 40 mg del producto. LC/MS (periodo largo): Tiempo de retención, 6.20 min; (M+H) = 433.

RMN ^1H (400 MHz, metanol- D_4) δ ppm: 1.68 - 1.85 (m, 1 H) 1.97 - 2.16 (m, 2 H)
2.31- 2.45 (m, 1 H) 3.38 (t, $J=7.47$ Hz, 2 H) 3.60 - 3.84 (m, 2 H) 4.26 (br s, 1 H)
4.75 (d, $J = 13.18$ Hz, 1H) 4.53 - 4.72 (m, 3 H) 7.20 (t, $J=8.57$ Hz, 2 H) 7.38 (t,
5 $J=9.23$ Hz, 1 H) 7.76 (br s, 2 H) 7.86 - 7.96 (m, 2 H) 8.00 (d, 1 H) 8.10 - 8.22 (m, 1
H) 8.24 (s, 1 H).

Ejemplos 81 y 82

10 El Ejemplo 80 se repite sustancialmente en los Ejemplos 81 y 82 con la
excepción en la utilización de los materiales de partida y reactivos respectivos en
cantidades apropiadas con el fin de preparar los Ejemplos 81 y 82 como se tabula
en la Tabla 9. También resumidos en la Tabla 9 están los datos LC/MS
observados para los ejemplos 81 y 82.

15

Tabla 9

agita a temperatura ambiente durante la noche, y luego se diluye con agua, las capas se separan y la fase acuosa se extrae con diclorometano. Las capas orgánicas combinadas se lavan secuencialmente con agua, solución de bicarbonato de sodio saturada y agua, se secan sobre sulfato de magnesio, se
5 filtran y se concentran para dar el producto crudo. La cromatografía (elución con metanol/diclorometano) suministra 400 mg del producto. LC/MS: Tiempo de retención, 2.66 min; (M+H) = 499.

Etapa 2: éster de terc-butilo de ácido 5-(3-[[[2-(terc-Butoxicarbonil-metil-amino)-etil]-(3-fluoro-bencil)-amino]-metil]-4-fluoro-fenil)-indazol-1-carboxílico: Se agregan
10 triacetoxiborohidruro de sodio (254 mg, 1.2 mmol) y ácido acético (48 mg, 0.8 mmol) a una mezcla de éster de terc-butilo de ácido 5-(3-[[[2-(terc-butoxicarbonil-metil-amino)-etilamino]-metil]-4-fluoro-fenil)-indazol-1-carboxílico (400 mg, 0.8 mmol) y 4-fluorobenzaldehído (99 mg, 0.8 mmol) en 15 mL de dicloroetano. La
15 mezcla se agita a temperatura ambiente durante 80 h, y luego se diluye con agua, las capas se separan y la fase acuosa se extrae con diclorometano. Las capas orgánicas combinadas se lavan secuencialmente con agua, solución de bicarbonato de sodio saturada y agua, se secan sobre sulfato de magnesio, se filtran y se concentran para dar el producto crudo. La cromatografía (elución con
20 acetato de etilo/pentano) suministra 360 mg del producto. LC/MS: Tiempo de retención, 4.10 min; (M+H) = 607.

Etapa 3: N-(3-Fluoro-bencil)-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N'-metil-etano-1,2-diamina: Una solución de éster de terc-butilo de ácido 2-(((4-fluoro-bencil)-[2-fluoro-5-(1-tritil-1H-benzotriazol-5-il)-bencil]-amino)-metil)-pirrolidina-1-carboxílico
25 (360 mg, 0.59 mmol) en 2 mL de dietil éter se trata con una solución de ácido clorhídrico en dioxano (4M, 12 mL) y la solución resultante se agita a temperatura

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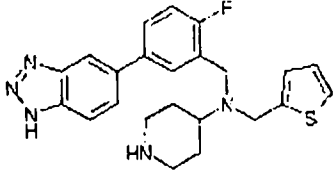
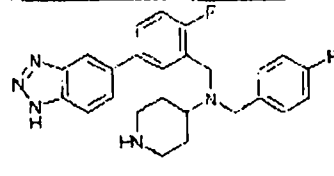
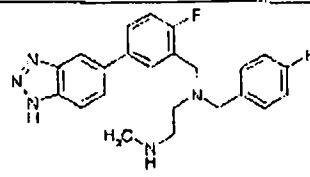
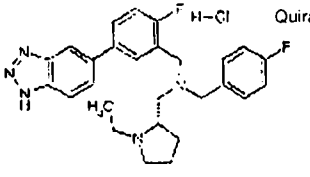
ambiente durante 4 h. Los volátiles se remueven en vacío y el residuo se disuelve en agua y se neutraliza con solución de bicarbonato de sodio saturada. El producto se extrae en acetato de etilo y las capas orgánicas combinadas se lavan secuencialmente con agua, se secan sobre sulfato de magnesio, se filtran y se concentran para dar el producto crudo. El residuo se disuelve en acetato de etilo caliente y el sólido obtenido luego de enfriamiento se recolecta para dar 65 mg del producto. LC/MS (periodo largo): Tiempo de retención, 6.02 min; (M+H) = 407.

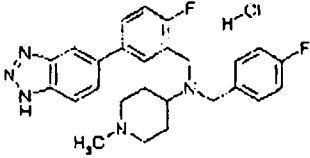
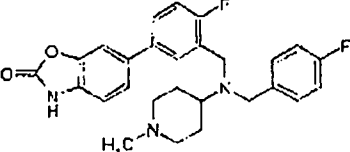
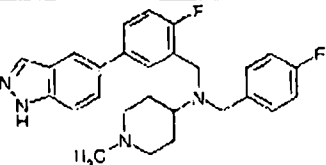
RMN ¹H (400 MHz, cloroformo-D) δ ppm: 2.29 (s, 3 H) 2.64 - 2.73 (m, 4 H) 3.60 (s, 2 H) 3.70 (s, 2 H) 6.95 (t, J=8.7 Hz, 2 H) 7.08 (t, J=8.7 Hz 1 H) 7.27 (dd, J=8.35, 5.49 Hz, 2 H) 7.39 - 7.46 (m, 1 H) 7.48 - 7.52 (m, 2 H) 7.53 - 7.57 (m, 1 H) 7.81 (s, 1 H) 8.07 (s, 1 H).

Ejemplos 84 a 90

El Ejemplo 83 se repite sustancialmente en los Ejemplos 84 a 90 con la excepción en la utilización de los materiales de partida y reactivos respectivos en cantidades apropiadas con el fin de preparar los Ejemplos 84 a 90 como se tabula en la Tabla 10. También resumidos en la Tabla 10 están los datos LC/MS observados para los ejemplos 84 a 90.

Tabla 10

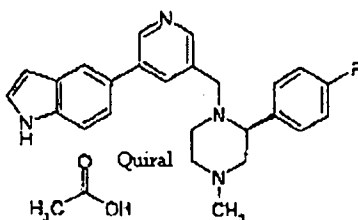
Ejemplo No.	Estructura Química y Nombre Químico	Datos LC/MS	
		RT (mins.)	M + H
84	 [5-(1H-Benzotriazol-5-il)-2-fluoro-bencil]-piperidin-4-il-tiofen-2-ilmetil-amina	4.73 ^b	422
85	 [5-(1H-Benzotriazol-5-il)-2-fluoro-bencil]-(4-fluoro-bencil)-piperidin-4-il-amina	4.74 ^h	434
86	 N-[5-(1H-Benzotriazol-5-il)-2-fluoro-bencil]-N-(4-fluoro-bencil)-N'-metil-etano-1,2-diamina	5.71 ^b	408
87	 Clorhidrato de [5-(1H-Benzotriazol-5-il)-2-fluoro-bencil]-(1-etil-pirrolidin-2S-ilmetil)-(4-fluoro-bencil)-amina	6.46 ^b	462

88	 Clorhidrato de [5-(1H-Benzotriazol-5-il)-2-fluoro-bencil]- (4-fluoro-bencil)-(1-metil-piperidin-4-il)-amina	4.95 ^b	448
89	 6-(4-Fluoro-3-(((4-fluoro-bencil)-(1-metil-piperidin- 4-il)-amino)-metil)-fenil)-3H-benzooxazol-2-ona	5.07 ^b	464
90	 (4-Fluoro-bencil)-[2-fluoro-5-(1H-indol-5-il)- bencil]-(1-metil-piperidin-4-il)-amina	4.71 ^b	447

^b= método LC/MS largo

Ejemplo 91

5 Acetato de 5-{5-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-piridin-3-il}-1H-indol



Etapa 1: Éster de *terc*-butilo de ácido (S)-4-(5-Bromo-piridin-3-ilmetil)-3-(4-
10 fluoró-fenil)-piperazina-1-carboxílico: Se agregan triacetoxiborohidruro de sodio
(1.27 g, 6 mmol) y ácido acético (120 mg, 2 mmol) a una mezcla de 5-bromo-
piridina-3-carboxaldehído (372 mg, 2 mmol) y éster de *terc*-butilo de ácido 3S-(4-
fluorofenil)-piperazina-1-carboxílico (560 mg, 2 mmol) en 10 mL de dicloroetano.

La mezcla se agita a temperatura ambiente durante la noche, y luego se diluye con diclorometano y agua, las capas se separan y la capa orgánica se lava con solución salina, se seca sobre sulfato de sodio, se filtra y se concentra para dar el producto crudo. La cromatografía (elusión con acetato de etilo/pentano) suministra
5 625 mg del producto. LC/MS: Tiempo de retención, 4.2 min; (M+H) = 452.

Etapa 2: (S)-1-(5-Bromo-piridin-3-ilmetil)-2-(4-fluoro-fenil)-piperazina: Se agrega una mezcla de ácido trifluoroacético y agua (TFA:agua = 19:1, 10 mL) a una solución de éster de terc-butilo de ácido (S)-4-(5-bromo-piridin-3-ilmetil)-3-(4-
10 fluoro-fenil)-piperazina-1-carboxílico (300 mg, 0.67 mmol) en 3 mL de diclorometano y la mezcla resultante se agita a temperatura ambiente durante 1.5 h, y luego los volátiles se remueven en vacío para dar 470 mg del producto. LC/MS: Tiempo de retención, 2.13 min; (M+H) = 351.

15 Etapa 3: (S)-1-(5-Bromo-piridin-3-ilmetil)-2-(4-fluoro-fenil)-4-metil-piperazina: Se agrega triacetoxiborohidruro de sodio (1.5 g, 7 mmol) a una mezcla de (S)-1-(5-bromo-piridin-3-ilmetil)-2-(4-fluoro-fenil)-piperazina (como sal de tris(trifluoroacetato)) (820 mg, 1.2 mmol) y formaldehído (37% de solución acuosa, 3 mL, 36.9 mmol) en 20 mL de metanol. La mezcla se agita a temperatura
20 ambiente durante la noche, y luego los volátiles se remueven en vacío y el residuo se disuelve en agua y el pH se ajusta a 11 por la adición de solución de hidróxido de sodio 10M. El producto se extrae en diclorometano y las capas orgánicas combinadas se lavan con solución salina, se secan sobre sulfato de sodio, se filtran y se concentran para dar 431 mg del producto. LC/MS: Tiempo de retención,
25 2.15 min; (M+H) = 366.

Etapa 4: 5-{5-[2S-(4-Fluoro-fenil)-4-metil-piperazin-1-ilmetil]-piridin-3-il}-1H-indol:

Una mezcla de (S)-1-(5-bromo-piridin-3-ilmetil)-2-(4-fluoro-fenil)-4-metil-piperazina (181 mg, 0.5 mmol), ácido 5-indolborónico (100 mg, 0.62 mmol), carbonato de cesio en agua (2M, 1 mL, 2 mmol) en 8 mL de dioxano se desgasifica (se evacua en vacío y se presuriza con nitrógeno, tres veces) se agrega PdCl₂(dppf).DCM (40 mg, 0.05 mmol) y la mezcla se desgasifica dos o más veces como se describió anteriormente. La mezcla resultante se calienta a 90° C durante 6 h, luego se le permite enfriar a temperatura ambiente y los volátiles se remueven en vacío. El residuo se tritura con agua, el agua se decanta y el residuo se disuelve en metanol. Este se filtra y el filtrado se evapora para dar el producto crudo. La cromatografía sobre gel de sílice (elución con DCE:MeOH:AcOH:H₂O = 240:15:3:2) proporciona 110 mg del producto. LC/MS (periodo largo): Tiempo de retención, 3.97 min; (M+H) = 401.

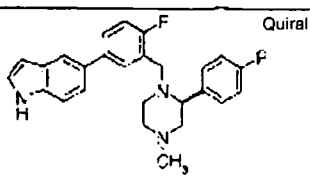
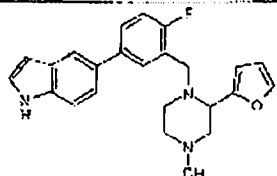
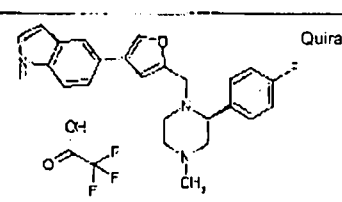
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Ejemplos 92 a 94

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El Ejemplo 91 se repite sustancialmente en los Ejemplos 92 a 94 con la excepción en la utilización de los materiales de partida y reactivos respectivos en cantidades apropiadas con el fin de preparar los Ejemplos 92 a 94 como se tabula en la Tabla 11. También resumidos en la Tabla 11 están los datos LC/MS observados para los ejemplos 92 a 94.

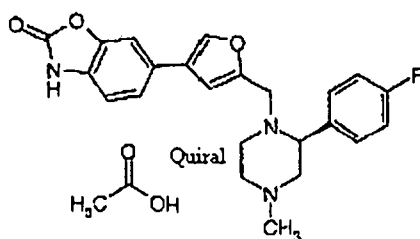
Tabla 11

Ejemplo No.	Estructura Química y Nombre Químico	Datos LC/MS	
		RT (mins.)	M + H
92	 5-{4-Fluoro-3-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-fenil}-3-metil-1H-indol	7.02 ^b	418
93	 5-[4-fluoro-3-(2-furan-2-il-4-metil-piperazin-1-ilmetil)-fenil]-1H-indol	5.43 ^b	390
94	 5-{5-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-furan-3-il}-1H-indol; compuesto con trifluoro-acetato	5.6 ^b	390

^b= método LC/MS largo

Ejemplo 95

5 6-{5-[2S-(4-Fluorofenil)-4-metilpiperazina-1-ilmetil]-furan-3-il}-3H-benzoxazol-2-ona



Etapas 1: 6-Bromo-3H-benzoxazol-2-ona: A una mezcla de 3H-benzoxazol-2-ona (20 g, 0.15 mol) en DCM (500 mL) se agrega bromo (8.34 mL, 0.16 mol). Después

de agitación a temperatura ambiente durante 19.5 h, el precipitado naranja que se ha formado se filtra y se lava con DCM hasta que el color naranja se lava. El filtrado se concentra hasta aproximadamente 33% de su volumen original y se filtra y se lava como antes. Los sólidos combinados pesan 28.36 g y contienen ca. 8-9% del material de partida.

Etapa 2: 6-Bromo-3-tritil-benzoxazol-2-ona: A una solución de 6-bromo-3H-benzoxazol-2-ona (15 g; ca. 0.07 mol, que contiene 8-9% de 3H-benzooxazol-2-ona) y trietilamina (11.1 mL, 0.08 mol) en DCM (250 mL) se agrega cloruro de tritilo (21.5 g, 0.08 mol). La solución se agita a temperatura ambiente durante 18 h y luego se lava con agua destilada (3 x 250 mL), solución salina (250 mL) y se seca (MgSO_4), se filtra y se evapora para dar un sólido coloreado blancuzco. El producto se disuelve en EtOAc que refluje luego se le permite enfriar a temperatura ambiente con agitación constante durante varias horas. Los sólidos se recolectan (21.16 g) y el filtrado se concentra hasta que ocurre precipitación, se recalienta (reflujo) durante varias horas y se permite enfriar con agitación hasta estimular una segunda cristalización (7.88 g).

Etapa 3: 6-(4,4,5,5-Tetrametil-[1,3,2]dioxaborolan-2-il)-3-tritil-3H-benzooxazol-2-ona: Una mezcla de 6-bromo-3-tritil-benzoxazol-2-ona (2.5 g, 5.48 mmol), bis(pinacolato)diboro (1.53 g, 6.03 mmol), acetato de potasio (2.15 g, 21.91 mmol) y $\text{PdCl}_2(\text{dppf})$.DCM (447 mg, 0.55 mmol) en DMSO anhidro, desgasificado se evacua y luego se represuriza con nitrógeno. Este proceso se repite varias veces para minimizar la cantidad de oxígeno en la mezcla de reacción. La mezcla se calienta a 85° C (temperatura de baño de aceite) bajo una atmósfera de nitrógeno durante 2.5 h. La reacción se diluye con DCM (700 mL) y se lava dos veces con

agua destilada (300 mL cada una), solución salina (300 mL), se seca (MgSO_4), se filtra y se evapora para dar un jarabe café oscuro.

La reacción se repite y el producto se combina con tal preparado anterior y
5 se cromatografía sobre una columna de gel de sílice, se eluye con 20% de Et_2O en heptano dando el producto deseado como un polvo blanco (3.76 g, 68%).

Etapa 4: Éster de *tert*-butilo de ácido 4-(4-Bromofuran-2-ilmetil)-3S-(4-fluorofenil)-piperazina-1-carboxílico: éster de *tert*-butilo de ácido 3S-(4-fluorofenil)-piperazina-
10 1-carboxílico (1.0 g, 3.57 mmol) y 4-bromo-2-furaldehído (0.63 g, 3.6 mmol) se disuelve en DCE (15 mL) y se agrega ácido acético glacial (0.23 mL, 3.55 mmol) seguido por triacetoxiborohidruro de sodio (2.30 g, 10.85 mmol). La reacción se agita durante la noche a temperatura ambiente. Se agrega DCM (50 mL) y la mezcla se lava con agua (1 x 50 mL) y solución salina (1 x 50 mL) y se seca sobre
15 Na_2SO_4 . El disolvente se remueve *in vacuo* para dar un aceite, que se solidifica en reposo para suministrar 1.6 g del producto. LC/MS: Tiempo de retención, 4.32 min; (M+H) = 439.

Etapa 5: Trifluoroacetato de 1-(4-bromofuran-2-ilmetil)-2S-(4-fluorofenil)-
20 piperazina: Éster de *tert*-butilo de ácido 4-(4-Bromofuran-2-ilmetil)-3S-(4-Fluorofenil)-piperazina-1-carboxílico (0.68 g, 1.55 mmol) se toma en una mezcla de 95% de TFA ac. y DCM [70:30] y se agita durante 30 mins. El disolvente se remueve *in vacuo* para producir una goma (0.90 g, rendimiento crudo cuantitativo). LCMS: Tiempo de retención, 2.33 min; (M+H) = 339.23.

25

Etapa 6: 1-(4-Bromofuran-2-ilmetil)-2S-(4-fluorofenil)-4-metilpiperazina: Una solución de di-trifluoroacetato de 1-(4-bromofuran-2-ilmetil)-2S-(4-fluorofenil)-

piperazina (0.60 g, 1.06 mmol) en metanol (15 mL) se trata con 37% de formaldehído acuoso (2.5 mL, ~30 mmol) seguido por triacetoxiborohidruro de sodio (1.25 g, 5.5 mmol). La reacción se agita a temperatura ambiente durante la noche después de que el disolvente se remueve *in vacuo* para dar una goma. Se
5 agrega agua (20 mL) y se ajusta el pH a 11 con NaOH ac 10M. La mezcla se extrae con DCM y las capas DCM combinadas se lavan con solución salina y se secan sobre Na₂SO₄. El disolvente removido *in vacuo* proporciona un aceite (0.35 g, 94%). Este compuesto se purifica por vía de cromatografía de gel de sílice flash utilizando DCM:MeOH: AcOH:agua (240:15:3:2) como eluyente. LC/MS: Tiempo
10 de retención, 2.28 min; (M+H) = 353.

Etapa 7: 6-{5-[2S-(4-Fluorofenil)-4-metilpiperazina-1-ilmetil]-furan-3-il}-3-tritil-3H-benzoxazol-2-ona: 1-(4-Bromofuran-2-ilmetil)-2S-(4-fluorofenil)-4-metilpiperazina (0.164 g, 0.33 mmol) y 6-(4,4,5,5-tetrametil-[1,3,2]dioxaborolan-2-il)-3-tritil-3H-
15 benzoaxazol-2-ona (0.105 g, 0.30 mmol) se disuelven en dioxano (8 mL) y se agrega Cs₂CO₃ ac. 2M (0.65 mL, 1.3 mmol). La mezcla se desgasifica y se introduce nitrógeno (tres veces) cuando se agrega PdCl₂(dppf).DCM (0.027 g, 0.03 mmol). Después de una desgasificación adicional, la reacción se calienta a 100° C durante 4 horas. Se agrega DCM (20 mL) a la mezcla y se lava con agua y
20 solución salina. La capa orgánica se seca sobre MgSO₄ y el disolvente remueve *in vacuo*. La cromatografía utilizando DCM:MeOH:AcOH:agua (240:15:3:2) como eluyente da 0.11 g del producto (68%). LC/MS: Tiempo de retención, 3.13 min; (M+H) = 650

25 Etapa 8: 6-{5-[2S-(4-Fluorofenil)-4-metilpiperazina-1-ilmetil]-furan-3-il}-3H-benzoxazol-2-ona: 6-{5-[2S-(4-Fluorofenil)-4-metilpiperazina-1-ilmetil]-furan-3-il}-3-tritil-3H-benzoxazol-2-ona (0.33 g, 0.51 mmol) se toma en 90% de TFA ac. (20 mL)

y se agita a temperatura ambiente durante 2 horas. El disolvente se remueve *in vacuo* y la coevaporación del TFA residual se logra utilizando agua (3 x ~2 mL) para proporcionar un sólido café. La cromatografía utilizando DCM:MeOH:AcOH:agua (180:20:3:2) como eluyente suministra 0.15 g del producto (73%). LC/MS (periodo largo): Tiempo de retención, 4.39 min; (M+H) = 408.

RMN ¹H (400 MHz, metanol-D₄) δ ppm: 2.73 (td, J=12.58, 2.75 Hz, 1 H) 2.83 (s, 3 H) 3.04 (t, J=11.76 Hz, 1 H) 3.16 - 3.26 (m, 2 H) 3.33 - 3.42 (m, 2 H) 3.50 (dd, J=12.09, 1.98 Hz, 1 H) 3.65 - 3.71 (m, 2 H) 6.54 (s, 1 H) 7.07 (d, J=8.13 Hz, 1 H) 7.20 (t, J=8.79 Hz, 2 H) 7.33 (dd, J=8.13, 1.54 Hz, 1 H) 7.39 (d, J=1.54 Hz, 1 H) 7.56 (dd, J=8.46, 5.39 Hz, 2 H) 7.83 (d, J=0.88 Hz, 1 H).

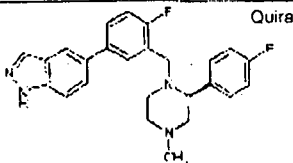
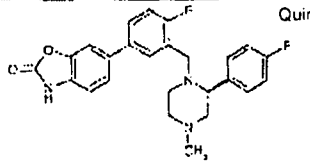
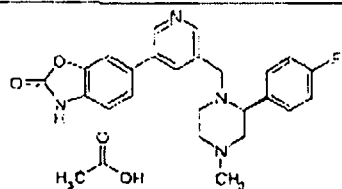
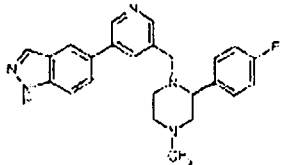
Ejemplos 96 a 99

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El Ejemplo 95 se repite sustancialmente en los Ejemplos 96 a 99 con la excepción en la utilización de los materiales de partida y reactivos respectivos en cantidades apropiadas con el fin de preparar los Ejemplos 96 a 99 como se tabula en la Tabla 12. También resumidos en la Tabla 12 están los datos LC/MS observados para los ejemplos 96 a 99.

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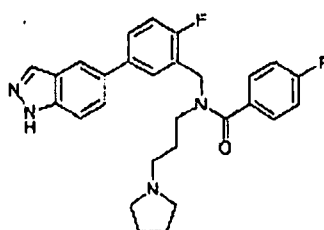
Tabla 12

Ejemplo No.	Estructura Química y Nombre Químico	Datos LC/MS	
		RT ^a (mins.)	M + H
96	 5-{4-Fluoro-3-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-fenil}-1H-indazol	6.22 ^b	419
97	 6-{4-Fluoro-3-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-fenil}-3H-benzooxazol-2-ona	6.19 ^b	436
98	 Acetato de 6-{5-[2S-(4-Fluoro-fenil)-4-metil-piperazin-1-ilmetil]-piridin-3-il}-3H-benzooxazol-2-ona	3.85 ^b	419
99	 5-{5-[2S-(4-Fluoro-fenil)-4-metil-piperazin-1-ilmetil]-piridin-3-il}-1H-indazol	3.55 ^b	402

^b= método LC/MS largo

Ejemplo 100

- 5 4-Fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(3-pirrolidin-1-il-propil)-benzamida



Etapa 1: Éster de terc-butilo de ácido 5-{4-Fluoro-3-[(3-pirrolidin-1-il-propilamino)-metil]-fenil}-indazol-1-carboxílico: Se agrega triacetoxiborohidruro de sodio (190 mg, 0.88 mmol) a una mezcla de éster de terc-butilo de ácido 5-(4-fluoro-3-formilfenil)-indazol-1-carboxílico (100 mg, 0.29 mmol) y N-(3-aminopropil)pirrolidina (74 mg, 0.59 mmol) y ácido acético (105 mg, 1.8 mmol) en dicloroetano. La mezcla se agita a temperatura ambiente durante la noche, y luego se diluye con diclorometano y se lava con solución de carbonato de sodio 1M. Las capas se separan y la fase acuosa se extrae con diclorometano. Las capas orgánicas combinadas se secan sobre sulfato de magnesio, se filtran y se concentran para dar el producto crudo. La cromatografía (elusión con metanol/diclorometano) suministra 130 mg del producto. LC/MS: Tiempo de retención, 1.98 min; (M+H) = 453.

Etapa 2: 4-Fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(3-pirrolidin-1-il-propil)-benzamida: Se agrega HATU (100 mg, 0.28 mmol) a una solución de éster de terc-butilo de ácido 5-{4-fluoro-3-[(3-pirrolidin-1-il-propilamino)-metil]-fenil}-indazol-1-carboxílico (125 mg, 0.28 mmol), ácido 4-fluorobenzoico (39 mg, 0.28 mmol) y diisopropiletilamina (89 mg, 0.69 mmol) en 3 mL de dimetilformamida, y la mezcla resultante se agita a temperatura ambiente durante 5 h. La mezcla se diluye con acetato de etilo se lava con solución de carbonato de sodio 1M. Las capas se separan y la fase acuosa se extrae con acetato de etilo. Las fases orgánicas combinadas se lavan con solución salina, se secan sobre sulfato de magnesio, se filtran y se concentran para dar el producto crudo. La cromatografía (elusión con metanol/diclorometano) suministra 100 mg del producto. Se agrega 2 mL de TFA a 98 mg de este material en 2 mL de diclorometano y la mezcla se agita a temperatura ambiente durante 5 h, y los volátiles se remueven en vacío. La

cromatografía (elusión con metanol/diclorometano) suministra 64 mg del producto.

LC/MS: Tiempo de retención, 2.65 min; (M+H) = 475.

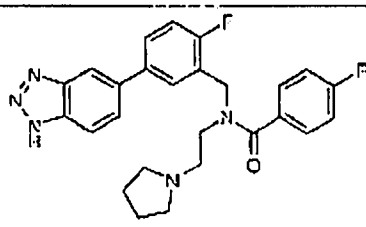
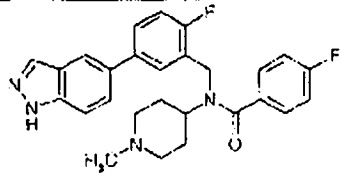
RMN ¹H (400 MHz, cloroformo-D) δ ppm: 1.98-2.21 (m, 6 H) 2.76 (br s, 2 H) 3.17
5 (br s, 2 H) 3.59 (br s, 2 H) 3.80 (br s, 2 H) 4.67 (br s, 2 H) 7.07-7.16 (m, 3 H) 7.34
(br s, 1 H) 7.41- 7.72 (m, 5 H) 7.84 (br s, 1 H) 8.11 (br s, 1 H) 12.98 (br s, 1 H).

Ejemplos 101 y 102

10 El Ejemplo 100 se repite sustancialmente en los Ejemplos 101 y 102 con la
excepción en la utilización de los materiales de partida y reactivos respectivos en
cantidades apropiadas con el fin de preparar los Ejemplos 101 y 102 como se
tabula en la Tabla 13. También resumidos en la Tabla 13 están los datos LC/MS
observados para los ejemplos 101 y 102.

15

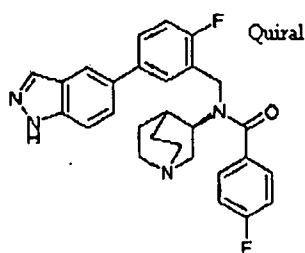
Tabla 13

Ejemplo No.	Estructura Química y Nombre Químico	Datos LC/MS	
		RT (mins.)	M + H
101	 N-[5-(1H-Benzotriazol-5-yl)-2-fluoro-bencil]-4-fluoro-N-(2-pirrolidin-1-yl-ethyl)-benzamida	4.87 ^b	462
102	 4-Fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-bencil]-N-(1-metil-piperidin-4-il)-benzamida	5 ^b	461

^b= método LC/MS largo

Ejemplo 103

- 5 N-(1-Aza-biciclo[2.2.2]oct-3*R*-il)-4-fluoro-N-[2-fluoro-5-(1H-indazol-5-yl)-bencil]-benzamida



- Etapa 1: Éster de *terc*-butilo de ácido 5-(4,4,5,5-Tetrametil-[1,3,2]dioxaborolan-2-il)-indazol-1-carboxílico: Una mezcla de éster de *terc*-butilo de ácido 5-bromo-indazol-1-carboxílico (1.8 g, 6.19 mmol), bis(pinacolato)diboro (1.73 g, 6.80 mmol), acetato de potasio (2.43 g, 24.7 mmol) y PdCl₂(dppf).DCM (505 mg, 0.62 mmol) en DMSO anhidro, desgasificado se evacua y luego se represuriza con nitrógeno. Este proceso se repite varias veces para minimizar la cantidad de oxígeno en la
- 10

mezcla de reacción. La mezcla se calienta a 85° C durante 4.5 h. La reacción se diluye con DCM y se lava con agua y solución salina, se seca sobre MgSO₄, se filtra y se evapora para dar un jarabe café oscuro. La cromatografía sobre gel de sílice, eluyendo con 75% de dietil éter/heptano da 1.47 g del producto.

5

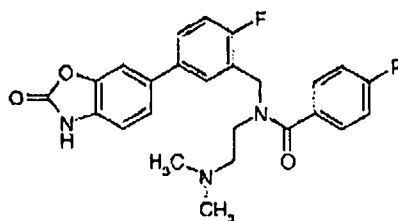
Etapa 2: N-(1-Aza-biciclo[2.2.2]oct-3*R*-il)-4-fluoro-N-[2-fluoro-5-(1*H*-indazol-5-il)-bencil]-benzamida: Una mezcla de (R)-N-(1-aza-biciclo[2.2.2]oct-3-il)-N-(5-bromo-2-fluoro-bencil)-4-fluoro-benzamida (180 mg, 0.41 mmol), éster de *terc*-butilo de ácido 5-(4,4,5,5-tetrametil-[1,3,2]dioxaborolan-2-il)-indazol-1-carboxílico (170 mg, 10 0.50 mmol), carbonato de cesio en agua (2M, 0.82 mL, 1.65 mmol) en 2 mL de dioxano se desgasifica (se evacua en vacío y se presuriza con nitrógeno) se agrega PdCl₂(dppf).DCM (34 mg, 0.04 mmol) y la mezcla se desgasifica como se hizo anteriormente. La mezcla resultante se calienta a 85° C durante 4 h, luego se le permite enfriar a temperatura ambiente se diluye con cloroformo y agua. Las 15 capas se separan y la fase orgánica se lava con solución salina, se seca sobre MgSO₄, se filtra y se evapora para dar el producto crudo. La cromatografía sobre gel de sílice (elusión con metanol/diclorometano) proporciona 100 mg del producto. Este material se disuelve en 95% de TFA acuoso y se agita a temperatura ambiente durante 4 h. Los volátiles se remueven *in vacuo* para dar el 20 producto crudo. La cromatografía (elusión con metanol/diclorometano) proporciona 38 mg del producto. LC/MS (periodo largo): Tiempo de retención, 5.88 min; (M+H) = 473.

RMN ¹H (400 MHz, metanol-D₄) δ ppm: 1.82 - 1.93 (m, 1 H) 1.94 - 2.06 (m, 2 H) 25 2.30 - 2.53 (m, 2 H) 3.22 - 3.40 (m, 1 H) 3.58 - 3.68 (m, 1 H) 3.72 (ddd, J=13.24, 6.65, 2.09 Hz, 1 H) 3.82 - 3.91 (m, 1 H) 4.25 - 4.33 (m, 1 H) 4.80 (d, J=16.93, 1 H)

4.91 (d, J=16.93, 1 H) 7.14 - 7.25 (m, 3 H) 7.37 (dd, J=7.25, 2.20 Hz, 1 H) 7.54 - 7.67 (m, 5 H) 7.93 (s, 1 H) 8.11 (s, 1 H).

Ejemplo 104

5 N-(2-Dimetilamino-etil)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-benzamida



Se agrega triacetoxiborohidruro de sodio (440 mg, 2.1 mmol) a una mezcla
10 de 2-fluoro-5-(2-oxo-2,3-dihidro-benzooxazol-6-il)-benzaldehído (180 mg, 0.7 mmol) y N',N'- dimetilaminoetilenediamina (184 mg, 2.1 mmol) y ácido acético (84 mg, 1.4 mmol) en 5 mL de dicloroetano. La mezcla se agita a temperatura ambiente durante la noche, y luego se diluye con diclorometano y se lava con solución de carbonato de sodio 1M. Las capas se separan y la fase acuosa se
15 extrae con diclorometano. Las capas orgánicas combinadas se lavan con solución salina, se secan sobre sulfato de magnesio, se filtran y se concentran para dar el producto crudo. La cromatografía (elusión con metanol/diclorometano) suministra 130 mg del producto. Se agrega HATU (76 mg, 0.2 mmol) a una solución del material anterior (65 mg, 0.2 mmol), ácido 4-fluorobenzoico (28 mg, 0.2 mmol) y
20 diisopropiletilamina (65 mg, 0.5 mmol) en 3 mL de dimetilformamida, y la mezcla resultante se agita a temperatura ambiente durante 4 h. La mezcla se diluye con acetato de etilo se lava con solución de carbonato de sodio 1M. Las capas se separan y la fase acuosa se extrae con acetato de etilo. Las fases orgánicas combinadas se lavan con solución salina, se secan sobre sulfato de magnesio, se
25 filtran y se concentran para dar el producto crudo. La cromatografía (dos veces,

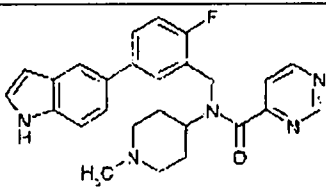
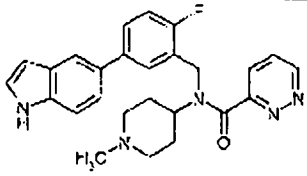
elusión con metanol/diclorometano) suministra 36 mg del producto. El producto se disuelve en acetato de etilo y se lava con solución de carbonato de sodio 1M. La fase acuosa se extrae con acetato de etilo, y las fases orgánicas combinadas se lavan con solución salina, se secan sobre sulfato de magnesio, se filtran y se concentran para dar 26 mg del producto. LCMS (periodo largo): Tiempo de retención: 5.64 min; (M+H) = 452.

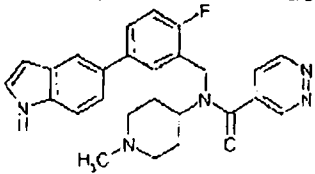
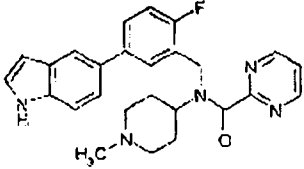
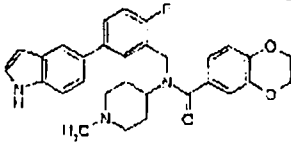
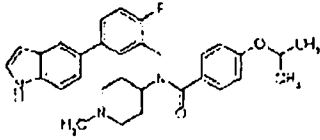
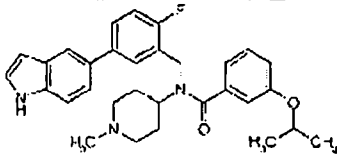
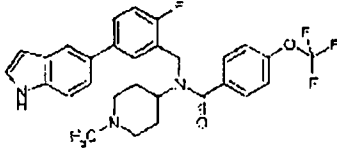
RMN ^1H (400 MHz, metanol- D_4) δ ppm: 2.03 (br s, 3 H) 2.27 (br s, 3 H) 2.38 - 2.68 (m, 2 H) 3.44 (br s, 1 H) 3.64 (br s, 1 H) 4.70 (br s, 1 H) 4.89 (br s, 1 H) 7.15 (d, J=8.13 Hz, 2 H) 7.17 - 7.27 (m, 2 H) 7.34 - 7.43 (m, 2 H) 7.46 (s, 1 H) 7.48 - 7.54 (m, 2 H) 7.54 - 7.61 (m, 1 H).

Ejemplos 105 a 112

Ejemplo 104 se repite sustancialmente en los Ejemplos 105 a 112 con la excepción en la utilización de los materiales de partida y reactivos respectivos en cantidades apropiadas con el fin de preparar los Ejemplos 105 a 112 como se tabula en la Tabla 14. También resumidos en la Tabla 14 están los datos LC/MS observados para los ejemplos 105 a 112.

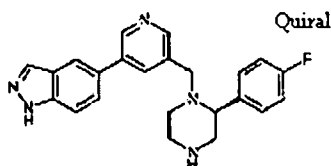
Tabla 14

Ejemplo No.	Estructura Química y Nombre Químico	Datos LC/MS	
		RT (mins.)	M + H
105	 [2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido pirimidina-4-carboxílico	5.24 ^b	444
106	 [2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido piridazina-3-carboxílico	5.18 ^b	444

107	 [2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)- amida de ácido piridazina-4-carboxílico	5.05 ^b	444
108	 [2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)- amida de ácido pirimidina-2-carboxílico	5 ^b	444
109	 [2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)- -amida de ácido 2,3-dihidro-benzo[1,4]dioxina-6- carboxílico	6.38 ^b	500
110	 N-[2-fluoro-5-(1H-indol-5-il)-bencil]-4-isopropoxi- N-(1-metil-piperidin-4-il)-benzamida	7.14 ^b	500
111	 N-[2-fluoro-5-(1H-indol-5-il)-bencil]-3-isopropoxi- N-(1-metil-piperidin-4-il)-benzamida	7.1 ^b	500
112	 N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin- 4-il)-4-trifluorometoxi-benzamida	7.37 ^b	526

^b= método LC/MS largo

5-{5-[2S-(4-Fluoro-fenil)-piperazin-1-ilmetil]-piridin-3-il}-1H-indazol



5

Etapa 1: Éster de terc-butilo de ácido 5-{5-[4-terc-Butoxicarbonil-2S-(4-fluoro-fenil)-piperazin-1-ilmetil]-piridin-3-il}-indazol-1-carboxílico: Éster de terc-butilo de ácido 4-(5-Bromo-piridin-3-ilmetil)-3-(4-fluoro-fenil)-piperazina-1-carboxílico (225 mg, 0.5 mmol) y éster de terc-butilo de ácido 5-(4,4,5,5- tetrametil-[1,3,2]dioxaborolan-2-il)-indazol-1-carboxílico (172 mg, 0.5 mmol) se disuelven en dioxano (8 mL) y se agrega Cs₂CO₃ ac. 2M (1 mL, 2 mmol). La mezcla se desgasifica y se introduce nitrógeno (tres veces) cuando se agrega PdCl₂(dppf).DCM (30 mg, 0.036 mmol). La reacción se calienta a 90° C durante 4 horas. Los volátiles se remueven en vacío y el residuo se disuelve en diclorometano. La fase orgánica se lava con agua y solución salina. La capa orgánica se seca sobre Na₂SO₄ y el disolvente remueve *in vacuo*. La purificación se logra por *vía* de cromatografía de gel de sílice flash (elusión con acetato de etilo/pentano) para dar 175 mg del producto. LC/MS: Tiempo de retención, 4.05 min; (M+H) = 587.

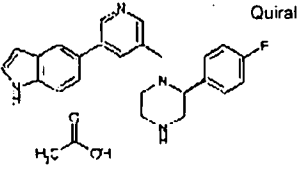
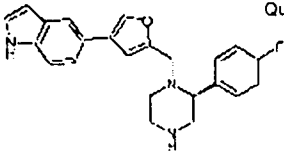
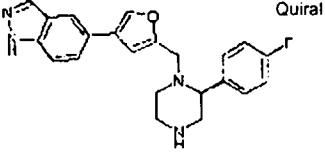
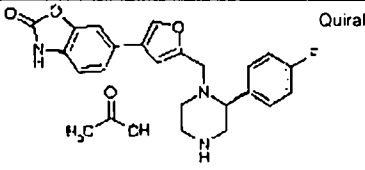
Etapa 2: 5-{5-[2S-(4-Fluoro-fenil)-piperazin-1-ilmetil]-piridin-3-il}-1H-indazol: Se agrega 7 mL de TFA acuoso al 95% a una solución de éster de terc-butilo de ácido 5-{5-[4-terc-butoxicarbonil-2S-(4-fluoro-fenil)-piperazin-1-ilmetil]-piridin-3-il}-indazol-1-carboxílico (170 mg, 0.29 mmol) en 3 mL de diclorometano, y la mezcla resultante se agita a temperatura ambiente durante 1 h. El disolvente se remueve para proporcionar el producto crudo. La purificación se logra por *vía* de

cromatografía de gel de sílice flash utilizando DCM:MeOH:AcOH:agua como eluyente. Las fracciones agrupadas se combinan y el disolvente se remueve *in vacuo* con coevaporación de AcOH residual utilizando agua (3 x ~2 mL) y MeOH:DCM (1:1, 10 mL) para dar 125 mg del producto. LCMS (periodo largo):

5 Tiempo de retención, 3.6 min; (M+H) = 388.

Ejemplos 114 a 117

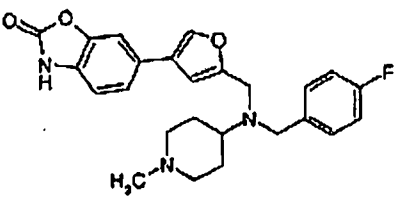
El Ejemplo 113 se repite sustancialmente en los Ejemplos 114 a 117 con la
10 excepción en la utilización de los materiales de partida y reactivos respectivos en cantidades apropiadas con el fin de preparar los Ejemplos 114 a 117 como se tabula en la Tabla 15. También resumidos en la Tabla 15 están los datos LC/MS observados para los ejemplos 114 a 117.

Ejemplo No.	Estructura Química y Nombre Químico	Datos LC/MS	
		RT (mins.)	M + H
114	 Acetato de 5-{5-[2S-(4-fluoro-fenil)-piperazin-1-ilmetil]-piridin-3-il}-1H-indol	3.72 ^a	387
115	 5-{5-[2S-(4-Fluoro-fenil)-piperazin-1-ilmetil]-furan-3-il}-1H-indol	5.52 ^b	376
116	 5-{5-[2S-(4-Fluoro-fenil)-piperazin-1-ilmetil]-furan-3-il}-1H-indol	4.86 ^b	377
117	 Acetato de 6-{5-[2S-(4-Fluoro-fenil)-piperazin-1-ilmetil]-furan-3-il}-3H-benzooxazol-2-ona	4.27 ^b	394

^b= método LC/MS largo

Ejemplo 118

5 6-(5-[[4-Fluoro-bencil)-(1-metil-piperidin-4-il)-amino]-metil]-furan-3-il)-3H-benzooxazol-2-ona



Etapa 1: 6-{5-[(1-Metil-piperidin-4-ilamino)-metil]-furan-3-il}-3-tritil-3H-benzooxazol-2-ona: Se agrega triacetoxiborohidruro de sodio (339 mg, 1.6 mmol) a una solución de 4-(2-oxo-3-tritil-2,3-dihidro-benzooxazol-6-il)-furan-2-carbaldehído (377 mg, 0.8 mmol) y 1-metil-piperidin-4-ilamina (219 mg, 1.92 mmol) y ácido acético (192 mg, 3.2 mmol) en 10 mL de 1,2-dicloroetano. La mezcla se agita a temperatura ambiente durante 21 h, y luego se diluye con diclorometano y se lava con solución de carbonato de sodio saturada. La fase acuosa se extrae con diclorometano, y las fases orgánicas combinadas se lavan con agua y solución salina, se secan sobre sulfato de magnesio, se filtran y se concentran para dar el producto crudo. La cromatografía (elusión con diclorometano/metanol/ácido acético/agua) da 189 mg del producto. LC/MS: Tiempo de retención, 2.38 min; (M+H) = 570.

Etapa 2: 6-(5-[(4-Fluoro-bencil)-(1-metil-piperidin-4-il)-amino]-metil)-furan-3-il}-3-tritil-3H-benzooxazol-2-ona: Se agrega triacetoxiborohidruro de sodio (71 mg, 0.33 mmol) a una solución de 6-{5-[(1-metil-piperidin-4-ilamino)-metil]-furan-3-il}-3-tritil-3H-benzooxazol-2-ona (95 mg, 0.17 mmol) y 4-fluorobenzaldehído (21 mg, 0.2 mmol) y ácido acético (20 mg, 0.33 mmol) en 1.5 mL de 1,2-dicloroetano. La mezcla se agita a temperatura ambiente durante 20 h, y luego se diluye con cloroformo y se lava con solución de carbonato de sodio saturada. La fase acuosa se extrae con cloroformo, y las fases orgánicas combinadas se lavan con agua y solución salina, se secan sobre sulfato de magnesio, se filtran y se concentran para dar el producto crudo. La cromatografía (elusión con diclorometano/metanol) da 64 mg del producto. LC/MS: Tiempo de retención, 2.99 min; (M+H) = 678.

Etapa 3: 6-(5-[[[4-Fluoro-bencil)-(1-metil-piperidin-4-il)-amino]-metil]-furan-3-il)-3H-benzooxazol-2-ona: Se agrega 1 mL de TFA acuoso al 95% a una solución de 6-(5-[[[4-fluoro-bencil)-(1-metil-piperidin-4-il)-amino]-metil]-furan-3-il)-3-tritil-3H-benzooxazol-2-ona (64 mg, 0.09 mmol) en 2 mL de diclorometano, y la mezcla

5 resultante se agita a temperatura ambiente durante 1 h. El disolvente se remueve para proporcionar el producto crudo. La purificación se logra por vía de cromatografía de gel de sílice flash (elusión con DCM:MeOH:AcOH:agua). Las fracciones agrupadas se combinan y el disolvente se remueve *in vacuo* con coevaporación de AcOH residual utilizando tolueno para dar 16 mg del producto.

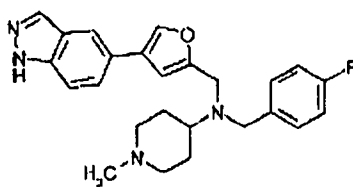
10 LC/MS (periodo largo): Tiempo de retención, 3.83 min; (M+H) = 436.

RMN ¹H (400 MHz, metanol-D₄) δ ppm: 1.86 (q, J = 13.14 Hz, 2 H) 2.14 (d, J = 13.8 Hz, 2 H) 2.84 (s, 3 H) 2.92 - 3.08 (m, 3 H) 3.55 (d, J = 13.14 Hz, 2 H) 3.75 (s, 2 H) 3.79 (s, 2 H) 6.62 (s, 1 H) 6.68-7.11 (m, 3H), 7.34 (d, J = 8.06 Hz, 1 H) 7.38-

15 7.44 (m, 3 H) 7.82 (s, 1 H).

Ejemplo 119

(4-Fluoro-bencil)-[4-(1H-indazol-5-il)-furan-2-ilmetil]-(1-metil-piperidin-4-il)-amina

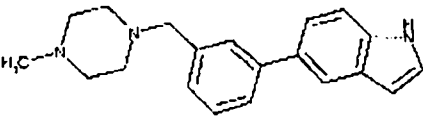


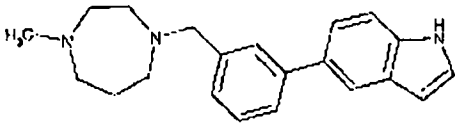
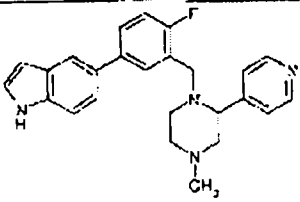
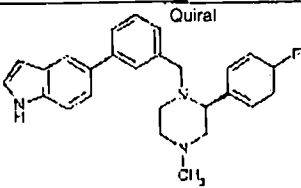
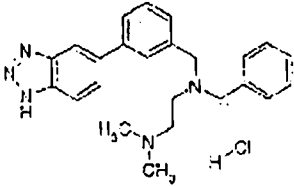
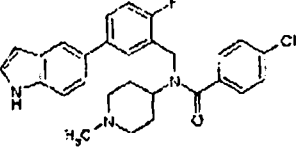
20 Ejemplo 118 se repite sustancialmente en Ejemplo 119 con la excepción en la utilización de los materiales de partida y reactivos respectivos en cantidades apropiadas con el fin de preparar el Ejemplo 119. LC/MS (periodo largo): Tiempo de retención, 4.07 min; (M+H) = 419.

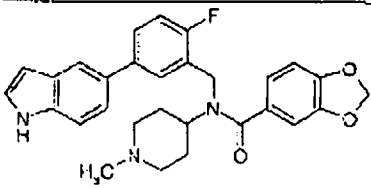
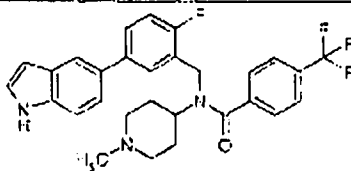
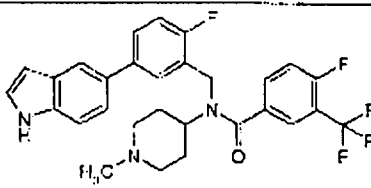
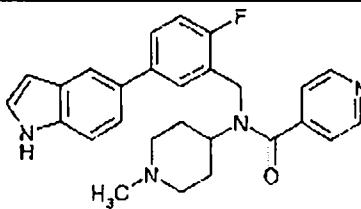
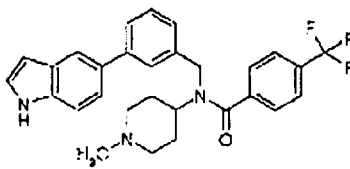
Los siguientes Ejemplos 120 a 169 se preparan siguiendo varios procedimientos como se describe aquí con la excepción en la utilización de los materiales de partida y reactivos respectivos en cantidades apropiadas con el fin de preparar los Ejemplos 120 a 169 como se tabula en la Tabla 16. También resumidos en la Tabla 16 están los métodos sintéticos utilizados para la preparación del respectivo Ejemplo y los datos observados LC/MS.

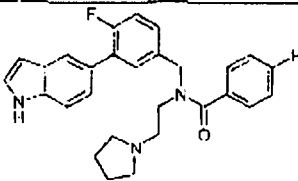
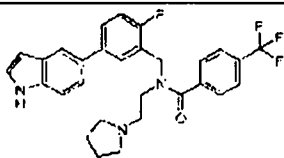
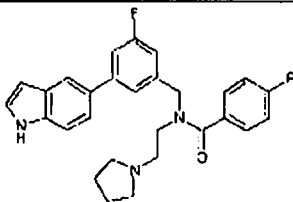
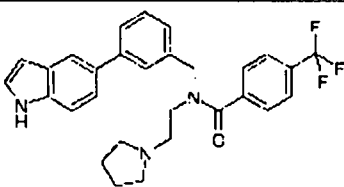
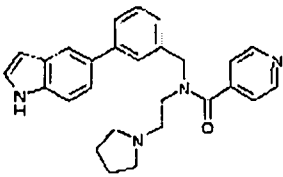
Tabla 16

10

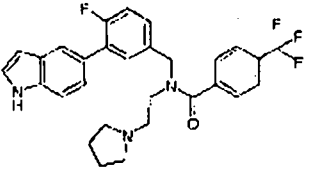
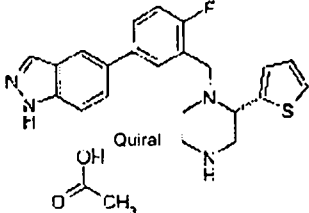
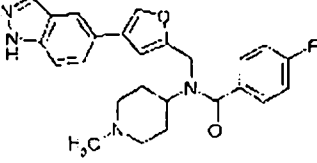
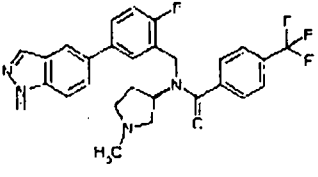
Ejemplo No.	Método Sintético Utilizado	Estructura Química y Nombre Químico	Datos LC/MS	
			RT (mins.)	M + H
120	Ejemplo 1	 5-[3-(4-metil-piperazin-1-ilmetil)-fenil]-1H-indol	n.a.	n.a.

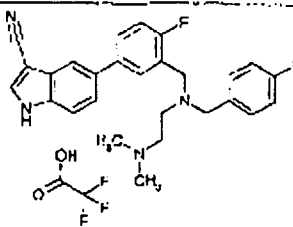
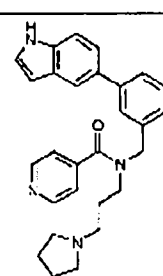
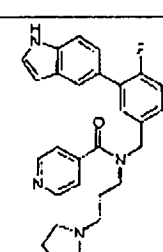
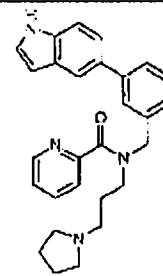
121	Ejemplo 1	 5-[3-(4-metil-[1,4]diazepan-1-ilmetil)-fenil]-1H-indol	n.a.	n.a.
122	Ejemplo 1	 5-[4-fluoro-3-(4-metil-2-piridin-4-il-piperazin-1-ilmetil)-fenil]-1H-indol	4.91 ^b	401
123	Ejemplo 1	 5-[3-[2S-(4-Fluoro-fenil)-4-metil-piperazin-1-ilmetil]-fenil]-1H-indol	7.02 ^b	400
124	Ejemplo 17	 Clorhidrato de N-[3-(1H-benzotriazol-5-il)-bencil]-N-bencil-N',N'-dimetil-etano-1,2-diamina	n.a.	n.a.
125	Ejemplo 20	 4-Cloro-N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-benzamida	6.72 ^b	476

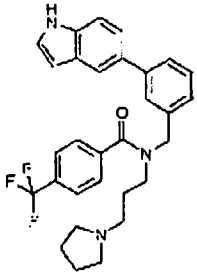
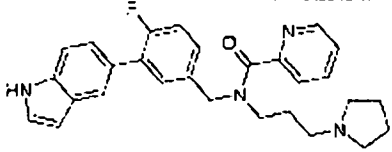
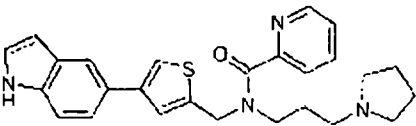
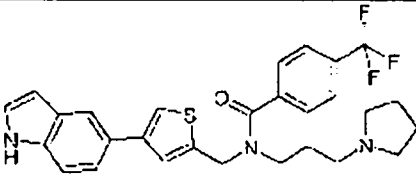
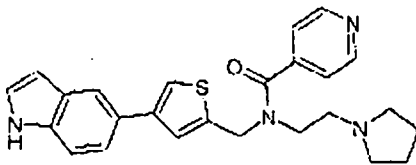
126	Ejemplo 20	 [2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido benzo [1,3]dioxol-5-carboxílico	6.15 ^b	486
127	Ejemplo 20	 N-[2-Fluoro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-4-trifluorometil-benzamida;	7.06 ^h	510
128	Ejemplo 20	 4-Fluoro-N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-3-trifluorometil-benzamida	7.11 ^b	528
129	Ejemplo 20	 N-[2-Fluoro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-isonicotinamida	4.99 ^b	443
130	Ejemplo 20	 N-[3-(1H-Indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-4-trifluorometil-benzamida	6.92 ^b	492

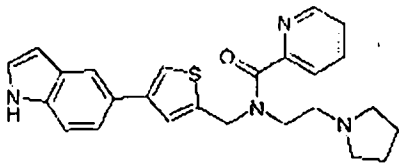
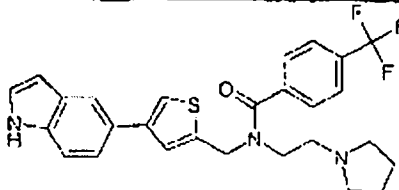
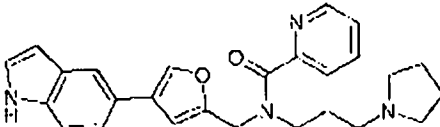
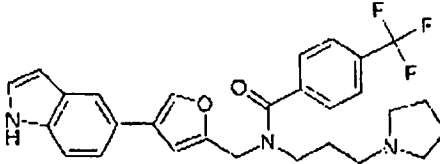
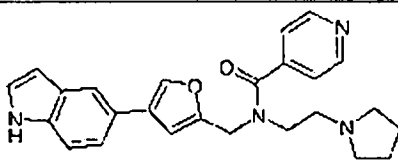
131	Ejemplo 20	 4-Fluoro-N-[4-fluoro-3-(1H-indol-5-yl)-benzyl]-N-(2-pirrolidin-1-il-etil)-benzamida	6.73 ^b	460
132	Ejemplo 20	 N-[2-fluoro-5-(1H-indol-5-il)-benzil]-N-(2-pirrolidin-1-il-etil)-4-trifluorometil-benzamida	6.85 ^b	510
133	Ejemplo 20	 4-Fluoro-N-[3-fluoro-5-(1H-indol-5-il)-benzil]-N-(2-pirrolidin-1-il-etil)-benzamida	6.75 ^b	460
134	Ejemplo 20	 N-[3-(1H-Indol-5-il)-benzil]-N-(2-pirrolidin-1-il-etil)-4-trifluorometil-benzamida	7.07 ^b	492
135	Ejemplo 20	 N-[3-(1H-indol-5-il)-benzil]-N-(2-pirrolidin-1-il-etil)-4-trifluorometil-benzamida	5.05 ^h	425

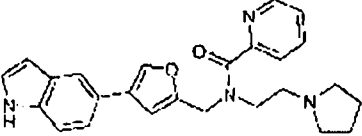
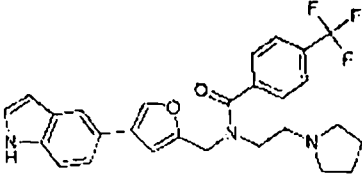
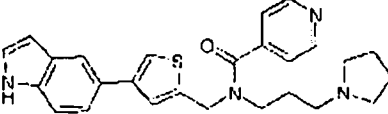
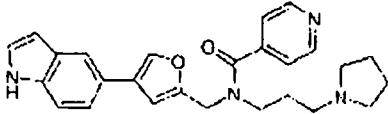
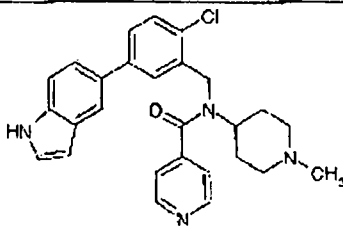
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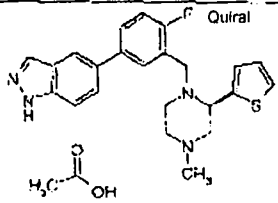
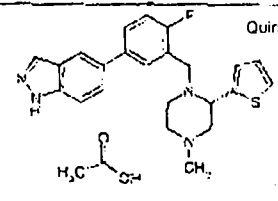
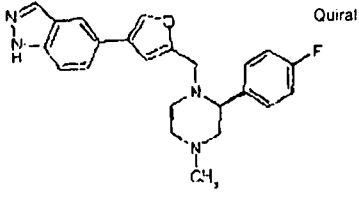
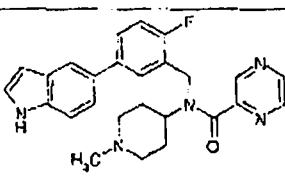
136	Ejemplo 20	 N-[4-fluoro-3-(1H-indol-5-yl)-benzil]-N-(2-pirrolidin-1-yl-ethyl)-4-trifluorometil-benzamida	7.16 ^b	510
137	Ejemplo 42	 Acetato de 5-[4-fluoro-3-(2R-tiofen-2-il-piperazin-1-ilmetil)-fenil]-1H-indazol	5.16 ^b	393
138	Ejemplo 53	 4-Fluoro-N-[4-(1H-indazol-5-yl)-furan-2-ilmetil]-N-(1-metil-piperidin-4-il)-benzamida	4.61 ^b	433
139	Ejemplo 53	 N-[2-Fluoro-5-(1H-indazol-5-yl)-benzil]-N-(1-metil-pirrolidin-3R-il)-4-trifluorometil-benzamida	6.64 ^b	497

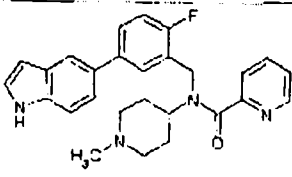
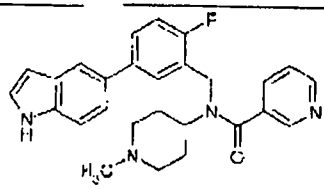
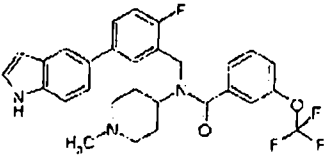
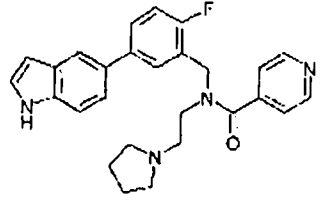
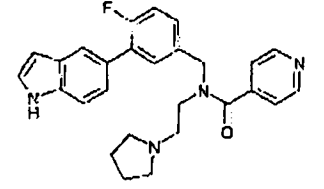
140	Ejemplo 70	 Trifluoro-acetato de 5-({[(2-Dimetilamino-etil)-(4-fluoro-bencil)amino]metil}-4-fluoro-fenil)-1H-indol-3-carbonitrilo	5.78 ^b	445
141	Ejemplo 77	 N-[3-(1H-Indol-5-il)-bencil]-N-(3-pirrolidin-1-il-propil)-isonicotinamida	2.12 ^c	439
142	Ejemplo 77	 N-[4-fluoro-3-(1H-indol-5-il)-bencil]-N-(3-pirrolidin-1-il-propil)-isonicotinamida	2.15 ^c	457
143	Ejemplo 77	 [3-(1H-indol-5-il)-bencil]-(3-pirrolidin-1-il-propil)-amida de ácido piridin-2-carboxílico	2.3 ^c	439

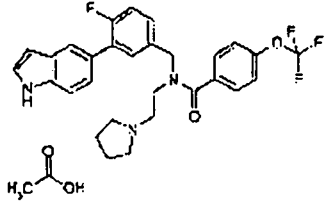
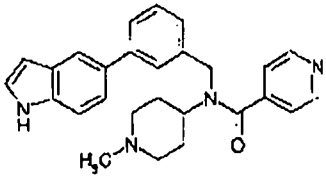
144	Ejemplo 77	 N-[3-(1H-Indol-5-yl)-benzil]-N-(3-pirrolidin-1-il-propil)-4-trifluorometil-benzamida	2.73 ^z	506
145	Ejemplo 77	 [4-fluoro-3-(1H-indol-5-il)-benzil]-(3-pirrolidin-1-il-propil)-amida de ácido piridin-2-carboxílico	2.35 ^c	457
146	Ejemplo 77	 [4-(1H-indol-5-il)-tiofen-2-ilmetil]-(3-pirrolidin-1-il-propil)-amida de ácido piridin-2-carboxílico	2.64 ^e	445
147	Ejemplo 77	 N-[4-(1-Indol-5-il)-tiofen-2-ilmetil]-N-(3-pirrolidin-1-il-propil)-4-trifluorometil-benzamida	3.0 ^c	512
148	Ejemplo 77	 N-[4-(1H-Indol-5-il)-tiofen-2-ilmetil]-N-(2-pirrolidin-1-il-etil)-isonicotinamida	2.47 ^c	431

149	Ejemplo 77	 <chem>C1CCNCC1CNC(=O)Cc2sc(c3cc[nH]3)-c4ccc5c2c[nH]5</chem> [4-(1H-indol-5-yl)-tiofen-2-ilmetil]-(2-pirrolidin-1-il-etil)-amida de ácido piridin-2-carboxílico	2.67 ^c	431
150	Ejemplo 77	 <chem>C1CCNCC1CNC(=O)Cc2sc(c3cc[nH]3)-c4ccc5c2c[nH]5C6=CC=C(C(F)(F)F)C=C6</chem> N-[4-(1H-Indol-5-il)-tiofen-2-ilmetil]-N-(2-pirrolidin-1-il-etil)-4-trifluorometil-benzamida	3.01 ^c	498
151	Ejemplo 77	 <chem>C1CCNCC1CNC(=O)Cc2oc(c3cc[nH]3)-c4ccc5c2c[nH]5</chem> [4-(1H-indol-5-il)-furan-2-ilmetil]-(3-pirrolidin-1-il-propil)-amida de ácido piridin-2-carboxílico	2.55 ^c	429
152	Ejemplo 77	 <chem>C1CCNCC1CNC(=O)Cc2oc(c3cc[nH]3)-c4ccc5c2c[nH]5C6=CC=C(C(F)(F)F)C=C6</chem> N-[4-(1H-indol-5-il)-furan-2-ilmetil]-N-(3-pirrolidin-1-il-propil)-4-trifluorometil-benzamida	2.95 ^c	496
153	Ejemplo 77	 <chem>C1CCNCC1CNC(=O)Cc2oc(c3cc[nH]3)-c4ccc5c2c[nH]5C6=CC=CC(=N6)C(=O)N</chem> N-[4-(1H-indol-5-il)-furan-2-ilmetil]-N-(2-pirrolidin-1-il-etil)-isonicotinamida	2.37 ^c	415

154	Ejemplo 77	 [4-(1H-indol-5-il)-furan-2-ilmetil]-(2-pirrolidin-1-il-etil)-amida de ácido piridin-2-carboxílico	2.55 ^c	415
155	Ejemplo 77	 N-[4-(1-Indol-5-il)-furan-2-ilmetil]-N-(2-pirrolidin-1-il-etil)-4-trifluorometil-benzamida	2.94 ^c	482
156	Ejemplo 77	 N-[4-(1H-Indol-5-il)-tiofen-2-ilmetil]-N-(3-pirrolidin-1-il-propil)-isonicotinamida	2.44 ^c	445
157	Ejemplo 77	 N-[4-(1H-Indol-5-il)-furan-2-ilmetil]-N-(3-pirrolidin-1-il-propil)-isonicotinamida	2.39 ^c	429
158	Ejemplo 77	 N-[2-cloro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-isonicotinamida	2.54 ^c	459

159	Ejemplo 95	 Acetato de 5-[4-fluoro-3-(4-metil-2<i>R</i>-tiofen-2-il-piperazin-1-ilmetil)-fenil]-1<i>H</i>-indazol	6.11 ^b	407
160	Ejemplo 95	 Acetato de 5-[4-Fluoro-3-(4-metil-2<i>R</i>-tiofen-2-il-piperazin-1-ilmetil)-fenil]-1<i>H</i>-indazol	6.04 ^b	407
161	Ejemplo 103	 5-[5-[2<i>S</i>-(4-Fluoro-fenil)-4-metil-piperazin-1-ilmetil]-furan-3-il]-1<i>H</i>-indazol	4.91 ^b	391
162	Ejemplo 104	 [2-fluoro-5-(1<i>H</i>-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido pirazina-2-carboxílico	5.63 ^b	444

163	Ejemplo 104	 <chem>CN1CCCCC1CN(C(=O)c2ccncc2)c3cc(F)ccc3c4c[nH]c5ccccc45</chem> [2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido piridina-2-carboxílico	5.55 ^b	443
164	Ejemplo 104	 <chem>CN1CCCCC1CN(C(=O)c2ccncc2)c3cc(F)ccc3c4c[nH]c5ccccc45</chem> N-[2-Fluoro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-nicotinamida	5.15 ^b	443
165	Ejemplo 104	 <chem>CN1CCCCC1CN(C(=O)c2cc(OC(F)(F)F)ccc2)c3cc(F)ccc3c4c[nH]c5ccccc45</chem> N-[2-Fluoro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-3-trifluorometoxi-benzamida	7.06 ^b	526
166	Ejemplo 104	 <chem>C1CCNCC1CN(C(=O)c2ccncc2)c3cc(F)ccc3c4c[nH]c5ccccc45</chem> N-[2-Fluoro-5-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-isonicotinamida	5.19 ^h	443
167	Ejemplo 104	 <chem>C1CCNCC1CN(C(=O)c2ccncc2)c3cc(F)ccc3c4c[nH]c5ccccc45</chem> N-[4-Fluoro-3-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-isonicotinamida	5.22 ^b	443

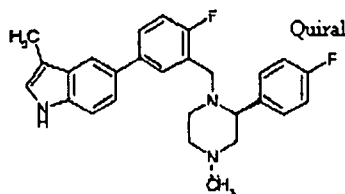
168		 Acetato de N-[4-Fluoro-3-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-4-trifluorometoxi-benzamida	7.34 ^b	460
169		 N-[3-(1H-indol-5 -il)-bencil]-N-(1-metil-piperidin-4-il)-isonicotinamida	4.69 ^b	425

^a = método LC/MS corto; ^b = método LC/MS largo; ^c = método 3; n.a. = no disponible.

5

Ejemplo 170

5-{4-Fluoro-3-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-fenil}-3-metil-1H-indol



- 10 Etapa 1: (S)-2-(4-Fluoro-fenil)-1-[2-fluoro-5-(4,4,5,5-tetrametil-[1,3,2]dioxaborolan-2-il)-bencil]-4-metil-piperazina: Una mezcla de (S)-1-(5-bromo-2-fluoro-bencil)-2-(4-fluoro-fenil)-4-metil-piperazina (0.87 g, 2.28 mmol), bis(pinacolato)diboro (0.61 g, 2.39 mmol), acetato de potasio (0.89 g, 9.11 mmol) y PdCl₂(dppf).DCM (186 mg, 0.23 mmol) en DMSO anhidro, desgasificado se evacua y luego se represuriza con
- 15 nitrógeno. Este proceso se repite varias veces para minimizar la cantidad de oxígeno en la mezcla de reacción. La mezcla se calienta a 85° C durante 4 h. La

reacción se diluye con DCM y se lava con agua y solución salina, se seca sobre MgSO_4 , se filtra y se evapora para dar un jarabe café oscuro. La cromatografía sobre gel de sílice, eluida con 2% de isopropanol/DCM da 709 mg del producto.

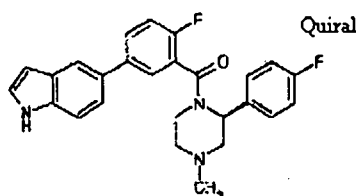
- 5 Etapa 2: 5-{4-Fluoro-3-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-fenil}-3-metil-1H-indol. Se agrega FibreCat 1001 (4 mg, 0.0006 mmol) a una mezcla de 5-bromo-3-metilindol (30 mg, 0.14mmol, (S)-2-(4-fluoro-fenil)-1-[2-fluoro-5-(4,4,5,5-tetrametil-[1,3,2]dioxaborolan-2-il)-bencil]-4-metil-piperazina (60 mg, 0.14 mmol), bromuro de tetrabutilamonio (45 mg, 0.14 mmol), y carbonato de cesio (2M, 280
10 μL , 0.56 mmol) en 4mL de 50% de dioxano acuoso. La mezcla se calienta a 150° C durante 5 min. con irradiación de microondas. La mezcla se filtra y los volátiles se remueven *in vacuo*. El residuo se particiona entre acetato de etilo y agua, las fases se separan y los orgánicos se secan sobre sulfato de magnesio, se filtran y se concentran. El residuo se cromatografía (gel de sílice, elusión con
15 metanol/DCM) para dar 32 mg del producto. LC/MS (periodo largo): Tiempo de retención, 6.54 min; (M+H) = 432.2

Ejemplo 171

[2-Fluoro-5-(1H-indol-5-il)-fenil]-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-il]-

20

metanona



- Etapa 1: (5-Bromo-2-fluoro-fenil)-[(S)-2-(4-fluoro-fenil)-piperazin-1-il]-metanona: Se
25 agregan diisopropilamina (0.47 g, 3.7mmol) y HATU (0.69 g, 1.8 mmol) a una

mezcla de ácido 5-bromo-2-fluorofenilcarboxílico 90.4 g, 1.8 mmol) y éster de terc-butilo de ácido (S)-3-(4-fluoro-fenil)-piperazina-1-carboxílico (0.34 g, 1.8 mmol) en 50 mL de dimetilformamida. La mezcla se agita a temperatura ambiente durante 15 h. Los volátiles se remueven *in vacuo*, y el residuo se particiona entre acetato de etilo y solución de bicarbonato de sodio 1M. La fase orgánica se lava con agua, se seca sobre sulfato de magnesio, se filtra y se concentra para dar 0.46 g del producto. Este material se disuelve en 4.5 mL de diclorometano y se agrega a 10 mL de 95% de trifluoroácido acético/agua. Esta mezcla se agita a temperatura ambiente durante 1.5 h y luego los volátiles se remueven *in vacuo*. El residuo se purifica por cromatografía sobre gel de sílice (elusión con 3% de etanol/diclorometano) para dar 0.32 g del producto. LC/MS: Tiempo de retención, 2.08 min; (M+H) = 381/383

Etapa 2: (5-Bromo-2-fluoro-fenil)-[(S)-2-(4-fluoro-fenil)-4-metil-piperazin-1-il]-metanona: Se agrega formaldehído (1.47 mL, 19.4 mmol de 37% de solución acuosa) a (5-Bromo-2-fluoro-fenil)-[(S)-2-(4-fluoro-fenil)-piperazin-1-il]-metanona (0.32 g, 0.65 mmol) en 10 mL de metanol. La mezcla se agita a temperatura ambiente durante 1 h y se agrega luego triacetoxiborohidruro de sodio (0.82 g, 3.9 mmol) y la mezcla resultante se agita durante la noche. Los volátiles se remueven *in vacuo*, y el residuo se particiona entre acetato de etilo y solución de bicarbonato de sodio 1M. La fase orgánica se lava con solución de bicarbonato de sodio 1M y solución salina, se seca sobre sulfato de magnesio, se filtra y se concentra para dar 0.21 g del producto. LC/MS: Tiempo de retención, 2.14 min; (M+H) = 395/397.

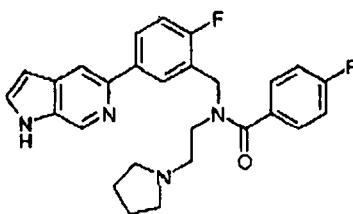
Etapa 3 [2-Fluoro-5-(1H-indol-5-il)-fenil]-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-il]-metanona: Una mezcla de (5-bromo-2-fluoro-fenil)-[(S)-2-(4-fluoro-fenil)-4-metil-piperazin-1-il]-metanona (0.2 g, 0.51 mmol) ácido Indol-5-borónico (0.086 g, 0.53

mmol), carbonato de cesio en agua (2M, 1.01 mL, 2.0 mmol) en 10 mL de dioxano se desgasifica (se evacua en vacío y se presuriza con nitrógeno, 3 veces). Se agrega PdCl₂(dppf).DCM (0.037 g, 0.0513 mmol) y la mezcla se calienta a 110 - 110° C durante 1.5 h. Los volátiles se remueven *in vacuo*, y el residuo se
5 particiona entre acetato de etilo y agua. La fase orgánica se lava con agua, se seca sobre MgSO₄, se filtra y se evapora para dar un jarabe café oscuro. La cromatografía sobre gel de sílice, se eluye con 2% de etanol/DCM da 74 mg del producto. LC/MS (periodo largo): Tiempo de retención, 5.24 min; (M+H)=432.

10

Ejemplo 172

4-Fluoro-N-[2-fluoro-5-(1H-pirrololo[2,3-c]piridin-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-
benzamida



15

Etapas 1: N-{5-[4-((E)-2-Dimetilamino-vinil)-5-nitro-piridin-2-il]-2-fluoro-bencil}-4-fluoro-N-(2-pirrolidin-1-il-etil)-benzamida: 4-Fluoro-N-[2-fluoro-5-(4-metil-5-nitro-piridin-2-il)-bencil]-N-(2-pirrolidin-1-il-etil)-benzamida (preparado de acuerdo con el ejemplo 20, 600 mg, 1.25 mmol) en 15 mL de dimetilformamida se trata con
20 dimetilformamida dimetil acetal (0.23 mL, 1.68 mmol), y la mezcla resultante se calienta a 80° C durante 5 h. La mezcla se le permite enfriar y los volátiles se remueven. El residuo se particiona entre acetato de etilo y agua. La fase orgánica se lava con agua, se seca sobre MgSO₄, se filtra y se evapora para dar un aceite. El anterior proceso se repite para dar 485 mg del producto.

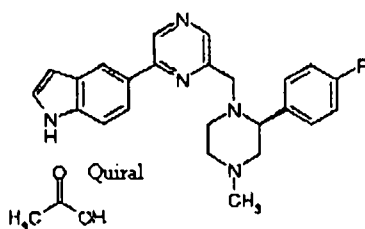
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341

Etapa 2: 4-Fluoro-N-[2-fluoro-5-(1H-pirrol[2,3-c]piridin-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-benzamida: N-{5-[4-((E)-2-Dimetilamino-vinil)-5-nitro-piridin-2-il]-2-fluoro-bencil}-4-fluoro-N-(2-pirrolidin-1-il-etil)-benzamida (485 mg, 0.9 mmol) en 30 mL de acetato de etilo se trata con 100 mg de 10% de Pd/C bajo 3 bar de hidrógeno durante 18 h. La mezcla se filtra a través de celita y el filtrado se concentra *in vacuo*. El residuo se cromatografía (alúmina, elusión con 2% de metanol/diclorometano) para proporcionar 230 mg del producto. LC/MS: Tiempo de retención, 1.79 min; (M+H)=461. RMN ¹H (400 MHz, DMSO-D₆) δ ppm: 1.61 (br s, 4 H) 2.37 (br ss, 2 H) 2.56 - 2.71 (br s, 2 H) 3.45 (t, J=6.26 Hz, 2 H) 4.75 (s, 2 H) 6.55 (s, 1 H) 7.17 - 7.28 (m, 3 H) 7.45 - 7.52 (m, 2 H) 7.56 (t, J=2.64 Hz, 1 H) 8.00 (ddd, J=8.30, 5.44, 2.31 Hz, 2 H) 8.07 (d, J=7.47 Hz, 1 H) 8.82 (s, 1 H) 11.40 (s, 1 H).

Ejemplo 173

Acetato de 5-{6-[2S-(4-Fluoro-fenil)-4-metil-piperazin-1-ilmetil]-pirazin-2-il}-1H-indol



Etapa 1: Éster de etilo de ácido 6-Cloro-ácido pirazina-2-carboxílico: Carboxilato de pirazina etilo (4.0 g, 13.14 mmol) en 200 mL de DCM se trata a 0° C con ácido meta-cloroperbenzoico (57- 80%, 5.67 g). La mezcla se le permite calentar a temperatura ambiente y se agita durante 72 h, cuando se agrega 4.28 g adicionales de ácido meta-cloroperbenzoico. Después de 4 d adicionales, se agrega 6 mL de acetona y se almacena durante 2.5 d. Luego se agrega 2.2 g de metabisulfito de sodio en 5 mL de agua y se agita durante 2 h. Se agrega acetato

de etilo y la mezcla se lava con solución salina, se seca sobre sulfato de sodio, se filtra y se concentra para dar un sólido que se purifica por cromatografía (gel de sílice, elución con acetato de etilo/pentano), para producir 3.35 g del N-óxido. El N-óxido así preparado (2.0 g, 11.89 mmol) en 10.53 mL de oxidocloruro de fósforo y 18 mL de tolueno se calienta a 100° C durante 1.5 h. La mezcla se trata cuidadosamente con hielo y luego con solución de carbonato de sodio acuosa saturada. El producto se extrae en acetato de etilo, y las capas orgánicas combinadas se lavan con solución salina, se secan sobre sulfato de sodio, se filtran y se concentran. El residuo se purifica por cromatografía de columna (elución con acetato de etilo/pentano) para dar 1.27 g de éster de etilo de ácido 6-cloro-pirazina-2-carboxílico.

Etapa 2: Éster de etilo de ácido 6-(1*H*-Indol-5-il)-pirazina-2-carboxílico: Se agrega éster de etilo de ácido 6-Cloro-pirazina-2-carboxílico (1.35 g, 7.23 mmol) a ácido indol-5-borónico (1.16 g, 7.23 mmol), carbonato de cesio (9.43 g, 28.9 mmol) y PdCl₂(dppf).DCM (591 mg, 0.72 mmol) en 30 mL de dioxano. La mezcla se desgasifica (se evacua en vacío y se presuriza con nitrógeno), se agrega 14.5 mL de agua y la mezcla se desgasifica. La mezcla se calienta a 85° C durante 2.5 h. y la mezcla se le permite enfriar y las capas se separan. La fase acuosa se extrae con cloroformo y las capas orgánicas combinadas se lavan con solución salina, se secan sobre sulfato de sodio, se filtran y se evaporan. La cromatografía del residuo sobre gel de sílice, eluida con acetato de etilo/pentano proporciona 1.07 g del producto. LC/MS: Tiempo de retención, 3.21 min; (M+η)=268.1.

Etapa 3: 6-(1*H*-Indol-5-il)-pirazin-2-ilo metanol: Se agrega una solución enfriada de éster de etilo de 6-(1*H*-indol-5-il)-ácido pirazina-2-carboxílico (1.07 g, 4.0 mmol) en 20 mL de THF a una solución de hidruro de aluminio litio (243 mg, 6.4 mmol) en 20

mL de THF a -78° C. La mezcla se agita a -78° C durante 45 min, y luego esta se calienta a 0° C y se agita durante unos 45 min adicionales, y finalmente se agita a temperatura ambiente durante 1.5 h. 0.25 mL de agua y se agrega 0.25 mL de 15% de solución de hidróxido sodio seguido por 0.75 mL adicionales de agua, la
5 mezcla se filtra a través de celita y la torta de filtro se lava con DCM. El filtrado se concentra y el residuo se disuelve en cloroformo, se lava con agua y solución salina, se seca sobre sulfato de sodio, se filtra y se concentra *in vacuo*. El residuo se recrystaliza a partir de acetato de etilo caliente para dar 486 mg de un sólido. La cromatografía (gel de sílice, elusión con metanol/DCM) proporciona 308 mg de 6-
10 (1*H*-indol-5-il)-pirazin-2-ilo metanol.

Etapa 4: Acetato de 5-{6-[2*S*-(4-Fluoro-fenil)-4-metil-piperazin-1-ilmetil]-pirazin-2-il}-1*H*-indol: Se agrega anhidro metanosulfónico (226 mg, 1.3 mmol) a 6-(1*H*-indol-5-il)-pirazin-2-ilo metanol (146 mg, 0.65 mmol) en THF. Se agrega trietilamina
15 (0.27 mL, 1.94 mmol) y la mezcla se le permite agitar a temperatura ambiente durante 45 min. En ese tiempo se agrega (S)-3-(4-fluoro-fenil)-1-metil-piperazina (315 mg, 1.62 mmol) y la mezcla se agita durante unas 18 h adicionales, cuando los volátiles se remueven *in vacuo* y se combinan con el producto de una reacción adicional desarrollada con 140 mg del alcohol. Este se diluye con DCM, y la fase
20 orgánica se lava con agua y solución salina, se seca sobre sulfato de sodio, se filtra y se concentra. El residuo se purifica por cromatografía de columna sobre gel de sílice (elusión con DCM/metanol/ácido acético/agua) para suministrar 110 mg del compuesto del título. LC/MS (periodo largo): Tiempo de retención, 2.34 min; (M+η)=402.

25

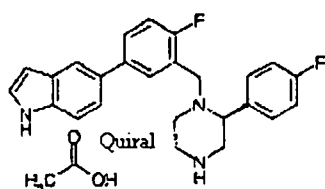
RMN ¹H (400 MHz, metanol-D₄) δ ppm: 1.97 (s, 3 H) 2.51 (s, 3 H) 2.57 (t, J = 11.7 Hz, 1 H) 2.66-2.74 (m, 2 H) 3.04 (dd, J=11.65, 2.42 Hz, 1 H) 3.10 - 3.17 (m, 2 H)

3.43 (d, J=14.6 Hz, 1 H) 3.69 (dd, J=10.88, 2.97 Hz, 1 H) 3.88 (d, J=14.6 Hz, 1 H) 6.57 (m, 1H) 7.12 (t, J=8.79 Hz, 2 H) 7.31 (d, J=3.08 Hz, 1 H) 7.50 (d, J=8.57 Hz, 1 H) 7.55 (dd, J=8.46, 5.39 Hz, 2 H) 7.82 (dd, J=8.57, 1.76 Hz, 1 H) 8.28 (d, J=1.32 Hz, 1 H) 8.34 (s, 1 H) 8.93 (s, 1 H).

5

Ejemplo 174

Acetato de 5-{4-Fluoro-3-[2S-(4-fluoro-fenil)-piperazin-1-ilmetil]-fenil}-1H-indol



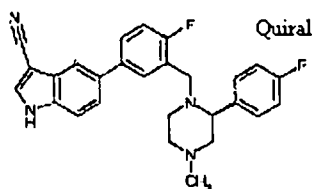
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El compuesto del título se prepara por los métodos del ejemplo 91, sin la mutilación en la etapa 3. LC/MS (periodo largo): Tiempo de retención, 5.76 min; (M+H)=404.

15

Ejemplo 175

5-{4-Fluoro-3-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-fenil}-1H-indol-3-carbonitrilo



20

Una mezcla de 5-{4-fluoro-3-[2S-(4-fluoro-fenil)-piperazin-1-ilmetil]-fenil}-1H-indol-3-carbonitrilo (preparado de acuerdo con los métodos en el ejemplo 113, 79 mg, 0.18 mmol), formaldehído (37% de solución ac., 0.13 mL), ácido acético

(0.011 mL, 0.18 mmol) en 2.5 mL de metanol se trata con triacetoxiborohidruro de sodio (214 mg, 1.01 mmol) durante la noche. Los volátiles se remueven *in vacuo* y se agrega una solución de bicarbonato de sodio saturada. El producto se extrae en DCM y los orgánicos combinados se lavan con agua, se secan sobre sulfato de sodio, se filtran y se concentran. La cromatografía (HPLC preparativa de fase inversa, elusión con acetonitrilo/agua suministra 52 mg del producto. LC/MS (periodo largo): Tiempo de retención, 5.96 min; (M+H)=443.

Ejemplos Biológicos

10 Ejemplo 176

Ensayo de Unión de Receptor

Cultivo Celular: células BHK que expresan establemente el receptor 5HT_{2A} humano se mantienen en Medio de Eagle modificado de Dulbecco complementado con 0.4 /ml de Geneticin, 1% de Piruvato de Sodio, 1% Pen-Strep y 10% de Suero de Becerro Fetal, y se trata con 5 mM de butirato de sodio durante 24 h para incrementar la extensión del receptor antes de cosecha. Las células se cosechan por raspado mecánico, se lavan con Salina Amortiguada con Fosfato, y se almacenan a -80° C en 10% de DMSO en alícuotas de 1 mg/ml hasta que se utilizan. La determinación de proteína se hace de acuerdo con Lowry.

Membranas de líneas celulares que expresan la dopamina humana D_{2L}, y los receptores α -adrenérgicos_{1A} (α 1A) se preparan como se describió previamente (Kongsamut et al., 1996 and Brooks et al., 1999). Las membranas de líneas celulares que expresan el receptor 5HT_{2c} humano se obtienen de Packard Bioscience

Ensayos de Unión del Receptor: Se conducen ensayos de 5HT_{2A} y D_{2L} a 37° C en sales que contienen amortiguador Tris (50 mM de Amortiguador Tris, pH 7.7; 120 mM de NaCl; 5 mM de KCl; 2 mM de CaCl₂; 1 mM de MgCl₂). Las membranas celulares se descongelan rápidamente (preparadas y congeladas previamente). Las membranas se diluyen a una concentración apropiada (para producir 100 µg de proteína/punto de ensayo para 5HT_{2A}, y 58 µg de proteína/punto de ensayo para D_{2L}) en amortiguador Tris y homogenizadas. Los ensayos se conducen en placas de 96 pozos, utilizando 2.5 y 1 nM de [³H]N-metil espiperona como radioligando para ensayos 5HT_{2A} y D_{2L} respectivamente. Las placas se incuban a 37° C en un baño de agitación de agua durante 30 y 60 min, para 5HT_{2A} y D_{2L}, respectivamente. La unión no específica se define utilizando 100 µM de metilsergida y eticloprida, para 5HT_{2A} y D_{2L}, respectivamente.

Se conduce el ensayo 5HT_{2C} a 37° C en amortiguador Tris (50 mM de Tris, 4 mM de CaCl₂ y 1% de ascorbato, pH 7.4). Membranas celulares (compradas de Packard Bioscience) se descongelan rápidamente. Las membranas se diluyen a una concentración apropiada (para producir 1 proteína unitaria/punto de ensayo) en amortiguador Tris y homogenizadas. Se conducen ensayos en placas de 96 pozos, utilizando 5 nM de [³H]mesulergina como radioligando. Las placas se incuban a 37° C en un baño de agitación de agua durante 60 min. La unión no específica se define utilizando 100 µM de mianserin.

Se conduce un ensayo α_{1A} a 37° C en amortiguador Tris (50 mM de Tris HCL, pH 7.7 que contiene 0.1% de ácido ascórbico). Las membranas celulares se descongelan rápidamente (preparadas y congeladas previamente). Las membranas se diluyen a una concentración apropiada (para producir 130 µg proteína/punto de ensayo) en amortiguador Tris y homogenizadas. Se conducen

ensayos en placas de 96 pozos, utilizando 1 nM de [^3H]prazosin como radioligando. Las placas se incuban a 37° C en un baño de agitación de agua durante 60 min. La unión no específica se define utilizando 100 μM fentolamina.

- 5 Los ensayos se determinan por filtración rápida a través de placas de filtro Millipore MAFB o MAFC (5HT_{2c}) (preenjuagadas en 50 mM de Tris HCl, pH 7.7, con 0.1% de Brij) utilizando un Cosechador de Células Millipore. Las placas de filtro luego se lavan con amortiguador Tris 50 mM enfriado con hielo, pH 7.7, y se le permite secar durante la noche. Se agrega cóctel de centelleo Microscint 50 μl y
- 10 las placas se cuentan en un contador de centelleo Packard Topcount.

- Se desarrollan cálculos IC₅₀ y K_i utilizando análisis de competición de un sitio de regresión no lineal (GraphPad, Prism), con límites inferiores y superiores mantenidos constantes a 0% y 100% de inhibición, respectivamente. El porcentaje
- 15 de inhibición en cada concentración de droga es el promedio de las determinaciones por duplicado. Excepto cuando se indique, cada determinación se desarrolla de 2 a 5 veces.

- Ensayo Funcional 5-HT_{2A}: se mantienen células BHK como se describió
- 20 anteriormente, y se siembran en la noche en placas cubiertas de colágeno de 96 pozos (pared negra, fondo claro) en una densidad de 45000/75 μl de medio en 0.5% de suero. Al siguiente día, el kit de tinte de calcio (Molecular Probes) se prepara en Solución de Sal Balanceada de Hank con la adición de 5 mM de probenecid (pH 7.4), y las células se incuban con esta solución durante 1 hora a
- 25 37° C. Los compuestos se preparan como un depósito DMSO de 10 mM y se diluyen a partir de allí; el agonista (serotonina) se prepara diariamente de forma fresca.

Se excitan células cargadas con tinte a 488 nm y la emisión detectada en 525 nm utilizando un filtro de corte 515 nm y una configuración de fotomulticapa alto en Molecular Devices FLEXstation™. Se leen los pozos (1 columna a la vez) en intervalos de 2 segundos para un periodo total de 375 segundos. El compuesto o vehículo se agrega a los 15 segundos seguido por la adición de 5-HT (1µM final) a 315 segundos (5 min de pretratamiento), o se agrega compuesto durante la carga de tinte (pretratamiento de 60 min).

La señal se calcula al sustraer la respuesta de pico del medio de la fluorescencia de línea base. El porcentaje de respuesta máximo para 1 µM 5-HT se calcula luego con el fin de generar las curvas IC₅₀

Referencias:

Brooks K. M., Cai J., Sandrasagra A., Roehr J. E., Errazo R., Vargas H. M.; Interaction of clozapine and other antipsychotic drugs with human alpha 1-adrenergic receptor subtypes, Proc. West Pharmacol. Soc. 1999; 42:67-69.

Kongsamut S., Roehr J. E., Cai J., Hartman H. B., Weissensee P., Kerman L. L.,

Tang L., Sandrasagra A.; Iloperidone binding to human and rat dopamina and 5-HT receptors, Eur. J. Pharmacol. 1996; 317(2-3):417-423.

Los valores K_i observados (expresados en concentración nanomolar, nM) en el sitio de receptor 5HT_{2A} para los compuestos de esta invención se tabulan en la Tabla 17.

Tabla 17

352

Ejemplo No.	5-HT _{2A} K _i (nM)
1	10.8
2	2.4
3	0.9
4	33.5
5	217.6
6	2.7
7	210.0
8	35.4
9	227.0
10	13.8
11	16.2
13	3.3
14	1.4
15	13.8
16	4.9
17	7.2
18	74.8
19	76.5
20	0.32
21	0.26
23	0.37
24	0.56
25	0.6
26	0.68
27	0.7
28	0.7
29	0.7
30	0.77
31	0.92
32	1.1
33	1.19
34	1.25
35	2.8
36	4.1
37	4.1

38	14.4
39	1.1
40	0.58
42	0.61
43	0.6
45	0.99
47	1.24
48	0.6
49	0.4
50	2.5
51	9.2
52	3.1
53	2.13
54	0.9
55	0.31
56	6.51
57	0.71
58	1.23
59	0.89
60	1.13
61	0.7
62	0.75
63	0.58
64	0.6
65	0.9
66	0.67
67	2.16
68	3.14
69	1.35
70	0.72
71	0.49
72	2.37
74	1.05
75	2.14
76	4.74
77	0.49
78	0.76

359

79	0.61
80	14.9
81	2.0
82	0.51
83	0.82
84	0.37
85	0.42
86	1.68
87	14.2
88	1.16
89	1.0
90	0.42
91	0.6
93	0.6
95	1.9
96	0.89
97	0.77
98	1.2
99	0.29
100	0.6
101	0.39
102	0.88
103	1.01
104	0.31
105	3.8
106	9.0
107	85.0
108	16.0
110	85.0
111	85.0
112	6.0
113	0.4
114	0.48
115	2.88
116	1.79
117	4.79
118	1.1

119	0.78
120	65.0
121	82.0
140	22.6
171	85.0
174	0.9
175	3.2

Ejemplo 177

Ensayo Head Twitch

5 Este Ejemplo 177 ilustra el estudio de eficacia de los compuestos de esta invención en el sitio del receptor 5HT_{2A} en modelos animales. En este Ejemplo 177, la inhibición de dimetiltriptamina (DMT) induce el head twitch en el ratón que se mide utilizando los compuestos de esta invención como se establece adelante.

10 Inhibición de 5-MeODMT (5-Metoxi-N,N-dimetiltriptamina): Se administran compuestos de ensayo a grupos de ratones machos en dosis seleccionadas. En un intervalo apropiado adelante 5-MeODMT (disuelto en 0.5% de ácido ascórbico) se administra en una dosis de 30 mg/kg i.p. Inmediatamente después de administración de 5-MeODMT, y continúa después de 6 min, el número de head
15 twitches para cada animal se continúa. Para efectos de inhibición, los animales no exhiben head twitches durante este periodo de 6 min que se considera bloqueado. El ED₅₀ se calcula como la dosis necesaria para bloquear el head twitch en 50% de los animales de ensayo. Todos los animales se desarrollan con al menos 10 animales por condición.

20

Los valores ED₅₀ (expresados como mg/kg) para los compuestos de esta invención se tabulan en la Tabla 18.

Tabla 18

Ejemplo No.	ED ₅₀ mg/kg, sc
3	<1(100% efecto@ 1mg/kg)
20	0.27
21	<3 (60% efecto @ 3 mg/kg)
23	0.16
26	0.82
27	0.59
34	1.09
42	1.73
44	0.54
47	~3 (50% efecto @ 3 mg/kg)
91	0.41
92	0.53
94	~3 (50% efecto @ 3 mg/kg)
95	0.5
98	0.49
104	6.36
133	0.92
159	0.04
161	0.16

5

Ejemplo 178

Estudios de Insomnio y Mantenimiento de Sueño

Este Ejemplo 178 ilustra el estudio de la eficacia de los compuestos de esta invención en mejorar la calidad de sueño en modelos animales.

10

Para registrar el electroencefalograma cortical (EEG), se preparan ratas macho Sprague-Dawley con cuatro electrodos de tornillo miniatura colocados a

través del cráneo (1.5 mm en el lado de la sutura central, 1.5, 3.0, 4.5 y 6.0 mm anterior a lambda) y se le permite recuperar durante 7 días. Los animales se mueven libremente y luego se colocan (en su propia jaula) en un cuarto a prueba de sonido que registra la humedad y temperatura controladas. Para cada rata, los registros se hacen a partir de dos terminales que suministran la mayor amplitud de ritmo theta. El ritmo theta (5-9Hz) y la menor actividad eléctrica (0 - 4Hz) se registran en animales despiertos (W). Solo las ondas lentas (0 - 4Hz) y los husos durmientes (12-14Hz) se observan durante la onda de sueño lenta (SWS). El ritmo theta solo se registra durante el sueño paradoxical (PS). Para cada rata y cada nivel de vigilancia (W, SWS, PS), un mínimo de espectro de energía promediado 90, que corresponde a episodios visualmente identificados se suman con el fin de obtener un espectro de referencia promedio. Los efectos de los compuestos de esta invención en cada uno de estos ritmos se miden.

Los compuestos de esta invención se administran 5 horas después que se enciende la luz o 18 horas después que se enciende la luz. Se incluyen seis animales en cada grupo de tratamiento. Todos compuestos de esta invención se administran intraperitonealmente. Se incluye un compuesto de referencia positivo y vehículo de control en cada estudio un grupo satélite de animales se dosifica para examinar los farmacocinéticos; sangre, de la cual, se obtienen fracciones de plasma y muestras de cerebros se recolectan de estos animales.

Ejemplo 179

Estudios de Apnea Obstructiva de Sueño

La aplicación intraperitoneal de L-triptofan (10mg/kg) y pargilina (50mg/kg) para ratas neonatas anestesiadas reduce la amplitud de las descargas de

inspiración del músculo genioglossal e induce la apnea obstructiva (OA). El siguiente procedimiento describe como determinar la eficacia de los compuestos de esta invención cuando se compara con la eficacia de la teofilina.

5 Se llevan a cabo experimentos en ratas Sprague Dawley neonatas. Los animales se anestesian mediante inyección intraperitoneal de bajas dosis de pentobarbitona de sodio (7-10mg/kg), se mantiene en reposo (cúbito dorsal) en una manta caliente y se ventila espontáneamente.

10 La actividad de electromiograma (EMG) de los músculos genioglossales y el diafragma se registran con cables finos aislados(registros bipolares) insertados dentro de los músculos, filtrados (100-3,000 Hz), amplificados (x 5-10,000) e integrados (tiempo constante 50 ms). Los movimientos de la jaula se registran por vía de un captador que toca las costillas inferiores y/o la pared abdominal. Los
15 cambios de flujo de aire que resultan de los movimientos respiratorios del pecho se registran por vía de una máscara facial y un registrador de presión altamente sensible.

Los efectos de un compuesto de esta invención en la depresión de un EMG
20 genioglossal inducido por L-triptofan y pargilina se pueden medir como sigue: Diez a quince minutos después de la inducción de anestesia, los animales reciben una primera inyección intraperitoneal de un compuesto de esta invención, y se toma un registro de control para definir la amplitud media del EMG integrado. Luego el animal recibe una inyección intraperitoneal de L-triptofan más pargilina ("L-
25 Trp+Parg") 10mg/kg y 50mg/kg, respectivamente, y los cambios en las amplitudes EMG se revisan cada 10 minutos se expresan como (%) de valores de control.

En general, el pre-tratamiento con un compuesto de esta invención en niveles de dosis de aproximadamente 0.1 mg/kg a aproximadamente 1.0 mg/kg pueden evitar la depresión de descarga genioglossal (GG) inducida por la inyección de L-Trp+Parg.

5

Los efectos del pretratamiento de compuestos en la ocurrencia de apnea obstructiva (OAs) inducida por inyección de L-triptofan y pargilina se pueden medir como sigue: Los movimientos respiratorios y que resultan de cambios de flujo de aire se pueden medir en 30 ratas neonatas que reciben un primer tratamiento con un compuesto de esta invención en 0.1, 1 o 3 mg/kg y 10 min después de inyección de L-Trp+Parg. Generalmente, la inyección L-Trp+Parg induce OAs ratas neonatas. Las ratas que reciben el compuesto de esta invención se espera que exhiban corta duración OA a ninguna OA dependiendo de la dosis administrada. Por ejemplo, las ratas que reciben 1 mg/kg a 1 mg/kg del compuesto de esta invención pueden exhibir corta duración OA. Mientras las ratas que reciben dosis mayores de aproximadamente 3 mg/kg se espera que no muestren OA.

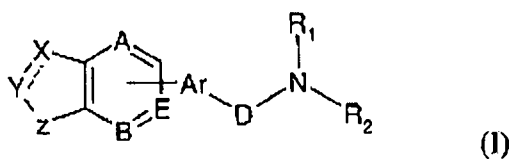
Efectos de pre-tratamiento de teofilina en la ocurrencia de apnea obstructiva inducida por inyección de L-triptofan y pargilina que se miden como sigue: Cinco ratas neonatas reciben teofilina en 10 mg/kg y los otros 5 animales reciben teofilina en 30 mg/kg. En ambos casos, la inyección L-Trp+Prg reduce la amplitud de descargas de inspiración de GG y este efecto no evita cualquier dosis de teofilina. En un segundo conjunto de experimentos, la inducción de OA después de inyección de L-Trp+Prg tampoco evita la teofilina en 10 o 30 mg/kg.

Aunque la invención se ha ilustrado por ciertos ejemplos precedentes, no se debe constituir como limitado de tal modo; pero a diferencia, la invención abarca el área genérica como se describió aquí anteriormente. Se pueden hacer varias modificaciones y modalidades sin apartarse del espíritu y alcance de la misma.

REIVINDICACIONES

Lo que se reivindica es:

- 5 1. Un compuesto que incluye los enantiómeros, estereoisómeros, y tautómeros de dicho compuesto y sales farmacéuticamente aceptables, solvatos o derivados de este, con dicho compuesto que tiene la estructura general mostrada en la fórmula I:



en donde:

$X \text{ --- } Y$ denota un enlace doble o sencillo entre X y Y;

X es CR, CHR, CO, N, O o S;

15 Y es CR, CHR, CO, S(O)₂, N o NR;

Z es NR, CO-NR, S(O)₂-NR;

A, B y E son los mismos o diferentes e independientemente uno del otro son CR o N;

D es CH₂ o CO;

20

Ar es arilo o heteroarilo sustituido o no sustituido;

cada R se escoge independientemente de hidrógeno, halógeno, CN, C(O)NR₃R₄,

alquilo C₁₋₄, alcoxi C₁₋₄, alquenilo C₁₋₄, arilo, heteroarilo, arilalquilo C₁₋₄,

heteroarilalquilo C₁₋₄, fluoroalquilo o fluoroalcoxi de la fórmula C_nH_xF_y o

25 OC_nH_xF_y en donde n es un entero entre 1 a 4, x es un entero entre 0 a 8, y es un entero entre 1 a 9 y la suma de x y y es 2n+1; en donde

R₃ y R₄ son hidrógeno o alquilo C₁₋₄; o

R₃ y R₄ tomados junto con el átomo de nitrógeno al cual ellos están adheridos

5 forman un heterociclo no sustituido o al menos monosustituido;

R₁ y R₂ son los mismos o diferentes y se seleccionan independientemente uno del

otro de arilo sustituido o no sustituido, heteroarilo, ariloilo, heteroariloilo,

arilsulfonilo, heteroarilsulfonilo, arilalquilo C₁₋₄, heteroarilalquilo C₁₋₄,

10 aminoalquilo C₁₋₄, alquilamino C₁₋₄alquilo C₁₋₄, cicloalquilo C₃₋

8aminoalquiloC₁₋₄, dicicloalquiloC₃₋₈aminoalquilo C₁₋₄, cicloalquilo C₃₋

8alquiloC₁₋₄aminoalquiloC₁₋₄, dialquilamino C₁₋₄alquilo, heterociclo,

heterocicloalquilo C₁₋₄, heterocicloalquilo C₁₋₄alquilo C₁₋₄; o

15 R₁ y R₂ tomados junto con el átomo de nitrógeno al cual ellos están adheridos

forman un heterociclo no sustituido o al menos monosustituido; y en donde

los sustituyentes se seleccionan del grupo que consiste de arilo sustituido o

no sustituido, heteroarilo, arilalquilo C₁₋₄, heteroarilalquilo C₁₋₄, heterociclo,

cicloalquilo C₃₋₈, alquilo C₁₋₄, alcoxi C₁₋₄, alquenilo C₁₋₄, fluoroalquilo o

20 fluoroalcoxi de la fórmula C_nH_xF_y o OC_nH_xF_y en donde n es un entero entre

1 a 4, x es un entero entre 0 a 8, y es un entero entre 1 a 9 y la suma de x y

y es 2n+1, -NO₂, -NH₂, -NH(alquilo C₁₋₄), -N(alquilo C₁₋₄)₂, -CN, -C(O)R₅, -

NHC(O)(alquilo C₁₋₄), -SO₂Cl, -SO₂(alquilo C₁₋₄), halógeno y hidroxil; en

donde

25

R₅ es hidroxil, alcoxi C₁₋₃, -O-fenilo, -NH₂, -NH(alquilo C₁₋₃), -N(alquilo C₁₋₃)₂ o

fenilo; heteroarilo es un heterociclo aromático, mono- o bicíclico de 5 a 10

miembros que contiene uno o más heteroátomos seleccionados del grupo que consiste de N, O y S;

arilo es un anillo aromático, mono- o bicíclico de 6 a 10 miembros; y

5

heterociclo es un heterociclo no aromático, mono- o bicíclico de 3 a 10 miembros que contiene uno o más heteroátomos seleccionados del grupo que consiste de N, O y S.

10 2. El compuesto como se establece en la reivindicación 1, en donde:

D es CH₂;

Ar es fenilo sustituido o no sustituido, piridinilo, pirazinilo, furanilo o tiofenilo; en donde los sustituyentes se seleccionan del grupo que consiste de flúor, cloro, alquilo C₁₋₄, alcoxi C₁₋₄ y -CF₃;

15

cada R se escoge independientemente de hidrógeno, CN o alquilo C₁₋₄;

R₁ y R₂ son los mismos o diferentes y se seleccionan independientemente uno del

20

otro de benzoilo sustituido o no sustituido, tiofenilcarbonilo, piridinilcarbonilo, pirazinilcarbonilo, pirimidinilcarbonilo, piridazinilcarbonilo, dihidro-benzo[1,4]dioxinilcarbonilo, benzo[1,3]dioxolilcarbonilo, fenilalquilo C₀₋₄, tiofenilalquilo C₁₋₄, aza-biciclo[2.2.2]octilalquilo C₀₋₄, aza-biciclo[3.2.1]octilalquilo C₀₋₄, piperidinilalquilo C₀₋₄, pirrolidinilalquilo C₀₋₄, alquilamino C₁₋₄alquiloC₁₋₄ y dialquilaminoC₁₋₄ alquilo C₁₋₄; en donde las porciones sustituidas se pueden sustituir con uno o más sustituyentes seleccionados

25

del grupo que consiste de flúor, cloro, alquilo C₁₋₄, cicloalquilo C₃₋₈, alcoxi C₁₋₄, OCF₃ y CF₃; o

R₁ y R₂ tomados junto con el átomo de nitrógeno al cual ellos están adheridos
5 forman un heterociclo no sustituido o al menos monosustituido seleccionado del grupo que consiste de piperazina y diazepan; en donde los sustituyentes se seleccionan del grupo que consiste de fenilo, fluorofenilo, trifluorometilfenilo, piridinilo, tiofenilo, furanilo y alquilo C₁₋₄.

10 3. El compuesto como se establece en la reivindicación 2, en donde:

X = Y denota un enlace doble entre X y Y;

X es CR;

Y es CR;

15 Z es NR;

A, B y E son los mismos o diferentes e independientemente uno del otro son CH o N;

Ar es fenilo, fluorofenilo, clorofenilo, piridinilo, pirazinilo, furanilo o tiofenilo;

20

cada R se escoge independientemente de hidrógeno, CN, metilo, etilo, metoxi, flúor, CF₃ o OCF₃;

R₁ y R₂ son los mismos o diferentes y se seleccionan independientemente uno del
25 otro de bencilo, fluorobencilo, fluorobenzoilo, clorobenzoilo, isopropoxibenzoilo, trifluorometilbenzoilo, fluoro-trifluorometilbenzoilo, trifluorometoxibenzoilo, tiofenilcarbonilo, piridinilcarbonilo, pirazinilcarbonilo,

pirimidinilcarbonilo, piridazinilcarbonilo, dihidro-benzo[1,4]dioxinilcarbonilo, benzo[1,3]dioxolilcarbonilo, aza-biciclo[2.2.2]octilo, aza-biciclo[2.2.2]octilmetilo, N-metil-piperidinilo, pirrolidinilmetilo, pirrolidiniletilo, pirrolidinilpropilo y dimetilaminoetilo; o

5

R₁ y R₂ tomados junto con el átomo de nitrógeno al cual ellos están adheridos forman un heterociclo no sustituido o al menos monosustituido seleccionado del grupo que consiste de piperazina y diazepam; en donde los sustituyentes se seleccionan del grupo que consiste de fenilo, fluorofenilo, trifluorometilfenilo, piridinilo, tiofenilo, furanilo y metilo.

10

4. El compuesto como se establece en la reivindicación 3 seleccionado del grupo que consiste de:

15

N-bencil-N-[3-(1H-indol-5-il)-bencil]-N',N'-dimetil-etano-1,2-diamina;

4-fluoro-N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-

benzamida;

N-(2-dimetilamino-etil)-4-fluoro-N-[2-fluoro-5-(2-metil-1H-indol-5-il)-bencil]-

benzamida;

20

N-(2-dimetilamino-etil)-4-fluoro-N-[2-fluoro-5-(1H-indol-5-il)-bencil]-

benzamida;

4-fluoro-N-[3-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-benzamida;

[3-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido tiofen-2-carboxílico;

25

[2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido tiofen-2-carboxílico;

(2-dimetilamino-etil)-[2-fluoro-5-(1H-indol-5-il)-bencil]-amida de ácido tiofen-2-carboxílico;

4-fluoro-N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-benzamida;

5 Trifluoro-acetato de N-(1-aza-biciclo[2.2.2]oct-4-ilmetil)-4-fluoro-N-[2-fluoro-5-(1H-indol-5-il)-bencil]-benzamida;

4-fluoro-N-[5-(1H-indol-5-il)-piridin-3-ilmetil]-N-(2-pirrolidin-1-il-etil)-benzamida;

4-fluoro-N-[4-fluoro-3-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-

10 benzamida;

Acetato de 4-fluoro-N-[4-(1H-indol-5-il)-tiofen-2-ilmetil]-N-(2-pirrolidin-1-il-etil)-benzamida;

(4-fluoro-bencil)-[2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amina;

15 N-(4-fluoro-bencil)-N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N',N'-dimetil-etano-1,2-diamina;

Acetato de (1-aza-biciclo[2.2.2]oct-4-ilmetil)-(4-fluoro-bencil)-[2-fluoro-5-(1H-indol-5-il)-bencil]-amina;

Trifluoroacetato de N-(2-dimetilamino-etil)-4-fluoro-N-[5-(1H-indol-5-il)-piridin-3-ilmetil]-benzamida;

20

4-fluoro-N-[5-(1H-indol-5-il)-tiofen-2-ilmetil]-N-(2-pirrolidin-1-il-etil)-benzamida;

4-fluoro-N-[4-(1H-indol-5-il)-furan-2-ilmetil]-N-(1-metil-piperidin-4-il)-benzamida;

25

N-(1-aza-biciclo[2.2.2]oct-3*R*-il)-4-fluoro-N-[2-fluoro-5-(1H-indol-6-il)-bencil]-benzamida;

[2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido
pirimidina-4-carboxílico;

[2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido
pirimidina-2-carboxílico;

5 [2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido
piridazina-3-carboxílico;

[2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido
piridazina-4-carboxílico;

10 [2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido 2,3-
dihidro-benzo[1,4]dioxina-6-carboxílico;

N-[2-fluoro-5-(1H-indol-5-il)-bencil]-4-isopropoxi-N-(1-metil-piperidin-4-il)-
benzamida;

N-[2-fluoro-5-(1H-indol-5-il)-bencil]-3-isopropoxi-N-(1-metil-piperidin-4-il)-
benzamida;

15 N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-4-
trifluorometoxi-benzamida;

4-cloro-N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-
benzamida;

20 [2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido
benzo[1,3]dioxol-5-carboxílico;

N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-4-trifluorometil-
benzamida;

4-fluoro-N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-3-
trifluorometil-benzamida;

25 N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-isonicotinamida;

N-[3-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-4-trifluorometil-
benzamida;

4-fluoro-N-[4-fluoro-3-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-
benzamida;

N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-4-trifluorometil-
benzamida;

5 4-fluoro-N-[3-fluoro-5-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-
benzamida;

N-[3-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-4-trifluorometil-benzamida;

N-[3-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-isonicotinamida;

10 N-[4-fluoro-3-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-4-trifluorometil-
benzamida;

N-[3-(1H-indol-5-il)-bencil]-N-(3-pirrolidin-1-il-propil)-isonicotinamida;

N-[4-fluoro-3-(1H-indol-5-il)-bencil]-N-(3-pirrolidin-1-il-propil)-
isonicotinamida;

15 [3-(1H-indol-5-il)-bencil]-(3-pirrolidin-1-il-propil)-amida de ácido piridin-2-
carboxílico;

N-[3-(1H-indol-5-il)-bencil]-N-(3-pirrolidin-1-il-propil)-4-trifluorometil-
benzamida;

[4-fluoro-3-(1H-indol-5-il)-bencil]-(3-pirrolidin-1-il-propil)-amida de ácido
piridin-2-carboxílico;

20 [4-(1H-indol-5-il)-tiofen-2-ilmetil]-(3-pirrolidin-1-il-propil)-amida de ácido
piridin-2-carboxílico;

N-[4-(1H-indol-5-il)-tiofen-2-ilmetil]-N-(3-pirrolidin-1-il-propil)-4-trifluorometil-
benzamida;

N-[4-(1H-indol-5-il)-tiofen-2-ilmetil]-N-(2-pirrolidin-1-il-etil)-isonicotinamida;

25 [4-(1H-indol-5-il)-tiofen-2-ilmetil]-(2-pirrolidin-1-il-etil)-amida de ácido piridin-
2-carboxílico;

N-[4-(1H-indol-5-il)-tiofen-2-ilmetil]-N-(2-pirrolidin-1-il-etil)-4-trifluorometil-benzamida;

[4-(1H-indol-5-il)-furan-2-ilmetil]-(3-pirrolidin-1-il-propil)-amida de ácido piridin-2-carboxílico;

5 N-[4-(1H-indol-5-il)-furan-2-ilmetil]-N-(3-pirrolidin-1-il-propil)-4-trifluorometil-benzamida;

N-[4-(1H-indol-5-il)-furan-2-ilmetil]-N-(2-pirrolidin-1-il-etil)-isonicotinamida;

[4-(1H-indol-5-il)-furan-2-ilmetil]-(2-pirrolidin-1-il-etil)-amida de ácido piridin-2-carboxílico;

10 N-[4-(1H-indol-5-il)-furan-2-ilmetil]-N-(2-pirrolidin-1-il-etil)-4-trifluorometil-benzamida;

N-[4-(1H-indol-5-il)-tiofen-2-ilmetil]-N-(3-pirrolidin-1-il-propil)-isonicotinamida;

N-[4-(1H-indol-5-il)-furan-2-ilmetil]-N-(3-pirrolidin-1-il-propil)-isonicotinamida;

N-[2-cloro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-isonicotinamida;

15 [2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido piridin-2-carboxílico;

N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-nicotinamida;

N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-3-trifluorometoxi-benzamida;

20 N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-isonicotinamida;

N-[4-fluoro-3-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-isonicotinamida;

Acetato de N-[4-fluoro-3-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-4-trifluorometoxi-benzamida;

N-[3-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-isonicotinamida;

25 [2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido pirazina-2-carboxílico;

Acetato de 5-[4-fluoro-3-(4-metil-2-piridin-3-il-piperazin-1-ilmetil)-fenil]-1H-indol;

5-{4-fluoro-3-[4-metil-2-(4-trifluorometil-fenil)-piperazin-1-ilmetil]-fenil}-1H-indol;

5 Acetato de 5-[4-fluoro-3-(4-metil-2-piridin-2-il-piperazin-1-ilmetil)-fenil]-1H-indol;

Acetato de 5-{5-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-piridin-3-il}-1H-indol;

5-{4-fluoro-3-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-fenil}-1H-indol;

10 5-[4-fluoro-3-(2-furan-2-il-4-metil-piperazin-1-ilmetil)-fenil]-1H-indol;

Trifluoro-acetato de 5-{5-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-furan-3-il}-1H-indol;

Acetato de 5-{5-[2S-(4-fluoro-fenil)-piperazin-1-ilmetil]-piridin-3-il}-1H-indol;

5-{5-[2S-(4-fluoro-fenil)-piperazin-1-ilmetil]-furan-3-il}-1H-indol;

15 5-[3-(4-metil-piperazin-1-ilmetil)-fenil]-1H-indol;

5-[4-fluoro-3-(4-metil-2-piridin-4-il-piperazin-1-ilmetil)-fenil]-1H-indol;

5-{3-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-fenil}-1H-indol;

Acetato de 5-{6-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-pirazin-2-il}-1H-indol;

20 Acetato de 5-{4-fluoro-3-[2S-(4-fluoro-fenil)-piperazin-1-ilmetil]-fenil}-1H-indol;

5-{4-fluoro-3-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-fenil}-1H-indol-3-carbonitrilo;

5-[3-(4-metil-[1,4]diazepan-1-ilmetil)-fenil]-1H-indol;

25 5-{4-fluoro-3-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-fenil}-3-metil-1H-indol;

N-[5-(3-ciano-1H-indol-5-il)-2-fluoro-bencil]-N-(2-dimetilamino-etil)-4-fluoro-benzamida;

5-{4-fluoro-3-[2S-(4-fluoro-fenil)-piperazin-1-ilmetil]-fenil}-1H-indol-3-carbonitrilo;

5 Trifluoro-acetato de 5-{6-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-pirazin-2-il}-1H-indol;

4-fluoro-N-[2-fluoro-5-(1H-pirrolo[3,2-b]piridin-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-benzamida;

10 5-{4-fluoro-3-[2-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-fenil}-1H-pirrolo[3,2-b]piridina; y

4-fluoro-N-[2-fluoro-5-(1H-pirrolo[2,3-c]piridin-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-benzamida;

o una sal farmacéuticamente aceptable de estos o un óptico o estereoisómero de estos.

15

5. El compuesto como se establece en la reivindicación 2, en donde:

X — Y denota un enlace doble entre X y Y;

X es CR;

20 Y es N;

Z es NR;

tanto A, B y E son CH;

Ar es fenilo, fluorofenilo, clorofenilo, piridinilo, pirazinilo, furanilo o tiofenilo;

25

cada R se escoge independientemente de hidrógeno, metilo, etilo, metoxi, flúor,

CF₃ o OCF₃;

R₁ y R₂ son los mismos o diferentes y se seleccionan independientemente uno del otro de bencilo, fluorobencilo, fluorobenzoilo, clorobenzoilo, isopropoxibenzoilo, trifluorometilbenzoilo, fluoro-trifluorometilbenzoilo, trifluorometoxibenzoilo, tiofenilcarbonilo, piridinilcarbonilo, pirazinilcarbonilo, 5 pirimidinilcarbonilo, piridazinilcarbonilo, dihidro-benzo[1,4]dioxinilcarbonilo, benzo[1,3]dioxolilcarbonilo, N-metil-aza-biciclo[2.2.2]octilo, aza-biciclo[2.2.2]octilo, aza-biciclo[2.2.2]octilmetilo, N-metil-piperidinilo, piperidinilo, N-metil-pirrolidinilo, pirrolidinilmetilo, pirrolidiniletilo, 10 pirrolidinilpropilo, metilaminoetilo, y dimetilaminoetilo; o

R₁ y R₂ tomados junto con el átomo de nitrógeno al cual ellos están adheridos forman un heterociclo no sustituido o al menos monosustituido seleccionado del grupo que consiste de piperazina y diazepan; en donde los 15 sustituyentes se seleccionan del grupo que consiste de fenilo, fluorofenilo, trifluorometilfenilo, piridinilo, tiofenilo, furanilo y metilo.

6. El compuesto como se establece en la reivindicación 5 seleccionado del grupo que consiste de:

20

Clorhidrato de N-bencil-N-[3-(1H-indazol-5-il)-bencil]-N',N'-dimetil-etano-1,2-diamina;

Acetato de N-(4-fluoro-bencil)-N-[5-(1H-indazol-5-il)-piridin-3-ilmetil]-N',N'-dimetil-etano-1,2-diamina;

25

(4-fluoro-bencil)-[2-fluoro-5-(1H-indazol-5-il)-bencil]-pirrolidin-2S-ilmetil-amina;

(4-fluoro-bencil)-[2-fluoro-5-(1H-indazol-5-il)-bencil]-piperidin-4-il-amina;

N-(4-fluoro-bencil)-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N'-metil-etano-1,2-diamina;

(4-fluoro-bencil)-[2-fluoro-5-(1H-indazol-5-il)-bencil]-(1-metil-piperidin-4-il)-amina;

5 (4-fluoro-bencil)-[4-(1H-indazol-5-il)-furan-2-ilmetil]-(1-metil-piperidin-4-il)-amina;

4-fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-benzamida; 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(exo-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-benzamida;

10 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(endo-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-benzamida;

4-fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(1-metil-piperidin-3-il)-benzamida;

15 Trifluoro-acetato de 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(1-metil-piperidin-3S-il)-benzamida;

Trifluoro-acetato de 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(1-metil-pirrolidin-3R-il)-benzamida;

Trifluoro-acetato de 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(1-metil-pirrolidin-3S-il)-benzamida;

20 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(3-pirrolidin-1-il-propil)-benzamida;

4-fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-benzamida;

25 N-(1-aza-biciclo[2.2.2]oct-3R-il)-4-fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-benzamida;

N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(1-metil-pirrolidin-3R-il)-4-trifluorometil-benzamida quiral;

4-fluoro-N-[4-(1H-indazol-5-il)-furan-2-ilmetil]-N-(1-metil-piperidin-4-il)-benzamida;

5-{4-fluoro-3-[2-(4-fluoro-fenil)-piperazin-1-ilmetil]-fenil}-1H-indazol;

Acetato de 5-[4-fluoro-3-(2S-tiofen-2-il-piperazin-1-ilmetil)-fenil]-1H-indazol;

5 5-[4-fluoro-3-(2-tiofen-2-il-piperazin-1-ilmetil)-fenil]-1H-indazol;

Acetato de 5-[4-fluoro-3-(2-tiofen-2-il-piperazin-1-ilmetil)-fenil]-1H-indazol quiral;

5-{4-fluoro-3-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-fenil}-1H-indazol;

5-{5-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-piridin-3-il}-1H-indazol;

10 5-{5-[2S-(4-fluoro-fenil)-piperazin-1-ilmetil]-piridin-3-il}-1H-indazol;

5-{5-[2S-(4-fluoro-fenil)-piperazin-1-ilmetil]-furan-3-il}-1H-indazol;

Acetato de 5-[4-fluoro-3-(4-metil-2R-tiofen-2-il-piperazin-1-ilmetil)-fenil]-1H-indazol;

Acetato de 5-[4-fluoro-3-(4-metil-2S-tiofen-2-il-piperazin-1-ilmetil)-fenil]-1H-indazol; y

5-{5-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-furan-3-il}-1H-indazol;

o una sal farmacéuticamente aceptable de estos o un óptico o estereoisómero de estos.

20 7. El compuesto como se establece en la reivindicación 2, en donde:

$X \equiv Y$ denota un enlace doble entre X y Y;

X es N;

Y es CR;

25 Z es NR;

tanto A, B y E son CH;

378

Ar es fenilo, fluorofenilo, clorofenilo, piridinilo, pirazinilo, furanilo o tiofenilo;

cada R se escoge independientemente de hidrógeno, metilo, etilo, metoxi, CF_3 o OCF_3 ;

5

R_1 y R_2 son los mismos o diferentes y se seleccionan independientemente uno del otro de bencilo, fluorobencilo, fluorobenzoilo, clorobenzoilo, isopropoxibenzoilo, trifluorometilbenzoilo, fluoro-trifluorometilbenzoilo, trifluorometoxibenzoilo, tiofenilcarbonilo, piridinilcarbonilo, pirazinilcarbonilo, pirimidinilcarbonilo, piridazinilcarbonilo, dihidro-benzo[1,4]dioxinilcarbonilo, benzo[1,3]dioxolilcarbonilo, N-metil-aza-biciclo[2.2.2]octilo, aza-biciclo[2.2.2]octilo, aza-biciclo[2.2.2]octilmetilo, N-metil-piperidinilo, piperidinilo, N-metil-pirrolidinilo, pirrolidinilmetilo, pirrolidiniletilo, pirrolidinilpropilo, metilaminoetilo, dimetilaminoetilo y dimetilaminopropilo;

10

15

o

R_1 y R_2 tomados junto con el átomo de nitrógeno al cual ellos están adheridos forman un heterociclo no sustituido o al menos monosustituido seleccionado del grupo que consiste de piperazina y diazepan; en donde los sustituyentes se seleccionan del grupo que consiste de fenilo, fluorofenilo, trifluorometilfenilo, piridinilo, tiofenilo, furanilo y metilo.

20

8. El compuesto como se establece en la reivindicación 7 seleccionado del grupo que consiste de:

25

Clorhidrato de N-[3-(1H-benzoimidazol-5-il)-bencil]-N-bencil-N',N'-dimetil-etano-1,2-diamina; y

Clorhidrato de N-[3-(1H-benzoimidazol-5-il)-bencil]-N-bencil-N',N'-dimetilpropano-1,3-diamina;

o una sal farmacéuticamente aceptable de estos o un óptico o estereoisómero de estos.

5

9. El compuesto como se establece en la reivindicación 2, en donde:

X = Y denota un enlace doble entre X y Y;

X es N;

10 Y es N;

Z es NR;

A, B y E son CH;

Ar es fenilo, fluorofenilo, clorofenilo, piridinilo, pirazinilo, furanilo o tiofenilo;

15

R es hidrógeno, metilo o etilo;

R₁ y R₂ son los mismos o diferentes y se seleccionan independientemente uno del

otro de bencilo, fluorobencilo, fluorobenzoilo, difluorobenzoilo,

20 clorobenzoilo, isopropoxibenzoilo, trifluorometilbenzoilo, fluoro-

trifluorometilbenzoilo, trifluorometoxibenzoilo, tiofenilcarbonilo,

piridinilcarbonilo, pirazinilcarbonilo, pirimidinilcarbonilo, piridazinilcarbonilo,

dihidro-benzo[1,4]dioxinilcarbonilo, benzo[1,3]dioxolilcarbonilo,

tiofenilmetilo, N-metil-aza-biciclo[2.2.2]octilo, aza-biciclo[2.2.2]octilo, aza-

25 biciclo[2.2.2]octilmetilo, N-metil-piperidinilo, N-isopropil-piperidinilo, N-

ciclopropil-piperidinilo, piperidinilo, N-metil-pirrolidinilo, N-etil-

pirrolidinilmetilo, pirrolidinilmetilo, pirrolidiniletilo, pirrolidinilpropilo, metilaminoetilo, dimetilaminoetilo y dimetilaminopropilo;

o

- 5 R₁ y R₂ tomados junto con el átomo de nitrógeno al cual ellos están adheridos forman un heterociclo no sustituido o al menos monosustituido seleccionado del grupo que consiste de piperazina y diazepan; en donde los sustituyentes se seleccionan del grupo que consiste de fenilo, fluorofenilo, trifluorometilfenilo, piridinilo, tiofenilo, furanilo y metilo.

10

10. El compuesto como se establece en la reivindicación 9 seleccionado del grupo que consiste de:

N-[3-(1H-benzotriazol-5-il)-bencil]-N-bencil-N',N'-dimetil-propano-1,3-
15 diamina;

Triclorhidrato de [5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-(4-fluoro-bencil)-
pirrolidin-2*R*-ilmetil-amina;

[5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-piperidin-4-il-tiofen-2-ilmetil-amina;

[5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-(4-fluoro-bencil)-piperidin-4-il-
20 amina;

N-[5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-N-(4-fluoro-bencil)-N'-metil-etano-
1,2-diamina;

Clorhidrato de [5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-(1-etil-pirrolidin-2*S*-
ilmetil)-(4-fluoro-bencil)-amina;

25

Clorhidrato de [5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-(4-fluoro-bencil)-(1-
metil-piperidin-4-il)-amina;

Clorhidrato de N-[3-(1H-benzotriazol-5-il)-bencil]-N-bencil-N',N'-dimetil-etano-1,2-diamina;

N-[5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-N-(1-etil-pirrolidin-2S-ilmetil)-4-fluoro-benzamida;

5 Clorhidrato de N-[3-(1H-benzotriazol-5-il)-bencil]-4-fluoro-N-(2-pirrolidin-1-il-etil)-benzamida;

Clorhidrato de [5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-(2-pirrolidin-1-il-etil)-amida de ácido tiofen-2-carboxílico;

10 Clorhidrato de N-[5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-2,4-difluoro-N-(2-pirrolidin-1-il-etil)-benzamida;

N-[5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-4-fluoro-N-(2-pirrolidin-1-il-etil)-benzamida;

N-[5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-4-fluoro-N-piperidin-4-il-benzamida;

15 N-[5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-4-fluoro-N-(1-isopropil-piperidin-4-il)-benzamida;

N-[5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-N-(1-ciclopropil-piperidin-4-il)-4-fluoro-benzamida;

20 N-[5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-N-(1-metil-piperidin-4-il)-4-fluoro-benzamida;

5-[3-(4-metil-piperazin-1-ilmetil)-fenil]-1H-benzotriazol;

5-[4-fluoro-3-(4-metil-piperazin-1-ilmetil)-fenil]-1H-benzotriazol; y

5-{4-fluoro-3-[2S-(4-fluoro-fenil)-piperazin-1-ilmetil]-fenil}-1H-benzotriazol;

25 o una sal farmacéuticamente aceptable de estos o un óptico o estereoisómero de estos.

11. El compuesto como se establece en la reivindicación 2, en donde:

X — Y denota un enlace sencillo entre X y Y;

X es CHR;

Y es CHR;

5 Z es NR;

A, B y E son CH;

Ar es fenilo, fluorofenilo, clorofenilo, piridinilo, pirazinilo, furanilo o tiofenilo;

10 cada R se escoge independientemente de hidrógeno, metilo o etilo;

R₁ y R₂ son los mismos o diferentes y se seleccionan independientemente uno del

otro de bencilo, fluorobencilo, fluorobenzoilo, difluorobenzoilo, clorobenzoilo, isopropoxibenzoilo, trifluorometilbenzoilo, fluoro-
15 trifluorometilbenzoilo, trifluorometoxibenzoilo, tiofenilcarbonilo, piridinilcarbonilo, pirazinilcarbonilo, pirimidinilcarbonilo, piridazinilcarbonilo, dihidro-benzo[1,4]dioxinilcarbonilo, benzo[1,3]dioxolilcarbonilo, tiofenilmetilo, N-metil-aza-biciclo[2.2.2]octilo, aza-biciclo[2.2.2]octilo, aza-biciclo[2.2.2]octilmetilo, N-metil-piperidinilo, N-isopropil-piperidinilo, N-ciclopropil-piperidinilo,
20 piperidinilo, N-metil-pirrolidinilo, N-etil-pirrolidinilmetilo, pirrolidinilmetilo, pirrolidiniletilo, pirrolidinilpropilo, metilaminoetilo, dimetilaminoetilo y dimetilaminopropilo; o

R₁ y R₂ tomados junto con el átomo de nitrógeno al cual ellos están adheridos

25 forman un heterociclo no sustituido o al menos monosustituido seleccionado del grupo que consiste de piperazina y diazepam; en donde los

sustituyentes se seleccionan del grupo que consiste de fenilo, fluorofenilo, trifluorometilfenilo, piridinilo, tiofenilo, furanilo y metilo.

12. El compuesto como se establece en la reivindicación 11 que es:

5

N-[5-(2,3-dihidro-1H-indol-5-il)-2-fluoro-bencil]-N-(2-dimetilamino-etil)-4-fluoro-benzamida;

o una sal farmacéuticamente aceptable de estos o un óptico o estereoisómero de estos.

10

13. El compuesto como se establece en la reivindicación 2, en donde:

$X - Y$ denota un enlace sencillo entre X y Y;

X es O, S o NR;

15 Y es CO;

Z es NR;

A, B y E son CH;

Ar es fenilo, fluorofenilo, clorofenilo, piridinilo, pirazinilo, furanilo o tiofenilo;

20

cada R se escoge independientemente de hidrógeno, metilo o etilo;

R_1 y R_2 son los mismos o diferentes y se seleccionan independientemente uno del

25

otro de bencilo, fluorobencilo, benzoilo, fluorobenzoilo, difluorobenzoilo, clorobenzoilo, isopropoxibenzoilo, trifluorometilbenzoilo, fluoro-trifluorometilbenzoilo, trifluorometoxibenzoilo, tiofenilcarbonilo, piridinilcarbonilo, pirazinilcarbonilo, pirimidinilcarbonilo, piridazinilcarbonilo,

dihidro-benzo[1,4]dioxinilcarbonilo, benzo[1,3]dioxolilcarbonilo, tiofenilmetilo, N-metil-aza-biciclo[2.2.2]octilo, aza-biciclo[2.2.2]octilo, aza-biciclo[2.2.2]octilmetilo, N-metil-piperidinilo, N-isopropil-piperidinilo, N-ciclopropil-piperidinilo, piperidinilo, N-metil-pirrolidinilo, N-etil-pirrolidinilmetilo, pirrolidinilmetilo, pirrolidiniletilo, pirrolidinilpropilo, metilaminoetilo, dimetilaminoetilo y dimetilaminopropilo; o

R₁ y R₂ tomados junto con el átomo de nitrógeno al cual ellos están adheridos forman un heterociclo no sustituido o al menos monosustituido seleccionado del grupo que consiste de piperazina y diazepam; en donde los sustituyentes se seleccionan del grupo que consiste de fenilo, fluorofenilo, trifluorometilfenilo, piridinilo, tiofenilo, furanilo y metilo.

14. El compuesto como se establece en la reivindicación 13 seleccionado del grupo que consiste de:

Clorhidrato de 6-(3-[[bencil-(2-dimetilamino-etil)-amino]-metil]-fenil)-3H-benzotiazol-2-ona;

Clorhidrato de N-(2-dimetilamino-etil)-N-[3-(2-oxo-2,3-dihidro-benzotiazol-6-il)-bencil]-benzamida;

Clorhidrato de 4-cloro-N-(2-dimetilamino-etil)-N-[3-(2-oxo-2,3-dihidro-benzotiazol-6-il)-bencil]-benzamida;

Clorhidrato de N-(3-dimetilamino-propil)-N-[3-(2-oxo-2,3-dihidro-benzotiazol-6-il)-bencil]-benzamida;

Clorhidrato de 6-(3-[[bencil-(2-dimetilamino-etil)-amino]-metil]-fenil)-3H-benzooxazol-2-ona;

6-(5-(((2-dimetilamino-etil)-(4-fluoro-bencil)-amino)-metil)-piridin-3-il)-3H-benzooxazol-2-ona;

6-(5-(((2-dimetilamino-etil)-(4-fluoro-bencil)-amino)-metil)-furan-3-il)-3H-benzooxazol-2-ona;

5 Trifluoro-acetato de 6-(3-(((1-etil-pirrolidin-2R-ilmetil)-(4-fluoro-bencil)-amino)-metil)-4-fluoro-fenil)-3H-benzooxazol-2-ona;

6-(4-fluoro-3-(((4-fluoro-bencil)-(1-metil-piperidin-4-il)-amino)-metil)-fenil)-3H-benzooxazol-2-ona;

10 6-(5-(((4-fluoro-bencil)-(1-metil-piperidin-4-il)-amino)-metil)-furan-3-il)-3H-benzooxazol-2-ona;

4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-N-(2-pirrolidin-1-il-etil)-benzamida;

Clorhidrato de N-(2-dimetilamino-etil)-N-[3-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-benzamida;

15 N-(1-etil-pirrolidin-2-ilmetil)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-benzamida;

Clorhidrato de 4-cloro-N-(2-dimetilamino-etil)-N-[3-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-benzamida;

20 Trifluoro-cetato de N-(1-etil-pirrolidin-2R-ilmetil)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-benzamida;

4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-N-(1-metil-piperidin-4-il)-benzamida;

Clorhidrato de N-(1-aza-biciclo[2.2.2]oct-3S-il)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-benzamida;

25 Clorhidrato de N-(1-aza-biciclo[2.2.2]oct-3R-il)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-benzamida;

N-(2-dimetilamino-etil)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-benzamida;

6-[3-(4-metil-piperazin-1-ilmetil)-fenil]-3H-benzooxazol-2-ona;

6-{5-[2*R*-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-furan-3-il}-3H-

5 benzooxazol-2-ona;

6-{5-[2*S*-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-furan-2-il}-3H-

benzooxazol-2-ona;

6-{5-[2*S*-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-tiofen-3-il}-3H-

benzooxazol-2-ona;

10 6-[4-fluoro-3-(2-tiofen-2-il-piperazin-1-ilmetil)-fenil]-3H-benzooxazol-2-ona;

6-{5-[2*S*-(4-fluorofenil)-4-metilpiperazina-1-ilmetil]-furan-3-il}-3H-benzoxazol-2-ona;

Acetato de 6-{5-[2*S*-(4-fluoro-fenil)-piperazin-1-ilmetil]-furan-3-il}-3H-benzooxazol-2-ona;

15 6-{4-fluoro-3-[2*S*-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-fenil}-3H-

benzooxazol-2-ona;

Acetato de 6-{5-[2*S*-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-piridin-3-il}-3H-benzooxazol-2-ona; y

20 Clorhidrato de 5-(3-{[bencil-(2-dimetilamino-etil)-amino]-metil}-fenil)-1,3-dihidro-benzoimidazol-2-ona;

o una sal farmacéuticamente aceptable de estos o un óptico o estereoisómero de estos.

15. El compuesto como se establece en la reivindicación 2, en donde:

25

X — Y denota un enlace sencillo entre X y Y;

X es O o CO;

Y es CHR o NR;

Z es CONR;

A, B y E son los mismos o diferentes e independientemente uno del otro son CH o N;

5

Ar es fenilo, fluorofenilo, clorofenilo, piridinilo, pirazinilo, furánilo o tiofenilo;

cada R se escoge independientemente de hidrógeno, metilo o etilo;

- 10 R₁ y R₂ son los mismos o diferentes y se seleccionan independientemente uno del otro de bencilo, fluorobencilo, benzoilo, fmorobenzoilo, difluorobenzoilo, clorobenzoilo, isopropoxibenzoilo, trifluorometilbenzoilo, fluoro-
- 15 trifluorometilbenzoilo, trifluorometoxibenzoilo, tiofenilcarbonilo, piridinilcarbonilo, pirazinilcarbonilo, pirimidinilcarbonilo, piridazinilcarbonilo, dihidro-benzo[1,4]dioxinilcarbonilo, benzo[1,3]dioxolilcarbonilo,
- 20 tiofenilmetilo, N-metil-aza-biciclo[2.2.2]octilo, aza-biciclo[2.2.2]octilo, aza-biciclo[2.2.2]octilmetilo, N-metil-piperidinilo, N-isopropil-piperidinilo, N-ciclopropil-piperidinilo, piperidinilo, N-metil-pirrolidinilo, N-etil-pirrolidinilmetilo, pirrolidinilmetilo, pirrolidiniletilo, pirrolidinilpropilo, metilaminoetilo, dimetilaminoetilo y dimetilaminopropilo;

o

- R₁ y R₂ tomados junto con el átomo de nitrógeno al cual ellos están adheridos forman un heterociclo no sustituido o al menos monosustituido seleccionado
- 25 del grupo que consiste de piperazina y diazepan; en donde los sustituyentes se seleccionan del grupo que consiste de fenilo, fluorofenilo, trifluorometilfenilo, piridinilo, tiofenilo, furanilo y metilo.

385

16. El compuesto como se establece en la reivindicación 15 seleccionado del grupo que consiste de:

5 Clorhidrato de 6-(3-{{bencil-(2-dimetilamino-etil)-amino}-metil}-fenil)-3-metil-1H-quinazolina-2,4-diona; y

Clorhidrato de 7-(3-{{bencil-(2-dimetilamino-etil)-amino}-metil}-fenil)-4H-pirido [3,2-b][1,4] oxazin-3-ona;

o una sal farmacéuticamente aceptable de estos o un óptico o
10 estereoisómero de estos.

17. El compuesto como se establece en la reivindicación 1, en donde:

$X \equiv Y$ denota un enlace doble entre X y Y;

15 X es CR;

Y es CR;

Z es NR;

A, B y E son los mismos o diferentes e independientemente uno del otro son CH o
N;

20 D es CO;

Ar es fenilo, fluorofenilo, clorofenilo, piridinilo, pirazinilo, furanilo o tiofenilo;

cada R se escoge independientemente de hidrógeno, metilo, etilo, metoxi, flúor,

25 CF_3 o OCF_3 ;

386

R₁ y R₂ son los mismos o diferentes y se seleccionan independientemente uno del otro de bencilo, fluorobencilo, benzoilo, fluorobenzoilo, difluorobenzoilo, clorobenzoilo, isopropoxibenzoilo, trifluorometilbenzoilo, fluoro-
trifluorometilbenzoilo, trifluorometoxibenzoilo, tiofenilcarbonilo,
5 piridinilcarbonilo, pirazinilcarbonilo, pirimidinilcarbonilo, piridazinilcarbonilo, dihidro-benzo[1,4]dioxinilcarbonilo, benzo[1,3]dioxolilcarbonilo, tiofenilmetilo, N-metil-aza-biciclo[2.2.2]octilo, aza-biciclo[2.2.2]octilo, aza-biciclo[2.2.2]octilmetilo, N-metil-piperidinilo, N-isopropil-piperidinilo, N-ciclopropil-piperidinilo, piperidinilo, N-metil-pirrolidinilo, N-etil-
10 pirrolidinilmetilo, pirrolidinilmetilo, pirrolidiniletilo, pirrolidinilpropilo, metilaminoetilo, dimetilaminoetilo y dimetilaminopropilo;

o

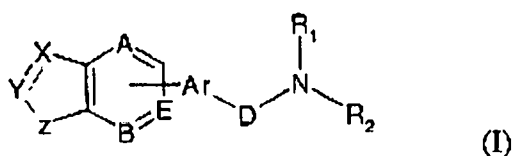
R₁ y R₂ tomados junto con el átomo de nitrógeno al cual ellos están adheridos
15 forman un heterociclo no sustituido o al menos monosustituido seleccionado del grupo que consiste de piperazina y diazepam; en donde los sustituyentes se seleccionan del grupo que consiste de fenilo, fluorofenilo, trifluorometilfenilo, piridinilo, tiofenilo, furanilo y metilo.

20 18. El compuesto como se establece en la reivindicación 17 que es:

[2-fluoro-5-(1H-indol-5-il)-fenil]-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-il]-
metanona;

o una sal farmacéuticamente aceptable de estos o un óptico o
25 estereoisómero de estos.

19. Una composición farmacéutica que comprende uno o más compuestos de fórmula I, que incluye enantiómeros, estereoisómeros, y tautómeros de dicho compuesto y sales farmacéuticamente aceptables, solvatos o derivados de este, en combinación con uno o más portadores farmacéuticamente aceptables, diluyentes o excipientes:



en donde:

10

$X \text{ --- } Y$ denota un enlace doble o sencillo entre X y Y;

X es CR, CHR, CO, N, O o S;

Y es CR, CHR, CO, S(O)₂, N o NR;

Z es NR, CO-NR, S(O)₂-NR;

- 15 A, B y E son los mismos o diferentes e independientemente uno del otro son CR o N;

D es CH₂ o CO;

Ar es arilo o heteroarilo sustituido o no sustituido;

- 20 cada R se escoge independientemente de hidrógeno, halógeno, CN, C(O)NR₃R₄, alquilo C₁₋₄, alcoxi C₁₋₄, alquenilo C₁₋₄, arilo, heteroarilo, arilalquilo C₁₋₄, heteroarilalquilo C₁₋₄, fluoroalquilo o fluoroalcoxi de la fórmula C_nH_xF_y o OC_nH_xF_y en donde n es un entero entre 1 a 4, x es un entero entre 0 a 8, y es un entero entre 1 a 9 y la suma de x y y es 2n+1; en donde

25

R₃ y R₄ son hidrógeno o alquilo C₁₋₄; o

R₃ y R₄ tomados junto con el átomo de nitrógeno al cual ellos están adheridos forman un heterociclo no sustituido o al menos monosustituido;

- 5 R₁ y R₂ son los mismos o diferentes y se seleccionan independientemente uno del otro de arilo sustituido o no sustituido, heteroarilo, ariloilo, heteroariloilo, arilsulfonilo, heteroarilsulfonilo, arilalquilo C₁₋₄, heteroarilalquilo C₁₋₄, aminoalquilo C₁₋₄, alquilaminoC₁₋₄alquiloC₁₋₄, cicloalquilo C₃₋₈aminoalquilo C₁₋₄, dicicloalquiloC₃₋₈aminoalquiloC₁₋₄, cicloalquiloC₃₋₈aminoalquiloC₁₋₄alquiloC₁₋₄, dialquilamino C₁₋₄ alquilo, heterociclo, heterocicloalquilo C₁₋₄, heterocicloalquilo C₁₋₄alquilo C₁₋₄; o
- 10

- R₁ y R₂ tomados junto con el átomo de nitrógeno al cual ellos están adheridos forman un heterociclo no sustituido o al menos monosustituido; y en donde
- 15 los sustituyentes se seleccionan del grupo que consiste de arilo sustituido o no sustituido, heteroarilo, arilalquilo C₁₋₄, heteroarilalquilo C₁₋₄, heterociclo, cicloalquilo C₃₋₈, alquilo C₁₋₄, alcoxi C₁₋₄, alquenilo C₁₋₄, fluoroalquilo o fluoroalcoxi de la fórmula C_nH_xF_y o OC_nH_xF_y en donde n es un entero entre 1 a 4, x es un entero entre 0 a 8, y es un entero entre 1 a 9 y la suma de x y y es 2n+1, -NO₂, -NH₂, -NH(alquilo C₁₋₄), -N(alquilo C₁₋₄)₂, -CN, -C(O)R₅, -NHC(O)(alquilo C₁₋₄), -SO₂Cl, -SO₂(alquilo C₁₋₄), halógeno y hidroxil; en donde
- 20

- R₅ es hidroxil, alcoxi C₁₋₃, -O-fenilo, -NH₂, -NH(alquilo C₁₋₃), -N(alquilo C₁₋₃)₂ o
- 25 fenilo;

heteroarilo es un heterociclo aromático, mono- o bicíclico de 5 a 10 miembros que contiene uno o más heteroátomos seleccionados del grupo que consiste de N, O y S;

arilo es un anillo aromático, mono- o bicíclico de 6 a 10 miembros; y

- 5 heterociclo es un heterociclo no aromático, mono- o bicíclico de 3 a 10 miembros que contiene uno o más heteroátomos seleccionados del grupo que consiste de N, O y S.

20. La composición como se establece en la reivindicación 19, en donde el
10 compuesto de fórmula (I) tiene:

D es CH₂;

- Ar es fenilo sustituido o no sustituido, piridinilo, pirazinilo, furanilo o tiofenilo; en donde los sustituyentes se seleccionan del grupo que consiste de flúor,
15 cloro, alquilo C₁₋₄, alcoxi C₁₋₄ y -CF₃;

cada R se escoge independientemente de hidrógeno, CN o alquilo C₁₋₄;

- R₁ y R₂ son los mismos o diferentes y se seleccionan independientemente uno del
20 otro de benzoilo sustituido o no sustituido, tiofenilcarbonilo, piridinilcarbonilo, pirazinilcarbonilo, pirimidinilcarbonilo, piridazinilcarbonilo, dihidro-benzo[1,4]dioxinilcarbonilo, benzo[1,3]dioxolilcarbonilo, fenilalquilo C₀₋₄, tiofenilalquilo C₁₋₄, aza-biciclo[2.2.2]octilalquilo C₀₋₄, aza-biciclo[3.2.1]octilalquilo C₀₋₄, piperidinilalquilo C₀₋₄, pirrolidinilalquilo C₀₋₄, alquilamino C₁₋₄
25 alquilo C₁₋₄ y dialquilamino C₁₋₄alquilo C₁₋₄; en donde las porciones sustituidas se pueden sustituir con uno o más sustituyentes seleccionados

del grupo que consiste de flúor, cloro, alquilo C₁₋₄, cicloalquilo C₃₋₈, alcoxi C₁₋₄, OCF₃ y CF₃; o

R₁ y R₂ tomados junto con el átomo de nitrógeno al cual ellos están adheridos forman un heterociclo no sustituido o al menos monosustituido seleccionado del grupo que consiste de piperazina y diazepan; en donde los sustituyentes se seleccionan del grupo que consiste de fenilo, fluorofenilo, trifluorometilfenilo, piridinilo, tiofenilo, furanilo y alquilo C₁₋₄.

- 10 21. La composición como se establece en la reivindicación 19, en donde el compuesto de fórmula (I) se selecciona del grupo que consiste de:

N-bencil-N-[3-(1H-indol-5-il)-bencil]-N',N'-dimetil-etano-1,2-diamina;

4-fluoro-N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-

15 benzamida;

N-(2-dimetilamino-etil)-4-fluoro-N-[2-fluoro-5-(2-metil-1H-indol-5-il)-bencil]-benzamida;

N-(2-dimetilamino-etil)-4-fluoro-N-[2-fluoro-5-(1H-indol-5-il)-bencil]-benzamida;

20 4-fluoro-N-[3-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-benzamida;

[3-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido tiofen-2-carboxílico;

[2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido tiofen-2-carboxílico;

25 (2-dimetilamino-etil)-[2-fluoro-5-(1H-indol-5-il)-bencil]-amida de ácido tiofen-2-carboxílico;

4-fluoro-N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-benzamida;

Trifluoro-acetato de N-(1-aza-biciclo[2.2.2]oct-4-ilmetil)-4-fluoro-N-[2-fluoro-5-(1H-indol-5-il)-bencil]-benzamida;

5 4-fluoro-N-[5-(1H-indol-5-il)-piridin-3-ilmetil]-N-(2-pirrolidin-1-il-etil)-benzamida;

4-fluoro-N-[4-fluoro-3-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-benzamida;

10 Acetato de 4-fluoro-N-[4-(1H-indol-5-il)-tiofen-2-ilmetil]-N-(2-pirrolidin-1-il-etil)-benzamida;

(4-fluoro-bencil)-[2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amina;

N-(4-fluoro-bencil)-N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N',N'-dimetil-etano-1,2-diamina;

15 Acetato de (1-aza-biciclo[2.2.2]oct-4-ilmetil)-(4-fluoro-bencil)-[2-fluoro-5-(1H-indol-5-il)-bencil]-amina;

Trifluoroacetato de N-(2-dimetilamino-etil)-4-fluoro-N-[5-(1H-indol-5-il)-piridin-3-ilmetil]-benzamida;

20 4-fluoro-N-[5-(1H-indol-5-il)-tiofen-2-ilmetil]-N-(2-pirrolidin-1-il-etil)-benzamida;

4-fluoro-N-[4-(1H-indol-5-il)-furan-2-ilmetil]-N-(1-metil-piperidin-4-il)-benzamida;

N-(1-aza-biciclo[2.2.2]oct-3*R*-il)-4-fluoro-N-[2-fluoro-5-(1H-indol-6-il)-bencil]-benzamida;

25 [2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido pirimidina-4-carboxílico;

[2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido
pirimidina-2-carboxílico;

[2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido
piridazina-3-carboxílico;

5 [2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido
piridazina-4-carboxílico;

[2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido 2,3-
dihidro-benzo[1,4]dioxina-6-carboxílico;

10 N-[2-fluoro-5-(1H-indol-5-il)-bencil]-4-isopropoxi-N-(1-metil-piperidin-4-il)-
benzamida;

N-[2-fluoro-5-(1H-indol-5-il)-bencil]-3-isopropoxi-N-(1-metil-piperidin-4-il)-
benzamida;

N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-4-
trifluorometoxi-benzamida;

15 4-cloro-N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-
benzamida;

[2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido
benzo[1,3]dioxol-5-carboxílico;

20 N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-4-trifluorometil-
benzamida;

4-fluoro-N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-3-
trifluorometil-benzamida;

N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-isonicotinamida;

25 N-[3-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-4-trifluorometil-
benzamida;

4-fluoro-N-[4-fluoro-3-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-
benzamida;

N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-4-trifluorometil-benzamida;

4-fluoro-N-[3-fluoro-5-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-benzamida;

5 N-[3-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-4-trifluorometil-benzamida;

N-[3-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-isonicotinamida;

N-[4-fluoro-3-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-4-trifluorometil-benzamida;

N-[3-(1H-indol-5-il)-bencil]-N-(3-pirrolidin-1-il-propil)-isonicotinamida;

10 N-[4-fluoro-3-(1H-indol-5-il)-bencil]-N-(3-pirrolidin-1-il-propil)-

isonicotinamida;

[3-(1H-indol-5-il)-bencil]-(3-pirrolidin-1-il-propil)-amida de ácido piridin-2-carboxílico;

N-[3-(1H-indol-5-il)-bencil]-N-(3-pirrolidin-1-il-propil)-4-trifluorometil-

15 benzamida;

[4-fluoro-3-(1H-indol-5-il)-bencil]-(3-pirrolidin-1-il-propil)-amida de ácido piridin-2-carboxílico;

[4-(1H-indol-5-il)-tiofen-2-ilmetil]-(3-pirrolidin-1-il-propil)-amida de ácido piridin-2-carboxílico;

20 N-[4-(1H-indol-5-il)-tiofen-2-ilmetil]-N-(3-pirrolidin-1-il-propil)-4-trifluorometil-benzamida;

N-[4-(1H-indol-5-il)-tiofen-2-ilmetil]-N-(2-pirrolidin-1-il-etil)-isonicotinamida;

[4-(1H-indol-5-il)-tiofen-2-ilmetil]-(2-pirrolidin-1-il-etil)-amida de ácido piridin-2-carboxílico;

25 N-[4-(1H-indol-5-il)-tiofen-2-ilmetil]-N-(2-pirrolidin-1-il-etil)-4-trifluorometil-benzamida;

- [4-(1H-indol-5-il)-furan-2-ilmetil]-(3-pirrolidin-1-il-propil)-amida de ácido piridin-2-carboxílico;
- N-[4-(1H-indol-5-il)-furan-2-ilmetil]-N-(3-pirrolidin-1-il-propil)-4-trifluorometil-benzamida;
- 5 N-[4-(1H-indol-5-il)-furan-2-ilmetil]-N-(2-pirrolidin-1-il-etil)-isonicotinamida;
- [4-(1H-indol-5-il)-furan-2-ilmetil]-(2-pirrolidin-1-il-etil)-amida de ácido piridin-2-carboxílico;
- N-[4-(1H-indol-5-il)-furan-2-ilmetil]-N-(2-pirrolidin-1-il-etil)-4-trifluorometil-benzamida;
- 10 N-[4-(1H-indol-5-il)-tiofen-2-ilmetil]-N-(3-pirrolidin-1-il-propil)-isonicotinamida;
- N-[4-(1H-indol-5-il)-furan-2-ilmetil]-N-(3-pirrolidin-1-il-propil)-isonicotinamida;
- N-[2-cloro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-isonicotinamida;
- [2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido piridin-2-carboxílico;
- 15 N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-nicotinamida;
- N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-3-trifluorometoxi-benzamida;
- N-[2-fluoro-5-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-isonicotinamida;
- N-[4-fluoro-3-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-isonicotinamida;
- 20 Acetato de N-[4-fluoro-3-(1H-indol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-4-trifluorometoxi-benzamida;
- N-[3-(1H-indol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-isonicotinamida;
- [2-fluoro-5-(1H-indol-5-il)-bencil]-(1-metil-piperidin-4-il)-amida de ácido pirazina-2-carboxílico;
- 25 Acetato de 5-[4-fluoro-3-(4-metil-2-piridin-3-il-piperazin-1-ilmetil)-fenil]-1H-indol;

5-{4-fluoro-3-[4-metil-2-(4-trifluorometil-fenil)-piperazin-1-ilmetil]-fenil}-1H-indol;

Acetato de 5-[4-fluoro-3-(4-metil-2-piridin-2-il-piperazin-1-ilmetil)-fenil]-1H-indol;

5 Acetato de 5-{5-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-piridin-3-il}-1H-indol;

5-{4-fluoro-3-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-fenil}-1H-indol;

5-[4-fluoro-3-(2-furan-2-il-4-metil-piperazin-1-ilmetil)-fenil]-1H-indol;

10 Trifluoro-acetato de 5-{5-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-furan-3-il}-1H-indol;

Acetato de 5-{5-[2S-(4-fluoro-fenil)-piperazin-1-ilmetil]-piridin-3-il}-1H-indol;

5-{5-[2S-(4-fluoro-fenil)-piperazin-1-ilmetil]-furan-3-il}-1H-indol;

5-[3-(4-metil-piperazin-1-ilmetil)-fenil]-1H-indol;

5-[4-fluoro-3-(4-metil-2-piridin-4-il-piperazin-1-ilmetil)-fenil]-1H-indol;

15 5-{3-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-fenil}-1H-indol;

Acetato de 5-{6-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-pirazin-2-il}-1H-indol;

Acetato de 5-{4-fluoro-3-[2S-(4-fluoro-fenil)-piperazin-1-ilmetil]-fenil}-1H-indol;

20 5-{4-fluoro-3-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-fenil}-1H-indol-3-carbonitrilo;

5-[3-(4-metil-[1,4]diazepan-1-ilmetil)-fenil]-1H-indol;

5-{4-fluoro-3-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-fenil}-3-metil-1H-indol;

25 N-[5-(3-ciano-1H-indol-5-il)-2-fluoro-bencil]-N-(2-dimetilamino-etil)-4-fluoro-benzamida;

5-{4-fluoro-3-[2S-(4-fluoro-fenil)-piperazin-1-ilmetil]-fenil}-1H-indol-3-carbonitrilo;

Trifluoro-acetato de 5-{6-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-pirazin-2-il}-1H-indol;

5 4-fluoro-N-[2-fluoro-5-(1H-pirrolo[3,2-b]piridin-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-benzamida;

5-{4-fluoro-3-[2-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-fenil}-1H-pirrolo[3,2-b]piridina; y

10 4-fluoro-N-[2-fluoro-5-(1H-pirrolo[2,3-c]piridin-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-benzamida;

o una sal farmacéuticamente aceptable de estos o un óptico o estereoisómero de estos.

22. La composición como se establece en la reivindicación 19, en donde el
15 compuesto de fórmula (I) se selecciona del grupo que consiste de:

Clorhidrato de N-bencil-N-[3-(1H-indazol-5-il)-bencil]-N',N'-dimetil-etano-1,2-diamina;

20 Acetato de N-(4-fluoro-bencil)-N-[5-(1H-indazol-5-il)-piridin-3-ilmetil]-N',N'-dimetil-etano-1,2-diamina;

(4-fluoro-bencil)-[2-fluoro-5-(1H-indazol-5-il)-bencil]-pirrolidin-2S-ilmetil-amina;

(4-fluoro-bencil)-[2-fluoro-5-(1H-indazol-5-il)-bencil]-piperidin-4-il-amina;

25 N-(4-fluoro-bencil)-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N'-metil-etano-1,2-diamina;

(4-fluoro-bencil)-[2-fluoro-5-(1H-indazol-5-il)-bencil]-(1-metil-piperidin-4-il)-amina;

(4-fluoro-bencil)-[4-(1H-indazol-5-il)-furan-2-ilmetil]-(1-metil-piperidin-4-il)-amina;

4-fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(2-pirrolidin-1-il-etil)-benzamida;

5 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(exo-8-metil-8-azabicyclo[3.2.1]oct-3-il)-benzamida;

4-fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(endo-8-metil-8-azabicyclo[3.2.1]oct-3-il)-benzamida;

10 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(1-metil-piperidin-3-il)-benzamida;

Trifluoro-acetato de 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(1-metil-piperidin-3S-il)-benzamida;

Trifluoro-acetato de 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(1-metil-pirrolidin-3R-il)-benzamida;

15 Trifluoro-acetato de 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(1-metil-pirrolidin-3S-il)-benzamida;

4-fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(3-pirrolidin-1-il-propil)-benzamida;

20 4-fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(1-metil-piperidin-4-il)-benzamida;

N-(1-aza-bicyclo[2.2.2]oct-3R-il)-4-fluoro-N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-benzamida;

N-[2-fluoro-5-(1H-indazol-5-il)-bencil]-N-(1-metil-pirrolidin-3R-il)-4-trifluorometil-benzamida quiral;

25 4-fluoro-N-[4-(1H-indazol-5-il)-furan-2-ilmetil]-N-(1-metil-piperidin-4-il)-benzamida;

5-{4-fluoro-3-[2-(4-fluoro-fenil)-piperazin-1-ilmetil]-fenil}-1H-indazol;

Acetato de 5-[4-fluoro-3-(2S-tiofen-2-il-piperazin-1-ilmetil)-fenil]-1H-indazol;

5-[4-fluoro-3-(2-tiofen-2-il-piperazin-1-ilmetil)-fenil]-1H-indazol;

Acetato de 5-[4-fluoro-3-(2-tiofen-2-il-piperazin-1-ilmetil)-fenil]-1H-indazol
quiral;

5 5-{4-fluoro-3-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-fenil}-1H-indazol;

5-{5-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-piridin-3-il}-1H-indazol;

5-{5-[2S-(4-fluoro-fenil)-piperazin-1-ilmetil]-piridin-3-il}-1H-indazol;

5-{5-[2S-(4-fluoro-fenil)-piperazin-1-ilmetil]-furan-3-il}-1H-indazol;

10 Acetato de 5-[4-fluoro-3-(4-metil-2R-tiofen-2-il-piperazin-1-ilmetil)-fenil]-1H-
indazol;

Acetato de 5-[4-fluoro-3-(4-metil-2S-tiofen-2-il-piperazin-1-ilmetil)-fenil]-1H-
indazol;

5-{5-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-furan-3-il}-1H-indazol;

15 Clorhidrato de N-[3-(1H-benzoimidazol-5-il)-bencil]-N-bencil-N',N'-dimetil-
etano-1,2-diamina;

Clorhidrato de N-[3-(1H-benzoimidazol-5-il)-bencil]-N-bencil-N',N'-dimetil-
propano-1,3-diamina;

N-[3-(1H-benzotriazol-5-il)-bencil]-N-bencil-N',N'-dimetil-propano-1,3-
diamina;

20 Triclorhidrato de [5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-(4-fluoro-bencil)-
pirrolidin-2*R*-ilmetil-amina;

[5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-piperidin-4-il-tiofen-2-ilmetil-amina;

[5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-(4-fluoro-bencil)-piperidin-4-il-
amina;

25 N-[5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-N-(4-fluoro-bencil)-N'-metil-etano-
1,2-diamina;

Clorhidrato de [5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-(1-etil-pirrolidin-2S-ilmetil)-(4-fluoro-bencil)-amina;

Clorhidrato de [5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-(4-fluoro-bencil)-(1-metil-piperidin-4-il)-amina;

5 Clorhidrato de N-[3-(1H-benzotriazol-5-il)-bencil]-N-bencil-N',N'-dimetil-etano-1,2-diamina;

N-[5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-N-(1-etil-pirrolidin-2S-ilmetil)-4-fluoro-benzamida;

10 Clorhidrato de N-[3-(1H-benzotriazol-5-il)-bencil]-4-fluoro-N-(2-pirrolidin-1-il-etil)-benzamida;

Clorhidrato de [5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-(2-pirrolidin-1-il-etil)-amida de ácido tiofen-2-carboxílico;

Clorhidrato de N-[5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-2,4-difluoro-N-(2-pirrolidin-1-il-etil)-benzamida;

15 N-[5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-4-fluoro-N-(2-pirrolidin-1-il-etil)-benzamida;

N-[5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-4-fluoro-N-piperidin-4-il-benzamida;

20 N-[5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-4-fluoro-N-(1-isopropil-piperidin-4-il)-benzamida;

N-[5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-N-(1-ciclopropil-piperidin-4-il)-4-fluoro-benzamida;

N-[5-(1H-benzotriazol-5-il)-2-fluoro-bencil]-N-(1-metil-piperidin-4-il)-4-fluoro-benzamida;

25 5-[3-(4-metil-piperazin-1-ilmetil)-fenil]-1H-benzotriazol;

5-[4-fluoro-3-(4-metil-piperazin-1-ilmetil)-fenil]-1H-benzotriazol;

5-{4-fluoro-3-[2S-(4-fluoro-phenyl)-piperazin-1-ilmetil]-fenil}-1H-benzotriazol;

y

N-[5-(2,3-dihidro-1H-indol-5-il)-2-fluoro-bencil]-N-(2-dimetilamino-etil)-4-fluoro-benzamida;

5 o una sal farmacéuticamente aceptable de estos o un óptico o estereoisómero de estos.

23. La composición como se establece en la reivindicación 19, en donde el compuesto de fórmula (I) se selecciona del grupo que consiste de:

10

Clorhidrato de 6-(3-[[bencil-(2-dimetilamino-etil)-amino]-metil]-fenil)-3H-benzotiazol-2-ona;

Clorhidrato de N-(2-dimetilamino-etil)-N-[3-(2-oxo-2,3-dihidro-benzotiazol-6-il)-bencil]-benzamida;

15

Clorhidrato de 4-cloro-N-(2-dimetilamino-etil)-N-[3-(2-oxo-2,3-dihidro-benzotiazol-6-il)-bencil]-benzamida;

Clorhidrato de N-(3-dimetilamino-propil)-N-[3-(2-oxo-2,3-dihidro-benzotiazol-6-il)-bencil]-benzamida;

20

Clorhidrato de 6-(3-[[bencil-(2-dimetilamino-etil)-amino]-metil]-fenil)-3H-benzooxazol-2-ona;

6-(5-[[2-dimetilamino-etil)-(4-fluoro-bencil)-amino]-metil]-piridin-3-il)-3H-benzooxazol-2-ona;

6-(5-[[2-dimetilamino-etil)-(4-fluoro-bencil)-amino]-metil]-furan-3-il)-3H-benzooxazol-2-ona;

25

Trifluoro-acetato de 6-(3-[[1-etil-pirrolidin-2R-ilmetil)-(4-fluoro-bencil)-amino]-metil]-4-fluoro-fenil)-3H-benzooxazol-2-ona;

6-(4-fluoro-3-[(4-fluoro-bencil)-(1-metil-piperidin-4-il)-amino]-metil)-fenil)-3H-benzooxazol-2-ona;

6-(5-[(4-fluoro-bencil)-(1-metil-piperidin-4-il)-amino]-metil)-furan-3-il)-3H-benzooxazol-2-ona;

5 4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-N-(2-pirrolidin-

1-il-etil)-benzamida;

Cloridrato de N-(2-dimetilamino-etil)-N-[3-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-benzamida;

10 N-(1-etil-pirrolidin-2-ilmetil)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-benzamida;

Cloridrato de 4-cloro-N-(2-dimetilamino-etil)-N-[3-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-benzamida;

15 Trifluoro-cetato de N-(1-etil-pirrolidin-2R-ilmetil)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-benzamida;

4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-N-(1-metil-piperidin-4-il)-benzamida;

Cloridrato de N-(1-aza-biciclo[2.2.2]oct-3S-il)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-benzamida;

20 Cloridrato de N-(1-aza-biciclo[2.2.2]oct-3R-il)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-benzamida;

N-(2-dimetilamino-etil)-4-fluoro-N-[2-fluoro-5-(2-oxo-2,3-dihidro-benzooxazol-6-il)-bencil]-benzamida;

6-[3-(4-metil-piperazin-1-ilmetil)-fenil]-3H-benzooxazol-2-ona;

25 6-{5-[2R-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-furan-3-il}-3H-benzooxazol-2-ona;

6-{5-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-furan-2-il}-3H-benzooxazol-2-ona;

6-{5-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-tiofen-3-il}-3H-benzooxazol-2-ona;

5 6-[4-fluoro-3-(2-tiofen-2-il-piperazin-1-ilmetil)-fenil]-3H-benzooxazol-2-ona;

6-{5-[2S-(4-fluorofenil)-4-metilpiperazina-1-ilmetil]-furan-3-il}-3H-benzoxazol-2-ona;

Acetato de 6-{5-[2S-(4-fluoro-fenil)-piperazin-1-ilmetil]-furan-3-il}-3H-benzooxazol-2-ona;

10 6-{4-fluoro-3-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-fenil}-3H-benzooxazol-2-ona;

Acetato de 6-{5-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-ilmetil]-piridin-3-il}-3H-benzooxazol-2-ona; y

15 Clorhidrato de 5-(3-{[bencil-(2-dimetilamino-etil)-amino]-metil}-fenil)-1,3-dihidro-benzoimidazol-2-ona;

o una sal farmacéuticamente aceptable de estos o un óptico o estereoisómero de estos.

24. La composición como se establece en la reivindicación 19, en donde el
20 compuesto de fórmula (I) se selecciona del grupo que consiste de:

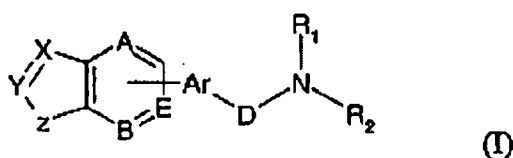
Clorhidrato de 6-(3-{[bencil-(2-dimetilamino-etil)-amino]-metil}-fenil)-3-metil-1H-quinazolina-2,4-diona;

25 Clorhidrato de 7-(3-{[bencil-(2-dimetilamino-etil)-amino]-metil}-fenil)-4H-pirido[3,2-b][1,4]oxazin-3-ona; y

[2-fluoro-5-(1H-indol-5-il)-fenil]-[2S-(4-fluoro-fenil)-4-metil-piperazin-1-il]-metanona;

o una sal farmacéuticamente aceptable de estos o un óptico o estereoisómero de estos.

25. Un método para tratar un trastorno del sueño en un paciente comprende administrar a dicho paciente una cantidad terapéuticamente efectiva de un compuesto de fórmula I, que incluye enantiómeros, estereoisómeros, y tautómeros de dicho compuesto y sales farmacéuticamente aceptables, solvatos o derivados de este, opcionalmente en combinación con uno o más portadores farmacéuticamente aceptables, diluyentes o excipientes:



en donde:

- 15 $X \text{ --- } Y$ denota un enlace doble o sencillo entre X y Y;

X es CR, CHR, CO, N, O o S;

Y es CR, CHR, CO, S(O)₂, N o NR;

Z es NR, CO-NR, S(O)₂-NR;

A, B y E son los mismos o diferentes e independientemente uno del otro son CR o N;

D es CH₂ o CO;

Ar es arilo o heteroarilo sustituido o no sustituido;

cada R se escoge independientemente de hidrógeno, halógeno, CN, C(O)NR₃R₄,

- 25 alquilo C₁₋₄, alcoxi C₁₋₄, alquenilo C₁₋₄, arilo, heteroarilo, arilalquilo C₁₋₄, heteroarilalquilo C₁₋₄, fluoroalquilo o fluoroalcoxi de la fórmula C_nH_xF_y o

404

$OC_nH_xF_y$ en donde n es un entero entre 1 a 4, x es un entero entre 0 a 8, y es un entero entre 1 a 9 y la suma de x y y es $2n+1$; en donde

R_3 y R_4 son hidrógeno o alquilo C_{1-4} ; o

5

R_3 y R_4 tomados junto con el átomo de nitrógeno al cual ellos están adheridos forman un heterociclo no sustituido o al menos monosustituido;

R_1 y R_2 son los mismos o diferentes y se seleccionan independientemente uno del

10

otro de arilo sustituido o no sustituido, heteroarilo, ariloilo, heteroariloilo, arilsulfonilo, heteroarilsulfonilo, arilalquilo C_{1-4} , heteroarilalquilo C_{1-4} , aminoalquilo C_{1-4} , aminoalquilo C_{1-4} alquilo C_{1-4} , cicloalquilo C_{3-8} aminoalquilo C_{1-4} , dicicloalquilo C_{3-8} aminoalquilo C_{1-4} , cicloalquilo C_{3-8} aminoalquilo C_{1-4} alquilo C_{1-4} , dialquilamino C_{1-4} alquilo, heterociclo, heterocicloalquilo C_{1-4} ,

15

heterocicloalquilo C_{1-4} alquilo C_{1-4} ; o

R_1 y R_2 tomados junto con el átomo de nitrógeno al cual ellos están adheridos forman un heterociclo no sustituido o al menos monosustituido; y en donde

20

los sustituyentes se seleccionan del grupo que consiste de arilo sustituido o no sustituido, heteroarilo, arilalquilo C_{1-4} , heteroarilalquilo C_{1-4} , heterociclo, cicloalquilo C_{3-8} , alquilo C_{1-4} , alcoxi C_{1-4} , alquenilo C_{1-4} , fluoroalquilo o fluoroalcoxi de la fórmula $C_nH_xF_y$ o $OC_nH_xF_y$ en donde n es un entero entre 1 a 4, x es un entero entre 0 a 8, y es un entero entre 1 a 9 y la suma de x y y es $2n+1$, $-NO_2$, $-NH_2$, $-NH$ (alquilo C_{1-4}), $-N$ (alquilo C_{1-4})₂, $-CN$, $-C(O)R_5$, $-NHC(O)$ (alquilo C_{1-4}), $-SO_2Cl$, $-SO_2$ (alquilo C_{1-4}), halógeno y hidroxilo; en donde

25

R₅ es hidroxil, alcoxi C₁₋₃, -O-fenilo, -NH₂, -NH(alquilo C₁₋₃), -N(alquilo C₁₋₃)₂ o fenilo;

heteroarilo es un heterociclo aromático, mono- o bicíclico de 5 a 10 miembros, que contiene uno o más heteroátomos seleccionados del grupo que consiste de N, O y S;

arilo es un anillo aromático, mono- o bicíclico de 6 a 10 miembros; y

heterociclo es un heterociclo no aromático, mono- o bicíclico de 3 a 10 miembros que contiene uno o más heteroátomos seleccionados del grupo que consiste de N, O y S.

26. El método como se establece en la reivindicación 25, en donde el compuesto de fórmula (I) tiene:

D es CH₂;

Ar es fenilo sustituido o no sustituido, piridinilo, pirazinilo, furanilo o tiofenilo; en donde los sustituyentes se seleccionan del grupo que consiste de flúor, cloro, alquilo C₁₋₄, alcoxi C₁₋₄ y -CF₃;

cada R se escoge independientemente de hidrógeno, CN o alquilo C₁₋₄;

R₁ y R₂ son los mismos o diferentes y se seleccionan independientemente uno del otro de benzoilo sustituido o no sustituido, tiofenilcarbonilo, piridinilcarbonilo, pirazinilcarbonilo, pirimidinilcarbonilo, piridazinilcarbonilo, dihidro-benzo[1,4]dioxinilcarbonilo, benzo[1,3]dioxolilcarbonilo, fenilalquilo C₀₋₄, tiofenilalquilo C₁₋₄, aza-biciclo[2.2.2]octilalquilo C₀₋₄, aza-biciclo[3.2.1]octilalquilo C₀₋₄, piperidinilalquilo C₀₋₄, pirrolidinilalquilo C₀₋₄, alquilamino C₁₋₄alquilo C₁₋₄ y dialquilamino C₁₋₄alquilo C₁₋₄; en donde las

porciones sustituidas se pueden sustituir con uno o más sustituyentes seleccionados del grupo que consiste de flúor, cloro, alquilo C₁₋₄, cicloalquilo C₃₋₈, alcoxi C₁₋₄, OCF₃ y CF₃; o

- 5 R₁ y R₂ tomados junto con el átomo de nitrógeno al cual ellos están adheridos forman un heterociclo no sustituido o al menos monosustituido seleccionado del grupo que consiste de piperazina y diazepam; en donde los sustituyentes se seleccionan del grupo que consiste de fenilo, fluorofenilo, trifluorometilfenilo, piridinilo, tiofenilo, furanilo y alquilo C₁₋₄.
- 10 27. El método como se establece en la reivindicación 25, en donde el trastorno del sueño es insomnio.
28. El método como se establece en la reivindicación 25, en donde el trastorno del sueño es insomnio primario.
- 15 29. El método como se establece en la reivindicación 25, en donde el trastorno del sueño es un trastorno del sueño relacionado con otro trastorno mental.
30. El método como se establece en la reivindicación 25, en donde el trastorno del sueño es un trastorno del sueño inducido por una sustancia.
- 20 31. El método como se establece en la reivindicación 25, en donde el trastorno del sueño es una apnea obstructiva del sueño

COMPUESTOS DE HETEROARILO Y BIS ARILO SUSTITUIDOS COMO
ANTAGONISTAS 5HT_{2A} SELECTIVOS

RESUMEN

5

La presente invención se relaciona con una serie de compuestos de arilo y heteroarilo sustituidos de fórmula (I): En donde X, Y, Z, A, B, D, Ar, R₁ y R₂ son como se define aquí. Los compuestos de esta invención son antagonistas 5HT_{2A} selectivos, y son por lo tanto, útiles en el tratamiento de una variedad de

10 enfermedades que incluyen pero no se limitan a una amplia variedad de trastornos del sueño como se describe y reivindica aquí.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference US20010107WO	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, Item 5 below.	
International application No. PCT/US2006/004879	International filing date (day/month/year) 10/02/2006	(Earliest) Priority Date (day/month/year) 10/02/2005
Applicant AVENTIS PHARMACEUTICALS INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ Certain claims were found unsearchable (See Box No. II)

3. ☐ Unity of invention is lacking (see Box No. III)

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant

☐ as selected by this Authority, because the applicant failed to suggest a figure

☐ as selected by this Authority, because this figure better characterizes the invention

b. ☐ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/004879

409

A. CLASSIFICATION OF SUBJECT MATTER		
INV.	C07D209/08	C07D277/68
	C07D231/56	C07D265/34
	C07D471/04	C07D405/04
	C07D263/58	C07D249/18
	C07D401/14	C07D413/14
	C07D413/12	C07D409/14
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) C07D A61K A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/53268 A (AGOURON PHARMACEUTICALS, INC) 26 July 2001 (2001-07-26) compound 91	1, 19
P, X	WO 2005/040131 A (AKZO NOBEL N.V; NEUROSEARCH A/S; HAMILTON, NIAL, MORTON; NAPIER, SUSA) 6 May 2005 (2005-05-06) examples 13, 20, 45, 46	1, 2, 19
P, X	WO 2006/015259 A (IRM LLC; MICHELLYS, PIERRE-YVES; PETRASSI, H. MICHAEL; RICHMOND, WENDY) 9 February 2006 (2006-02-09) example 327	1, 19
	----- -/--	
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents:		
A document defining the general state of the art which is not considered to be of particular relevance		
E earlier document but published on or after the international filing date		
I document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)		
O document referring to an oral disclosure, use, exhibition or other means		
P document published prior to the international filing date but later than the priority date claimed		
T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention		
X document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone		
Y document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art		
Z document member of the same patent family		
Date of the actual completion of the international search 16 June 2006		Date of mailing of the international search report 29/06/2006
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Diederien, J

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/004879

410

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/07435 A (MERCK PATENT GMBH; BOETTCHER, HENNING; GREINER, HARTMUT; HARTING, JUER) 1 February 2001 (2001-02-01) the whole document -----	1, 19, 25

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/004879

411

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 25-31 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

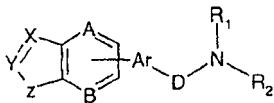
Information on patent family members

International application No

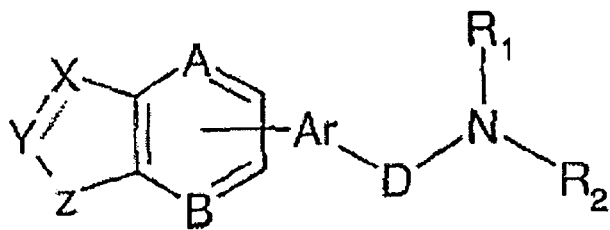
PCT/US2006/004879

412

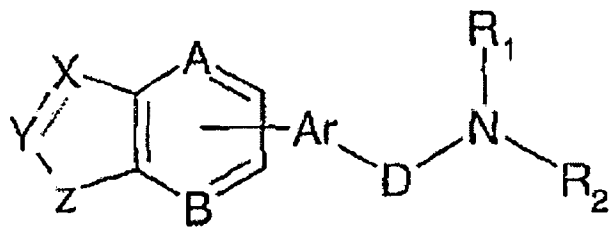
Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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(I)



(I)



415

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-081882- -00000-0000

Fecha: 2007-08-10 16:40:51 Dep: 2020 NUECREACION
Tra: 11 PATENTEIYII Eve: 379 FASENACIONALII
Act: 411 PRESENTACION Folios: 415

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 61,641
FECHA : JULIO 31 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	63769915	31/07/2007	55,200,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		1 TRAMITES DE SOL. DE PATENTE DE IN	482,000.00
		TOTAL :	\$ 482,000.00

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

660 15896-841-018-9



No. 07-081882- -00000-0000

Fecha: 2007-08-10 16:40:51 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act 411 PRESENTACION Folios: 415**Industria y Comercio**
SUPERINTENDENCIA**REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT**

PATENTE DE INVENCION []

MODELO DE UTILIDAD []

- ◆ Indicación de que se solicita la concesión de 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 [☒]

COMPLETA []

INCOMPLETA []

DISEÑO INDUSTRIAL []

- ◆ Indicación de que se solicita el registro de 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 []

- ◆ Indicación de que se solicita el registro de un Esquema de Trazado [☐]
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud [☐]
- ◆ Representación gráfica del esquema trazado [☐]
- ◆ Comprobante de pago de las tasas establecidas [☐]

COMPLETA []

INCOMPLETA []

Andrés M Nevac
Firma Responsable

Fecha _____

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