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Fecha (MM): 2003-01-20 17 32 18
Tramite 011 PCT-PATENT 378 FASE NACI 411 PRESENTACION radicación
Dependencia 0920 DIVISION DE NUEVAS CREACIONES

0001

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

(1) SOLICITUD DE

[X]	Patente de Invención	[ ]	Patente de Modelo de Utilidad
[ ]	Capítulo I	[X]	Capítulo II

(2) SOLICITANTE (71)

Nombre: WARNER LAMBERT COMPANY

Dirección: 201 Tabor Road, Morris Plains, NJ 07950 Estados Unidos de América.

Nacionalidad o Domicilio: ESTADOUNIDENSE

Lugar de Constitución: Estado de Delaware Estados Unidos de América

Teléfono: Fax:

E-Mail:

IDENTIFICACION

C C [ ] NIT [ ]

C E [ ] Otro [ ]

Cual: _____

Número: _____

(3) REPRESENTANTE O APODERADO

Nombre: CARLOS R OLARTE

Dirección: Avda 82 No 10-62 Piso 6

Teléfono: 634-1500 Fax. 376-2211

E Mail: patents bogota@bakernet com

IDENTIFICACION

C C [X] NIT [ ]

C E [ ] Otro [ ]

Cual: _____

Número: 79 782 747 Btá TP 74 295

(4) INVENTOR (ES) (72)

Nombre: Douglas Stephen Barrett, Cathlin Biwersi, Michael Kaufman, Haile Tecle, Scott Joseph Warmus

Dirección: 2800 Plymouht Road, Ann Arbor MI 48105 EUA

Nacionalidad o Domicilio: ESTADOUNIDENSE

(5) PCT (85)

Solicitud Internacional No: PCT/US01/22331 Fecha: Julio 12, 2001

Publicación Internacional No: WO 02/06213 Fecha: Enero 24 2002

(6) Título (54): ÉSTERES OXIGENADOS DE ÁCIDOS 4-YODO FENILAMINO BENZHIDROXÁMICOS

(7) Clasificación Internacional (51): A61K 31/166, C07C 259/00

(8) Prioridad	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
SI [X] NO [ ]	US	Julio 19, 2000	60/219,372

(9) Comprobante de pago No 82,174, 1,691 **Fecha** 06-12-02, 10-01-03

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

2

(10) **ANEXOS**

0002

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

(11) **FIGURA CARATERISTICA**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

FIRMA:

C.C. 79.782.747 de Btá T.P. 74295

Instrucciones para la presentación de los anexos, ver reverso de esta página

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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800172085-2

RECIBO OFICIAL DE CAJA : 03 - 1,692
FECHA : ENERO 10 DE 2003

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
JULIAN ANDRES VARGAS	CONSIGNACION	BANCO POPULAR	050-00110-6	8285310	10/01/2003	15,879,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	998	VALOR COMPLEMENTO TARIFA A&O ANTR	22,000.00
			TOTAL : $	22,000.00

SON: VEINTIDOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador 382 0840
Fax 350 5220
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

4

Industria y Comercio

SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03003336 00000000 Folios: 612
Fecha (AMD): 2003-01-20 17:32:18
Tramite : 011 PCT-PATENT 370 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 02 - 82,174
FECHA : DICIEMBRE 6 DE 2002

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
JORGE LUIS GOMEZ	CONSIGNACION	BANCO POPULAR	050-00110-6	7973876	06/12/2002	20,670,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	378,000.00
		TOTAL : $	378,000.00

SON: TRESCIENTOS SETENTA Y OCHO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador 382 0840
Fax 350 5220
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

TRADUCCION OFICIAL No. 030/01 de un documento escrito en inglés, el cual para su identificación se sella con el sello del Traductor. Esta es una Traducción Oficial efectuada el día 23 de enero de 2001 por la Sra. María Teresa Lara R., c.c. 41.568.055 de Bogotá, Traductora Oficial según Resolución No. 01016 del 2 de octubre de 1998, expedida por el Ministerio de Justicia.

= =

Poder otorgado por WARNER-LAMBERT COMPANY para su representación en asuntos de propiedad industrial en Colombia. Certificación notarial suscrita por Kenneth Greenwood, Notario Público de Egham, Surrey, Inglaterra, y legalizaciones subsiguientes.

MARIA TERESA LARA R.
TRADUCTORA OFICIAL
RESOLUCION No. 01016
DE MINJUSTICIA

PODER

La abajo firmada, WARNER-LAMBERT COMPANY, sociedad constituida conforme a las leyes del estado de Delaware, Estados Unidos de América, domiciliada en 201 Tabor Road, Morris Plains, Nueva Jersey 07950, Estados Unidos de América, declara por el presente otorgar a CARLOS R. OLARTE y/o ALVARO CORREA ORDOÑEZ poder especial amplio y bastante para recabar de las oficinas y autoridades nacionales que correspondan, la obtención de: Patentes de invención, patentes de modelo de utilidad, diseños industriales, fusiones, cambios de nombre, cesiones, presentación y trámite de oposiciones, cambios de dirección, a cuyo efecto los faculta para dar ante dichas autoridades todos los pasos necesarios al objeto indicado, elevar solicitudes, formular descripciones, protestas, declaraciones, apelaciones y reclamos, oblar impuestos, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede a los expresados mandatarios poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones

COMO NOTARIO ONCE DE ESTE CIRCULO HAGO CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE TUVE A LA VISTA.
2001
BOGOTA D.C. - COLOMBIA
ARMANDO SANCHEZ PARRA
NOTARIO ONCE (11) E.

o demandas que por motivo de las marcas se presentaren y hacer cuanto fuere necesario ante las autoridades administrativas o judiciales de cualquier orden, dándoles así mismo facultad para sustituir el presente y en caso necesario revocar dichas sustituciones.

Dado y firmado en Nueva York, Nueva York, E.U.A., a los 12 días del mes de diciembre de 2000.

WARNER-LAMBERT COMPANY

(Fdo.) J. Trevor Lumb

J. TREVOR LUMB
ASESOR GENERAL ASISTENTE DE PATENTES

[Sello] Certificado, verificado y autenticado
en la ciudad de Egham en Surrey

A los4 días del mes de enero de 2001

KENNETH GREENWOOD
NOTARIO PUBLICO
HORNE ENGALL AND FREEMAN

(Adherida, oblea dorada
con el sello notarial)

REINO UNIDO DE LA GRAN BRETAÑA E IRLANDA DEL NORTE

No. **D653053**

Fecha **4 de enero de 2001**

Este documento lleva la firma/sello de **K. Greenwood**

actuando en calidad de **Notari Públic**

COMO NOTARIO ONCE (E) DEL CIRCULO HAGO CONSTAR QUE ESTA FOTOCOPIA CONCUERDA CON EL ORIGINAL QUE HE TENIDO A LA VISTA.
24 ENE 2001
BOGOTA D.C. - COLOMBIA
ARMANDO SANCHEZ PARRA
NOTARIO ONCE (11) E.

0007

Firmado por: **T.S. Cunningham**

Por el Secretario de Estado Principal de Su Majestad para Asuntos Exteriores y de la Commonwealth

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EN ESPAÑOL: Certificación del Consulado General de Colombia en Londres, bajo el No. 01/0043 de fecha 5 de enero de 2001. Legalización de la firma de la funcionaria consular por el Ministerio de Relaciones Exteriores de Colombia, bajo el No. 004033 de fecha 23 de enero de 2001.

= =

La anterior es traducción fiel y completa del documento en referencia, de la cual se deja copia en este archivo para su confrontación.

María Teresa Lara R.
c.c. 41.568.055 de Bogotá
Traductora Oficial según
Resolución No. 01016 del
2 de octubre de 1998, del
Ministerio de Justicia

COMO NOTARIO ONCE (E) DEL ESTE CIRCULO HAGO CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA.
24 ENE 2001
BOGOTA, D.C.
ARMANDO SANCHEZ FARFA
NOTARIO ONCE (11) E.

CONSULADO GENERAL DE COLOMBIA
3RD FLOOR, 15-19 GREAT TITCHFIELD STREET, LONDON W1P 7FB
TELEPHONE 020-7637 9883 • TELEFAX 020-7637 5804
E-MAIL consulco@consulco.demon.co.uk

La suscrita Cónsul General (E) de Colombia en Londres, vistos los documentos presentados ante este Despacho,

CERTIFICA

Que, **KENNETH GREENWOOD**, Notario Público de Egham, Surrey, Inglaterra, legalizó la firma del documento precedente y su firma se encuentra certificada por **T.S. CUNNINGHAM**, Oficial del Ministerio de Relaciones Exteriores Británico, firma que a su vez se encuentra registrada en este Consulado General.

Que, **WARNER-LAMBERT COMPANY**, es una Sociedad constituída, organizada y existente en New Jersey, Estado de Delaware, Estados Unidos de América y que cumple con su objeto social de acuerdo con las leyes de ese país.

Que, **J. TREVOR LUMB**, en su calidad de Representante Legal de la mencionada Sociedad, debidamente autorizado otorga el documento precedente y su firma se encuentra legalizada por **KENNETH GREENWOOD**, Notario Público de Egham, Surrey, Inglaterra Gran Bretaña.

La Cónsul General (E) no asume responsabilidad por el contenido del mencionado documento.

Dado en Londres, Inglaterra, Gran Bretaña, a los cinco (05) días del mes de Enero de dos mil uno (2001).

Certificación No.01 /0043
Derechos: U$ 106,00 CANCELADOS

MINISTERIO DE RELACIONES EXTERIORES
CUYA FIRMA APARECE EN EL FACSIMILE DESEMPEÑA LAS FUNCIONES INDICADAS

ANA GEORGINA CHARRY
Cónsul General (E)

JAN 23

COMO NOTARIO ONCE (E) DE BOGOTÁ
CÍRCULO HAGO CONSTAR QUE ESTA
FOTOCOPIA CONCUERDA CON EL
ORIGINAL QUE HE TENIDO A LA VISTA.
24 ENE 2001
BOGOTÁ, D.C. - COLOMBIA
ARMANDO SÁNCHEZ PINTO
NOTARIO ONCE (11) E.

PC5953-01-CA/20132
CO-2

POWER OF ATTORNEY

The undersigned, WARNER-LAMBERT COMPANY,
a corporation organized under the laws of
the State of Delaware, United States of America
located in
201 Tabor Road, Morris Plains, New Jersey
07950, United States of America

declares that it hereby grants to
CARLOS R. OLARTE and/or
ALVARO CORREA ORDOÑEZ

a full and sufficient power of attorney to apply to the proper national officers and authorities for the issue of: Patents of Invention, Patents for Utility Models, Industrial Designs, changes of name, assignments, filing and prosecution of oppositions, changes of address to which end it empowers them to take all steps necessary before said authorities for the objects stated, to file petitions, prepare descriptions, make protests, declarations, appeals and objections, pay imposts, apply for certifications, receive documents and securities, abandon applications and collect refunds. To the said mandatories sufficient power is granted hereby to receive notifications for and on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the marks, and to do everything that may be required, before administrative or judicial officers of any class giving them likewise power to substitute these presents and revoke such substitutions if necessary.

Done and subscribed in New York, New York, U.S.A.

Dated 12 December 2000

WARNER-LAMBERT COMPANY

J. Trevor Lumb

J. TREVOR LUMB
ASSISTANT GENERAL PATENT COUNSEL

Certified And Authenticated
By The Town Of Egham In Surrey
This 4th Day Of January 2001

KENNETH GREENWOOD
NOTARY PUBLIC
HORNE ENGALL AND FREEMAN

PODER

La abajo firmada
WARNER-LAMBERT COMPANY
domiciliada en

declara por el presente otrogar a
CARLOS R. OLARTE y/o
ALVARO CORREA ORDOÑEZ
poder especial amplio y bastante para recabar de las oficinas y autoridades nacionales que correspondan, la obtención de: Patentes de Invención, Patentes de Modelo de Utilidad, Diseños Industriales, fusiones, cambios de nombre, cesiones, presentación * a cuyo efecto los faculta para dar ante dichas autoridades, todos los pasos necesarios al objeto indicado, elevar solicitudes, formular descripciones, protestas, declaraciones, apelaciones y reclamos, oblar impuestos, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede a los expresados mandatarios poder bastante para recibir notificaciones a nombre de la compañía, otrogar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de las marcas se presentaren y hacer cuanto fuere necesario, ante las autoridades administrativas o judiciales de cualquier orden, dándoles asimismo facultad para sustituir el presente y en caso necesario revocar dichas sustituciones.

Dado y firmado en _____

a los _____

COTEJO NOTARIAL
CIRCULO I VAGO CON
FOTOCOPIA CONFORME
ORIGINAL QUE HE TENIDO A LA VISTA
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BOGOTA, D.C.
ARMANDO
NOTARIO ORCE (11) L.

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* y trámite de oposiciones, cambios de dirección.

MARIA TERESA LARA R.
TRADUCTORA OFICIAL
RESOLUCION No. 01616
DE MINJUSTICIA
030/01

COMO NOTARIO ONCE (E) DE ESTE CIRCULO HAGO CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL, QUE HE TENIDO A LA VISTA.

24 ENE 2001

BOGOTA D.C. COLOMBIA
ARNULFO SANCHEZ PARRA
NOTARIO ONCE (11) E.

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UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

No. **D653053**

Date **4 January, 2001**

This document bears
the signature / seal of **K Greenwood**

Acting in the capacity of **Notary Public**

Signed by: **T.S. Cunningham**

FOREIGN AND COMMONWEALTH OFFICE
LONDON

For Her Majesty's Principal Secretary of State
For Foreign and Commonwealth Affairs

COMO NOTARIO ONCE (E) DE ESTE CIRCULO HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

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BOGOTA
ARMANDO
NOTARIO

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60/219,372 19 July 2000 (19.07.2000) US

(71) Applicant *(for all designated States except US)*: WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: BARRETT, Stephen, Douglas [US/US]; Pfizer, PGRD, Ann Arbor Laboratories, 2800 Plymouth Road, Ann Arbor, MI 48105 (US). BIWERSI, Catibiu [US/US]; Pfizer, PGRD, Ann Arbor Laboratories, 2800 Plymouth Road, Ann Arbor, MI 48105 (US). KAUFMAN, Michael [US/US]; Pfizer, PGRD, Ann Arbor Laboratories, 2800 Plymouth Road, Ann Arbor, MI 48105 (US). TECLE, Haile [US/US]; Pfizer, PGRD, Ann Arbor Laboratories, 2800 Plymouth Road, Ann Arbor, MI 48105 (US). WARMUS, Joseph, Scott [US/US]; Pfizer, PGRD, Ann Arbor Laboratories, 2800 Plymouth Road, Ann Arbor, MI 48105 (US).

(74) Agents: FEDERMAN, Evan, J.; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 et al. (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/06213 A2

(54) Title: OXYGENATED ESTERS OF 4-IODO PHENYLAMINO BENZHYDROXAMIC ACIDS

(57) Abstract: The present invention relates to oxygenated esters of 4-iodophenylamino benzhydroxamic acid derivatives, pharmaceutical compositions and methods of use thereof. The present invention also relates to crystaline forms of oxygenated esters of 4-iodophenylamino benzhydroxamic acid derivatives, pharmaceutical compositions and methods of use thereof.

OXYGENATED ESTERS OF 4-IODO PHENYLAMINO BENZHYDROXAMIC ACIDS

FIELD OF THE INVENTION

The present invention relates to oxygenated esters of 4-iodophenylamino benzhydroxamic acid derivatives, pharmaceutical compositions and methods of use thereof. The present invention also relates to crystalline forms of oxygenated esters of 4-iodophenylamino benzhydroxamic acid derivatives, pharmaceutical compositions and methods of use thereof.

BACKGROUND OF THE INVENTION

MAPK/ERK Kinase ("MEK") enzymes are dual specificity kinases involved in, for example, immunomodulation, inflammation, and proliferative diseases such as cancer and restenosis.

Proliferative diseases are caused by a defect in the intracellular signaling system, or the signal transduction mechanism of certain proteins. Defects include a change either in the intrinsic activity or in the cellular concentration of one or more signaling proteins in the signaling cascade. The cell may produce a growth factor that binds to its own receptors, resulting in an autocrine loop, which continually stimulates proliferation. Mutations or overexpression of intracellular signaling proteins can lead to spurious mitogenic signals within the cell. Some of the most common mutations occur in genes encoding the protein known as Ras, a G-protein that is activated when bound to GTP, and inactivated when bound to GDP. The above-mentioned growth factor receptors, and many other mitogenic receptors, when activated, lead to Ras being converted from the GDP-bound state to the GTP-bound state. This signal is an absolute prerequisite for proliferation in most cell types. Defects in this signaling system, especially in the deactivation of the Ras-GTP complex, are common in cancers, and lead to the signaling cascade below Ras being chronically activated.

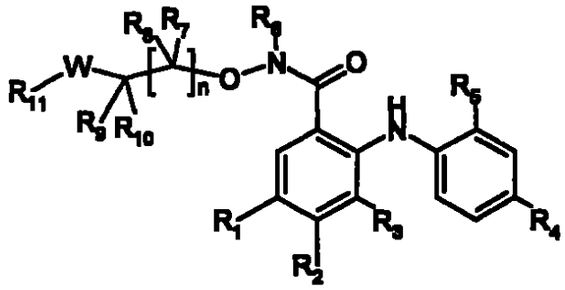
Activated Ras leads in turn to the activation of a cascade of serine/threonine kinases. One of the groups of kinases known to require an active Ras-GTP for its own activation is the Raf family. These in turn activate MEK (e.g., MEK_1 and MEK_2) which then activates the MAP kinase, ERK (ERK_1 and ERK_2). Activation of MAP kinase by mitogens appears to be essential for proliferation; constitutive activation of this kinase is sufficient to induce cellular transformation. Blockade of downstream Ras signaling, for example by use of a dominant negative Raf-1 protein, can completely inhibit mitogenesis, whether induced from cell surface receptors or from oncogenic Ras mutants. Although Ras is not itself a protein kinase, it participates in the activation of Raf and other kinases, most likely through a phosphorylation mechanism. Once activated, Raf and other kinases phosphorylate MEK on two closely adjacent serine residues, S^{218} and S^{222} in the case of MEK-1, which are the prerequisite for activation of MEK as a kinase. MEK in turn phosphorylates MAP kinase on both a tyrosine, Y^{185}, and a threonine residue, T^{183}, separated by a single amino acid. This double phosphorylation activates MAP kinase at least 100-fold. Activated MAP kinase can then catalyze the phosphorylation of a large number of proteins, including several transcription factors and other kinases. Many of these MAP kinase phosphorylations are mitogenically activating for the target protein, such as a kinase, a transcription factor, or another cellular protein. In addition to Raf-1 and MEKK, other kinases activate MEK, and MEK itself appears to be a signal integrating kinase. Current understanding is that MEK is highly specific for the phosphorylation of MAP kinase. In fact, no substrate for MEK other than the MAP kinase, ERK, has been demonstrated to date and MEK does not phosphorylate peptides based on the MAP kinase phosphorylation sequence, or even phosphorylate denatured MAP kinase. MEK also appears to associate strongly with MAP kinase prior to phosphorylating it, suggesting that phosphorylation of MAP kinase by MEK may require a prior strong interaction between the two proteins. Both this requirement and the unusual specificity of MEK are suggestive that it may have enough difference in its mechanism of action to other protein kinases that selective inhibitors of MEK, possibly operating

through allosteric mechanisms rather than through the usual blockade of the ATP binding site, may be found.

It has been found that the compounds of the present invention are inhibitors of MEK and are useful in the treatment of a variety of proliferative disease states, such as conditions related to the hyperactivity of MEK, as well as diseases modulated by the MEK cascade.

SUMMARY OF THE INVENTION

The present invention provides a compound of formula



I

wherein

R_1 is hydrogen, halogen, or nitro;

R_2 is hydrogen or fluorine;

R_3 is hydrogen or fluorine;

R_4 is hydrogen, iodine, bromine, chlorine, or fluorine;

R_5 is hydrogen, halogen, hydroxy, C_{1-8} alkyl, C_{1-8} alkoxy, trifluoromethyl, or cyano;

n is 1 to 5;

R_6, R_7, R_8, R_9, and R_{10} are independently hydrogen, C_{1-8} alkyl, C_{3-8} cycloalkyl, hydroxy, C_{1-8} alkoxy, perhalo(C_{1-3})alkyl, hydroxy(C_{1-8})alkyl, (C_{1-5})alkoxy(C_{1-5})alkyl, [(C_{1-4})alkyl]$_2$aminomethyl, (C_{2-7})heterocycle(C_{1-5})alkyl, or aryloxy(C_{1-5})alkyl, or may be independently joined to complete a 3-10 member cyclic ring optionally containing

additional heteroatoms selected from the group consisting of O, S, NH, and N-alkyl, wherein R_7 and R_8 are independently selected for n>1;

Ra and Rb are independently hydrogen or C_{1-4} alkyl;

W is O or NRa;

R_{11} is hydrogen, C_{1-8} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, hydroxy(C_{1-8})alkyl, (C_{1-5})alkoxy(C_{1-5})alkyl, phenyl, C_{2-7} heteroaryl, (C_{1-8})alkylcarbonyl, (phenyl)carbonyl, (phenyl)(C_{1-3} alkyl)carbonyl, or trifluoro(C_{1-6})alkyl;

wherein the above alkyl, alkoxy, cycloalkyl, heteroaryl, and phenyl groups can be optionally substituted with between 1 and 5 substituents independently selected from the group consisting of hydroxy, amino, monoalkylamino, dialkylamino, halogen, cyano, (C_{1-3})alkoxy, COOR, OCORa, CONRaRb, NRaCORb, SO, SO_2, SO_4, and SO_2NRaRb;

and pharmaceutically acceptable salts, (C_{1-6}) amides and (C_{1-6}) esters thereof;

provided that when R_{11} is phenyl and n is 1, W cannot be O;

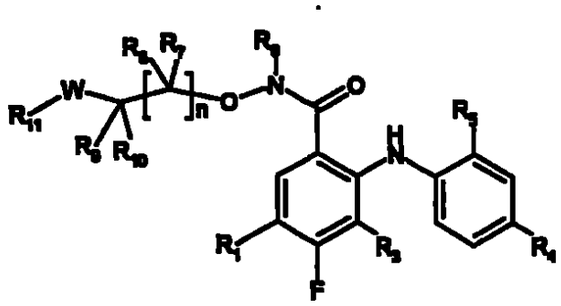
further provided that the compound is not

5-Bromo-N-(2-diethylamino-ethoxy)-3,4-difluoro-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-(2-dimethylamino-propoxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide; or

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-N-(2-dimethylamino-ethoxy)-3,4-difluoro-benzamide.

The present invention also provides a compound is of formula



Ia

wherein

R_1 is hydrogen or halogen;

R_3 is hydrogen or fluorine;

R_4 is hydrogen, iodine, bromine, chlorine, or fluorine;

R_5 is hydrogen, halogen, or C_{1-8} alkyl;

n is 1 to 5;

R_6, R_7, R_8, R_9, and R_{10} are independently hydrogen, C_{1-8} alkyl, hydroxy, C_{1-8} alkoxy, perhalo(C_{1-3})alkyl, (C_{2-7})heterocycle(C_{1-5})alkyl, or aryloxy(C_{1-5})alkyl, or may be independently joined to complete a 3-10 member cyclic ring optionally containing additional heteroatoms selected from the group consisting of O, S, NH, and N-alkyl, wherein R_7 and R_8 are independently selected for n>1;

Ra and Rb are independently hydrogen or C_{1-4} alkyl;

W is O or NRa;

R_{11} is hydrogen, C_{1-8} alkyl, C_{2-6} alkenyl, (C_{1-5})alkoxy(C_{1-5})alkyl, phenyl, (C_{1-8})alkylcarbonyl, or trifluoro(C_{1-6})alkyl;

wherein the above alkyl, alkoxy, cycloalkyl, heteroaryl, and phenyl groups can be optionally substituted with between 1 and 5 substituents independently selected from the group consisting of hydroxy, amino, monoalkylamino, dialkylamino, halogen, cyano, (C_{1-3})alkoxy, COOR, OCORa, CONRaRb, NRaCORb, SO, SO_2, SO_4, and SO_2NRaRb;

and pharmaceutically acceptable salts, (C_{1-6}) amides and (C_{1-6}) esters thereof;

provided that when R_{11} is phenyl and n is 1, W cannot be O;

further provided that the compound is not

5-Bromo-N-(2-diethylamino-ethoxy)-3,4-difluoro-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-(2-dimethylamino-propoxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide; or

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-N-(2-dimethylamino-ethoxy)-3,4-difluoro-benzamide.

The invention also provides a pharmaceutical composition comprising a compound of formula I or Ia and a pharmaceutically acceptable carrier.

Additionally, the invention provides a method of treating a proliferative disease in a patient in need thereof comprising administering a therapeutically effective amount of a compound of formula I or Ia.

The invention also provides the use of a compound of formula I or Ia for the manufacture of a medicament for the treatment of a proliferative disease.

Furthermore, the invention provides methods of treating cancer, restenosis, psoriasis, autoimmune disease, atherosclerosis, osteoarthritis, rheumatoid arthritis, heart failure, chronic pain, and neuropathic pain in a patient in need thereof comprising administering a therapeutically effective amount of a compound of formula I or Ia.

The invention also provides the use of a compound of formula I or Ia for the manufacture of a medicament for the treatment of cancer, restenosis, psoriasis, autoimmune disease, atherosclerosis, osteoarthritis, rheumatoid arthritis, heart failure, chronic pain, and neuropathic pain.

In addition, the invention provides a method for treating cancer in a patient in need thereof comprising administering a therapeutically effective amount of a compound of formula I or Ia in combination with radiation therapy or at least one chemotherapeutic agent.

In another aspect, the present invention provides a crystalline Form I *N*-(2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing at least one of the following 2θ values measured using CuK_α radiation: 7.1, 19.2, or 32.1.

The present invention also provides a crystalline Form I *N*-(2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing the following 2θ values measured using CuK_α radiation: 7.1, 19.2, and 32.1.

Additionally, the present invention provides a crystalline Form I *N*-(2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing the following 2θ values measured using CuK_α radiation: 7.1, 14.1, 15.3, 15.8, 16.9, 18.1, 19.2, 20.3, 21.4,

22.3, 23.4, 24.5, 25.5, 26.2, 26.8, 27.8, 28.3, 29.5, 32.1, 33.2, 33.6, 40.0, 42.9, and 44.1.

Also provided by the present invention is a crystalline Form II *N*-(2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing at least one of the following 2θ values measured using CuK_α radiation: 11.6, 12.6 or 24.9.

The present invention also provides a crystalline Form II *N*-(2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing the following 2θ values measured using CuK_α radiation: 11.6, 12.6 and 24.9.

Additionally, the present invention provides a crystalline Form II *N*-(2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing the following 2θ values measured using CuK_α radiation: 11.6, 12.6, 15.6, 17.3, 17.9, 20.3, 21.1, 22.1, 24.9, 25.9, 26.7, 27.8, 30.1, 30.9, 33.8, 35.4, 38.2, 39.3, 40.8, 41.6, 43.6, and 47.0.

Additionally, the present invention provides a crystalline Form I *N*-[(R)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing at least one of the following 2θ values measured using CuK_α radiation: 10.6, 13.7, 19.0 or 23.7.

In addition, the present invention provides a crystalline Form I *N*-[(R)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing the following 2θ values measured using CuK_α radiation: 10.6, 13.7, 19.0 and 23.7.

Also provided by the present invention is crystalline Form I *N*-[(R)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing the following 2θ values measured using CuK_α radiation: 10.6, 13.7, 14.6, 17.3, 18.0, 18.2, 98.0, 19.3, 20.1, 21.0, 21.9, 22.4, 23.7, 24.0, 24.9, 26.3, 27.6, 28.0, 30.1, 32.1, 32.3, 32.9, 35.8, and 37.7.

Furthermore, the present invention provides a crystalline Form II *N*-[(R)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing at least one of the following 2θ values measured using CuK_α radiation: 5.5 or 19.6.

The present invention also provides a crystalline Form II *N*-[(R)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing at least one of the following 2θ values measured using CuK_α radiation: 5.5 and 19.6.

Additionally, the present invention provides a crystalline Form II *N*-[(R)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing the following 2θ values measured using CuK_α radiation: 5.5, 10.7, 16.5, 19.6, 22.0, 22.5, 23.6, 24.1, 25.0, 26.2, 27.6, 29.1, 30.5, 31.7, 33.3, and 39.0.

In addition, the present invention provides a crystalline Form I *N*-[(S)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing at least one of the following 2θ values measured using CuK_α radiation: 10.5, 13.7, 19.0, or 23.6.

Also provided by the present invention is crystalline Form I *N*-[(S)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing the following 2θ values measured using CuK_α radiation: 10.5, 13.7, 19.0, and 23.6.

Furthermore, the present invention provides a crystalline Form I *N*-[(S)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing the following 2θ values measured using CuK_α radiation: 10.548, 13.703, 17.887, 18.958, 20.122, 21.950, 22.321, 23.640, 24.803, 26.244, 27.570, 28.000, 29.566, 32.234, 32.769, 35.804, 37.641, 41.402, 41.956, and 44.600.

The present invention also provides a crystalline Form II *N*-[(S)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing at least one of the following 2θ values measured using CuK_α radiation: 5.6 or 19.6.

Additionally, the present invention provides a crystalline Form II *N*-[(S)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing at least one of the following 2θ values measured using CuK_α radiation: 5.6 and 19.6.

In addition, the present invention provides a crystalline Form II *N*-[(S)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing the following 2θ values measured using CuK_α radiation: 5.6, 10.7, 16.5, 19.6, 20.9, 22.0, 23.7, 24.2, 25.0, 26.2, 27.7, 28.0, 29.1, 31.7, 32.8, 33.3, 34.1, 42.0, and 42.3.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is further described by the following nonlimiting examples which refer to the accompanying Figures 1 to 6, short particulars of which are given below.

FIG. 1

Diffractogram of Form I *N*-(2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide (Y-axis = 0 to maximum intensity of about 350 counts per second (cps))

FIG. 2

Diffractogram of Form II *N*-(2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide (Y-axis = 0 to maximum intensity of about 1200 cps)

FIG. 3

Diffractogram of Form I *N*-[(R)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide (Y-axis = 0 to maximum intensity of about 600 cps).

FIG. 4

Diffractogram of Form II *N*-[(R)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide (Y-axis = 0 to maximum intensity of about 1250 cps).

FIG. 5

Diffractogram of Form I *N*-[(S)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide (Y-axis = 0 to maximum intensity of about 2600 cps).

FIG. 6

Diffractogram of Form II *N*-[(S)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide (Y-axis = 0 to maximum intensity of about 700 cps).

DETAILED DESCRIPTION OF THE INVENTION

Certain terms are defined below and by their usage throughout this disclosure.

The terms "halogen" or "halo" in the present invention refer to a fluorine, bromine, chlorine, and iodine atom or fluoro, bromo, chloro, and iodo. The terms fluorine and fluoro, for example, are understood to be equivalent herein.

Alkyl groups, such as "C_1-$_8$ alkyl", include aliphatic chains (i.e., hydrocarbyl or hydrocarbon radical structures containing hydrogen and carbon atoms) with a free valence. Alkyl groups are understood to include straight chain and branched structures. Examples include methyl, ethyl, propyl, isopropyl, butyl, n-butyl, isobutyl, t-butyl, pentyl, isopentyl, 2,3-dimethylpropyl, hexyl, 2,3-dimethylhexyl, 1,1-dimethylpentyl, heptyl, octyl, and the like. The term "C_1-$_8$ alkyl" includes within its definition the terms "C_1-$_6$ alkyl", "C_1-$_5$ alkyl", "C_1-$_4$ alkyl" and "C_1-$_3$ alkyl".

Alkyl groups can be substituted with 1, 2, 3 or more substituents which are independently selected from halo (fluoro, chloro, bromo, or iodo), cyano, hydroxy, amino, alkoxy, alkylamino, dialkylamino, cycloalkyl, aryl, aryloxy, arylalkyloxy, heterocyclic radical, and (heterocyclic radical)oxy. Specific examples include fluoromethyl, hydroxyethyl, 2,3-dihydroxyethyl, (2- or 3-furanyl)methyl, cyclopropylmethyl, benzyloxyethyl, (3-pyridinyl)methyl, (2- or 3-furanyl)methyl, (2-thienyl)ethyl, hydroxypropyl, aminocyclohexyl, 2-

dimethylaminobutyl, methoxymethyl, *N*-pyridinylethyl, diethylaminoethyl, and cyclobutylmethyl.

The term "alkoxy" as used herein refers to a straight or branched alkyl chain attached to an oxygen atom. The term "C_1-g alkoxy" as used herein refers to a straight or branched alkyl chain having from one to eight carbon atoms attached to an oxygen atom. Typical C_1-g alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, pentoxy and the like. The term "C_1-g alkoxy" includes within its definition the terms "C_1-6 alkoxy" and "C_1-4 alkoxy".

Alkenyl groups are analogous to alkyl groups, but have at least one double bond (two adjacent sp^2 carbon atoms). Depending on the placement of a double bond and substituents, if any, the geometry of the double bond may be *entgegen* (E), or *zusammen* (Z), *cis*, or *trans*. Similarly, alkynyl groups have at least one triple bond (two adjacent sp carbon atoms). Unsaturated alkenyl or alkynyl groups may have one or more double or triple bonds, respectively, or a mixture thereof; like alkyl groups, unsaturated groups may be straight chain or branched, and they may be substituted as described both above for alkyl groups and throughout the disclosure by example. Examples of alkenyls, alkynyls, and substituted forms include cis-2-butenyl, trans-2-butenyl, 3-butynyl, 3-phenyl-2-propynyl, 3-(2'-fluorophenyl)-2-propynyl, 3-methyl(5-phenyl)-4-pentynyl, 2-hydroxy-2-propynyl, 2-methyl-2-propynyl, 2-propenyl, 4-hydroxy-3-butynyl, 3-(3-fluorophenyl)-2-propynyl, and 2-methyl-2-propenyl. In formula I, the term "alkenyl" includes C_{2-6} alkenyl or C_{2-4} alkenyl.

Cycloalkyl groups, such as C_3-10 cycloalkyl, refer to a saturated hydrocarbon ring structure containing from 3 to 10 atoms. Typical C_3-10 cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like.

The term "aryl" means an unsubstituted aromatic carbocyclic group having a single ring (e.g., phenyl), multiple rings (e.g., biphenyl), or multiple condensed rings in which at least one is aromatic (e.g., 1,2,3,4-tetrahydronaphthyl, naphthyl, anthryl, or phenanthryl). The aryl group can be optionally substituted with between 1 and 5 substituents independently selected from the group consisting of

hydroxy, amino, monoalkylamino, dialkylamino, halogen, cyano, (C_{1-3})alkoxy, COOR, OCORa, CONRaRb, NRaCORb, SO, SO_2, SO_4, and SO_2NraRb, where Ra and Rb are independently hydrogen or C_{1-4} alkyl.

The term "aryloxy" as used herein refers to an aryl group attached to an oxygen atom.

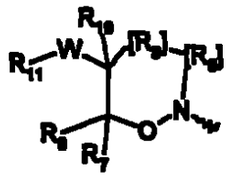
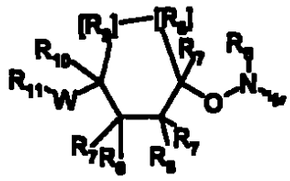
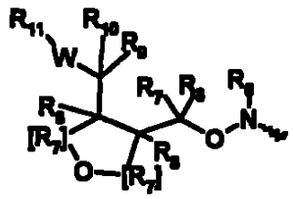
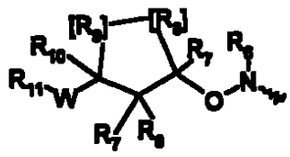
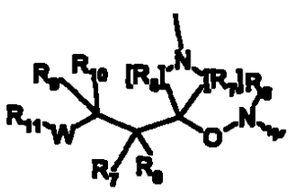
As used herein, the terms "heterocycle", "C_{2-7} heterocycle", "C_{2-9} heterocycle", or "C_{2-7} heteroaryl" in the present invention refers to a stable 5-, 6-, or 7-membered monocyclic or 7- to 10-membered bicyclic heterocyclic ring which is saturated or unsaturated, and consists of carbon atoms and from one to four heteroatoms selected from the group consisting of nitrogen, oxygen, or sulfur. The heterocyclic ring may be attached at any heteroatom or carbon atom which affords a stable structure.

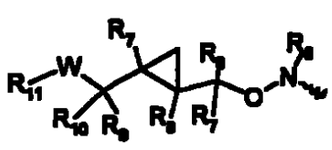
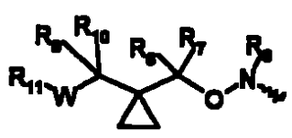
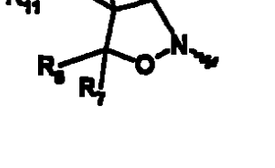
Heterocyclic radicals, which include but are not limited to heteroaryls, include: furyl, (is)oxazolyl, isoxazolyl, thiophenyl, thiazolyl, pyrrolyl, imidazolyl, 1,3,4-triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyridazinyl, indolyl, and their nonaromatic counterparts. Further examples of heterocyclic radicals include thienyl, piperidyl, quinolyl, isothiazolyl, piperidinyl, morpholinyl, piperazinyl, tetrahydrofuryl, tetrahydropyrrolyl, pyrrolidinyl, octahydroindolyl, octahydrobenzothiofuranyl, octahydrobenzofuranyl, (iso)quinolinyl, naphthyridinyl, benzimidazolyl, and benzoxazolyl.

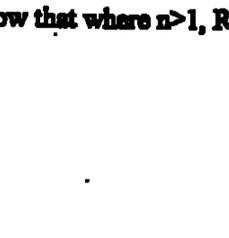
More general forms of substituted hydrocarbon radicals include hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, hydroxycycloalkyl, hydroxyaryl, and corresponding forms for the prefixes amino-, halo- (e.g., fluoro-, chloro-, or bromo-), nitro-, alkyl-, phenyl-, cycloalkyl- and so on, or combinations of substituents. According to formula (I), therefore, substituted alkyls include, but are not limited to, hydroxyalkyl, alkoxyalkyl, aminoalkyl, nitroalkyl, haloalkyl, cyanoalkyl, alkylalkyl (branched alkyls, such as methylpentyl), (cycloalkyl)alkyl, phenylalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylalkyl, aryloxyalkyl, arylalkyloxyalkyl, (heterocyclic radical)alkyl, and (heterocyclic radical)oxyalkyl. Formula I thus includes hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, hydroxycycloalkyl, hydroxyaryl, aminoalkyl, aminoalkenyl, aminoalkynyl, aminocycloalkyl, aminoaryl, alkylalkenyl, (alkylaryl)alkyl, (haloaryl)alkyl,

(hydroxyaryl)alkynyl, and so forth. R_6, R_7, R_8, R_9, and R_{10} include hydroxy(C_{1-8})alkyl, (C_{1-5})alkoxy(C_{1-5})alkyl, aminoalkyl, (e.g., [(C1-4)alkyl]$_2$aminomethyl), perhalo(C_{1-3})alkyl (e.g., trifluoromethyl or trifluoroethyl), (C_{2-7})heterocycle(C_{1-5})alkyl, and aryloxy(C_{1-5})alkyl. Similarly, R_{10} includes hydroxy(C_{1-8})alkyl, (C_{1-5})alkoxy(C_{1-5})alkyl and trifluoro(C_{1-6})alkyl.

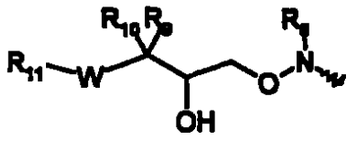
Representative examples of the independent union of R_6, R_7, R_8, R_9, and R_{10} to complete a 3-10 member cyclic ring optionally containing additional heteroatoms selected from O, S, NH, or N-alkyl are demonstrated in the fragments shown below.

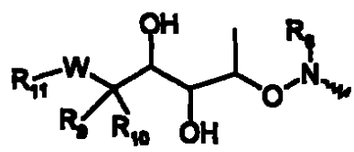






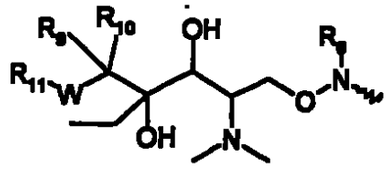
Representative examples of formula I where R_7 and R_8 are independently selected for n>1 are illustrated in the fragments shown below. The fragments below also show that where n>1, R_7 and R_8 are independently selected for each (CR_7R_8) unit.



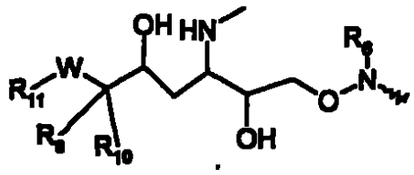
n=2



n=3



n=4



n=5

The present invention includes the hydrates and the pharmaceutically acceptable salts and solvates of the compounds defined by formula I. The compounds of this invention can possess a sufficiently basic functional group, and accordingly react with any of a number of inorganic and organic acids, to form a pharmaceutically acceptable salt.

The term "pharmaceutically acceptable salt" as used herein, refers to salts of the compounds of formula I which are substantially non-toxic to living organisms. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a pharmaceutically acceptable mineral or organic acid. Such salts are also known as acid addition salts. Such salts include the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, 66, 2-19 (1977), which are know to the skilled artisan.

Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as *p*-tohuenesulfonic, methanesulfonic acid, benzenesulfonic acid, oxalic acid, *p*-bromophenylsulfonic acid; carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Example of such pharmaceutically acceptable salts are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, bromide, hydrobromide, iodide, acetate, propionate, decanoate, caprate, caprylate, acrylate, ascorbate,

formate, hydrochloride, dihydrochloride, isobutyrate, caproate, heptanoate, propiolate, glucuronate, glutamate, propionate, phenylpropionate, salicylate, oxalate, malonate, succinate, suberate, sebacate, fumarate, malate, maleate, hydroxymaleate, mandelate, mesylate, nicotinate, isonicotinate, cinnamate, hippurate, nitrate, stearate, phthalate, teraphthalate, butyne-1,4-dioate, butyne-1,4-dicarboxylate, hexyne-1,4-dicarboxylate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, hydroxybenzoate, methoxybenzoate, dinitrobenzoate, *o*-acetoxybenzoate, naphthalene-2-benzoate, phthalate, *p*-toluenesulfonate, *p*-bromobenzenesulfonate, *p*-chlorobenzenesulfonate, xylenesulfonate, phenylacetate, trifluoroacetate, phenylpropionate, phenylbutyrate, citrate, lactate, α-hydroxybutyrate, glycolate, tartrate, hemi-tartrate, benzenesulfonate, methanesulfonate, ethanesulfonate, propanesulfonate, hydroxyethanesulfonate, 1-naphthalenesulfonate, 2-naphthalenesulfonate, 1,5-naphthalenedisulfonate, mandelate, tartarate, and the like. A preferred pharmaceutically acceptable salt is hydrochloride.

It should be recognized that the particular counterion forming a part of any salt of this inventions is usually not of a critical nature, so long as the salt as a whole is pharmacologically acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole. It is further understood that such salts may exist as a hydrate.

As used herein, the term "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures which are not interchangeable. The three-dimensional structures are called configurations. As used herein, the term "enantiomer" refers to each of two stereoisomers whose molecules are nonsuperimposable mirror images of one another. The term "chiral center" refers to a carbon atom to which four different groups are attached. As used herein, the term "diastereomers" refers to stereoisomers which are not enantiomers. The terms "racemate" or "racemic mixture" refer to a mixture of enantiomers.

The enantiomers of compounds of the present invention can be resolved by one of ordinary skill in the art using standard techniques well-known in the art, such as those described by J. Jacques, et al., "Enantiomers, Racemates, and

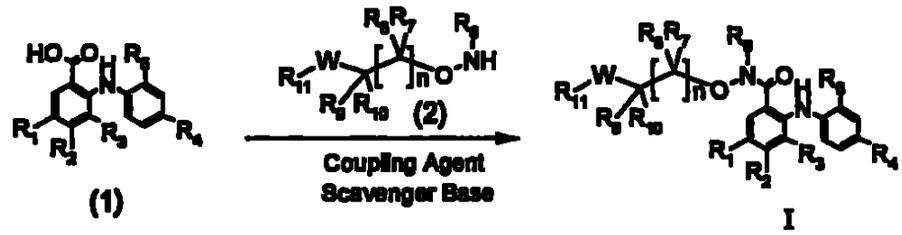
Resolutions", John Wiley and Sons, Inc. 1981. Examples of resolutions include recrystallization techniques or chiral chromatography.

Some of the compounds of the present invention have one or more chiral centers and may exist in a variety of stereoisomeric configurations. As a consequence of these chiral centers, the compounds of the present invention occur as racemates, mixtures of enantiomers and as individual enantiomers, as well as diastereomers and mixtures of diastereomers. All such racemates, enantiomers, and diastereomers are within the scope of the present invention.

The compounds of formula I can be prepared by techniques and procedures readily available to one of ordinary skill in the art, for example by following the procedures as set forth in the following Schemes. These schemes are not intended to limit the scope of the invention in any way. All substituents, unless otherwise indicated, are previously defined. The reagents and starting materials are readily available to one of ordinary skill in the art.

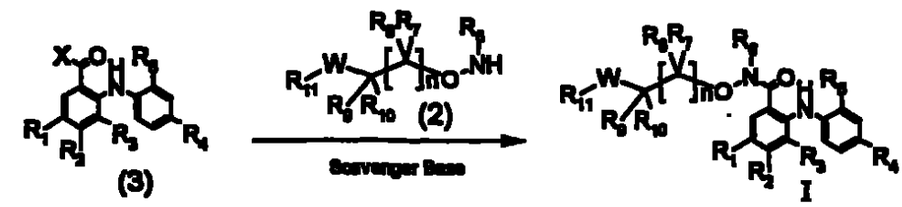
The compounds of formula I are generally obtained by the union of 2-(arylamino)-benzoic acids (1) with alkoxyamines (2) by the action of a peptide coupling agent in the presence of a base, as shown in Scheme 1. Preferred coupling agents include diphenylphosphinic chloride (DPP-Cl), benzotriazol-yl-oxy-tripyrolidinophosphonium hexafluorophosphate (PyBOP), benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP), N,N'-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI), or 1,1'-carbonyldimidazole (CDI). Preferred bases include diisopropylethylamine, triethylamine, 4-methylmorpholine, or pyridine or a substituted pyridine, for example, 4-dimethyaminopyridine or 2,6-dimethylpyridine. Preferred solvents are polar aprotic solvents such as dichloromethane, tetrahydrofuran, or dimethylformamide. The reactions are generally carried out at a temperature between about –78 °C to about 25 °C, and are normally complete within about 2 hours to about 5 days. The product amides can be isolated by removing the solvent, for example by evaporation under reduced pressure, and further purified, if desired, by standard methods such as chromatography, crystallization, or distillation.

Scheme 1: General Preparation of Benzamides from Benzoic Acids



Alternately, disclosed compounds are also generally prepared as shown in Scheme 2 by the contact of alkoxyamine (2) with "activated" benzoic acid derivatives (3), wherein the activating group "X" completes an acid halide, anhydride, mixed anhydride, or an activated ester, such as a pentafluorophenyl ester, nitrophenyl ester or thioester. Preferred bases include diisopropylethylamine, triethylamine, 4-methylmorpholine, imidazole, pyridine or a substituted pyridine, for example, 4-dimethyaminopyridine or 2,6-dimethylpyridine. Preferred solvents are polar aprotic solvents such as dichloromethane, tetrahydrofuran, or dimethylformamide. These synthetic strategies, which are suitable for both conventional or combinatorial (parallel synthesis) synthetic methods are further exemplified in examples below.

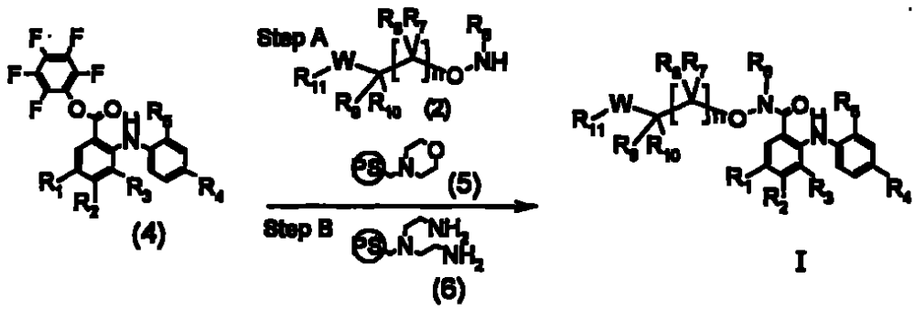
Scheme 2: General Preparation of Benzamides from "Activated" Benzoic Acid Derivatives



Preferred combinatorial methods are outlined in Scheme 3, wherein the compounds of formula I are obtained by the reaction of an excess of pentafluorophenyl esters (4) with alkoxyamines (2) in the presence of polymer supported (PS) 4-methylmorpholine (5) in dimethylformamide with mechanical shaking. After a reaction period of about 16 to 72 hours, polymer supported

amine (6) is added with dichloromethane. After an additional several hours of mechanical agitation, targets I are obtained by filtration, solvent evaporation and chromatographic purification.

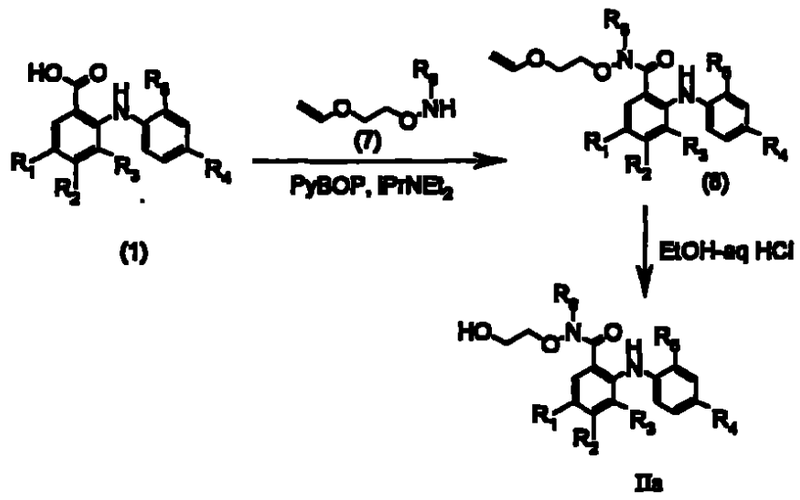
Scheme 3: General Combinatorial Preparation of Benzamides from Benzoic Acid Pentafluorophenyl Esters



For the preparation of compounds of formula I wherein R_{11} = hydrogen, preferred synthetic modes may utilize a reagent of formula (2), wherein R_6, R_7, R_8, R_9, R_{10} are defined as for formula I, above, and R_{11} is a standard hydroxyl (W = O) or amino (W = NRa) protecting group. In such instances, general schemes 1-3, above may be modified to include a standard removal of the said protecting group. Suitable protecting groups include, but are not limited to, vinyl ethers, silyl ethers, acetals, acetonides, and carbamates. Examples of such modifications are outlined below.

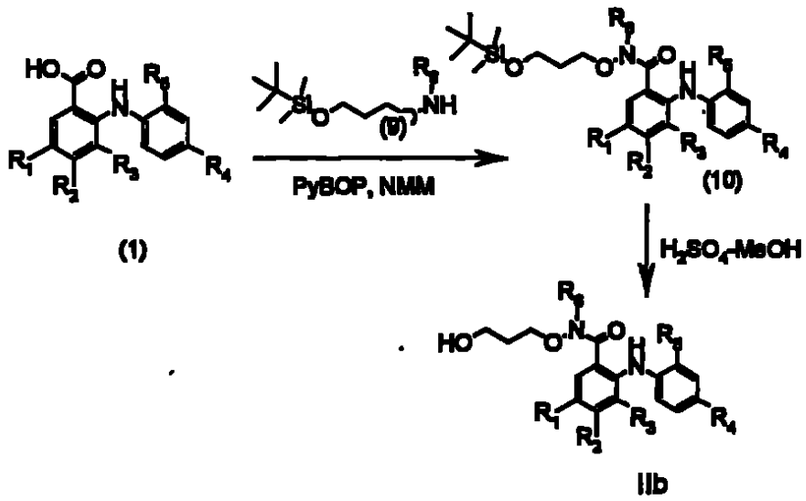
As illustrated in Scheme 4, preferred compounds of formula IIa may be obtained by the reaction of benzoic acids (1) with vinyl ether (7), a peptide coupling agent (for example, PyBOP) and a base (for example, diisopropylethylamine) to afford vinyl ether amide (8). Further treatment of vinyl ether (8) with acid affords the compounds of formula IIa.

Scheme 4: Representative Preparation of Hydroxylated Benzamides Using a Vinyl Ether as a Hydroxyl Protecting Group



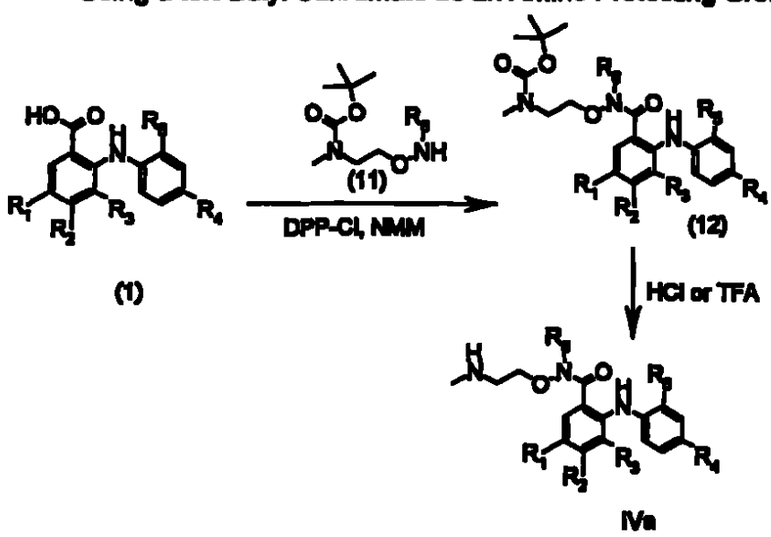
As shown below in Scheme 5, preferred compounds of formula IIb may also be obtained by the reaction of benzoic acids (1) with a suitable protecting group, such as tert-butyldimethylsilyl ether (9), in the presence a peptide coupling agent (for example, PyBOP) and a tertiary amine base (for example, diisopropylethylamine) to afford tert-butyldimethylsilyl ether amide (10). Further treatment of silyl ether (10) with acid in a protic solvent affords the compounds of formula IIb.

Scheme 5: Representative Preparation of Hydroxylated Benzamides Using a Silyl Ether as a Hydroxyl Protecting Group



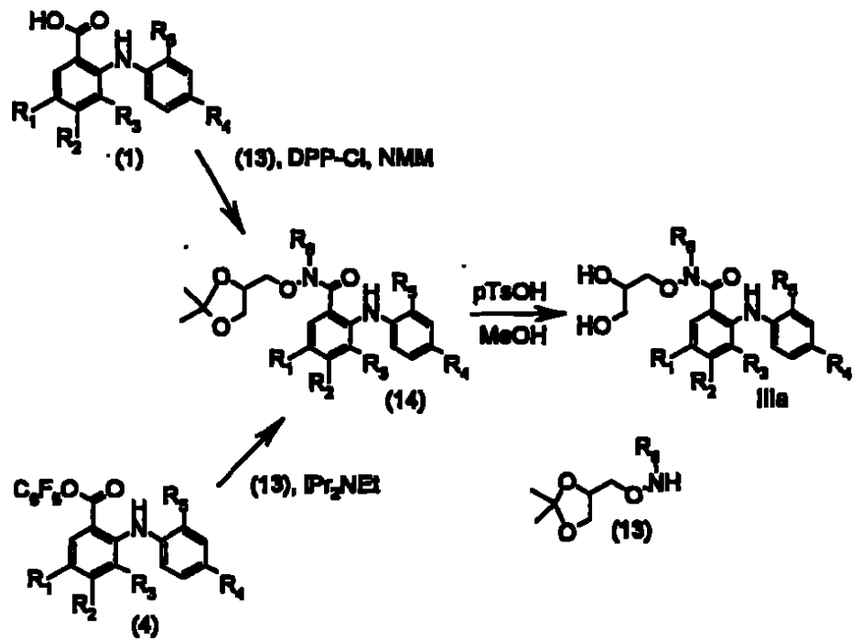
Preferred compounds of formula IVa can be prepared by similar methods, as illustrated in Scheme 6. For example, treatment of benzoic acids (1) with carbamate (11) in the presence of a peptide coupling agent, for example diphenylphosphinic chloride (DPP-Cl), in the presence of a tertiary amine base, for example 4-methylmorpholine (NMM) affords carbamate amide (12). Subsequent treatment of (12) with a suitable acid, for example trifluoracetic acid or hydrogen chloride, gives rise to the amines of general formula IVa, which may be isolated as acid salts or neutralized under standard conditions to afford free bases.

Scheme 6: Representative Preparation of Amino-Substituted Benzamides Using a tert-Butyl Carbamate as an Amino Protecting Group



Further examples of the use of protecting group stategies are illustrated in the synthesis of preferred compounds of formula IIIa shown in Scheme 7. Acetonide-amides (14) are readily obtained by the union of acetonide (13) with benzoic acid (1) in the presence of a peptide coupling agent (for example, DPP-Cl) and a tertiary base, for example, 4-methylmorpholine (NMM). Alternately, they may be prepared according to Scheme 2 by the treatment of benzoic acid pentafluorophenyl esters (4) with acetonide (13) in the presence of a tertiary amine base (for example, diisopropylethylamine). Conversion of acetonide-amides (14) to preferred compounds IIIa can be accomplished by treatment under standard acidic hydrolysis conditions, for example p-toluenesulfonic acid in methanol.

Scheme 7: Representative Preparation of Dihydroxylated Benzamides Using an Acetonide as a Diol Protecting Group



The compounds of formula I can also be prepared by the modification of other compounds of formula I. For example, compounds of formula I, where R_6=H (15) may be converted to compounds of formula I, where R_6=alkyl (16) by treatment with alkylating agents (for example, iodomethane) in the presence of a base (for example, potassium carbonate). Alternately, compounds of formula I, where R_{11}= H (17) may be converted to compounds of formula I, where R_{11} = alkylcarbonyl (18) by treatment with an acid chloride (for example, acetyl chloride) and a base, such as triethylamine. Additionally, a compound of formula I, where R_4=H (19) can be prepared from a compound of formula I, where R_4=Iodo (20). Illustrations of these examples are found in Schemes 8-10.

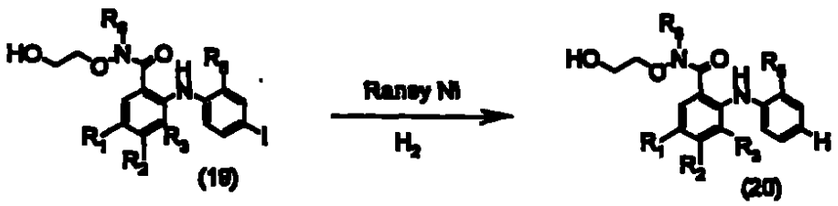
Scheme 8: Representative Preparation of Tertiary Benzamides by N-Alkylation



Scheme 9: Representative Preparation of Acetates by Acetylation



Scheme 10: Representative Hydrogenolysis of Aryl Iodides



Specific compounds provided by the invention include:

Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-butoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-1-methyl-ethoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-methoxy-ethoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(2-hydroxy-butoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(2-hydroxy-1-methyl-ethoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(2-methoxy-ethoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(2-hydroxy-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(3-hydroxy-2,2-dimethyl-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(2-hydroxy-2-methyl-propoxy)-benzamide

3,4,5-Trifluoro-N-(2-hydroxy-3-phenoxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4,5-Trifluoro-N-(2-hydroxy-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4,5-Trifluoro-N-(2-hydroxy-1-methyl-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-methoxy-ethoxy)-benzamide

3,4,5-Trifluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4,5-Trifluoro-N-(2-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4,5-Trifluoro-N-(3-hydroxy-2,2-dimethyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4,5-Trifluoro-N-(2-hydroxy-2-methyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-butoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-1-methyl-ethoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-methoxy-ethoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-propoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-2-methyl-propoxy)-benzamide

5-Bromo-3,4-difluoro-N-(2-hydroxy-3-phenoxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-3,4-difluoro-N-(2-hydroxy-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-3,4-difluoro-N-(2-hydroxy-1-methyl-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-methoxy-ethoxy)-benzamide

5-Bromo-3,4-difluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-3,4-difluoro-N-(2-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-3,4-difluoro-N-(2-hydroxy-2-methyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4-Difluoro-N-(2-hydroxy-3-phenoxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4-Difluoro-N-(2-hydroxy-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4-Difluoro-N-(2-hydroxy-1-methyl-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-methoxy-ethoxy)-benzamide

3,4-Difluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4-Difluoro-N-(2-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4-Difluoro-N-(3-hydroxy-2,2-dimethyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4-Difluoro-N-(2-hydroxy-2-methyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-butoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-1-methyl-ethoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-methoxy-ethoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-propoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-2,2-dimethyl-propoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-2-methyl-propoxy)-benzamide

5-Chloro-3,4-difluoro-N-(2-hydroxy-3-phenoxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-3,4-difluoro-N-(2-hydroxy-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-3,4-difluoro-N-(2-hydroxy-1-methyl-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-methoxy-ethoxy)-benzamide

5-Chloro-3,4-difluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-3,4-difluoro-N-(2-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-3,4-difluoro-N-(3-hydroxy-2,2-dimethyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-3,4-difluoro-N-(2-hydroxy-2-methyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-propoxy)-benzamide

3,4,5-Trifluoro-N-(3-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(3-hydroxy-propoxy)-benzamide

5-Bromo-3,4-difluoro-N-(3-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4-Difluoro-N-(3-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide

3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide

Additionally, the claims provide for the following compounds:
5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-*N*-(2-hydroxy-ethoxy)-benzamide,
5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-*N*-(2-hydroxy-ethoxy)-benzamide,
2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-*N*-(2-hydroxy-ethoxy)-benzamide,
5-Bromo-3,4-difluoro-*N*-(2-hydroxy-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide,
5-Chloro-3,4-difluoro-*N*-(2-hydroxy-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide,
5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-*N*-(2-hydroxy-propoxy)-benzamide,
5-Chloro-3,4-difluoro-*N*-(2-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide,
2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-2,2-dimethyl-propoxy)-benzamide,
5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-2,2-dimethyl-propoxy)-benzamide,
5-Bromo-3,4-difluoro-N-(3-hydroxy-2,2-dimethyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide,
2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-2-methyl-propoxy)-benzamide,
5-Chloro-2-(2-chloro-4-iodo-phenylamino)-N-(2,3-dihydroxy-propoxy)-3,4-difluoro-benzamide,
5-Chloro-N-(2,3-dihydroxy-propoxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide,
5-Chloro-2-(2-chloro-4-iodo-phenylamino)-N-(3,4-dihydroxy-butoxy)-3,4-difluoro-benzamide,

5-Chloro-N-(3,4-dihydroxy-butoxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide,

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide,

5-Chloro-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide.

Additional Compounds described by the invention include:

4-Fluoro-N-(2-hydroxy-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-N-(3-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide

4-Fluoro-N-(2-hydroxy-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-N-(2-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-N-(2-hydroxy-2-methyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-N-(2-hydroxy-1-methyl-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-methoxy-ethoxy)-benzamide

N-(3,4-Dihydroxy-butoxy)-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-(2,3-Dihydroxy-propoxy)-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-N-(2-hydroxy-3-phenoxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-N-(3-hydroxy-2,2-dimethyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-ethoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(3-hydroxy-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-butoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-2-methyl-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-1-methyl-ethoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(2-methoxy-ethoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-N-(3,4-dihydroxy-butoxy)-4-fluoro-benzamide

2-(2-Chloro-4-iodo-phenylamino)-N-(2,3-dihydroxy-propoxy)-4-fluoro-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(3-hydroxy-2,2-dimethyl-propoxy)-benzamide

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-ethoxy)-benzamide

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-propoxy)-benzamide

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-butoxy)-benzamide

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-propoxy)-benzamide

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-2-methyl-propoxy)-benzamide

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-1-methyl-ethoxy)-benzamide

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-methoxy-ethoxy)-benzamide

N-(3,4-Dihydroxy-butoxy)-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

N-(2,3-Dihydroxy-propoxy)-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-2,2-dimethyl-propoxy)-benzamide

4,5-Difluoro-N-(2-hydroxy-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4,5-Difluoro-N-(3-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4,5-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide

4,5-Difluoro-N-(2-hydroxy-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4,5-Difluoro-N-(2-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4,5-Difluoro-N-(2-hydroxy-2-methyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4,5-Difluoro-N-(2-hydroxy-1-methyl-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4,5-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-methoxy-ethoxy)-benzamide

N-(3,4-Dihydroxy-butoxy)-4,5-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-(2,3-Dihydroxy-propoxy)-4,5-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

4,5-Difluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4,5-Difluoro-N-(2-hydroxy-3-phenoxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4,5-Difluoro-N-(3-hydroxy-2,2-dimethyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-N-(2-hydroxy-ethoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-N-(3-hydroxy-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-N-(2-hydroxy-butoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-N-(2-hydroxy-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-N-(2-hydroxy-2-methyl-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-N-(2-hydroxy-1-methyl-ethoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-N-(2-methoxy-ethoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-N-(3,4-dihydroxy-butoxy)-4,5-difluoro-benzamide

2-(2-Chloro-4-iodo-phenylamino)-N-(2,3-dihydroxy-propoxy)-4,5-difluoro-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-N-(3-hydroxy-2,2-dimethyl-propoxy)-benzamide

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-ethoxy)-benzamide

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-propoxy)-benzamide

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-butoxy)-benzamide

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-propoxy)-benzamide

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-2-methyl-propoxy)-benzamide

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-1-methyl-ethoxy)-benzamide

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-methoxy-ethoxy)-benzamide

N-(3,4-Dihydroxy-butoxy)-4,5-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

N-(2,3-Dihydroxy-propoxy)-4,5-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-2,2-dimethyl-propoxy)-benzamide

5-Chloro-4-fluoro-N-(2-hydroxy-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-4-fluoro-N-(3-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide

5-Chloro-4-fluoro-N-(2-hydroxy-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-4-fluoro-N-(2-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-4-fluoro-N-(2-hydroxy-2-methyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-4-fluoro-N-(2-hydroxy-1-methyl-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-methoxy-ethoxy)-benzamide

5-Chloro-N-(3,4-dihydroxy-butoxy)-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-N-(2,3-dihydroxy-propoxy)-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-4-fluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-4-fluoro-N-(2-hydroxy-3-phenoxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-4-fluoro-N-(3-hydroxy-2,2-dimethyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-ethoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(3-hydroxy-propoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-butoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-propoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-2-methyl-propoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-1-methyl-ethoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(2-methoxy-ethoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-N-(3,4-dihydroxy-butoxy)-4-fluoro-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-N-(2,3-dihydroxy-propoxy)-4-fluoro-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(3-hydroxy-2,2-dimethyl-propoxy)-benzamide

5-Chloro-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-ethoxy)-benzamide

5-Chloro-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-propoxy)-benzamide

5-Chloro-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide

5-Chloro-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-butoxy)-benzamide

5-Chloro-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-propoxy)-benzamide

5-Chloro-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-2-methyl-propoxy)-benzamide

5-Chloro-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-1-methyl-ethoxy)-benzamide

5-Chloro-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-methoxy-ethoxy)-benzamide

5-Chloro-N-(3,4-dihydroxy-butoxy)-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

5-Chloro-N-(2,3-dihydroxy-propoxy)-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

5-Chloro-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide

5-Chloro-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide

5-Chloro-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-2,2-dimethyl-propoxy)-benzamide

5-Bromo-4-fluoro-N-(2-hydroxy-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-4-fluoro-N-(3-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide

5-Bromo-4-fluoro-N-(2-hydroxy-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-4-fluoro-N-(2-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-4-fluoro-N-(2-hydroxy-2-methyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-4-fluoro-N-(2-hydroxy-1-methyl-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-methoxy-ethoxy)-benzamide

5-Bromo-N-(3,4-dihydroxy-butoxy)-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-N-(2,3-dihydroxy-propoxy)-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-4-fluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-4-fluoro-N-(2-hydroxy-3-phenoxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-4-fluoro-N-(3-hydroxy-2,2-dimethyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-ethoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(3-hydroxy-propoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-butoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-propoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-2-methyl-propoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-1-methyl-ethoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(2-methoxy-ethoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-N-(3,4-dihydroxy-butoxy)-4-fluoro-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-N-(2,3-dihydroxy-propoxy)-4-fluoro-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(3-hydroxy-2,2-dimethyl-propoxy)-benzamide

5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-ethoxy)-benzamide

5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-propoxy)-benzamide

5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide

5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-butoxy)-benzamide

5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-propoxy)-benzamide

5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-2-methyl-propoxy)-benzamide

5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-1-methyl-ethoxy)-benzamide

5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-methoxy-ethoxy)-benzamide

5-Bromo-N-(3,4-dihydroxy-butoxy)-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

5-Bromo-N-(2,3-dihydroxy-propoxy)-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide

5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide

5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-2,2-dimethyl-propoxy)-benzamide

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-ethoxy)-benzamide

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-propoxy)-benzamide

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-butoxy)-benzamide

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-propoxy)-benzamide

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-2-methyl-propoxy)-benzamide

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-1-methyl-ethoxy)-benzamide

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-methoxy-ethoxy)-benzamide

N-(3,4-Dihydroxy-butoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

N-(2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-2,2-dimethyl-propoxy)-benzamide

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-ethoxy)-benzamide

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-propoxy)-benzamide

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-butoxy)-benzamide

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-propoxy)-benzamide

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-2-methyl-propoxy)-benzamide

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-1-methyl-ethoxy)-benzamide

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-methoxy-ethoxy)-benzamide

N-(3,4-Dihydroxy-butoxy)-3,4,5-trifluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

N-(2,3-Dihydroxy-propoxy)-3,4,5-trifluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-2,2-dimethyl-propoxy)-benzamide

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-ethoxy)-benzamide

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-propoxy)-benzamide

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-butoxy)-benzamide

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-propoxy)-benzamide

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-2-methyl-propoxy)-benzamide

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-1-methyl-ethoxy)-benzamide

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-methoxy-ethoxy)-benzamide

5-Chloro-N-(3,4-dihydroxy-butoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

5-Chloro-N-(2,3-dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-2,2-dimethyl-propoxy)-benzamide

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-ethoxy)-benzamide

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-propoxy)-benzamide

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-butoxy)-benzamide

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-propoxy)-benzamide

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-2-methyl-propoxy)-benzamide

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-1-methyl-ethoxy)-benzamide

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-methoxy-ethoxy)-benzamide

5-Bromo-N-(3,4-dihydroxy-butoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

5-Bromo-N-(2,3-dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-2,2-dimethyl-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-methoxy-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-pentyloxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-methyl-butoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-4-methyl-pentyloxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(1-hydroxy-cyclopropylmethoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(1-hydroxy-cyclobutylmethoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(1-hydroxymethyl-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-1,1-dimethyl-ethoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(1-hydroxymethyl-cyclopropoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-N-(2-ethoxy-ethoxy)-3,4-difluoro-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-2-methoxy-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-pentyloxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-butoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-3-methyl-butoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-[2-(1-hydroxy-cyclopropyl)-ethoxy]-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxymethyl-cyclopropylmethoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-1,1-dimethyl-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-1-methyl-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-N-(2,3-dihydroxy-1,1-dimethyl-propoxy)-3,4-difluoro-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(2-hydroxy-3-methoxy-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(2-hydroxy-pentyloxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(2-hydroxy-3-methyl-butoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(2-hydroxy-4-methyl-pentyloxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(1-hydroxy-cyclopropylmethoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(1-hydroxy-cyclobutylmethoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(1-hydroxymethyl-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(2-hydroxy-1,1-dimethyl-ethoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(1-hydroxymethyl-cyclopropoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-N-(2-ethoxy-ethoxy)-3,4,5-trifluoro-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(3-hydroxy-2-methoxy-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(3-hydroxy-pentyloxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(3-hydroxy-butoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(3-hydroxy-3-methyl-butoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-[2-(1-hydroxy-cyclopropyl)-ethoxy]-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(2-hydroxymethyl-cyclopropylmethoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(3-hydroxy-1,1-dimethyl-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(3-hydroxy-1-methyl-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-N-(2,3-dihydroxy-1,1-dimethyl-propoxy)-3,4,5-trifluoro-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-methoxy-propoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-pentyloxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-methyl-butoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-4-methyl-pentyloxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(1-hydroxy-cyclopropylmethoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(1-hydroxy-cyclobutylmethoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(1-hydroxymethyl-propoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-1,1-dimethyl-ethoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(1-hydroxymethyl-cyclopropoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-N-(2-ethoxy-ethoxy)-3,4-difluoro-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-2-methoxy-propoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-pentyloxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-butoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-3-methyl-butoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-[2-(1-hydroxy-cyclopropyl)-ethoxy]-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxymethyl-cyclopropylmethoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-1,1-dimethyl-propoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-1-methyl-propoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-N-(2,3-dihydroxy-1,1-dimethyl-propoxy)-3,4-difluoro-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-methoxy-propoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-pentyloxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-methyl-butoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-4-methyl-pentyloxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(1-hydroxy-cyclopropylmethoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(1-hydroxy-cyclobutylmethoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(1-hydroxymethyl-propoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-1,1-dimethyl-ethoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(1-hydroxymethyl-cyclopropoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-N-(2-ethoxy-ethoxy)-3,4-difluoro-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-2-methoxy-propoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-pentyloxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-butoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-3-methyl-butoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-[2-(1-hydroxy-cyclopropyl)-ethoxy]-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxymethyl-cyclopropylmethoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-1,1-dimethyl-propoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-1-methyl-propoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-N-(2,3-dihydroxy-1,1-dimethyl-propoxy)-3,4-difluoro-benzamide

3,4-Difluoro-N-(2-hydroxy-3-methoxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4-Difluoro-N-(2-hydroxy-pentyloxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide

3,4-Difluoro-N-(2-hydroxy-3-methyl-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4-Difluoro-N-(2-hydroxy-4-methyl-pentyloxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4-Difluoro-N-(1-hydroxy-cyclopropylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4-Difluoro-N-(1-hydroxy-cyclobutylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4-Difluoro-N-(1-hydroxymethyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4-Difluoro-N-(2-hydroxy-1,1-dimethyl-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4-Difluoro-N-(1-hydroxymethyl-cyclopropoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-(2-Ethoxy-ethoxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4-Difluoro-N-(3-hydroxy-2-methoxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4-Difluoro-N-(3-hydroxy-pentyloxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4-Difluoro-N-(3-hydroxy-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4-Difluoro-N-(3-hydroxy-3-methyl-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4-Difluoro-N-[2-(1-hydroxy-cyclopropyl)-ethoxy]-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4-Difluoro-N-(1-hydroxymethyl-cyclopropylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4-Difluoro-N-(2-hydroxymethyl-cyclopropylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4-Difluoro-N-(3-hydroxy-1,1-dimethyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4-Difluoro-N-(3-hydroxy-1-methyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-(2,3-Dihydroxy-1,1-dimethyl-propoxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4,5-Trifluoro-N-(2-hydroxy-3-methoxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4,5-Trifluoro-N-(2-hydroxy-pentyloxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide

3,4,5-Trifluoro-N-(2-hydroxy-3-methyl-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4,5-Trifluoro-N-(2-hydroxy-4-methyl-pentyloxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4,5-Trifluoro-N-(1-hydroxy-cyclopropylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4,5-Trifluoro-N-(1-hydroxy-cyclobutylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4,5-Trifluoro-N-(1-hydroxymethyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4,5-Trifluoro-N-(2-hydroxy-1,1-dimethyl-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4,5-Trifluoro-N-(1-hydroxymethyl-cyclopropoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-(2-Ethoxy-ethoxy)-3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4,5-Trifluoro-N-(3-hydroxy-2-methoxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4,5-Trifluoro-N-(3-hydroxy-pentyloxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4,5-Trifluoro-N-(3-hydroxy-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4,5-Trifluoro-N-(3-hydroxy-3-methyl-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4,5-Trifluoro-N-[2-(1-hydroxy-cyclopropyl)-ethoxy]-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4,5-Trifluoro-N-(1-hydroxymethyl-cyclopropylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4,5-Trifluoro-N-(2-hydroxymethyl-cyclopropylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4,5-Trifluoro-N-(3-hydroxy-1,1-dimethyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4,5-Trifluoro-N-(3-hydroxy-1-methyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-(2,3-Dihydroxy-1,1-dimethyl-propoxy)-3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-3,4-difluoro-N-(2-hydroxy-3-methoxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-3,4-difluoro-N-(2-hydroxy-pentyloxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide

5-Chloro-3,4-difluoro-N-(2-hydroxy-3-methyl-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-3,4-difluoro-N-(2-hydroxy-4-methyl-pentyloxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-3,4-difluoro-N-(1-hydroxy-cyclopropylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-3,4-difluoro-N-(1-hydroxy-cyclobutylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-3,4-difluoro-N-(1-hydroxymethyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-3,4-difluoro-N-(2-hydroxy-1,1-dimethyl-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-3,4-difluoro-N-(1-hydroxymethyl-cyclopropoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-N-(2-ethoxy-ethoxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-3,4-difluoro-N-(3-hydroxy-2-methoxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-3,4-difluoro-N-(3-hydroxy-pentyloxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-3,4-difluoro-N-(3-hydroxy-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-3,4-difluoro-N-(3-hydroxy-3-methyl-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-3,4-difluoro-N-[2-(1-hydroxy-cyclopropyl)-ethoxy]-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-3,4-difluoro-N-(1-hydroxymethyl-cyclopropylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-3,4-difluoro-N-(2-hydroxymethyl-cyclopropylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-3,4-difluoro-N-(3-hydroxy-1,1-dimethyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-3,4-difluoro-N-(3-hydroxy-1-methyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-N-(2,3-dihydroxy-1,1-dimethyl-propoxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-3,4-difluoro-N-(2-hydroxy-3-methoxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-3,4-difluoro-N-(2-hydroxy-pentyloxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide

5-Bromo-3,4-difluoro-N-(2-hydroxy-3-methyl-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-3,4-difluoro-N-(2-hydroxy-4-methyl-pentyloxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-3,4-difluoro-N-(1-hydroxy-cyclopropylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-3,4-difluoro-N-(1-hydroxy-cyclobutylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-3,4-difluoro-N-(1-hydroxymethyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-3,4-difluoro-N-(2-hydroxy-1,1-dimethyl-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-3,4-difluoro-N-(1-hydroxymethyl-cyclopropoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-N-(2-ethoxy-ethoxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-3,4-difluoro-N-(3-hydroxy-2-methoxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-3,4-difluoro-N-(3-hydroxy-pentyloxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-3,4-difluoro-N-(3-hydroxy-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-3,4-difluoro-N-(3-hydroxy-3-methyl-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-3,4-difluoro-N-[2-(1-hydroxy-cyclopropyl)-ethoxy]-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-3,4-difluoro-N-(1-hydroxymethyl-cyclopropylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-3,4-difluoro-N-(2-hydroxymethyl-cyclopropylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-3,4-difluoro-N-(3-hydroxy-1,1-dimethyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-3,4-difluoro-N-(3-hydroxy-1-methyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-N-(2,3-dihydroxy-1,1-dimethyl-propoxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-N-(2-hydroxy-3-methoxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-N-(2-hydroxy-pentyloxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide

4-Fluoro-N-(2-hydroxy-3-methyl-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-N-(2-hydroxy-4-methyl-pentyloxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-N-(1-hydroxy-cyclopropylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-N-(1-hydroxy-cyclobutylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-N-(1-hydroxymethyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-N-(2-hydroxy-1,1-dimethyl-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-N-(1-hydroxymethyl-cyclopropoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-(2-Ethoxy-ethoxy)-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-N-(3-hydroxy-2-methoxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-N-(3-hydroxy-pentyloxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-N-(3-hydroxy-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-N-(3-hydroxy-3-methyl-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-N-[2-(1-hydroxy-cyclopropyl)-ethoxy]-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-N-(1-hydroxymethyl-cyclopropylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-N-(2-hydroxymethyl-cyclopropylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-N-(3-hydroxy-1,1-dimethyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-N-(3-hydroxy-1-methyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-(2,3-Dihydroxy-1,1-dimethyl-propoxy)-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-3-methoxy-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-pentyloxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-3-methyl-butoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-4-methyl-pentyloxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(1-hydroxy-cyclopropylmethoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(1-hydroxy-cyclobutylmethoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(1-hydroxymethyl-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-1,1-dimethyl-ethoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(1-hydroxymethyl-cyclopropoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-N-(2-ethoxy-ethoxy)-4-fluoro-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(3-hydroxy-2-methoxy-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(3-hydroxy-pentyloxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(3-hydroxy-butoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(3-hydroxy-3-methyl-butoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-[2-(1-hydroxy-cyclopropyl)-ethoxy]-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxymethyl-cyclopropylmethoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(3-hydroxy-1,1-dimethyl-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(3-hydroxy-1-methyl-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-N-(2,3-dihydroxy-1,1-dimethyl-propoxy)-4-fluoro-benzamide

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-methoxy-propoxy)-benzamide

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-pentyloxy)-benzamide

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-methyl-butoxy)-benzamide

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-4-methyl-pentyloxy)-benzamide

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxy-cyclopropylmethoxy)-benzamide

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxy-cyclobutylmethoxy)-benzamide

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxymethyl-propoxy)-benzamide

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-1,1-dimethyl-ethoxy)-benzamide

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxymethyl-cyclopropoxy)-benzamide

N-(2-Ethoxy-ethoxy)-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-2-methoxy-propoxy)-benzamide

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-pentyloxy)-benzamide

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-butoxy)-benzamide

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-3-methyl-butoxy)-benzamide

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-[2-(1-hydroxy-cyclopropyl)-ethoxy]-benzamide

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxymethyl-cyclopropylmethoxy)-benzamide

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-1,1-dimethyl-propoxy)-benzamide

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-1-methyl-propoxy)-benzamide

N-(2,3-Dihydroxy-1,1-dimethyl-propoxy)-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

4,5-Difluoro-N-(2-hydroxy-3-methoxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4,5-Difluoro-N-(2-hydroxy-pentyloxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4,5-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide

4,5-Difluoro-N-(2-hydroxy-3-methyl-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4,5-Difluoro-N-(2-hydroxy-4-methyl-pentyloxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4,5-Difluoro-N-(1-hydroxy-cyclopropylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4,5-Difluoro-N-(1-hydroxy-cyclobutylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4,5-Difluoro-N-(1-hydroxymethyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4,5-Difluoro-N-(2-hydroxy-1,1-dimethyl-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4,5-Difluoro-N-(1-hydroxymethyl-cyclopropoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-(2-Ethoxy-ethoxy)-4,5-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

4,5-Difluoro-N-(3-hydroxy-2-methoxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4,5-Difluoro-N-(3-hydroxy-pentyloxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4,5-Difluoro-N-(3-hydroxy-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4,5-Difluoro-N-(3-hydroxy-3-methyl-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4,5-Difluoro-N-[2-(1-hydroxy-cyclopropyl)-ethoxy]-2-(4-iodo-2-methyl-phenylamino)-benzamide

4,5-Difluoro-N-(1-hydroxymethyl-cyclopropylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4,5-Difluoro-N-(2-hydroxymethyl-cyclopropylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4,5-Difluoro-N-(3-hydroxy-1,1-dimethyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4,5-Difluoro-N-(3-hydroxy-1-methyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-(2,3-Dihydroxy-1,1-dimethyl-propoxy)-4,5-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-N-(2-hydroxy-3-methoxy-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-N-(2-hydroxy-pentyloxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-N-(2-hydroxy-3-methyl-butoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-N-(2-hydroxy-4-methyl-pentyloxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-N-(1-hydroxy-cyclopropylmethoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-N-(1-hydroxy-cyclobutylmethoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-N-(1-hydroxymethyl-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-N-(2-hydroxy-1,1-dimethyl-ethoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-N-(1-hydroxymethyl-cyclopropoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-N-(2-ethoxy-ethoxy)-4,5-difluoro-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-N-(3-hydroxy-2-methoxy-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-N-(3-hydroxy-pentyloxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-N-(3-hydroxy-butoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-N-(3-hydroxy-3-methyl-butoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-N-[2-(1-hydroxy-cyclopropyl)-ethoxy]-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-N-(2-hydroxymethyl-cyclopropylmethoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-N-(3-hydroxy-1,1-dimethyl-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-N-(3-hydroxy-1-methyl-propoxy)-benzamide

2-(2-Chloro-4-iodo-phenylamino)-N-(2,3-dihydroxy-1,1-dimethyl-propoxy)-4,5-difluoro-benzamide

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-methoxy-propoxy)-benzamide

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-pentyloxy)-benzamide

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-methyl-butoxy)-benzamide

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-4-methyl-pentyloxy)-benzamide

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxy-cyclopropylmethoxy)-benzamide

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxy-cyclobutylmethoxy)-benzamide

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxymethyl-propoxy)-benzamide

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-1,1-dimethyl-ethoxy)-benzamide

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxymethyl-cyclopropoxy)-benzamide

N-(2-Ethoxy-ethoxy)-4,5-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-2-methoxy-propoxy)-benzamide

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-pentyloxy)-benzamide

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-butoxy)-benzamide

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-3-methyl-butoxy)-benzamide

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-[2-(1-hydroxy-cyclopropyl)-ethoxy]-benzamide

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxymethyl-cyclopropylmethoxy)-benzamide

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-1,1-dimethyl-propoxy)-benzamide

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-1-methyl-propoxy)-benzamide

N-(2,3-Dihydroxy-1,1-dimethyl-propoxy)-4,5-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

5-Chloro-4-fluoro-N-(2-hydroxy-3-methoxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-4-fluoro-N-(2-hydroxy-pentyloxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide

5-Chloro-4-fluoro-N-(2-hydroxy-3-methyl-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-4-fluoro-N-(2-hydroxy-4-methyl-pentyloxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-4-fluoro-N-(1-hydroxy-cyclopropylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-4-fluoro-N-(1-hydroxy-cyclobutylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-4-fluoro-N-(1-hydroxymethyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-4-fluoro-N-(2-hydroxy-1,1-dimethyl-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-4-fluoro-N-(1-hydroxymethyl-cyclopropoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-N-(2-ethoxy-ethoxy)-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-4-fluoro-N-(3-hydroxy-2-methoxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-4-fluoro-N-(3-hydroxy-pentyloxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-4-fluoro-N-(3-hydroxy-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-4-fluoro-N-(3-hydroxy-3-methyl-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-4-fluoro-N-[2-(1-hydroxy-cyclopropyl)-ethoxy]-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-4-fluoro-N-(1-hydroxymethyl-cyclopropylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-4-fluoro-N-(2-hydroxymethyl-cyclopropylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-4-fluoro-N-(3-hydroxy-1,1-dimethyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-4-fluoro-N-(3-hydroxy-1-methyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-N-(2,3-dihydroxy-1,1-dimethyl-propoxy)-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-3-methoxy-propoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-pentyloxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-3-methyl-butoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-4-methyl-pentyloxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(1-hydroxy-cyclopropylmethoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(1-hydroxy-cyclobutylmethoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(1-hydroxymethyl-propoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-1,1-dimethyl-ethoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(1-hydroxymethyl-cyclopropoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-N-(2-ethoxy-ethoxy)-4-fluoro-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(3-hydroxy-2-methoxy-propoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(3-hydroxy-pentyloxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(3-hydroxy-butoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(3-hydroxy-3-methyl-butoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-[2-(1-hydroxy-cyclopropyl)-ethoxy]-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxymethyl-cyclopropylmethoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(3-hydroxy-1,1-dimethyl-propoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(3-hydroxy-1-methyl-propoxy)-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-N-(2,3-dihydroxy-1,1-dimethyl-propoxy)-4-fluoro-benzamide

5-Chloro-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-methoxy-propoxy)-benzamide

5-Chloro-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-pentyloxy)-benzamide

5-Chloro-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide

5-Chloro-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-methyl-butoxy)-benzamide

5-Chloro-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-4-methyl-pentyloxy)-benzamide

5-Chloro-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxy-cyclopropylmethoxy)-benzamide

5-Chloro-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxy-cyclobutylmethoxy)-benzamide

5-Chloro-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxymethyl-propoxy)-benzamide

5-Chloro-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-1,1-dimethyl-ethoxy)-benzamide

5-Chloro-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxymethyl-cyclopropoxy)-benzamide

5-Chloro-N-(2-ethoxy-ethoxy)-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

5-Chloro-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-2-methoxy-propoxy)-benzamide

5-Chloro-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-pentyloxy)-benzamide

5-Chloro-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-butoxy)-benzamide

5-Chloro-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-3-methyl-butoxy)-benzamide

5-Chloro-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-[2-(1-hydroxy-cyclopropyl)-ethoxy]-benzamide

5-Chloro-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide

5-Chloro-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxymethyl-cyclopropylmethoxy)-benzamide

5-Chloro-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-1,1-dimethyl-propoxy)-benzamide

5-Chloro-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-1-methyl-propoxy)-benzamide

5-Chloro-N-(2,3-dihydroxy-1,1-dimethyl-propoxy)-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

5-Bromo-4-fluoro-N-(2-hydroxy-3-methoxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-4-fluoro-N-(2-hydroxy-pentyloxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide

5-Bromo-4-fluoro-N-(2-hydroxy-3-methyl-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-4-fluoro-N-(2-hydroxy-4-methyl-pentyloxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-4-fluoro-N-(1-hydroxy-cyclopropylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-4-fluoro-N-(1-hydroxy-cyclobutylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-4-fluoro-N-(1-hydroxymethyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-4-fluoro-N-(2-hydroxy-1,1-dimethyl-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-4-fluoro-N-(1-hydroxymethyl-cyclopropoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-N-(2-ethoxy-ethoxy)-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-4-fluoro-N-(3-hydroxy-2-methoxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-4-fluoro-N-(3-hydroxy-pentyloxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-4-fluoro-N-(3-hydroxy-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-4-fluoro-N-(3-hydroxy-3-methyl-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-4-fluoro-N-[2-(1-hydroxy-cyclopropyl)-ethoxy]-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-4-fluoro-N-(1-hydroxymethyl-cyclopropylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-4-fluoro-N-(2-hydroxymethyl-cyclopropylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-4-fluoro-N-(3-hydroxy-1,1-dimethyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-4-fluoro-N-(3-hydroxy-1-methyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-N-(2,3-dihydroxy-1,1-dimethyl-propoxy)-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-3-methoxy-propoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-pentyloxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-3-methyl-butoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-4-methyl-pentyloxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(1-hydroxy-cyclopropylmethoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(1-hydroxy-cyclobutylmethoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(1-hydroxymethyl-propoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-1,1-dimethyl-ethoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(1-hydroxymethyl-cyclopropoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-N-(2-ethoxy-ethoxy)-4-fluoro-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(3-hydroxy-2-methoxy-propoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(3-hydroxy-pentyloxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(3-hydroxy-butoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(3-hydroxy-3-methyl-butoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-[2-(1-hydroxy-cyclopropyl)-ethoxy]-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxymethyl-cyclopropylmethoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(3-hydroxy-1,1-dimethyl-propoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(3-hydroxy-1-methyl-propoxy)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-N-(2,3-dihydroxy-1,1-dimethyl-propoxy)-4-fluoro-benzamide

5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-methoxy-propoxy)-benzamide

5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-pentyloxy)-benzamide

5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide

5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-methyl-butoxy)-benzamide

5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-4-methyl-pentyloxy)-benzamide

5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxy-cyclopropylmethoxy)-benzamide

5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxy-cyclobutylmethoxy)-benzamide

5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxymethyl-propoxy)-benzamide

5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-1,1-dimethyl-ethoxy)-benzamide

5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxymethyl-cyclopropoxy)-benzamide

5-Bromo-N-(2-ethoxy-ethoxy)-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-2-methoxy-propoxy)-benzamide

5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-pentyloxy)-benzamide

5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-butoxy)-benzamide

5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-3-methyl-butoxy)-benzamide

5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-[2-(1-hydroxy-cyclopropyl)-ethoxy]-benzamide

5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide

5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxymethyl-cyclopropylmethoxy)-benzamide

5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-1,1-dimethyl-propoxy)-benzamide

5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-1-methyl-propoxy)-benzamide

5-Bromo-N-(2,3-dihydroxy-1,1-dimethyl-propoxy)-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-methoxy-propoxy)-benzamide

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-pentyloxy)-benzamide

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-methyl-butoxy)-benzamide

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-4-methyl-pentyloxy)-benzamide

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxy-cyclopropylmethoxy)-benzamide

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxy-cyclobutylmethoxy)-benzamide

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxymethyl-propoxy)-benzamide

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-1,1-dimethyl-ethoxy)-benzamide

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxymethyl-cyclopropoxy)-benzamide

N-(2-Ethoxy-ethoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-2-methoxy-propoxy)-benzamide

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-pentyloxy)-benzamide

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-butoxy)-benzamide

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-3-methyl-butoxy)-benzamide

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-[2-(1-hydroxy-cyclopropyl)-ethoxy]-benzamide

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxymethyl-cyclopropylmethoxy)-benzamide

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-1,1-dimethyl-propoxy)-benzamide

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-1-methyl-propoxy)-benzamide

N-(2,3-Dihydroxy-1,1-dimethyl-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-methoxy-propoxy)-benzamide

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-pentyloxy)-benzamide

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-methyl-butoxy)-benzamide

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-4-methyl-pentyloxy)-benzamide

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxy-cyclopropylmethoxy)-benzamide

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxy-cyclobutylmethoxy)-benzamide

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxymethyl-propoxy)-benzamide

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-1,1-dimethyl-ethoxy)-benzamide

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxymethyl-cyclopropoxy)-benzamide

N-(2-Ethoxy-ethoxy)-3,4,5-trifluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-2-methoxy-propoxy)-benzamide

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-pentyloxy)-benzamide

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-butoxy)-benzamide

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-3-methyl-butoxy)-benzamide

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-[2-(1-hydroxy-cyclopropyl)-ethoxy]-benzamide

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxymethyl-cyclopropylmethoxy)-benzamide

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-1,1-dimethyl-propoxy)-benzamide

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-1-methyl-propoxy)-benzamide

N-(2,3-Dihydroxy-1,1-dimethyl-propoxy)-3,4,5-trifluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-methoxy-propoxy)-benzamide

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-pentyloxy)-benzamide

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-methyl-butoxy)-benzamide

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-4-methyl-pentyloxy)-benzamide

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxy-cyclopropylmethoxy)-benzamide

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxy-cyclobutylmethoxy)-benzamide

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxymethyl-propoxy)-benzamide

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-1,1-dimethyl-ethoxy)-benzamide

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxymethyl-cyclopropoxy)-benzamide

5-Chloro-N-(2-ethoxy-ethoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-2-methoxy-propoxy)-benzamide

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-pentyloxy)-benzamide

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-butoxy)-benzamide

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-3-methyl-butoxy)-benzamide

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-[2-(1-hydroxy-cyclopropyl)-ethoxy]-benzamide

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxymethyl-cyclopropylmethoxy)-benzamide

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-1,1-dimethyl-propoxy)-benzamide

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-1-methyl-propoxy)-benzamide

5-Chloro-N-(2,3-dihydroxy-1,1-dimethyl-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-methoxy-propoxy)-benzamide

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-pentyloxy)-benzamide

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-methyl-butoxy)-benzamide

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-4-methyl-pentyloxy)-benzamide

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxy-cyclopropylmethoxy)-benzamide

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxy-cyclobutylmethoxy)-benzamide

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxymethyl-propoxy)-benzamide

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-1,1-dimethyl-ethoxy)-benzamide

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxymethyl-cyclopropoxy)-benzamide

5-Bromo-N-(2-ethoxy-ethoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-2-methoxy-propoxy)-benzamide

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-pentyloxy)-benzamide

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-butoxy)-benzamide

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-3-methyl-butoxy)-benzamide

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-[2-(1-hydroxy-cyclopropyl)-ethoxy]-benzamide

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxymethyl-cyclopropylmethoxy)-benzamide

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-1,1-dimethyl-propoxy)-benzamide

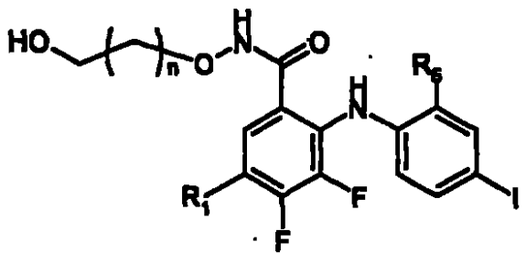
5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-1-methyl-propoxy)-benzamide, and

5-Bromo-N-(2,3-dihydroxy-1,1-dimethyl-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide.

Preferred compounds are those of formula I wherein R_1 is hydrogen or halogen; and more preferably, hydrogen, F, Br, or Cl; and most preferably,

hydrogen; R_2 and R_3 are fluoro; R_4 is hydrogen, iodine, bromine, chlorine, or fluorine; and more preferably hydrogen, iodine, chlorine, or fluorine; and most preferably is iodo; R_5 is fluoro, chloro, or methyl; more preferably is fluoro or chloro; and most preferably is fluoro; n is 1 or 2; or combinations thereof.

Preferred compounds are selective MEK inhibitors. The most preferred compounds within are those wherein R_6, R_7, R_8, R_9, R_{10}, and R_{11} are hydrogen, W is oxygen, and n is 1 or 2 and also those wherein, R_6, R_7, R_9, R_{10}, and R_{11} are hydrogen, W is oxygen, n is 2, and $R_8(1)$ is hydrogen and $R_8(2)$ is hydroxy. Such compounds have the formulae II and III.



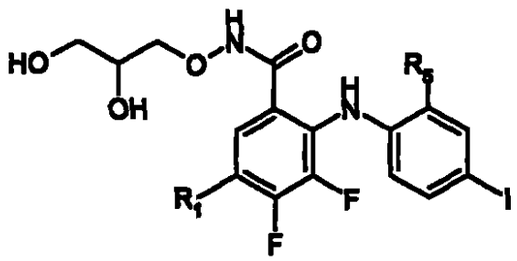
II

wherein

R_1 is hydrogen or halogen;

R_5 is fluorine, chlorine, or methyl; and

n is 1 or 2.



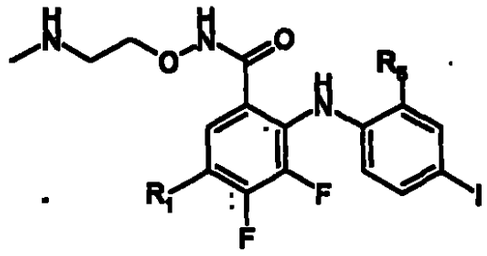
III

wherein

R_1 is hydrogen or halogen; and

R_5 is fluorine, chlorine, or methyl.

Other most preferred compounds are those of formula I wherein R_1 is hydrogen or halo such as F, Br, or Cl; R_2 and R_3 are fluoro; R_4 is iodo; R_5 is fluoro, chloro, or methyl; n is 1; R_6, R_7, R_8, R_9, and R_{10} are hydrogen, W is NRa and Ra is H; R_{11} is methyl or phenyl; and pharaceutically accepted salts thereof. These compounds have formulae IV and V.

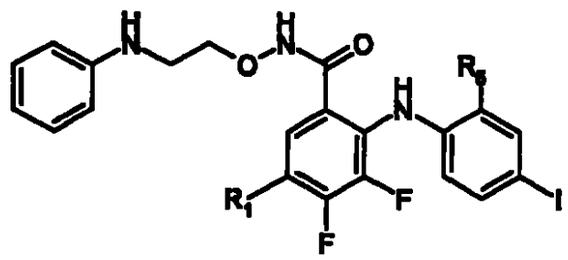


IV

wherein

R_1 is hydrogen or halogen; and

R_5 is fluorine, chlorine, or methyl.



V

wherein

R_1 is hydrogen or halogen; and

R_5 is fluorine, chlorine, or methyl.

Preferred compounds of the present invention include, but are not limited to the following compounds:

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-N-(2,3-dihydroxy-propoxy)-3,4-difluoro-benzamide;

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-ethoxy)-benzamide;

N-(2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

5-Chloro-N-(2,3-dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

5-Chloro-N-((R)-2,3-dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-methylamino-ethoxy)-benzamide; hydrochloride;

N-((R)-2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

N-((S)-2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-N-((S)-2,3-dihydroxy-propoxy)-3,4-difluoro-benzamide;

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-N-((R)-2,3-dihydroxy-propoxy)-3,4-difluoro-benzamide;

5-Chloro-N-((S) 2,3-dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-1-hydroxymethyl-ethoxy)-benzamide; and

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)- N-(2-hydroxy-1-hydroxymethyl-ethoxy)-benzamide.

In another aspect, the present invention provides Crystalline Form I and Form II of *N*-(2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide (hereinafter referred to as "Form I of Compound A" and "Form II of Compound A", respectively) or hydrates thereof, Crystalline Form I and Form II of *N*-[(R)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide (hereinafter referred to as "Form I of Compound B" and "Form II of Compound B", respectively) or hydrates thereof, and Crystalline Form I and Form II of *N*-[(S)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide (hereinafter referred to as "Form I of Compound C" and "Form II of Compound C", respectively) or hydrates thereof.

The present invention also provides Crystalline Form I and Form II of Compound A or hydrates thereof, Crystalline Form I and Form II of Compound B or hydrates thereof, and Crystalline Form I or Form II of Compound C or hydrates

thereof (hereinafter referred to collectively as "crystal forms" or "crystal forms" of the present invention, unless specified otherwise) which are useful as pharmaceutical agents, to methods for their production and isolation, to pharmaceutical compositions which include these compounds and a pharmaceutically acceptable carrier, and to pharmaceutical methods of treatment. The novel crystalline compounds of the present invention are useful as inhibitors of MEK.

The crystal forms provided by the present invention may be characterized by their X-ray powder diffraction patterns.

Crystalline Form I and Form II of Compound A, Crystalline Form I and Form II of Compound B, and Crystalline Form I and Form II of Compound C were characterized by their X-ray powder diffraction pattern. Thus, the X-ray diffraction patterns of the crystal forms of the present invention were measured on a Rigaku Ultima + diffractometer with CuK_α radiation.

Equipment

Rigaku Ultima + Diffractometer with an IBM-compatible interface equipped with 6 position autosampler, software = RigMeas v2.0 (Rigaku, December 1995) and JADE 3.1 (Materials Data, Inc.).

CuK_α radiation (40 mA, 40 kV, λ = 1.5419 Å). Slits I and II at 0.5°, slit III at 0.3°.

Methodology

The silicon standard is run once a week to check the X-ray tube alignment.

Continuous $\theta/2\theta$ coupled scan: 3.00° to 50.00° in 2θ, scan rate of 1°/min: 1.0 sec/0.04° step.

Sample tapped out of vial and pressed onto zero-background silicon in aluminum holder. Sample width 5 mm.

Samples are stored and run at room temperature.

Samples are being spun at 40 rpm around vertical axis during data collection.

Table 1 lists the X-ray powder diffraction pattern for crystalline Form I of Compound A, expressed in terms of the 2-theta ("2θ"), d-spacings or d(A), and relative intensities by peak area with a relative intensity of >10% measured on a Rigaku Ultima + diffractometer with CuK_α radiation. It should be noted that the computer-generated, unrounded numbers are listed in Table 1.

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TABLE 1

2-Theta	d(A)	Relative Intensity (>10%)
7.078	12.4779	15.2
14.123	6.2659	15.4
15.280	5.7939	58.7
15.836	5.5917	31.4
16.880	5.2481	42.2
18.082	4.9019	41.4
19.162	4.6280	67.4
20.279	4.3754	21.1
21.360	4.1565	73.6
22.325	3.9789	14.4
23.400	3.7984	79.3
24.522	3.6271	11.0
25.480	3.4929	24.6
26.159	3.4037	100.0
26.801	3.3237	48.9
27.842	3.2017	22.8
28.280	3.1531	45.4
29.475	3.0280	16.0
32.118	2.7845	19.7
33.248	2.6924	10.6
33.645	2.6615	16.3
40.008	2.2517	10.6
42.885	2.1071	12.1
44.095	2.0520	12.8

Table 2 lists the X-ray powder diffraction pattern for crystalline Form II of Compound A, expressed in terms of the 2-theta ("2θ"), d-spacings or d(A), and relative intensities by peak area with a relative intensity of >10% measured on a Rigaku Ultima + diffractometer with CuK_α radiation. It should be noted that the computer-generated, unrounded numbers are listed in Table 2.

TABLE 2

2-Theta	d(A)	Relative Intensity (>10%)
11.582	7.6344	11.2 *
12.598	7.0205	13.0 *
15.622	5.6678	17.1
17.302	5.1211	29.3
17.886	4.9551	13.3
20.345	4.3614	49.8
21.140	4.1991	31.0
22.137	4.0123	81.7
24.855	3.5793	100.0 *
25.885	3.4391	15.1
26.699	3.3362	23.3
27.842	3.2018	23.7
30.059	2.9704	11.8
30.948	2.8871	33.4
33.799	2.6498	24.8
35.399	2.5336	16.2
38.242	2.3516	33.9
39.282	2.2916	11.3
40.755	2.2122	12.6
41.641	2.1671	11.7
43.570	2.0756	24.5
46.958	1.9334	19.5

Table 3 lists the X-ray powder diffraction pattern for crystalline Form I of Compound B, expressed in terms of the 2-theta ("2θ"), d-spacings or d(A), and relative intensities by peak area with a relative intensity of >10% measured on a Rigaku Ultima + diffractometer with CuK_α radiation. It should be noted that the computer-generated, unrounded numbers are listed in Table 3.

TABLE 3

2-Theta	d(A)	Relative Intensity (>10%)
10.560	8.3702	14.9 *
13.720	6.4488	10.3 *
14.619	6.0543	13.9
17.258	5.1340	12.4
17.958	4.9354	44.5
18.219	4.8654	15.8
18.998	4.6675	38.1 *
19.258	4.6052	12.3
20.142	4.4050	17.7
21.002	4.2264	18.5
21.940	4.0479	53.2
22.360	3.9727	19.3
23.680	3.7541	100.0 *
24.043	3.6983	16.9
24.919	3.5702	67.3
26.278	3.3886	20.1
27.603	3.2289	40.6
28.024	3.1813	30.7
30.100	2.9665	14.6
32.142	2.7825	15.8
32.298	2.7694	14.6
32.938	2.7171	14.7
35.841	2.5034	16.3
37.660	2.3865	15.6

Table 4 lists the X-ray powder diffraction pattern for crystalline Form II of Compound B, expressed in terms of the 2-theta ("2θ"), d-spacings or d(A), and relative intensities by peak area with a relative intensity of >10% measured on a Rigaku Ultima + diffractometer with CuK_α radiation. It should be noted that the computer-generated, unrounded numbers are listed in Table 4.

TABLE 4

2-Theta	d(A)	Relative Intensity (>10%)
5.482	16.1076	39.6 *
10.721	8.2453	20.3
16.478	5.3751	21.9
19.563	4.5340	73.2 *
22.019	4.0334	100.0
22.478	3.9521	16.1
23.621	3.7634	11.1
24.100	3.6896	31.9
24.959	3.5647	98.2
26.181	3.4010	15.1
27.621	3.2269	31.7
29.081	3.0681	17.7
30.476	2.9307	11.4
31.698	2.8204	38.9
33.263	2.6913	19.4
39.020	2.3064	10.2

Table 5 lists the X-ray powder diffraction pattern for crystalline Form I of Compound C, expressed in terms of the 2-theta ("2θ"), d-spacings or d(A), and relative intensities by peak area with a relative intensity of >10% measured on a Rigaku Ultima + diffractometer with CuK_α radiation. It should be noted that the computer-generated, unrounded numbers are listed in Table 5.

TABLE 5

2-Theta	d(A)	Relative Intensity (>10%)
10.548	8.3798	14.6 *
13.703	6.4568	11.3 *
17.887	4.9549	19.9
18.958	4.6772	27.3 *
20.122	4.4093	10.9
21.950	4.0460	58.3
22.321	3.9796	13.4
23.640	3.7604	100.0 *
24.803	3.5867	66.6
26.244	3.3929	12.1
27.570	3.2327	21.6
28.000	3.1840	31.9
29.566	3.0189	23.1
32.234	2.7748	18.3
32.769	2.7307	16.4
35.804	2.5059	13.8
37.641	2.3877	16.8
41.402	2.1791	14.4
41.956	2.1516	10.0
44.600	2.0300	13.9

Table 6 lists the X-ray powder diffraction pattern for crystalline Form II of Compound C, expressed in terms of the 2-theta ("2θ"), d-spacings or d(A), and relative intensities by peak area with a relative intensity of >10% measured on a Rigaku Ultima + diffractometer with CuK_α radiation. It should be noted that the computer-generated, unrounded numbers are listed in Table 6.

TABLE 6

2-Theta	d(A)	Relative Intensity (>10%)
5.550	15.91107	21.8 *
10.763	8.2128	22.3
16.485	5.3729	11.8
19.636	4.5173	73.5 *
20.922	4.2425	20.6
22.043	4.0291	54.0
23.683	3.7538	18.0
24.153	3.6817	52.6
24.996	3.5595	100.0
26.236	3.3939	11.4
27.680	3.2201	25.2
28.037	3.1799	22.4
29.120	3.0641	21.5
31.718	2.8187	36.4
32.794	2.7287	13.3
33.314	2.6872	10.8
34.085	2.6282	13.6
41.999	2.1494	14.6
42.278	2.1359	10.3

The crystal forms of the present invention may exist in anhydrous forms as well as hydrated forms. In general, the hydrated forms, are equivalent to unhydrated forms and are intended to be encompassed within the scope of the present invention.

The present invention provides a process for the preparation of crystalline Form I of Compound A which comprises crystallizing Compound A from a solution in solvents under conditions which yield crystalline Form I of Compound A.

The precise conditions under which crystalline Form I of Compound A is formed may be empirically determined and it is only possible to give a number of methods which have been found to be suitable in practice. The desired Form I may be obtained by suspending the solid in a suitable solvent, such as ethanol and precipitating with water; by dissolving the solid in a minimum amount of a boiling solvent, such as ethanol and adding water to the boiling solvent; and by dissolving the solid in a minimum amount of boiling solvent, such as ethyl acetate, and adding a suitable solvent, such as heptane to the boiling solvent, as is more fully set forth in Example 39A below.

The present invention provides a process for the preparation of crystalline Form II of Compound A which comprises crystallizing Compound A from a solution in solvents under conditions which yield crystalline Form II of Compound A.

The precise conditions under which crystalline Form II of Compound A is formed may be empirically determined and it is only possible to give a number of methods which have been found to be suitable in practice. The desired Form II may be obtained by suspending the solid in a suitable solvent, such as ethyl acetate/hexanes or suspending the solid in a suitable solvent, such as heptane – CH_2Cl_2 (1 : 1), as is more fully set forth in Example 39 below.

The present invention provides a process for the preparation of crystalline Form I of Compound B which comprises crystallizing Compound B from a solution in solvents under conditions which yield crystalline Form I of Compound B.

The precise conditions under which crystalline Form I of Compound B is formed may be empirically determined and it is only possible to give a method which has been found to be suitable in practice. The desired Form I may be obtained by suspending the solid in hexane-AcOEt. A more detailed procedure is set forth in Example 49 below.

The present invention provides a process for the preparation of crystalline Form II of Compound B which comprises crystallizing Compound B from a solution in solvents under conditions which yield crystalline Form II of Compound B.

The precise conditions under which crystalline Form II of Compound B is formed may be empirically determined and it is only possible to give a method which has been found to be suitable in practice. The desired Form II may be obtained by suspending the solid in ethyl acetate and heptane or by suspending the solid in by suspending the solid in hexane-AcOEt, as is more fully set forth in Examples 49 and 49A below.

The present invention provides a process for the preparation of crystalline Form I of Compound C which comprises crystallizing Compound C from a solution in solvents under conditions which yield crystalline Form I of Compound C.

The precise conditions under which crystalline Form I of Compound C is formed may be empirically determined and it is only possible to give a method which has been found to be suitable in practice. The desired Form I may be obtained by suspending the solid in hexane-AcOEt. A more detailed procedure is set forth in Example 50 below.

The present invention provides a process for the preparation of crystalline Form II of Compound C which comprises crystallizing Compound C from a solution in solvents under conditions which yield crystalline Form II of Compound C.

The precise conditions under which crystalline Form II of Compound C is formed may be empirically determined and it is only possible to give a method which has been found to be suitable in practice. The desired Form II may be obtained by suspending the solid in ethyl acetate and heptane, or by suspending the solid in hexane-AcOEt, as is more fully set forth in Examples 50 and 50A below.

As used herein, the term "patient" refers to any warm-blooded animal such as, but not limited to, a human, horse, dog, guinea pig, or mouse. Preferably, the patient is human.

The term "treating" for purposes of the present invention refers to prophylaxis or prevention, amelioration or elimination of a named condition once the condition has been established.

Selective MEK 1 or MEK 2 inhibitors are those compounds which inhibit the MEK 1 or MEK 2 enzymes, respectively, without substantially inhibiting other enzymes such as MKK3, PKC, Cdk2A, phosphorylase kinase, EGF, and PDGF receptor kinases, and C-src. In general, a selective MEK 1 or MEK 2 inhibitor has an IC_{50} for MEK 1 or MEK 2 that is at least one-fiftieth (1/50) that of its IC_{50} for one of the above-named other enzymes. Preferably, a selective inhibitor has an IC_{50} that is at least 1/100, more preferably 1/500, and even more preferably 1/1000, 1/5000, or less than that of its IC_{50} or one or more of the above-named enzymes.

The disclosed compositions are useful as both prophylactic and therapeutic treatments for diseases or conditions related to the hyperactivity of MEK, as well as diseases or conditions modulated by the MEK cascade. Examples include, but are not limited to, stroke, septic shock, heart failure, osteoarthritis, rheumatoid arthritis, organ transplant rejection, and a variety of tumors such as ovarian, lung, pancreatic, brain, prostatic, and colorectal.

The invention further relates to a method for treating proliferative diseases, such as cancer, restenosis, psoriasis, autoimmune disease, and atherosclerosis. Other aspects of the invention include methods for treating MEK-related (including ras-related) cancers, whether solid or hematopoietic. Examples of cancers include brain, breast, lung, such as non-small cell lung, ovarian, pancreatic, prostate, renal, colorectal, cervical, acute leukemia, and gastric cancer.

Further aspects of the invention include methods for treating or reducing the symptoms of xenograft (cell(s), skin, limb, organ or bone marrow transplant) rejection, osteoarthritis, rheumatoid arthritis, cystic fibrosis, complications of diabetes (including diabetic retinopathy and diabetic nephropathy), hepatomegaly, cardiomegaly, stroke (such as acute focal ischemic stroke and global cerebral ischemia), heart failure, septic shock, asthma, Alzheimer's disease, and chronic or neuropathic pain. Compounds of the invention are also useful as antiviral agents for treating viral infections such as HIV, hepatitis (B) virus (HBV), human papilloma virus (HPV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV). These methods include the step of administering to a patient in need of such treatment, or suffering from such a disease or condition, a therapeutically effective amount of a disclosed compound, including crystal forms, or pharmaceutical composition thereof.

The term "chronic pain" for purposes of the present invention includes, but is not limited to, neuropathic pain, idiopathic pain, and pain associated with chronic alcoholism, vitamin deficiency, uremia, or hypothyroidism. Chronic pain is associated with numerous conditions including, but not limited to, inflammation, arthritis, and post-operative pain.

As used herein, the term "neuropathic pain" is associated with numerous conditions which include, but are not limited to, inflammation, postoperative pain, phantom limb pain, burn pain, gout, trigeminal neuralgia, acute herpetic and postherpetic pain, causalgia, diabetic neuropathy, plexus avulsion, neuroma, vasculitis, viral infection, crush injury, constriction injury, tissue injury, limb amputation, post-operative pain, arthritis pain, and nerve injury between the peripheral nervous system and the central nervous system.

The invention also features methods of combination therapy, such as a method for treating cancer, wherein the method further includes providing radiation therapy or chemotherapy, for example, with mitotic inhibitors such as a taxane or a vinca alkaloid. Examples of mitotic inhibitors include paclitaxel, docetaxel, vincristine, vinblastine, vinorelbine, and vinflunine. Other therapeutic combinations include a MEK inhibitor of the invention and an anticancer agent such as cisplatin, 5-fluorouracil or 5-fluoro-2-4(1H,3H)-pyrimidinedione (5FU), flutamide, and gemcitabine.

The chemotherapy or radiation therapy may be administered before, concurrently, or after the administration of a disclosed compound according to the needs of the patient.

Those skilled in the art will be able to determine, according to known methods, the appropriate therapeutically-effective amount or dosage of a compound of the present invention to administer to a patient, taking into account factors such as age, weight, general health, the compound administered, the route of administration, the type of pain or condition requiring treatment, and the presence of other medications. In general, an effective amount or a therapeutically-effective amount will be between about 0.1 and about 1000 mg/kg per day, preferably between about 1 and about 300 mg/kg body weight, and daily dosages will be between about 10 and about 5000 mg for an adult subject of normal weight. Commercially available capsules or other formulations (such as liquids and film-coated tablets) of 100 mg, 200 mg, 300 mg, or 400 mg can be administered according to the disclosed methods.

The compounds of the present invention, including crystal forms, are preferably formulated prior to administration. Therefore, another aspect of the present invention is a pharmaceutical composition comprising a compound of formula I and a pharmaceutically acceptable carrier. In making the compositions of the present invention, the active ingredient, such as a compound of formula I, will usually be mixed with a carrier, or diluted by a carrier or enclosed within a carrier. Dosage unit forms or pharmaceutical compositions include tablets, capsules, pills, powders, granules, aqueous and nonaqueous oral solutions and suspensions, and parenteral solutions packaged in containers adapted for subdivision into individual doses.

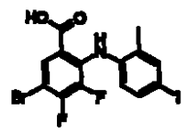
Dosage unit forms can be adapted for various methods of administration, including controlled release formulations, such as subcutaneous implants. Administration methods include oral, rectal, parenteral (intravenous, intramuscular, subcutaneous), intracisternal, intravaginal, intraperitoneal, intravesical, local (drops, powders, ointments, gels, or cream), and by inhalation (a buccal or nasal spray).

Parenteral formulations include pharmaceutically acceptable aqueous or nonaqueous solutions, dispersion, suspensions, emulsions, and sterile powders for

the preparation thereof. Examples of carriers include water, ethanol, polyols (propylene glycol, polyethylene glycol), vegetable oils, and injectable organic esters such as ethyl oleate. Fluidity can be maintained by the use of a coating such as lecithin, a surfactant, or maintaining appropriate particle size. Carriers for solid dosage forms include (a) fillers or extenders, (b) binders, (c) humectants, (d) disintegrating agents, (e) solution retarders, (f) absorption accelerators, (g) adsorbants, (h) lubricants, (i) buffering agents, and (j) propellants.

Compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents; antimicrobial agents such as parabens, chlorobutanol, phenol, and sorbic acid; isotonic agents such as a sugar or sodium chloride; absorption-prolonging agents such as aluminum monostearate and gelatin; and absorption-enhancing agents.

The following examples represent typical syntheses of the compounds of the present invention as described generally above. These examples are illustrative only and are not intended to limit the invention in any way. The reagents and starting materials are readily available to one of ordinary skill in the art.



PREPARATION 1

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid

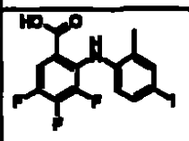
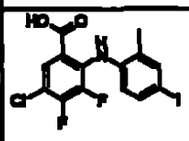
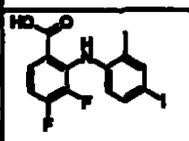
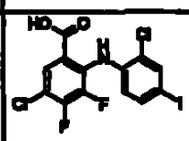
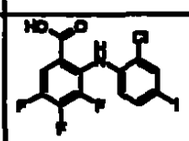
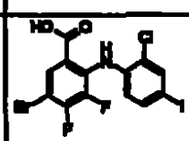
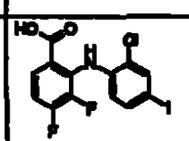
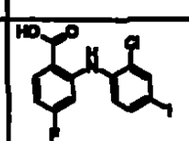
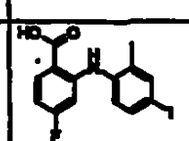
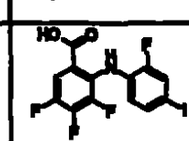
To a stirred solution comprised of 1.88 g (0.00791 mol) of 2-amino-5-iodotoluene in 10 mL of tetrahydrofuran at -78°C was added 6 mL (0.012 mol) of a 2.0 M lithium diisopropylamide in tetrahydrofuran/heptane/ethylbenzene (Aldrich) solution. The resulting green suspension was stirred vigorously for 10 minutes, after which time a solution of 1.00 g (0.00392 mol) of 5-bromo-2,3,4-trifluorobenzoic acid in 15 mL of tetrahydrofuran was added. The cold bath was subsequently removed, and the reaction mixture stirred for 18 hours. The mixture was concentrated, and the concentrate was treated with 100 mL of dilute (10%) aqueous hydrochloric acid. The resulting suspension was extracted with ether (2 × 150 mL), and the combined organic extractions were dried ($MgSO_4$)

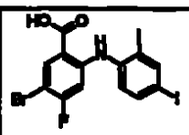
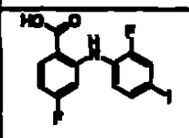
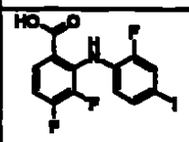
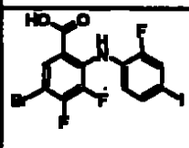
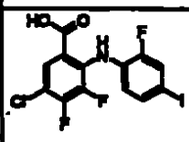
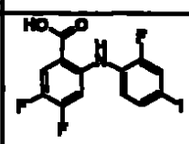
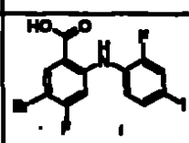
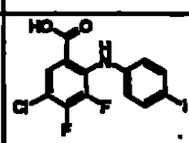
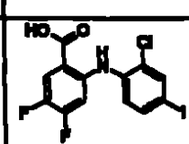
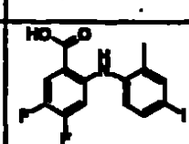
and concentrated in vacuo to give an orange solid. The solid was triturated with boiling dichloromethane, cooled to ambient temperature, and collected by filtration. The solid was rinsed with dichloromethane, and dried in the vacuum-oven (80°C) to afford 1.39 g (76%) of a yellow-green powder; mp 259.5-262°C; ^{1}H NMR (400 MHz, DMSO): δ 9.03 (s, 1H), 7.99 (dd, 1H, J=7.5, 1.9 Hz), 7.57 (dd, 1H, J=1.5 Hz), 7.42 (dd, 1H, J=8.4, 1.9 Hz), 6.70 (dd, 1H, J=8.4, 6.0 Hz), 2.24 (s, 3H); ^{19}F NMR (376 MHz, DMSO): δ -123.40 to -123.47 (m); -139.00 to -139.14 (m); IR (KBr) 1667 (C=O stretch)cm^{-1}; MS (CI) M+1 = 469. Anal. Calcd/found for $C_{14}H_9BrF_2INO_2$:

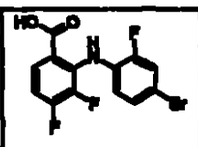
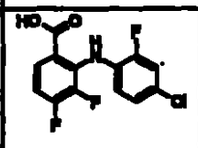
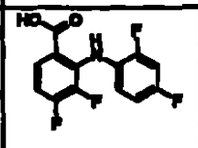
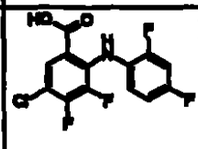
C, 35.93/36.15; H, 1.94/1.91; N, 2.99/2.70; Br, 17.07/16.40; F, 8.12/8.46; I, 27.11/26.05.

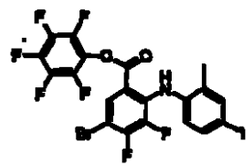
PREPARATIONS

Preparations 2 to 25 in Table 7 below were prepared by the general procedure of Example 1.

Preparation		Compound	MP °C
2		3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	206-210
3		5-Chloro-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	249-251
4		3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	240.5-244.5
5		5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-benzoic acid	293.3-293.6
6		2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-benzoic acid	237-239
7		5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-benzoic acid	302-304
8		2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-benzoic acid	226-228
9		2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-benzoic acid	242-247
10		4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	224-229.5
11		3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-benzoic acid	

12		5-bromo-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	
13		4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-benzoic acid	215-217
14		3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzoic acid	200-201
15		5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzoic acid	258-259
16		5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzoic acid	256-258
17		4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzoic acid	244-245
18		5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-benzoic acid	296-298
19		5-Chloro-3,4-difluoro-2-(4-iodo-phenylamino)-benzoic acid	267-269
20		2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-benzoic acid	245, dec
21		4,5-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	238-239

22		2-(4-Bromo-2-fluoro-phenylamino)-3,4-difluoro-benzoic acid	214.4-214.9
23		2-(4-Chloro-2-fluoro-phenylamino)-3,4-difluoro-benzoic acid	215.4-215.6
24		2-(2,4-Difluoro-phenylamino)-3,4-difluoro-benzoic acid	191.8-192.0
25		5-Chloro-2-(2,4-difluoro-phenylamino)-3,4-difluoro-benzoic acid	240-240.3



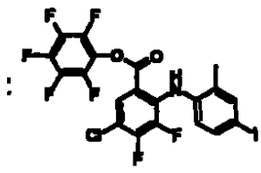
PREPARATION 26

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid pentafluorophenyl ester

To a solution of 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid (prepared as described in WO 99/01426) (1.61 g, 3.4 mmol) and pyridine (0.31 mL, 3.83 mmol) in anhydrous dimethylformamide (7 mL) was added pentafluorophenyl trifluoroacetate (0.71 mL, 4.13 mmol). The resultant solution was stirred at ambient temperature for 18 h. The reaction mixture was diluted with ether (100 mL) and washed with water (40 mL), 0.1 M aqueous hydrochloric acid (40 mL), saturated aqueous sodium bicarbonate (40 mL), and saturated brine (40 mL). The organics were dried over anhydrous magnesium sulfate and concentrated under reduced pressure to afford a foam that was purified on silica gel. Elution with hexanes-ethyl acetate (19:1) afforded 5-Bromo-3,4-difluoro-2-

(4-iodo-2-methyl-phenylamino)-benzoic acid pentafluorophenyl ester (1.95 g; 89%) as a pale-yellow powder: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1 H), 8.24 (d, J = 5.8 Hz, 1 H), 7.54 (s, 1 H), 7.45 (d, J = 8.4 Hz, 1 H), 6.70 (dd, J = 8.4, 5.3 Hz, 1 H), 2.26 (s, 3 H).

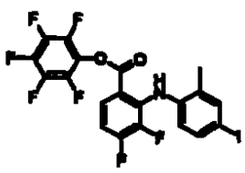
Preparations 27-46 were prepared by the general procedure of Preparation 26.



PREPARATION 27

5-Chloro-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid pentafluorophenyl ester

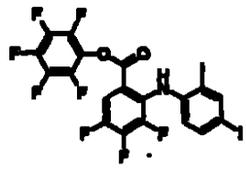
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1 H), 8.12 (dd, J = 7.5, 2.0 Hz, 1 H), 7.54 (s, 1 H), 7.46 (dd, J = 8.3, 1.5 Hz, 1 H), 6.70 (dd, J = 8.3, 5.4 Hz, 1 H), 2.28 (s, 3 H); ^{19}F-NMR (376 MHz, $CDCl_3$) δ -125.1 (dd, J = 17.7, 5.0 Hz, 1 F), -139.1 (d, J = 17.7 Hz, 1 F), -152.6 (d, J = 17.7 Hz, 2 F), -156.9 (t, J = 20.3 Hz, 1 H), -161.9 (t, J = 20.2 Hz, 2 H); MS (APCI-) = 587.9.



PREPARATION 28

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid pentafluorophenyl ester

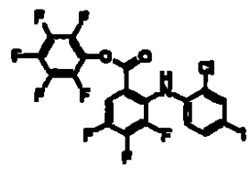
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1 H), 8.04 (dd, J = 7.5, 7.0 Hz, 1 H), 7.53 (s, 1 H), 7.45 (d, J = 8.4 Hz, 1 H), 6.77 (m, 1 H), 6.70 (dd, J = 7.2, 6.9 Hz, 1 H), 2.27 (s, 3 H); MS (APCI-) = 554.0



PREPARATION 29

3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid pentafluorophenyl ester

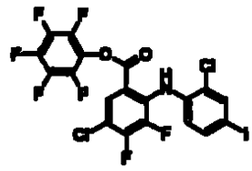
MP: 108.5-110.6 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.89 (ddd, J=10.4, 8.0, 2.2 Hz, 1H), 7.53 (s, 1H), 7.44 (dd, J=8.2, 1.9 Hz, 1H), 6.64 (dd, J=8.2, 5.5 Hz, 1H), 2.27 (s, 3H); ^{19}F-NMR (376 MHz, $CDCl_3$) δ -137.25 (d, J=16.8 Hz, 1F), -144.18 (dd, J=21.4, 10.7 Hz, 1F), -145.55 (td, J=21.4, 7.6 Hz, 1F), -152.31 (d, J=18.3 Hz, 2F), -156.60 (t, J=21.4 Hz, 1F), -161.62 (t, J=18.3 Hz, 2F). Anal. Calcd/found for $C_{20}H_8NO_2F_8I$: C, 41.91/41.52; H, 1.41/1.32; N, 2.44/2.36; F, 26.52/26.34; I, 22.14/22.19.



PREPARATION 30

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-benzoic acid pentafluorophenyl ester

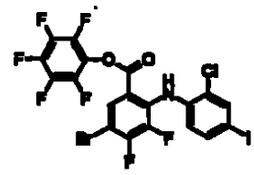
MP: 98.2-99.2 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.93 (ddd, J=10.1, 8.0, 2.2 Hz, 1 H), 7.70 (d, J=1.7 Hz, 1H), 7.48 (dd, J=8.7, 1.7 Hz, 1H), 6.62 (t, J=7.6 Hz, 1H); ^{19}F-NMR (376 MHz, $CDCl_3$) δ -134.42 (d, J=18.3 Hz, 1F), -141.59 (dd, J=21.4, 9.2 Hz, 1F), -145.26 (td, J=21.4, 7.6 Hz, 1F), -152.26 (d, J=18.3 Hz, 2F), -156.46 (t, J=21.4 Hz, 1F), -161.53 (t, J=18.3 Hz, 2F). Anal. Calcd/found for $C_{19}H_5NO_2F_5ClI$: C, 38.45/38.39; H, 0.85/0.91; N, 2.36/2.32; Cl, 5.97/6.32; F, 25.60/25.68; I, 21.38/21.32.



PREPARATION 31

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-benzoic acid pentafluorophenyl ester

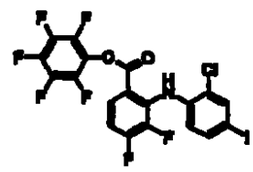
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1 H), 8.15 (dd, J = 7.3, 2.0 Hz, 1 H), 7.71 (d, J = 2.0 Hz, 1 H), 7.49 (dd, J = 8.4, 2.0 Hz, 1 H), 6.68 (dd, J = 8.4, 7.1 Hz, 1 H); MS (APCI-) = 607.8.



PREPARATION 32

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-benzoic acid pentafluorophenyl ester

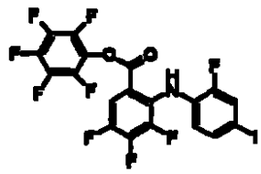
Yield, 1.99 g (61%); mp. 112-114 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.28 (dd, J=7.0, 2.2 Hz, 1H), 7.50 (dd, J = 8.4, 1.9 Hz, 1H), 7.713 (d, J=1.9 Hz, 1H), 6.68 (dd, J=8.4, 7.0 Hz, 1H); ^{19}F-NMR (376 MHz, $CDCl_3$) δ -116.43 (dd, J=19.8, 6.1 Hz, 1F), -135.59 (dd, J=18.3, 6.1 Hz, 1F), -152.2 (d, J=16.8 Hz, 2F), -156.47 (t, J=21.4 Hz, 1F), -161.53 (t, J=18.3 Hz, 2F). Anal. Calcd/found for $C_{19}H_5NO_2F_7BrCl$: C, 34.87/34.72; H, 0.77/0.65; N, 2.14/2.07; F, 20.32/20.68; Cl, 5.42/6.06; Br, 12.21/11.67; I, 19.39/19.75.



PREPARATION 33

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-benzoic acid pentafluorophenyl ester

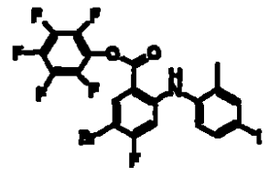
Yield, 2.15g (75%); mp. 108.5-110.0 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.77 (br s , 1H), 8.07 (br s, 1 H), 7.69 (br s, 1H), 7.48 (br d, J=7.0 Hz, 1H), 6.91 (br d, J=7.2 Hz, 1H), 6.67 (br s., 1H); ^{19}F-NMR (376 MHz, $CDCl_3$) δ -123.74 (s, 1F), -139.17 (d, J=16.8 Hz, 1F), -152.35 (d, J=21.4 Hz, 2F), -156.96 (t, J=21.4 Hz, 1F), -161.81 (t, J=21.4 Hz, 2F). Anal. Calcd/found for $C_{19}H_6NO_2F_7ClI$: C, 39.65/39.32; H, 1.05/0.91; N, 2.43/2.35; F, 23.10/22.85; Cl, 6.16/6.92; I, 22.05/22.50.



PREPARATION 34

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-benzoic acid pentafluorophenyl ester

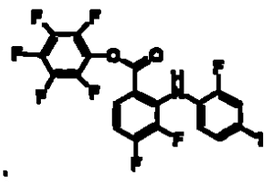
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.85-7.91 (m, 1H), 7.35-7.43 (m, 2H), 6.67-6.73 (m, 1H);); MS (APCI)=575.9.



PREPARATION 35

5-Bromo-4-fluoro-2-(4-iodo-2-methylphenylamino)-benzoic acid pentafluorophenyl ester

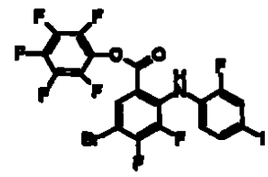
^{1}H-NMR (400 MHz, acetone-d_6) δ 9.04 (br. s., 1H), 8.44 (d, 1H, J=7.81 Hz), 7.74 (d, 1H, J=1.22 Hz), 7.64 (dd, 1H, J=8.31, 1.96 Hz), 7.19 (d, 1H, 8.3 Hz), 6.67 (d, 1H, J=11.48 Hz), 2.22 (s, 3H). ^{19}F-NMR (376 MHz, acetone-d_6) δ –97.1 (t), -155.0 (t), -160.2 (t), -165.1 (t). MS (APCI-) 415.8 m/z, 429.9 m/z, 447.9 m/z, 615.8 m/z.



PREPARATION 36

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzoic acid pentafluorophenyl ester

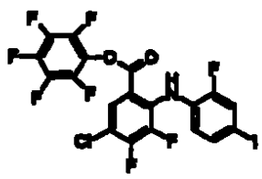
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1 H), 8.04 (ddd, J = 9.3, 5.6, 2.2 Hz, 1 H), 7.42 9dd, J = 10.0, 1.9 Hz, 1 H), 7.38 (d, J = 8.8 Hz, 1 H), 6.84 (td, J = 9.1, 6.8 Hz, 1 H), 6.77 (td, J = 8.5, 5.1 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –124.3, -125.1, -143.5, -152.6, -157.3, -162.1; MS (APCI-) = 557.9.



PREPARATION 37

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzoic acid pentafluorophenyl ester

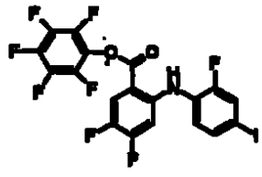
^{1}H NMR (400 MHz, acetone-d_6) δ 8.60 (s, 1 H), 8.39 (ddd, J = 7.1, 2.3, 0.7 Hz, 1 H),7.58 (dd, J = 10.5, 1.7 Hz, 1 H), 7.49 (dt, J = 7.5, 1.5 Hz, 1 H), 7.06 (td, J = 8.5, 4.4 Hz, 1 H); ^{19}F NMR (376 MHz, acetone-d_6) δ -120.5, -127.1, -141.5, -154.7, -159.8, -164.8; MS (APCI-) = 635.8, 637.8.



PREPARATION 38

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzoic acid pentafluorophenyl ester

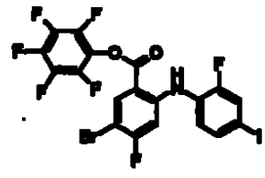
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1 H), 8.10 (dd, J = 7.5, 2.3 Hz, 1 H), 7.44 (dd, J = 10.0, 1.7 Hz, 1 H), 7.41 (dd, J = 8.4 , 1.1 Hz, 1 H), 6.76 (td, J = 8.3, 4.6 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –124.6, -124.9, -140.3, -152.5, -156.8, -161.9; MS (APCI-) = 591.8, 593.8.



PREPARATION 39

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzoic acid pentafluorophenyl ester

^{1}H-NMR (400 MHz, acetone-d_6) δ 8.99 (br. s.), 8.17 (dd, 1H, J=10.99, 8.79 Hz), 7.69 (dd, 1H, J=10.0, 1.95 Hz), 7.63 (m, 1H), 7.38 (t, 1H, J=8.55 Hz), 7.04 (qd, 1H, J=6.84, 1.47 Hz). ^{19}F-NMR (376 MHz, acetone-d_6) δ –123.0 (t), -125.7 (p), -150.8 (m), -155.1 (d), -160.1 (t), -165.0 (t). MS (APCI-) 355.9 m/z, 391.9 m/z, 558.0 m/z. Anal. Calcd for $C_{14}H_{10}F_2INO_2$: C, 40.81; H, 1.08; N, 2.50. Found: C, 40.92; H, 1.00; N, 2.32.

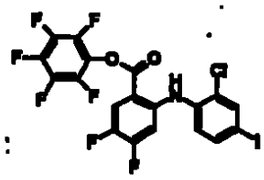


PREPARATION 40

5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-benzoic acid pentafluorophenyl ester

0061

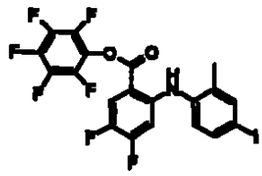
^{1}H-NMR (400 MHz, acetone-d_6) δ 9.11 (br. s.), 8.2 (dd, 1H, J=11.24, 8.79 Hz), 7.9 (d, 1H, J=1.95 Hz), 7.73 (dd, 1H, J=8.55, 2.2 Hz), 7.45 (d, 1H, J=8.55 Hz), 7.17 (dd, 1H, J=13.18, 6.83 Hz). ^{19}F-NMR (376 MHz, acetone-d_6) δ –96.8, -122.4, -155.0, -160.0, -165.0. MS (APCI-) 415.8 m/z (d), 453.8 m/z (d), 617.8 m/z (d). Anal. Calcd for $C_{13}H_7BrF_2INO_2$: C, 34.39; H, 0.98; N, 2.26. Found: C, 36.61; H, 0.99; N, 2.09.



PREPARATION 41

2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-benzoic acid pentafluorophenyl ester

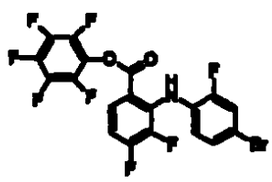
^{1}H-NMR (400 MHz, acetone-d_6) δ 9.11 (br. s.), 8.2 (dd, 1H, J=11.24, 8.79 Hz), 7.9 (d, 1H, 1.95 Hz), 7.73 (dd, 1H, J=8.55, 2.2 Hz), 7.45 (d, 1H, J=8.55 Hz), 7.17 (dd, 1H, J=13.18, 6.83 Hz). ^{19}F-NMR (376 MHz, acetone-d_6) δ –125.5 (p), -150.1 (m), -155.1 (d), -160.0 (t), -164.9 (t). MS (APCI-) 355.9 m/z, 389.9 m/z, 407.9 m/z, 573.9 m/z.



PREPARATION 42

4,5-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid pentafluorophenyl ester

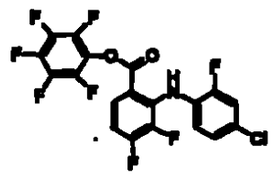
^{1}H-NMR (400 MHz, acetone-d_6) δ 8.92 (br. s.), 8.14 (dd, 1H, J=11.23, 8.79 Hz), 7.75 (d, 1H, J=1.46 Hz), 7.64 (dd, 1H, J=8.31, 2.2 Hz), 7.2 (d, 1H J=8.31 Hz), 6.76 (dd, 1H, J=13.19, 6.84 Hz), 2.24 (s, 3H). ^{19}F-NMR (376 MHz, acetone-d_6) δ –125.78 (p), -152.41 (m), -155.1 (d), -160.2 (t), -165.0 (t). MS (APCI-): 355.9 m/z, 369.9 m/z, 386.9 m/z (d), 554.0 m/z.



PREPARATION 43

2-(4-Bromo-2-fluoro-phenylamino)-3,4-difluoro-benzoic acid pentafluorophenyl ester

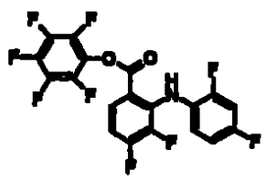
m.p. 100.9-101.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (s, 1 H), 8.07 (ddd, J = 9.3, 5.9, 2.0 Hz, 1 H), 7.54 (dd, J = 11.0, 2.2 Hz, 1 H), 7.35-7.22 (cm, 2 H), 7.04 (td, J = 8.9, 2.0 Hz, 1 H); ^{19}F-NMR (376 MHz, DMSO-d_6) δ –125.8 (t, J = 10.1 Hz); -126.7 (m), -145.3 (d, J = 20.2 Hz), -153.3 (d, J = 20.2 Hz), -157.8 (t, J = 22.7 Hz), -162.9 (t, J = 21.5 Hz); MS (APCI-) = 510.0/512.0.



PREPARATION 44

2-(4-Chloro-2-fluoro-phenylamino)-3,4-difluoro-benzoic acid pentafluorophenyl ester

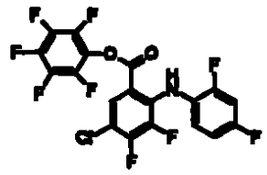
m.p. 99.0-99.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (s, 1 H), 8.07 (ddd, J = 9.0, 5.8, 2.0 Hz, 1 H), 7.45 (dd, J = 11.2, 2.2 Hz, 1 H), 7.30 (dt, J = 7.3, 9.2 Hz, 1 H), 7.19-7.08 (m, 2 H); ^{19}F NMR (376 MHz, DMSO-d_6) δ -125.6 (t, J = 10.1 Hz), -126.7 (m, 1 H), -145.6 (d, J = 15.2 Hz), -153.3 (d, J = 20.2 Hz); -157.7 (t, J = 22.8 Hz), -162.8 (t, J = 20.2 Hz); MS (APCI-) = 466.0.



PREPARATION 45

2-(2,4-Difluoro-phenylamino)-3,4-difluoro-benzoic acid pentafluorophenyl ester

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (s, 1 H), 8.07 (ddd, J = 9.0, 5.9, 2.0 Hz, 1 H), 7.34-7.12 (cm, 3 H), 7.01 (m, 1 H); ^{19}F NMR (376 MHz, DMSO-d_6) δ –116.9 (s), -122.6 (t, J = 10.1 Hz), -126.7 (m), -147.9 (d, J = 20.2 Hz), -153.5 (d, J = 20.2 Hz), -157.7 (t, J = 22.8 Hz), -162.8 (t, J = 20.2 Hz); MS (APCI-) = 450.0.



PREPARATION 46

5-Chloro-2-(2,4-difluoro-phenylamino)-3,4-difluoro-benzoic acid pentafluorophenyl ester

m.p. 92.5-93.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (s, 1 H), 8.21 (dd, J = 7.7, 2.1 Hz, 1 H), 7.34-7.24 (m, 2 H), 7.02 (m, 1 H); ^{19}F NMR (376 MHz, DMSO-d_6) δ –116.7(m), -122.4 (m), -128.1 (dd, J = 20.2, 7.6 Hz), -143.4 (d, J = 17.7 Hz), -153.2 (d, J = 20.2 Hz), -157.4 (t, J = 22.7 Hz), -162.8 (t, J = 20.2 Hz); MS (APCI-) = 483.9.



PREPARATION 47

O-(2-Vinyloxy-ethyl)-hydroxylamine

Part A: Synthesis of 2-(2-Vinyloxy-ethoxy)-isoindole-1,3-dione

Ethylene glycol vinyl ether (9.88 g, 112 mmol), triphenylphosphine (29.4 g, 112 mmol), and N-hydroxyphthalimide (18.22 g, 111.7 mmol) were combined in 300 mL of anhydrous tetrahydrofuran and cooled to 0 °C (ice bath). Diethylazodicarboxylate (18.0 mL, 114 mmol) was added dropwise over 15 min and the resultant reaction mixture was allowed to warm to ambient temperature over 18 h. The reaction mixture was concentrated to a paste and the solids were filtered and washed with chloroform. The filtrate was further concentrated and filtered again, washing the solids with chloroform. The remaining chloroform solution was concentrated to an oil. The oil was dissolved in absolute ethanol (75 mL). Scratching with a glass rod induced crystallization. The crystals were

collected and recrystallized from hot ethanol to afford colorless needles of 2-(2-vinyloxy-ethoxy)-isoindole-1,3-dione (13.8 g, 53% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (m, 2 H), 7.75 (m, 2 H), 6.46 (dd, J = 14.3, 6.7 Hz, 1 H), 4.45 (m, 2 H), 4.16 (dd, J = 14.4, 2.2 Hz), 4.02 (m 3 H).

Part B: Synthesis of *O* -(2-Vinyloxy-ethyl)-hydroxylamine

2-(2-vinyloxy-ethoxy)-isoindole-1,3-dione (13.8 g, 59.2 mmol) was dissolved in dichloromethane (45 mL). Methylhydrazine (3.2 mL, 60 mmol) was added dropwise and the resultant solution was stirred 30 min at ambient temperature. The resultant suspension was diluted with diethyl ether (150 mL) and was filtered. The filtrate was concentrated in vacuo. The residual oil was distilled (bp 60-65 °C @ 20 mm Hg) to afford the amine as a colorless liquid (4.6 g, 75% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 (dd, J = 14.3, 6.7 Hz, 1 H), 5.59 (br s, J = 2 H), 4.19 (dd, J = 14.3, 2.2 Hz, 1 H), 4.01 (dd, J = 6.8, 2.2 Hz, 1 H), 3.90-3.83 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 86.8, 73.7, 66.0.

Preparations 48-51 were prepared by the general procedure of preparation 47, part A.



PREPARATION 48

O-(2-Methoxy-ethyl)-hydroxylamine

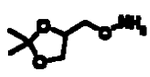
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.21 (br s, 2 H), 3.82 (m, 2 H), 3.54 (m, 2 H), 3.37 (s, 3 H).



PREPARATION 49

3-Aminooxy-2,2-dimethyl-propan-1-ol

BP 148 °C @ 20 mm Hg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.50 (s, 2H), 3.37 (s, 2H), 0.86 (s, 6H).



PREPARATION 50

O-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethyl)-hydroxylamine

^{1}H NMR (400MHz, $CDCl_3$) δ 5.50 (bs, 1 H), 4.32 (m, 1 H), 4.04 (t, J = 6.81 Hz, 1 H), 3.72 (m, 2 H), 3.67 (m, 1 H), 1.41 (s, 3 H), 1.34 (s, 3 H); MS(APCI+)=148.



PREPARATION 51

O-[2-(2-Methoxy-ethoxy)-ethyl]-hydroxylamine

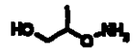
BP 95-100 °C @ 20 mm Hg; ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.96 (br s, 2 H), 3.62 (t, J = 4.3 Hz, 2 Hz), 3.55-3.47 (m, 4 H), 3.42 (m, 2 H) 3.24 (s, 3 H); MS (APCI+) = 136.1.



PREPARATION 52

2-Aminooxy-ethanol

2-Aminooxy-ethanol was prepared by the literature procedure: Dhanak, D.; Reese, C. B. J. Chem. Soc.; Perkin Trans. 1 1987, 2829.



PREPARATION 53

2-Aminooxy-propan-1-ol

2-Aminooxy-propan-1-ol was prepared according to the literature procedure (Cannon, J. G; Mulligan, P. J.; Garst, J. E.; Long, J. P.; Heintz, S. *J. Med. Chem.* 1973, *16*, 287). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 (br s, 2 H), 3.77 (m, 1 H), 3.58 (dd, J = 11.7, 2.8 Hz, 1 H), 3.52 (dd, J = 11.7, 6.9 Hz, 1 H), 1.02 (d, J = 6.4 Hz, 3 H).

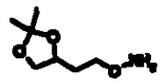


PREPARATION 54

3-Aminooxy-propan-1-ol

3-Aminooxy-propan-1-ol was prepared by the literature procedure (Ludwig, B. J.; Reisner, D. B.; Meyer, M.; Powell, L. S.; Simet, L.; Stiefel, F. J. *J. Med. Chem.*

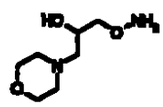
1970, *13*, 60). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (t, J = 5.8 Hz, 2 H), 3,74 (t, J = 5.8 Hz, 2 H), 1.85 (quintet, J = 5.8 Hz, 2 H).



PREPARATION 55

O-(2,2-Dimethyl-[1,3]dioxolan-4-ylethyl)-hydroxylamine

To a vigorously stirring suspension of 1,2,4-butanetriol (5.8g, 54.6 mmol) in dichloromethane (20 mL) was added 2,2-dimethoxypropane (6.8 mL, 54.6 mmol) and catalytic *p*-toluenesulfonic acid. After 5 minutes, the solution became homogenous and was allowed to stir for an additional 30 minutes. The reaction mixture was then concentrated *in vacuo* to afford (2,2-Dimethyl-[1,3]dioxolan-4-yl)-ethanol (7.72g, 96.7%). To a stirring solution of (2,2-Dimethyl-[1,3]dioxolan-4-yl)-ethanol (6.95g, 47.5 mmol), triphenylphosphine (12.5g, 47.5 mmol) and *N*-hydroxyphthalimide in freshly distilled tetrahydrofuran (200 mL) at 0 °C was slowly added (over 20 minutes) diethylazodicarboxylate. The dark red solution was allowed to stir for 2 hours at 0 °C and then allowed to warm to room temperature while stirring for 17 hours. The yellow solution was concentrated *in vacuo* and dissolved in chloroform (100mL). The solids were filtered and filtrate concentrated. This filtration was repeated twice. The remaining yellow oil was purified on silica gel eluting with hexanes-ethyl acetate (4:1) to afford 2-[2-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-ethoxy]-isoindole-1,3-dione (8.1g, 58.7%). To a stirring solution of 2-[2-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-ethoxy]-isoindole-1,3-dione (0.86g, 2.95 mmol) in dichloromethane (10mL) at 0 °C was added methylhydrazine (0.16 mL, 2.95 mmol). The resultant solution was allowed to warm to room temperature and stirred for 3 days. The resulting suspension was diluted with diethyl ether (20 mL) and filtered. The filtrate concentrated *in vacuo* to afford *O*-(2,2-dimethyl-[1,3]dioxolan-4-ylethyl)-hydroxylamine (0.36g, 75.3%): ^{1}H NMR (400MHz; $CDCl_3$) δ 4.18 (quint, 1H, J=5.9), 4.07 (dd, 1H, J=5.9, 7.8), 3.86 (t, 2H, J=6.2), 3.56 (t, 1H, J=7.6), 1.89 (m, 2H), 1.36 (s, 3H), 1.20 (s, 3H); MS(APCI+)=162.



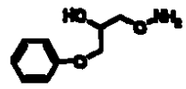
PREPARATION 56

1-Aminooxy-3-morpholin-4-yl-propan-2-ol

Step A. Synthesis of 2-(2-hydroxy-3-morpholin-4-yl-propoxy)-isoindole-1,3-dione: Triethylamine (15.0 mL, 108 mmol) was added to a solution of *N*-hydroxyphthalimide (17.1 g, 105 mmol) and 4-Oxiranylmethyl-morpholine (14.3 g, 100 mmol) in anhydrous dimethylformamide (200 mL). The resultant deep red-colored reaction mixture was heated to 85 °C for 18 h. After removal of the solvent in vacuo, the residue was diluted with ethyl acetate (200 mL) and washed with water (3 x 100 mL) and brine (2 x 75 mL). The organics were dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel (chloroform-methanol, 19:1) to afford 2-(2-Hydroxy-3-morpholin-4-yl-propoxy)-isoindole-1,3-dione (7.96 g, 25% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (m, 2 H), 7.77 (m, 2 H), 4.26 (dd, J = 10.8, 3.4 Hz, 1 H), 4.18-4.10 (m, 2 H), 3.72 (m, 4 H), 2.70-2.47 (m, 6 H); MS (APCI+) = 307.2.

Step B. Synthesis of 1-aminooxy-3-morpholin-4-yl-propan-2-ol: A solution of 2-(2-hydroxy-3-morpholin-4-yl-propoxy)-isoindole-1,3-dione (7.96 g, 26.0 mmol) in dichloromethane (50 mL) was chilled to 0 °C and treated with methylhydrazine (1.45 mL, 27.3 mmol). The reaction mixture was stirred 5 min at 0 °C and 2 h at ambient temperature. Ether (200 mL) was added, the heterogenous solution was filtered, and the collected precipitate was washed with ether (300 mL). The ethereal solutions were concentrated in vacuo, and the residue was chromatographed on silica gel. Elution with chloroform-methanol (4:1) afforded 1-aminooxy-3-morpholin-4-yl-propan-2-ol (3.21 g, 70% yield) as a colorless solid. Recrystallization (ether-dichloromethane) afforded colorless needles: mp 83-85 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.96 (br s, 2 H), 4.56 (d, J = 4.4 Hz, 1 H), 3.81 (m, 1 H), 3.53 (apparent t, J = 4.6 Hz, 4 H), 3.50-3.38 (m, 2 H), 2.41-2.30 (m, 4 H), 2.29-2.17 (m, 2 H). Anal. Calcd/found for $C_7H_{16}N_2O_3$: C, 47.71/47.54; H, 9.15/9.23; N, 15.90/15.65.

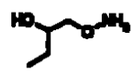
Preparations 57-62 were prepared by the general procedure of Preparation 56.



PREPARATION 57

1-Aminooxy-3-phenoxy-propan-2-ol

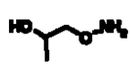
m.p. 67.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.27 (m, 2 H), 6.91 (m, 3 H), 6.06 (s, 2 H), 5.07 (d, J = 3.7 Hz, 1 H), 4.02 (m, 1 H), 3.92 (dd, J = 10.0, 4.3 Hz, 1 H), 3.84 (dd, J = 10.0, 6.1 Hz, 1 H), 3.59 (m, 2 H); MS (APCI+) = 183.0.



PREPARATION 58

1-Aminooxy-butan-2-ol

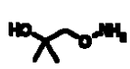
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49 (br s, 2 H), 3.78 (m, 1 H), 3.65 (dd, J = 11.2, 2.4 Hz, 1 H), 3.54-3.45 (m, 2 H), 1.42 (m, 2 H), 0.91 (t, J = 7.6 hz, 3 H); MS (APCI+) = 105.9.



PREPARATION 59

1-Aminooxy-propan-2-ol

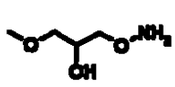
BP 85-87 °C @ 20 mm Hg; ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.96 (br s, 2H), 4.58 (d, J = 3.9 Hz, 1 H), 3.80 (m, 1 H), 3.41-3.28 (m, 2 H), 0.99 (d, J = 6.4 Hz, 3 H).



PREPARATION 60

1-Aminooxy-2-methyl-propan-2-ol

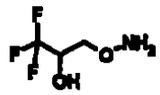
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 (br s, 2 H), 3.50 (s, 2 H), 1.15 (s, 6 H).



PREPARATION 61

1-Aminooxy-3-methoxy-propan-2-ol

^{1}H NMR (400 MHz; DMSO-d_6) δ 5.95 (2H, br, NH_2), 4.76 (1H, br, -OH), 3.72-3.78(1H, m), 3.36-3.46 (2H, m), 3.19-3.26 (2H, m), 3.19 (3H, s); MS (APCI+) = 121.9.



PREPARATION 62

1-Aminooxy-4,4,4-trifluoro-butan-2-ol

^{1}H NMR (400 MHz; $CDCl_3$) δ 5.40 (2H, br, NH_2), 3.60-4.10 (3H, m); MS (APCI+) = 145.9.



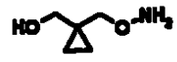
PREPARATION 63

trans-(2-Aminooxymethyl-cyclopropyl)-methanol

Step A: To a suspension of lithium aluminum hydride (7.6 g, 0.3 mol) in tetrahydrofuran (150ml) at 0 °C was added diethyl trans-1,2-cyclopropanedicarboxylate (18.6 g, 0.1mol) dropwise over a period of 15 minutes. The resultant reaction mixture was removed from the cooling bath and heated at reflux for 20 h. The reaction mixture was cooled to 0°C and quenched cautiously with water (7.7 mL), 10% aqueous sodium hydroxide (7.7 mL), and water (23 mL). The resultant solids were filtered and the filtrate was dried over sodium sulfate and concentrated under reduced pressure. The residual oil was distilled under reduced pressure to afford trans 2-hydroxymethyl-cyclopropyl)-methanol (7.5 g, 73% yield) as a colorless liquid: b.p. 142-144 °C @ 20 mm Hg.

Step B: A solution of trans 2-hydroxymethyl-cyclopropyl)-methanol (7.5g, 73 mmol), triphenylphosphine (19.3 g, 73 mmol), *N*-hydroxyphthalimide (73 mmol) in anhydrous tetrahydrofuran (200 mL) was chilled to 0°C and treated with diethyl azodicarboxylate. The resulting mixture was allowed to warm naturally to room temperature and stirred overnight. The reaction mixture was concentrated to

about 1/8 volume and filtered. The filtered precipitate was washed with ether and the combined washings and filtrate were concentrated in vacuo. The crude product was dissolved in dichloromethane. Methylhydrazine (73 mmol) was added and the reaction mixture was stirred overnight at ambient temperature. The resultant precipitate was removed by filtration. Concentration of the filtrate afforded additional precipitate which was also removed by filtration. The final filtrate was concentrated and distilled under reduced pressure to afford *trans*-(2-aminooxymethyl-cyclopropyl)-methanol (3.84 g, 45% yield) as a colorless oil: bp 183 °C @ 20 mm Hg; ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.80 (br, NH_2), 3.50-3.70 (2H, m), 3.30-3.42 (2H, m), 0.95-1.15 (2H, m), 0.40-0.60 (2H, m); MS (APCI+) = 117.9



PREPARATION 64

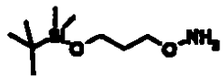
(1-Aminooxymethyl-cyclopropyl)-methanol

Step A: Diethyl 1,1-cyclopropanedicarboxylate (25 g, 0.13 mol) was added dropwise over 1 h to a stirring suspension of lithium aluminum hydride in tetrahydrofuran (150 mL) at 0°C. After addition was complete, the reaction mixture was heated at reflux for additional 18 h. The mixture was cooled to 0 °C and sequentially treated with water (10g), then 10% aqueous sodium hydroxide (10g) and water (30g). The mixture was filtered, and the filtrate was dried over potassium carbonate and concentrated under reduced pressure. Distillation provided (1-hydroxymethyl-cyclopropyl)-methanol (8.8 g, 66% yield) as a colorless viscous oil: ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.57 (4H, s), 3.26 (2H, s), 0.48 (4H, s).

Step B: (1-Hydroxymethyl-cyclopropyl)-methanol (4.08g, 0.04mol), *N*-hydroxyphthalimide (6.53g, 0.04 mol) and triphenylphosphine (10.50g, 0.04mol) were combined in anhydrous tetrahydrofuran (100 mL)and stirred at 0°C for 1.5 hours. Diethyl azodicarboxylate (6.97g, 0.04mol) was added at 0°C and the reaction mixture was stirred at room temperature overnight. Repeated concentration of the reaction mixture from chloroform and filtration of the

resulting precipitate (triphenylphosphine oxide) afforded the crude product which was further purified by silica gel chromatography. Elution with hexane/ethyl acetate (3:2) provided 2-(1-Hydroxymethyl-cyclopropylmethoxy)-isoindole-1,3-dione (5.63 g, 57% yield) as a white solid: ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.82-7.85 (2H, m), 7.74-7.78 (2H, m), 4.19 (2H, s), 3.72 (2H, s), 0.63 (4H, s)

Step C: To a stirring solution of 2-(1-Hydroxymethyl-cyclopropylmethoxy)-isoindole-1,3-dione (5.63 g, 22.8 mmol) in dichloromethane (60ml) at 0°C was added methylhydrazine (1.1 g, 23.8). The reaction mixture was stirred at room temperature overnight, filtered and concentrated under reduced pressure. Distillation afforded pure 1-Aminooxymethyl-cyclopropyl)-methanol (2.9 g, 71% yield) as a colorless oil: bp 140 °C @ 20 mm Hg; ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.00 (br s, NH_2), 3.61 (2H, s), 3.43 (2H, s), 0.49 (4H, s); MS (APCI+) = 117.9.



PREPARATION 65

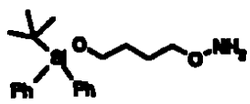
O-[3-(tert-Butyl-dimethyl-silanyloxy)-propyl]-hydroxylamine

Step A: Diisopropylethylamine (43 mL, 246 mmol) was added to a stirring solution of N-hydroxphthalimide (20.6g, 123 mmol) in dimethylformamide (95 mL). After 5 minutes, 3-bromopropanol (11.5 mL, 127 mmol) was added and the reaction mixture was heated to 80 °C for 18 h. The cooled solution was diluted with ethyl acetate (700 mL) and was washed with water (4 x 500 mL) and saturated brine (2 x 500 mL), dried over sodium sulfate and concentrated to an oil that solidified on standing to afford 2-(3-hydroxy-propoxy)-isoindole-1,3-dione (17.5 g, 65% yield) as a tan-colored solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (m, 2H), 7.74 (m, 2H), 4.36 (t, 2H, J=5.6 Hz), 3.92 (t, 2H, J=5.9 Hz), 1.98 (quintet, 2H, J=5.9 Hz).

Step B: To a solution of 2-(3-hydroxy-propoxy)-isoindole-1,3-dione (17.5 g, 79.1 mmol) and imidazole (5.92 g, 86.1 mmol) in dichloromethane (200 mL) was added tert-butyldimethylsilyl chloride (13.2 g, 86.1 mmol). After 30 min, the reaction was transferred to a separatory funnel and shaken with dilute aqueous hydrochloric acid (400 mL). The organic layer was washed with saturated

aqueous sodium bicarbonate, dried over magnesium sulfate and concentrated in vacuo to afford 2-[3-(tert-Butyl-dimethyl-silanyloxy)-propoxy]-isoindole-1,3-dione (26.3 g, 99% yield) as a viscous liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (m, 2H), 7.67 (m, 2H), 4.25 (t, 2H, J=5.9 Hz), 3.77 (t, 2H, J=6.0 Hz), 1.91 (quintet, 2H, J=6.1 Hz), 0.82 (s, 9H), 0.00 (s, 6H).

Step C: A solution of 2-[3-(tert-butyl-dimethyl-silanyloxy)-propoxy]-isoindole-1,3-dione (26.3 g, 78.3 mmol) in dichloromethane (120 mL) was cooled to 0 °C and treated with methylhydrazine (16.1 g, 78.3 mmol). The reaction mixture was stirred for 30 min at 0 °C and filtered. The filtrate was concentrated under reduced pressure, redissolved in ether, and refrigerated (4 °C) overnight. The resultant crytalline material was removed by filtration and the filtrate was concentrated under reduced pressure to afford O-[3-(tert-butyl-dimethyl-silanyloxy)-propyl]-hydroxylamine (15.95 g, 99% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (br s, 2 H), 3.74 (t, J = 6.3 Hz, 2 H), 3.67 (t, J = 6.3 Hz, 2 H), 1.78 (quintet, J = 6.3 Hz, 2 H), 0.88 (s, 9 H), 0.00 (s, 6 H); MS (APCI+) = 206.1. Anal. Calcd./Found for $C_9H_{23}NO_2Si$: C, 52.64/52.22; H, 11.29/10.94; N, 6.82/6.46.



PREPARATION 66

O-[4-(*tert*-butyl-diphenyl-silanyloxy)-butyl]-hydroxylamine

Step A: To a solution of 1,4-butanediol (5g, 55 mol) in dichloromethane (10mL) containing diisopropylethylamine (10mL) was added tert-butylchlorodiphenylsilane (5 mL, 18 mmol) dropwise under N_2 atmosphere at 18°C over 2 h. The resultant solution was stirred at room temperature for 4 hours and concentrated under reduced pressure. Purification by column chromatography with hexane/ethyl acetate (1/1) gave 4-(tert-butyl-diphenyl-silanyloxy)-butan-1-ol (10.2 g, 85% yield) as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.71 (4H, m); 7.32-7.43 (6H, m), 3.63-3.69 (4H, m), 1.83 (1H, br s), 1.59-1.71 (4H, m), 1.03 (9H, s).

Step B: 4-(tert-Butyl-diphenyl-silanyloxy)-butan-1-ol (10.0 g , 30.5 mmol), triphenylphosphine (8.0 g, 30 mmol), and *N*-hydroxyphthalimide (4.97g, 30.5 mmol) were combined in anhydrous tetrahydrofuran (200 ml) att 0 °C and the resultant solution was stirred at 0°C for 1 hour. Diethyl azodicarboxylate (5.31g, 30.5 mmol) was added at 0°C, and the reaction mixture was allowed to gradually warm to room temperature and stirred overnight. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in chloroform. Precipitation ensued, and the white solid was removed by filtration. The filtrate was concentrated and purified with column chromatography (hexane/ethyl acetate(3/1)) to afford 2-[4-(tert-butyl-diphenyl-silanyloxy)-butoxy]-isoindole-1,3-dione (11.06g, 77% yield) as colorless crystals: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (4H, s), 7.59 (4H, dd, J=7.6, 1.0 Hz), 7.39-7.43 (6H, m), 4.13 (2H, t, J = 6.4 Hz), 3.68 (2H, t, J = 5.8 Hz),1.67-1.78 (4H, m), 0.95 (9H, s).

Step C: A solution of 2-[4-(tert-butyl-diphenyl-silanyloxy)-butoxy]-isoindole-1,3-dione (11.1 g, 23.4 mmol) in dichloromethane (100ml) was treated with methylhydrazine. The reaction mixture was stirred overnight and was filtered. The filtrate was concentrated and purified by column chromatography [hexane/ethyl acetate (3.5/1)] to afford *O*-[4-(*tert*-butyl-diphenyl-silanyloxy)-butyl]-hydroxylamine (7.2 g, 90% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.66(4H, m), 7.33-7.42 (6H, m), 3.64-3.68(4H), 1.54-1.70 (4H, m), 1.02 (9H, s); MS (APCI+) =344.2.



PREPARATION 67

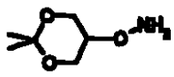
2-Aminooxy-2-methyl-propan-1-ol

Step A: To a stirring solution of *t*-butyl-*N*-hydroxycarbamate (2.38g, 17.87 mmol) in absolute ethanol (50 mL) is added potassium hydroxide (1.2g, 21.45 mmol) and ethyl-2-bromoisobutyrate (3.15 mL, 21.45 mmol). The reaction mixture was heated at reflux for 17 hours. The solids were filtered off and filtrate concentrated. The afforded residue was partitioned between diethyl ether and water. The aqueous layers were extracted twice with ether. The organic layers were collected and dried over Na_2SO_4, filtered and concentrated *in vacuo*,

affording 2-Boc-aminooxy-2-methyl-propionic acid ethyl ester as a clear oil (4.2g, 95%): ^{1}H NMR (400 MHz;$CDCl_3$) δ 7.34 (bs, 1H), 4.16 (q, 2H, J=13.9,6.6), 1.45 (s, 6H), 1.42 (s, 9H), 1.16 (t, 3H, J=7.1); MS (APCI-)=246.0.

Step B: 2-Boc-aminooxy-2-methyl-propionic acid ethyl ester (2.54g, 10.27 mmol) was dissolved in freshly distilled THF (100 mL), cooled to 0°C and charged with 2.0 M lithium borohydride solution (10.3 mL, 20.54 mmol) in THF. The ice bath was removed and reaction was heated to reflux. After 17 hours, the reaction was cooled to 0°C and quenched with methanol and concentrated *in vacuo*. The afforded residue was partitioned between ethyl acetate and 1M sodium hydroxide solution. The organic layers were washed twice with 1M sodium hydroxide solution, twice with saturated sodium chloride solution, collected and dried over Na_2SO_4, filtered and concentrated *in vacuo*, affording 2-Boc-aminooxy-2-methyl-propan-1-ol (1.50g, 71%) as a white solid: ^{1}H NMR (400 MHz;$CDCl_3$) δ 6.84 (bs, 1H), 3.37 (s, 2H), 1.45 (s, 9H), 1.18 (s, 6H); MS (APCI)=204.0.

STEP C: 2-Boc-aminooxy-2-methyl-propan-1-ol (0.21g, 1.02 mmol) was dissolved in methanol (5 mL) and charged with anhydrous hydrogen chloride gas for 1 minute. After stirring for 1 hour , the reaction mixture was concentrated *in vacuo* and to the resulting residue was added diethylether, affording white solids. The solids were washed several times with diethylether and dried *in vacuo* to afford 2-aminooxy-2-methyl-propan-1-ol as the hydrogen chloride salt (0.091g, 63%). ^{1}H NMR (400MHz;$CDCl_3$) δ 3.61 (s, 2H), 1.16 (s, 6H); MS (APCI+)=105.9.



PREPARATION 68

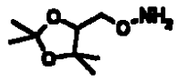
<u>*O*-(2,2-Dimethyl-[1,3]dioxan-5-yl)-hydroxylamine</u>

Step A: 2,2-Dimethyl-[1,3]dioxan-5-ol was prepared as described previously (Forbes, D.C. et. al.; *Synthesis*; 1998, *6*, 879-882). ^{1}H NMR (400MHz;DMSO-d_6)

δ 4.91 (d, 1H, J=5.1), 3.70-3.75 (m, 2H), 3.41-3.46 (m, 3H), 1.30 (s, 3H), 1.24 (s, 3H); MS (APCI+)=132.9.

Step B: To a stirring solution of 2,2-dimethyl-[1,3]dioxan-5-ol (1.50g, 11.35 mmol), *N*-hydroxyphthalimide (1.85g, 11.35 mmol) and triphenylphosphine (2.98g, 11.35 mmol) in anhydrous tetrahydrofuran (30 mL) at 0°C was added diethyl azodicarboxylate (2.3 mL, 14.75 mmol). The resultant solution was allowed to warm to room temperature. After stirring for 3 hours, the mixture was concentrated *in vacuo* and charged with chloroform affording white solids. The solids were filtered off and filtrate was collected and concentrated. The residue was purified via silica column chromatography (4:1 hexanes/ethyl acetate) affording 2-(2,2-dimethyl-[1,3]dioxan-5-yloxy)-isoindole-1,3-dione as clear crystals (1.74g, 55% over 2 steps): ^{1}H NMR (400MHz;DMSO-d_6) δ 7.83 (s, 4H), 4.11-4.12 (m, 1H), 4.04-4.09 (m, 2H), 3.92-3.96 (m, 2H), 1.32 (s, 3H), 1.25 (s, 3H); MS (APCI+)=278.0.

Step C: To a stirring solution of 2-(2,2-dimethyl-[1,3]dioxan-5-yloxy)-isoindole-1,3-dione (1.72g, 6.20mmol) in dichloromethane (15 mL) at 0°C under nitrogen was added methylhydrazine (0.36 mL, 6.82 mmol) and allowed to warm to room temperature. After stirring for two hours the reaction mixture was concentrated *in vacuo* and charged with diethylether. The solids were filtered off and the filtrate was collected and concentrated to afford *O*-(2,2-dimethyl-[1,3]dioxan-5-yl)-hydroxylamine as a yellow oil (0.97g, 100%). ^{1}H NMR (400MHz;DMSO-d_6) δ 5.98 (bs, 2H), 3.84-3.87 (m, 2H), 3.66-3.68 (m, 2H), 3.30-3.35 (m, 1H), 1.29 (s, 3H), 1.22 (s, 3H); MS (APCI+)=147.9.



PREPARATION 69

<u>*O*-(2,2,5,5-Tetramethyl-[1,3]dioxolan-4-ylmethyl)-hydroxylamine</u>

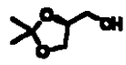
Step A: To a stirring solution of *N*-hydroxyphthalimide (Aldrich, 1.63g, 10.0 mmol) in anhydrous ethanol (50 mL) was added 1-bromo-3-methyl-but-2-ene (Aldrich, 1.4 mL, 12.0 mmol) and potassium hydroxide (0.67g, 12.0 mmol). After the reaction was allowed to stir at 50 °C for 4 hours, it was concentrated *in vacuo*

and then dissolved in ethyl acetate and partitioned with water. The organic layer was washed twice with water, twice with saturated sodium chloride solution, collected and dried over Na_2SO_4, filtered and concentrated *in vacuo*, affording a white solid. The collected solid was purified via silica column in 10% methanol in dichloromethane to afford 2-(3-methyl-but-2-enyloxy)-isoindole-1,3-dione (0.53 g, 23%): ^{1}H NMR (400MHz;DMSO-d_6) δ 7.81 (s, 4H), 5.38 (t, 1H, J=1.5), 4.57 (d, 2H, J=7.6). 1.67 (s, 3H), 1.62 (s, 3H); MS (APCI+)=232.0

Step B: 2-(3-Methyl-but-2-enyloxy)-isoindole-1,3-dione was dissolved in a *t*-butanol/THF/H_2O solution (10mL/3mL/1mL) and charged with *N*-methylmorpholine *N*-oxide (0.085g, 0.73 mmol) and a catalytic amount of potassium osmate dihydrate. After stirring for 17 hours the reaction was diluted with a saturated solution of sodium metabisulfite and partitioned with ethyl acetate. The organic layer was washed twice with saturated solution of sodium metabisulfite, twice with saturated sodium chloride solution, collected and dried over Na_2SO_4, filtered and concentrated *in vacuo* affording 2-(2,3-dihydroxy-3-methyl-butoxy)-isoindole-1,3-dione as a clear oil, which was charged with dichloromethane (10 mL), 2,2-dimethoxypropane (0.12 mL, 0.75 mmol) and a catalytic amount of *p*-toluenesulfonic acid. After stirring for 17 hours, the reaction was concentrated *in vacuo*, and partitioned between ethyl acetate and water. The organic layer was washed twice with water, once with saturated sodium chloride solution, collected and dried over Na_2SO_4, filtered and concentrated *in vacuo*, affording 2-(2,2,5,5-tetramethyl-[1,3]dioxolan-4-ylmethoxy)-isoindole-1,3-dione as a light brown solid (0.158g, 77.1%): ^{1}H NMR (400 MHz;DMSO-d_6) δ 7.82 s, (4H), 4.12-4.26 (m, 2H), 4.04-4.07 (m, 1H), 1.22 (s, 9H), 1.17 (s, 3H), 0.97 s(3H).

Step C: 2-(2,2,5,5-tetramethyl-[1,3]dioxolan-4-ylmethoxy)-isoindole-1,3-dione (0.158g, 0.52 mmol) was dissolved in dichloromethane (3 mL), cooled to 0 °C, and charged with methylhydrazine (30μL, 0.57 mmol). The ice bath was removed and the reaction was allowed to stir at ambient temperature for 1 hour. The reaction mixture was diluted with diethylether and the solids were filtered off and filtrate concentrated *in vacuo* to afford *O*-(2,2,5,5-tetramethyl-[1,3]dioxolan-4-ylmethyl)-hydroxylamine as a yellow oil (0.042g, 46%). ^{1}H NMR (400

MHz;DMSO-d_6) δ 6.06 (bs, 2H), 3.84-3.87 (m, 1H), 3.50-3.59 (m, 2H), 1.26 (s, 3H), 1.19 (s, 3H), 1.16 (s, 3H), 0.94 (s, 3H); MS (APCI+)=176.9.



PREPARATION 70

(*S*)-(+)-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-methanol

Step A: To a stirring suspension of D-Mannitol (1.82 g, 10.0 mmol) in tetrahydrofuran (21 mL) and dimethylformamide (9 mL) was added *p*-toluenesulfonic acid monohydrate (0.02 g, 0.1mmol,) at ambient temperature, followed by 2,2-dimethoxypropane (2.8 ml, 0.023 mole). The reaction mixture was stirred for 18 h at room temperature, then additional 2,2-dimethoxypropane (0.3 ml, 2.4 mmol) was added. The suspension was heated to 40-45 °C, and stirred for 2 hrs. Sodium bicarbonate (1.8 g, 0.016 mol) was added to neutralize the acid and the mixture was stirred for 30 minutes. The excess Na_2CO_3 was filtered and washed with tetrahydrofuran (5ml). The filtrate was concentrated. To the remaining light yellow oil was added toluene (15mL) and the mixture was stirred at 3-5 °C until a light-yellow gelatinous solid formed. The solid was filtered and washed with hexane (2 x 5mL). The product was dried in a vacuum oven for 18 h to give 1,2:5,6-Di-*O*-isopropylidene-D-mannitol (1.24 g, 47.3%) as an off-white solid, mp 110-113 °C.

Step B: To a solution of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (50 g, 0.191 mol) in water (700 mL), was added solid sodium bicarbonate (20 g). The resultant solution was stirred until all the solid dissolved, and then cooled in an ice-water bath. Solid sodium periodate (81.5 g, 0.381 mol) was slowly added to the solution portionwise. Gas evolution observed. The white mixture was stirred at ambient temperature for 2 hrs. Solid sodium chloride (30 g) was added, and the mixture was stirred for 15 min. The white solid was filtered. The filtrate was cooled in an ice-water bath. Solid sodium borohydride was added slowly. Gas bubble evolved. The mixture was warmed to ambient temperature, and stirred overnight. The milky mixture turned to a clear solution. The aqueous solution was extracted with dichloromethane (3 X). The organic solution was washed with brine, and dried over magnesium sulfate. The solvent was removed *in vacuo* to give (*S*)-(+)-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-methanol as a colorless oil, which was dried

under high vacuum at ambient temperature overnight, 34.82 g (60%); MS (APCI+) = 133 (M^++1).



PREPARATION 71

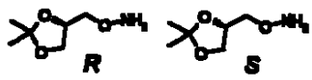
(*R*)-(+)-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-methanol

Step A: To a solution of L-ascorbic acid (83.9 g, 0.477 mole) in water (600 mL) was added Pd/C (10%, 8.3 g). The mixture was subjected to hydrogenation in a Parr hydrogenator at 48 psi, 18 °C for 62 hrs. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* to afford L-gulonic γ-lactone (81.0 g, 96%) as an off-white solid, after drying at 50 °C in a vacuum oven for 18 hrs: m.p. 182-184 °C.

Step B: L-Gulonic γ-lactone (25.0 g, 140.3 mmol) was dissolved in mixture of tetrahydrofuran (140 mL) and dimethylformamide (200 mL). *p*-Toluenesulfonic acid monohydrate (2.67 g, 14.0 mmol) was added and the reaction mixture was cooled to 0 – 5 °C in an ice-water bath. 2,2-dimethoxypropane (22.4 mL, 182.4 mmol) was added dropwise and the reaction mixture was stirred at ambient temperature for 18 hours. The mixture was neutralized with solid sodium carbonate (24.0 g), and stirred for 1 hour. The solid was filtered and washed with tetrahydrofuran. The THF was removed under vacuo, and DMF by distillation under high vacuum. The resulting orange solid was triturated with toluene (300 mL), filtered, washed with toluene (20 mL), and dried in a vacuum oven at 40 °C for 3 days, to yield 5,6-Isopropylidene-L-gulonic Acid γ-lactone (28.9 g, 94%) as a pale orange solid: mp 155-158 °C; MS(APCI+) = 219.0 (M^++1).

Step C: To a stirring suspension of 5,6-*O*-isopropylidene-L-gulono-1,4-lactone (15.16 g, 69.5 mmol) in water (0.3 L) was added solid sodium periodate in small portions at 3-5°C. The pH of the mixture was adjusted to 5.5 with 1N aqueous sodium hydroxide. The suspension was stirred for 2 hrs at ambient temperature, then saturated with sodium chloride (20.0 g) and filtered. To the filtrate, at 3-5°C, was added sodium borohydride (10.5 g, 0.278 mol) in small portions. The reaction

mixture was stirred for 18 h at ambient temperature. Acetone (100 mL) was added to destroy the excess of sodium borohydride, and the stirring was continued for 30 minutes. The acetone was removed under reduced pressure and the aqueous residue was extracted with dichloromethane (3 x 300 mL) and EtOAc (3 x 300 mL). The combined organic layers were dried over magnesium sulfate, filtered, and evaporated to give *(R)*-(+)-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-methanol (5.07g, 55.7%) as a colorless clear liquid: MS(APCI+) = 132.9 (M^++1).



PREPARATION 72

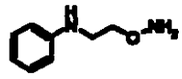
Preparation of *(R)*-O-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-hydroxylamine and *(S)*-O-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-hydroxylamine

(R)-O-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-hydroxylamine and *(S)*-O-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-hydroxylamine were prepared from *(S)*-(+)-(2,2-dimethyl-[1,3]dioxolan-4-yl)-methanol and *(R)*-(-) -(2,2-dimethyl-[1,3]dioxolan-4-yl)-methanol respectively by the following procedure:

Step A: A 3-L round-bottomed flask equipped with mechanical stirrer and additional funnel was charged with *N*-hydroxyphthalimide (68.0 g, 0.416 mol) and tetrahydrofuran (1.2 L) under nitrogen atmosphere. To this solution was added triphenylphosphine (109.2 g, 0.416 mol) and *(R)*- or *(S)*-(2,2-dimethyl-[1,3]dioxolan-4-yl)-methanol (55.0 g, 0.416 mol). The mixture was cooled to 3-5°C and diethyl azodicarboxylate (85.2 mL, 0.541 mol) was added dropwise, while keeping the inner temperature below 15 ^{o}C. The reaction mixture was warmed to ambient temperature, and stirred for 18 hrs. The tetrahydrofuran was evaporated under reduced pressure. To the remaining orange solid was added dichloromethane (0.5 L) and the mixture was stirred for 1h. The white solid (Ph_3PO) was filtered and washed with dichloromethane (0.1 L). The solvent was removed and ethanol (0.5 L) was added to the resulting solid. The mixture was stirred for 2 h at 3-5 ^{o}C. The white solid was filtered, washed with a small amount of cold EtOH and dried in vacuum oven at 40 ^{o}C to give *(S)*- or *(R)*-2-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethoxy)-isoindole-1,3-dione (112.5 g, 97%) as a white solid: ^{1}H NMR ($CDCl_3$): δ 1.33 (s, 3H), 1.99 (s, 3H), 3.96 (m, 1H), 4.15

(m, 2H), 4.30 (m, 1H), 4.48 (m, 1H), 7.59 (m, 2H), 7.84 (m, 2H); MS (APCI+) = 278 (M^++1).

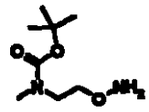
Step B: To a stirring solution of *(S)*- or *(R)*-2-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethoxy)-isoindole-1,3-dione (74.9 g, 0.27 mol) in dichloromethane (480 mL) at 3-5°C was added methylhydrazine (15.8 mL, 0.29 mole) dropwise. The color of the suspension turned from yellow to white. The cooling bath was removed and the mixture was stirred for 2 hrs at ambient temperature. The resulting suspension was concentrated on a rotary evaporator. To the white solid was added ether (0.5 L) and the resulting mixture was stirred for 1.5 h at ambient temperature. The white precipitate was filtered and washed with ether (0.2L). The filtrate was concentrated on rotary evaporator to give *(S)*- or *(R)*-O-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-hydroxylamine (39.0 g, 98.3 %): ^{1}H NMR ($CDCl_3$): δ 1.35 (s, 3H), 1.42 (s, 3H), 3.73 (m, 3H), 4.05 (m, 1H), 4.33 (m, 1H), 5.39 (m, 2H); MS (APCI+) = 148.1 (M^++1)



PREPARATION 73

O-(2-Phenylamino-ethyl)-hydroxylamine: hydrochloride

O-(2-Phenylamino-ethyl)-hydroxylamine was prepared from 2-Phenylamino-ethanol by the general procedure of Preparation 48 and was isolated as the hydrochloride salt by precipitation from etheral hydrogen chloride. ^{1}H NMR (DMSO-d_6): δ 7.12 (t, J = 7.7 Hz, 2 H), 6.72-6.61 (m, 3 H), 4.16 (t, J = 5.4 Hz, 2 H), 3.35 (t, J = 5.4 Hz, 2 H); MS (APCI+) = 153.1 (M^++1).



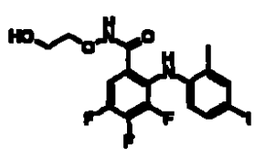
PREPARATION 74

(2-Aminooxy-ethyl)-methyl-carbamic acid tert-butyl ester

Step A: (2-Hydroxy-ethyl)-methyl-carbamic acid tert-butyl ester was prepared as previously described: Mewshaw, R. E.; et. al. *J.Med.Chem.* 1999, *42*, 2007.

Step B: Diethylazodicarboxylate was added dropwise over 45 min to a stirring solution of (2-hydroxy-ethyl)-methyl-carbamic acid tert-butyl ester (7.10 g, 40.5 mmol), N-hydroxyphthalimide (7.17 g, 44.0 mmol) and triphenylphosphine (11.5 g, 43.8 mmol) in tetrahydrofuran (150 mL). The resultant reaction mixture was stirred 22 h at ambient temperature and was concentrated in vacuo to a thick oil. Chloroform (200 mL) was added and the resultant solution was chilled to affect crystallization of diethyl 1,2-hydrazaine dicarboxylate. The precipitate was filtered and the filtrate was concentrated and further diluted with hexanes. A single crystal of triphenylphosphine oxide was added. The resultant crystals of triphenylphosphine oxide were removed by filtration and the filtrate was concentrated in vacuo and chromatographed on silica gel to afford [2-(1,3-dioxo-1,3-dihydro-isoindol-2-yloxy)-ethyl]-methyl-carbamic acid tert-butyl ester (12.8 g, 98% yield) as a colorless oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (bs, 4 H), 8.55 (bs, H), 4.24 (t, J =5.5 Hz, 2 H), 3.50 br t, J = 5.4 Hz, 2 H), 2.92 and 2.88 (br s, 3 H), 1.39 and 1.36 (br s, 9 H).

Step C: A solution of [2-(1,3-dioxo-1,3-dihydro-isoindol-2-yloxy)-ethyl]-methyl-carbamic acid tert-butyl ester (4.50 g, 14.0 mmol) in dichloromethane (40 mL) was treated with methylhydrazine (0.78 mL, 14.7 mmol) and the reaction mixture was stirred 6 h at ambient temperature. Diethyl ether (80 mL) was added and the heterogeneous solution was allowed to stand overnight. The precipitate was removed by filtration and was washed with ether (80 mL). The filtrate was further concentrated and the resultant precipitate was filtered and the second filtrate concentrated to afford (2-Aminooxy-ethyl)-methyl-carbamic acid tert-butyl ester (2.83 g) as a viscous oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (t, J = 5.2 Hz, 2 H), 5.45 (br s, NH_2), 3.46 and 3.42 (br s, 2 H), 2.86 br s, 3 H), 1.25 (br s, 9 H); MS (APCI+) = 191.1.



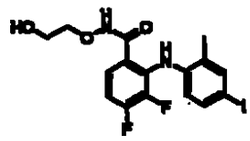
EXAMPLE 1

3,4,5-Trifluoro-*N*-(2-hydroxy-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

Step A: To a solution comprised of 2-(4-iodo-2-methyl-phenylamino)-3,4,5-trifluoro-benzoic acid (3.60 g, 8.84 mmol), O-(2-vinyloxyethyl)hydroxylamine (1.09 g, 10.5 mol) and diisopropylethylamine (2.80 mL, 16.0 mmol) in dichloromethane (50 mL) was added benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium-hexafluorophosphate (5.26 g, 10.1 mmol). The resultant solution was stirred 90 min at ambient temperature. The reaction mixture was diluted with ether (100 mL) and washed with water (3 x 50 mL) and saturated brine (50 mL). The organics were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography to afford 2-(4-iodo-2-methyl-phenylamino)-3,4,5-trifluoro-N-(2-vinyloxyethoxy) benzamide (3.17 g, 73 %) as a pale-yellow foam.

Step B: A solution of 2-(4-iodo-2-methyl-phenylamino)-3,4,5-trifluoro-N-(2-vinyloxyethoxy)-benzamide (3.00 g, 6.09 mmol) in ethanol (80 mL) was treated with 1 M aqueous hydrochloric acid (16 mL, 16 mol). The resultant solution was stirred for 2.5 h at ambient temperature. Water (50 mL) was added and the slurry was filtered. The solids were washed with ethanol-water (1:1, 150 mL) and recrystallized from methanol-acetone to afford N-(2-hydroxyethoxy)-2-(4-iodo-2-methyl-phenylamino)-3,4,5-trifluoro- benzamide (2.12 g, 75%): m.p. 205-207 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.85 (br s, 1 H), 8.13 (s, 1 H), 7.54 (dd, J = 8.9, 8.7 Hz, 1 H), 7.47 (d, J = 1.0 Hz, 1 H), 7.32 9d, J = 8.5 Hz, 1 H), 6.41 (dd, J = 8.1, 5.0 Hz, 1 H), 4.69 (br s, 1 H), 3.79 (br s, 2 H), 3.52 (br s, 2 H), 2.20 (s, 3 H); MS (APCI+) = 467.1; MS (APCI-) = 465.1; Anal. Calcd/found for $C_{16}H_{14}F_3IN_2O_3$: C, 41.22/41.28; H, 3.03/2.91; N, 6.01/5.79.

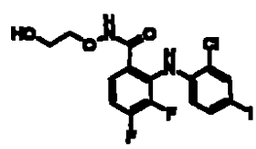
Examples 2-11 were prepared by the general procedure of Example 1.



EXAMPLE 2

3,4-Difluoro-*N*-(2-hydroxy-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

MP 181-183 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.87 (s, 1 H), 8.50 (s, 1 H), 7.49 (s, 1 H), 7.40 (dd, 7.3, 6.6 Hz, 1 H), 7.35 (dd, J = 8.3, 1.7 Hz, 1 H), 7.16 (dt, J =7.3, 9.3 Hz, 1 H), 6.46 (dd, J = 8.5, 5.6 Hz, 1 H), 4.70 (br s, 1 H), 3.81 (br s, 2 H), 3.54 (br s, 2 H), 2.21 (s, 3 H); MS (APCI+) = 449.1; MS (APCI-) = 447.1; Anal. Calcd/found for $C_{16}H_{15}F_2IN_2O_3$: C, 42.88/42.94; H, 3.37/3.39; N, 6.25/6.05.



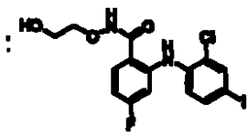
EXAMPLE 3

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-*N*-(2-hydroxy-ethoxy)-benzamide

Method A: By the general procedure of Example 1: m.p. 173-175 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.93 (br s, 1 H), 8.85 (br s, 1 H), 7.76 (d, J = 1.7 Hz, 1 H), 7.48 (dd, J = 8.6, 1.7 Hz, 1 H), 7.44 (dd, J =8.5, 6.2 Hz, 1 H), 7.25 (dt, J = 8.5, 9.3 Hz, 1H), 6.58 (dd, J = 8.5, 6.4 Hz, 1 H), 4.70 (br s, 1 H), 3.86 (br s, 2 H), 3.56 (br d, J = 3.9 Hz, 2 H); MS (APCI+) = 469.0; MS (APCI-) = 467.0; Anal. Calcd/found for $C_{15}H_{12}ClF_2IN_2O_3$: C, 38.45/38.60; H, 2.58/2.53; N, 5.98/5.91; F, 8.11/8.08; I, 27.08/27.43.

Method B: To a solution of 2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-benzoic acid pentafluorophenyl ester (10.0g, 17.4 mmol) in anhydrous dimethylformamide (36 mL) was added 2-(aminooxy)-ethanol (1.6 g, 20.8 mmol) and N,N-diisopropylethylamine (6.0 mL, 34.8 mmol). The resultant solution was stirred at ambient temperature for 16 h. The reaction mixture was concentrated to 20% volume then diluted with ethyl acetate (360 mL). The resultant solution was

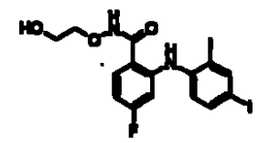
washed with water (6 x 60 mL) and brine (2 x 60 mL). The organics were dried over anhydrous magnesium sulfate and concentrated under reduced pressure to afford a white solid that was purified on silica gel. Elution with ethyl acetate-methanol (9:1) afforded 2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-*N*-(2-hydroxy-ethoxy)-benzamide (7.31 g, 90%) as a white solid. Recrystallization from methanol afforded analytically pure material, identical in all respects to the material prepared by method A.



EXAMPLE 4

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-ethoxy)-benzamide

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88 (br s, 1 H), 9.81 (s, 1 H), 7.85 (d, J = 2.0 Hz, 1 H), 7.64 (m, 1 H), 7.60 (dd, J = 8.5, 1.9 Hz, 1 H), 7.31 (d, J = 8.3 Hz, 1 H), 7.00 (dd, J = 11.7, 2.5 Hz, 1 H), 6.75 (td, J = 8.5, 2.5 Hz, 1 H), 4.73 br s, 1 H), 3.90 (t, J = 4.6 Hz, 2 H), 3.60 (br t, J = 4.2 Hz, 2 H); MS (APCI+) = 451.0; MS (APCI-) = 449.0; Anal. Calcd/found for $C_{15}H_{13}ClF_1IN_2O_3$: C, 39.98/40.07; H, 2.91/2.83; N, 6.22/6.11.



EXAMPLE 5

4-Fluoro-N-(2-hydroxy-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (br s, 1 H), 8.67 (s, 1 H), 7.60 (d, J = 1.7 Hz, 1 H), 7.51 (dd, J = 8.4, 1.7 Hz, 1 H), 7.37 (dd, J = 7.8, 6.6 Hz, 1 H), 7.02 (d, 8.3 Hz, 1 H), 6.59 (dd, J = 12.2, 2.4 Hz, 1 H), 6.41 (m, 1 H), 4.08 (t, J = 4.2 Hz, 2 H), 3.80 (t, J = 4.2 Hz, 2 H), 2.22(s, 3 H); MS (APCI+) = 431.0; MS (APCI-) = 429.0.

EXAMPLE 6

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(2-hydroxy-ethoxy)-benzamide

Yield: 96%; m.p. 183-184.5 °C; ^{1}H-NMR (400 MHz; DMSO-d_6) δ 8.46 (s, 1H), 7.73 (d, 1H, J=1.7 Hz), 7.58 (m, 1H), 7.44 (dd, 1H, J=8.5, 2.0 Hz), 6.54 (dd, 1H, J=8.5, 5.4 Hz), 4.70 (broad s, 1H), 3.84 (m, 2H), 3.54 (s, 2H); ^{19}F-NMR (376 MHz; DMSO-d_6) δ -137.03 (d, 1F, J=20.2 Hz), -141.04 (s, 1F), -154.73 (s, 1F); MS (APCI$^+$) 486.9 (M+1, 100); MS (APCI$^-$) 484.9 (M-1, 50), 424.9 (100); IR (KBr) 3337 (O-H stretch), 1652 (C=O stretch), 1502 cm^{-1}. Anal. Calcd./found for $C_{15}H_{11}ClF_3IN_2O_3$: C, 37.02/37.16; H, 2.28/2.29; N, 5.76/5.49.

EXAMPLE 7

5-Chloro-3,4-difluoro-N-(2-hydroxy-ethoxy)-2-(4-iodo-phenylamino)-benzamide

Yield: 21%; m.p. 174-176 °C; ^{1}H-NMR (400 MHz; DMSO-d_6) δ 11.72 (s, 1H), 8.47 (s, 1H), 7.53 (d, 1H, J=7.1 Hz), AB[7.43 (d, 2H, J=8.3 Hz), 6.63 (d, 2H, J=7.6 Hz)], 4.67 (s, 1H), 3.74 (s, 2H), 3.49 (s, 2H); ^{19}F-NMR (376 MHz; DMSO-d_6) δ -134.59 (s, 1F), -139.07 (d, 1F, J=17.7 Hz); MS (APCI$^+$)469.0 (M+1, 100); MS (APCI$^-$) 467.0 (M-1, 40), 406.9 (100); IR (KBr) 1636 cm^{-1} (C=O stretch). Anal.Calcd./found for $C_{15}H_{12}ClF_2IN_2O_3$: C, 38.45/38.61; H, 2.58/2.43; N, 5.98/5.94.

EXAMPLE 8

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-ethoxy)-benzamide

Yield: 96%; m.p. 117-119 °C; ^{1}H-NMR (400 MHz; DMSO-d_6) δ 11.83 (s, 1H), 9.62 (s, 1H), 7.69 (d, 1H, J=10.5 Hz), 7.60 (m, 1H), 7.49 (d, 1H, J=8.6 Hz), 7.27 (m, 1H), 6.84 (d, 1H, J=11.2 Hz), 6.70 (m, 1H), 4.73 (broad s, 1H), 3.90 (m, 2H), 3.60 (m, 2H); ^{19}F-NMR (376 MHz; DMSO-d_6) δ -106.74 (s, 1F), -124.58 (s, 1F); MS (APCI$^+$) 435.0 (M+1, 100); MS (APCI$^-$)433.0 (M-1, 82), 373.0 (100); IR (KBr) 1638 (C=O stretch), 1597 cm^{-1}. Anal.Calcd./found for $C_{15}H_{12}F_2IN_2O_3$: C, 41.49/41.52; H, 3.02/2.97; N, 6.45/6.18.

EXAMPLE 9

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-ethoxy)-benzamide

Method A: By the general procedure of example 32. Yield: 54%; m.p. 155-156 °C; ^{1}H-NMR (400 MHz; DMSO-d_6) δ 11.83 (s, 1H), 8.69 (s, 1H), 7.56 (dd, 1H, J=11.0, 1.5 Hz), 7.36 (m, 2H), 7.19 (m, 1H), 6.65 (m, 1H), 3.82 (s, 2H), 3.55 (s, 2H); ^{19}F-NMR (376 MHz; DMSO-d_6) δ -128.18 (s, 1F), -133.11 (s, 1F), -144.16 (s, 1F); MS (APCI$^+$) 453.0 (M+1, 100); MS (APCI$^-$) 451.0 (M-1, 100); IR (KBr) 3349 (O-H stretch), 1641 (C=O stretch), 1610 cm^{-1}. Anal.Calcd./found for $C_{15}H_{12}F_3IN_2O_3$: C, 39.84/39.99; H, 2.67/2.81; N, 6.20/6.20.

EXAMPLE 10

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-ethoxy)-benzamide

Yield: 96%; m.p. 180-180.5 °C; ^{1}H-NMR (400 MHz; DMSO-d_6) δ 11.89 (s, 1H), 8.68 (s, 1H), 7.59 (m, 2H), 7.34 (d, 1H, J=6.8 Hz), 6.72 (m, 1H), 4.70 (broad s, 1H), 3.82 (m, 2H), 3.55 (s, 2H); ^{19}F-NMR (376 MHz; DMSO-d_6) δ -127.72 (s, 1F), -134.13 (s, 1F), -140.35 (d, 1F, J=17.7 Hz); MS (APCI$^+$) 487.0 (M+1, 100); MS (APCI$^-$) 484.9 (M-1, 63), 424.9 (100); IR (KBr) 3333 (O-H stretch), 1643 (C=O stretch), 1609, 1490 cm^{-1}. Anal.Calcd./found for $C_{15}H_{11}ClF_3IN_2O_3$: C, 37.02/37.30; H, 2.28/2.23; N, 5.76/5.69.

EXAMPLE 11

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-ethoxy)-benzamide

Yield: 100%; m.p. 189-190 °C; ^{1}H-NMR (400 MHz; DMSO-d_6) δ 11.89 (s, 1H), 8.70 (s, 1H), 7.69 (d, 1H, J=6.1 Hz), 7.57 (d, 1H, J=10.7 Hz), 7.34 (d, 1H, J=7.8 Hz), 6.73 (m, 1H), 4.70 (broad s, 1H), 3.81 (s, 2H), 3.54 (s, 2H); ^{19}F-NMR (376 MHz; DMSO-d_6) δ -126.43 (s, 1F), -127.65 (s, 1F), -140.20 (d, 1F, J=17.7 Hz); MS (APCI$^+$) 533.0 (95), 531.0 (M+1, 100); MS (APCI$^-$) 531.0 (40), 529.0 (M-1, 42), 470.9 (95), 468.9 (100); IR (KBr) 3341 (O-H stretch), 1647 (C=O stretch), 1606, 1509, 1484 cm^{-1}. Anal.Calcd./found for $C_{15}H_{11}BrF_3IN_2O_3$: C, 33.93/33.89; H, 2.09/2.02; N, 5.27/5.13.

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EXAMPLE 12

4,5-Difluoro-N-(2-hydroxy-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

To a solution of 4,5-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzoic acid pentafluorophenyl ester (2.96 g, 0.533 mmol) in dimethylformamide at rt was added diisopropylethylamine (0.184 mL, 1.1 mmol). After the reaction stirred overnight, the reaction mixture was concentrated to about half volume. The solution was diluted with ether (30 mL) then washed with water (4 x 10 mL) and brine (10 mL). The ether layer was dried over magnesium sulfate and the resultant mixture was filtered. The filtrate solvent was removed *in vacuo* to obtain an oily solid. The oily solid was purified by flash chromatography (35 g silica gel), eluting with a gradient of ethyl acetate in hexanes. The solvent was removed *in vacuo* to obtain a solid which was dried on a vacuum pump overnight. Recrystalization from hexanes-acetone afforded 4,5-difluoro-N-(2-hydroxy-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide as a solid (0.107g, 45 % yield): m.p. 151.2-152.5 C; ^{1}H-NMR (400 MHz, $(CD_3)_2CO$) δ 9.22 (br. S, 1H), 7.63 (m, 2H), 7.53 (dd, 1H, J=8.3, 1.95 Hz), 7.14 (d, 1H, J=8.3 Hz), 6.41 (m, 1H), 4.03 (t, 2H, J=4.4 Hz), 3.69 (t, 2H, J=4.88 Hz), 2.23 (s, 3H); ^{19}F-NMR (376 MHz, $(CD_3)_2CO$) δ -132.75, -152.61; MS 478.9 m/z (APCI+); 476.9 m/z (APCI-). Anal. Calcd. for $C_{16}H_{15}F_2IN_2O_3$: C, 42.88; H, 3.39; N, 6.25. Found: C, 42.79; H, 3.19; N, 6.02.

Examples 13 to 20 were prepared by the general procedure of Example 12.

EXAMPLE 13

5-Bromo-3,4-difluoro-N-(2-hydroxy-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

m.p. 208.2-209.6 C; ^{1}H-NMR (400 MHz, $(CD_3)_2CO$) δ 8.62 (br. S, 1H), 7.79 (dd, 1H, J=7.08, 1.47 Hz), 7.55 (s, 1H), 7.42 (d, 1H, J=8.79 Hz), 6.65 (dd, 1H, J=8.30, 5.86 Hz), 4.02 (t, 2H, J=4.64 Hz), 3.67 (t, 2H, J=4.64 Hz), 2.32 (s, 3H); ^{19}F-NMR (376 MHz, $(CD_3)_2CO$) δ -126.85, -139.3 (d, J=15.16 Hz). Anal. Calcd. for $C_{16}H_{14}BrF_2IN_2O_3$: C, 36.46; H, 2.68; N, 5.31; F,

7.21; Br, 15.16; I, 24.08. Found: C, 36.67; H, 2.62; N, 5.23; F, 7.23; Br, 15.32; I, 23.3.

EXAMPLE 14

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-ethoxy)-benzamide

m.p. 190.2-200.2 C; ^{1}H-NMR (400 MHz, $(CD_3)_2CO$) δ 11.11 (br s, 1H), 8.92 (br. s., 1H), 7.84 (dd, 1H, J=6.84, 2.2 Hz), 7.76 (d, 1H, J=1.95 Hz), 7.54 (dd, 1H, J=8.54, 6.59 Hz), 6.77 (dd, 1H, J=8.54, 6.59 Hz), 4.40 (t, 2H, J=4.39 Hz), 3.69 (t, 2H, J=4.89 Hz). ^{19}F-NMR (376 MHz, $(CD_3)_2CO$) δ -126.16, -137.47 (d, J=17.69 Hz); MS 546.9 m/z, 548.9 m/z (AP+); 544.9 m/z, 546.9 m/z (AP-). Anal. Calcd. for $C_{15}H_{11}BrClF_2IN_2O_3$: C, 32.91; H, 2.03; N, 5.12; F, 6.94; Br, 14.58; I, 23.18. Found: C, 32.94; H, 1.95; H, 5.30; F, 6.87; Br, 14.79; I, 22.91.

EXAMPLE 15

5-Chloro-3,4-difluoro-N-(2-hydroxy-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

m.p. 199.1-200.8 C; ^{1}H-NMR (400 MHz, $(CD_3)_2CO$) δ 8.57 (br. S, 1H), 7.68 (dd, 1H, J=7.32, 2.2 Hz), 7.55 (s, 1H), 7.41 (dd, 1H, J=8.3, 1.71 Hz), 6.64 (dd, 1H, J=8.3, 5.86), 4.02 (t, 2H, J=4.63 Hz), 3.67 (t, 2H, J=4.88 Hz), 2.32 (s, 3H). ^{19}F-NMR (376 MHz, $(CD_3)_2CO$) δ -134.75, -139.56 (t, J=15.17 Hz); MS 483.0 m/z (AP+); 481.0 m/z (AP-). Anal. Calcd. for $C_{16}H_{14}ClF_2IN_2O_3$: C, 39.82; H, 2.92; N, 5.8; F, 7.87; Cl, 7.35; I, 26.29. Found: C, 39.91; H, 2.92; N, 6.0; F, 7.91; Cl, 7.39; I, 27.06.

EXAMPLE 16

5-Bromo-4-fluoro-N-(2-hydroxy-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

m.p. 154.4-156.4; ^{1}H-NMR (400 MHz, $(CD_3)_2CO$) δ 9.42 (br. s, 1H), 7.86 (d, 1H, J=7.57 Hz), 7.66 (d, 1H, J=1.46 Hz), 7.56 (dd, 1H, J=8.3, 2.2 Hz), 7.16 (d, 1H, J=8.55 Hz), 6.8 (dd, 1H, J=11.72, 6.59 Hz), 4.04 (t, 2H, J=7.9, 4.4 Hz), 3.69 (t, 2 H, J=6.84, 4.64 Hz), 2.23 (s, 3H). ^{19}F-NMR (376 MHz, $(CD_3)_2CO$) δ -103.3; MS

508.9 m/z, 510.9 m/z (AP+); 506.9 m/z, 508.9 m/z (AP-). Anal. Calcd. for $C_{16}H_{15}BrFIN_2O_3$: C, 37.75; H, 2.97; N, 5.50. Found: C, 37.68; H, 2.7; N, 5.31.

EXAMPLE 17

2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-N-(2-hydroxy-ethoxy)-benzamide

^{1}H-NMR (400 MHz, $(CD_3)_2CO$) δ 11.01 (br. s, 1H), 9.53 (br. s, 1H), 7.79 (br. s, 1H), 7.67 (br. s, 1H), 7.59 (br. d, 1H, J=7.82 Hz), 7.32 (d, 1H, J=8.55 Hz), 7.26 (br. s, 1H), 4.03 (br. s, 2H), 3.7 (br. s, 2H); ^{19}F-NMR (376 MHz, $(CD_3)_2CO$) δ -132.54, -149.93; MS 469.0 (AP+); 467.0 (AP-).

EXAMPLE 18

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-ethoxy)-benzamide

m.p. 189.6-190.6 C; ^{1}H-NMR (400 MHz, $(CD_3)_2CO$) δ 11.00 (br s, 1H), 9.39 (br. s, 1H), 7.65 (dd, 1H, J=11.23, 8.79 Hz), 7.59 (dd, 1H, J=10.26, 1.96 Hz), 7.51 (m, 1H), 7.31 (t, 1H, J=8.8 Hz), 7.13 (m, 1H), 4.02 (t, 2H, J=4.64 Hz), 3.69 (t, 2H, J=4.89 Hz); ^{19}F-NMR (376 MHz, $(CD_3)_2CO$) δ -125.9 (d, J=50.55 Hz), -132.74, -151.05; MS 453.0 m/z (AP+); 451.0 m/z (AP-). Anal. Calcd. for $C_{15}H_{12}F_3IN_2O_3$: C, 39.84; H, 2.67; N, 6.20. Found: C, 40.22; H, 2.62; N, 6.03.

EXAMPLE 19

5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-ethoxy)-benzamide

m.p. 173-175 C; ^{1}H-NMR (400 MHz, $(CD_3)_2CO$) δ 9.59 (br. s.), 7.89 (d, 1H, J=7.57 Hz), 7.62 (dd, 1H, J=10.26, 1.95 Hz), 7.55 (m, 1H), 7.34 (t, 1H, J=8.64 Hz), 7.03 (d, 1H, J=11.48 Hz), 4.04 (d, 2H, J=4.39 Hz), 3.70 (d, 2H, J=4.64 Hz); ^{19}F-NMR (376 MHz, $(CD_3)_2CO$) δ -103.07, -124.7 (d, J=53.1 Hz); MS 512.8 m/z, 514.8 m/z (AP+); 510.9 m/z, 512.9 m/z (AP-). Anal. Calcd. for $C_{15}H_{12}BrF_2IN_2O_3 \cdot 0.17\ C_4H_8O_2 \cdot 0.13\ C_6H_{14}$: C, 36.66; H, 2.84 N, 5.19. Found: C, 36.65; H, 2.57; N, 5.16.

EXAMPLE 20

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-*N*-(2-hydroxy-ethoxy)-benzamide

m.p.=178-181°C; ^{1}NMR (400MHz; DMSO-d_6) δ 12.00 (s, 1H), 8.80 (s, 1H), 7.76 (s, 1H), 7.66 (d, 1H, J=7.1), 7.47 (d, 1H, J=8.5), 6.66 (t, 1H, J=7.6), 4.70 (bs, 1H), 3.85 (m, 2H), 3.56 (m, 2H); MS(APCI+)=502.9/504.9. Anal.calcd/found for $C_{15}H_{11}Cl_2F_2IN_2O_3$: C 35.81/35.69, H 2.20/2.25, N 5.57/5.22, F 7.55/7.72.

Examples 21-24 and 26-27 were prepared by the general method of Example 38.

EXAMPLE 21

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)- N-(2-hydroxy-ethoxy)-benzamide

m.p.=185-187°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.79 (s, 1H), 8.32 (s, 1H), 7.53 (m, 2H), 7.30 (d, 1H, J=8.5), 6.60-6.55 (m,1H), 4.69 (bs, 1H), 3.80 (bs, 2H), 3.50 (bs, 2H); MS(APCI+)=471.0. Anal.calcd/found for $C_{15}H_{11}F_4IN_2O_3$: C, 38.32/38.38; H, 2.36/2.15; N, 5.96/5.76; F, 16.16/15.87.

EXAMPLE 22

2-(4-Bromo-2-fluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-ethoxy)-benzamide

m.p. 146.1-146.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.82 (1H, s), 8.71 (1H, s), 7.47 (1H, dd, J=11.1Hz, 2.1Hz), 7.30-7.40 (1H, m), 7.15-7.20 (2H, m), 6.76-6.81 (1H, m), 4.69 (1H, br s), 3.80 (2H, t, J≤4.0Hz), 3.52 (2H, t, J≤4.0Hz). Anal. Calcd/Found for $C_{15}H_{12}F_3BrN_2O_3$: C, 44.47/44.58; H, 2.99/2.88; N, 6.91/6.72; F, 14.07/14.01; Br, 19.72/19.60.

EXAMPLE 23

2-(4-Bromo-2-fluoro-phenylamino)-4,5-difluoro-N-(2-hydroxy-ethoxy)-benzamide

m.p. 190.8-192.5 °C; ^{1}H NMR (400 MHz, Acetone-d_6) δ 9.40 (br s, 1 H), 7.67 (1H, dd, J=11.48Hz, 8.79 Hz), 7.48 (2H, m), 7.37 (1H, m), 7.12 (1H, m), 4.05

(2H, t, J=4.64 Hz), 3.71 (2H, t, J=4.64 Hz). Anal Calcd/Found $C_{15}H_{12}BrF_3N_2O_3$: C, 44.47/45.55; H, 2.99/2.98; N, 6.91/6.29.

EXAMPLE 24

2-(4-Chloro-2-fluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-ethoxy)-benzamide

m.p. 142.1-142.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.83 (1H, s), 8.72 (1H,s), 7.36-7.39 (2H, m), 7.16 (1H, dd, J=16.5Hz, 9.4Hz), 7.07 (1H, dd, J=8.5Hz, 1.3 Hz), 6.82-6.88 (1H, m), 4.69 (1H, br s), 3.80 (2H, t, J=4.6Hz), 3.52 (2H, t, J=4.6Hz). Anal Calcd/Found for $C_{15}H_{12}ClF_3N_2O_3$: C, 49.95/50.18; H, 3.35/3.21; N, 7.77/7.70; F, 15.80/15.70; Cl 9.83/9.94.

EXAMPLE 25

3,4-Difluoro-2-(2-fluoro-phenylamino)-N-(2-hydroxy-ethoxy)-benzamide

Prepared from 3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-ethoxy)-benzamide by the general method of Example 86. m.p. 129.6-130.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.85 (1H, s), 8.72 (1H, s), 7.36-7.39 (1H, m), 6.82-7.18 (5H, m), 4.69 (1H, br s), 3.82 (2H, t, J=4.7Hz), 3.53 (2H, t, J=4.7Hz). Anal Calcd/Found for $C_{15}H_{13}F_3N_2O_3$: C, 55.22/55.16; H, 4.02/3.97; N, 8.59/8.51; F, 17.47/17.15.

EXAMPLE 26

5-Chloro-2-(2,4-difluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-ethoxy)-benzamide

m.p. 161.6-162.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89 (1H, s), 8.69 (1H, s), 7.56 (1H, dd, J=7.5Hz, 1.9Hz), 7.21-7.27 (1H, m), 6.94-7.06 (1H, m), 6.89-6.92 (1H, m), 4.69 (1H, br s), 3.81 (2H, t, J=4.6 Hz), 3.53 (2H, t, J=4.6Hz). Anal Calcd/Found for $C_{15}H_{11}ClF_4N_2O_3$: C, 47.57/47.74; H, 2.93/2.83; N, 7.40/7.31; F, 20.07/19.76; Cl, 9.36/9.39.

EXAMPLE 27

2-(2,4-Difluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-ethoxy)-benzamide

m.p.141.1-141.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.84 (1H, s), 8.73 (1H, s); 7.34-7.37 (1H, m), 7.11-7.27 (1H, m), 7.04-7.09 (1H, m), 6.89-6.99 (2H, m), 4.70 (1H, br s), 3.82 (2H, t, J=4.9 Hz); 3.53 (2H, t, J=4.8Hz). Anal Calcd/Found for $C_{15}H_{12}F_4N_2O_3$: C, 52.33/52.34; H, 3.51/3.39; N 8.14/8.01; F, 22.07/21.93.

EXAMPLE 28

4-Fluoro-N-(3-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

Step A: To a mixture of 4-fluoro-2-(4-iodo-2-methyl-phenylamino) benzoic acid (3.32g, 8.95 mmol) in dichloromethane at ambient temperature was added diisopropylethylamine (2.82 mL, 16.2 mmol). To the resultant solution was added O-[3-(tert-butyl-dimethyl-silanyloxy)-propyl]-hydroxylamine (2.19g, 10.65 mmol) and PyBOP. After 1.5 h of stirring, the solution was diluted with ether (100 mL) and was washed with water (3x50 mL) and brine (50 mL), dried over magnesium sulfate and filtered, and concentrated *in vacuo* to obtain a gum. Chromatographed the gum using a gradient of 100% hexanes to 30% ethyl acetate in hexanes over 45 min. The solvent of the combined fractions was removed *in vacuo* to obtain a yellow gum. The gum was dried on a vacuum pump for c. a. 18h which afforded N-[3-(tert -Butyl-dimethyl-silanyloxy)-propoxy]-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide as a solid. (4.06g, 81% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.3 (br. s., 1H), 9.0 (br. s., 1H), 7.58 (s, 1H), 7.49 (dd, 1H, J=8.3, 1.95Hz)), 7.36 (br. t., 1H, =5.71 Hz), 7.05 (d, 1H, J=8.3 Hz), 6.65 (dd, 1H, J=11.96, 2.44 Hz), 6.4 (br. t., J=7.1 Hz), 4.14 (t, 2H, J=5.61 Hz), 3.812 (t, 2H, J=5.62 Hz), 2.28 (s, 3H), 1.94 (p, 2H, J=5.86 Hz), 0.9 (s, 9H), 0.08 (s, 6H). ^{19}F-NMR (376 MHz, $CDCl_3$) δ –105.25. MS (AP+) 559.2 m/z, (AP-) 557.1 m/z.

Step B: To a solution of N-[3-(tert -Butyl-dimethyl-silanyloxy)-propoxy]-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide (4.0g, 7.27 mmol) in methanol (5 mL) at ambient temperature was added 5 M H_2SO_4 in methanol (0.073 mL, 0.364 mmol). After 1h of stirring, to the reaction was added additional 5 M H_2SO_4 in methanol (0.035 mL, 0.182 mmol). After 2h of stirring, the reaction was adjusted to pH 7 using saturated $NaHCO_3$ (aq) (c. a. 1.5 mL), followed by addition of water (35 mL). The aqueous layer was extracted with ethyl acetate (1x20 mL, 2x10 mL). The extracts were combined, washed with

brine, and dried over magnesium sulfate. The resultant mixture was filtered, and the filtrate solvent was removed *in vacuo* to obtain an oil that was dried on a vacuum pump over the weekend. The oil was purified by flash chromatography, eluted with a gradient of 100% hexanes to 100% ethyl acetate in 50 min. The solvent was removed *in vacuo* of combined fractions to obtain a solid which was dried on a vacuum pump for c. a. 6 h. Recrystalized solid in a mixture of hexanes and ethyl acetate to afford 4-fluoro-N-(3-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide as a solid (2.4g, 74% yield): m.p. 120.8-122.4 C; ^{1}H-NMR (400 MHz, $(CD_3)_2CO$) δ 10.91 (br s, 1 H), 9.59 (br. S, 1H), 9.68 (m, 2H), 7.57 (d, 1H, J=8.54 Hz), 7.18 (d, 1H, J=8.34 Hz), 6.72 (m, 1H); 6.53 (m, 1H); 4.12 (t, 2H, J=6.11 Hz), 3.71 (t, 2H, J=5.86 Hz), 2.26 (s, 3H), 1.86 (m, 2H); ^{19}F-NMR (376 MHz, $(CD_3)_2CO$) δ -108.14; MS 445.1 m/z (AP+), 443.1 m/z (AP-). Anal. Calcd. for $C_{17}H_{18}FIN_2O_3$: C, 45.96; H, 4.08; N, 6.31; F, 4.28; I, 28.57. Found: C, 45.78; H, 3.88; N, 6.14; F, 4.30; I, 28.27.

Examples 29-33 were prepared by the general procedure of example 28.

EXAMPLE 29

5-Chloro-3,4-difluoro-N-(3-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

m.p. 155.2-156.6 C; ^{1}H-NMR (400 MHz, $(CD_3)_2CO$) δ 10.98 (br s, 1H), 8.70 (br. S, 1H), 7.66 (dd, 1H, J=7.33, 1.95 Hz), 7.55 (s, 1H), 7.42 (dd, 1H, J=8.54, 1.95 Hz), 6.64 (dd, 1H, J=8.55, 6.11 Hz), 4.08 (t, 2H; J=6.11 Hz), 3.67 (t, 2H, J=6.10 Hz), 2.32 (s, 3H), 1.83 (m, 2H); ^{19}F-NMR (376 MHz, $(CD_3)_2CO$) δ -135.0, -139.63 (d, J=17.67 Hz); MS 497.1 m/z (AP+); 495.1 m/z (AP-). Anal. Calcd. for $C_{17}H_{16}ClF_2IN_2O_3$: C, 41.11; H, 3.25; N, 5.64; F, 7.65; Cl, 7.14; I, 25.55. Found: C, 41.09; H, 3.07; N, 5.46; F, 7.63; Cl, 7.24; I, 25.57.

EXAMPLE 30

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(3-hydroxy-propoxy)-benzamide

m.p. 158.8-160.8 C; ^{1}H-NMR (400 MHz, $(CD_3)_2CO$) δ 10.90 (br s, 1H), 9.93 (br. S, 1H), 7.84 (d, 1H, J=1.95 Hz), 7.72. (dd, 1H, J=8.55, 1.96 Hz), 7.65 (dd, 1H, J=8.55, 1.96 Hz), 7.39 (d, 1H, J=8.54 Hz), 7.05 (dd, 1H, J=11.72, 2.44 Hz), 6.67

(td, 1H, J=8.55, 2.69Hz), 4.13 (t, 2H, J=6.34 Hz), 3.71 (t, 2H, J=6.10 Hz), 1.86 (m, 2H). ^{19}F-NMR (376 MHz, $(CD_3)_2CO$) δ -108.0; . MS 465.1 m/z (AP+), 463.1 m/z (AP-). Anal. Calcd. for $C_{16}H_{15}ClFIN_2O_3$: C, 41.36; H, 3.25; N, 6.03; F, 4.09; Cl, 7.63; I, 27.31. Found: C, 41.41; H, 3.13; N, 5.84; F, 4.10; Cl, 7.62; I, 27.41

EXAMPLE 31

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-*N*-(3-hydroxy-propoxy)-benzamide

m.p. 120-121°C; ^{1}NMR (400MHz;DMSO-d_6) δ 11.90 (bs, 1H), 8.91 (bs, 1H), 7.76 (bs, 2H), 7.47 (d, 1H, J=8.1), 6.67 (m, 1H), 4.48 (bs, 1H), 3.89 (bs, 2H), 3.47 (bs, 2H), 1.73 (m, 2H); MS(APCI+)=560.8/562.8. Anal calcd/found for $C_{16}H_{13}BrClF_2IN_2O_3$: C 34.22/34.45, H 2.33/2.36, N 4.99/4.91, F 6.77/6.72.

EXAMPLE 32

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-propoxy)-benzamide

m.p. 151.8-152.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.74 (1H, s), 8.71 (1H, s), 7.56 (1H, d, J=11.0Hz), 7.20-7.30 (2H, m), 7.16-7.22 (1H, m), 6.62-6.68 (1H, m), 4.46 (1H, br s), 3.83 (2H, t, J=5.6Hz), 3.46 (2H, t, J=4.6Hz), 1.67-1.70 (2H, m). Anal. Calcd/Found for $C_{16}H_{14}F_3IN_2O_3$: C,41.22/41.27; H, 3.03/2.87; N, 6.01/5.92; F, 12.23/11.97; I, 27.22/27.44.

EXAMPLE 33

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(4-hydroxy-butoxy)-benzamide

m.p. 131.4-131.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.71 (1H, s), 8.68 (1H, s), 7.54 (1H, d, J=11.0Hz), 7.20-7.36 (2H, m), 7.14-7.18 (1H, m), 6.60-6.66 (1H, m), 4.38 (1H, br s), 3.74 (2H, t, J=6.1Hz), 3.36 (2H, t, J=4.2Hz), 1.41-1.55 (4H, m). Anal. Calcd/Found for $C_{17}H_{16}F_3IN_2O_3$: C, 42.52/42.91; H, 3.36/3.27; N, 5.83/5.58; F, 11.87/11.61; I, 26.43/26.67.

EXAMPLE 34

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-*N*-(2,3-dihydroxy-propoxy)-3,4-difluoro-benzamide

Step A: To a stirring solution of 5-chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-benzoic acid pentafluorophenyl ester (5.80 g, 9.51 mmol) is freshly distilled tetrahydrofuran (40 mL) was added *O*-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-hydroxylamine (1.54g, 10.5 mmol) and diisopropylethylamine (1.8 mL, 10.5 mmol). After 20 hours, the mixture was partitioned between ethyl acetate and water. The organic layer was washed twice with water and twice with saturated brine solution. The organic layer was collected, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by crystallization in ethyl acetate/hexanes affording 5-chloro-2-(2-chloro-4-iodo-phenylamino)-*N*-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-3,4-difluoro-benzamide as a white solid (3.7 g, 67.9%): ^{1}H NMR (400 MHz,$CDCl_3$) δ 9.82 (bs, 1H), 8.10 (bs, 1H), 7.68 (s, 1H), 7.47 (bs, 1H), 7.40-7.43 (m, 1H), 6.44-6.47 (m, 1H), 4.40 (bs, 1H), 3.97-4.20 (m, 3H), 3.77 (t, 1H, J=8.0), 1.44 (s, 3H), 1.37 (s, 3H); MS (APCI+) = 573.0/575.0.

Step B: To a stirring solution of 5-chloro-2-(2-chloro-4-iodo-phenylamino)-*N*-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-3,4-difluoro-benzamide (3.7g, 6.45 mmol) in methanol (20 mL) and water (2 mL) was added *p*-toluenesulfonic acid (0.12g, 0.65 mmol). After 20 hours the reaction was concentrated *in vacuo*. The afforded residue was partitioned between ethyl acetate and water. The organic layer was washed twice with saturated $NaHCO_3$ solution and twice with saturated brine solution. The organic layers were collected, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by crystallization with methanol/water and the solids were dried in a vacuum oven at 40°C to afford 5-chloro-2-(2-chloro-4-iodo-phenylamino)-*N*-(2,3-dihydroxy-propoxy)-3,4-difluoro-benzamide: m.p.=152-154°C; ^{1}NMR (400 MHz, DMSO-d_6) δ 12.03 (s, 1H), 8.83 (s, 1H), 7.76 (s, 1H), 7.66 (d, 1H, J=6.8), 7.47 (d, 1H, J=8.5), 6.68 (t, 1H, J=6.6), 4.83 (bs, 1H), 4.60 (bs, 1H), 3.89-3.92 (m, 1H), 3.68-3.76 (m, 2H), 3.30 (2H, partially hidden by HDO); MS(APCI+)=533.0/535.0; Anal.calcd/found for $C_{16}H_{13}Cl_2F_2IN_2O_4$: C, 36.05/36.23; H, 2.46/2.40; N, 5.25/5.03; F, 7.13/7.14.

Examples 35-37 were prepared by the general procedure described in example 34.

EXAMPLE 35

5-Chloro-*N*-(2,3-dihydroxy-propoxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

m.p.=67-69°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.46 (d, 1H, J=6.3), 7.38 (d, 1H, J=8.5), 6.44 (dd, 1H, J=8.3, 4.9), 3.94-3.98 (m, 2H), 3.89 (m, 1H), 3.74 (A of abx, 1H, J=11.7, 3.9), 3.61 (B of abx, 1H, J=11.5, 4.9), 2.30 (s, 3H); MS(APCI+)=513.0/515.0. Anal.calcd/found for $C_{17}H_{16}ClF_2IN_2O_4$: C, 39.83/39.90; H, 3.15/3.23; N, 5.46/5.03; F, 7.41/7.20.

EXAMPLE 36

5-Chloro-*N*-(3,4-dihydroxy-butoxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

m.p.=135-138°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.86 (bs, 1H), 8.55 (bs, 1H), 7.85 (s, 1H), 7.60 (d, 1H, J=7.1), 7.51 (s, 1H), 7.35 (d, 1H, J=8.5), 6.53 (dd, 1H, J=8.3,5.4), 4.51-4.52 (m, 2H), 3.86-3.88 (m, 2H), 3.53 (bs, 1H), 3.23-3.28 (m, 1H), 2.20 (s, 3H), 1.73-1.77 (m, 1H), 1.45-1.48 (m, 1H); MS(APCI+)=527.0. Anal.calcd/found for $C_{18}H_{18}ClF_2IN_2O_4$: C, 41.05/41.12; H, 3.44/3.41; N, 5.32/5.13; F, 7.21/6.83.

EXAMPLE 37

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-N-(3,4-dihydroxy-butoxy)-3,4-difluoro-benzamide

m.p.=146-148°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, 1H), 8.84 (s, 1H), 7.76 (s, 1H), 7.65 (d, 1H, J=7.1), 7.47 (d, 1H, J=8.8), 6.67 (dd, 1H, J=8.3,6.3), 4.54-4.50 (m, 2H), 3.93 (t, 2H, J=6.3), 3.54 (t, 1H, J=4.2), 3.28-3.20 (m, 2H), 1.76 (m, 1H), 1.52-1.47 (m, 1H); MS (APCI+)=547.0/549.0. Anal.calcd/found for $C_{17}H_{15}Cl_2F_2IN_2O_4$: C, 37.32/37.26; H, 2.76/2.62; N, 5.12/4.99; F, 6.94/7.07.

EXAMPLE 38

N-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

To a stirring solution of 3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzoic acid (4.52g, 11.5 mmol) in freshly distilled tetrahydrofuran (20 mL) at -15°C was added diphenylphosphinic chloride (2.85 mL, 14.95 mmol). The resultant reaction mixture was stirred for 30 minutes at -15°C. *N*-Methylmorpholine (1.26 mL, 11.5 mmol) was added and stirring was continued for 90 minutes at -15°C. The reaction was then charged with *O*-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-hydroxylamine (2.03g, 13.8 mmol) and allowed to stir at -15°C for 30 minutes. *N*-methylmorpholine (1.9 mL, 17.25 mmol) was added and the reaction was allowed to warm to room temperature. After 17 hours, the mixture was diluted with ethyl acetate and partitioned twice with saturated $NaHCO_3$ solution, then twice with water, and twice with saturated brine solution. Organic layers were collected, dried over sodium sulfate, filtered and concentrated *in vacuo*. The afforded residue was purified by silica column chromatography in 3:1 hexanes/ethyl acetate. The corresponding fractions were collected, dried *in vacuo*, and crystallized from ethyl acetate/hexanes affording *N*-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide (4.12g, 68.6%) as light brown solid: m.p.=114-115°C; ^{1}NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 8.62 (s, 1H), 7.53-7.55 (m, 1H), 7.31-7.37 (m, 2H), 7.17 (dd, 1H, J=16.9, 9.3), 6.60-6.65 (m, 1H), 4.22 (t, 1H, J=6.1), 3.96 (t, 1H, J=8.3), 3.76-3.77 (m, 2H), 3.63 (t, 1H, J=4.9), 1.26 (s, 3H), 1.21 (s, 3H); MS(APCI+)=522.9; Anal.calcd/found for $C_{19}H_{18}F_3IN_2O_4$: C, 43.70/43.88; H, 3.47/3.43; N, 5.36/5.20; F, 10.91/10.87.

EXAMPLE 39

N-(2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide (Form II of Compound A)

To a stirring solution of *N*-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide (3.03g, 5.81 mmol) in methanol (30 mL) and water (3 mL) at ambient temperature was added *p*-toluene

sulfonic acid (0.11g, 0.581 mmol). After 18 hours another 0.11g of added *p*-toluene sulfonic acid and 2 mL of water was added. After an additional 24 hours the reaction mixture was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water. The organic layer was washed twice with saturated $NaHCO_3$ solution and twice with saturated brine solution. The organic layers were collected, dried over Na_2SO_4, filtered and concentrated *in vacuo* affording a light brown solid, which was crystallized from ethyl acetate/hexanes to afford *N*-(2,3-dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide as a white solid. m.p.=135.5-137.3°C; ^{1}NMR (400MHz, DMSO-d_6) δ 11.87 (s, 1H), 8.69 (s, 1H), 7.54 (dd, 1H, J=10.9, 1.5), 7.32-7.38 (m, 2H), 7.17 (dd, 1H, J=16.8, 9.0), 6.61-6.66 (m, 1H), 4.82 (bs, 1H), 4.58 (bs, 1H), 3.84-3.85 (m, 1H), 3.71-3.64 (m, 2H), 3.33 (2H, partially hidden by HDO); MS(APCI+)=483.0; Anal.calcd/found for $C_{16}H_{14}F_3IN_2O_4$: C, 39.85/40.12; H, 2.93/2.84; N, 5.81/5.65; F, 11.82/11.47.

Alternatively, the crude white solid of *N*-(2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide was suspended in heptane – CH_2Cl_2 (1 : 1). The ratio was 6 mL of the solvent per gram of solid. The suspension was stirred at ambient temperature for 30 min. The solid was filtered, and dried at a vacuum oven (20 mmHg), 45 °C for 18 hrs, to give white crystals, mp 131 – 132 °C.

EXAMPLE 39A

N-(2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide (Form I of Compound A)

To a stirring solution of *N*-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide (0.907g, 1.74 mmol) in methanol (10 mL) and water (1 mL) at ambient temperature was added *p*-toluene sulfonic acid (0.032g, 0.17 mmol). After stirring for 18 hours the reaction mixture was concentrated *in vacuo* and the affording residue was partitioned between ethyl acetate and water. The organic layers were washed twice with water and once with saturated brine solution. Organic layers were collected, dried over Na_2SO_4,

filtered and concentrated *in vacuo* affording a light brown solid, which was dissolved in ethanol and precipitated with water to afford *N*-(2,3-dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide as a white solid (0.387g). m.p.=83-85°C; ^{1}NMR (400MHz, DMSO-d_6) 11.87 (s, 1H), 8.69 (s, 1H), 7.56 (d, 1H, J=11.0), 7.33-7.39 (m, 2H), 7.19 (dd, 1H, J=16.6, 9.0), 6.62-6.68 (cm, 1H), 4.82 (d, 1H, J=4.2), 4.58 (t, 1H, J=5.5), 3.84-3.87 (m, 1H), 3.66-3.72 (m, 2H), 3.3 (2H, partially hidden by HDO); MS(APCI+)=483.0; Anal.calcd/found for $C_{16}H_{14}F_3IN_2O_4 \cdot 0.3\ H_2O$: C, 39.41/39.02; H, 3.02/2.93; N, 5.75, 5.81; F, 11.69/11.68.

Alternatively, the crude solid *N*-(2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide was dissolved in minimum amount of boiling ethanol (95%). Water was added to this boiling solvent until slightly cloudy. The mixture was cooled to ambient temperature and then at 0 °C for 18 hrs. Solid formed was filtered and dried at a vacuum oven (20 mmHg), 45 °C for 18 hrs, mp 81 – 84 °C.

Furthermore, the crude solid *N*-(2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide was dissolved in minimum amount of boiling ethyl acetate, and heptane was added to this solution until slight cloudy. The mixture was cooled to ambient temperature and then at 0 °C for 18 hrs. Solid formed was filtered and dried at a vacuum oven (20 mmHg), 45 °C for 18 hrs, mp 86 °C.

The compounds of examples 40-48 were prepared by the procedures described in Examples 38 and 39.

EXAMPLE 40

5-Bromo-*N*-(2,3-dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

m.p.=172-174°C; ^{1}H NMR (400MHz, DMSO-d_6) δ 11.92 (s, 1H), 8.69 (s, 1H), 7.67 (d, 1H, J=6.8), 7.56 (d, 1H, J=10.7), 7.34 (d, 1H, J=8.3), 6.73 (cm, 1H), 4.81 (m, 1H), 4.58-4.57 (m, 1H), 3.86-3.84 (m, 1H), 3.70-3.67 (m, 2H), 3.30 (2H,

partially under HDO); MS(APCI+)=561.0. Anal.calcd/found for $C_{16}H_{13}BrF_3IN_3O_4$: C, 34.25/34.27; H, 2.34/2.22; N, 4.99/4.75.

EXAMPLE 41

5-Chloro-*N*-(2,3-dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

m.p.=152-155°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.91 (s, 1H), 8.66 (s, 1H), 7.58-7.55 (m, 2H), 7.34 (d, 1H, J=8.1 Hz), 6.72 (m, 1H), 4.81 (d, 1H, J=4.1 Hz), 4.58 (t, 1H, J=5.9 Hz), 3.87-3.84 (m, 1H), 3.70-3.68 (m, 2H), 3.33 (2H, partially under HDO); MS(APCI+)=517.0. Anal.calcd/found for $C_{16}H_{13}ClF_3IN_3O_4$: C 37.20/36.88, H 2.54/2.43, N 5.42/5.14, F 11.03/11.70.

EXAMPLE 42

N-(2,3-Dihydroxy-propoxy)-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

m.p.= 173-175°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.86 (s, 1H), 9.59 (s, 1H), 7.69 (d, 1H, J=10.3), 7.58 (t, 1H, J=7.8), 7.49 (d, 1H, J=8.5), 7.27 (t, 1H, J=8.5), 6.82 (d, 1H, J=11.5), 6.69 (t, 1H, J=7.8), 3.94-3.92 (m, 1H), 3.78-3.71 (m, 2H), 3.4 (2H, under HDO); MS(APCI+)=465.0.

EXAMPLE 43

N-(2,3-Dihydroxy-propoxy)-3,4,5-trifluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

m.p.=157-160°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.82 (s, 1H), 8.32 (s, 1H), 7.53-7.48 (m, 2H), 7.29 (d, 1H) J=8.3), 6.58-6.55 (m, 1H), 4.80 (d, 1H, J=3.0), 4.57 (t, 1H, J=5.9), 3.83-3.81 (m, 1H), 3.67-3.65 (m, 2H), 3.30 (2H, under HDO); MS(APCI+)=500.9. Anal.calcd/found for $C_{16}H_{13}F_4IN_2O_4$: C, 38.42/38.48; H, 2.62/2.54; N, 5.60/5.55; F, 15.19/14.96.

EXAMPLE 44

2-(4-Bromo-2-fluoro-phenylamino)-N-(2,3-dihydroxy-propoxy)-3,4-difluoro-benzamide

Prepared in the manner of *N*-(2,3-dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide (Example 39): m.p. 110-117 °C (dec). Anal. Calcd/Found for $C_{16}H_{14}BrF_2BrN_2O_4$: C, 44.16/43.86; H, 3.24/2.97; N, 6.44/6.13; F, 13.10/12.76; Br, 18.36/18.64.

EXAMPLE 45

2-(4-Chloro-2-fluoro-phenylamino)-N-(2,3-dihydroxy-propoxy)-3,4-difluoro-benzamide

m.p. 114.0-114.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.87 (1H, s), 8.74 (1H, s), 7.38 (1H, dd, J=11.3Hz, 2.3Hz), 7.36 (1H, m), 7.07-7.20 (2H, m), 6.84-6.90 (1H, m), 4.83 (1H, br s), 4.59 (1H, br s), 3.84-3.87 (1H, m), 3.65-3.72 (2H, m), 3.20-3.40 (2H, m). Anal Calcd/Found for $C_{16}H_{14}F_3ClN_2O_4$: C, 49.18/49.09; H, 3.61/3.56; N, 7.07/7.03; F, 14.59/14.45; Cl, 9.07/9.16.

EXAMPLE 46

***N*-(2,2-Dimethyl-[1,3]dioxan-5-yloxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide**

m.p.=154-155°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H), 8.64 (s, 1H), 7.55 (dd, 1H, J=10.7, 1.7), 7.40 (t, 1H, J=7.1), 7.33 (d, 1H, J=8.3), 7.21-7.14 (m, 1H), 6.69-6.65 (m, 1H), 3.95 (A of AB, 2H, J=10.7), 3.80 (B of AB, 2H, J=12.2), 3.65 (bs, 1H), 1.33 (s, 3H), 1.25 (s, 3H); MS (APCI+)=523.1; Anal.calc/found for $C_{19}H_{18}F_3IN_2O_4$: C, 43.70/43.76; H, 3.47/3.44; N, 5.36/5.21; F, 10.91/10.73.

EXAMPLE 47

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)- *N*-(2-hydroxy-1-hydroxymethyl-ethoxy)-benzamide

m.p. 111-114°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.82 (bs, 1H), 8.64 (bs, 1H), 7.55 (dd, 1H, J=10.7, 1.9), 7.40 (t, 1H, J=7.3), 7.34-7.31 (m, 1H), 7.20 (dd, 1H, J=16.6,9.3), 6.65-6.60 (m, 1H), 4.64 (bs, 2H), 3.75-3.72 (m, 1H), 3.48-3.44 (m, 4H); MS (APCI+)=482.9; Anal.calc/found for $C_{16}H_{14}F_3IN_2O_4$: C, 39.85/39.93; H, 2.93/2.93; N, 5.81/5.51; F, 11.82/11.72.

EXAMPLE 48

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-*N*-(2-hydroxy-1-hydroxymethyl-ethoxy)-benzamide

m.p. 173–175°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.87 (s, 1H), 8.56 (s, 1H), 7.61 (d, 1H, J-6.3), 7.55 (d, 1H, J=9.3), 7.32 (d, 1H, J=9.5), 6.69 (m, 1H), 4.61 (m, 2H), 3.73 (m, 1H), 3.48 (m, 4H); MS(APCI+)=516.9/518.9.

EXAMPLE 49

N-[(R)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide (Form I of Compound B)

Step A: To a solution of 3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzoic acid (39.3 g, 100.0 mmol) in dry tetrahydrofuran (500 mL, 0.2 M), under nitrogen atmosphere, was added *(R)*-O-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-hydroxylamine (14.7 g, 100.0 mmol), followed by *N*-methylmorpholine (27.5 mL, 0.25 mole). The orange-colored solution was cooled with an ice-water bath. Diphenylphosphinic chloride (22.9 mL, 0.12 mole) was added dropwise. Some solid formed. The mixture was warmed to ambient temperature and stirred for 18 hrs. Water was added to quench the reaction and the tetrahydrofuran was evaporated *in vacuo*. The remaining oil was dissolved in ethyl acetate (500 mL), washed with a mixture of saturated brine and saturated sodium bicarbonate (1:1) two times. The ethyl acetate was removed and the crude oily solid was purified by flash chromatography (silica gel, hexane-acetone / 2 : 1) to give N-((R)-2,2-Dimethyl-[1,3]dioxolan-4-ylmethoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide as an off-white solid after drying in a vacuum oven at 40 °C for 20 hrs: 41.7 g (79.8%), m.p. 124–125 °C. The impure fractions were combined and purified by a second column chromatography using the same condition to give a 2nd batch of 6.4 g (12.3%), mp 124–125 °C, total yield 48.1 g (92.1%). ^{1}H NMR (d^6-DMSO): δ 11.9 (s, br, 1H), 8.7 (s, br, 1H), 7.6 (d, 1H, J=10.99 Hz), 7.4 (m, 2H), 7.2 (m, 1H), 6.7 (m, 1H), 4.2 (m, 1H), 4.0 (t, 1H, J1=8.3 Hz, J2=6.8 Hz), 3.8 (m, 2H), 3.7 (m, 1H), 1.3 (s, 3H), 1.2 (s, 3H); ^{19}F NMR (d^6-DMSO): δ -128.0, -133.1, -144.3; MS: 523 (M^++1).

Step B: N-((R)-2,2-Dimethyl-[1,3]dioxolan-4-ylmethoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide (22.3 g, 42.7 mmol) was suspended in methanol (223 mL, 10mL/g), and a solution of pTsOH·H_2O (4.1 g, 21.35 mmol) in water (22.3 mL) was added. The mixture was stirred at ambient temperature for 18 hrs, during which all solids dissolved to give a colorless, clear solution. The solution was concentrated and extracted with ethyl acetate (2 x 300 mL). The organic solution was washed with sodium bicarbonate, dried over $MgSO_4$. After filtration, the filtrate was concentrated, and co-evaporated with heptane to give a foaming solid. To this solid was added hexane-CH_2Cl_2 (1 : 1, 100 mL) and the mixture was stirred for 30 min. A white solid formed, which was filtered, washed with hexane. The solid was recrystallized from hexane-AcOEt to give N-((R)-2,3-dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide as white crystals, 13.57 g (65.9%), after drying at 60 °C vacuum oven for 3 days. A second crop of 5.05 g was obtained from the mother liquor, after recrystallization from the same solvent system. The total yield was 18.62 g (90.4%): m.p. 89-90 °C (Form II of Compound B). The combined crystals were ground with a set of mortar and pestle to fine powder, and dried at 60 °C in a vacuum oven for 3 days: m.p. 117-118 °C (Form I of Compound B); $[\alpha]$= -2.05° (c=1.12, methanol); Analysis: Calcd. For: $C_{16}H_{14}F_3I_1N_2O_4$: C, 39.85; H, 2.93; N, 5.81; F, 11.82, I, 26.32. Found: C, 39.95; H, 2.76; N, 5.72; F, 11.71; I, 26.53. ^{1}NMR (400MHz, DMSO-d_6) δ 11.87 (s, 1H), 8.69 (s, 1H), 7.54 (dd, 1H, J=10.9, 1.5), 7.32-7.38 (m, 2H), 7.17 (dd, 1H, J=16.8, 9.0), 6.61-6.66 (cm, 1H), 4.82 (bs, 1H), 4.58 (bs, 1H), 3.84-3.85 (m, 1H), 3.71-3.64 (cm, 2H), 3.33 (2H, partially hidden by HDO).

EXAMPLE 49A

N-[(R)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide (Form II of Compound B)

Step A: To a solution of 3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzoic acid (2.25 g, 5.10 mmol) in dry tetrahydrofuran under nitrogen atmosphere, at –15C was added diphenylphosphinic chloride (1.26 mL, 6.63 mols) dropwise. After stirring 20 min., N-methyl morpholine (0.70 mL, 6.375 mmol) was added and the reaction stirred an additional 20 min. *(R)*-O-(2,2-dimethyl-[1,3]dioxolan-

4-ylmethyl)-hydroxylamine (0.748 g, 5.1 mmol) was added and the reaction stirred for 1 hour, at which point *N*-methylmorpholine (0.7 mL, 6.37 mmol) was added. The mixture was warmed to ambient temperature and stirred for 12 h. The reaction was concentrated in vacuo and then diluted with EtOAc. The organic layer was washed with sat'd $NaHCO_3$ (2x), brine (1x), dried over Na_2SO_4, filtered and concentrated. The crude product was purified on SiO2 using 4:1 hexane/EtOAc as elutant to provide 1.82g (68%) of a brownish red solid.

Step B: N-((R)-2,2-Dimethyl-[1,3]dioxolan-4-ylmethoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide (0.210 g, 0.40 mmol) was suspended in 10:1 methanol/H_2O and $pTsOH \cdot H_2O$ (0.008 g, 0.04 mmol) was added. The mixture was stirred at ambient temperature for 18 hrs, during which all solids dissolved to give a colorless, clear solution. The solution was diluted with EtOAc. The organic solution was washed with sodium bicarbonate (2x), brine (1x) and dried over Na_2SO_4. After filtration, the filtrate was concentrated, and recrystallized from EtOAc and heptane. This solid was washed with heptane-CH_2Cl_2 (1 : 1and dried in vacuo at 60C to give N-((R)-2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide as a white solid, (0.136g, 70%). Product shrinks at 90.8C, melts at 115-117C. Analysis shows C 40.92, H 3.16, N 5.41, F 11.30, I 23.92 (6.75% EtOAc, 0.96 % heptane).

EXAMPLE 50

N-[(S)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide (Form I of Compound C)

Prepared from *(S)*-O-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-hydroxylamine and 3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzoic acid by the procedure described above for *N*-[(R)-2,3-dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide: m.p. 116-118 °C (Form II of Compound C); and m.p. 116-118 °C (Form I of Compound C); $[\alpha]$= +1.77° (c=1.13, methanol). Analysis: Calcd. For: $C_{16}H_{14}F_3I_1N_2O_4$: C, 39.85; H, 2.93; N, 5.81; F, 11.82, I, 26.32. Found: C, 40.01; H, 2.73; N, 5.84; F, 11.45; I, 26.42.

EXAMPLE 50A

N-[(S)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide (Form II of Compound C)

Prepared from *(S)*-O-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-hydroxylamine and 3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzoic acid by the alternative procedure described above for *N*-[(R)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide: m.p. 118-119 °C.

EXAMPLE 51

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-*N*-[(R)-2,3-dihydroxy-propoxy]-3,4-difluoro-benzamide

Prepared from *(R)*-O-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-hydroxylamine and 5-chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-benzoic acid by the procedure described for *N*-(2,3-dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide: m.p. 155-156 °C; $[\alpha]$= -5.1° (c=3.5 mg/mL, ethanol); ^{1}NMR (400 MHz, DMSO-d_6) δ 12.03 (s, 1H), 8.83 (s, 1H), 7.76 (s, 1H), 7.66 (d, 1H, J=6.8 Hz), 7.47 (d, 1H, J=8.5 Hz), 6.68 (t, 1H, J=6.6 Hz), 4.83 (bs, 1H), 4.60 (bs, 1H), 3.89-3.92 (m, 1H), 3.68-3.76 (m, 2H), 3.30 (2H, partially hidden by HDO); MS (APCI+)=533.0/535.0; Anal.calcd/found for $C_{16}H_{13}Cl_2F_2IN_2O_4$: C, 36.05/36.04; H, 2.46/2.25; N, 5.25/5.10; F, 7.13/7.18; Cl, 13.30, 13.50; I, 23.80, 24.02.

EXAMPLE 52

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-*N*-[(S)-2,3-dihydroxy-propoxy]-3,4-difluoro-benzamide

Step A: A 1L single necked round-bottomed flask equipped with a magnetic stirrer was charged with a solution of 5-chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-benzoic acid (59.6 g, 135 mmol) in dry tetrahydrofuran (300 mL). The solution was cooled to 0 °C in an ice-acetone bath. To this solution was added diisopropylethylamine (34.8 g, 270 mmol), *(S)*-O-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-hydroxylamine (29.7 g, 202 mmol), 1-hydroxybenzotriazole (30.93 g, 202 mmol), and benzotriazol-1-yloxy-

tris(dimethylamino)phosphonium hexafluorophosphate (BOP) (89.32g, 202 mmol). After 30 minutes, the cooling bath was removed, and the reaction was stirred at ambient temperature for 18 hrs. The solvent was evaporated *in vacuo*, and the residue was dissolved in diethyl ether. The organic solution was washed with 10% aqueous sodium hydroxide (3 x 500 mL) and brine, and dried ($MgSO_4$). The solution was concentrated to afford 5-chloro-2-(2-chloro-4-iodo-phenylamino)-N-((S)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-3,4-difluoro-benzamide (69.9 g) as a pale yellow solid that was used directly in the next hydrolysis reaction.

Step B: A 3L single necked round bottomed flask equipped with a magnetic stirrer was charged with a solution of 5-chloro-2-(2-chloro-4-iodo-phenylamino)-N-((S)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-3,4-difluoro-benzamide (69.9 g, 122 mmol) in tetrahydrofuran (1.5 L). Aqueous 1N hydrochloric acid (500 mL) solution was added and the reaction mixture was stirred at ambient temperature for 18 hrs. The reaction mixture was concentrated and extracted with ethyl acetate (3 x 800 mL). The organic extracts were washed with saturated aqueous sodium bicarbonate (500 ml) and brine (500 ml), and dried ($MgSO_4$). The crude pale yellow solid was recrystallized from ethyl acetate/hexane and dried at 70 °C in vacuum oven to afford 5-Chloro-2-(2-chloro-4-iodo-phenylamino)-N-((S)-2,3-dihydroxy-propoxy)-3,4-difluoro-benzamide (35 g, 54%) as pale yellow crystals: m.p. 153-154 °C; $[\alpha]$= +3.36° (c=1.04, methanol); ^{1}H NMR (d^6-DMSO) δ 12.02 (s, 1H), 8.85 (s, 1H), 7.74 (s, 1H), 7.64 (d, 1H), 7.45 (d, 1H), 6.66 (t, 1H), 4.82 (s, 1H), 4.58 (s, 1H), 3.88 (m, 2H), 3.74 (m, 3H); ^{19}F NMR (d^6-DMSO) δ -133.21 (s, 1F), -137.18 (s, 1F); MS (m/z): 534 (68), 532 (100), 483 (28), 481 (41), 440 (51). Anal.calcd/found for $C_{16}H_{13}Cl_2F_2IN_2O_4$: C, 36.05/36.36; H, 2.46/2.38; N, 5.25/5.30; F, 7.13/7.15; Cl, 13.30/13.76; I, 23.80/23.83.

EXAMPLE 53

5-Chloro-*N*-[(2(R),3-dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

Prepared from from *(R)*-O-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-hydroxylamine and 5-dhloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-

benzoic acid by the procedure described above for *N*-[(R)-2,3-dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide: m.p. 142-143 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.91 (s, 1H), 8.66 (s, 1H), 7.58-7.55 (m, 2H), 7.34 (d, 1H, J=8.1 Hz), 6.72 (cm, 1H), 4.81 (d, 1H, J=4.1 Hz), 4.58 (t, 1H, J=5.9 Hz), 3.87-3.84 (m, 1H), 3.70-3.68 (m, 2H), 3.33 (2H, partially under HDO).

EXAMPLE 54

5-Chloro-*N*-[2(S),3-dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

Prepared from from *(S)*-O-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-hydroxylamine and 5-dhloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzoic acid by the procedure described above for *N*-[(R)-2,3-dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide: m.p. 157-158 °C; [α]= +5.29° (c=1.02, methanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.91 (s, 1H), 8.66 (s, 1H), 7.58-7.55 (m, 2H), 7.34 (d, 1H, J=8.1 Hz), 6.72 (cm, 1H), 4.81 (d, 1H, J=4.1 Hz), 4.58 (t, 1H, J=5.9 Hz), 3.87-3.84 (m, 1H), 3.70-3.68 (m, 2H), 3.33 (2H, partially under HDO). Anal.calcd/found for $C_{16}H_{13}ClF_3IN_2O_4$: C, 37.20/37.47; H, 2.54/2.57; N 5.42/5.32; F, 11.03/11.09; Cl, 6.86/6.87; I, 24.56/24.80.

EXAMPLE 55

2-(4-Bromo-2-fluoro-phenylamino)-N-((R)-2,3-dihydroxy-propoxy)-3,4-difluoro-benzamide

Prepared in the manner of *N*-[2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide (Example 39) with the following exception: Organics were dried over sodium sulfate and concentrated to afford a white foam. This was heated to 100 °C under vacuum (0.5mm) for 1 hr to afford a glass: m.p. 52 °C (shrink), 70 °C melt; [α] = -4.4 °(c = 6.8, ethanol); ^{1}H NMR (400 MHz, CD_3OD) δ 7.40 [cm, 1H]; 7.29 [dd, J = 11.0, 2.2 Hz, 1H]; 7.16 [d, J = 8.5 Hz, 1H]; 6.98 [dd, J = 16.4, 9 Hz, 1H]; 6.73 [cm, 1H]; 3.94 [cm, 1H]; 3.83 [m, 2H]; 3.55 [m, 2H]. Anal. Calcd/Found for $C_{16}H_{14}BrF_3BrN_2O_4$: C, 44.16/43.77; H, 3.24/3.36; N, 6.44/6.09; F, 13.10/12.64; Br, 18.36/18.24.

The compounds of examples 56-61 were prepared by the general procedure of example 1.

EXAMPLE 56

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-vinyloxy-ethoxy)-benzamide

Yield: 55%; m.p. 141.5-143.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.01 (s, 1 H), 8.84 (s, 1 H), 7.77 (d, J = 1.7 Hz, 1 H), 7.51-7.42 (m, 2 H), 7.27 (ddd, J = 9.0, 8.8, 7.8 Hz, 1 H), 6.59 (dd, J = 8.6, 6.4 Hz, 1 H), 6.49 (dd, J = 14.2, 6.6 Hz, 1 H), 4.19 (d, J = 14.1 Hz, 1 H), 4.06 (br s, 2 H), 3.98 (d, J = 6.6 Hz, 1 H), 3.87 (br s, 2 H); ^{19}F NMR (376 MHz, DMSO-d_6) δ -132.4, -141.4; MS (APCI+) = 495.1; MS (APCI-) = 493.0. Anal. Calcd/found for $C_{17}H_{14}ClF_2N_2O_3$ with 0.08 moles residual C_6H_{14}: C, 41.86/41.90; H, 3.04/2.91; N, 5.59/5.72.

EXAMPLE 57

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(2-vinyloxy-ethoxy)-benzamide

Yield: 25%; m.p. 115-116 °C; ^{1}H-NMR (400 MHz; DMSO-d_6) δ 11.96 (s, 1H), 8.42 (s, 1H), 7.73 (d, 1H, J=1.7 Hz), 7.59 (m, 1H), 7.44 (dd, 1H, J=8.6, 1.7 Hz), 6.54 (m, 1H), 6.47 (dd, 1H, J=14.2, 6.6 Hz), 4.15 (d, 1H, J=14.2 Hz), 4.02 (s, 2H), 3.96 (dd, 1H, J=6.9, 1.7 Hz), 3.83 (s, 2H); ^{19}F-NMR (376 MHz; DMSO-d_6) δ -137.08 (d, 1F, J=20.2 Hz), -140.97 (s, 1F), -154.65 (s, 1F); MS (APCI$^+$) 513.0 (M+1, 100); MS (APCI) 511.0 (M-1, 65), 424.9 (100); IR (KBr) 1647 (C=O stretch), 1621, 1488 cm^{-1}. Anal. Calcd./found for $C_{17}H_{13}ClF_3IN_2O_3$: C, 39.83/40.04; H, 2.56/2.54; N, 5.46/5.32.

EXAMPLE 58

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-vinyloxy-ethoxy)-benzamide

Yield: 44%; m.p. 103.5-104 °C; ^{1}H-NMR (400 MHz; DMSO-d_6) δ 11.90 (s, 1H), 9.62 (s, 1H), 7.69 (dd, 1H, J=10.5, 2.0 Hz), 7.60 (m, 1H), 7.49 (d, 1H, J=8.3 Hz), 7.27 (m, 1H), 6.84 (d, 1H, J=11.7 Hz), 6.70 (m, 1H), 6.52 (dd, 1H, J=14.4, 6.8

Hz), 4.20 (dd, 1H, J=14.4, 2.0 Hz), 4.09 (m, 2H), 3.98 (dd, 1H, J=6.8, 1.7 Hz), 3.90 (m, 2H); ^{19}F-NMR (376 MHz; DMSO-d_6) δ -106.73 (s, 1F), -124.58 (s, 1F); MS (APCI$^+$) 461.0 (M+1, 100); MS (APCI) 459.0 (M-1, 100); IR (KBr) 1641 (C=O stretch), 1602 cm^{-1}. Anal.Calcd./found for $C_{17}H_{13}F_2IN_2O_3$: C, 44.37/44.42; H, 3.29/3.28; N, 6.09/5.89.

EXAMPLE 59

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-vinyloxy-ethoxy)-benzamide

^{1}H-NMR (400 MHz; DMSO-d_6) δ 11.89 (s, 1 H), 8.67 (s, 1 H), 7.57 (dd, 11.0, 1.7 Hz, 1 H), 7.41-7.32 (m, 2 H), 7.20 (m, 1 H), 6.66 (m, 1 H), 6.46 (dd, J = 14.2, 6.8 Hz, 1 H), 4.17 (dd, J = 14.2, 1.5 Hz, 1 H), 4.00 (br s, 2 H), 3.97 (dd, J = 6.7, 1.8 Hz, 1 H), 3.84 (br s, 2 H); ^{19}F-NMR (376 MHz; DMSO-d_6) δ -128.1(s, 1 F), -133.1 (s, 1 F), -144.3 (d, 17.7 Hz, 1 F). Anal.Calcd./found for $C_{17}H_{14}F_2IN_2O_3$: C, 42.70/42.30; H, 2.95/2.92; N, 5.86/5.52.

EXAMPLE 60

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-vinyloxy-ethoxy)-benzamide

Yield: 34%; m.p. 119-120 °C; ^{1}H-NMR (400 MHz; DMSO-d_6) δ 11.96 (s, 1H), 8.64 (s, 1H), 7.59 (m, 2H), 7.35 (d, 1H, J=8.3 Hz), 6.71 (m, 1H), 6.48 (dd, 1H, J=14.4, 6.8 Hz), 4.17 (d, 1H, J=14.2 Hz), 3.98 (m, 3H), 3.84 (m, 2H); ^{19}F-NMR (376 MHz; DMSO-d_6) δ -127.60 (s, 1F), -134.09 (d, 1F, J=15.2 Hz), -140.45 (d, 1F, J=17.7 Hz); MS (APCI) 511.0 (M-1, 100); IR (KBr) 1646 (C=O stretch), 1608 cm^{-1}. Anal.Calcd./found for $C_{17}H_{13}ClF_2IN_2O_3$: C, 39.83/39.78; H, 2.56/2.57; N, 5.46/5.36.

EXAMPLE 61

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-vinyloxy-ethoxy)-benzamide

Yield: 39%; m.p. 128-130 °C; ^{1}H-NMR (400 MHz; DMSO-d_6) δ 11.95 (s, 1H), 8.67 (s, 1H), 7.69 (d, 1H, J=6.4 Hz), 7.57 (dd, 1H, J=10.7, 1.7 Hz), 7.35 (d, 1H, J=8.1 Hz), 6.72 (m, 1H), 6.48 (dd, 1H, J=14.4, 6.6 Hz), 4.17 (d, 1H, J=14.2 Hz),

3.98 (m, 3H), 3.83 (s, 2H); ^{19}F-NMR (376 MHz; DMSO-d_6) δ -126.37 (s, 1F); -127.54 (s, 1F), -140.31 (d, 1F, J=17.7 Hz); MS (APCI$^+$) 558.9 (100), 556.9 (M+1, 98); MS (APCI) 556.9 (31), 554.9 (M-1, 32), 468.9 (100); IR (KBr) 1644 (C=O stretch), 1607, 1515, 1490 cm^{-1}. Anal.Calcd./found for $C_7H_{13}BrF_3IN_2O_3$: C, 36.65/36.71; H, 2.35/2.23; N, 5.03/4.97.

The compounds of Examples 62-64 were prepared by the general procedure of example 12.

EXAMPLE 62

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-*N*-(2-hydroxy-1,1-dimethyl-ethoxy)-benzamide

m.p.=179-181°C; ^{1}H NMR (400 MHz;DMSO-d_6) δ 11.36 (s, 1H), 8.48 (s, 1H), 7.76 (d, 1H, J=6.8), 7.72 (s, 1H), 7.43 (d, 1H, J=8.5), 6.59 (m, 1H), 4.55 (t, 1H, J=6.4), 3.20 (d, 2H, J=5.9), 1.09 (s, 6H); MS (APCI+) = 574.9/576.9. Anal.calcd/found for $C_{17}H_{15}BrClF_2IN_2O_3$: C 35.48/35.56, H 2.63/2.53, N 4.87/4.71, F 6.60/6.68.

EXAMPLE 63

3,4-Difluoro-*N*-(2-hydroxy-1,1-dimethyl-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

m.p.=175-176°C; ^{1}H NMR (400MHz;DMSO-d_6) δ 11.29 (s, 1H), 8.15 (s, 1H), 7.46 (s, 1H), 7.41 (m, 1H), 7.32 (d, 1H, J=8.3), 7.32 (q, 1H, J=16.4,8.8), 6.38 (m, 1H), 4.59 (bs, 1H), 3.15 (d, 2H, J=4.9), 2.17 (s, 3H), 1.08 (s, 6H); MS(APCI+)=477.0. Anal.calcd/found for $C_{18}H_{19}F_2IN_2O_3$ (0.05eq CH_2Cl_2): C 45.12/44.73, H 4.01/3.96, N 5.83/5.54, F 7.91/7.71.

EXAMPLE 64

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-2-methyl-propoxy)-benzamide

Yield: 17%; m.p. 140-153 °C; ^{1}H-NMR (400 MHz; DMSO-d_6) δ 11.94 (s, 1H), 8.82 (s, 1H), 7.76 (d, 1H, J=1.5 Hz), 7.48 (dd, 1H, J=8.5, 2.0 Hz), 7.42 (m, 1H),

7.25 (m, 1H), 6.57 (m, 1H), 4.58 (s, 1H), 3.63 (s, 2H), 1.12 (s, 6H); ^{19}F-NMR (376 MHz; DMSO-d_6) δ -132.53 (s, 1F), -141.45 (d, 1F); MS (APCI$^+$) 496.9 (M+1, 100); MS (APCI$^-$) 495.0 (M-1, 45), 406.9 (100); IR (KBr) 1637 cm^{-1} (C=O stretch).. Anal.Calcd./found for $C_{17}H_{16}ClF_2IN_2O_3$ with 0.03 mole residual acetone: C, 41.18/41.57; H, 3.27/3.14; N, 5.62/5.31.

The compounds of examples 65-76 were prepared by the general procedure of example 38.

EXAMPLE 65

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)- *N*-(2-hydroxy-1,1-dimethyl-ethoxy)-benzamide

m.p.=182-183°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.25 (s, 1H), 8.38 (s, 1H), 7.54 (d, 1H, J=11.0), 7.39 (m, 1H), 7.31 (d, 1H, J=8.1), 7.24 (dd, 1H, J=16.9, 9.5), 6.59-6.56 (m, 1H), 4.58, (m, 1H), 3.16 (d, 2H, J=6.3), 1.08 (s, 6H); MS(APCI+)=481.0. Anal.calcd/found for $C_{17}H_{16}F_3IN_2O_3$ (+0.47 $C_4H_8O_2$): C, 43.47/43.86; H, 3.82/3.40; N, 5.37/5.60.

EXAMPLE 66

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)- *N*-(2-hydroxy-1,1-dimethyl-ethoxy)-benzamide

m.p.=178-180°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.31 (s, 1H), 8.41 (s, 1H), 7.64 (d, 1H, J=7.1), 7.56 (d, 1H, J=11.0), 7.33 (d, 1H, J=8.3), 6.69-6.65 (m, 1H), 4.57 (t, 1H, J=6.1), 3.19 (d, 2H, J=6.6), 1.10 (s, 6H); MS(APCI+) = 514.9/516.9. Anal.calcd/found for $C_{17}H_{15}ClF_3IN_2O_3$: C, 39.67/39.99; H, 2.94/2.74; N, 5.44/5.31; F, 11.07/ 11.05.

EXAMPLE 67

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-2-methyl-propoxy)-benzamide

m.p. 156.7-156.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.85 (1H, s), 8.70 (1H, s), 7.55 (1H, dd, J=10.8Hz, 1.9Hz), 7.33-7.37 (2H, m), 7.17 (1H, dd, J=16.7Hz,

9.4Hz), 6.62-6.67 (1H, m), 4.57 (1H, br s), 3.58 (2H, s), 1.09 (6H, s). Anal. Calcd/Found for $C_{17}H_{16}F_2IN_2O_3$: C, 42.52/42.48; H, 3.36/3.21; N, 5.83/5.67; F, 11.87/11.51; I, 26.43/26.38.

EXAMPLE 68

3,4-Difluoro-N-(2-hydroxy-3-methoxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

m.p. 136.2-136.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (1H, s), 8.49 (1H, s), 7.50 (1H, d, J=1.7Hz), 7.34-7.41(2H, m), 7.14 (1H, dd, J=16.6Hz, 9.3Hz), 6.45 (1H, dd, J=8.4Hz, 5.6Hz), 4.97 (1H, s), 3.69-3.79 (3H, m), 3.25-3.31 (2H, m), 3.21 (3H, s), 2.21 (3H). Anal. Calcd/Found for $C_{18}H_{19}F_2IN_2O_4$: C,43.92/44.14; H,3.89/3.88; N,5.69/5.59; F, 7.72/7.79; I, 25.78/25.89.

EXAMPLE 69

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-methoxy-propoxy)-benzamide

m.p. 139.5-140.1°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.03 (1H, s), 8.83 (1H, s), 7.50-7.76 (2H, m), 7.47 (1H, dd, J=8.6Hz, 1.5Hz), 6.65-6.69(1H,m), 4.98 (1H, s), 3.70-3.90 (3H, m), 3.31 (2H, m), 3.22 (3H, s).

Anal. Calcd/Found for $C_{17}H_{13}BrClF_2IN_2O_4$: C,34.52/34.92; H,2.56/2.54; N, 4.74/4.67; F, 6.42/6.48; I, 21.45/21.12.

EXAMPLE 70

3,4-Difluoro-N-(1-hydroxymethyl-cyclopropylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

m.p. 165.4-165.6°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.74 (1H, s), 8.49 (1H, s), 7.47 (1H, d, J=1.5Hz), 7.31-7.36 (2H, m), 7.11 (1H, dd, J=16.5Hz, 9.4Hz), 6.43 (1H, dd, J=8.3Hz, 5.6Hz), 4.55 (1H, br s), 3.67 (2H, s), 3.33 (2H, s), 2.17 (3H, s), 0.36 (4H, J=4.9Hz). Anal. Calcd/Found for $C_{19}H_{19}F_2IN_2O_3$: C,46.74/46.87; H,3.92/3.93; N, 5.74/5.99; F, 7.78/7.64; I, 25.99/25.84.

EXAMPLE 71

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide

m.p. 152.6-153.9°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88(1H, s), 8.81 (1H, s), 7.75 (1H, s), 7.69 (1H, d, J=6.6Hz), 7.45 (1H, d, J=8.5Hz), 6.63-6.67 (1H, m), 4.53 (1H, br s), 3.73 (2H, s), 3.33 (2H, s), 0.36 (4H, J=4.9Hz). Anal. Calcd/Found for $C_{18}H_{13}BrClF_2IN_2O_3$: C:36.79/37.21; H,2.57/2.57; N,4.77/4.64; F, 6.47/6.58; I, 21.60/21.78.

EXAMPLE 72

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide

m.p. 175.2-175.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.00 (1H, s), 8.41 (1H, s), 7.47 (1H), 7.40 (1H, m), 7.33 (1H, d), 7.12 (1H, dd, J=16.6Hz, 9.3Hz), 6.54 (1H, br s), 6.44 (1H, dd, J=8.3Hz, 5.3Hz), 4.24 (1H,m), 3.83-3.98 (2H, m), 2.18 (3H, s). Anal. Calcd/Found for $C_{17}H_{14}F_5IN_2O_3$: C,39.56/39.87; H, 2.73/2.66; N, 5.43/5.30; F, 18.40/18.32; I, 24.58/24.63.

EXAMPLE 73

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide

m.p. 186.9-187.3°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.16 (1H, s), 8.77 (1H, s), 7.80 (1H, dd, J=7.0Hz, 1.5Hz), 7.75 (1H, d, J=1.7Hz), 7.47 (1H, dd, J=8.6Hz, 1.9Hz), 6.66 (1H, dd, J=8.5Hz, 5.9Hz), 6.55 (1H, br s), 4.31 (1H, m), 3.92-4.07 (2H, m). Anal. Calcd/Found for $C_{16}H_{10}BrClF_5IN_2O_3$: C, 31.22/31.52; H,1.64/1.60; N,4.55/4.46; F, 15.43/15.39; I, 20.62/20.87.

EXAMPLE 74

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-[trans-(2-hydroxymethyl-cyclopropylmethoxy)]-benzamide

m.p. 128.5-128.7 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.71(1H, s), 8.69 (1H, s), 7.54 (1H, dd, J=10.9Hz, 1.8Hz), 7.32-7.36 (2H, m), 7.17 (1H, dd, J=16.6Hz,

9.3Hz), 6.60-6.66 (1H, m), 4.43 (1H, t, J=5.6Hz), 3.54-3.65 (2H, m), 3.14-3.34 (2H, m), 0.85-0.89 (2H, m), 0.34-0.41 (2H, m). Anal. Calcd/Found for $C_{18}H_{16}F_3IN_2O_3$: C,43.92/44.23; H,3.28/3.23; N, 5.69/5.54; F, 11.58/11.47; I, 25.78/25.58.

EXAMPLE 75

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-[trans-(2-hydroxymethyl-cyclopropylmethoxy)]-benzamide

m.p. 152.5-153.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.76 (1H, s), 8.65 (1H, s), 7.56 (1H, m), 7.52-7.53 (1H, m), 7.32 (1H, d, J=8.5Hz), 6.66-6.72 (1H, m), 4.44-4.47 (1H, m), 3.54-3.62 (2H, m), 3.12-3.42 (2H, m), 0.81-0.89 (2H, m), 0.32-0.40 (2H, m). Anal. Calcd/Found for $C_{18}H_{15}ClF_3IN_2O_3$: C, 41.05/41.00; H, 2.87/2.96; N, 5.31/5.13; F, 10.82/10.48; I, 24.09/24.33.

EXAMPLE 76

N-(2,3-Dihydroxy-3-methyl-butoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

m.p.=180-183°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.85 (s, 1H), 8.69 (bs, 1H), 7.56 (d, 1H, J=10.7), 7.40 (m, 1H), 7.35 (d, 1H, J=9.0), 7.20 (dd, 1H, J=16.6, 8.3), 6.65 (m, 1H), 4.87 (bs, 1H), 4.31 (s, 1H), 4.07 (d, 1H, J=9.8), 3.65 (t, 1H, J=9.8), 3.44-3.41 (m, 1H), 1.05 (s, 3H), 0.97 (s, 3H); MS(APCI+)=511.1.
Anal.calcd/found for $C_{18}H_{18}F_3IN_2O_4$ (+0.22 eq $C_4H_8O_2$): C, 42.82/43.20; H, 3.76/3.61; N, 5.29/5.15.

EXAMPLE 77

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-phenylamino-ethoxy)-benzamide

The title compound was prepared in the manner described for example 1. A white solid: m.p.157.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.3 (s, 1H), 7.70 (m, 2H), 7.44 (dd, J=8.6 Hz, 1.95 Hz, 1H), 7.01 (t, J=8.1 Hz, 2H), 6.94 (t, J=9.2 Hz, 1H), 6.47 (m, 4H), 5.58 (br t, J=5.1 Hz, 1H), 3.91 (t, J=5.6 Hz, 2H), 3.19 (q, J=5.6 Hz, 2H); ^{19}F NMR (376 MHz, DMSO-d_6) δ -139.77 (s, 1F), -143.39 (d, J=20.2 Hz, 1F).

EXAMPLE 78

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-methylamino-ethoxy)-benzamide

Step A: To a solution of (2-aminooxy-ethyl)-methyl-carbamic acid tert-butyl ester (0.63 g, 3.31 mmol) and diisopropylethylamine (0.6 mL, 3.44 mmol) in dimethylformamide (10 mL) was added 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid pentafluorophenyl ester (1.66 g, 2.99 mmol). The resultant reaction mixture was stirred 5 h at ambient temperature and concentrated under reduced pressure. The residue was diluted with ether (100 mL), washed with water (2 x 25 mL) and brine (2x 25 mL), dried over magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography. Elution with dichloromethane afforded [2-({1-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanoyl}-aminooxy)-ethyl]-methyl-carbamic acid tert-butyl ester (1.05 g, 62%) as a white foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.85 and 11.80 (br s, 1 H), 8.49 (br s, 1 H), 7.50 (s, 1 H), 7.39 (m, 1 H), 7.35 (d, J = 8.3 Hz, 1 H), 7.14 (m, 1 H), 6.46 (dd, J = 7.8, 5.9 Hz, 1 H), 3.85 (br s, 2 H), 3.35 (br s, 2 H), 2.79 (br s, 3 H), 2.21 (s, 3 H), 1.36 and 1.33 (s, 9 H); ^{19}F NMR (376 MHz, DMSO-d_6) δ -132.9, -143.3 (d, J = 17.7 Hz); MS (APCI+) = 562.1.

Step B: Trifluoroacetic acid (3.0 mL, 39 mmol) was added to a 0 °C solution of [2-({1-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanoyl}-aminooxy)-ethyl]-methyl-carbamic acid tert-butyl ester (0.75 g, 1.3 mmol) in dichlormethane (12 mL). The resultant solution was stirred 2.5 h at 0 °C and diluted with ether (50 mL). Water (20 mL) was added and, with vigorous stirring, the pH of the aqueous layer was adjusted to pH 8 with saturated aqueous sodium bicarbonate. The heterogeneous mixture was stirred 30 min and the precipitate was removed by filtration and washed with water-ethanol (2:1) and acetone. The solid (471 mg) was dried overnight *in vacuo* and was further triturated with hot methanol and dried at 70 °C under reduced pressure to afford 3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-methylamino-ethoxy)-benzamide (272 mg) as a white powder: m.p. 183-185 (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.33 (s, 1 H), 7.69 (t, J = 7.0 Hz, 1 H), 7.46 (d, J = 1.7 Hz, 1 H), 7.33 (dd, J = 8.6, 2.0 Hz, 1

H), 6.95 (app q, J = 9.0 Hz, 1 H), 6.40 (t, J = 7.8 Hz, 1 H), 3.87 (br t, J = 4.4 Hz, 2 H), 2.82 (br s, 2 H), 2.47 (s, 3 H), 2.24 (s, 3 H); ^{19}F NMR (376 MHz, DMSO-d_6) δ -137.7 (d, J = 7.6 Hz), -143.3 (d, J = 20.2 Hz). Anal Calcd./Found for $C_{17}H_{18}F_2IN_3O_2$+0.07 $C_4H_{10}O$: C, 44.50/44.61; H, 4.01/3.97; N, 9.01/8.72.

EXAMPLE 79

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-methylamino-ethoxy)-benzamide, hydrochloride salt

Step A: A solution of 3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzoic acid (3.11 g, 7.91 mmol) in tetrahydrofuran (20 mL) was cooled with a –40 °C bath and treated with N-methylmorpholine (0.87 mL, 7.9 mmol). Diphenylphosphinic chloride (2.00 mL, 10.5 mmol) was added dropwise over 5 min and the reaction mixture was stirred for 90 min, during which time the temperature of the cooling bath slowly warmed to 0 °C. The reaction mixture was again cooled to –40 °C and (2-aminooxy-ethyl)-methyl-carbamic acid tert-butyl ester (2.00 g, 10.5 mmol) was added as a solution in tetrahydrofuran (6 mL). After an additional 10 min, N-methylmorpholine (1.33 mL, 12.1 mmol) was added. The temperature of the cooling bath was allowed to warm to ambient temperature over 4 h and the reaction mixture was further stirred overnight. The reaction was diluted with ethyl acetate (40 mL) and washed with saturated aqueous ammonium chloride (2 x 10 mL). The organics were dried over magnesium sulfate, concentrated and purified by silica gel chromatography. Elution with 35% ethyl acetate-hexanes afforded [2-({1-[3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-phenyl]-methanoyl}-aminooxy)-ethyl]-methyl-carbamic acid tert-butyl ester (3.28 g, 73% yield) as an off-white foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.84 and 11.75 (br s, 1 H total), 8.66 (br s, 1 H), 7.54 (dd, J = 10.9, 1.6 Hz, 1 H), 7.36 (br t, J = 8.8 Hz, 1 H), 7.33 (br d, J = 8.8 Hz), 7.20 (m, 1 H), 6.64 (m, 1 H), 3.85 (t, J = 5.2 Hz, 2 H), 3.34 (br s, 2 H), 2.81 and 2.79 (br s, 3 H total), 1.34 and 1.32 (s, 9 H total); ^{19}F NMR (376 MHz, DMSO-d_6) δ -128.0 (d, J = 32.9 Hz), -133.0, -144.2 (d, J = 17.7 Hz); MS (APCI-) = 564.1.

Step B: [2-({1-[3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-phenyl]-methanoyl}-aminooxy)-ethyl]-methyl-carbamic acid tert-butyl ester (3.28 g, 5.80

mmol) was dissolved in ethereal hydrogen chloride solution (20 mL, 1.0 M in diethyl ether). The resultant solution was stirred at ambient temperature for 48 h, during which precipitation of a white solid ensued. Hexanes (20 mL) was added and the reaction mixture was stirred vigorously for an additional 20 min. The reaction mixture was filtered, and the filter cake was broken up with a spatuala. The solid was washed with hexanes (50 mL) and ether (20 mL) and was dried in vacuo to afford a free-flowing, tan-colored powder (2.46 g, 85% yield). Recrystallization from acetonitrile afforded colorless needles: m.p. 173-176 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.27 (s, 1 H), 8.76 (br s, 2 H), 8.64 (s, 1 H), 7.55 (dd, J = 11.0, 1.9 Hz, 1 H), 7.47 (dd, J = 7.1, 6.3 Hz, 1 H), 7.33 (d, J = 8.3 Hz, 1 H), 7.23 (dt, J = 7.6, 9.2 Hz, 1 H), 6.64 (td, J = 8.8, 4.2 Hz, 1 H), 4.05 (t, 4.9 Hz, 2 H), 3.11 (br s, 2 H), 2.56 (t, J = 4.6 Hz, 3 H); ^{19}F NMR (376 MHz, DMSO-d_6) δ -128.2 (t, J = 10.1 Hz), -132.5 (d, J = 20.2 Hz), -144.0 (d, 20.2 Hz). Anal Calcd./Found for $C_{16}H_{16}F_5IN_3O_2Cl$: C, 38.31/38.20; H, 3.21/3.10; N, 8.38/8.34; F, 11.36/11.21; Cl, 7.07/7.05.

EXAMPLE 80

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-[2-(2,2,2-trifluoro-ethylamino)-ethoxy]-benzamide; hydrochloride

Step A: Diethylazodicarboxylate (3.60 mL, 22.9 mmol) was added dropwise over 30 min to a solution comprised of O-[2-(2,2,2-trifluoro-ethylamino)-ethyl]-hydroxylamine (3.19 g, 22.3 mmol, prepared as in *J. Am. Chem. Soc.* 1979, *101*, 4300), triphenylphosphine (6.05 g, 23.1 mmol), and N-hydroxyphthalimide (3.65 g, 22.4 mmol). The resultant reaction mixture was stirred at ambient temperature. After 20 h, the reaction mixture was concentrated and the residue was dissolved in 60 mL of warm chloroform. Upon cooling, crystallization of diethyl 1,2-hydrazaine dicarboxylate ensued. The precipitate was filtered and the filtrate was concentrated and further diluted with ether. A single crystal of triphenylphosphine oxide was added, initiating copious precipitation. The resultant precipitate was removed by filtration and the filtrate was concentrated in vacuo and chromatographed on silica gel. Elution with hexanes-ethyl acetate (2:1) afforded 2-[2-(2,2,2-trifluoro-ethylamino)-ethoxy]-isoindole-1,3-dione (4.05

g, 63% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84-7.73 (m, 4H), 4.30 (t, J=4.8 Hz, 2H), 3.26 (q, J=9.5 Hz, 2H), 3.00 (t, J=4.9 Hz, 2H), 2.33 (br s, 1H); MS (APCI+) = 289.0.

Step B: Dichloromethane (5 mL) was added to 2-[2-(2,2,2-trifluoro-ethylamino)-ethoxy]-isoindole-1,3-dione (0.46 g, 1.6 mmol) and the resultant solution was cooled to 0 °C. Methylhydrazine (0.086 mL, 1.62 mmol) was added and the resultant solution was stirred at ambient temperature for 1 h. Ether (20 mL) was added and the precipitate was filtered and the filtrate was concentrated in vacuo. Dimethylformamide (5 mL) was added and the resultant solution was treated sequentially with 3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid pentafluorophenyl ester (0.847 g, 1.51 mmol) and diisopropylethylamine (0.60 mL, 3.4 mmol). The resultant reaction mixture was stirred overnight, diluted with ethyl acetate and washed with water (4x) and saturated brine, dried over magnesium sulfate and concentrated in vacuo. Purification by silica gel chromatography (hexanes-ethyl acetate, 1:1) afforded 3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-[2-(2,2,2-trifluoro-ethylamino)-ethoxy]-benzamide (0.70 g, 83% yield) as a waxy foam: ^{1}H NMR (400 MHz, Acetone-d_6) δ 10.98 (br s, 1H), 8.69 (br s, 1H), 7.52 (br s, 2H), 7.39 (dd, J=8.6 Hz, 2.0 Hz, 1H), 7.00 (m, 1H), 6.55 (dd, J=8.6 Hz, 6.4 Hz, 1H), 3.27 (q, J=10.0 Hz, 2H), 2.90 (br t, J=4.9 Hz, 2H), 2.82 (br s, 2H), 2.30 (s, 3H); ^{19}F NMR (376 MHz, Acetone-d_6) δ -73.1 (t, J=10.0Hz, 3F), -133.8 (s, 1F), -143.2 (s, 1F); MS (APCI+) = 530.0.

Step C: The hydrochloride salt was prepared by treatment of a solution of 3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-[2-(2,2,2-trifluoro-ethylamino)-ethoxy]-benzamide (375 mg, 0.708 mmol) in ether (5 mL) with ethereal hydrogen chloride (2 mL, 1.0 M in ether) and precipitation by addition of hexanes (50 mL). The resultant solid was dried in vacuo at 75 °C overnight to afford a straw-colored powder: ^{1}H NMR (400 MHz, Acetone-d_6) δ 12.35 (br s, 1H), 8.84 (br s, 1H), 7.73 (br s, 1H), 7.54 (s, 1H), 7.40 (dd, J=8.4 Hz, 1.9 Hz, 1H), 7.00 (apparent q, J=8.4 Hz, 1H), 6.58 (dd, J=8.4 Hz, 6.40 Hz, 1H), 4.43 (br s, 2H), 4.17 (br q, 2H), 3.59 (br s, 2H), 2.30 (s, 3H); ^{19}F NMR (376 MHz, Acetone-d_6) δ -68.39 (s, 3F), -133.07 (s, 1F), -143.20 (s, 1F). Anal Calcd./Found for $C_{18}H_{17}F_5IN_3O_2$+0.86 HCl: C, 38.57/38.77; H, 3.21/3.04; N, 7.49/7.19; Cl, 5.44/5.66.

EXAMPLE 81

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-ethoxy)-N-methyl-benzamide

A solution of 2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-ethoxy)-benzamide (0.460 g, 1.02 mmol) in dimethylformamide (10 mL) was sequentially treated with potassium carbonate (0.61 g, 4.4 mmol) and iodomethane (0.075 mL, 1.2 mmol). The resultant reaction mixture was stirred 1 h at ambient temperature, was diluted with excess water and was extracted with ethyl acetate. The organic extracts were washed with brine, dried over magnesium sulfate and concentrated in vacuo. Chromatography on silica gel afforded a white solid (200 mg). Further purification by chromatography on C-18 reverse phase silica gel (30% water-acetonitrile) afforded 2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-ethoxy)-N-methyl-benzamide (139 mg, 29% yield) as a white foam: ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.45 (s, 1 H), 7.79 (d, J = 2.0 Hz, 1 H), 7.69 (dd, J = 8.8, 6.6 Hz, 1 H), 7.60 (dd, J = 8.5, 2.0 Hz, 1 H), 7.28 (d, J = 8.5 Hz, 1 H), 7.09 (dd, J = 11.4, 2.3 Hz, 1 H), 6.77 (td, J = 8.6, 2.5 Hz, 1 H), 3.90 (t, J = 2 H), 3.85 (br m, OH), 3.58 (t, J = 4.5 Hz, 2 H), 3.38 (s, 3 H); ^{19}F-NMR (376 MHz, Acetone-d_6) δ -109.8 (dd, J = 10.1, 7.6 Hz); MS (APCI+) = 465.0.

EXAMPLE 82

Acetic acid 2-({1-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanoyl}-aminooxy)-ethyl ester

To a 0 °C solution of 3,4,5-trifluoro-N-(2-hydroxy-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide (0.25g, 0.536 mmol) in THF (10.72 mL) was added triethylamine (0.113 mL, 0.804 mmol). After 5 min, acetyl chloride (0.039 mL, 0.536 mmol) was added to the cold solution, which immediately produced a precipate. After stirring for 50 min between 0-5 °C, the reaction mixture was partitioned between water (20 mL) and ethyl acetate (20mL). The aqueous layer was extracted with ethyl acetate (20 mL). The organic layers were combined and dried over anhydrous magnesium sulfate. The resultant mixture was filtered and the filter cake was thoroughly rinsed with ethyl acetate. The filtrate was

concentrated *in vacuo* to obtain a yellow oil (0.1755g). Chromatographed crude oil using a gradient of hexanes and ethyl acetate. Combined fractions and removed the solvent *in vacuo* to obtain a solid. The solid was recrystalized in a mixture of hexanes/acetone to afford 0.0221g (8%) of a solid; ^{1}H NMR (400 MHz, Acetone-d_6): δ 10.15 (br s, 1H), 8.49 (br s, 1H), 7.88 (t, J=0.9Hz, 1H),7.56 (s, 1H), 7.43 (d, J=8.3Hz, 1H), 6.69 (dd, J=8.55, 5.86Hz, 1H), 4.53 (br s, 2H), 4.19 (br s, 2H), 2.33 (s, 3H), 1.81 (br s, 3H). ^{19}F NMR (375 MHz, Acetone-d_6): δ -139.52 (br t, 1F), -146.62 (br q, 1F), -153.43 (br s, 1F). Anal. Calcd/Found for $C_{18}H_{16}F_3IN_2O_4$: C, 42.54/40.87; H, 3.17/2.98; N, 5.51/5.17.

EXAMPLE 83

[3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-phenyl]-(4-hydroxy-isoxazolidin-2-yl)-methanone

To a stirring solution of 3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzoic acid pentafluorophenyl ester (171 mg, 0.306 mmol) and 4-hydroxytetrahydroisoxazol-2-inm chloride (BIONET, 58 mg, 0.46 mmol) in dimethylformamide (2 mL) was added 4-methylmorpholine (0.1 mL, 0.91 mmol). The resultant reaction mixture was stirred at ambient temperature for 3 h. Ethyl acetate (50 mL) was added the mixture was washed with water (3 x 10 mL) and saturated brine solution (10 mL). The extracts were dried over magnesium sulfate and concentrated in vacuo. Chromatography (10% methanol-dichloromethane) afforded a tan-colored oil that solidified upon standing. Recrystallization from acetone-ether afforded [3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-phenyl]-(4-hydroxy-isoxazolidin-2-yl)-methanone (61 mg, 43% yield) as a white powder: m.p. 122-124 °C; ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.97 (br s, 1 H), 7.51-7.45 (m, 2 H), 7.38 (ddd, J = 8.6, 1.7, 1.2 Hz, 1 H), 7.12 (m, 1 H), 6.68 (td, J = 8.8, 5.2 Hz, 1 H), 4.82 (m, 1 H), 4.71 (br d, J = 4.2 Hz, OH), 3.98 (dd, J = 8.8, 4.2 Hz, 1 H), 3.96-3.88 (m, 2 H), 3.75 (dd, J = 11.8, 0.9 Hz, 1 H); ^{19}F-NMR (376 MHz, Acetone-d_6) δ -30.5, -135.4, -144.4. Anal Calcd/Found $C_{16}H_{12}F_3IN_2O_2$: C, 41.40/41.52; H, 2.61/2.53; N, 6.03/6.05.

EXAMPLE 84

5-Bromo-*N*-(2,3-dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-phenylamino)-benzamide

A solution of 5-bromo-*N*-(2,3-dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide (0.240g, 0.429 mmol) and triethylamine (0.2g, 1.98 mmol) in tetrahydrofuran (16 mL) was hydrogenated over Raney Nickel (0.12g, pre-rinsed with tetrahydrofuran) at 10 psig at room temperature for a total of 7 hours. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The afforded residue was partitioned between ethyl acetate and water. The organics were washed twice with water, twice with saturated brine, collected, dried over sodium sulfate, filtered and concentrated *in vacuo*. HPLC purification was performed using a YMC 30x100mm 5u (C18) column in 0-100% acetonitrile (3.0% n-propanol)/100-0% water (3.0% n-propanol)at 30 mL/min. The desired fractions were collected, concentrated and dried in a vacuum oven overnight at 50°C to afford 5-bromo-*N*-(2,3-dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-phenylamino)-benzamide as a white solid (0.054g, 30%): m.p.=143.5-144.5°C; ^{1}NMR (400 MHz, DMSO-d_6) δ 11.95 (bs, 1H), 8.74 (bs, 1H), 7.68 (d, 1H, J=6.1 Hz), 7.17 (t, 1H, J=9.8 Hz), 7.01-7.04 (m, 1H), 6.94 (m, 2H), 4.81 (m, 1H), 4.57 (m, 1H), 3.86 (m, 1H), 3.69-3.71 (m, 2H), 3.3, (2H, under HDO); MS(APCI+)=435.0/437.0.

EXAMPLE 85

N-(2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-phenylamino)-benzamide

A solution of *N*-(2,3-dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide (0.260g, 0.539 mmol) and triethylamine (2.0 mL, 14.3mmol) in tetrahydrofuran (14 mL) was hydrogenated over Raney Nickel (0.2g wet) at 50 psig at room temperature for 20 hours. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The afforded residue was partitioned between ethyl acetate and water. The organics were washed twice with saturated sodium bicarbonate solution, twice with water, collected, dried over sodium sulfate, filtered and concentrated *in vacuo*. HPLC purification was performed using a YMC 30x100mm 5u (C18) column in 0-100% acetonitrile

(3.0% n-propanol)/100-0% water (3.0% n-propanol) at 30 mL/min. The desired fractions were collected and concentrated. The afforded residue was extracted with ethyl acetate/water. Organic layers were washed with saturated NaCl solution, collected and dried *in vacuo* to afford *N*-(2,3-dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-phenylamino)-benzamide as a white solid (0.061g, 31%): m.p.=113-115°C; ^{1}NMR (400 MHz,DMSO-d_6) δ 11.90 (s, 1H), 8.73 (s, 1H), 7.37 (m, 1H), 7.10-7.19 (m, 2H), 7.02 (t, 1H, J=7.4 Hz), 6.84-6.93 (m, 2H), 4.82 (m, 1H), 4.57-4.58 (m, 1H), 3.86-3.88 (m, 1H), 3.67-3.73 (m, 2H), 3.3 (2H, under HDO); MS(APCI+)=357.1; Anal.calcd/found for $C_{16}H_{15}F_3N_2O_4$: C, 53.94/53.97; H, 4.24/4.37; N, 7.86/7.83.

EXAMPLES 86-97

Examples 86 to 97 were prepared utilizing combinatorial synthetic methods, as detailed below, by the combination of the respective alkoxyamine and pentafluorophenyl ester, prepared as described above. General Procedure:

Step A: An array of 2-dram vials was charged with the appropriate pentafluorophenyl ester diarylamine (0.12 mmol) as a solid and diluted with 2 mL of *N,N*-dimethylformamide. Using a bulk dispenser, each reaction was charged with 0.2 grams of polymer-supported morpholine resin (commercially available from Novabiochem or prepared by the method of Booth and Hodges: *J. Am. Chem. Soc.*, 1997, *119*, 4842). Solutions were prepared of the hydroxylamine acetonides in *N,N*-dimethylformamide (0.8M, 1.6mL) and dispensed (0.1 mmol, 0.2 mL) into the corresponding reaction vial. The reactions were sealed with teflon coated caps and were allowed to shake on an orbital shaker for 5 days at ambient temperature. The 14 reactions were charged with 0.2 grams of polymer-supported tris(2-aminoethyl)amine [Novabiochem; see also: Booth, R. J.; Hodges, J. C. *J. Am. Chem. Soc.*, 1997, *119*, 4842.], 0.1 grams of polymer-supported methylisocyanate [Novabiochem; see also: Booth, R. J.; Hodges, J. C. *J. Am. Chem. Soc.*, 1997, *119*, 4842.], and 1 mL of dichloromethane. The reaction vessels were resealed and allowed to shake an additional 6 hours at ambient temperature. The reactions were filtered through a Specdisk 3A filter and rinsed

with 6 mL of a 10% methanol/dichloromethane solution and concentrated via a nitrogen stream.

Step B: The resulting acetonide benzamides were charged with 2 mL of methanol, 0.05 mL of deionized water, approximately 2 milligrams of *p*-toluenesulfonic acid, and 0.1 grams of glycerol resin. Reactions were sealed with teflon coated caps and allowed to shake for 17 hours. The reactions were filtered through a Specdisk 3A filter and washed with 6 mL of 50% methanol in dichloromethane and concentrated via a nitrogen stream. Purification was performed on all samples using a SQ1600 Combi-Flash column eluting with acetonitrile/water (0.05% trifluoroacetic acid). LC/MS was performed using CPI 120SE C18 column (4.6x 50 μm) eluting with acetonitrile/water (0.05% trifluoroacetic acid).

Example No.	Compound	Formula	Exact Mass Found
86	2-(2-Chloro-4-iodo-phenylamino)-*N*-(2,3-dihydroxy-propoxy)-3,4-difluoro-benzamide	$C_{16}H_{16}ClF_2IN_2O_4$	499 (APCI +)
87	2-(2-Chloro-4-iodo-phenylamino)-*N*-(2,3-dihydroxy-propoxy)-3,4,5-trifluoro-benzamide	$C_{16}H_{13}ClF_3IN_2O_4$	517 (APCI +)
88	5-Bromo-2-(2-chloro-4-iodo-phenylamino)-*N*-(2,3-dihydroxy-propoxy)-3,4-difluoro-benzamide	$C_{16}H_{13}BrClF_2IN_2O_4$	577/579 (APCI +)
89	*N*-(2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	$C_{17}H_{17}F_2IN_2O_4$	479 (APCI+)
90	*N*-(2,3-Dihydroxy-propoxy)-3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	$C_{17}H_{16}F_3IN_2O_4$	495 (APCI⁻)
91	5-Bromo-*N*-(2,3-dihydroxy-propoxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	$C_{17}H_{16}BrF_2IN_2O_4$	557/559 (APCI +)
92	2-(2-Chloro-4-iodo-phenylamino)-*N*-(3,4-dihydroxy-butoxy)-3,4-difluoro-benzamide	$C_{17}H_{16}ClF_2IN_2O_4$	513 (APCI +)
93	2-(2-Chloro-4-iodo-phenylamino)-N-(3,4-	$C_{17}H_{13}ClF_3IN_2O_4$	531 (APCI +)

	dihydroxy-butoxy)-3,4,5-trifluoro-benzamide		
94	5-Bromo-2-(2-chloro-4-iodo-phenylamino)-*N*-(3,4-dihydroxy-butoxy)-3,4-difluoro-benzamide	$C_{17}H_{15}BrClF_2IN_2O_4$	591/593 (APCI +)
95	*N*-(3,4-Dihydroxy-butoxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	$C_{18}H_{19}F_2IN_2O_4$	493 (APCI +)
96	*N*-(3,4-Dihydroxy-butoxy)-3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	$C_{18}H_{18}F_3IN_2O_4$	511 (APCI +)
97	5-Bromo-*N*-(3,4-dihydroxy-butoxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	$C_{18}H_{18}BrF_2IN_2O_4$	571/573 (APCI +)

EXAMPLES 98-235

Examples 98-235 were prepared utilizing combinatorial synthetic methods, as detailed below, by the combination of the respective alkoxyamine and pentafluorophenyl ester, prepared as described above. General Procedure: Two-dram vials were each charged with 100-110 mg of polymer-supported morpholine (3.55 mmol N/g) employing a bulk resin dispenser. [Polymer–supported morpholinomethyl resin is commercially available (Novabiochem) or may be prepared by the method of Booth and Hodges: *J. Am. Chem. Soc.*, 1997, *119*, 4842.] The appropriate vials were treated sequentially with a 0.08 M stock solution of the alkoxyamine in DMF (0.6 mL, 0.048 mmol) and a 0.12 M stock solution of the pentafluorophenyl ester in DMF (0.48 mL, 0.0576 mmol, 1.2 eq). The vials were sealed with Teflon-lined caps and agitated on an orbital shaker at ambient temperature. After 48 h, the reaction mixtures were treated with

polymer-supported tris(2-aminoethyl)amine (100 mg, 4.28 mmol/g) [Novabiochem; see also: Booth, R. J.; Hodges, J. C. *J. Am. Chem. Soc.*, 1997, *119*, 4842.] and dichloromethane (1.0 mL). The vials were capped again and shaken an additional 6 h. The solids were removed by filtration though a Speckdisc 3A filter and washed with 10% methanol-dichloromethane solution (3 x 2mL). The filtrates were concentrated under a stream of nitrogen and purified by HPLC using a SQ1600 Combiflash column eluting with acetonitrile/water (0.05% trifluoroacetic acid). LC/MS was performed using CPI 120SE C18 column (0.0046x 0.050 mm) eluting with acetonitrile/water (0.05% trifluoroacetic acid).

Example No.	Compound	Formula	Exact Mass (APCI+)
98	5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-propoxy)-benzamide	$C_{16}H_{13}BrClF_2IN_2O_3$	561/563 (M+1)
99	2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-propoxy)-benzamide	$C_{16}H_{14}ClF_2IN_2O_3$	483 (M+1)
100	3,4,5-Trifluoro-N-(3-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide	$C_{17}H_{16}F_3IN_2O_3$	481 (M+1)
101	2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(3-hydroxy-propoxy)-benzamide	$C_{16}H_{13}ClF_3IN_2O_3$	501 (M+1)
102	5-Bromo-3,4-difluoro-N-(3-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide	$C_{17}H_{16}BrF_2IN_2O_3$	541/543 (M+1)
103	3,4-Difluoro-N-(3-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide	$C_{17}H_{17}F_2IN_2O_3$	463 (M+1)
104	2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-butoxy)-benzamide	$C_{17}H_{16}ClF_2IN_2O_3$	496.9 (M+1)
105	2-(2-Chloro-4-iodo-phenylamino)-3,4,5-	$C_{17}H_{15}ClF_3IN_2O_3$	514.9 (M+1)

	trifluoro-N-(2-hydroxy-butoxy)-benzamide		
106	3,4,5-Trifluoro-N-(2-hydroxy-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide	$C_{18}H_{18}F_3IN_2O_3$	494.9 (M+1)
107	5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-butoxy)-benzamide.	$C_{17}H_{15}BrClF_2IN_2O_3$	574.8/576.8 (M+1)
108	5-Bromo-3,4-difluoro-N-(2-hydroxy-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide	$C_{18}H_{18}BrF_2IN_2O_3$	554.9/556.9 (M+1)
109	3,4-Difluoro-N-(2-hydroxy-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide	$C_{18}H_{19}F_2IN_2O_3$	476.9 (M+1)
110	5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-butoxy)-benzamide	$C_{17}H_{15}Cl_2F_2IN_2O_3$	530.8 (M+1)
111	5-Chloro-3,4-difluoro-N-(2-hydroxy-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide	$C_{18}H_{18}ClF_2IN_2O_3$	510.9 (M+1)
112	3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-butoxy)-benzamide	$C_{17}H_{16}F_3IN_2O_3$	481.1 (M+1)
113	5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-butoxy)-benzamide	$C_{17}H_{15}BrF_3IN_2O_3$	559.0/561.0 (M+1)

114	5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-butoxy)-benzamide	$C_{17}H_{15}ClF_3IN_2O_3$	515.1 (M+1)
115	4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-butoxy)-benzamide	$C_{17}H_{16}F_3IN_2O_3$	481.1 (M+1)
116	5-Chloro-2-(2,4-difluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-butoxy)-benzamide	$C_{17}H_{15}ClF_4N_2O_3$	407.4 (M+1)
117	2-(2,4-Difluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-butoxy)-benzamide	$C_{17}H_{16}F_4N_2O_3$	373.5 (M+1)
118	2-(4-Bromo-2-fluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-butoxy)-benzamide	$C_{17}H_{16}BrF_3N_2O_3$	433.3/435.3 (M+1)
119	5-Chloro-3,4-difluoro-N-(2-hydroxy-1-methyl-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide	$C_{17}H_{16}ClF_2IN_2O_3$	496.9 (M+1)
120	2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-1-methyl-ethoxy)-benzamide	$C_{16}H_{14}ClF_2IN_2O_3$	482.9 (M+1)
121	2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(2-hydroxy-1-methyl-ethoxy)-benzamide	$C_{16}H_{13}ClF_3IN_2O_3$	500.9 (M+1)
122	3,4,5-Trifluoro-N-(2-	$C_{17}H_{16}F_3IN_2O_3$	480.9 (M+1)

	hydroxy-1-methyl-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide		
123	5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-1-methyl-ethoxy)-benzamide	$C_{16}H_{13}BrClF_2IN_2O_3$	560.8/562.8 (M+1)
124	5-Bromo-3,4-difluoro-N-(2-hydroxy-1-methyl-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide	$C_{17}H_{16}BrF_2IN_2O_3$	540.8/542.8 (M+1)
125	2-(4-Chloro-2-fluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-1-methyl-ethoxy)-benzamide	$C_{16}H_{14}ClF_3N_2O_3$	375.0 (M+1)
126	3,4-Difluoro-N-(2-hydroxy-1-methyl-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide	$C_{17}H_{17}F_2IN_2O_3$	462.9 (M+1)
127	5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-1-methyl-ethoxy)-benzamide	$C_{16}H_{13}Cl_2F_2IN_2O_3$	516.8 (M+1)
128	3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-1-methyl-ethoxy)-benzamide	$C_{16}H_{14}F_3IN_2O_3$	466.9 (M+1)
129	5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-1-methyl-ethoxy)-benzamide	$C_{16}H_{13}BrF_3IN_2O_3$	545.0/547.0 (M+1)
130	5-Chloro-3,4-difluoro-2-(2-	$C_{16}H_{13}ClF_3IN_2O_3$	500.9 (M+1)

	fluoro-4-iodo-phenylamino)-N-(2-hydroxy-1-methyl-ethoxy)-benzamide		
131	4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-1-methyl-ethoxy)-benzamide	$C_{16}H_{14}F_3IN_2O_3$	466.9 (M+1)
132	5-Chloro-2-(2,4-difluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-1-methyl-ethoxy)-benzamide	$C_{16}H_{13}ClF_4N_2O_3$	393.4 (M+1)
133	2-(2,4-Difluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-1-methyl-ethoxy)-benzamide	$C_{16}H_{14}F_4N_2O_3$	359.4 (M+1)
134	2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-methoxy-ethoxy)-benzamide	$C_{16}H_{14}ClF_2IN_2O_3$	482.9 (M+1)
135	2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(2-methoxy-ethoxy)-benzamide	$C_{16}H_{13}ClF_3IN_2O_3$	500.9 (M+1)
136	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-methoxy-ethoxy)-benzamide	$C_{17}H_{17}F_2IN_2O_3$	462.9 (M+1)
137	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-methoxy-ethoxy)-benzamide	$C_{17}H_{16}BrF_2IN_2O_3$	540.8/542.8 (M+1)
138	3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-	$C_{17}H_{16}F_3IN_2O_3$	480.9 (M+1)

	methoxy-ethoxy)-benzamide		
139	5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-methoxy-ethoxy)-benzamide	$C_{16}H_{13}BrClF_2IN_2O_3$	560.8/562.8 (M+1)
140	5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-methoxy-ethoxy)-benzamide	$C_{16}H_{13}Cl_2F_2IN_2O_3$	516.8 (M+1)
141	5-Chloro-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-methoxy-ethoxy)-benzamide	$C_{17}H_{16}ClF_2IN_2O_3$	496.9 (M+1)
142	5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-methoxy-ethoxy)-benzamide	$C_{16}H_{13}ClF_3IN_2O_3$	501.1 (M+1)
143	2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide	$C_{20}H_{21}ClF_2IN_3O_4$	568.0 (M+1)
144	5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide	$C_{20}H_{20}BrClF_2IN_3O_4$	645.9/647.9 (M+1)
145	2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide	$C_{20}H_{20}ClF_3IN_3O_4$	585.9 (M+1)
146	3,4,5-Trifluoro-N-(2-	$C_{21}H_{23}F_3IN_3O_4$	566.0 (M+1)

	hydroxy-3-morpholin-4-yl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide		
147	5-Bromo-3,4-difluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide	$C_{21}H_{23}BrF_2IN_3O_4$	625.9/627.9 (M+1)
148	3,4-Difluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide	$C_{21}H_{24}F_2IN_3O_4$	548.0 (M+1)
149	5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide	$C_{20}H_{20}Cl_2F_2IN_3O_4$	601.9 (M+1)
150	5-Chloro-3,4-difluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide	$C_{21}H_{23}ClF_2IN_3O_4$	582.0 (M+1)
151	3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide	$C_{20}H_{21}F_3IN_3O_4$	551.9 (M+1)
152	5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide	$C_{20}H_{20}ClF_3IN_3O_4$	585.8 (M+1)
153	4,5-Difluoro-2-(2-fluoro-4-	$C_{20}H_{21}F_3IN_3O_4$	551.9 (M+1)

	iodo-phenylamino)-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide		
154	5-Chloro-2-(2,4-difluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide	$C_{20}H_{20}ClF_4N_3O_4$	478.4 (M+1)
155	2-(4-Chloro-2-fluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide	$C_{20}H_{21}ClF_3N_3O_4$	460.0 (M+1)
156	2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-propoxy)-benzamide	$C_{16}H_{14}ClF_2IN_2O_3$	482.9 (M+1)
157	3,4,5-Trifluoro-N-(2-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide	$C_{17}H_{16}F_3IN_2O_3$	480.9 (M+1)
158	5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-propoxy)-benzamide	$C_{16}H_{13}BrClF_2IN_2O_3$	560.8/562.8 (M+1)
159	5-Bromo-3,4-difluoro-N-(2-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide	$C_{17}H_{16}BrF_2IN_2O_3$	540.8/542.8 (M+1)
160	2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(2-hydroxy-propoxy)-benzamide	$C_{16}H_{13}ClF_3IN_2O_3$	500.8 (M+1)
161	5-Chloro-2-(2-chloro-4-	$C_{16}H_{13}Cl_2F_2IN_2O_3$	516.8 (M+1)

	iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-propoxy)-benzamide		
162	3,4-Difluoro-N-(2-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide	$C_{17}H_{17}F_2IN_2O_3$	462.9 (M+1)
163	5-Chloro-3,4-difluoro-N-(2-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide	$C_{17}H_{16}ClF_2IN_2O_3$	496.9 (M+1)
164	3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-propoxy)-benzamide	$C_{16}H_{14}F_3IN_2O_3$	466.9 (M+1)
165	5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-propoxy)-benzamide	$C_{16}H_{13}ClF_3IN_2O_3$	500.8 (M+1)
166	5-Chloro-2-(2,4-difluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-propoxy)-benzamide	$C_{16}H_{13}ClF_4N_2O_3$	393.1 (M+1)
167	2-(2,4-Difluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-propoxy)-benzamide	$C_{16}H_{14}F_4N_2O_3$	359.4 (M+1)
168	2-(4-Chloro-2-fluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-propoxy)-benzamide	$C_{16}H_{14}ClF_3N_2O_3$	375.1 (M+1)
169	4,5-Difluoro-2-(2-fluoro-4-	$C_{16}H_{14}F_3IN_2O_3$	466.9 (M+1)

	iodo-phenylamino)-N-(2-hydroxy-propoxy)-benzamide		
170	2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(2-hydroxy-2-methyl-propoxy)-benzamide	$C_{17}H_{15}ClF_3IN_2O_3$	514.9 (M+1)
171	3,4,5-Trifluoro-N-(2-hydroxy-2-methyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide	$C_{18}H_{18}F_3IN_2O_3$	494.9 (M+1)
172	5-Bromo-3,4-difluoro-N-(2-hydroxy-2-methyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide	$C_{18}H_{18}BrF_2IN_2O_3$	554.9/556.9 (M+1)
173	5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-2-methyl-propoxy)-benzamide	$C_{17}H_{15}BrClF_2IN_2O_3$	574.8/576.8 (M+1)
174	3,4-Difluoro-N-(2-hydroxy-2-methyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide	$C_{18}H_{19}F_2IN_2O_3$	477.0 (M+1)
175	5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-2-methyl-propoxy)-benzamide	$C_{17}H_{15}Cl_2F_2IN_2O_3$	530.9 (M+1)
176	5-Chloro-3,4-difluoro-N-(2-hydroxy-2-methyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide	$C_{18}H_{18}ClF_2IN_2O_3$	510.9 (M+1)
177	3,4-Difluoro-2-(2-fluoro-4-	$C_{17}H_{16}F_3IN_2O_3$	481.1 (M+1)

	iodo-phenylamino)-N-(2-hydroxy-2-methyl-propoxy)-benzamide		
178	5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-2-methyl-propoxy)-benzamide	$C_{17}H_{15}BrF_2IN_2O_3$	559.0/561.0 (M+1)
179	5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-2-methyl-propoxy)-benzamide	$C_{17}H_{15}ClF_2IN_2O_3$	515.1 (M+1)
180	5-Chloro-2-(2,4-difluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-2-methyl-propoxy)-benzamide	$C_{17}H_{15}ClF_4N_2O_3$	407.4 (M+1)
181	2-(2,4-Difluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-2-methyl-propoxy)-benzamide	$C_{17}H_{16}F_4N_2O_3$	373.5 (M+1)
182	2-(4-Bromo-2-fluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-2-methyl-propoxy)-benzamide	$C_{17}H_{16}BrF_3N_2O_3$	433.3/435.3 (M+1)
183	Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide	$C_{22}H_{18}ClF_2IN_2O_4$	575.0 (M+1)
184	2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide	$C_{22}H_{17}ClF_3IN_2O_4$	592.9 (M+1)

185	3,4,5-Trifluoro-N-(2-hydroxy-3-phenoxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide	$C_{23}H_{20}F_3IN_2O_4$	573.0 (M+1)
186	5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide	$C_{22}H_{17}BrClF_2INO_4$	652.8/654.8 (M+1)
187	5-Bromo-3,4-difluoro-N-(2-hydroxy-3-phenoxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide	$C_{23}H_{20}BrF_2IN_2O_4$	632.9/634.9 (M+1)
188	3,4-Difluoro-N-(2-hydroxy-3-phenoxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide	$C_{23}H_{21}F_2IN_2O_4$	555.0 (M+1)
189	5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide	$C_{22}H_{17}Cl_2F_2IN_2O_4$	608.9 (M+1)
190	5-Chloro-3,4-difluoro-N-(2-hydroxy-3-phenoxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide	$C_{23}H_{20}ClF_2IN_2O_4$	588.9 (M+1)
191	3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-phenoxy-	$C_{22}H_{18}F_3IN_2O_4$	558.9 (M+1)

	propoxy)-benzamide		
192	5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide	$C_{22}H_{17}ClF_3IN_2O_4$	592.8 (M+1)
193	4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide	$C_{22}H_{18}F_3IN_2O_4$	558.9 (M+1)
194	5-Chloro-2-(2,4-difluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide	$C_{22}H_{17}ClF_4N_2O_4$	485.4 (M+1)
195	2-(2,4-Difluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide	$C_{22}H_{18}F_4N_2O_4$	451.5 (M+1)
196	2-(4-Chloro-2-fluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide	$C_{22}H_{18}ClF_3N_2O_4$	467.0 (M+1)
197	3,4-Difluoro-N-(3-hydroxy-2,2-dimethyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide	$C_{19}H_{21}F_2IN_2O_3$	491.0 (M+1)
198	2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(3-hydroxy-2,2-dimethyl-propoxy)-benzamide	$C_{19}H_{17}ClF_3IN_2O_3$	528.9 (M+1)
199	3,4,5-Trifluoro-N-(3-hydroxy-2,2-dimethyl-	$C_{19}H_{20}F_3IN_2O_3$	508.9 (M+1)

	propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide		
200	5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-2,2-dimethyl-propoxy)-benzamide	$C_{19}H_{17}Cl_2F_2IN_2O_3$	544.9 (M+1)
201	5-Chloro-3,4-difluoro-N-(3-hydroxy-2,2-dimethyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide	$C_{19}H_{20}ClF_2IN_2O_3$	524.9 (M+1)
202	3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-2,2-dimethyl-propoxy)-benzamide	$C_{19}H_{19}F_3IN_2O_3$	495.1 (M+1)
203	5-Chloro-2-(2,4-difluoro-phenylamino)-3,4-difluoro-N-(3-hydroxy-2,2-dimethyl-propoxy)-benzamide	$C_{18}H_{17}ClF_4N_2O_3$	421.4 (M+1)
204	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide	$C_{19}H_{21}F_2IN_2O_4$	507 (M+1)
205	3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide	$C_{19}H_{20}F_3IN_2O_4$	525 (M+1)
206	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-[2-(2-	$C_{19}H_{20}BrF_2IN_2O_4$	585/587 (M+1)

	methoxy-ethoxy)-ethoxy]-benzamide		
207	2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide	$C_{18}H_{18}ClF_2IN_2O_4$	527 (M+1)
208	2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide	$C_{18}H_{17}ClF_3IN_2O_4$	545 (M+1)
209	5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide	$C_{18}H_{17}BrClF_2IN_2O_4$	605/607 (M+1)
210	3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide	$C_{16}H_{10}F_7IN_2O_3$	539.1 (M+1)
211	5-Chloro-2-(2,4-difluoro-phenylamino)-3,4-difluoro-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide	$C_{16}H_{10}ClF_7N_2O_3$	447.4 (M+1)
212	2-(2,4-Difluoro-phenylamino)-3,4-difluoro-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide	$C_{16}H_{11}F_7N_2O_3$	413.4 (M+1)
213	2-(4-Chloro-2-fluoro-phenylamino)-3,4-difluoro-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-	$C_{16}H_{11}ClF_6N_2O_3$	429.0 (M+1)

	benzamide		
214	5-Chloro-2-(2,4-difluoro-phenylamino)-3,4-difluoro-N-(2-hydroxymethyl-cyclopropylmethoxy)-benzamide	$C_{18}H_{15}ClF_4N_2O_3$	419.4 (M+1)
215	2-(2,4-Difluoro-phenylamino)-3,4-difluoro-N-(2-hydroxymethyl-cyclopropylmethoxy)-benzamide	$C_{18}H_{16}F_4N_2O_3$	385.4 (M+1)
216	2-(4-Chloro-2-fluoro-phenylamino)-3,4-difluoro-N-(2-hydroxymethyl-cyclopropylmethoxy)-benzamide	$C_{18}H_{16}ClF_3N_2O_3$	401.0 (M+1)
217	4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxymethyl-cyclopropylmethoxy)-benzamide	$C_{18}H_{16}F_3IN_2O_3$	492.9 (M+1)
218	3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide	$C_{18}H_{16}F_3IN_2O_3$	493.5 (M+1)
219	3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide	$C_{18}H_{15}F_4IN_2O_3$	511.1 (M+1)
220	5-Bromo-3,4-difluoro-2-(2-	$C_{18}H_{15}BrF_3IN_2O_3$	571.0/573.0 (M+1)

	fluoro-4-iodo-phenylamino)-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide		
221	4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide	$C_{18}H_{16}F_3IN_2O_3$	493.1 (M+1)
222	2-(2,4-Difluoro-phenylamino)-3,4-difluoro-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide	$C_{18}H_{16}F_4N_2O_3$	385.4 (M+1)
223	2-(4-Bromo-2-fluoro-phenylamino)-3,4-difluoro-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide	$C_{18}H_{16}BrF_3N_2O_3$	445.3/447.3 (M+1)
224	2-(4-Chloro-2-fluoro-phenylamino)-3,4-difluoro-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide	$C_{18}H_{16}ClF_3N_2O_3$	401.4 (M+1)
225	5-Chloro-2-(2,4-difluoro-phenylamino)-3,4-difluoro-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide	$C_{18}H_{15}ClF_4N_2O_3$	419.1 (M+1)
226	2-(2,4-Difluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-methoxy-	$C_{17}H_{16}F_4N_2O_4$	389.4 (M+1)

	propoxy)-benzamide		
227	5-Chloro-2-(2,4-difluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-methoxy-propoxy)-benzamide	$C_{17}H_{15}ClF_4N_2O_4$	423.4 (M+1)
228	2-(4-Bromo-2-fluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-methoxy-propoxy)-benzamide	$C_{17}H_{16}BrF_3N_2O_4$	449.3/451.3 (M+1)
229	2-(4-Chloro-2-fluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-methoxy-propoxy)-benzamide	$C_{17}H_{16}ClF_3N_2O_4$	405.4 (M+1)
230	3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-phenylamino-ethoxy)-benzamide	$C_{22}H_{19}F_3IN_3O_2$	542.0 (M+1)
231	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-phenylamino-ethoxy)-benzamide	$C_{22}H_{19}BrF_2IN_3O_2$	574.0/576.0 (M+1)
232	2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-phenylamino-ethoxy)-benzamide	$C_{21}H_{17}ClF_2IN_3O_2$	544.0 (M+1)
233	2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(2-phenylamino-ethoxy)-benzamide	$C_{21}H_{16}ClF_3IN_3O_2$	562.0 (M+1)
234	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-	$C_{22}H_{20}F_2IN_3O_2$	524.0 (M+1)

	phenylamino-ethoxy)-benzamide		
235	5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-phenylamino-ethoxy)-benzamide	$C_{21}H_{16}BrClF_2IN_3O_2$	622.0/624.0 (M+1)

EXAMPLE 236

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-((S)-3-hydroxy-2-methylamino-propoxy)-benzamide

Step A: N-Boc-O-Benzyl-L-Serine (8.86 g, 30.0 mmol) was dissolved in tetrahydrofuran (94 mL) and the resultant solution was cooled with a 0 °C ice bath. Methyl iodide (15.0 mL, 241 mmol) was added in one portion. After 5 min, sodium hydride (60 % dispersion in mineral oil, 3.6 g, 90 mmol) was added in three portions during 10 min. The resultant reaction mixture was stirred under nitrogen for 76 h while the cooling bath temperature was maintained at 0 °C. The reaction mixture was diluted with cold (0-5 °C) ethyl acetate (150 mL) and water (1.5 mL) was added dropwise over 10 min. The cooling bath temp was allowed to slowly warm to ambient temperature overnight. The reaction mixture was concentrated to a viscous oil on a rotary evaporator without heating. The residue was partitioned between ether (100 mL) and water (300 mL). The ethereal layer was further washed with saturated aqueous sodium bicarbonate (150 mL). The combined aqueous portions were acidified to pH 3 using aqueous citric acid (2 M) and were extracted with ethyl acetate (3 x 150 mL). The combined extracts were washed with water (2 x 150 mL) and 5% aqueous sodium thiosulfate (150 mL), dried over magnesium sulfate and concentrated on a rotary evaporator (without heating) to afford (S)-3-Benzyloxy-2-(tert-butoxycarbonyl-methyl-amino)-propionic acid as viscous, colorless oil (8.98 g).

Step B: The acid prepared in Step A (8.95 g, 28.9 mmol) was dissolved in methanol (50 mL) and dichloromethane (50 mL). The resultant solution was

cooled to 0 °C. Trimethylsilyldiazomethane (2.0 M in hexane, 26 mL) was added dropwise over 1 h and the resultant reaction mixture was stirred an additional h at 0 °C. An additional portion of trimethylsilyldiazomethane (2.0 M in hexane, 3 mL) was added and the reaction was stirred an additional 30 min at 0 °C. The reaction mixture was concentrated in vacuo, taking care not to heat the solution above 20 °C. The residual liquid was dissolved in tetrahydrofuran-methanol (3:1, 200 mL) and the resultant solution was cooled to 0 °C. A solution of lithium borohydride (2.0 M in tetrahydrofuran, 20 mL) was added dropwise over 30 min. The reaction mixture was stirred and additional 1 h at 0 °C and 1 h at ambient temperature. An additional portion of lithium borohydride solution (20 mL) was added and the reaction mixture was stirred overnight . Water (30 mL) was cautiously added with vigorous stirring . After gas evolution had subsided, 50% aqueous sodium hydroxide (1 mL) was added and the stirring was continued for 20 min. The reaction mixture was concentrated in vacuo to about 1/4 volume and was diluted with ethyl acetate (300 mL) and washed with water (50 mL), saturated aqueous ammonium chloride (50 mL) and saturated brine (50 mL). The extracts were dried over magnesium sulfate and concentrated in vacuo. Chromatography of the residual oil (40% ethyl acetate in hexanes) on silica gel provided the product ((R)-1-Benzyloxymethyl-2-hydroxy-ethyl)-methyl-carbamic acid tert-butyl ester (6.02 g, 68% from N-Boc-O-Benzyl serine) as a colorless oil: ^{1}H NMR (400 MHz, CDCl3) δ 7.39-7.28 (m, 5 H), 4.55 (ABquartet, J = 8.0 Hz, Δv =16.4 Hz, 2 H), 4.13 (br s, 1 H), 3.85-3.55 (cm, 4 H), 2.86 (s, 3 H), 1.45 (s, 9 H); $[\alpha]_D$ = +77 (methanol, c = 1 mg/mL); MS (APCI+) 296.2 (M+1, 10%), 222.1 (M+1-$C_4H_{10}O$, 60%), 196.1 (M+1-$C_5H_8O_2$, 100%).

Step C, D: According to the procedure of Preparation 74, ((R)-1-Benzyloxymethyl-2-hydroxy-ethyl)-methyl-carbamic acid tert-butyl ester can be converted to ((S)-2-Aminooxy-1-benzyloxymethyl-ethyl)-methyl-carbamic acid tert-butyl ester.

Step E: [(S)-1-Benzyloxymethyl-2-({1-[3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-phenyl]-methanoyl}-aminooxy)-ethyl]-methyl-carbamic acid tert-butyl ester can be prepared from to ((S)-2-Aminooxy-1-benzyloxymethyl-ethyl)-

methyl-carbamic acid tert-butyl ester and 3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzoic acid by the procedure of Example 80, Step A.

Step F: Treatment of the product of Step E with iodotrimethylsilane followed by a workup with aqueous hydrochloric acid will provide 3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-((S)-3-hydroxy-2-methylamino-propoxy)-benzamide, which may be isolated as a pharmaceutically acceptable salt.

EXAMPLE 237

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-((R)-3-hydroxy-2-methylamino-propoxy)-benzamide

Step A: Treatment of ((R)-1-Benzyloxymethyl-2-hydroxy-ethyl)-methyl-carbamic acid tert-butyl ester with tert-butyldimethylsilyl chloride and imidazole in dimethylformamide will afford [(S)-1-Benzyloxymethyl-2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-carbamic acid tert-butyl ester.

Step B: Exposure of the compound prepared in Step A to a pressurized atmosphere of hydrogen in the presence of activated palladium on charcoal will provide [(S)-2-(tert-Butyl-dimethyl-silanyloxy)-1-hydroxymethyl-ethyl]-methyl-carbamic acid tert-butyl ester.

Step C,D: The compound of step B can be converted to [(S)-1-Aminooxymethyl-2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-methyl-carbamic acid tert-butyl ester by the general procedure of Preparation 74.

Step E: [(S)-2-(tert-Butyl-dimethyl-silanyloxy)-1-({1-[3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-phenyl]-methanoyl}-aminooxymethyl)-ethyl]-methyl-carbamic acid tert-butyl ester can be prepared by the procedure of Example 80, Step A.

Step F: Treatment of the product of Step E with iodotrimethylsilane followed by a workup with tetrabutylammonium fluoride will provide 3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-((R)-3-hydroxy-2-methylamino-propoxy)-benzamide, which may be isolated as a pharmaceutically acceptable salt.

EXAMPLE 238

(S)- and (R)-5-Chloro-3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-2-methylamino-propoxy)-benzamide

(S)- and (R)-5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-2-methylamino-propoxy)-benzamide may be prepared from 5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzoic acid by analogy to examples 236 and 237 respectively.

EXAMPLE 239

(S)- and (R)-5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-2-methylamino-propoxy)-benzamide

(S)- and (R)-5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-2-methylamino-propoxy)-benzamide may be prepared from 5-chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-benzoic acid by analogy to examples 236 and 237 respectively.

EXAMPLE 240

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-methylamino-propoxy)-benzamide

Step A: N-(tert-butoxycarbonyl)-N-methyl-2,3-epoxypropylamine (available by the literature procedure: Edwards, M. L.; Snyder, R. D.; Stemerick, D. M. *J. Med. Chem.* 1991, *34*, 2414) can be converted to (3-aminooxy-2-hydroxy-propyl)-methyl-carbamic acid tert-butyl ester by the general procedure of example 56.

Step B, C: 3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-methylamino-propoxy)-benzamide can be prepared from (3-aminooxy-2-hydroxy-propyl)-methyl-carbamic acid tert-butyl ester and 3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzoic acid by the general procedure of example 236, steps E and F.

EXAMPLE 241

Cellular Assay for Measuring MEK Inhibition

The evaluation of the compounds as MEK inhibitors was performed in an assay that measures their ability to inhibit phosphorylation of MAP kinase (ERK) in murine colon 26 (C26) carcinoma cells. Since ERK1 and ERK2 represent the only known substrates for MEK, measurement of inhibition of ERK phosphorylation in cells provides direct readout of cellular MEK inhibition by the

compounds of the invention. Briefly, the assay involves treating exponentially growing C26 cells with varying concentrations of the test compound (or vehicle control) for one hour at 37° C. Cells are then rinsed free of compound/vehicle and lysed in a solution containing 70 mM NaCl, 50 mM glycerol phosphate, 10 mM HEPES, pH 7.4, 1% Triton X-100, 1 mM Na_3VO_4, 100 μM PMSF, 10 μM leupeptin and 10 μM pepstatin. Supernatants are then subjected to gel electrophoresis and Western blotting using a primary antibody recognizing dually phosphorylated ERK1 and ERK2. To evaluate total MAPK levels, blots were subsequently 'stripped' and re-probed with a 1:1 mixture of polyclonal antibodies recognizing unphosphorylated ERK1 and ERK2.

The inhibition data generated by the above protocol is disclosed in Table 1. If several concentrations of inhibitor were tested, IC_{50} values (the concentration which gives 50% inhibition) were determined graphically from the dose response curve for % inhibition. Otherwise, percent inhibitions at measured concentrations are reported.

Table 8. Cellular Inhibition of ERK Phosphorylation by Compounds of the Invention

Compound of Example No.	IC_{50} (μM)	% Inhibition @ 0.1 μM	% Inhibition @ 1 μM	% Inhibition @ 10 μM
1	0.008			
2	0.003			
3	0.004			
4	0.002			
5	0.003			
6	0.005			
7	0.005			
8	0.0003			
9	0.00007			
10	0.0003			

11	0.002			
12	0.022			
13	0.002			
14	0.002			
15	0.001			
16	0.02			
17	0.045			
18	0.002			
19	0.001			
20	0.003			
21	0.0018			
22	0.0077			
23	0.032			
24	0.026			
25	0.052			
26	0.24			
27	0:12			
28	0.12			
29	0.047			
30	0.13			
32	0.0044			
33	0.005			
34	0.001			
35	0.006			
36	0.053			
37	0.03			
38	> 1.00			
39	0.0004			
40	0.0014			
41	0.00073			
42	0.0027			

43	0.0018			
44	0.003			
45	0.019			
46	0.582			
47	0.001			
48	0.0016			
49	0.00033			
50	0.00083			
51	0.0038			
52	0.0078			
53	0.0012			
54	0.0012			
55	0.0045			
58	0.06			
61	0.15			
62	0.018			
63	0.047			
64	0.013			
65	0.014			
66	0.002			
67	0.006			
68	0.024			
69	0.06			
70	0.2			
71	0.12			
72	0.019			
73	0.08			
74	0.018			
75	0.042			
76	0.006			
77	0.24			

78	0.23			
79	0.02			
80	0.49			
81	0.134			
82	>1			
83	0.041			
85	0.054			
86	0.019			
87	0.025			
88	0.11			
89	0.012			
90	0.04			
91		89.4	98.9	
92		51.8	92.4	
93		4	79.1	
94	0.28			
95	0.19			
96		35	87.1	
97		30.1	91.9	
98	0.011			
99	0.018			
100	0.058			
101	0.225			
102	0.275			
103	0.487			
104	0.024			
105		3.3	71.3	
106		13.2	81.6	
107	0.076			
108		74	94.6	
109	0.038			

111		78	93.4	
112		95.2	95.5	
113		89.9	94.6	
114		90.5	97.3	
115		94.8	98.5	
116			62.8	75.8
117		0	66.7	86.9
118		74.6	95.6	
119		87.4	97.9	
120	0.014			
121		46.9	85.5	
122		49.6	87.3	
123	0.021			
124		78	96.9	
125		9.1	89	
126	0.026			
127	0.025			
128	0.009			
129		100	100	
130	0.004			
131		78.7	91.3	
132			45.7	80.6
133		0	26.4	
134	0.37			
135		0	41.4	
136	0.25			
137	0.1			
138		0	19.6	
139	0.36			
140	0.45			
141		38	92.7	

142		31	91.4	
143	0.6			
145	0.1			
146		0	40.5	
147	0.1			
148	0.23			
149	0.17			
150		49	99.9	
151	0.041			
152		59.2	90.3	
153		13.9	89.5	
154			8.9	51
155		0	30.9	
156	0.011			
157		50.7	91.5	
159		88.4	100	
160		71.9	96.8	
161	0.015			
162	0.00785			
163		88.9	95.1	
164	0.003			
165	0.004			
166		0	31.9	88.7
167			80.5	89.2
168		48.8	89.5	
169	0.014			
170		19	85.7	
171		35.6	94.6	
172		41.9	92.9	
173	0.3			
174	0.1			

175	0.18			
176		14.1	87.7	
177		91.6	95.7	
178		61.8	94.9	
179		90.4	99.3	
180			34	58.6
181			0	65.1
182		13.1	81.9	
183	0.053			
184		16.1	82.5	
185		6.2	71.9	
186	0.034			
187		13.8	83.3	
188	0.044			
190		51.5	94.6	
191	0.006			
192	0.007			
193	0.01			
194		0	0	
195			26.7	82.6
196		10.2	82.8	
197	0.051			
198		0	43.5	
199	0.1			
200	0.3			
201	0.1			
202		59.7	94.6	
203			0	37.4
206	0.14			
207	0.212			
208	1.029			

210		79.7	99.2	
211			35	71.9
212			20.1	85.1
213		6.2	78.7	
214			15.4	38.2
215			11.7	84.8
216		41.2	87.6	
217		26.9	93.1	
218		87	96.9	
219		65.3	96.2	
220		35.4	88.8	
221		46	92.4	
222			9.6	55.6
223		5.2	56.7	
224		0	18.1	
225		0	8.7	36.9
226			41.5	84.1
227			24.2	63
228		48.6	92.4	
229		9.8	76.5	
230	0.051			
231	0.067			
232	0.022			
233	0.033			
234	0.054			
235	0.062			

EXAMPLE 242

Carrageenan-induced Footpad Edema (CFE) Rat Model

Male outbred Wistar rats (135-150 g, Charles River Labs) were dosed orally with 10 ml/kg vehicle or test compound one hour prior to administration of a sonicated suspension of carrageenan (1 mg/0.1 ml saline). Carrageenan was

injected into the subplantar region of the right hind paw. Paw volume was determined by mercury plethysmography immediately after injection and again five hours after carrageenan injection. Percent inhibition of edema was determined, and the ID40 calculated by linear regression. Differences in swelling compared to control animals were assessed by a 1-way ANOVA, followed by Dunnett's test.

EXAMPLE 243

Collagen-Induced Arthritis in Mice

Type II collagen-induced arthritis (CIA) in mice is an experimental model of arthritis that has a number of pathologic, immunologic, and genetic features in common with rheumatoid arthritis. The disease is induced by immunization of DBA/1 mice with 100 μg type II collagen, which is a major component of joint cartilage, delivered intradermally in Freund's complete adjuvant. The disease susceptibility is regulated by the class II MHC gene locus, which is analogous to the association of rheumatoid arthritis with HLA-DR4.

A progressive and inflammatory arthritis develops in the majority of mice immunized, characterized by paw width increases of up to 100%. A test compound is administered to mice in a range of amounts, such as 20, 60, 100, and 200 mg/kg body weight/day. The duration of the test can be several weeks to a few months, such as 40, 60, or 80 days. A clinical scoring index is used to assess disease progression from erythema and edema (stage 1), joint distortion (stage 2), to joint ankylosis (stage 3). The disease is variable in that it can affect one or all paws in an animal, resulting in a total possible score of 12 for each mouse. Histopathology of an arthritic joint reveals synovitis, pannus formation, and cartilage and bone erosions. All mouse strains that are susceptible to CIA are high antibody responders to type II collagen, and there is a marked cellular response to CII.

EXAMPLE 244

SCW-induced monoarticular arthritis

Arthritis is induced as described by Schwab, *et al.*, *Infection and Immunity*, 59:4436-4442 (1991) with minor modifications. Rats receive 6 μg sonicated SCW [in 10 μl Dulbecco's PBS (DPBS)] by an intraarticular injection into the right tibiotalar joint on day 0. On day 21, the DTH is initiated with 100 μg of SCW (250 μl) administered i.v. For oral compound studies, compounds are suspended in vehicle (0.5% hydroxypropyl-methylcellulose/0.2% Tween 80), sonicated, and administered twice daily (10 ml/kg volume) beginning 1 hr prior to reactivation with SCW. Compounds are administered in amounts between 10 and 500 mg/kg body weight/day, such as 20, 30, 60, 100, 200, and 300 mg/kg/day. Edema measurements are obtained by determining the baseline volumes of the sensitized hindpaw before reactivation on day 21, and comparing them with volumes at subsequent time points such as day 22, 23, 24, and 25. Paw volume is determined by mercury plethysmography.

EXAMPLE 245

Mouse ear-heart transplant model

Fey, T.A. *et al.* describe methods for transplanting split-heart neonatal cardiac grafts into the ear pinna of mice and rats (*J. Pharm. and Toxic. Meth.* 39:9-17 (1998)). Compounds are dissolved in solutions containing combinations of absolute ethanol, 0.2% hydroxypropyl methylcellulose in water, propylene glycol, cremophor, and dextrose, or other solvent or suspending vehicle. Mice are dosed orally or intraperitoneally once, twice or three times daily from the day of transplant (day 0) through day 13 or until grafts have been rejected. Rats are dosed once, twice, or three times daily from day 0 through day 13. Each animal is anesthetized and an incision is made at the base of the recipient ear, cutting only the dorsal epidermis and dermis. The incision is spread open and down to the cartilage parallel to the head, and sufficiently wide to accommodate the appropriate tunneling for a rat or insertion tool for a mouse. A neonatal mouse or rat pup less than 60 hours old is anesthetized and cervically dislocated. The heart is removed from the chest, rinsed with saline, bisected

longitudinally with a scalpel, and rinsed with sterile saline. The donor heart fragment is placed into the preformed tunnel with the insertion tool and air or residual fluid is gently expressed from the tunnel with light pressure. No suturing, adhesive bonding, bandaging, or treatment with antibiotics is required.

Implants are examined at 10-20-fold magnification with a stereoscopic dissecting microscope without anesthesia. Recipients whose grafts are not visibly beating may be anesthetized and evaluated for the presence of electrical activity using Grass E-2 platinum subdermal pin microelectodes placed either in the pinna or directly into the graft and a tachograph. Implants can be examined 1-4 times a day for 10, 20, 30 or more days. The ability of a test compound to ameliorate symptoms of transplant rejection can be compared with a control compound such as cyclosporine, tacrolimus, or orally-administered leflunomide.

EXAMPLE 246

The analgesic activity of the compounds of the present invention was assessed by a test with rats. Rats weighing from 175 to 200 g were injected with carrageenan (2% in 0.9% sodium chloride aqueous solution, 100 μL injection volume) into the footpad of one hind limb. The rats were placed on a glass plate with illumination from a halogen lamp placed directly under the injected paw. The time (in seconds) from beginning illumination until the hindlimb was withdrawn from the glass was measured and scored as Paw Withdrawal Latency (PWL). Drug substances were given by oral gavage injection 2 ½ hours after carrageenan injection to the footpad. PWL was measured prior to carrageenan injection, just prior to drug injection, and 1, 2 (and sometimes 3) hours after drug injection.

Carrageenan (a polysaccharide extracted from seaweed) causes a sterile inflammation when injected under the skin. Injection into the rat footpad causes little or no spontaneous pain-related behavior but induces hyperalgesia (pain-related behavioral responses of greater intensity than expected) to peripheral thermal or mechanical stimuli. This hyperalgesia is maximal 2 to 3 hours after injection. Treatment of rats with various analgesic drugs reduces hyperalgesia measured in this way and is a conventional test for detection of analgesic activity

in rats. (Hargreaves K, Dubner R, Brown F, Flores C, Joris J. A new and sensitive method for measuring thermal nociception in cutaneous hyperalgesia. Pain 1988;32:77-88 and Kayser V, Guilbaud G. Local and remote modifications of nociceptive sensitivity during carrageenan-induced inflammation in the rat. Pain 1987;28:99-108). Untreated rats had a PWL of approximately 10 seconds. Carrageenan injection reduced PWL to approximately 3 seconds for at least 4 hours, indicating thermal hyperalgesia. Inhibition of the carrageenan thermal hyperalgesia response was determined by the difference between reduced PWL prior to drug and subsequent to drug treatment, and was expressed as percent inhibition of the response. Administration of MEK inhibitors dose-dependently reduced thermal hyperalgesia (Table 9).

In Table 9, doses were given by oral gavage (PO) and inhibition of the response was measured 1 hour (1 hr), 2 hours (2 hr) or in some cases, 3 hours (3 hr) after drug administration. Inhibition indicates and analgesic effect.

TABLE 9

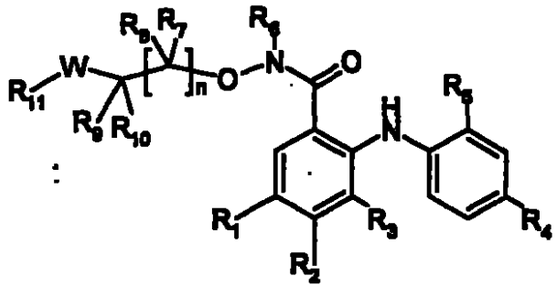
Administration of MEK Inhibitors to Rats Reduces Thermal Hyperalgesia from Intraplantar Carrageenan.

EXAMPLE NO.	DOSE (PO)	%Inhibition (1 hr)	% Inhibition (2 hr)	% Inhibition (3 hr)
9	30	103.0	114.4	65.2
	10	57.2	80.0	50.8
	3	38.1	44.3	26.1
34	10	39.6	61.5	
41	10	26.7	61.0	
55	10	36.8	60	22
54	10	49	52.9	29.6

CLAIMS

What is claimed is:

1. A compound of formula



I

wherein

R_1 is hydrogen, halogen, or nitro;

R_2 is hydrogen or fluorine;

R_3 is hydrogen or fluorine;

R_4 is hydrogen, iodine, bromine, chlorine, or fluorine;

R_5 is hydrogen, halogen, hydroxy, C_{1-8} alkyl, C_{1-8} alkoxy, trifluoromethyl, or cyano;

n is 1 to 5;

R_6, R_7, R_8, R_9, and R_{10} are independently hydrogen, C_{1-8} alkyl, C_{3-8} cycloalkyl, hydroxy, C_{1-8} alkoxy, perhalo(C_{1-3})alkyl, hydroxy(C_{1-8})alkyl, (C_{1-5})alkoxy(C_{1-5})alkyl, [(C_{1-4})alkyl]$_2$aminomethyl, (C_{2-7})heterocycle(C_{1-5})alkyl, or aryloxy(C_{1-5})alkyl, or may be independently joined to complete a 3-10 member cyclic ring optionally containing additional heteroatoms selected from the group consisting of O, S, NH, and N-alkyl, wherein R_7 and R_8 are independently selected for n>1;

Ra and Rb are independently hydrogen or C_{1-4} alkyl;

W is O or NRa;

R_{11} is hydrogen, C_{1-8} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, hydroxy(C_{1-8})alkyl, (C_{1-5})alkoxy(C_{1-5})alkyl, phenyl, C_{2-7} heteroaryl, (C_{1-8})alkylcarbonyl, (phenyl)carbonyl, (phenyl)(C_{1-3} alkyl)carbonyl, or trifluoro(C_{1-6})alkyl;

wherein the above alkyl, alkoxy, cycloalkyl, heteroaryl, and phenyl groups can be optionally substituted with between 1 and 5 substituents independently selected from the group consisting of hydroxy, amino, monoalkylamino, dialkylamino, halogen, cyano, (C_{1-3})alkoxy, COOR, OCORa, CONRaRb, NRaCORb, SO, SO_2, SO_4, and SO_2NRaRb;

and pharmaceutically acceptable salts;

provided that when R_{11} is phenyl and n is 1, W cannot be O;

further provided that the compound is not

5-Bromo-N-(2-diethylamino-ethoxy)-3,4-difluoro-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-(2-dimethylamino-propoxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide; or

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-N-(2-dimethylamino-ethoxy)-3,4-difluoro-benzamide.

2. The compound of Claim 1 wherein R_1 is hydrogen or halogen.

3. The compound of Claim 2 wherein halogen is fluorine, bromine or chlorine.

4. The compound of Claim 1 wherein R_2 is fluorine.

5. The compound of Claim 1 wherein R_3 is fluorine.

6. The compound of Claim 1 wherein R_4 is iodine.

7. The compound of Claim 1 wherein R_5 is fluorine, chlorine, or methyl.

8. The compound of claim 1 wherein n is 1 or 2.

9. The compound of claim 1 wherein R_6, R_7, R_8, R_9, R_{10}, and R_{11} are hydrogen.

10. The compound of claim 1 wherein R_6, R_7, R_8, R_9, and R_{10} are hydrogen.

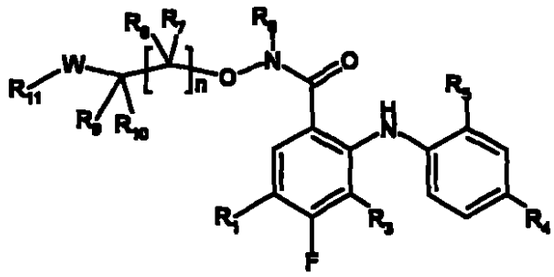
11. The compound of claim 1 wherein R_6, R_7, R_9, R_{10}, and R_{11} are hydrogen.

12. The compound of claim 1 wherein W is oxygen.

13. The compound of claim 1 wherein W is NRa and Ra is hydrogen.

14. The compound of claim 1 wherein R_{11} is methyl or phenyl.

15. The compound of Claim 1 wherein the compound is of formula



Ia

wherein

R_1 is hydrogen or halogen;

R_5 is hydrogen, halogen, or C_{1-8} alkyl;

R_6, R_7, R_8, R_9, and R_{10} are independently hydrogen, C_{1-8} alkyl, hydroxy, C_{1-8} alkoxy, perhalo(C_{1-3})alkyl, (C_{2-7})heterocycle(C_{1-5})alkyl, or aryloxy(C_{1-5})alkyl, or may be independently joined to complete a 3-10 member cyclic

ring optionally containing additional heteroatoms selected from the group consisting of O, S, NH, and N-alkyl, wherein R_7 and R_8 are independently selected for n>1; and

R_{11} is hydrogen, C_{1-8} alkyl, C_{2-6} alkenyl, (C_{1-5})alkoxy(C_{1-5})alkyl, phenyl, (C_{1-8})alkylcarbonyl, or trifluoro(C_{1-6})alkyl.

16. The compound of Claim 15 wherein R_1 is hydrogen.

17. The compound of Claim 15 wherein R_3 is hydrogen.

18. The compound of Claim 15 wherein R_3 is fluorine.

19. The compound of Claim 15 wherein R_4 is iodine.

20. The compound of Claim 15 wherein R_5 is fluorine, chlorine, or methyl.

21. The compound of Claim 15 wherein n is 1 or 2.

22. The compound of claim 15 wherein R_6, R_7, R_8, R_9, R_{10}, and R_{11} are hydrogen.

23. The compound of claim 15 wherein R_6, R_7, R_8, R_9, and R_{10} are hydrogen.

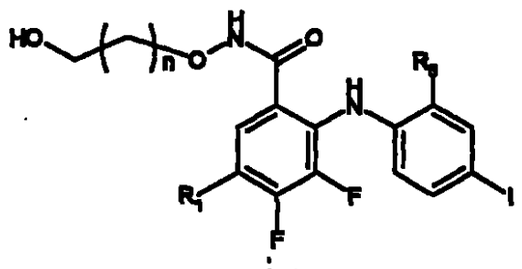
24. The compound of claim 15 wherein R_6, R_7, R_9, R_{10}, and R_{11} are hydrogen.

25. The compound of claim 15 wherein W is O.

26. The compound of claim 15 wherein W is NRa and Ra is hydrogen.

27. The compound of claim 15 wherein R_{11} is methyl or phenyl.

28. A compound of Claim 1 wherein the compound is of formula



II

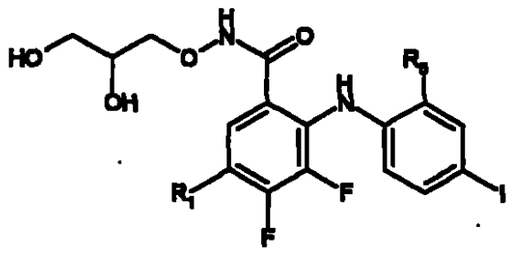
wherein

R_1 is hydrogen or halogen;

R_5 is fluorine, chlorine, or methyl; and

n is 1 or 2.

29. A compound of Claim 1 wherein the compound is of formula



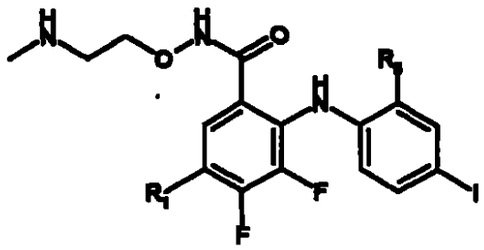
III

wherein

R_1 is hydrogen or halogen; and

R_5 is fluorine, chlorine, or methyl.

30. A compound of Claim 1 wherein the compound is of formula



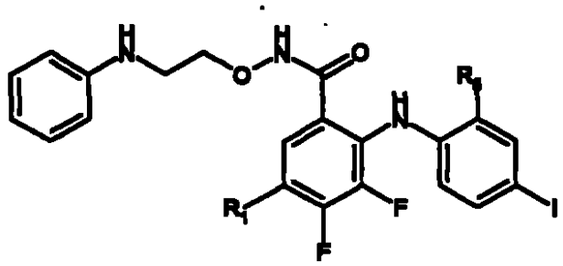
IV

wherein

R_1 is hydrogen or halogen; and

R_5 is fluorine, chlorine, or methyl.

31. A compound of Claim 1 wherein the compound is of formula



V

wherein

R_1 is hydrogen or halogen; and

R_5 is fluorine, chlorine, or methyl.

32. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

33. A method of treating a proliferative disease in a patient in need thereof comprising administering a therapeutically effective amount of a compound of claim 1.

34. A method of claim 33 wherein the proliferative disease is selected from the group consisting of cancer, restenosis, psoriasis, and atherosclerosis.

35. A method of treating psoriasis in a patient in need thereof comprising administering a therapeutically effective amount of a compound of claim 1.

36. A method of treating cancer in a patient in need thereof comprising administering a therapeutically effective amount of a compound of claim 1.

37. A method of claim 36 wherein the cancer is MEK-related.

38. A method of claim 36 wherein the cancer is brain, breast, lung, ovarian, pancreatic, prostate, renal, or colorectal cancer.

39. A method of treating osteoarthritis in a patient in need thereof comprising administering a therapeutically effective amount of a compound of claim 1.

40. A method of treating rheumatoid arthritis in a patient in need thereof comprising administering a therapeutically effective amount of a compound of claim 1.

41. A method of treating heart failure in a patient in need thereof comprising administering a therapeutically effective amount of a compound of claim 1.

42. A method of treating chronic pain in a patient in need thereof comprising administering a therapeutically effective amount of a compound of claim 1.

43. The method of claim 42, wherein the chronic pain is selected from the group consisting of neuropathic pain, idiopathic pain, and pain associated with chronic alcoholism, vitamin deficiency, uremia, and hypothyroidism.

44. The method of claim 42, wherein the chronic pain is associated with inflammation.

45. The method of claim 42, wherein the chronic pain is associated with arthritis.

46. The method of claim 42, wherein the chronic pain is associated with post-operative pain.

47. A method of treating neuropathic pain in a patient in need thereof comprising administering a therapeutically effective amount of a compound of claim 1.

48. The method of claim 47, wherein the neuropathic pain is associated with a condition selected from the group consisting of inflammation, postoperative pain, phantom limb pain, burn pain, gout, trigeminal neuralgia, acute herpetic and postherpetic pain, causalgia, diabetic neuropathy, plexus avulsion, neuroma, vasculitis, viral infection, crush injury, constriction injury, tissue injury, limb amputation, post-operative pain, arthritis pain, and nerve injury between the peripheral nervous system and the central nervous system.

49. A method for treating cancer in a patient in need thereof comprising administering a therapeutically effective amount of a compound of claim 1 in combination with radiation therapy.

50. A method for treating cancer in a patient in need thereof comprising administering a therapeutically effective amount of a compound of claim 1 in combination with at least one chemotherapeutic agent.

51. A method of claim 50 wherein the chemotherapeutic agent is a mitotic inhibitor.

52. A method of claim 51 wherein the mitotic inhibitor is selected from the group consisting of paclitaxel, docetaxel, vincristine, vinblastine, vinorelbine, and vinflunine.

53. A crystalline Form I *N*-(2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing at least one of the following 2θ values measured using CuK_α radiation: 7.1, 19.2, or 32.1.

54. A crystalline Form I *N*-(2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing the following 2θ values measured using CuK_α radiation: 7.1, 19.2, and 32.1.

55. A crystalline Form I *N*-(2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing the following 2θ values measured using CuK_α radiation: 7.1, 14.1, 15.3, 15.8, 16.9, 18.1, 19.2, 20.3, 21.4, 22.3, 23.4, 24.5, 25.5, 26.2, 26.8, 27.8, 28.3, 29.5, 32.1, 33.2, 33.6, 40.0, 42.9, and 44.1.

56. A crystalline Form I *N*-(2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing the following 2θ values measured using CuK_α radiation: 7.078, 14.123, 15.280, 15.836, 16.880, 18.082, 19.162, 20.279, 21.360, 22.325, 23.400, 24.522, 25.480, 26.159, 26.801, 27.842, 28.280, 29.475, 32.118, 33.248, 33.645, 40.008, 42.885, and 44.095.

57. A crystalline Form II *N*-(2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing at least one of the following 2θ values measured using CuK_α radiation: 11.6, 12.6 or 24.9.

58. A crystalline Form II *N*-(2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing the following 2θ values measured using CuK_α radiation: 11.6, 12.6 and 24.9.

59. A crystalline Form II *N*-(2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing the following 2θ values measured using CuK_α radiation: 11.6, 12.6, 15.6, 17.3, 17.9, 20.3, 21.1, 22.1, 24.9, 25.9, 26.7, 27.8, 30.1, 30.9, 33.8, 35.4, 38.2, 39.3, 40.8, 41.6, 43.6, and 47.0.

60. A crystalline Form II *N*-(2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing the following 2θ values measured using CuK_α radiation: 11.582, 12.598, 15.622, 17.302, 17.886, 20.345, 21.140, 22.137, 24.855, 25.885, 26.699, 27.842, 30.059, 30.948, 33.799, 35.399, 38.242, 39.282, 40.755, 41.641, 43.570, and 46.958.

61. A crystalline Form I *N*-[(R)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing at least one of the following 2θ values measured using CuK_α radiation: 10.6, 13.7, 19.0 or 23.7.

62. A crystalline Form I *N*-[(R)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction

powder diffraction containing the following 2θ values measured using CuK_α radiation: 10.6, 13.7, 19.0 and 23.7.

63. A crystalline Form I *N*-[(R)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing the following 2θ values measured using CuK_α radiation: 10.6, 13.7, 14.6, 17.3, 18.0, 18.2, 98.0, 19.3, 20.1, 21.0, 21.9, 22.4, 23.7, 24.0, 24.9, 26.3, 27.6, 28.0, 30.1, 32.1, 32.3, 32.9, 35.8, and 37.7.

64. A crystalline Form I *N*-[(R)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing the following 2θ values measured using CuK_α radiation: 10.560, 13.720, 14.619, 17.258, 17.958, 18.219, 18.998, 19.258, 20.142, 21.002, 21.940, 22.360, 23.680, 24.043, 24.919, 26.278, 27.603, 28.024, 30.100, 32.142, 32.298, 32.938, 35.841, and 37.660.

65. A crystalline Form II *N*-[(R)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing at least one of the following 2θ values measured using CuK_α radiation: 5.5 or 19.6.

66. A crystalline Form II *N*-[(R)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing at least one of the following 2θ values measured using CuK_α radiation: 5.5 and 19.6.

67. A crystalline Form II *N*-[(R)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing the following 2θ values measured using

CuK_α radiation: 5.5, 10.7, 16.5, 19.6, 22.0, 22.5, 23.6, 24.1, 25.0, 26.2, 27.6, 29.1, 30.5, 31.7, 33.3, and 39.0.

68. A crystalline Form II *N*-[(R)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing the following 2θ values measured using CuK_α radiation: 5.482, 10.721, 16.478, 19.563, 22.019, 22.478, 23.621, 24.100, 24.959, 26.181, 27.621, 29.081, 30.476, 31.698, 33.263, and 39.020.

69. A crystalline Form I *N*-[(S)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing at least one of the following 2θ values measured using CuK_α radiation: 10.5, 13.7, 19.0, or 23.6.

70. A crystalline Form I *N*-[(S)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing the following 2θ values measured using CuK_α radiation: 10.5, 13.7, 19.0, and 23.6.

71. A crystalline Form I *N*-[(S)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing the following 2θ values measured using CuK_α radiation: 10.548, 13.703, 17.887, 18.958, 20.122, 21.950, 22.321, 23.640, 24.803, 26.244, 27.570, 28.000, 29.566, 32.234, 32.769, 35.804, 37.641, 41.402, 41.956, and 44.600.

72. A crystalline Form I *N*-[(S)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing the following 2θ values measured using CuK_α radiation: 10.548, 13.703, 17.887, 18.958, 20.122, 21.950, 22.321,

23.640, 24.803, 26.244, 27.570, 28.000, 29.566, 32.234, 32.769, 35.804, 37.641, 41.402, 41.956, and 44.600.

73. A crystalline Form II *N*-[(S)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing at least one of the following 2θ values measured using CuK_α radiation: 5.6 or 19.6.

74. A crystalline Form II *N*-[(S)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing at least one of the following 2θ values measured using CuK_α radiation: 5.6 and 19.6.

75. A crystalline Form II *N*-[(S)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing the following 2θ values measured using CuK_α radiation: 5.6, 10.7, 16.5, 19.6, 20.9, 22.0, 23.7, 24.2, 25.0, 26.2, 27.7, 28.0, 29.1, 31.7, 32.8, 33.3, 34.1, 42.0, and 42.3.

76. A crystalline Form II *N*-[(S)-2,3-Dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide having an X-ray diffraction powder diffraction containing the following 2θ values measured using CuK_α radiation: 5.550, 10.763, 16.485, 19.636, 20.922, 22.043, 23.683, 24.153, 24.996, 26.236, 27.680, 28.037, 29.120,31.718, 32.794, 33.314, 34.085, 41.999, and 42.278.

77. A compound which is selected from the group consisting of

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-N-(2,3-dihydroxy-propoxy)-3,4-difluoro-benzamide;

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-ethoxy)-benzamide;

N-(2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

5-Chloro-N-(2,3-dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

5-Chloro-N-((R)-2,3-dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-methylamino-ethoxy)-benzamide; hydrochloride;

N-((R)-2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

N-((S)-2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-N-((S)-2,3-dihydroxy-propoxy)-3,4-difluoro-benzamide;

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-N-((R)-2,3-dihydroxy-propoxy)-3,4-difluoro-benzamide;

5-Chloro-N-((S) 2,3-dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-1-hydroxymethyl-ethoxy)-benzamide; and

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)- N-(2-hydroxy-1-hydroxymethyl-ethoxy)-benzamide.

78. A compound which is selected from the group consisting of

3,4,5-Trifluoro-N-(2-hydroxy-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

3,4-Difluoro-N-(2-hydroxy-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-ethoxy)-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-ethoxy)-

benzamide;

4-Fluoro-N-(2-hydroxy-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(2-hydroxy-ethoxy)-benzamide;

5-Chloro-3,4-difluoro-N-(2-hydroxy-ethoxy)-2-(4-iodo-phenylamino)-benzamide;

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-ethoxy)-benzamide;

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-ethoxy)-benzamide;

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-ethoxy)-benzamide;

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-ethoxy)-benzamide;

4,5-Difluoro-N-(2-hydroxy-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-3,4-difluoro-N-(2-hydroxy-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-ethoxy)-benzamide;

5-Chloro-3,4-difluoro-N-(2-hydroxy-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-4-fluoro-N-(2-hydroxy-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-4,5-difluoro-N-(2-hydroxy-ethoxy)-benzamide;

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-ethoxy)-benzamide;

5-Bromo-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-ethoxy)-benzamide;

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-

ethoxy)-benzamide;

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-ethoxy)-benzamide;

2-(4-Bromo-2-fluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-ethoxy)-benzamide;

2-(4-Bromo-2-fluoro-phenylamino)-4,5-difluoro-N-(2-hydroxy-ethoxy)-benzamide;

2-(4-Chloro-2-fluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-ethoxy)-benzamide;

3,4-Difluoro-2-(2-fluoro-phenylamino)-N-(2-hydroxy-ethoxy)-benzamide;

5-Chloro-2-(2,4-difluoro-phenylamino)-3,4-difluoro-N -(2-hydroxy-ethoxy)-benzamide;

2-(2,4-Difluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-ethoxy)-benzamide;

4-Fluoro-N-(3-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-3,4-difluoro-N-(3-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(3-hydroxy-propoxy)-benzamide;

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-propoxy)-benzamide;

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-propoxy)-benzamide;

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(4-hydroxy-butoxy)-benzamide;

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-N-(2,3-dihydroxy-propoxy)-3,4-difluoro-benzamide;

5-Chloro-N-(2,3-dihydroxy-propoxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-(3,4-dihydroxy-butoxy)-3,4-difluoro-2-(4-iodo-2-methyl-

phenylamino)-benzamide;

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-N-(3,4-dihydroxy-butoxy)-3,4-difluoro-benzamide;

N-(2,2-Dimethyl-1,3-dioxolan-4-ylmethoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

N-(2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

5-Bromo-N-(2,3-dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

5-Chloro-N-(2,3-dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

N-(2,3-Dihydroxy-propoxy)-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

N-(2,3-Dihydroxy-propoxy)-3,4,5-trifluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

2-(4-Bromo-2-fluoro-phenylamino)-N-(2,3-dihydroxy-propoxy)-3,4-difluoro-benzamide;

2-(4-Chloro-2-fluoro-phenylamino)-N-(2,3-dihydroxy-propoxy)-3,4-difluoro-benzamide;

N-(2,2-Dimethyl-1,3-dioxinan-5-yloxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-1-hydroxymethyl-ethoxy)-benzamide;

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)- N-(2-hydroxy-1-hydroxymethyl-ethoxy)-benzamide;

N-((R)-2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

N-((S)-2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-N-((R)-2,3-dihydroxy-propoxy)-3,4-difluoro-benzamide;

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-N-((S)-2,3-dihydroxy-

propoxy)-3,4-difluoro-benzamide;

5-Chloro-N-((R)-2,3-dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

5-Chloro-N-((S) 2,3-dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

2-(4-Bromo-2-fluoro-phenylamino)-N-((R)-2,3-dihydroxy-propoxy)-3,4-difluoro-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-vinyloxy-ethoxy)-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(2-vinyloxy-ethoxy)-benzamide;

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-vinyloxy-ethoxy)-benzamide;

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-vinyloxy-ethoxy)-benzamide;

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-vinyloxy-ethoxy)-benzamide;

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-vinyloxy-ethoxy)-benzamide;

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-1,1-dimethyl-ethoxy)-benzamide;

3,4-Difluoro-N-(2-hydroxy-1,1-dimethyl-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-2-methyl-propoxy)-benzamide;

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)- N-(2-hydroxy-1,1-dimethyl-ethoxy)-benzamide;

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-1,1-dimethyl-ethoxy)-benzamide;

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-2-methyl-propoxy)-benzamide;

3,4-Difluoro-N-(2-hydroxy-3-methoxy-propoxy)-2-(4-iodo-2-methyl-

phenylamino)-benzamide;

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-methoxy-propoxy)-benzamide;

3,4-Difluoro-N-(1-hydroxymethyl-cyclopropylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide;

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide;

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxymethyl-cyclopropylmethoxy)-benzamide;

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxymethyl-cyclopropylmethoxy)-benzamide;

N-(2,3-Dihydroxy-3-methyl-butoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-phenylamino-ethoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-methylamino-ethoxy)-benzamide;

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-methylamino-ethoxy)-benzamide; hydrochloride;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-[2-(2,2,2-trifluoro-ethylamino)-ethoxy]-benzamide; hydrochloride;

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-(2-hydroxy-ethoxy)-N-methyl-benzamide;

Acetic acid 2-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzoylaminooxy]-ethyl ester;

[3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-phenyl]-(4-hydroxy-isoxazolidin-2-yl)-methanone;

5-Bromo-N-(2,3-dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-

phenylamino)-benzamide;

N-(2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-phenylamino)-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-N-(2,3-dihydroxy-propoxy)-3,4-difluoro-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-N-(2,3-dihydroxy-propoxy)-3,4,5-trifluoro-benzamide;

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-N-(2,3-dihydroxy-propoxy)-3,4-difluoro-benzamide;

N-(2,3-Dihydroxy-propoxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(2,3-Dihydroxy-propoxy)-3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-(2,3-dihydroxy-propoxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-N-(3,4-dihydroxy-butoxy)-3,4-difluoro-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-N-(3,4-dihydroxy-butoxy)-3,4,5-trifluoro-benzamide;

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-N-(3,4-dihydroxy-butoxy)-3,4-difluoro-benzamide;

N-(3,4-Dihydroxy-butoxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(3,4-Dihydroxy-butoxy)-3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-(3,4-dihydroxy-butoxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-propoxy)-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-propoxy)-benzamide;

3,4,5-Trifluoro-N-(3-hydroxy-propoxy)-2-(4-iodo-2-methyl-

phenylamino)-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(3-hydroxy-propoxy)-benzamide;

5-Bromo-3,4-difluoro-N-(3-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

3,4-Difluoro-N-(3-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-butoxy)-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(2-hydroxy-butoxy)-benzamide;

3,4,5-Trifluoro-N-(2-hydroxy-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-butoxy)-benzamide;

5-Bromo-3,4-difluoro-N-(2-hydroxy-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

3,4-Difluoro-N-(2-hydroxy-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-butoxy)-benzamide;

5-Chloro-3,4-difluoro-N-(2-hydroxy-butoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-butoxy)-benzamide;

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-butoxy)-benzamide;

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-butoxy)-benzamide;

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-butoxy)-benzamide;

5-Chloro-2-(2,4-difluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-

butoxy)-benzamide;

2-(2,4-Difluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-butoxy)-benzamide;

2-(4-Bromo-2-fluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-butoxy)-benzamide;

5-Chloro-3,4-difluoro-N-(2-hydroxy-1-methyl-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-1-methyl-ethoxy)-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(2-hydroxy-1-methyl-ethoxy)-benzamide;

3,4,5-Trifluoro-N-(2-hydroxy-1-methyl-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-1-methyl-ethoxy)-benzamide;

5-Bromo-3,4-difluoro-N-(2-hydroxy-1-methyl-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

2-(4-Chloro-2-fluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-1-methyl-ethoxy)-benzamide;

3,4-Difluoro-N-(2-hydroxy-1-methyl-ethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-1-methyl-ethoxy)-benzamide;

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-1-methyl-ethoxy)-benzamide;

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-1-methyl-ethoxy)-benzamide;

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-1-methyl-ethoxy)-benzamide;

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-1-methyl-ethoxy)-benzamide;

5-Chloro-2-(2,4-difluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-1-

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methyl-ethoxy)-benzamide;

2-(2,4-Difluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-1-methyl-ethoxy)-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-methoxy-ethoxy)-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(2-methoxy-ethoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-methoxy-ethoxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-methoxy-ethoxy)-benzamide;

3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-methoxy-ethoxy)-benzamide;

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-methoxy-ethoxy)-benzamide;

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-methoxy-ethoxy)-benzamide;

5-Chloro-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-methoxy-ethoxy)-benzamide;

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-methoxy-ethoxy)-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide;

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide;

3,4,5-Trifluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-3,4-difluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

3,4-Difluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-2-(4-iodo-2-

methyl-phenylamino)-benzamide;

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide;

5-Chloro-3,4-difluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide;

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide;

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide;

5-Chloro-2-(2,4-difluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide;

2-(4-Chloro-2-fluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-morpholin-4-yl-propoxy)-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-propoxy)-benzamide;

3,4,5-Trifluoro-N-(2-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-propoxy)-benzamide;

5-Bromo-3,4-difluoro-N-(2-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(2-hydroxy-propoxy)-benzamide;

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-propoxy)-benzamide;

3,4-Difluoro-N-(2-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-3,4-difluoro-N-(2-hydroxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-propoxy)-

benzamide;

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-propoxy)-benzamide;

5-Chloro-2-(2,4-difluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-propoxy)-benzamide;

2-(2,4-Difluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-propoxy)-benzamide;

2-(4-Chloro-2-fluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-propoxy)-benzamide;

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-propoxy)-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(2-hydroxy-2-methyl-propoxy)-benzamide;

3,4,5-Trifluoro-N-(2-hydroxy-2-methyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-3,4-difluoro-N-(2-hydroxy-2-methyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-2-methyl-propoxy)-benzamide;

3,4-Difluoro-N-(2-hydroxy-2-methyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-2-methyl-propoxy)-benzamide;

5-Chloro-3,4-difluoro-N-(2-hydroxy-2-methyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-2-methyl-propoxy)-benzamide;

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-2-methyl-propoxy)-benzamide;

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-2-methyl-propoxy)-benzamide;

5-Chloro-2-(2,4-difluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-2-

methyl-propoxy)-benzamide;

2-(2,4-Difluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-2-methyl-propoxy)-benzamide;

2-(4-Bromo-2-fluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-2-methyl-propoxy)-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide;

3,4,5-Trifluoro-N-(2-hydroxy-3-phenoxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide;

5-Bromo-3,4-difluoro-N-(2-hydroxy-3-phenoxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

3,4-Difluoro-N-(2-hydroxy-3-phenoxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide;

5-Chloro-3,4-difluoro-N-(2-hydroxy-3-phenoxy-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide;

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide;

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide;

5-Chloro-2-(2,4-difluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide;

2-(2,4-Difluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-phenoxy-propoxy)-benzamide;

2-(4-Chloro-2-fluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-

phenoxy-propoxy)-benzamide;

3,4-Difluoro-N-(3-hydroxy-2,2-dimethyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(3-hydroxy-2,2-dimethyl-propoxy)-benzamide;

3,4,5-Trifluoro-N-(3-hydroxy-2,2-dimethyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-2,2-dimethyl-propoxy)-benzamide;

5-Chloro-3,4-difluoro-N-(3-hydroxy-2,2-dimethyl-propoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-2,2-dimethyl-propoxy)-benzamide;

5-Chloro-2-(2,4-difluoro-phenylamino)-3,4-difluoro-N-(3-hydroxy-2,2-dimethyl-propoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide;

3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide;

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-[2-(2-methoxy-ethoxy)-ethoxy]-benzamide;

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide;

5-Chloro-2-(2,4-difluoro-phenylamino)-3,4-difluoro-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide;

2-(2,4-Difluoro-phenylamino)-3,4-difluoro-N-(3,3,3-trifluoro-2-hydroxy-

propoxy)-benzamide;

2-(4-Chloro-2-fluoro-phenylamino)-3,4-difluoro-N-(3,3,3-trifluoro-2-hydroxy-propoxy)-benzamide;

5-Chloro-2-(2,4-difluoro-phenylamino)-3,4-difluoro-N-(2-hydroxymethyl-cyclopropylmethoxy)-benzamide;

2-(2,4-Difluoro-phenylamino)-3,4-difluoro-N-(2-hydroxymethyl-cyclopropylmethoxy)-benzamide;

2-(4-Chloro-2-fluoro-phenylamino)-3,4-difluoro-N-(2-hydroxymethyl-cyclopropylmethoxy)-benzamide;

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxymethyl-cyclopropylmethoxy)-benzamide;

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide;

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide;

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide;

4,5-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide;

2-(2,4-Difluoro-phenylamino)-3,4-difluoro-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide;

2-(4-Bromo-2-fluoro-phenylamino)-3,4-difluoro-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide;

2-(4-Chloro-2-fluoro-phenylamino)-3,4-difluoro-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide;

5-Chloro-2-(2,4-difluoro-phenylamino)-3,4-difluoro-N-(1-hydroxymethyl-cyclopropylmethoxy)-benzamide;

2-(2,4-Difluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-methoxy-propoxy)-benzamide;

5-Chloro-2-(2,4-difluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-methoxy-propoxy)-benzamide;

2-(4-Bromo-2-fluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-

methoxy-propoxy)-benzamide;

2-(4-Chloro-2-fluoro-phenylamino)-3,4-difluoro-N-(2-hydroxy-3-methoxy-propoxy)-benzamide;

3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-phenylamino-ethoxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-phenylamino-ethoxy)-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-phenylamino-ethoxy)-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-(2-phenylamino-ethoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-phenylamino-ethoxy)-benzamide;

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(2-phenylamino-ethoxy)-benzamide;

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-((S)-3-hydroxy-2-methylamino-propoxy)-benzamide;

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-((R)-3-hydroxy-2-methylamino-propoxy)-benzamide;

(S)-5-Chloro-3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-2-methylamino-propoxy)-benzamide;

(R)-5-Chloro-3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(3-hydroxy-2-methylamino-propoxy)-benzamide;

(S)-5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-2-methylamino-propoxy)-benzamide;

(R)-5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-(3-hydroxy-2-methylamino-propoxy)-benzamide; and

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-(2-hydroxy-3-methylamino-propoxy)-benzamide.

FIG. 1

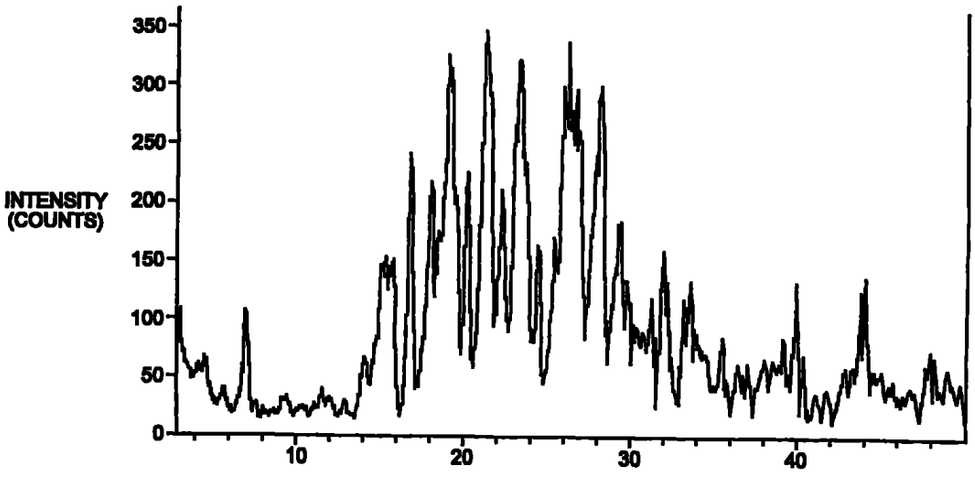


FIG. 2

FIG. 3

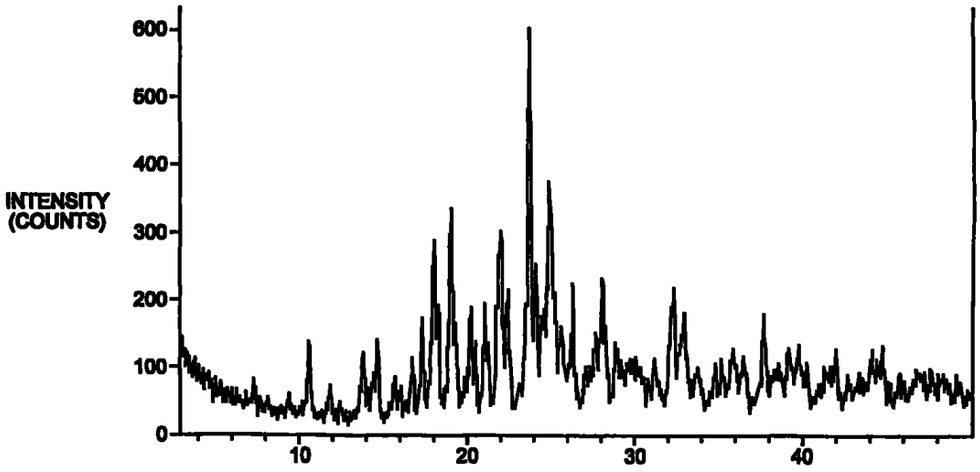
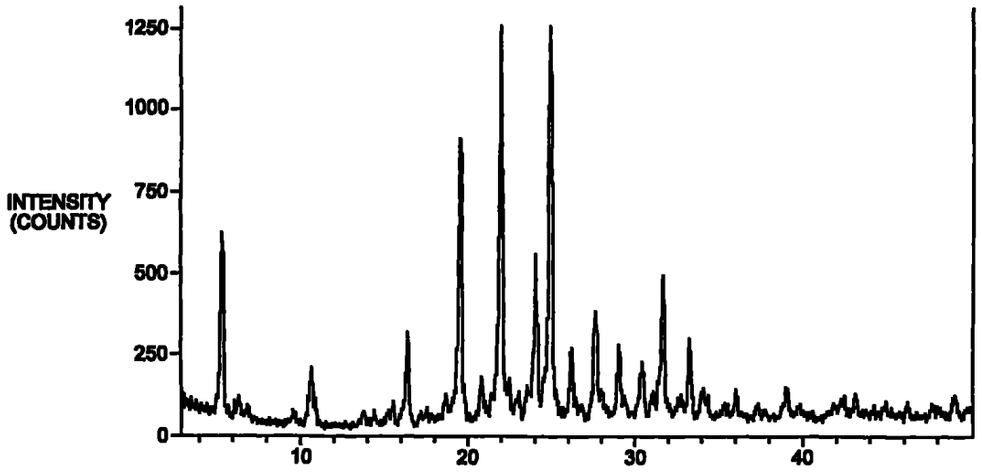


FIG. 4



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FIG. 5

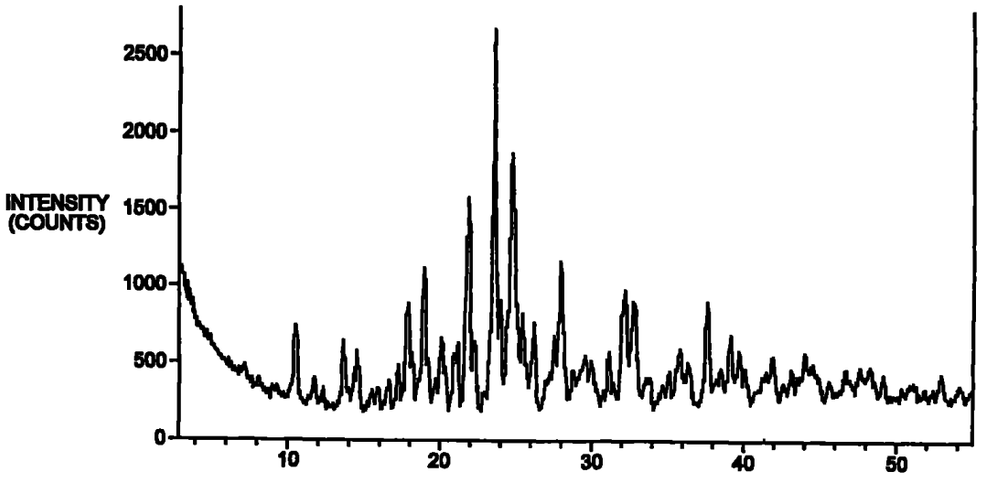
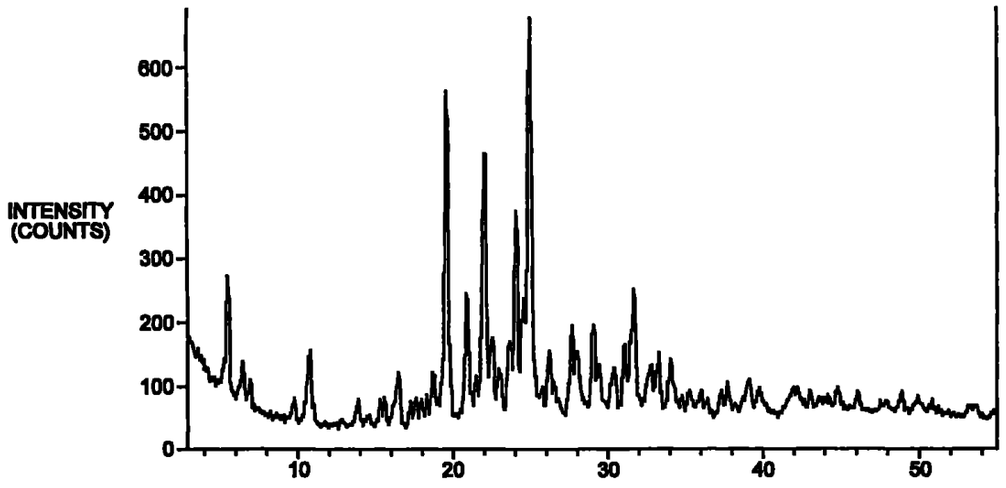


FIG. 6



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ÉSTERES OXIGENADOS DE ÁCIDOS 4-YODO FENILAMINO BENZHIDROXÁMICOS

CAMPO DE LA INVENCIÓN

La presente invención se relaciona con ésteres oxigenados de derivados del ácido 4-yodofenilamino benzhidroxámico, composiciones farmacéuticas y métodos de uso de aquellos. La presente invención también se relaciona con formas cristalinas de ésteres oxigenados de derivados del ácido 4-yodofenilamino benzhidroxámico, composiciones farmacéuticas y métodos de uso de ellos.

ANTECEDENTES DE LA INVENCIÓN

Las enzimas quinasa MAPK/ERK ("MEK") son quinasas de especificidad doble involucradas, por ejemplo, en la inmunomodulación, la inflamación y las enfermedades proliferativas tales como cáncer y restenosis.

Las enfermedades proliferativas están causadas por un defecto en el sistema de señalización intracelular, o el mecanismo de transducción de señales de ciertas proteínas. Los defectos incluyen un cambio en la actividad intrínseca o en la concentración celular de una o más proteínas señalizadoras en

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la cascada de señalización. La célula puede producir un factor de crecimiento que se une a sus propios receptores, lo cual deriva en un lazo autócrino, que estimula continuamente la proliferación. Las mutaciones o la sobreexpresión de las proteínas de señalización intracelular puede llevar a señales mitogénicas espurias dentro de la célula. Algunas de las mutaciones más comunes ocurren en los genes que codifican la proteína llamada Ras, una proteína G que se activa cuando se une a GTP, y se inactiva cuando se une a GDP. Los receptores del factor de crecimiento mencionados anteriormente, y muchos otros receptores mitogénicos, cuando son activados, conducen a que Ras sea convertida del estado unido a GDP al estado unido a GTP. Esta señal es un prerequisito absoluto para la proliferación en la mayor parte de los tipos de células. Los defectos en este sistema de señalización, especialmente en la desactivación del complejo de Ras-GTP, son comunes en el cáncer, y llevan a la cascada de señalización debajo de la Ras que está activada crónicamente.

Ras activada conduce a su vez a la activación de la cascada de quinasas de serina/treonina. Uno de los grupos de quinasas que se sabe que requieren Ras activa-GTP para su propia activación es la familia Raf. Éstas a su vez activan MEK (ej. MEK_1 y MEK_2) que luego activa la quinasa de MEK, ERK (ERK_1 y ERK_2). La activación de una quinasa MAP por mitogenes parece ser

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esencial para la proliferación; la activación constitutiva de esta quinasa es suficiente para inducir la transformación celular. El bloqueo de la señalización de Ras corriente abajo, por ejemplo mediante el uso de una proteína Raf-1 negativa dominante, puede inhibir completamente la mitogénesis, sea inducida desde los receptores de la superficie celular o desde mutantes de Ras oncogénicos. Aunque Ras no es ella misma una quinasa de proteína, participa en la activación de Raf y otras quinasas, más probablemente a través de un mecanismo de fosforilación. Una vez activada, la Raf y otras quinasas fosforilan MEK en dos residuos de serina estrechamente adyacentes, S^{128} y S^{222} en el caso de MEK-1, que son el prerequisito para la activación de MEK como una quinasa. MEK a su vez fosforila la quinasa MAP tanto en un residuo de tirosina, Y^{185}, como como de treonina, T^{183}, separados por un solo aminoácido. Esta fosforilación doble activa la quinasa MAP al menos 100 veces. La quinasa MAP activada puede luego catalizar la fosforilación de una gran cantidad de proteínas, incluyendo varios factores de transcripción y otras quinasas. Muchas de estas fosforilaciones de quinasas MAP son activadaras mitogénicas para la proteína objetivo, tal como una quinasa, un factor de transcripción, u otra proteína celular. Además de Raf-1 y MEKK, otras quinasas activan MEK, y la propia MEK parece ser una quinasa integradora de señales. Actualmente se entiende que MEK es altamente específica para

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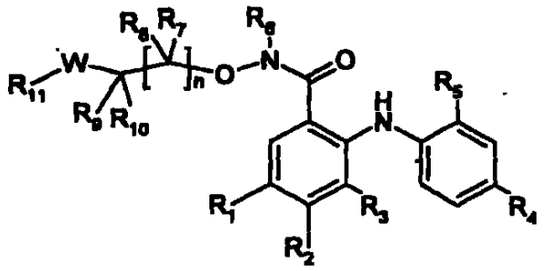
la fosforilación de la quinasa MAP. De hecho, no se ha demostrado hasta la fecha ningún sustrato para MEK salvo la quinasa MAP, ERK, y MEK no fosforila péptidos basados en la secuencia de fosforilación de la quinasa MAP, o siquiera fosforila la quinasa MAP desnaturalizada. MEK también parece asociarse fuertemente con la quinasa MAP antes de fosforilarla, lo cual sugiere que la fosforilación de la quinasa MAP por MEK puede requerir una fuerte interacción previa entre las dos proteínas. Tanto este requisito como al especificidad inusual de MEK sugieren que puede haber suficiente diferencia en este mecanismo de acción con otras quinasas de proteínas para que se puedan hallar inhibidores selectivos de MEK, que posiblemente operan a través de mecanismos alostéricos en lugar de a través del bloqueo habitual del sitio de unión a ATP.

Se ha descubierto que los compuestos de la presente invención son inhibidores de MEK y son útiles en el tratamiento de una veriedad de estados de enfermedades proliferativas, tales como las condiciones relacionadas con la hiperactividad de MEK, así como enfermedades moduladas por la cascada de MEK.

RESUMEN DE LA INVENCIÓN

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La invención proporciona un compuesto de la fórmula



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en donde

R_1 es hidrógeno, halógeno, o nitro;

R_2 es hidrógeno o flúor;

R_3 es hidrógeno o flúor;

R_4 es hidrógeno, yodo, bromo, cloro, o flúor;

R_5 es hidrógeno, halógeno, hidroxi, alquilo de C_{1-8}, alcoxi de C_{1-8}, trifluorometlo, o ciano;

n es 1 a 5;

R_6, R_7, R_8, R_9, y R_{10} son independientemente hidrógeno, alquilo de C_{1-8}, cicloalquilo de C_{3-8}, hidroxi, alcoxi de C_{1-8}, perhaloalquilo (de C_{1-3}), hidroxialquilo (de C_{1-8}), alcoxi (de C_{1-5})alquilo (de C_{1-5}), [alquilo (de C_{1-4})]$_3$aminometilo, heterociclo (de C_{2-7})alquilo (de C_{1-5}), o ariloxialquilo (de C_{1-5}), o puede ser unido independientemente para completar un anillo cíclico de 3-10 miembros que contiene optativamente heteroátomos adicionales seleccionados del grupo formado por

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O, S, NH, y N-alquilo, en donde R_7 y R_8 se seleccionan independientemente para n>1;

R_a y R_b son independientemente hidrógeno o alquilo de C_{1-4};

W es O o NR_a;

R_{11} es hidrógeno, alquilo de C_{1-8}, alquenilo de C_{2-6}, cicloalquilo de C_{3-8}, hidroxialquilo (de C_{1-8}), alcoxi (de C_{1-5})alquilo (de C_{1-5}), fenilo, heteroarilo de C_{2-7}, alquilcarbonilo (de C_{1-8}), (fenil)carbonilo, (fenil)(alquilo de C_{1-3})carbonilo, o trifluoroalquilo (de C_{1-6});

en donde los grupos alquilo, alcoxi, cicloalquilo, heteroarilo, y fenilo se pueden sustituir optativamente con entre 1 y 5 sustituyentes seleccionados independientemente del grupo formado por hidroxi, amino, monoalquilamino, dialquilamino, halógeno, ciano, alcoxi (de C_{1-3}), COOR, $OCOR_a$, $CONR_aR_b$, NR_aCOR_b, SO, SO_2, SO_4 y $SO_2NR_aR_b$;

y las sales farmacéuticamente aceptables, amidas (de C_{1-6}) y ésteres (de C_{1-6}) de ellos;

siempre que cuando R_{11} es fenilo y n es 1, W no puede ser O;

además siempre que el compuesto no sea

5-bromo-N-(2-dietilamino-etoxi)-3,4-difluoro-(4-yodo-2-metil-fenilamino)-benzamida;

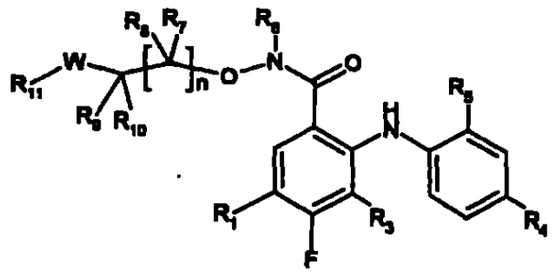
5-bromo-N-(2-dimetilamino-propoxi)-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-benzamida; o

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5-bromo-2-(2-cloro-4-yodo-fenilamino)-N-(2-dimetilamino-etoxi)-3,4-difluoro-benzamida.

La presente invención también proporciona un compuesto que tiene la fórmula



Ia

en donde

R_1 es hidrógeno o halógeno;

R_3 es hidrógeno o flúor;

R_4 es hidrógeno, yodo, bromo, cloro, o flúor;

R_5 es hidrógeno, halógeno o alquilo de C_{1-8};

n es 1 a 5;

R_6, R_7, R_8, R_9, y R_{10} son independientemente hidrógeno, alquilo de C_{1-8}, cicloalquilo de C_{3-8}, hidroxi, alcoxi de C_{1-8}, perhaloalquilo (de C_{1-3}), hidroxialquilo (de C_{1-8}), o ariloxi (de C_{1-5})alquilo (de C_{1-5}), o puede ser unido independientemente para completar un anillo cíclico de 3-10 miembros que contiene optativamente heteroátomos adicionales seleccionados del grupo formado por O, S, NH, y N-alquilo, en donde R_7 y R_8 se seleccionan independientemente para n>1;

R_a y R_b son independientemente hidrógeno o alquilo de C_{1-4};

W es O o NR_a;

R_{11} es hidrógeno, alquilo de C_{1-8}, alquenilo de C_{2-6}, alcoxi (de C_{1-5})alquilo (de C_{1-5}), fenilo, alquilcarbonilo (de C_{1-8}), o trifluoroalquilo (de C_{1-6});

en donde los grupos alquilo, alcoxi, cicloalquilo, heteroarilo, y fenilo se pueden sustituir optativamente con entre 1 y 5 sustituyentes seleccionados independientemente del grupo formado por hidroxi, amino, monoalquilamino, dialquilamino, halógeno, ciano, alcoxi (de C_{1-3}), COOR, $OCOR_a$, $CONR_aR_b$, NR_aCOR_b, SO, SO_2, SO_4 y $SO_2NR_aR_b$;

y las sales farmacéuticamente aceptables, amidas (de C_{1-6}) y ésteres (de C_{1-6}) de ellos;

siempre que cuando R_{11} es fenilo y n es 1, W no puede ser O;

además siempre que el compuesto no sea

5-bromo-N-(2-dietilamino-etoxi)-3,4-difluoro-(4-yodo-2-metil-fenilamino)-benzamida;

5-bromo-N-(2-dimetilamino-propoxi)-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-benzamida; o

5-bromo-2-(2-cloro-4-yodo-fenilamino)-N-(2-dimetilamino-etoxi)-3,4-difluoro-benzamida.

La invención también proporciona una composición farmacéutica que comprende un compuesto de la fórmula I o Ia y un portador farmacéuticamente aceptable.

Además, la invención proporciona un método para tratar una enfermedad proliferativa en un paciente que lo necesita que comprende administrar una cantidad terapéuticamente efectiva de un compuesto de la Fórmula I o Ia.

La invención también proporciona el uso de un compuesto de la fórmula I o Ia para la fabricación de un medicamento para el tratamiento de una enfermedad proliferativa.

Más aún, la invención provee métodos para tratar el cáncer, restenosis, psorisis, enfermedad autoinmune, aterosclerosis, osteoartritis, artritis reumatoide, insuficiencia cardíaca, dolor crónico, y dolor neuropático en un paciente que lo necesita, que comprenden administrar una cantidad terapéuticamente efectiva de un compuesto de la fórmula I o Ia.

La invención también provee el uso de un compuesto de la fórmula I o Ia para la fabricación de un medicamento para el tratamiento de cáncer, restenosis, psoriasis, enfermedad autoinmune, aterosclerosis, osteoartritis, artritis

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reumatoide, insuficiencia cardíaca, dolor crónico, y dolor neuropático.

Además, la invención provee un método para tratar el cáncer en un paciente que lo necesita, que comprende administrar una cantidad terapéuticamente efectiva de un compuesto de la fórmula I o Ia en combinación con terapia de radiación o por lo menos un agente quimioterapéutico.

En otro aspecto, la presente invención provee una Forma I cristalina de N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene por lo menos uno de los siguientes valores de 2θ medidos usando la radiación de CuK_α: 7,1, 19,2, o 32,1.

La presente invención también provee una Forma I cristalina de N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 7,1, 19,2, y 32,1.

Además, la presente invención provee una Forma I cristalina de N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-

fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 7,1, 14,1, 15,3, 15,8, 16,9, 18,1, 19,2, 20,3, 21,4, 22,3, 23,4, 24,5, 25,5, 26,2, 26,8, 27,8, 28,3, 29,5, 32,1, 33,2, 33,6, 40,0, 42,9 y 44,1.

La presente invención también provee una Forma II cristalina de N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 11,6, 12,6, o 24,9.

La presente invención también provee una Forma II cristalina de N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 11,6, 12,6 y 24,9.

Además, la presente invención provee una Forma II cristalina de N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 11,6, 12,6, 15,6, 17,3,

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17,9, 20,3, 21,2, 22,1, 24,9, 25,9, 26,7, 27,8, 30,1, 30,9, 33,8, 35,4, 38,2, 39,3, 40,8, 41,6, 43,6, y 47,0.

Además, la presente invención provee una Forma I cristalina de N-[(R)-2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 10,6, 13,7, 19,0 o 23,7.

Además, la presente invención provee una Forma I cristalina de N-[(R)-2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 10,6, 13,7, 19,0 y 23,7.

La presente invención también provee una Forma I cristalina de N-[(R)-2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 10,6, 13,7, 14,6, 17,3, 18,0, 18,2, 19,0, 19,3, 20,1, 21,0, 21,9, 22,4, 23,7, 24,0, 24,9, 26,3, 27,6, 28,0, 30,1, 32,1, 32,3, 32,9, 35,8, y 37,7.

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Más áun, la presente invención provee una Forma II cristalina de N-[(R)-2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 5,5 o 19,6.

La presente invención también provee una Forma II cristalina de N-[(R)-2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 5,5 y 19,6.

Además, la presente invención provee una Forma II cristalina de N-[(R)-2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 5,5, 10,7, 16,5, 19,6, 22,0, 22,5, 23,6, 24,1, 25,0, 26,2, 27,6, 29,1, 30,5, 31,7, 33,3 y 39,0.

Además, la presente invención provee una Forma I cristalina de N-[(S)-2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de

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difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 10,5, 13,7, 19,0 y 23,6.

La presente invención también provee una Forma I cristalina de N-[(S)-2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 10,5, 13,7, 19,0 y 23,6.

Más aún, la presente invención provee una Forma I cristalina de N-[(S)-2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 10,548, 13,703, 17,887, 18,958, 20,122, 21,950, 22,321, y 23,640, 24,803, 26,244, 27,570, 28,000, 29,566, 32,234, 32,769, 35,804, 37,641, 41,402, 41,956 y 44,600.

La presente invención también provee una Forma II cristalina de N-[(S)-2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 5,6 o 19,6.

Además, la presente invención provee una Forma II cristalina de N-[(S)-2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 5,6, y 19,6.

Además, la presente invención provee una Forma II cristalina de N-[(S)-2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 5,6, 10,7, 16,5, 19,6, 20,9, 22,0, y 23,7, 24,2, 25,0, 26,2, 27,7, 28,0, 29,1, 31,7, 32,8, 33,3, 34,1, 42,0 y 42,3.

BREVE DESCRIPCIÓN DE LOS DIBUJOS

La invención se describe también con los siguientes ejemplos no taxativos que hacen referencia a las Figuras 1 a 6 que los acompañan, cuyos detalles se dan a continuación..

FIGURA 1

Difractograma de la Forma I N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida (eje Y = 0 hasta la intensidad máxima de 350 cuentas por segundo (cps)).

FIGURA 2

Difractograma de la Forma II N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida (eje Y = 0 hasta la intensidad máxima de 1200 cps).

FIGURA 3

Difractograma de la Forma I N-[(R)-2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida (eje Y = 0 hasta la intensidad máxima de 600 cps).

FIGURA 4

FIGURA 2

Difractograma de la Forma II N-[(R)-2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida (eje Y = 0 hasta la intensidad máxima de 1250 cps).

FIGURA 5

Difractograma de la Forma I N-[(S)-2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida (eje Y = 0 hasta la intensidad máxima de 2600 cps).

FIGURA 6

Difractograma de la Forma II N-[(S)-2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida (eje Y = 0 hasta la intensidad máxima de 700 cps).

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DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Ciertos términos se definen a continuación y por su uso en toda la invención.

Los términos "halógeno" o "halo" en la presente invención se refieren a átomos de flúor, cloro, y yodo o fluro, bromo, cloro y yodo. Se entiende que los términos flúor y fluoro, por ejemplo, son equivalentes aquí.

Los grupos alquilo, tales como "alquilo de C_{1-8}" incluyen alifáticos (es decir, estructuras de radicales hidrocarbilo o hidrocarburo que contienen átomos de hidrógeno y carbono) con una valencia libre. Se entiende que los grupos alquilo se incluyen estructuras de cadena recta y ramificadas. Ejemplos de ellos incluyen metilo, etilo, propilo, isopropilo, butilo, n-butilo, isobutilo, t-butilo, pentilo, isopentilo, 2,3-dimetilpropilo, hexilo, 2,3-dimetilhexilo, 1,1-dimetilpentilo, heptilo, octilo y similares. El término "alquilo de C_{1-8}" incluye dentro de su definición los términos "alquilo de C_{1-6}", "alquilo de C_{1-5}", "alquilo de C_{1-4}" y "alquilo de C_{1-3}".

Los grupos alquilo pueden sustituirse con 1, 2, o 3 sustituyentes que se seleccionan independientemente de halo (fluoro, cloro, bromo o yodo), ciano hidroxi, amino, alcoxi,

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alquilamino, dialquilamino, cicloalquilo, arilo, ariloxi, arilalquiloxi, radical heterocíclico y (radical heterocíclico)oxi. Ejemplos específicos incluyen fluorometilo, hidroxietilo, 2,3-dihidroxietilo, (2- o 3-furanil)metilo, ciclopropilmetilo, benciloxietilo, (3-piridil)metilo, (2- o 3-furanil)metilo, (2-tienil)etilo, hidroxipropilo, aminociclohexilo, 2-dimetilaminobutilo, metoximetilo, N-piridiniletilo, dietilaminoetilo, y ciclobutilmetilo.

El término "alcoxi" usado aquí se refiere a una cadena recta o ramificada de alquilo unida a un átomo de oxígeno. El término "alcoxi de C_{1-8}" usado aquí se refiere a una cadena recta o ramificada de alquilo que tiene de uno a ocho átomos de carbono unida a un átomo de oxígeno. Los grupos alcoxi de C_{1-8} típicos incluyen metoxi, etoxi, propoxi, isopropoxi, butoxi, t-butoxi, pentoxi, y similares. El término "alcoxi de C_{1-8}" incluye dentro de su definición los términos "alcoxi de C_{1-6}" y "alcoxi de C_{1-4}".

Los grupos alquenilo son análogos a los grupos alquilo, pero tienen por lo menos un enlace doble (dos átomos de carbono sp^2 adyacentes). Según la ubicación de un enlace doble y los sustituyentes, si hubiera, la geometría del enlace doble puede ser *entgegen* (E), o *zusammen* (Z), *cis* o *trans*. En forma similar, los grupos alquinilo tienen por lo menos un enlace

triple (dos átomos de carbono sp adyacentes). Los grupos alquenilo o alquinilo pueden tener uno o más enlaces dobles o triples, respectivamente, o una mezcla de ellos; como los grupos alquilo, los grupos insaturados pueden ser de cadena recta o ramificados, y pueden sustituirse como se describió anteriormente tanto para los grupos alquilo como en toda la invención en forma de ejemplo. Ejemplos de alquenilos, alquinilos y formas sustituidas incluyen cis-2-butenilo, trans-2-butenilo, 3-butinilo, 3-fenil-2-propinilo, 3-(2'-fluorofenilo)-2-propinilo, 3-metil(5-fenil)-4-pentinilo, 2-hidroxi-2-propinilo, 2-metil-2-propinilo, 2-propenilo, 4-hidroxi-3-butinilo, 3-(3-fluorofenil)-2-propinilo, y 2-metil-2-propenilo. En la fórmula (I), el término "alquenilo" incluye alquenilo de C_{2-4}, o alquenilo de C_{2-8}.

Los grupos cicloalquilo, tales como cicloalqulo de C_{3-10}, se refieren a una estructura de anillo de hidrocarburo saturado que contiene de 3 a 10 átomos. Los grupos cicloalquilo de C_{3-10} incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo y similares.

El término "arilo" significa un grupo carbocíclico aromático no sustituido que tiene un solo anillo (ej. fenilo), múltiples anillos (ej. bifenilo), o múltiples anillos condensados en los cuales al menos uno es aromático (ej. 1,2,3,4-

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tetrahidronaftilo, naftilo, antrilo, o fenantrilo). El grupo arilo se puede sustituir optativamente con entre 1 y 5 sustituyentes seleccionados independientemente del grupo formado por hidroxi, amino, monoalquilamino, dialquilamino, halógeno, ciano, alcoxi (de C_{1-3}), COOR, $OCOR_a$, $CONR_aR_b$, SO, SO_2, SO_4 y $SO_2NR_aR_b$, donde R_a y R_b son independientemente hidrógeno o alquilo de C_{1-4}.

El término "ariloxi" usado aquí se refiere a un grupo arilo unido a un átomo de oxígeno.

Como se usa aquí, los términos "heterociclo", "heterociclo de C_{2-7}", "heterociclo de C_{2-9}" o "heteroarilo de C_{2-7}" en la presente invención se refiere a un anillo monocíclico estable de 5, 6 o 7 miembros o un anillo heterocíclico bicíclico de 7 a 10 miembros que es saturado o insaturado, y comprende átomos de carbono y de uno a cuatro heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno, o azufre. El anillo heterocíclico puede ser unido a cualquier heteroátomo o átomo de carbono que da una estructura estable.

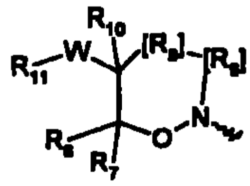
Los radicales heterocíclicos, que incluyen en forma no taxativa heteroarilos, incluyen: furilo, (is)oxazolilo, isoxazolilo, tiofenilo, tiazolilo, pirrolilo, imidazolilo, 1,3,4-triazolilo, tetrazolilo, piridinilo, pirimidinilo,

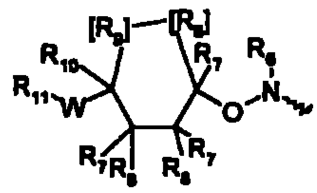
piridazinilo, indolilo, y sus contrapartes no aromáticas. Otros ejemplos de radicales heterocíclicos incluyen tienilo, piperidilo, quinolilo, isotiazolilo, piperidinilo, morfolinilo, piperazinilo, tetrahidrofurilo, tetrahidropirrolilo, pirrolidinilo, octahidroindolilo, octahidrobenzotiofuranilo, octahidrobenzofuranilo, (iso)quinolinilo, naftiridinilo, bencimidazolilo o benzoxazolilo.

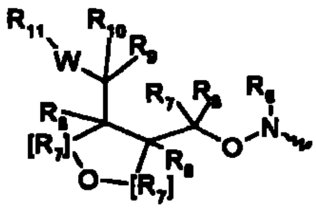
Formas más generales de radicales hidrocarburo sustituido incluyen hidroxialquilo, hidroxialquenilo, hidroxialquinilo, hidroxicicloalquilo, hidroxiarilo y las formas correspondientes de los prefijos amino-, halo- (ej. fluoro-, cloro- o bromo-), nitro-, alquilo-, fenilo-, cicloalquilo-, etc, o combinaciones de los sustituyentes. De acuerdo con la fórmula (I), en consecuencia, los alquilos sustituidos incluyen, en forma no taxativa, hidroxialquilo, alcoxialquilo aminoalquilo, nitroalquilo, haloalquilo, cianoalquilo, alquilalquilo (alquilos ramificados, tales como metilpentilo), (cicloalquil)alquilo, fenilalquilo, alquilamioalquilo, dialquilaminoalquilo, arilalquilo, ariloxialquilo, arilalquiloxialquilo, (radical heterocíclico)alquilo, y (radical heterocíclico)oxialquilo. La Fórmula I incluye por lo tanto, hidroxialquilo, hidroxialquenilo, hidroxialquinilo, hidroxicicloalquilo, hidroxiarilo, aminoalquilo,

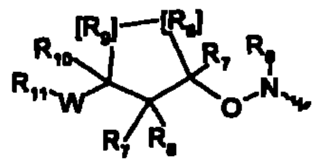
aminoalquenilo, aminoalquinilo, aminocicloalquilo, aminoarilo, alquilalquenilo, (alquilaril)alquilo, (haloaril)alquilo, (hidroxiaril)alquinilo, etc. En forma similar, R_6, R_7, R_8, R_9 y R_{10} incluyen hidroxialquilo (de C_{1-8}), alcoxi (de C_{1-5}) alquilo (de C_{1-5}), aminoalquilo, (ej. [alquilo (de C_{1-4})]$_2$aminometilo), perhaloalquilo (de C_{1-3}) (ej. trifluorometilo o trifluoroetilo), heterociclo (de C_{2-7}) alquilo (de C_{1-5}), y ariloxi alquilo (de C_{1-5}). En forma similar, R_{10} incluye hidroxialquilo (de C_{1-8}), alcoxi (de C_{1-5}) alquilo (de C_{1-5}) y trifluoro alquilo (de C_{1-6}).

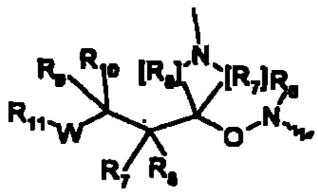
Ejemplos representativos de la unión independiente de R_6, R_7, R_8, R_9 y R_{10} para completar un anillo cíclico de 3-10 miembros que optativamente contienen heteroátomos adicionales seleccionados de O, S, NH o N-alquilo se demuestran en los fragmentos que se muestran a continuación.

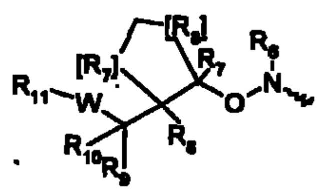


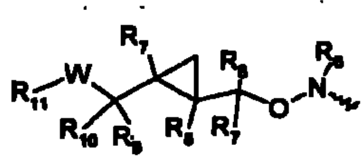


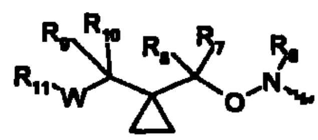


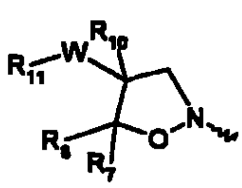






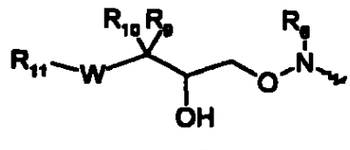




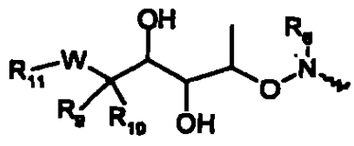


Ejemplos representativos de la fórmula I donde R_7 y R_8 se seleccionan independientemente de n>1 se ejemplifican en los fragmentos que se muestran a continuación. Los fragmentos

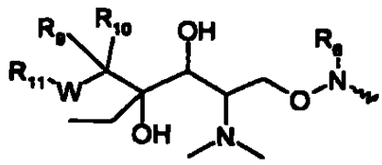
siguientes muestran que cuando n>1, R_7 y R_8 se seleccionan independientemente para cada unidad (CR_7R_8).



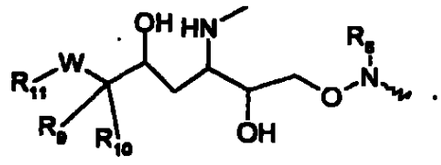
n=2



n=3



n=4



n=5

La presente invención incluye los hidratos y las sales farmacéuticamente aceptables y solvatos de los compuestos definidos por la fórmula I. Los compuestos de esta invención pueden poseer un grupo funcional suficientemente básico y por consiguiente reaccionan con cualquiera de la cantidad de ácidos inorgánicos y orgánicos, para formar una sal farmacéuticamente aceptable.

El término "sal farmacéuticamente aceptable" como se usa aquí, se refiere a las sales de los compuestos de la fórmula I que son sustancialmente no tóxicos para los organismos vivos. La

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sales farmacéuticamente aceptables típicas incluyen aquellas sales preparadas mediante la reacción de los compuestos de la presente invención con un mineral o ácido orgánico farmacéuticamente aceptable. Tales sales se denominan también sales de adición ácidas. Tales sales incluyen las sales farmacéuticamente aceptables enumeradas en la lista de Journal of Pharmaceutical Science, 66, 2-19 (1977), conocidas para el experto.

Los ácidos comúnmente empleados para formar las sales de adición ácidas son ácidos orgánicos tales como ácido clorhídrico, ácido bromhídrico, ácido yodhídrico, ácido sulfúrico, ácido fosfórico, y similares, y ácidos orgánicos tales como ácido p-toluensulfónico, ácido metanosulfónico, ácido bencensulfónico, ácido oxálico, ácido p-bromofenilsulfónico, ácido carónico, ácido succínico, ácido cítrico, ácido benzoico, ácido acético, y similares. Ejemplos de tales sales farmacéuticamente aceptables son las sales de sulfato, pirosulfato, bisulfato, sulfito, bisulfito, fosfato, monohidrogenfosfato, dihidrogenfosfato, metafosfato, pirofosfato, bromuro, bromhidrato, yoduro, acetato, propionato, decanoato, caprato, caprilato, acrilato, ascorbato, formato, clorhidrato, diclorhidrato, isobutirato, caproato, heptanoato, propiolato, glucuronato, glutamato, propionato, fenilpropionato, salicilato, oxalato, malonato,

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succinato, suberato, sebacato, fumarato, malato, maleato, hidroximaleato, mandelato, mesilato, nicotinato, isonicotinato, cinamato, hipurato, nitrato, estearato, ftalato, tetraftalato, butin-1,4-dioato, butin-1,4-dicarboxilato, hexin-1,4-dicarboxilato, hexin-1,6-dioato, benzoato, clorobenzoato, metilbenzoato, hidroxibenzoato, metoxibenzoato, dinitrobenzoato, o-acetoxibenzoato, naftalen-2-benzoato, ftalato, p-toluensulfonato, p-bromobencensulfonato, p-clorobencensulfonato, xilensulfonato, fenilacetato, trifluoroacetato, fenilpropionato, fenilbutirato, citrato, lactato, α-hidroxibutirato, glicolato, tartrato, hemitartrato, bencensulfonato, metanosulfonato, etanosulfonato, propanosulfonato, hidroxietanosulfonato, 1-naftalensulfonato, 2-naftalensulfonato, 1,5-naftalendisulfonato, mandelato, tartrato, y similares. Una sal farmacéuticamente aceptable preferida es el clorhidrato.

Se debe reconocer que el contra ion particular que forma parte de cualquier sal de esta invención generalmente no es de carácter crítico, en la medida en que la sal en su totalidad sea farmacológicamente aceptable y en la medida en que el contra ion no contribuya con cualidades indeseadas para la sal en su totalidad. Se entiende también que tales sales pueden existir como un hidrato.

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Como se usa aquí, el término "estereoisómero" se refiere a un compuesto hecho de los mismos átomos unidos por los mismos enlaces pero que tiene diferentes estructuras tridimensionales que no son intercambiables. Las estructuras tridimensionales se denominan configuraciones. Como se usa aquí, el término "enantiómero" se refiere a cada uno de dos estereoisómeros cuyas moléculas son imágenes especulares una de otra que pueden superponerse. El término "centro quiral" se refiere a un átomo de carbono al cual se unen cuatro grupos diferentes. Como se usa aquí, el término "diastereoisómeros" se refiere a estereoisómeros que no son enantiómeros. Los términos "racemato" o "mezcla racémica" se refieren a una mezcla de enantiómeros.

Los enantiómeros de los compuestos de la presente invención pueden ser resueltos por un conocedor del arte que usa técnicas estándar conocidas en el arte, tales como aquellas descriptas por J. Jacques et al, "Enantiómeros, Racematos y Resoluciones", John Wiley and Sons, Inc., 1981. Ejemplos de resoluciones incluyen técnicas de recristalización o cromatografía quiral.

Algunos de los compuestos de la presente invención tienen uno o más centros quirales y pueden existir en una variedad de configuraciones estereoisoméricas. Como consecuencia de estos

centros quirales, los compuestos de la presente invención ocurren como racematos, mezclas de enantiómeros y como enantiómeros individuales, así como diastereómeros y mezclas de diastereómeros. Todos los racematos, enantiómeros, y diastereómeros están dentro del alcance de la presente invención.

Los compuestos de la fórmula I se pueden preparar mediante técnicas y procedimientos rápidamente disponibles para un conocedor del arte, por ejemplo mediante los siguientes procedimientos expuestos en los siguientes Esquemas. Estos esquemas, salvo que se indique lo contrario, se definen previamente. Los reactivos y los materiales iniciales son rápidamente disponibles para un experto en el arte.

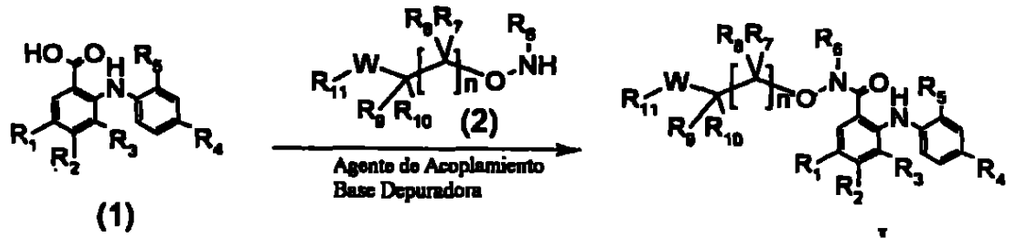
Los compuestos de la fórmula I generalmente se obtienen mediante la unión de ácidos 2-(arilamino)-benzoicos (1) con alcoxiaminas (2) mediante la acción de un agente de acoplamiento de péptido en la presencia de una base, como se muestra en el Esquema 1. Los agentes de acoplamiento preferidos incluyen cloruro difenilfosfínico (DPP-Cl), hexafluorofosfato de benzotriazol-il-oxi-tripirrolidinofosfonio (PyBOP), hexafluorofosfato de benzotriazol-1-iloxi-tris(dimetilamino)fosfonio (BOP), N,N'-diciclohexilcarbodiimida (DCC), clorhidrato de 1-etil-3-(3-

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dimetilaminopropil)carbodiimida (EDCI), o 1,1'-carbonildiimidazol (CDI). Las bases preferidas incluyen diisopropiletilamina, trietilamina, 4-metilmorfolina, o piridina o una piridina sustituida, por ejemplo, 4-dimetilaminopiridina o 2,6-dimetilpiridina. Los solventes preferidos son solventes apróticos polares tales como diclorometano, tetrahidrofurano, o dimetilformamida. Las reacciones generalmente se llevan a cabo a una temperatura de entre -78°C y 25°C, y normalmente son completas dentro de las 2 horas a 5 días. Las amidas producto pueden aislarse removiendo el solvente, por ejemplo mediante la evaporación bajo presión reducida, y purificarse más, si se desea, mediante métodos estándar tales como cromatografía, cristalización o destilación.

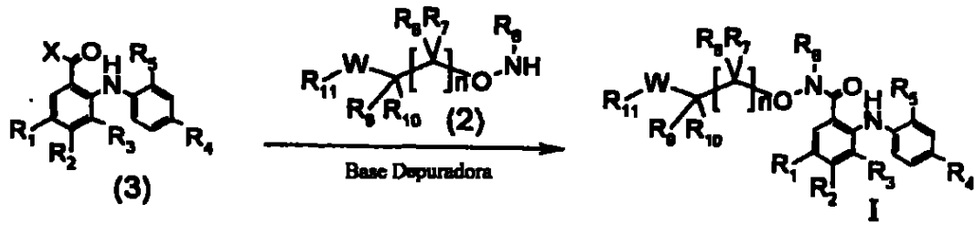
Esquema 1: Preparación General de Benzamidas desde Ácidos Benzoicos



Alternativamente, los compuestos revelados también generalmente se preparan como se muestra en el Esquema 2

mediante el contacto de alcoxiamina (2) con derivados de ácido benzoico "activado" (3), en donde el grupo activador "X" completa un haluro ácido, anhídrido, anhídrido mezclado o un éster activado, tal como pentafluorofenil éster, nitrofenil éster o tioéster. Las bases preferidas incluyen diisopropiletilamina, trietilamina, 4-metilmorfolina, imidazol, piridina o una piridina sustituida, por ejemplo, 4-dimetilaminopridina o 2,6-dimetilpiridina. Los solventes preferidos son solventes apróticos polares tales como diclorometano, tetrahidrofurano, o dimetilformamida. Estas estrategias sintéticas, que son adecuadas para los métodos sintéticos convencionales así como combinatorios (síntesis paralela), se ejemplifican en los siguientes ejemplos.

Esquema 2: Preparación General de Benzamidas desde Derivados de Ácido Benzoico "Activados"



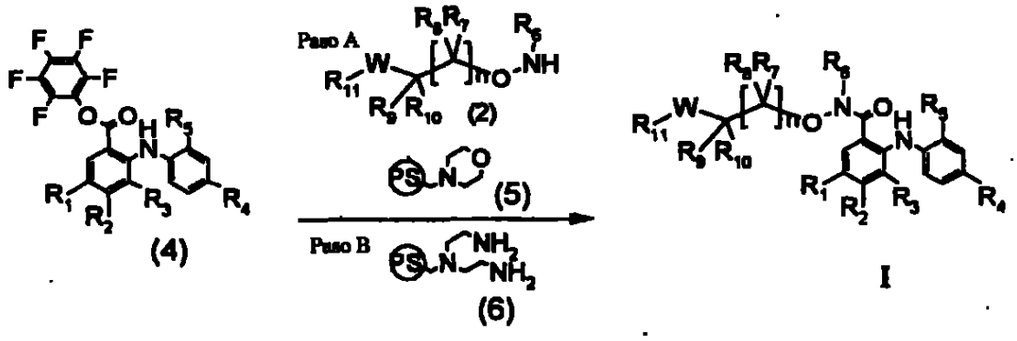
Los métodos combinatorios preferidos se describen en el Esquema 3, donde los compuestos de la fórmula I se obtienen

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mediante la reacción de un exceso de pentafluorofenil ésteres (4) con alcoxiaminas (2) en la presencia de 4-metilmorfolina soportada por polímeros (PS) (5) en dimetilformamida con agitación mecánica. Después de un período de reacción de 16 a 72 horas, la amina soportada por polímeros (6) se agrega con diclorometano. Después de varias horas adicionales de agitación mecánica, los objetivos I se obtienen mediante filtración, evaporación del solvente y purificación cromatográfica.

Esquema 3: Preparación Combinatoria General de Benzamidas desde Pentafluorofenil Ésteres del Ácido Benzoico



Para la preparación de compuestos de la fórmula I donde R_{11}= hidrógeno, los modos sintéticos preferidos pueden utilizar un reactivo de la fórmula (2), en donde R_6, R_7, R_8, R_9, R_{10} se definen como la fórmula I, precedente, y R_{11} es un grupo protector estándar hidroxilo (W = O) o amino (W = NR_8). En tales casos, los esquemas 1-3, precedentes pueden modificarse

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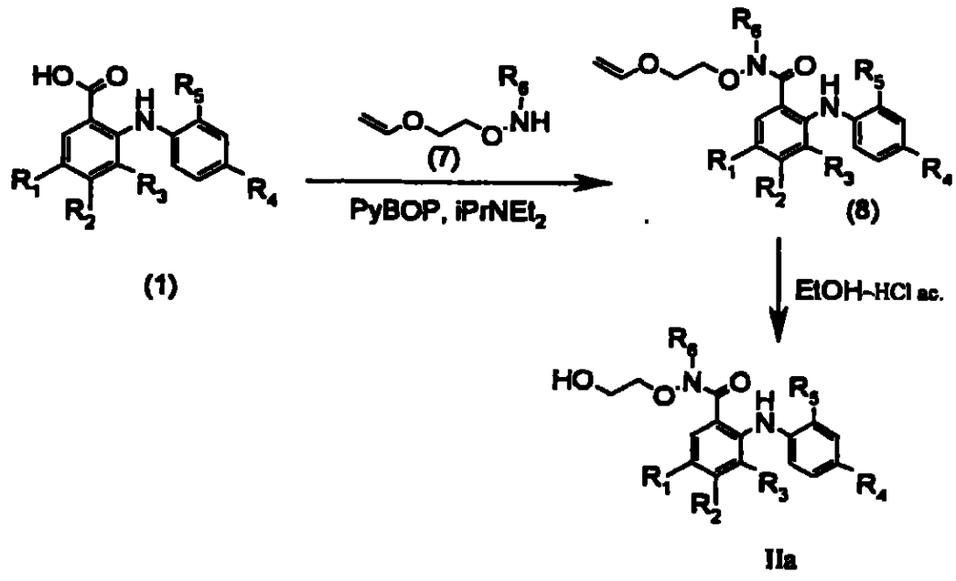
para incluir una remoción estándar de dicho grupo protector. Los grupos protectores adecuados incluyen, en forma no taxativa, vinil ésteres, silil éteres, acetales, acetonuros, y carbamatos. A continuación se describen ejemplos de tales modificaciones.

Como se representa en el Esquema 4, los compuestos preferidos de la fórmula IIa se pueden obtener mediante la reacción de ácidos benzoicos (1) con vinil éter (7), un agente de acoplamiento de péptido (por ejemplo, PyBOP) y una base (por ejemplo, diisopropiletilamina) para dar vinil éter amida (8). Otro tratamiento de vinil éter (8) con ácido da los compuestos de la fórmula IIa.

(61)

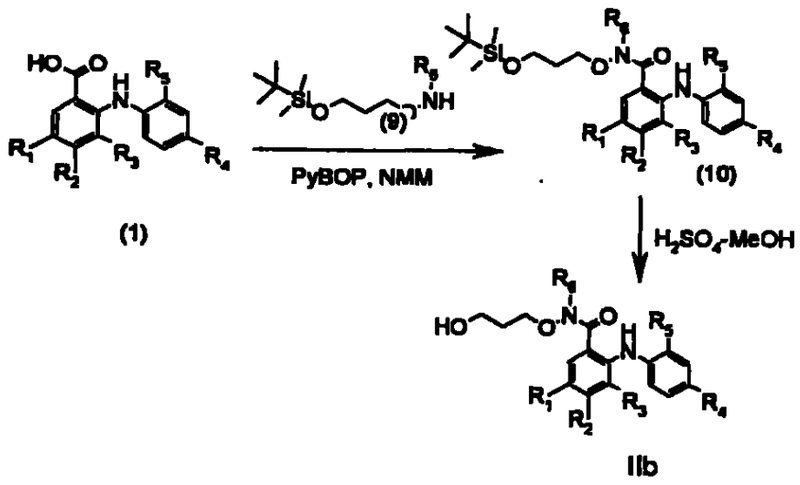
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Esquema 4: Preparación Representativa de Benzamidas Hidroxiladas Usando un Vinil Éter como un Grupo Protector Hidroxilo



Como se muestra abajo en el Esquema 5, los compuestos preferidos de la fórmula IIb también pueden obtenerse mediante la reacción de ácidos benzoicos (1) con un grupo protector adecuado, tal como terc-butildimetilsilil éter (9), en la presencia de un agente de acoplamiento de péptido (por ejemplo, PyBOP) y una base de amina terciaria (por ejemplo, diisopropiletilamina) para dar una terc-butildimetilsilil éter amida (10). Otro tratamiento del silil éter (10) con ácido en un solvente prótico da los compuestos de la fórmula IIb.

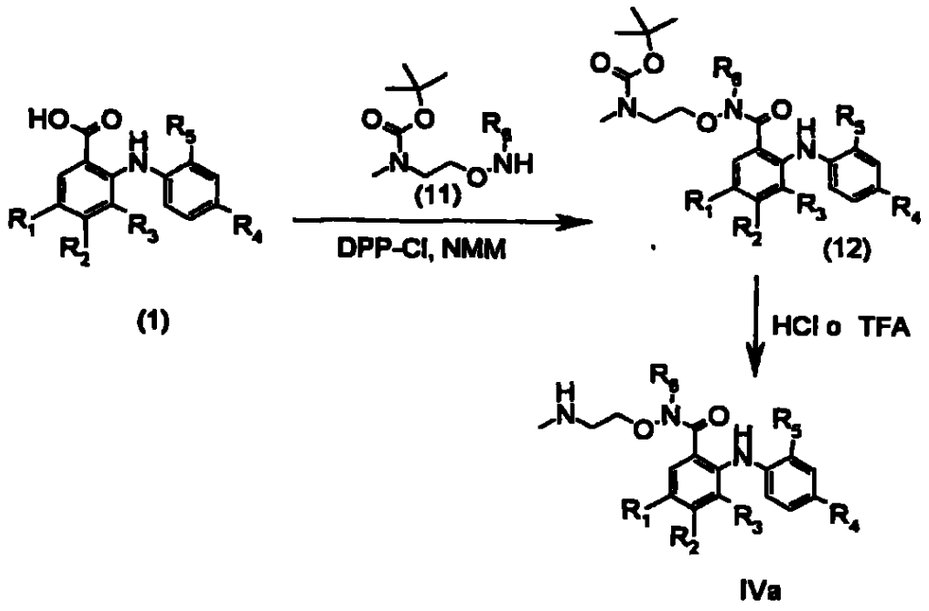
Esquema 5: Preparación Representativa de Benzamidas Hidroxiladas Usando un Silil Éter como un Grupo Protector Hidroxilo



Los compuestos de la fórmula IVa pueden prepararse mediante métodos particulares, como se ilustra en el Esquema 6. Por ejemplo, el tratamiento de ácidos benzoicos (1) con carbamato (11) en la presencia de un agente de acoplamiento de péptido, por ejemplo cloruro difenilfosfínico (DPP-Cl), en la presencia de una base de amina terciaria, por ejemplo 4-metilmorfilina (NMM) da amida de carbamato (12). El tratamiento posterior de (12) con un ácido adecuado, por ejemplo ácido trifluoroacético o cloruro de hidrógeno, da origen a las aminas de la fórmula

general IVa, que pueden aislarse como sales ácidas o nutralizarse en condiciones estándar para dar bases libres.

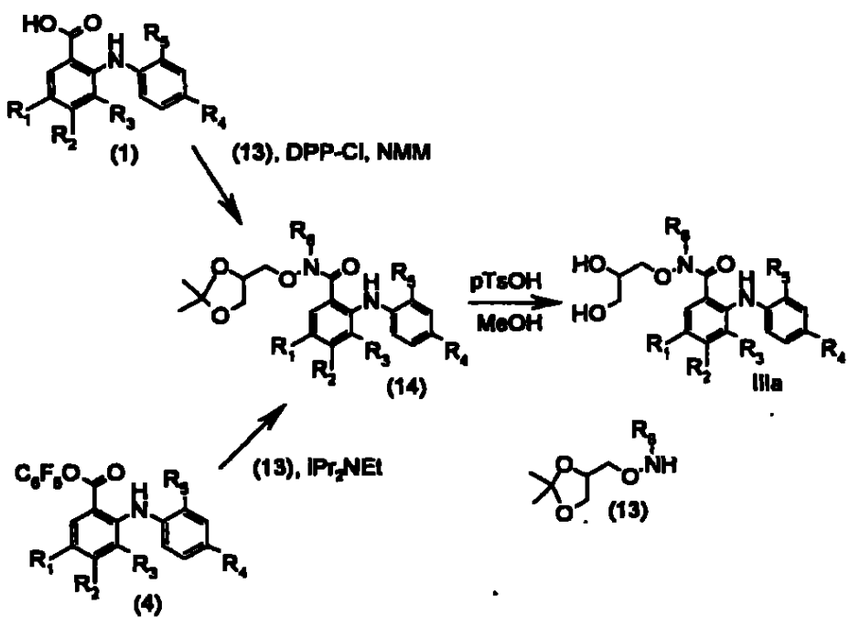
Esquema 6: Preparación Representativa de Benzamidas Benzo-Sustituidas Usando un terc-Butil Carbamato como un Grupo Protector Amino



Otros ejemplos del uso de estrategias de grupos protectores se representan en la síntesis de compuestos preferidos de la fórmula IIIa mostrada en el Esquema 7. Se obtienen rápidamente acetonuro-amidas (14) mediante la unión del acetonuro (13) con ácido benzoico (1) en la presencia de un agente de acoplamiento de péptido (por ejemplo, DPP-Cl) y una base

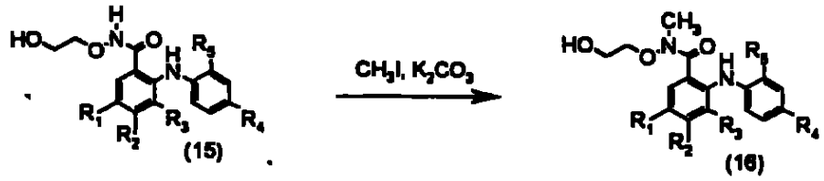
terciaria, por ejemplo, 4-metilmorfolina (NMM). Alternativamente, éstas se pueden preparar de acuerdo con el Esquema 2 mediante el tratamiento de pentafluorofenil ésteres del ácido benzoico (4) con acetonuro (13) en la presencia de una base de amina terciaria (por ejemplo, diisopropiletilamina). La conversión de acetonuro-amidas (14) en compuestos preferidos IIIa se pueden lograr mediante el tratamiento en condiciones de hidrólisis ácida estándar, por ejemplo ácido p-toluensulfónico en metanol.

Esquema 7: Preparación Representativa de Benzamidas Dihidroxiladas Usando un Acetonuro como un Grupo Protector Diol



Los compuestos de la fórmula I también pueden prepararse mediante la modificación de otros compuestos de la fórmula I. Por ejemplo, los compuestos de la fórmula I, donde R_6=H (15) se pueden convertir en compuestos de la fórmula I, donde R_6= alquilo (16) mediante el tratamiento con agentes de alquilación (por ejemplo, yodometano) en la presencia de una base (por ejemplo, carbonato de potasio). Alternativamente, los compuestos de la fórmula I, donde R_{11} = H (17) puede convertirse en compuestos de la fórmula I, donde R_{11} = alquilcarbonilo (18) mediante el tratamiento con un cloruro ácido (por ejemplo, cloruro de acetilo) y una base, tal como trietilamina. Además, un compuesto de la fórmula I, donde R_4= H (19) puede prepararse desde un compuesto de la fórmula I, donde R_4 = Yodo (20). La representación de estos ejemplos se hallan en los Esquemas 8-10.

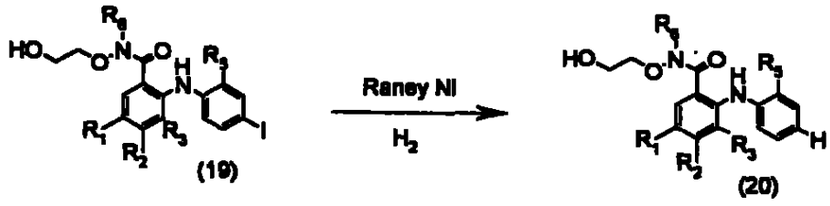
Esquema 8: Preparación Representativa de Benzamidas Terciarias mediante N-Alquilación



Esquema 9: Preparación Representativa de Acetatos mediante Acetilación



Esquema 10: Hidrogenólisis Representativa de Yoduros de Arilo



Los compuestos específicos provistos por la invención incluyen:

Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-butoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-1-metil-etoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-metoxi-etoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-hidroxi-butoxi)-benzamida

2-(2-Cloro-4-yodo-fenilarnino)-3,4,5-trifluoro-N-(2-hidroxi-1-metil-etoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-metoxi-etoxi)-benzamida

2-(2-Cloro-4-yodo-fenylamino)-3,4,5-trifluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-hidroxi-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(3-hidroxi-2,2-dimetil-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-hidroxi-2-metil-propoxi)-benzamida

3,4,5-Trifluoro-N-(2-hidroxi-3-fenoxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4,5-Trifluoro-N-(2-hidroxi-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4,5-Trifluoro-N-(2-hidroxi-1-metil-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4,5-Trifluoro-2-(4-yodo-2-metil-fenilamino)-N-(2-metoxi-etoxi)-benzamida

3,4,5-Trifluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4,5-Trifluoro-N-(2-hidroxi-propoxi)-2-(4-yodo-2-metil-fenilamíno)-benzamida

3,4,5-Trifluoro-N-(3-hidroxi-2,2-dimetil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4,5-Trifluoro-N-(2-hidroxi-2-metil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-butoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-1-metil-etoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-metoxi-etoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-propoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-2-metil-propoxi)-benzamida

5-Bromo-3,4-difluoro-N-(2-hidroxi-3-fenoxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-3,4-difluoro-N-(2-hidroxi-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-3,4-difluoro-N-(2-hidroxi-1-metil-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-N-(2-metoxi-etoxi)-benzamida

5-Bromo-3,4-difluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-3,4-difluoro-N-(2-hidroxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-3,4-difluoro-N-(2-hidroxi-2-metil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4-Difluoro-N-(2-hidroxi-3-fenoxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4-Difluoro-N-(2-hidroxi-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4-Difluoro-N-(2-hidroxi-1-metil-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

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3,4-Difluoro-2-(4-yodo-2-metil-fenilamino)-N-(2-metoxi-etoxi)-benzamida

3,4-Difluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4-Difluoro-N-(2-hidroxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4-Difluoro-N-(3-hidroxi-2,2-dimetil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4-Difluoro-N-(2-hidroxi-2-metil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-diflúoro-N-(2-hidroxi-butoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-1-metil-etoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-metoxi-etoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-propoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-2,2-dimetil-propoxi)-henzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-2-metil-propoxi)-benzamida

5-Cloro-3,4-difluoro-N-(2-hidroxi-3-fenoxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-3,4-difluoro-N-(2-hidroxi-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-3,4-difluoro-N-(2-hidroxi-1-metil-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-N-(2-metoxi-etoxi)-benzamida

5-Cloro-3,4-difluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-3,4-difluoro-N-(2-hidroxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-3,4-difluoro-N-(3-hidroxi-2,2-dimetil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-3,4-dilfluoro-N-(2-hidroxi-2-metil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-propoxi)-benzamida

3,4,5-Trifluoro-N-(3-hidroxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzarnida

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2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(3-hidroxi-propoxi)-benzamida

5-Bromo-3,4-difluoro-N-(3-hidroxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4-Difluoro-N-(3-hidroxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4-Difluoro-2-(4-yodo-2-metil-fenilamino)-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida

3,4,5-Trifluoro-2-(4-yodo-2-metil-fenilamino)-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida

5-Bromo-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida

Además, las reivindicaciones proveen los siguientes compuestos:

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-etoxi)-benzamida,

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-etoxi)-benzamida

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2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-hidroxi-etoxi)-benzamida,

5-Bromo-3,4-difluoro-N-(2-hidroxi-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida,

5-Cloro-3,4-difluoro-N-(2-hidroxi-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida,

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-propoxi)-benzamida,

5-Cloro-3,4-difluoro-N-(2-hidroxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida,

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-2,2-dimetil-propoxi)-benzamida,

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-2,2-dimetil-propoxi)-benzamida,

5-Bromo-3,4-difluoro-N-(3-hidroxi-2,2-dimetil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida,

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-2-metil-propoxi)-benzamida,

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-N-(2,3-dihidroxi-propoxi)-3,4-difluoro-benzamida,

5-Cloro-N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-benzamida,

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-N-(3,4-dihidroxi-butoxi)-3,4-difluoro-benzamida,

5-Cloro-N-(3,4-dihidroxi-butoxi)-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-benzamida,

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida,

5-Cloro-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida.

Compuestos adicionales descriptos por la invención incluyen:

4-Fluoro-N-(2-hidroxi-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4-Fluoro-N-(3-hidroxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida,

4-Fluoro-2-(4-yodo-2-metil-fenilamino)-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida,

4-Fluoro-N-(2-hidroxi-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4-Fluoro-N-(2-hidroxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4-Fluoro-N-(2-hidroxi-2-metil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida,

4-Fluoro-N-(2-hidroxi-1-metil-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4-Fluoro-2-(4-yodo-2-metil-fenilamino)-N-(2-metoxi-etoxi)-benzamida

N-(3,4-Dihidroxi-butoxi)-4-fluoro-2-(4-yodo-2-metil-fenilamino)-benzamida

N-(2,3-Dihidroxi-propoxi)-4-fluoro-2-(4-yodo-2-metil-fenilamino)-benzamida

4-Fluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4-Fluoro-N-(2-hidroxi-3-fenoxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4-Fluoro-N-(3-hidroxi-2,2-dimetil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-etoxi)-benzamida

(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(3-hidroxi-propoxi)-benzamida

(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-butoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-2-metil-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-1-metil-etoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(2-metoxi-etoxi)-benzamida

2-(2-Cloro-4-yodo-fenolamino-N-(3,4-dihidroxi-butoxi)-4-fluoro-benzamida

2-(2-Chioro-4-yodo-fenilamino)-N-(2,3-díhidroxi-propoxi)-4-fluoro-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(3-hidroxi-2,2-dimetil-propoxi)-benzamída

4-Fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-etoxi)-benzamida

4-Fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-propoxi)-benzamida

4-Fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida

4-Fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-butoxi)-benzamida

4-Fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-propoxi)-benzamida

4-Fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-2-metil-propoxi)-benzamida

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4-Fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1-metil-etoxi)-benzamida

4-Fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-metoxi-etoxi)-benzamida

N-(3,4-Dihidroxi-butoxi)-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

N-(2,3-Dihidroxi-propoxi)-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

4-Fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-morfolin-4-il-propoxi)-benzamida

4-Fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida

4-Fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-2,2-dimetil-propoxi)-benzamida

4,5-Difluoro-N-(2-hidroxi-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4,5-Difluoro-N-(3-hidroxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4,5-Difluoro-2-(4-yodo-2-metil-fenilamino)-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida

4,5-Difluoro-N-(2-hidroxi-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4,5-Difluoro-N-(2-hidroxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4,5-Difluoro-N-(2-hidroxi-2-metil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4,5-Difluoro-N-(2-hidroxi-1-metil-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4,5-Difluoro-2-(4-yodo-2-metil-fenilamino)-N-(2-metoxi-etoxi)-benzamida

N-(3,4-Dihidroxi-butoxi)-4,5-difluoro-2-(4-yodo-2-metil-fenilamino)-benzamida

N-(2,3-Dihidroxi-propoxi)-4,5-difluoro-2-(4-yodo-2-metil-fenilamino)-benzamida

4,5-Difluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4,5-Difluoro-N-(2-hidroxi-3-fenoxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4,5-Difluoro-N-(3-hidroxi-2,2-dimetil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4,5-difluoro-N-(2-hidroxi-etoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4,5-difluoro-N-(3-hidroxi-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino-4,5-difluoro-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4,5-difluoro-N-(2-hidroxi-butoxi)-benzamida

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2-(2-Cloro-4-yodo-fenilamino)-4,5-difluoro-N-(2-hidroxi-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4,5-difluoro-N-(2-hidroxi-2-metil-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4,5-difluoro-N-(2-hidroxi-1-metil-etoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4,5-difluoro-N-(2-metoxi-etoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-N-(3,4-dihidroxi-butoxi)-4,5-difluoro-benzamida

2-(2-Cloro-4-yodo-fenilamino)-N-(2,3-dihidroxi-propoxi)-4,5-difluoro-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4,5-difluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4,5-difluoro-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4,5-difluoro-N-(3-hidroxi-2,2-dimetil-propoxi)-benzamida

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-etoxi)-benzamida

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-propoxi-benzamida

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida

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4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-butoxi)-benzamida

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-propoxi)-benzamida

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-2-metil-propoxi)-benzamida

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1-metil-etoxi)-benzamida

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-metoxi-etoxi)-benzamida

N-(3,4-Dihidroxi-butoxi)-4,5-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

N-(2,3-Dihidroxi-propoxi)-4,5-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-morfolin-4-il-propoxi)-benzamida

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-2,2-dimetil-propoxi)-benzamida

5-Cloro-4-fluoro-N-(2-hidroxi-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-4-fluoro-N-(3-hidroxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

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0719

5-Cloro-4-fluoro-2-(4-yodo-2-metil-fenilamino)-N-[2-(2-metoxi-etoxi)-ethoxi]-benzamida

5-Cloro-4-fluoro-N-(2-hidroxi-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-4-fluoro-N-(2-hidroxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-4-fluoro-N-(2-hidroxi-2-metil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-4-fluoro-N-(2-hidroxi-1-metil-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-4-fluoro-2-(4-yodo-2-metil-fenilamino)-N-(2-metoxi-etoxi)-benzamida

5-Cloro-N-(3,4-dihidroxi-butoxi)-4-fluoro-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-N-(2,3-dihidroxi-propoxi)-4-fluoro-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-4-fluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-4-fluoro-N-(2-hidroxi-3-fenoxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-4-fluoro-N-(3-hidroxi-2,2-dimetil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-etoxi)-benzamida

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5-Cloro-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(3-hidroxi-propoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-butoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-propoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-2-metil-propoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-1-metil-etoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(2-metoxi-etoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-N-(3,4-dihidroxi-butoxi)-4-fluoro-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-N-(2,3-dihidroxi-propoxi)-4-fluoro-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(3-hidroxi-2,2-dimetil-propoxi)-benzamida

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0181

5-Cloro-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-etoxi)-benzamida

5-Cloro-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-propoxi)-benzamida

5-Cloro-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida

5-Cloro-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-butoxi)-benzamida

5-Cloro-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-propoxi)-benzamida

5-Cloro-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-2-metil-propoxi)-benzamida

5-Cloro-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1-metil-etoxi)-benzamida

5-Cloro-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-metoxi-etoxi)-benzamida

5-Cloro-N-(3,4-dihidroxi-butoxi)-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

5-Cloro-N-(2,3-dihidroxi-propoxi)-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

5-Cloro-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-morfolin-4-il-propoxi)-benzamida

5-Cloro-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida

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5-Cloro-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-2,2-dimetil-propoxi)-benzamida

5-Bromo-4-fluoro-N-(2-hidroxi-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-4-fluoro-N-(3-hidroxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-4-fluoro-2-(4-yodo-2-metil-fenilamino)-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida

5-Bromo-4-fluoro-N-(2-hidroxi-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-4-fluoro-N-(2-hidroxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-4-fluoro-N-(2-hidroxi-2-metil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-4-fluoro-N-(2-hidroxi-1-metil-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-4-fluoro-2-(4-yodo-2-metil-fenilamino)-N-(2-metoxi-etoxi)-benzamida

5-Bromo-N-(3,4-dihidroxi-butoxi)-4-fluoro-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-N-(2,3-dihidroxi-propoxi)-4-fluoro-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-4-fluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

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0183

5-Bromo-4-fluoro-N-(2-hidroxi-3-fenoxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-4-fluoro-N-(3-hidroxi-2,2-dimetil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-etoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(3-hidroxi-propoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-butoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-propoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-2-metil-propoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-1-metil-etoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(2-metoxi-etoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-N-(3,4-dihidroxi-butoxi)-4-fluoro-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-N-(2,3-dihidroxi-propoxi)-4-fluoro-benzamida

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5-Bromo-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(3-hidroxi-2,2-dimetil-propoxi)-benzamida

5-Bromo-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-etoxi)-benzamida

5-Bromo-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-propoxi)-benzamida

5-Bromo-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida

5-Bromo-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-butoxi)-benzamida

5-Bromo-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-propoxi)-benzamida

5-Bromo-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-2-metil-propoxi)-benzamida

5-Bromo-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1-metil-etoxi)-benzamida

5-Bromo-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-metoxi-etoxi)-benzamida

5-Bromo-N-(3,4-dihidroxi-butoxi)-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

5-Bromo-N-(2,3-dihidroxi-propoxi)-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

5-Bromo-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-morfolin-4-il-propoxi)-benzamida

5-Bromo-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida

5-Bromo-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-2,2-dimetil-propoxi)-benzamida

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-etoxi)-benzamida

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-propoxi)-benzamida

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-butoxi)-benzamida

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-propoxi)-benzamida

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-2-metil-propoxi)-benzamida

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1-metil-etoxi)-benzamida

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-metoxi-etoxi)-benzamida

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N-(3,4-Dihidroxi-butoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

N-(2,3-Dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-morfolin-4-il-propoxi)-benzamida

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-2,2-dimetil-propoxi)-benzamida

3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-etoxi)-benzamida

3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-propoxi)-benzamida

3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida

3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-butoxi)-benzamida

3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-propoxi)-benzamida

3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-2-metil-propoxi)-benzamida

3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1-metil-etoxi)-benzamida

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3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-metoxi-etoxi)-benzamida

N-(3,4-Dihidroxi-butoxi)-3,4,5-trifluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

N-(2,3-Dihidroxi-propoxi)-3,4,5-trifluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-morfolin-4-il-propoxi)-benzamida

3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida

3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-2,2-dimetil-propoxi)-benzamida

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-etoxi)-benzamida

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-propoxi)-benzamida

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-butoxi)-benzamida

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-propoxi)-benzamida

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-2-metil-propoxi)-benzamida

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5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1-metil-etoxi)-benzamida

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-metoxi-etoxi)-benzamida

5-Cloro-N-(3,4-dihidroxi-butoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

5-Cloro-N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-morfolin-4-il-propoxi)-benzamida

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-2,2-dimetil-propoxi-benzamida

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-etoxi)-benzamida

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-propoxi)-benzamida

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-butoxi)-benzamida

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-propoxi)-benzamida

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5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-2-metil-propoxi)-benzamida

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1-metil-etoxi)-benzarnida

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-metoxi-etoxi)-benzamida

5-Bromo-N-(3,4-dihidroxi-butoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

5-Bromo-N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-morfolin-4-il-propoxi)-benzamida

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-2,2-dimetil-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-metoxi-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-pentiloxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-metil-butoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-4-metil-pentiloxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(1-hidroxi-ciclopropilmetoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(1-hidroxi-ciclobutilmetoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(1-hidroximetil-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-1,1-dimetil-etoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(1-hidroximetil-ciclopropoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-N-(2-etoxi-etoxi)-3,4-difluoro-benzamida.

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-2-metoxi-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-pentiloxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-butoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-3-metil-butoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-[2-(1-hidroxi-ciclopropil)-etoxi]-benzamida

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2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(1-hidroximetil-ciclopropilmetoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroximetil-ciclopropilmetoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-1,1-dimetil-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-1-metil-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-N-(2,3-dihidroxi-1,1-dimetil-propoxi)-3,4-difluoro-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-hidroxi-3-metoxi-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-hidroxi-pentiloxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-hidroxi-3-metil-butoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-hidroxi-4-metil-pentiloxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(1-hidroxi-ciclopropilmetoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(1-hidroxi-ciclobutilmetoxi)-benzamida

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2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(1-hidroxymetil-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-hidroxi-1,1-dimetil-etoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(1-hidroximetil-ciclopropoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-N-(2-etoxi-etoxi)-3,4,5-trifluoro-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(3-hidroxi-2-metoxi-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(3-hidroxi-pentiloxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(3-hidroxi-butoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(3-hidroxi-3-metil-butoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-[2-(1-hidroxi-ciclopropil)-etoxi]-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(1-hidroximetil-ciclopropilmetoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-hidroximetil-ciclopropilmetoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(3-hidroxi-1,1-dimetil-propoxi)-benzamida

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2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(3-hidroxi-1-metil-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-N-(2,3-dihidroxi-1,1-dimetil-propoxi)-3,4,5-trifluoro-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-metoxi-propoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-pentiloxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-metil-butoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-4-metil-pentiloxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(1-hidroxi-ciclopropilmetoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(1-hidroxi-ciclobutilmetoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(1-hidroximetil-propoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-1,1-dimetil-etoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(1-hidroximetil-ciclopropoxi)-benzamida

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5-Cloro-2-(2-cloro-4-yodo-fenilamino)-N-(2-etoxi-etoxi)-3,4-difluoro-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-2-metoxi-propoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-pentiloxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-butoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-3-metil-butoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-[2-(1-hidroxi-ciclopropil)-etoxi]-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(1-hidroximetil-ciclopropilmetoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroximetil-ciclopropilmetoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-1,1-dimetil-propoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-1-metil-propoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-N-(2,3-dihidroxi-1,1-dimetil-propoxi)-3,4-difluoro-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-metoxi-propoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-pentiloxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-metil-butoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-4-metil-pentiloxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(1-hidroxi-ciclopropilmetoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(1-hidroxi-ciclobutilmetoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(1-hidroximetil-propoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-1,1-dimetil-etoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(1-hidroximetil-ciclopropoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-N-(2-etoxi-etoxi)-3,4-difluoro-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-2-metoxi-propoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-pentiloxi)-benzamida

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5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-butoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-3-metil-butoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-[2-(1-hidroxi-ciclopropil)-etoxi]-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(1-hidroximetil-ciclopropilmetoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroximetil-ciclopropilmetoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-1,1-dimetil-propoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-1-metil-propoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-N-(2,3-dihidroxi-1,1-dimetil-propoxi)-3,4-difluoro-benzamida

3,4-Difluoro-N-(2-hidroxi-3-metoxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4-Difluoro-N-(2-hidroxi-pentiloxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4-Difluoro-2-(4-yodo-2-metil-fenilamino)-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida

3,4-Difluoro-N-(2-hidroxi-3-metil-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

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3,4-Difluoro-N-(2-hidroxi-4-metil-pentiloxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4-Difluoro-N-(1-hidroxi-ciclopropilmetoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4-Difluoro-N-(1-hidroxi-ciclobutilmetoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4-Difluoro-N-(1-hidroximetil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4-Difluoro-N-(2-hidroxi-1,1-dimetil-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4-Difluoro-N-(1-hidroximetil-ciclopropoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

N-(2-Etoxi-etoxi)-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4-Difluoro-N-(3-hidroxi-2-metoxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4-Difluoro-N-(3-hidroxi-pentiloxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4-Difluoro-N-(3-hidroxi-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4-Difluoro-N-(3-hidroxi-3-metil-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4-Difluoro-N-[2-(1-hidroxi-ciclopropil)-etoxi]-2-(4-yodo-2-metil-fenilamino)-benzamida

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3,4-Difluoro-N-(1-hidroximetil-ciclopropilmetoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4-Difluoro-N-(2-hidroximetil-ciclopropilmetoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4-Difluoro-N-(3-hidroxi-1,1-dimetil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4-Difluoro-N-(3-hidroxi-1-metil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

N-(2,3-Dihidroxi-1,1-dimetil-propoxi)-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4,5-Trifluoro-N-(2-hidroxi-3-metoxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4,5-Trifluoro-N-(2-hidroxi-pentiloxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4,5-Trifluoro-2-(4-yodo-2-metil-fenilamino)-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida

3,4,5-Trifluoro-N-(2-hidroxi-3-metil-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4,5-Trifluoro-N-(2-hidroxi-4-metil-pentiloxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4,5-Trifluoro-N-(1-hidroxi-ciclopropilmetoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4,5-Trifluoro-N-(1-hidroxi-ciclobutilmetoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4,5-Trifluoro-N-(1-hidroximetil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4,5-Trifluoro-N-(2-hidroxi-1,1-dimetil-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4,5-Trifluoro-N-(1-hidroximetil-ciclopropoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

N-(2-Etoxi-etoxi)-3,4,5-trifluoro-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4,5-Trifluoro-N-(3-hidroxi-2-metoxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4,5-Trifluoro-N-(3-hidroxi-pentiloxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4,5-Trifluoro-N-(3-hidroxi-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4,5-Trifluoro-N-(3-hidroxi-3-metil-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4,5-Trifluoro-N-[2-(1-hidroxi-ciclopropil)-etoxi]-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4,5-Trifluoro-N-(1-hidroximetil-ciclopropilmetoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4,5-Trifluoro-N-(2-hidroximetil-ciclopropilmetoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

3,4,5-Trifluoro-N-(3-hidroxi-1,1-dimetil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

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3,4,5-Trifluoro-N-(3-hidroxi-1-metil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

N-(2,3-Dihidroxi-1,1-dimetil-propoxi)-3,4,5-trifluoro-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-3,4-difluoro-N-(2-hidroxi-3-metoxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-3,4-difluoro-N-(2-hidroxi-pentiloxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida

5-Cloro-3,4-difluoro-N-(2-hidroxi-3-metil-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-3,4-difluoro-N-(2-hidroxi-4-metil-pentiloxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-3,4-difluoro-N-(1-hidroxi-ciclopropilmetoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-3,4-difluoro-N-(1-hidroxi-ciclobutilmetoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-3,4-difluoro-N-(1-hidroximetil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-3,4-difluoro-N-(2-hidroxi-1,1-dimetil-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-3,4-difluoro-N-(1-hidroximetil-ciclopropoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

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5-Cloro-N-(2-etoxi-etoxi)-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-3,4-difluoro-N-(3-hidroxi-2-metoxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-3,4-difluoro-N-(3-hidroxi-pentiloxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-3,4-difluoro-N-(3-hidroxi-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-3,4-difluoro-N-(3-hidroxi-3-metil-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-3,4-difluoro-N-[2-(1-hidroxi-ciclopropil)-etoxi]-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-3,4-difluoro-N-(1-hidroximetil-ciclopropilmetoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-3,4-difluoro-N-(2-hidroximetil-ciclopropilmetoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-3,4-difluoro-N-(3-hidroxi-1,1-dimetil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-3,4-difluoro-N-(3-hidroxi-1-metil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-N-(2,3-dihidroxi-1,1-dimetil-propoxi)-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-3,4-difluoro-N-(2-hidroxi-3-metoxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

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5-Bromo-3,4-difluoro-N-(2-hidroxi-pentiloxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida

5-Bromo-3,4-difluoro-N-(2-hidroxi-3-metil-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-3,4-difluoro-N-(2-hidroxi-4-metil-pentiloxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-3,4-difluoro-N-(1-hidroxi-ciclopropilmetoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-3,4-difluoro-N-(1-hidroxi-ciclobutilmetoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-3,4-difluoro-N-(1-hidroximetil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-3,4-difluoro-N-(2-hidroxi-1,1-dimetil-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-3,4-difluoro-N-(1-hidroximetil-ciclopropoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-N-(2-etoxi-etoxi)-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-3,4-difluoro-N-(3-hidroxi-2-metoxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-3,4-difluoro-N-(3-hidroxi-pentiloxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

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5-Bromo-3,4-difluoro-N-(3-hidroxi-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-3,4-difluoro-N-(3-hidroxi-3-metil-hutoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-3,4-difluoro-N-[2-(1-hidroxi-ciclopropil)-etoxi]-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-3,4-difluoro-N-(1-hidroximetil-ciclopropilmetoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-3,4-difluoro-N-(2-hidroximetil-ciclopropilmetoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-3,4-difluoro-N-(3-hidroxi-1,1-dimetil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-3,4-difluoro-N-(3-hidroxi-1-metil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida-

5-Bromo-N-(2,3-dihidroxi-1,1-dimetil-propoxi)-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-benzamida

4-Fluoro-N-(2-hidroxi-3-metoxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4-Fluoro-N-(2-hidroxi-pentiloxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4-Fluoro-2-(4-yodo-2-metil-fenilamino)-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida

4-Fluoro-N-(2-hidroxi-3-metil-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4-Fluoro-N-(2-hidroxi-4-metil-pentiloxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4-Fluoro-N-(1-hidroxi-ciclopropilmetoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4-Fluoro-N-(1-hidroxi-ciclobutilmetoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4-Fluoro-N-(1-hidroximetil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4-Fluoro-N-(2-hidroxi-1,1-dimetil-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4-Fluoro-N-(1-hidroximetil-ciclopropoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

N-(2-Etoxi-etoxi)-4-fluoro-2-(4-yodo-2-metil-fenilamino)-benzamida

4-Fluoro-N-(3-hidroxi-2-metoxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4-Fluoro-N-(3-hidroxi-pentiloxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4-Fluoro-N-(3-hidroxi-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4-Fluoro-N-(3-hidroxi-3-metil-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4-Fluoro-N-[2-(1-hidroxi-ciclopropil)-etoxi]-2-(4-yodo-2-metil-fenilamino)-benzamida

4-Fluoro-N-(1-hidroximetil-ciclopropilmetoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4-Fluoro-N-(2-hidroximetil-ciclopropilmetoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4-Fluoro-N-(3-hidroxi-1,1-dimetil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4-Fluoro-N-(3-hidroxi-1-metil-propoxi)-2-(4-yodo-2-metil-fenilamíno)-benzamida

N-(2,3-Dihidroxi-1,1-dimetil-propoxi)-4-fluoro-2-(4-yodo-2-metil-fenilamino)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-3-metoxi-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-pentiloxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidrox-3-metil-butoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-4-metil-pentiloxi)- benzamida

2-(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(1-hidroxi-ciclopropilmetoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(1-hidroxi-ciclobutilmetoxi)-benzamida

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2-(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(1-hidroximetil-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-1,1-dimetil-etoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(1-hidroximetil-ciclopropoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-N-(2-etoxi-etoxi)-4-fluoro-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(3-hidroxi-2-metoxi-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(3-hidroxi-pentiloxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(3-hidroxi-butoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(3-hidroxi-3-metil-butoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-[2-(1-hidroxi-ciclopropil)-etoxi]-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(1-hidroximetil-ciclopropilmetoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroximetil-ciclopropilmetoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(3-hidroxi-1,1-dimetil-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(3-hidroxi-1-metil-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-N-(2,3-dihidroxi-1,1-dimetil-propoxi)-4-fluoro-benzamida

4-Fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-metoxi-propoxi)-benzamida

4-Fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-pentiloxi)-benzamida

4-Fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida

4-Fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-metil-butoxi)-benzamida

4-Fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-4-metil-pentiloxi)-benzamida

4-Fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroxi-ciclopropilmetoxi)-benzamida

4-Fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroxi-ciclobutilmetoxi)-benzamida

4-Fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroximetil-propoxi)-benzamida

4-Fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1,1-dimetil-etoxi)-benzamida

4-Fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroximetil-ciclopropoxi)-benzamida

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N-(2-Etoxi-etoxi)-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

4-Fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-2-metoxi-propoxi-benzamida

4-Fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-pentiloxi)-benzamida

4-Fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-butoxi)-benzamida

4-Fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-3-metil-butoxi)-benzamida

4-Fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-[2-(1-hidroxi-ciclopropil)-etoxi]-benzamida

4-Fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroximetil-ciclopropilmetoxi)-benzamida

4-Fluoro-2-(2-fluoro-4-iodo-fenilamino)-N-(2-hidroximetil-ciclopropilmetoxi)-benzamida

4-Fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-1,1-dimetil-propoxi)-benzamida

4-Fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-1-metil-propoxi)-benzamida

N-(2,3-Dihidroxi-1,1-dimetil-propoxi)-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

4,5-Difluoro-N-(2-hidroxi-3-metoxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4,5-Difluoro-N-(2-hidroxi-pentiloxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4,5-Difluoro-2-(4-yodo-2-metil-fenilamino)-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida

4,5-Difluoro-N-(2-hidroxi-3-metil-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4,5-Difluoro-N-(2-hidroxi-4-metil-pentiloxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4,5-Difluoro-N-(1-hidroxi-ciclopropilmetoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4,5-Difluoro-N-(1-hidroxi-ciclobutilmetoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4,5-Difluoro-N-(1-hidroximetil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4,5-Difluoro-N-(2-hidroxi-1,1-dimetil-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4,5-Difluoro-N-1I-hidroximetil-ciclopropoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

N-(2-Etoxi-etoxi)-4,5-difluoro-2-(4-yodo-2-metil-fenilamino)-benzamida

4,5-Difluoro-N-(3-hidroxi-2-metoxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4,5-Difluoro-N-(3-hidroxi-pentiloxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

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4,5-Difluero-N-(3-hidroxi-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4,5-Difluoro-N-(3-hidroxi-3-metil-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4,5-Difluoro-N-[2-(1-hidroxi-ciclopropil)-etoxi]-2-(4-yodo-2-metil-fenilamino)-benzamida

4,5-Difluoro-N-(1-hidroximetil-ciclopropilmetoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4,5-Difluoro-N-(2-hidroximetil-ciclopropilmetoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4,5-Difluoro-N-(3-hidroxi-1,1-dimetil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

4,5-Difluoro-N-(3-hidroxi-1-metil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

N-(2,3-Dihidroxi-1,1-dimetil-propoxi)-4,5-difluoro-2-(4-yodo-2-metil-fenilamino)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4,5-difluoro-N-(2-hidroxi-3-metoxi-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4,5-difluoro-N-(2-hidroxi-pentiloxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4,5-difluoro-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4,5-difluoro-N-(2-hidroxi-3-metil-butoxi)-benzamida

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2-(2-Cloro-4-yodo-fenilamino)-4,5-difluoro-N-(2-hidroxi-4-metil-pentiloxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4,5-difluoro-N-(1-hidroxi-ciclopropilmetoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4,5-difluoro-N-(1-hidroxi-ciclobutilmetoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4,5-difluoro-N-(1-hidroximetil-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4,5-difluoro-N-(2-hidroxi-1,1-dimetil-etoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4,5-difluoro-N-(1-hidroximetil-ciclopropoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-N-(2-etoxi-etoxi)-4,5-difluoro-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4,5-difluoro-N-(3-hidroxi-2-metoxi-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4,5-difluoro-N-(3-hidroxi-pentiloxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4,5-difluoro-N-(3-hidroxi-butoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4,5-difluoro-N-(3-hidroxi-3-metil-butoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4,5-difluoro-N-[2-(1-hidroxi-ciclopropil)-etoxi]-benzamida

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2-(2-Cloro-4-yodo-fenilamino)-4,5-difluoro-N-(1-hidroximetil-ciclopropilmetoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4,5-difluoro-N-(2-hidroximetil-ciclopropilmetoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4,5-difluoro-N-(3-hidroxi-1,1-dimetil-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamino)-4,5-difluoro-N-(3-hidroxi-1-metil-propoxi)-benzamida

2-(2-Cloro-4-yodo-fenilamíno)-N-(2,3-dihidroxi-1,1-dimetil-propoxi)-4,5-difluoro-benzamida

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-metoxi-propoxi)-benzamida

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-pentiloxi)-benzamida

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-metil-butoxi)-benzaniida

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-4-metil-pentiloxi)-benzamida

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamíno)-N-(1-hidroxi-ciclopropilmetoxi)-benzamida

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilaniino)-N-(1-hidroxi-ciclobutilmetoxi)-benzamida

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroximetil-propoxi)-benzamida

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1,1-dimetil-etoxi)-benzamida

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroximetil-ciclopropoxi)-benzamida

N-(2-Etoxi-etoxi)-4,5-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-2-metoxi-propoxi)-benzamida

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-pentiloxi)-benzamida

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-butoxi)-benzamida

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-3-metil-butoxi)-benzamida

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-[2-(1-hidroxi-ciclopropil)-etoxi]-benzamida

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroximetil-ciclopropilmetoxi)-benzamida

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroximetil-ciclopropilmetoxi)-benzamida

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-1,1-dimetil-propoxi)-benzamida

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-1-metil-propoxi)-benzamida

N-(2,3-Dihidroxi-1,1-dimetil-propoxi)-4,5-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

5-Cloro-4-fluoro-N-(2-hidroxi-3-metoxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-4-fluoro-N-(2-hidroxi-pentiloxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-4-fluoro-2-(4-yodo-2-metil-fenilamino)-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida

5-Cloro-4-fluoro-N-(2-hidroxi-3-metil-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-4-fluoro-N-(2-hidroxi-4-metil-pentiloxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-4-fluoro-N-(1-hidroxi-ciclopropilmetoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-4-fluoro-N-(1-hidroxi-ciclobutilmetoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-4-fluoro-N-(1-hidroximetil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-4-fluoro-N-(2-hidroxi-1,1-dimetil-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-4-fluoro-N-(1-hidroximetil-ciclopropoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-N-(2-etoxi-etoxi)-4-fluoro-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-4-fluoro-N-(3-hidroxi-2-metoxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-4-fluoro-N-(3-hidroxi-pentiloxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-4-fluoro-N-(3-hidroxi-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-4-fluoro-N-(3-hidroxi-3-metil-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-4-fluoro-N-[2-(1-hidroxi-ciclopropil)-etoxi]-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-4-fluoro-N-(1-hidroximetil-ciclopropilmetoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-4-fluoro-N-(2-hidroximetil-ciclopropilmetoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Chioro-4-fluoro-N-(3-hidroxi-1,1-dimetil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-4-fluoro-N-(3-hidroxi-1-metil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-N-(2,3-dihidroxi-1,1-dimetil-propoxi)-4-fluoro-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-3-metoxi-propoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-pentiloxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-3-metil-butoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-4-metil-pentiloxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(1-hidroxi-ciclopropilmetoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(1-hidroxi-ciclobutilmetoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(1-hidroximetil-propoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-1,1-dimetil-etoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(1-hidroximetil-ciclopropoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-N-(2-etoxi-etoxi)-4-fluoro-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(3-hidroxi-2-metoxi-propoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(3-hidroxi-pentiloxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(3-hidroxi-butoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(3-hidroxi-3-metil-butoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-[2-(1-hidroxi-ciclopropil)-etoxi]-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(1-h hidroximetil-ciclopropilmetoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroximetil-ciclopropilmetoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(3-hidroxi-1,1-dimetil-propoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(3-hidroxi-1-metil-propoxi)-benzamida

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-N-(2,3-dihidroxi-1,1-dimetil-propoxi)-4-fluoro-benzamida

5-Cloro-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-metoxi-propoxi)-benzamida

5-Cloro-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-pentiloxi)-benzamida

5-Cloro-4-fluoro-2-(2-fluoro-4-yodo-fenlamino)-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida

5-Cloro-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-metil-butoxi)-benzamida

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5-Cloro-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-4-metil-pentiloxi)-benzamida

5-Cloro-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroxi-ciclopropilmetoxi)-benzamida

5-Cloro-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroxi-ciclobutilmetoxi)-benzamida

5-Cloro-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroximetil-propoxi)-benzamida

5-Cloro-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1,1-dimetil-etoxi)-benzamida

5-Cloro-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroximetil-ciclopropoxi)-benzamida

5-Cloro-N-(2-etoxi-etoxi)-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

5-Cloro-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-2-metoxi-propoxi)-benzamida

5-Cloro-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-pentiloxi)-benzamida

5-Cloro-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-butoxi)-benzamida

5-Cloro-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-3-metil-butoxi)-benzamida

5-Cloro-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-[2-(1-hidroxi-ciclopropil)-etoxi]-benzamida

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5-Cloro-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroximetil-ciclopropilmetoxi)-benzamida

5-Cloro-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroximetil-ciclopropilmetoxi)-benzamida

5-Cloro-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-1,1-dimetil-propoxi)-benzamida

5-Cloro-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-1-metil-propoxi)-benzamida

5-Cloro-N-(2,3-dihidroxi-1,1-dimetil-propoxi)-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

5-Bromo-4-fluoro-N-(2-hidroxi-3-metoxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-4-fluoro-N-(2-hidroxi-pentiloxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-4-fluoro-2-(4-yodo-2-metil-fenilamino)-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida

5-Bromo-4-fluoro-N-(2-hidroxi-3-metil-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-4-fluoro-N-(2-hidroxi-4-metil-pentiloxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

S-Bromo-4-fluoro-N-(1-hidroxi-ciclopropilmetoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-4-fluoro-N-(1-hidroxi-ciclobutilmetoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-4-fluoro-N-(1-hidroximetil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzaniida

5-Bromo-4-fluoro-N-(2-hidroxi-1,1-dimetil-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-4-fluoro-N-(1-hidroximetil-ciclopropoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-N-(2-etoxi-etoxi)-4-fluoro-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-4-fluoro-N-(3-hidroxi-2-metoxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-4-fluoro-N-(3-hidroxi-pentiloxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-4-fluoro-N-(3-hidroxi-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-4-fluoro-N-(3-hidroxi-3-metil-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-4-fluoro-N-[2-(1-hidroxi-ciclopropil)-etoxi]-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-4-fluoro-N-(1-hidroximetil-ciclopropilmetoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-4-fluoro-N-(2-hidroximetil-ciclopropilmetoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-4-fluoro-N-(3-hidroxi-1,1-dimetil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

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5-Bromo-4-fluoro-N-(3-hidroxi-1-metil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-N-(2,3-dihidroxi-1,1-dimetil-propoxi)-4-fluoro-2-(4-yodo-2-metil-fenilamino)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-3-metoxi-propoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-pentiloxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-3-metil-butoxi)-benzamida

5-Brorno-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-4-metil-pentiloxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(1-hidroxi-ciclopropilmetoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(1-hidroxi-ciclobutilmetoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(1-hidroximetil-propoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-1,1-dimetil-etoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(1-hidroximetil-ciclopropoxi)-benzamida

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5-Bromo-2-(2-cloro-4-yodo-fenilamino)-N-(2-etoxi-etoxi)-4-fluoro-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(3-hidroxi-pentiloxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(3-hidroxi-2-metoxi-propoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(3-hidroxi-butoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(3-hidroxi-3-metil-butoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-[2-(1-hidroxi-ciclopropil)-etoxi]-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(1-hidroximetil-ciclopropilmetoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroximetil-ciclopropilmetoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(3-hidroxi-1,1-dimetil-propoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(3-hidroxi-1-metil-propoxi)-benzamida

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-N-(2,3-dihidroxi-1,1-dimetil-propoxi)-4-fluoro-benzamida

5-Bromo-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-metoxi-propoxi)-henzamida

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5-Bromo-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-pentiloxi)-benzamida

5-Bromo-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida

5-Bromo-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-metil-butoxi)-benzamida

5-Bromo-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-4-metil-pentiloxi)-benzamida

5-Bromo-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroxi-ciclopropilmetoxi)-benzamida

5-Bromo-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroxi-ciclobutilmetoxi)-benzamida

5-Bromo-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroximetil-propoxi)-benzamida

5-Bromo-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1,1-dimetil-etoxi)-benzamida

5-Bromo-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroximetil-ciclopropoxi)-benzamida

5-Bromo-N-(2-etoxi-etoxi)-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

5-Bromo-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-2-metoxi-propoxi)-benzamida

5-Bromo-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-pentiloxi)-benzamida

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5-Bromo-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-butoxi)-benzamida

5-Bromo-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-3-metil-butoxi)-benzamida

5-Bromo-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-[2-(1-hidroxi-ciclopropil)-etoxi]-benzamida

5-Bromo-4-fluoro-2-(2-fluoro-4-yiodo-fenilamino)-N-(1-hidroximetil-ciclopropilmetoxi)-benzamida

5-Bromo-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroximetil-ciclopropilmetoxi)-benzamida

5-Bromo-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-1,1-dimetil-propoxi)-benzamida

5-Bromo-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-1-metil-propoxi)-benzamida

5-Bromo-N-(2,3-dihidroxi-1,1-dimetil-propoxi)-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-metoxi-propoxi)-benzamida

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-pentiloxi)-benzamida

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-metil-butoxi)-benzamida

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3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-4-metil-pentiloxi)-benzamida

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroxi-ciclopropilmetoxi)-benzamida

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroxi-ciclobutilmetoxi)-benzamida

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroximetil-propoxi)-benzamida

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1,1-dimetil-etoxi)-benzamida

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroximetil-ciclopropoxi)-benzamida

N-(2-Etoxi-etoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-2-metoxi-propoxi)-benzamida

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-pentiloxi)-benzamida

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-butoxi)-benzamida

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-3-metil-butoxi)-benzamida

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-[2-(1-hidroxi-ciclopropil)-etoxi]-benzamida

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroximetil-ciclopropilmetoxi)-benzamida

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroximetil-ciclopropilmetoxi)-benzamida

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-1,1-dimetil-propoxi)-benzamida

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-1-metil-propoxi)-benzamida

N-(2,3-Dihidroxi-1,1-dimetil-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-metoxi-propoxi)-benzamida

3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-pentiloxi)-benzamida

3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida

3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-metil-butoxi)-benzamida

3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-4-metil-pentiloxi)-benzamida

3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroxi-ciclopropilmetoxi)-henzamida

3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroxi-ciclobutilmetoxi)-benzamida

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3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroximetil-propoxi)-benzamida

3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1,1-dimetil-etoxi)-benzamida

3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroximetil-ciclopropoxi)-benzamida

N-(2-Etoxi-etoxi)-3,4,5-trifluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-2-metoxi-propoxi)-benzamida

3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-pentiloxi)-benzamida

3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-butoxi)-benzamida

3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-3-metil-butoxi)-benzamida

3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-[2-(1-hidroxi-ciclopropil)-etoxi]-benzamida

3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroximetil-ciclopropilmetoxi)-benzamida

3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroximetil-ciclopropilmetoxi)-benzamida

3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-1,1-dimetil-propoxi)-benzamida

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3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-1-metil-propoxi)-benzamida

N-(2,3-Dihidroxi-1,1-dimetil-propoxi)-3,4,5-trifluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-metoxi-propoxi)-benzamida

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-pentiloxi)-benzamida

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-metil-butoxi)-benzamida

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-4-metil-pentiloxi)-benzamida

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroxi-ciclopropilmetoxi)-benzamida

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroxi-ciclobutilmetoxi)-benzamida

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroxymetil-propoxi)-benzamida

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1,1-dimetil-etoxi)-benzamida

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroximetil-ciclopropoxi)-benzamida

5-Cloro-N-(2-etoxi-etoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-2-metoxi-propoxi)-benzamida

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-pentiloxi)-benzamida

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-butoxi)-benzamida

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-3-metil-butoxi)-benzamida

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-[2-(1-hidroxi-ciclopropil)-etoxi]-benzamida

4-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroximetil-ciclopropilmetoxi)-benzamida

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroximetil-ciclopropilmetoxi-benzamida

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-1,1-dimetil-propoxi)-henzamida

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-1-metil-propoxi)-benzamida

5-Cloro-N-(2,3-dihidroxi-1,1-dimetil-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-metoxi-propoxi)-benzamida

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5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-pentiloxi)-benzamida

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-metil-butoxi)-benzamida

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-4-metil-pentiloxi)-benzamida

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroxi-ciclopropilmetoxi)-benzamida

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroxi-ciclobutlmetoxi)-benzamida

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroxietil-propoxi)-benzamida

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1,1-dimetil-etoxi)-benzamida

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroximetil-ciclooopropoxi)-benzamida

5-Bromo-N-(2-etoxi-etoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-2-metoxi-propoxi)-benzamida

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-pentiloxi)-benzamída

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-butoxi)-benzamida

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-3-metil-butoxi)-benzamida

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-[2-(1-hidroxi-ciclopropil)-etoxi]-benzamida

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(i-hidroximetil-ciclopropilmetoxi)-benzamida

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroximetil-ciclopropilmetoxi)-benzamida

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamíno)-N-(3-hidroxi-1,1-dimetil-propoxi)-benzamida

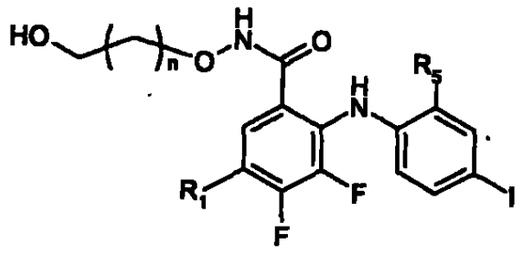
5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-1-metil-propoxi)-benzamida, y

5-Bromo-N-(2,3-dihidroxi-1,1-dimetil-propoxi-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida.

Los compuestos preferidos son aquellos de la fórmula I donde R_1 es hidrógeno o halógeno y más preferentemente hidrógeno, F, Br, o Cl; y más preferentemente hidrógeno; R_2 y R_3 son fluoro; R_4 es hidrógeno, yodo, bromo, cloro, o flúor; y más preferentemente hidrógeno, yodo, cloro o flúor; más preferentemente es flúor o cloro; y más preferentemente es flúor; n es 1 o 2; o combinaciones de ellos. Los compuestos preferidos son inhibidores de MEK selectivos. Los compuestos

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más preferidos son aquellos donde R_6, R_7, R_8, R_9, R_{10} y R_{11} son hidrógeno, W es oxígeno, y n es 1 o 2, y $R_8(1)$ es hidrógeno y $R_8(2)$ es hidroxi. Tales compuestos tienen las fórmulas II y III.



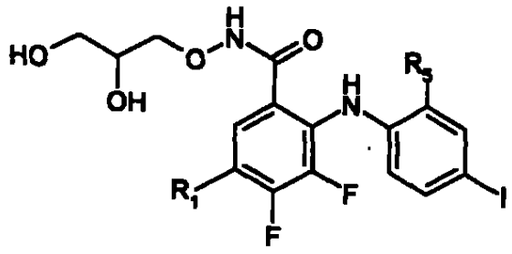
II

en donde

R_1 es hidrógeno o halógeno;

R_5 es flúor, cloro o metilo; y

n es 1 o 2.



III

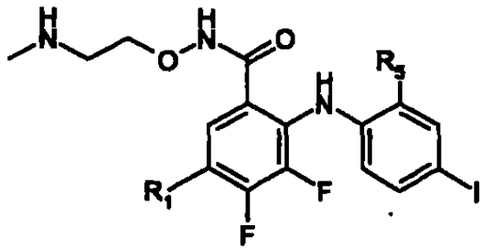
en donde

R_1 es hidrógeno o halógeno y

R_5 es flúor, cloro o metilo.

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Otros compuestos más preferidos son aquellos de la fórmula I donde R_1 es hidrógeno o halo tal como F, Br, o Cl; R_2 y R_3 son fluoro, R_4 es yodo, R_5 es fluoro, cloro o metilo, n es 1, R_6, R_7, R_8, R_9 y R_{10} son hidrógeno, W es NR_a, y R_a es H. R_{11} es metilo o fenilo; y sales farmacéuticamente aceptadas de ellos. Estos compuestos tienen las fórmulas IV y V.

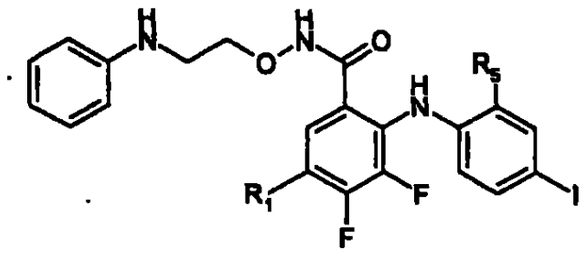


IV

en donde

R_1 es hidrógeno o halógeno y

R_5 es flúor, cloro o metilo.



V

en donde

R_1 es hidrógeno o halógeno y

R_5 es flúor, cloro o metilo.

Los compuestos preferidos de la presente invención incluyen en forma no taxativa los siguientes compuestos:

5-cloro-2-(2-cloro-4-yodo-fenilamino)-N-(2,3-dihidroxi-propoxi)-3,4-difluoro-benzamida;

3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-etoxi)-benzamida

N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-cloro-4-yodo-fenilamino)-benzamida

5-cloro-N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

5-cloro-N-((R)-2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

clorhidrato de 3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-metilamino-etoxi)-benzamida

N-((R)-2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

N-((S)-2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

5-cloro-2-(2-cloro-4-yodo-fenilamino)-N-((S)-2,3-dihidroxi-propoxi)-3,4-difluoro-benzamida

5-cloro-2-(2-cloro-4-yodo-fenilamino)-N-((R)-2,3-dihidroxi-propoxi)-3,4-difluoro-benzamida

5-cloro-N-((S)-2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

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3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1-hidroximetil-etoxi)-benzamida y 5-cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1-hidroximetil-etoxi)-benzamida.

En otro aspecto, la presente invención provee la forma I cristalina y la forma II de N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida (en adelante denominadas "Forma I del Compuesto A" y "Forma II del Compuesto A", respectivamente) o hidratos de ellas, la Forma I Cristalina y la Forma II de N-[(R)-2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida (en adelante denominadas "Forma I del Compuesto B" y "Forma II del Compuesto B", respectivamente) o hidratos de ellas, y la Forma I Cristalina y la Forma II de N-[(S)-2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida (en adelante denominadas "Forma I del Compuesto C" y "Forma II del Compuesto C", respectivamente) o hidratos de ellas.

La presente invención también provee la Forma I Cristalina y la Forma II del Compuesto A o hidratos de ellas, la Forma I Cristalina y la Forma II del Compuesto B o hidratos de ellas, y la Forma I Cristalina y la Forma II del Compuesto C o hidratos de ellas (en adelante denominadas colectivamente "formas cristalinas" de la presente invención, a menos que se

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especifique lo contrario) que son útiles como agentes farmacéuticos, los métodos para su producción y aislación, las composiciones farmacéuticas que incluyen estos compuestos y un portador farmacéuticamente aceptable y los métodos de tratamiento farmacéutico. Los compuestos cristalinos novedosos de la presente invención son útiles como inhibidores de MEK.

Las formas cristalinas provistas por la presente invención pueden ser caractarizadas por sus patrones de difracción de polvo de rayos X.

La Forma I cristalina y la Forma II del Compuesto A, la Forma I cristalina y la Forma II del Compuesto B y la Forma I cristalina y la Forma II del Compuesto C se caracterizan por su patrón de difracción de polvo de rayos X. Por lo tanto los patrones de difracción de rayos X de las formas cristalinas de la presente invención se miden en un Rigaku Ultima + difractómetro con radiacción de CuK_a.

Equipo

Rigaku Ultima + Difractómetro con una interfaz compatible con IBM equipado con automuestreadores de posición, software = RigMeas v2.0 (Rigaku, diciembre de 1995) Y JADE 3.1 (Materials Data, Inc.).

radiación de Cu K_α (40 mA, 40 kV, λ = 1,5419 A). Ranuras I y I a 0,5°, ranura III a 0,3°.

Metodología

El modelo de silicio se realiza una vez por semana para controlar la alineación del tubo de rayos X.
Barrido acoplado de $\theta/2\theta$ continuo: 3,00° a 50,00° en 2 θ, velocidad de barrido,de 1°/min: 1,0 seg/paso de 0,04°.

Muestra extraída de un tubo y prensada sobre silicio de fondo cero en soporte de aluminio. Ancho de la muestra 5 mm.

Las muestras se almacenan y realizan a temperatura ambiente.

Las muestras se centrifugan a 40 rpm alrededor de un eje vertical durante la recolección de datos.
La tabla 1 muestra una lista de patrones de difracción de polvo rayos X para la Forma I cristalina del Compuesto A, expresados en términos de 2-theta ("2θ"), d-espacios o d(A) e intensidades relativas por área de pico con una intensidad relativa de >10% medida en un Rigaku Ultima + difractómetro con una radiación de CuK_α. Se debe indicar que se dan números no redondeados, generados por computadora en la Tabla 1.

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Tabla 1

2-Theta	d(A)	Intensidad Relativa (>10%)
7.078	12.4779	15.2
14.123	6.2659	15.4
15.280	5.7939	58.7
15.836	5.5917	31.4
16.880	5.2481	42.2
18.082	4.9019	41.4
19.162	4.6280	67.4
20.279	4.3754	21.1
21.360	4.1565	73.6
22.325	3.9789	14.4
23.400	3.7984	79.3
24.522	3.6271	11.0
25.480	3.4929	24.6
26.159	3.4037	100.0
26.801	3.3237	48.9
27.842	3.2017	22.8
28.280	3.1531	45.4
29.475	3.0280	16.0
32.118	2.7845	19.7
33.248	2.6924	10.6
33.645	2.6615	16.3
40.008	2.2517	10.6
42.885	2.1071	12.1
44.095	2.0520	12.8

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La Tabla 2 da una lista de los patrones de difracción de polvo de rayos X para la Forma II cristalina del Compuesto A, expresados en términos de 2 theta ("2θ"), d-espacios o d(A) e intensiades relativas por área de pico con una intensidad relativa de >10% medida en un Rigaku Ultima + difractómetro con una radiación de CuK_{α}. Se debe indicar que se dan números no redondeados, generados por una computadora en la Tabla 2.

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Tabla 2

2-Theta	d(A)	Intensidad Relativa (>10%)
11.582	7.6344	11.2 *
12.598	7.0205	13.0 *
15.622	5.6678	17.1
17.302	5.1211	29.3
17.886	4.9551	13.3
20.345	4.3614	49.8
21.140	4.1991	31.0
22.137	4.0123	81.7
24.855	3.5793	100.0 *
25.885	3.4391	15.1
26.699	3.3362	23.3
27.842	3.2018	23.7
30.059	2.9704	11.8
30.948	2.8871	33.4
33.799	2.6498	24.8
35.399	2.5336	16.2
38.242	2.3516	33.9
39.282	2.2916	11.3
40.755	2.2122	12.6
41.641	2.1671	11.7
43.570	2.0756	24.5
46.958	1.9334	19.5

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La Tabla 3 da una lista de los patrones de difracción de polvo de rayos X para la Forma I cristalina del Compuesto B, expresados en términos de 2-theta ("2θ"), d-espacios o d(A) e intensidad relativa por área de pico con una intensidad relativa de >10% medida en un Rigaku Ultima + difractómetro con una radiación de CuK_{α}. Se debe indicar que se dan números no redondeados generados por computadora en la Tabla 3.

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2-Theta	d(A)	Intensidad Relativa (>10%)
10.560	8.3702	14.9 *
13.720	6.4488	10.3 *
14.619	6.0543	13.9
17.258	5.1340	12.4
17.958	4.9354	44.5
18.219	4.8654	15.8
18.998	4.6675	38.1 *
19.258	4.6052	12.3
20.142	4.4050	17.7
21.002	4.2264	18.5
21.940	4.0479	53.2
22.360	3.9727	19.3
23.680	3.7541	100.0 *
24.043	3.6983	16.9
24.919	3.5702	67.3
26.278	3.3886	20.1
27.603	3.2289	40.6
28.024	3.1813	30.7
30.100	2.9665	14.6
32.142	2.7825	15.8
32.298	2.7694	14.6
32.938	2.7171	14.7
35.841	2.5034	16.3
37.660	2.3865	15.6

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La Tabla 4 da una lista de los patrones de difracción de polvo de rayos X para la Forma II cristalina del Compuesto B, expresados en términos de 2-theta ("2θ"), d-espacios o d(A) e intensidades relativas por área de pico con una intensidad relativa de >10% medida en un Rigaku Ultima + difractómetro con una radiación de CuK_{α}. Se debe indicar que se dan números no redondeados generados por computadora en la Tabla 4.

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Tabla 4

2-Theta	d(A)	Intensidad Relativa (>10%)
5.482	16.1076	39.6 *
10.721	8.2453	20.3
16.478	5.3751	21.9
19.563	4.5340	73.2 *
22.019	4.0334	100.0
22.478	3.9521	16.1
23.621	3.7634	11.1
24.100	3.6896	31.9
24.959	3.5647	98.2
26.181	3.4010	15.1
27.621	3.2269	31.7
29.081	3.0681	17.7
30.476	2.9307	11.4
31.698	2.8204	38.9
33.263	2.6913	19.4
39.020	2.3064	10.2

La Tabla 5 da una lista de patrones de difracción de polvo de rayos X para la Forma I cristalina del Compuesto C, expresados en términos de 2-theta ("2θ"), d-espacios o d(A) e intensidades relativas por área de pico con una intensidad relativa de >10% medida en un Rigaku Ultima + difractómetro con una radiación

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de CuK_α. Se debe indicar que se dan números no redondeados generados por computadora en la Tabla 5.

Tabla 5

2-Theta	d(A)	Intensidad Relativa (>10%)
10.548	8.3798	14.6 *
13.703	6.4568	11.3 *
17.887	4.9549	19.9
18.958	4.6772	27.3 *
20.122	4.4093	10.9
21.950	4.0460	58.3
22.321	3.9796	13.4
23.640	3.7604	100.0 *
24.803	3.5867	66.6
26.244	3.3929	12.1
27.570	3.2327	21.6
28.000	3.1840	31.9
29.566	3.0189	23.1
32.234	2.7748	18.3
32.769	2.7307	16.4
35.804	2.5059	13.8
37.641	2.3877	16.8
41.402	2.1791	14.4
41.956	2.1516	10.0
44.600	2.0300	13.9

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La Tabla 6 da una lista de patrones de difracción de polvo de rayos X para la Forma II cristalina del Compuesto C, expresados en términos de 2-theta ("2θ"), d-espacios o d(A) e intensidades relativas por área de pico con una intensidad relativa de >10% medida en un Rigaku Ultima + difractómetro con una radiación de CuK_{α}. Se debe indicar que se dan números no redondeados generados por computadora en la Tabla 6.

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Tabla 6

2-Theta	d(A)	Intensidad Relativa (>10%)
5.550	15.91107	21.8 *
10.763	8.2128	22.3
16.485	5.3729	11.8
19.636	4.5173	73.5 *
20.922	4.2425	20.6
22.043	4.0291	54.0
23.683	3.7538	18.0
24.153	3.6817	52.6
24.996	3.5595	100.0
26.236	3.3939	11.4
27.680	3.2201	25.2
28.037	3.1799	22.4
29.120	3.0641	21.5
31.718	2.8187	36.4
32.794	2.7287	13.3
33.314	2.6872	10.8
34.085	2.6282	13.6
41.999	2.1494	14.6
42.278	2.1359	10.3

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Las formas cristalinas de la presente invención pueden existir como formas anhidras así como formas hidratadas. En general, las formas hidratadas, son equivalentes a las formas no hidratadas y se intenta abarcarlas dentro del alcance de la presente invención.

La presente invención provee un proceso para la preparación de la Forma I cristalina del Compuesto A que comprende cristalizar el Compuesto A desde una solución en solventes en condiciones que dan la Forma I cristalina del Compuesto A.

Las condiciones precisas en las que se forma la Forma I cristalina del Compuesto A pueden determinarse empíricamente y solamente es posible dar el número de métodos que se ha hallado que son adecuados en la práctica. La Forma I deseada puede obtenerse suspendiendo el sólido en un solvente adecuado, tal como etanol y precipitando con agua, disolviendo el sólido en una cantidad mínima de un solvente en ebullición, tal como etanol y agregando agua al solvente en ebullición; y disolviendo el sólido en una cantidad mínima de solvente en ebullición, tal como acetato de etilo, y agregando un solvente adecuado, tal como heptano al solvente en ebullición, como se expone en forma más completa en el Ejemplo 39A abajo.

La presente invención provee un proceso para la preparación de la Forma II cristalina del Compuesto A que comprende cristalizar el Compuesto A desde una solución en solventes en condiciones que dan la Forma II cristalina del Compuesto A.

Las condiciones precisas en las cuales se forma la Forma II cristalina del Compuesto A se pueden determinar empíricamente y solamente es posible dar un número de métodos que se ha hallado que son adecuados en la práctica. La Forma II deseada puede obtenerse suspendiendo el sólido en un solvente adecuado, tal como acetato de etilo/heptanos o suspendiendo el sólido en un solvente adecuado, tal como heptano - CH_2Cl_2 (1:1), como se expone en forma más completa en el Ejemplo 39 abajo.

La presente invención provee un proceso para la preparación de la Forma I cristalina del Compuesto B que comprende cristalizar el Compuesto B desde una solución en solventes en condiciones que dan la Forma I cristalina del Compuesto B.

Las condiciones precisas en que se forma la Forma I cristalina del Compuesto B pueden determinarse empíricamente y solamente es posible dar un método que se ha hallado que son adecuados en la práctica. La Forma I deseada puede obtenerse

suspendiendo el sólido en hexano-AcOEt. Se expone un procedimiento más detallado en el Ejemplo 49 abajo.

La presente invención provee un proceso para la preparación de la Forma II cristalina del Compuesto B que comprende cristalizar el Compuesto B desde una solución en solventes en condiciones que dan la Forma II cristalina del Compuesto B.

Las condiciones precisas en que se forma la Forma II cristalina del Compuesto B pueden determinarse empíricamente y solamente es posible dar un método que se ha hallado que es adecuado en la práctica. La Forma II deseada puede obtenerse suspendiendo el sólido en acetato de etilo y heptano o suspendiendo el sólido en hexano-AcOEt, como se expone en forma más completa en los Ejemplos 49 y 49A abajo.

La presente invención provee un proceso para la preparación de la Forma I cristalina del Compuesto C que comprende cristalizar el Compuesto C desde una solución en solventes en condiciones que dan la Forma I cristalina del Compuesto C.

Las condiciones precisas en las cuales se forma la Forma I cristalina del Compuesto C pueden determinarse empíricamente y solamente es posible dar un método que se ha hallado que es adecuado en la práctica. La Forma I deseada puede obtenerse

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suspendiendo el sólido en hexano-AcOEt. Se expone un procedimiento más detallado en el Ejemplo 50 abajo.

La presente invención provee un proceso para la preparación de la Forma II cristalina del Compuesto C que comprende cristalizar el Compuesto C desde una solución en solventes en condiciones que dan la Forma II cristalina del Compuesto C.

Las condiciones precisas en las que se forma la Forma II del Compuesto C pueden determinarse empíricamente y solamente es posible dar un método que se ha hallado que es adecuado en la práctica. La Forma II deseada puede obtenerse suspendiendo el sólido en acetato de etilo y heptano, o suspendiendo el sólido en hexano-AcOEt, como se expone en forma más completa en los Ejemplos 50 y 50A abajo.

Como se usa aquí, el término "paciente" se refiere a cualquier animal de sangre caliente tal como, en forma no taxativa, un ser humano, caballo, perro, conejillo de Indias, o ratón. Preferentemente, el paciente es humano.

El término "tratar" para los propósitos de la presente invención se refiere a la profilaxis o prevención, mejoramiento o eliminación de una condición nombrada una vez que la condición se ha establecido.

Los inhibidores de MEK 1 o MEK 2 son aquellos compuestos que inhiben las enzimas MEK 1 o MEK 2, respectivamente, sin inhibir sustancialmente otras enzimas tales como MKK3, PKC, Cdk2A, fosforilasa quinasa, EGF, y quinasas de receptor de PDGE, y C-src. En general, un inhibidor selectivo de MEK1 o MEK 2 tiene un IC_{50} para MEK 1 o MEK 2 que es por lo menos un quincuagésimo (1-50) de su IC_{50} para una de las otras enzimas mencionadas anteriormente. Preferentemente un inhibidor selectivo tiene un IC_{50} que es por lo menos 1/100, más preferentemente 1/500, y aún más preferentemente 1/1.000, 1/5.000, menor que aquel de su IC_{50} para una o más de las enzimas mencionadas anteriormente.

Las composiciones reveladas son útiles cómo tratamientos profilácticos así como terapéuticos para enfermedades o condiciones relacionadas con la hiperactividad de MEK, así como enfermedades o condiciones moduladas por la cascada de MEK. Los ejemplos incluyen, en forma no taxativa, ataque, choque séptico, insuficiencia cardíaca, osteoartritis, artritis reumatoide, rechazo de transplantes de órganos, y una variedad de tumores tales como tumores de ovarios, pulmón, páncreas, cerebro, próstata y colorectal.

La invención además se relaciona con un método para tratar enfermedades proliferativas tales como cáncer, restenosis,

psoriasis, enfermedad autoinmune, y aterosclerosis. Otros aspectos de la invención incluyen métodos para tratar cánceres relacionados con MEK (incluyendo los relacionados con ras), sean sólidos o hematopoyéticos. Los ejemplos de cánceres incluyen cáncer de cerebro, mamas, pulmón, tal como pulmón de células no pequeñas, ovario, páncreas, próstata, riñón, colorectal, de cuello de útero, leucemia aguda, y de estómago. Otros aspectos de la invención incluyen métodos para tratar o reducir los síntomas del rechazo de xenoinjerto (transplante de célula(s), piel, miembros, órganos o médula), osteoartritis, artritis reumatoide, fibrosis cística, complicaciones de la diabetes (incluyendo retinopatía diabética y nefropatía diabética), hepatomegalia, cardiomégalia, ataque (tal como ataque isquémico focal agudo e isquemia cerebral global), insuficiencia cardíaca, choque séptico, asma, enfermedad de Alzheimer, y dolor crónico o neuropático. Los compuestos de la invención son también útiles como agentes antivirales para tratar infecciones virales tales como HIV, virus de la hepatitis (B) (HBV), virus de papiloma humano (HPV), citomegalovirus (CMV), y virus de Epstein-Barr (EBV). Estos métodos incluyen el paso de administrar a un paciente que necesita tal tratamiento, o sufre de tal enfermedad o condición, una cantidad terapéuticamente efectiva de un compuesto revelado, que incluye formas cristalinas, o composiciones farmacéuticas de ellas.

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El término "dolor crónico" para los propósitos de la presente invención incluye, en forma no taxativa, dolor neuropático, dolor idiopático, y dolor asociado con el alcoholismo crónico, deficiencia de vitaminas, uremia, o hipotiroidismo. El dolor crónico está asociado con numerosas condiciones que incluyen, en forma no taxativa, inflamación, artritis y dolor post-operatorio.

Como se usa aquí, el término "dolor neuropático" está asociado con numerosas condiciones que incluyen, en forma no taxativa, inflamación, dolor post-operatorio, dolor de miembro fantasma, dolor por quemaduras, gota, neuralgia trigeminal, dolor herpético o postherpético agudo, causalgia, neuropatía diabética, avulsión del plexo, neuroma, vasculitis, infección viral, lesión por aplastamiento, lesión por constricción, lesión de tejidos, amputación de un miembro, dolor post-operatorio, dolor de artritis, y lesión nerviosa entre el sistema nervioso periférico y el sistema nervioso central.

La invención también caracteriza métodos de terapia de combinación, tales como un método para tratar el cáncer, en donde el método además incluye proveer terapia de radiación o quimioterapia, por ejemplo, con inhibidores mitóticos tales como un taxano o un alcaloide de vincapervinca. Los ejemplos de inhibidores mitóticos incluyen paclitaxel, docetaxel,

vincristina, vinblastina, vinorelbina, y vinflunina. Otras combinaciones terapéuticas incluyen un inhbidor de MEK d ela invención y un agente anticáncer tal como cisplatina, 5-fluorouracilo o 5-fluoro-2-4(1H,3H)-pirimidindiona (5FU), flutamida, y gemcitabina.

La quimioterapia o la terapia de radiación se puede administrar antes, simultáneamente o después de la administración de un compuesto revelado de acuerdo con las necesidades del paciente.

Los expertos en el arte podrán determinar, de acuerdo con los métodos conocidos, la cantidad o dosificación terapéuticamente efectiva apropiada de un compuesto de la presente invención para administrar a un paciente, tomando en cuenta factores como la edad, peso, salud general, el compuesto administrado, la vía de administración, el tipo de dolor o condición que requiere el tratamiento, y la presencia de otras medicaciones. En general, una cantidad efectiva o una cantidad terapéuticamente efectiva es entre 0,1 mg/kg y 1.000 mg/kg por día, preferentemente entre 1 mg/kg y 300 mg/kg de peso corporal, y las dosificaciones diarias son entre 10 mg y 5.000 mg para un sujeto adulto de peso normal. Las cápsulas u otras formulaciones comercialmente disponibles (tales como líquidos y tabletas recubiertas con películas) de 100 mg, 200 mg, 300

mg o 400 mg pueden administrarse de acuerdo con los métodos revelados.

Los compuestos de la presente invención, que incluyen formas cristalinas, preferentemente se formulan antes de la administración. En consecuencia, otro aspecto de la presente invención es una composición farmacéutica que comprende un compuesto de la fórmula I y un portador farmacéuticamente aceptable. En la fabricación de las composiciones d ela presente invención, el ingrediente activo, tal como un compuesto de la fórmula I, generalmente se mezcla con un portador, o es diluido por un portador o encerrado dentro de un portador. Las formas unitarias de dosificación o composiciones farmacéuticas incluyen tabletas, cápsulas, píldoras, polvos, gránulos, soluciones y suspensiones acuosas y no acuosas, y soluciones parenterales empaquetadas en recipientes adaptados para la subdivisión en dosis individuales.

Las formas unitarias de dosificación pueden adaptarse para diversos métodos de administración, que incluyen formulaciones de liberación controlada, tales como implantes subcutáneos. Los métodos de administración incluyen oral, rectal, parenteral (intravenosa, intramuscular, subcutánea), intracisternal, intravaginal, intraperitoneal, intravesicular,

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local (gotas, polvos, ungüentos, geles o cremas), y mediante inhalación (una aspersión bucal o nasal).

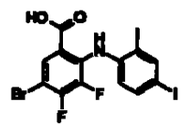
Las formulaciones parenterales incluyen soluciones acuosas o no acuosas farmacéuticamente aceptables, dispersión, suspensiones, emulsiones, y polvos estériles para su preparación. Los ejemplos de portadores incluyen agua, etanol, polioles (propilenglicol, polietilenglicol), aceites vegetales, y ésteres orgánicos inyectables tales como oleato de etilo. La fluidez se puede mantener mediante el uso de un recubrimiento tal como lecitina, un agente tensoactivo o manteniendo el tamaño de partícula adecuado. Los portadores para formas de dosificación sólidas incluyen (a) rellenos o extendedores, (b) ligantes, (c) humectantes, (d) agentes desintegradores, (e) retardadores de la solición, (f) aceleradores de la absorción, (g) adsorbentes, (h) lubricantes, (i) agentes tampones y (j) propulsores.

Las composiciones también pueden contener coadyuvantes tales como agentes conservantes, humidificantes, emulsionadores, y dispersantes; agentes antimicrobianos tales como parabenos, clorobutanol, fenol y ácido sórbico; agentes isotónicos tales como azúcar o cloruro de sodio; agentes prolongadores de la absorción tales como monoestearato de aluminio y gelatina; y agentes mejoradores de la absorción.

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Los siguientes ejemplos representan síntesis típicas de los compuestos de la presente invención descriptas en general anteriormente. Estos ejemplos son solamente ilustrativos y no intentan limitar de ninguna manera la invención. Los reactivos y materiales iniciales están disponibles fácilmente para los expertos en el arte.



PREPARACIÓN 1

Ácido 5-Bromo-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-benzoico

A una solución agitada comprendida por 1,88 g (0,00791 mol) de 2-amino-5-yodotolueno en 10 ml de tetrahidrofurano a -78°C se agregaron 6 ml (0,012 mol) de 2,0 M diisopropilamida de litio en una solución de tetrahidrofurano/heptano/etilbenceno (Aldrich). La suspensión verde resultante se agitó vigorosamente durante 10 minutos, después de cuyo tiempo se agregó una solución de 1,00 g (0,00392 mol) de ácido 5-bromo-2,3,4-trifluorobenzoico en 15 ml de tetrahidrofurano. El baño frío se removió posteriormente, y la mezcla de la reacción se agitó durante 18 horas. La mezcla se concentró, y el concentrado se trató con 100 ml de ácido clorhídrico acuoso

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diluido (10%). La suspensión resultante se extrajo con éter (2 x 150 ml) y las extracciones orgánicas combinadas se secaron ($MgSO_4$) y se concentraron en vacío para far un sólido naranja. El sólido se trituró con diclorometano en ebullición, se enfrió a temperatura ambiente y se recogió mediante filtración. El sólido se enjuagó con diclorometano, y se secó en el horno de vacío (80°C) para dar 1,39 g (76%) de un polvo verde amarillento; punto de fusión 259,5°C-262°C;

^1H NMR (400 MHz, DMSO): δ 9,03 (s, 1H), 7,99 (dd, 1H, J=7,5, 1,9 Hz), 7,57 (dd, 1H, J= 1,5 Hz), 7,42 (dd, 1H, J=8,4, 1,9 Hz), 6,70 (dd, 1H, J=8,4, 6,0 Hz), 2,24 (s, 3H); ^{19}F NMR (376 MHz, DMSO): δ -123,40 a -123,47 (m); -139,00 a -139,14 (m); IR (KBr) 1667 (C=O estiramiento) cm^{-1}; MS (CI) M+1 = 469.

Análisis calculado/hallado para $C_{14}H_9BrF_2IN_2$:

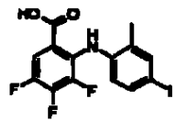
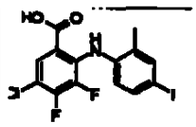
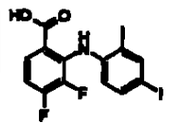
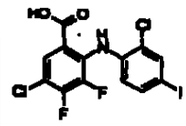
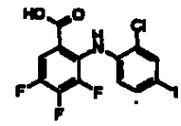
C, 35,93/36,15; H, 1,94/1,91; N, 2,99/2,70; Br, 17,07/16,40; F, 8,12/8,46; I, 27,11/26,05.

PREPARACIONES

Las preparaciones 2 a 25 de la Tabla 7 siguiente se preparan mediante el procedimiento del Ejemplo 1.

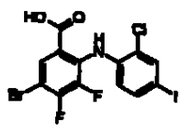
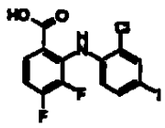
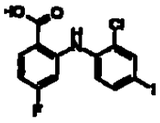
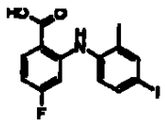
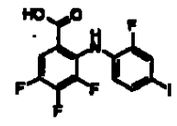
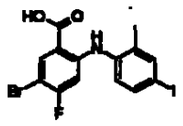
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Preparación		Compuesto	Punto de Fusión °C
2		ácido 3,4,5-trifluoro-2-(4-yodo-2-metil-fenilamino)-benzoico	206-210
3		ácido 5-cloro-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-benzoico	249-251
4		ácido 3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-benzoico	240-244,5
5		ácido 5-cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-benzoico	293,3-293,6
6		ácido 2-(2-cloro-4-yodo-fenilamino)-3,4,5-trifluoro-benzoico	237-239

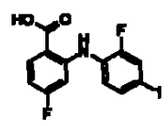
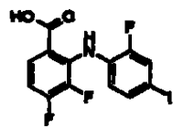
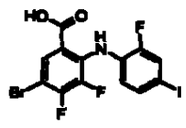
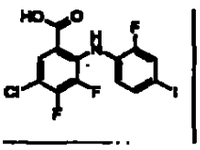
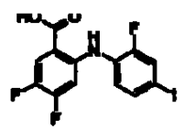
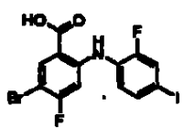
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7		ácido 5-bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-benzoico	302-304
8		ácido 2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-benzoico	226-228
9		ácido 2-(2-cloro-4-yodo-fenilamino)-4-fluoro-benzoico	242-247
10		ácido 4-fluoro-2-(4-yodo-2-metil-fenilamino)-benzoico	224-229,5
11		ácido 3,4,5-trifluoro-2-(2-fluoro-4-yodo-fenilamino)-benzoico	
12		ácido 5-bromo-4-fluoro-2-(4-yodo-2-metil-fenilamino)-benzoico	

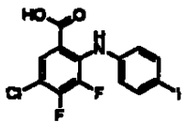
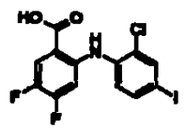
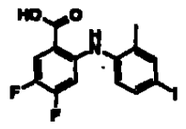
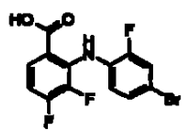
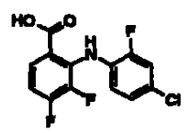
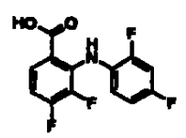
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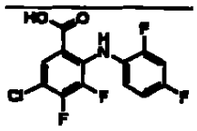
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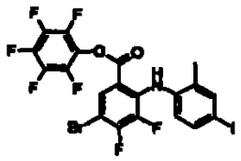
13		ácido 4-fluoro-2-(2-fluoro-4-yodo-2-fenilamino)-benzoico	215-217
14		ácido 3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzoico	200-201
15		ácido 5-bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzoico	258-259
16		ácido 5-cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzoico	256-258
17		ácido 4,5-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzoico	244-245
18		ácido 5-bromo-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-benzoico	296-298

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.- 0263

19		ácido 5-cloro-3,4-difluoro-2-(4-yodo-fenilamino)-benzoico	267-269
20		ácido 2-(2-cloro-4-yodo-fenilamino)-4,5-difluoro-benzoico	245
21		ácido 4,5-difluoro-2-(4-yodo-2-metil-fenilamino)-benzoico	238-239
22		ácido 2-(4-bromo-2-fluoro-fenilamino)-3,4-difluoro-benzoico	214,4-214,9
23		ácido 2-(4-cloro-2-fluoro-fenilamino)-3,4-difluoro-benzoico	215,4-215,6
24		ácido 2-(2,4-difluoro-fenilamino)-3,4-difluoro-benzoico	191,8-192,0

25		ácido 5-cloro-2-(2,4-difluoro-fenilamino)-3,4-difluoro-benzoico	240-240,3



PREPARACIÓN 26

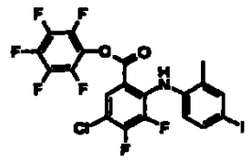
Pentafluorofenil éster del ácido 5-bromo-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-benzoico

A una solución de ácido 5-bromo-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-benzoico (preparado como se describe en WO 99/01426) (1,61 g, 3,4 mmol) y piridina (0,31 ml, 3,83 mmol) en dimetilformamida anhidra (7 ml) se agregó pentafluorofenil trifluoroacetato (0,71 ml, 4,13 mmol). La solución resultante se agitó a temperatura ambiente durante 18 h. La mezcla de la reacción se diluyó con éter (100 ml) y se lavó con agua (40 ml), 0,1 M ácido clorhídrico acuoso (40 ml), bicarbonato de sodio acuoso saturado, y solución salina saturada (40 ml). Los orgánicos se secaron sobre sulfato de magnesio anhidro y se

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concentraron bajo presión reducida para dar una espuma que se purificó sobre gel de sílice. La elución con hexanos-acetato de etilo (19:1) dio pentafluorofenil éster del ácido 5-bromo-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-benzoico (1,95 g, 89%) como un polvo amarillo pálido. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8,59 (s, 1H), 8,24 (d, J=5,8 Hz, 1 H), 7,54 (s, 1H), 7,45 (d, J= 8,4 Hz, 1 H), 6,70 (dd, J=8,4, 5,3 Hz, 1 H), 2,26 (s, 3H).

Las preparaciones 27-46 se prepararon mediante el procedimiento general de la Preparación 26.

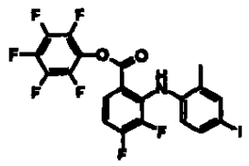


PREPARACIÓN 27

Pentafluorofenil éster del ácido 5-cloro-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-benzoico

^{1}H NMR (400 MHz, $CDCl_3$): δ 8,58 (s, 1H), 8,12 (dd, J=7,5, 2,0 Hz, 1 H), 7,54 (s, 1H), 7,46 (dd, J= 8,3, 1,5 Hz, 1 H), 6,70 (dd, J=8,3, 5,4 Hz, 1 H), 2,28 (s, 3H); ^{19}F-NMR (376 MHz, $CDCl_3$) δ -125,1 (dd, J= 17,7, 5,0 Hz, 1 F), -139,1 (d, J = 17,7 Hz, 1 F), -152,6 (d, J = 17,7 Hz, 2 F), -156,9 (t, J = 20,3 Hz, 1 H), -161,9 (t, J = 20,2 Hz, 2 H); MS (APCI-) = 587,9.

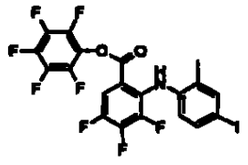
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0266



PREPARACIÓN 28

Pentafluorofenil éster del ácido 3,4-difuoro-2-(4-yodo-2-metil-fenilamino)-benzoico

^{1}H NMR (400 MHz, $CDCl_3$): δ 8,59 (s, 1H), 8,04 (dd, J=7,5, 7,0 Hz, 1 H), 7,53 (s, 1H), 7,45 (d, J= 8,4 Hz, 1 H), 6,77 (m, 1 H), 6,70 (dd, J=7,2, 6,9 Hz, 1 H), 2,27 (s, 3H); MS(APCI-)= 554,0.



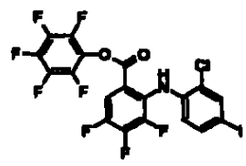
PREPARACIÓN 29

Pentafluorofenil éster del ácido 3,4,5-trifluoro-2-(4-yodo-2-metil-fenilamino)-benzoico

Punto de fusión: 108,5°C-110,6°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8,35 (s, 1H), 7,89 (ddd, J=10,4, 8,0, 2,2 Hz, 1 H), 7,53 (s, 1H), 7,44 (dd, J= 8,2, 1,9 Hz, 1 H), 6,64 (dd, J=8,2, 5,5 Hz, 1H), 2,27 (s, 3H); ^{19}F-NMR (376 MHz, $CDCl_3$) δ -137,25 (d, J= 16,8 Hz, 1F), -144,18 (dd, J = 21,4, 10,7 Hz, 1F), -145,55 (td, J = 21,4, 7,6 Hz, 1F), -152,31 (d, J = 18,3 Hz, 2H), -

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156,60 (t, J = 21,4 Hz, 1F), -161,62 (t, J=18,3 Hz, 2F). Análisis calculado/hallado para $C_{20}H_8NO_2F_8I$: C, 41,91/41,52; H, 1,41/1,32; N, 2,44/2,36; F, 26,52/26,34; I, 22,14/22,19.

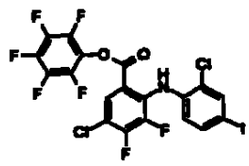


PREPARACIÓN 30

Pentafluorofenil éster del ácido 2-(2-cloro-4-yodo-fenilamino)-3,4,5-trifluoro-benzoico

Punto de fusión: 98,2°C-99,2°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8,50 (s, 1H), 7,93 (ddd, J=10,1, 8,0, 2,2 Hz, 1 H), 7,70 (d, J=1,7 Hz, 1H), 7,48 (dd, J= 8,7, 1,7 Hz, 1H), 6,62 (t, J=7,6 Hz, 1H); ^{19}F-NMR (376 MHz, $CDCl_3$) δ -134,42 (d, J= 18,3 Hz, 1F), -141,59 (dd, J = 21,4, 9,2 Hz, 1F), -145,26 (td, J = 21,4, 7,6 Hz, 1F), -152,26 (d, J = 18,3 Hz, 2H), -156,46 (t, J = 21,4 Hz, 1F), -161,53 (t, J=18,3 Hz, 2F). Análisis calculado/hallado para $C_{19}H_5NO_2F_8ClI$: C, 38,45/38,39; H, 0,85/0,91; N, 2,36/2,32; Cl, 5,97/6,32; F, 25,60/25,68; I, 21,38/21,32.

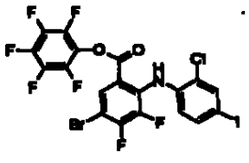
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PREPARACIÓN 31

Pentafluorofenil éster del ácido 5-cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-benzoico

^{1}H NMR (400 MHz, $CDCl_3$): δ 8,74 (s, 1H), 8,15 (dd, J=7,3, 2,0 Hz, 1 H), 7,71 (d, J=2,0 Hz, 1 H), 7,49 (dd, J= 8,4, 2,0 Hz, 1 H), 6,68 (dd J=8,4, 7,1 Hz, 1 H); MS (APCI-)=607,8.



PREPARACIÓN 32

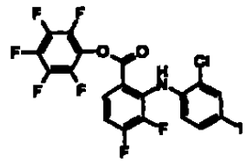
Pentafluorofenil éster del ácido 5-bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-benzoico

Rendimiento, 1,99 g (61%); punto de fusión: 112°C-114°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8,75 (s, 1H), 8,28 (dd, J= 7,0, 2,2 Hz, 1H), 7,50 (dd, J=8,4, 1,9 Hz, 1H), 7,713 (d, J= 1,9 Hz, 1H), 6,68 (dd, J=8,4, 7,0 Hz, 1H); ^{19}F-NMR (376 MHz, $CDCl_3$) δ -116,43 (dd, J= 19,8, 6,1 Hz, 1F), -135,59 (dd, J = 18,3, 6,1 Hz, 1F), -152,2 (d, J = 16,8 Hz, 2F), -156,47 (t, J = 21,4 Hz, 1F), -161,53 (t, J=18,3 Hz, 2F). Análisis calculado/hallado para

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$C_{19}H_5NO_2F_7BrClI$: C, 34,87/34,72; H, 0,77/0,65; N, 2,14/2,07; F, 20,32/20,68; Cl, 5,42/6,06; Br, 12,21/11,67; I, 19,39/19,75.

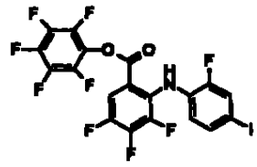


PREPARACIÓN 33

Pentafluorofenil éster del ácido 2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-benzoico

Rendimiento, 2,15 g (75%); punto de fusión: 108,5°C-110,0°C; ^1H NMR (400 MHz, $CDCl_3$): δ 8,77 (br s, 1H), 8,07 (br s, 1 H), 7,69 (br s, 1H), 7,48 (br d, J= 7,0, 1H), 6,91 (br d, J=7,2 Hz, 1H), 6,67 (br s, 1H); ^{19}F-NMR (376 MHz, $CDCl_3$). δ -123,74 (s, 1F), -139,17 (d, J= 16,8 Hz, 1F), -152,35 (d, J = 21,4 Hz, 2F), -156,96 (t, J = 21,4 Hz, 1F), -161,81 (t, J=21,4 Hz, 2F). Análisis calculado/hallado para $C_{19}H_6NO_2F_7ClI$: C, 39,65/39,32; H, 1,05/0,91; N, 2,43/2,35; F, 23,10/22,85; Cl, 6,16/6,92; I, 22,05/22,50.

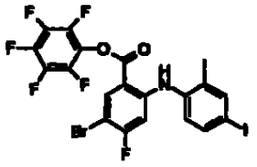
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0210



PREPARACIÓN 34

Pentafluorofenil éster del ácido 3,4,5-trifluoro-2-(2-fluoro-4-yodo-fenilamino)-benzoico

^{1}H NMR (400 MHz, $CDCl_3$): δ 8,40 (s, 1H), 7,85-7,91 (m, 1H), 7,35-7,43 (m, 2H), 6,67-6,73 (m, 1H), MS ($APCI^-$)=575,9.

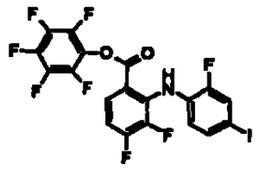


PREPARACIÓN 35

Pentafluorofenil éster del ácido 5-bromo-4-fluoro-2-(4-yodo-2-metilfenilamino)-benzoico

^{1}H NMR (400 MHz, acetona-d_6): δ 9,04 (br s, 1H), 8,44 (d, 1H, J= 7,81 Hz), 7,74 (d, 1H, J= 1,22 Hz), 7,64 (dd, 1H, J=8,31, 1,96 Hz), 7,19 (d, 1H, J=8,3 Hz), 6,67 (d, 1H, J=11,48 Hz), 2,22 (s, 3H). ^{19}F-NMR (376 MHz, acetona-d_6) δ -97,1 (t), -155,0 (t), -160,2 (t), -165,1 (t). MS(APCI-) 415,8 m/z, 429,9 m/z, 447,9 m/z, 615,8 m/z.

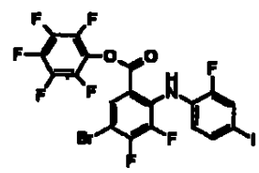
273
0271



PREPARACIÓN 36

Pentafluorofenil éster del ácido 3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzoico

^{1}H NMR (400 MHz, $CDCl_3$): δ 8,67 (s, 1H), 8,04 (ddd, J= 9,3, 5,6, 2,2 Hz, 1H), 7,42 (dd, J=10,0, 1,9 Hz, 1H), 7,38 (d, J= 8,8 Hz, 1H), 6,84 (td, J=9,1, 6,8 Hz, 1H), 6,77 (td, J=8,5, 5,1 Hz, 1 H); ^{19}F-NMR (376 MHz, $CDCl_3$) δ -124,3, -125,1, -143,5, -152,6, -157,3, -162,1; MS (APCI-)=557,9.



PREPARACIÓN 37

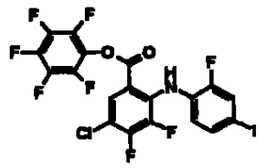
Pentafluorofenil éster del ácido 5-bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzoico

^{1}H NMR (400 MHz, acetona-d_6): δ 8,60 (s, 1H), 8,39 (ddd, J= 7,1, 2,3, 0,7 Hz, 1 H), 7,58 (dd, J=10,5, 1,7 Hz, 1 H), 7,49 (dt, J=7,5, 1,5 Hz, 1 H), 7,06 (td, J=8,5, 4,4 Hz, 1 H); ^{19}F

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0272

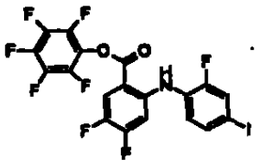
NMR (376 MHz, acetona-d_6) δ -120,5, -127,1, -141,5, -154,7, -159,8, -164,8; MS(APCI-) 535,8, 637,8.



PREPARACIÓN 38

Pentafluorofenil éster del ácido 5-cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzoico

^{1}H NMR (400 MHz, $CDCl_3$): δ 8,62 (s, 1H), 8,10 (dd, J= 7,5, 2,3 Hz, 1 H), 7,44 (dd, J=10,0, 1,7 Hz, 1 H), 7,41 (dd, J=8,4, 1,1 Hz, 1 H), 6,76 (td, J=8,3, 4,6 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -124,6, -124,9, -140,3, -152,5, -156,8, -161,9; MS(APCI-) 591,8, 593,8.

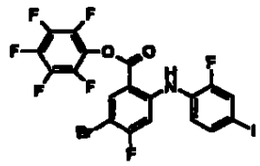


PREPARACIÓN 39

Pentafluorofenil éster del ácido 4,5-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzoico

^{1}H NMR (400 MHz, acetona-d_6): δ 8,99 (br. s.), 8,17 (dd, 1H, J= 10,99, 8,79 Hz), 7,69 (dd, 1H, J=10,0, 1,95 Hz), 7,63 (m, 1H),

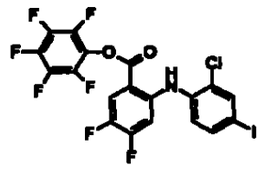
7,38 (t, 1H, J=8,55), 7,04 (qd, 1H, J=6,84, 1,47 Hz); ^{19}F NMR (376 MHz, acetona-d_6) δ -123,0 (t), -125,7 (p), -150,8 (m), -155,1 (d), -160,1 (t), -165,0 (t); MS(APCI-) 355,9 m/z, 391,9 m/z, 558,0 m/z. Análisis calculado para $C_{14}H_{10}F_2INO_2$: C, 40,81; H, 1,08; N, 2,50. Hallado: C, 40,92; H, 1,00; N, 2,32.



PREPARACIÓN 40

Pentafluorofenil éster del ácido 5-bromo-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-benzoico

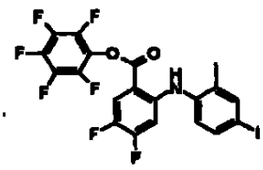
^1H NMR (400 MHz, acetona-d_6): δ 9,11 (br. s.), 8,2 (dd, 1H, J= 11,24, 8,79 Hz), 7,9 (d, 1H, J= 1,95 Hz), 7,73 (dd, 1H, J=8,55, 2,2 Hz), 7,45 (d, 1H, J=8,55), 7,17 (dd, 1H, J=13,18, 6,83 Hz); ^{19}F NMR (376 MHz, acetona-d_6) δ -96,8, -122,4, -155,0, -160,0, -165,0; MS(APCI-) 415,8 m/z (d), 453,8 m/z (d), 617,8 m/z (d). Análisis calculado para $C_{13}H_7BrF_2INO_2$: C, 34,39; H, 0,98; N, 2,26. Hallado: C, 36,61; H, 0,99; N, 2,09.



PREPARACIÓN 41

Pentafluorofenil éster del ácido 2-(2-cloro-4-yodo-fenilamino)-4,5-difluoro-benzoico

^{1}H NMR (400 MHz, acetona-d_6): δ 9,11 (br. s.), 8,2 (dd, 1H, J= 11,24, 8,79 Hz), 7,9 (d, 1H, J= 1,95 Hz), 7,73 (dd, 1H, J=8,55, 2,2 Hz), 7,45 (d, 1H, J=8,55 Hz), 7,17 (dd, 1H, J=13,18, 6,83 Hz); ^{19}F NMR (376 MHz, acetona-d_6) δ -125,5 (p), -150,1 (m), -155,1 (d), -160,0 (t), -164,9 (t). MS(APCI-) 355,9 m/z, 389,9 m/z, 407,9 m/z, 573,9 m/z.



PREPARACIÓN 42

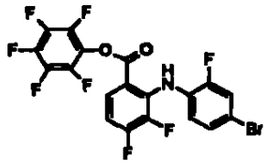
Pentafluorofenil éster del ácido 4,5-difluoro-2-(4-yodo-2-metil-fenilamino)-benzoico

^{1}H NMR (400 MHz, acetona-d_6): δ 8,92 (br. s.), 8,14 (dd, 1H, J= 11,23, 8,79 Hz), 7,75 (d, 1H, J= 1,46 Hz), 7,64 (dd, 1H, J=8,31, 2,2 Hz), 7,2 (d, 1H, J=8,31 Hz), 7,76 (dd, 1H,

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J=13,19, 6,84 Hz), 2,24 (s, 3H); ^{19}F NMR (376 MHz, acetona-d_6) δ -125,78 (p), -152,41 (m), -155,1 (d), -160,2 (t), -165,0 (t). MS(APCI-) 355,9 m/z, 369,9 m/z (d), 554,0 m/z.

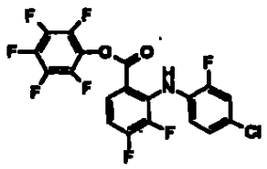


PREPARACIÓN 43

Pentafluorofenil éster del ácido 2-(4-bromo-2-fluoro-fenilamino)-3,4-difluoro-benzoico

Punto de fusión: 100,9°C-101,5°C; ^1H NMR (400 MHz, DMSO-d_6): δ 8,56 (s, 1 H), 8,07 (ddd, J= 9,3, 5,9, 2,0 Hz, 1 H), 7,54 (dd, J=11,0, 2,2 Hz, 1 H), 7,35-7,22 (cm, 2 H), 7,04 (td, J=8,9, 2,0 Hz, 1 H); ^{19}F NMR (376 MHz, DMSO-d_6) δ -125,8 (t, J=10,1 Hz), -126,7 (m), -145,3 (d, J=20,2 Hz), -153,3 (d, J=20,2 Hz), -157,8 (t, J=22,7 Hz), -162,9 (t, J=21,5 Hz). MS(APCI-) 510,0/512,0.

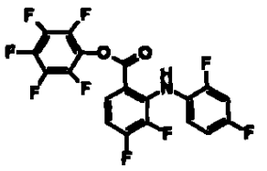
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PREPARACIÓN 44

Pentafluorofenil éster del ácido 2-(4-cloro-2-fluoro-fenilamino)-3,4-difluoro-benzoico

Punto de fusión: 99,0°C-99,4°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8,59 (s, 1 H), 8,07 (ddd, J= 9,0, 5,8, 2,0 Hz, 1 H), 7,45 (dd, J=11,2, 2,2 Hz, 1 H), 7,30 (dt, J=7,3, 9,2 Hz, 1 H), 7,19-7,08 (m, 2 H); ^{19}F NMR (376 MHz, DMSO-d_6) δ -125,6 (t, J=10,1 Hz), -126,7 (m, 1 H), -145,6 (d, J=15,2 Hz), -153,3 (d, J=20,2 Hz), -157,7 (t, J=22,8 Hz), -162,8 (t, J=20,2 Hz. MS(APCI-) 466,0.



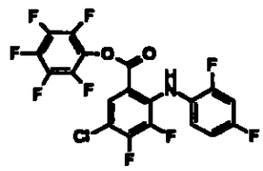
PREPARACIÓN 45

Pentafluorofenil éster del ácido 2-(2,4-difluoro-fenilamino)-3,4-difluoro-benzoico

^{1}H NMR (400 MHz, DMSO-d_6): δ 8,58 (s, 1 H), 8,07 (ddd, J= 9,0, 5,9, 2,0 Hz, 1 H), 7,34-7,12 (cm, 3 H), 7,01 (m, 1 H); ^{19}F NMR (376 MHz, DMSO-d_6) δ -116,9 (s), -122,6 (t, J=10,1 Hz), -126,7

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(m), 147,9 (d, J=20,2 Hz), -153,5 (t, J=20,2 Hz), -157,7 (t, J=22,8 Hz), -162,8 (t, J=20,2 Hz); MS(APCI-) 450,0.



PREPARACIÓN 46

Pentafluorofenil éster del ácido 5-cloro-2-(2,4-difluoro-fenilamino)-3,4-difluoro-benzoico

Punto de fusión 92,5°C-93,2°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8,62 (s, 1 H), 8,21 (dd, J= 7,7, 2,1 Hz, 1 H), 7,34-7,24 (m, 3 H), 7,02 (m, 1 H); ^{19}F NMR (376 MHz, DMSO-d_6) δ -116,7 (m), -122,4 (m), -128,1 (dd, J=20,2, 7,6 Hz), -143,4 (d, J=17,7 Hz), -153,2 (d, J=20,2 Hz), -157,4 (t, J=22,7 Hz), -162,8 (t, J=20,2 Hz); MS(APCI-) 483,9



PREPARACIÓN 47

O-(2-Viniloxi-etil)-hidroxilamina

Parte A: Síntesis de 2-(2-viniloxi-etoxi)-isoindol-1,3-diona

Vinil éter de etilenglicol (9,88 g, 112 mmol), trifenilfosfina (29,4 g, 112 mmol) y N-hidroxiftalimida (18,22 g, 111,7 mmol)

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se combinaron en 300 ml de tetrahidrofurano anhidro y se enfriaron a 0°C (baño de hielo).

Se agregó dietilazodicarboxilato (18,0 ml, 114 mmol) gota a gota durante 15 minutos y la mezcla de la reacción resultante se dejó calentar a temperatura ambiente durante 18 h. La mezcla de la reacción se concentró en una pasta y los sólidos se filtraron y se lavaron con cloroformo. El filtrado se concentró más y se filtró nuevamente, lavando los sólidos con cloroformo. La solución de cloroformo restante se concentro en un aceite. El aceite se disolvió en etanol absoluto (75 ml). El raspado con una varilla de vidrio indujo la cristalización. Los cristales se recogierion y recristalizaron desde etanol caliente para dar agujas incoloras de 2-(2-viniloxi-etoxi)-isoindol-1,3-diona (13,8 g, 53% de rendimiento): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7,85 (m, 2 H), 7,75 (m, 2 H), 6,46 (dd, J= 14,3, 6,7 Hz, 1 H), 4,45 (m, 2 H), 4,16 (dd, J=14,4, 2,2 Hz), 4,02 (m, 3 H).

Parte B: Síntesis de O-(2-viniloxi-etil)-hidroxilamina

2-(2-Viniloxi-etoxi)-isoindol-1,3-diona (13,8 g, 59,2 mmol) se disolvió en diclorometano (45 ml). Se agregó metilhidrazina (3,2 ml, 60 mmol) gota a gota y la solución resultante se agitó durante 30 minutos a temperatura ambiente. La suspensión resultante se diluyó con dietil éter (150 ml) y se filtró. El filtrado se concentró en vacío. El aceite residual se destiló (punto de ebullición 60°C-65°C a 20 mm Hg) para dar la amina

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como un líquido incoloro (4,6 g, 75% de rendimiento). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6,49 (dd, J= 14,3, 6,7 Hz, 1 H), 5,59 (br s, J=2 H), 4,19 (dd, J=14,3, 2,2 Hz, 1 H), 4,01 (dd, J=6,8, 2,2 Hz, 1 H), 3,90-3,83 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151,7, 86,8, 73,7, 66,0.

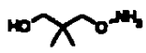
Las preparaciones 48-51 se prepararon mediante el procedimiento general de la preparación 47, parte A.



PREPARACIÓN 48

O-(2-Metoxi-etil)-hidroxilamina

^{1}H NMR (400 MHz, $CDCl_3$): δ 5,21 (br s, 2 H), 3,82 (m, 2 H), 3,54 (m, 2 H), 3,37 (s, 3 H).



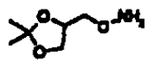
PREPARACIÓN 49

3-Aminooxi-2,2-dimetil-propan-1-ol

Punto de ebullición 148°C a 20 mm Hg; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3,50 (s, 2H), 3,37 (s, 2H), 0,86 (s, 6H).

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PREPARACIÓN 50

O-(2,2-Dimetil-[1,3]dioxolan-4-ilmetil)-hidroxilamina

^{1}H NMR (400 MHz, $CDCl_3$): δ 5,50 (bs, 1 H), 4,32 (m, 1 H), 4,04 (t, J=6,81 Hz, 1 H), 3,72 (m, 2 H), 3,67 (m, 1 H), 1,41 (s, 3 H), 1,34 (s, 3 H); MS (APCI+) =148.



PREPARACIÓN 51

O-[2-(2-Metoxi-etoxi)-etil]-hidroxilamina

Punto de ebullición 95°C-100°C a 20 mm Hg; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5,96 (br s, 2 H), 3,62 (t, J=4,3 Hz, 2 Hz), 3,55-3,47 (m, 4 H), 3,42 (m, 2 H), 3,24 (s, 3 H); MS (APCI+) =136,1

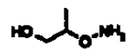


PREPARACIÓN 52

2-Aminooxi-etanol

2-Aminooxi-etanol se preparó mediante el procedimiento de la bibliografía: Dhanak, D.; Reese, C.B. J.Chem. Soc., Perkin Trans. 1, 1987, 2829.

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0281



PREPARACIÓN 53

2-Amnooxi-propan-1-ol

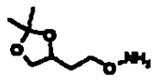
2-Aminooxi-propan-1-ol se preparó de acuerdo con el procedimiento de la bibliografía (Cannon, J.G.; Mulligan, P.J.; Garst, J.E.; Long, J.P.; Heintz, S. *J. Med. Chem.*, 1973, 16, 287). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5,41 (br s, 2 H), 3,77 (m, 1 H), 3,58 (dd, J=11,7, 2,8 Hz, 1 H), 3,52 (dd, J=11,7, 6,9 Hz, 1 H), 1,02 (d, J=6,4 Hz, 3 H).



PREPARACIÓN 54

3-Aminooxi-propan-1-ol

3-Aminooxi-propan-1-ol se preparó mediante el procedimiento de la bibliografía (Ludwig, B.J.; Reisner, D.B.; Meyer, M.; Powell, L.S.; Simet, L.; Stiefel, F.J. *J. Med. Chem.*, 1970, 13, 60). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3,84 (t, J=5,8 Hz, 2 H), 3,74 (t, J=5,8 Hz, 2 H), 1,85 (quinteto, J= 5,8 Hz, 2 H).



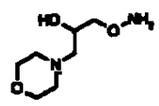
PREPARACIÓN 55

O-(2,2-Dimetil-[1,3]dioxolan-4-iletil)-hidroxilamina

A una suspensión que se agita vigorosamente de 1,2,4-butanotriol (5,8 g, 54,6 mmol) en diclorometano (20 ml) se agregó 2,2-dimetoxipropano (6,8 ml, 54,6 mmol) y ácido p-toluensulfónico catalítico. Después de 5 minutos, la solución se hizo homogénea y se la dejó agitar durante 30 minutos adicionales. La mezcla de la reacción se concentró luego en vacío para dar (2,2-dimetil-[1,3]dioxolan-4-il)-etanol (7,72 g, 96,7%). A una solución en agitación de (2,2-dimetil-[1,3]dioxolan-4-il)-etanol (6,95 g, 47,5 mmol), trifenilfosfina (12,5 g, 47,5 mmol) y N-hidroxiftalimida en tetrahidrofurano recién destilado (200 ml) a 0°C se agregó lentamente (durante 20 minutos) dietilazodicarboxilato. La solución rojo oscuro se dejó agitar durante 2 horas a 0°C y luego se la dejó calentar a temperatura ambiente mientras se agitaba durante 17 horas. La solución amarilla se concentró en vacío y se disolvió en cloroformo (100 ml). Los sólidos se filtraron y el filtrado se concentró. Esta filtración se repitió dos veces. El aceite amarillo restante se purificó sobre gel de sílice eluyendo con hexanos-acetato de etilo (4:1) para dar 2-[2-(2,2-dimetil-[1,3]dioxolan-4-il)-etoxi]-isoindol-1,3-diona (8,1 g, 58,7%). A una solución en agitación

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de 2-[2-(2,2-dimetil-[1,3]dioxolan-4-il)-etoxi]-isoindol-1,3-diona (0,86 g, 2,95 mmol) en diclorometano (10 ml) a 0°C se agregó metilhidrazina (0,16 ml, 2,95 mmol). La solución resultante se dejó calentar a temperatura ambiente y se agitó durante 3 días. La suspensión resultante se diluyó con dietil éter (20 ml) y se filtró. El filtrado se concentró en vacío para dar O-(2,2-dimetil-[1,3]dioxolan-4-iletil)-hidroxilamina (0,36 g, 75,3%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 4,18 (quint, 1H, J=5,9), 4,07 (dd, 1H, J=5,9, 7,8), 3,86 (t, 2H, J=6,2), 3,56 (t, 1H, J=7,6), 1,89 (m, 2H), 1,36 (s, 3H), 1,20 (s, 3H); MS(APCI+)=162.



PREPARACIÓN 56

1-Aminooxi-3-morfolin-4-il-propan-2-ol

Paso A: Síntesis de 2-(2-hidroxi-3-morfolin-4-il-propoxi)-isoindol-1,3-diona: Trietilamina (15,0 ml, 108 mmol) se agregó a una solución de N-hidroxilftalimida (17,1 g, 105 mmol) y 4-oxiranilmetil-morfolina (14,3 g, 100 mmol) en dimetilformamida anhidra (200 ml). La mezcla de la reacción de color rojo profundo se calentó a 85°C durante 18 h. Después de la remoción del solvente en vacío, el residuo se diluyó con acetato de etilo (200 ml) y se lavó con agua (3 x 100 ml) y

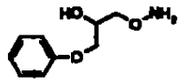
solución salina (2 x 75 ml). Los orgánicos se secaron sobre sulfato de magnesio anhidro y se concentraron en vacío. El residuo se cromatografió sobre gel de sílice (cloroformo-metanol, 19:1) para dar 2-(2-hidroxi-3-morfolin-4-il-propoxi)-isoindol-1,3-diona (7,96 g, 25% de rendimiento): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7,84 (m, 2 H), 7,77 (m, 2 H), 4,26 (dd, J=10,8, 3,4 Hz, 1 H), 4,18-4,10 (m, 2 H), 3,72 (m, 4 H), 2,70-2,47 (m, 6 H); MS(APCI+)= 307,2.

Paso B: Síntesis de 1-aminooxi-3-morfolin-4-il-propan-2-ol: Una solución de 2-(2-hidroxi-3-morfolin-4-il-propoxi)-isoindol-1,3-diona (7,96 g, 26,0 mmol) en diclorometano (50 ml) se enfrió a 0°C y se trató con metilhidrazina (1,45 ml, 27,3 mmol). La mezcla de la reacción se agitó durante 5 minutos a 0°C y durante 2 h a temperatura ambiente. Se agregó éter (200 ml), la solución heterogénea se filtró y el precipitado recogido se lavó con éter (30 ml). Las soluciones etéreas se concentraron en vacío, y el residuo se cromatografió sobre gel de sílice. La elución con cloroformo-metanol (4:1) dio 1-aminooxi-3-morfolin-4-il-propan-2-ol (3,21 g, 70% de rendimiento) como un sólido incoloro. La recristalización (éter-diclorometano) dio agujas incoloras: punto de fusión 83°C-85°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5,96 (br s, 2 H), 4,56 (d, J=4,4 Hz, 1 H), 3,81 (m, 1 H), 3,53 (t aparente, J=4,6 Hz, 4 H), 3,50-3,38 (m, 2 H), 2,41-2,30 (m, 4

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H), 2,29-2,17 (m, 2 H). Análisis calculado/hallado para $C_7H_{16}N_2O_3$: C, 47,71/47,54; H, 9,15/9,23; N, 15,90/15,65.

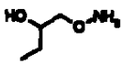
Las preparaciones 57-62 se prepararon mediante el procedimiento general de la Preparación 56.



PREPARACIÓN 57

1-Aminooxi-3-fenoxi-propan-2-ol

Punto de fusión 67,5°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7,27 (m, 2 H), 6,91 (m, 3 H), 6,06 (s, 2 H), 5,07 (d, J=3,7 Hz, 1 H), 4,02 (m, 1 H), 3,92 (dd, J=10,0, 4,3 Hz, 1 H), 3,84 (dd, J= 10,0, 6,1 Hz, 1 H), 3,59 (m, 2 H); MS (APCI+) = 183,0.



PREPARACIÓN 58

1-Aminooxi-butan-2-ol

^{1}H NMR (400 MHz, $CDCl_3$): δ 5,49 (br s, 2 H), 3,78 (m, 1 H), 3,65 (dd, J=11,2, 2,4 Hz, 1 H), 3,54-3,45 (m, 2 H), 1,42 (m, 2 H), 0,91 (t, J=7,6 Hz, 3 H); MS(APCI+)= 105,9.



PREPARACIÓN 59

1-Aminooxi-propan-2-ol

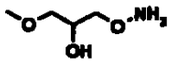
Punto de ebullición 85°C-87°C a 20 mm Hg; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5,96 (br s, 2H), 4,58 (d, J=3,9 Hz, 1 H), 3,80 (m, 1 H), 3,41-3,28 (m, 2 H), 0,99 (d, J=6,4 Hz, 3 H).



PREPARACIÓN 60

1-Aminooxi-2-metil-propan-2-ol

^{1}H NMR (400 MHz, $CDCl_3$): δ 4,84 (br s, 2 H), 3,50 (s, 2 H), 1,15 (s, 6 H)



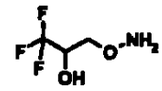
PREPARACIÓN 61

1-Aminooxi-3-metoxi-propan-2-ol

^{1}H NMR (400 MHz, DMSO-d_6): δ 5,95 (2H, br, NH_2), 4,76 (1H, br, -OH), 3,72-3,78 (1H, m), 3,36-3,46 (2H, m), 3,19-3,26 (2H, m), 3,19 (3H, s); MS (APCI+) = 121,9.

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PREPARACIÓN 62

1-Aminooxi-4,4,4-trifluoro-butan-2-ol

^{1}H NMR (400 MHz, $CDCl_3$): δ 5,40 (2H, br, NH_2), 3,60-4,10 (3H, m); MS (APCI+) 145,9.



PREPARACIÓN 63

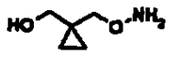
trans-(2-Aminooximetil-ciclopropil)-metanol

Paso A: A una suspensión de hidruro de litio y aluminio (7,6 g, 0,3 mol) en tetrahidrofurano (150 ml) a 0°C se agregó dietil trans-1,2-ciclopropandicarboxilato (18,6 g, 0,1 mol) gota a gota durante un período de 15 minutos. La mezcla de la reacción resultante se removió del baño de enfriamiento y se calentó a reflujo durante 20 h. La mezcla de la reacción se enfrió a 0°C y se enfrió con precaución con agua (7,7 ml), 10% de hidróxido de sodio acuoso (7,7 ml) y agua (23 ml). Los sólidos resultantes se filtraron y el filtrado se secó sobre sulfato de sodio y se concentró bajo presión reducida. El aceite residual se destiló bajo presión reducida para dar trans-2-hidroximetil-ciclopropil)-metanol (7,5 g, 73% de

rendimiento) como un líquido incoloro: punto de ebullición 142°C-144°C a 20 mm Hg.

Paso B: Una solución de trans 2-hidroximetil-ciclopropil)-metanol (7,5 g, 73 mmol), trifenilfosfina (19,3 g, 73 mmol), N-hidroxiftalimida (73 mmol) en tetrahidrofurano anhidro (200 ml) se enfrió a 0°C y se trató con dietil azodicarboxilato. Se dejó calentar la mezcla resultante naturalmente a la temperatura ambiente y se agito toda la noche. La mezcla de la reacción se concentró a 1/8 del volumen y se filtró. El precipitado filtrado se lavó con éter y los lavados combinados y el filtrado se concentraron en vacío. El producto crudo se disolvió en diclorometano. Se agregó metilhidrazina (73 mmol) y la mezcla de la reacción se agitó toda la noche a temperatura ambiente. El precipitado resultante se removió mediante filtración. La concentración del filtrado dio un precipitado adicional que también se removió mediante filtración. El filtrado final se concentró y se destiló bajo presión reducida para dar *trans*-(2-aminooximetil-ciclopropil)-metanol (3,84 g, 45% de rendimiento) como un aceite incoloro: punto de ebullición 183°C a 20 mm Hg; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3,80 (br, NH_2), 3,50-3,70 (2H, m), 3,30-3,42 (2H, m), 0,95-1,15 (2H, m); MS (APCI+) 117,9.

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PREPARACIÓN 64

(1-Aminooximetil-ciclopropil)-metanol

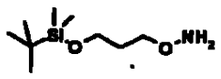
Paso A: Se agregó dietil 1,1-ciclopropanodicarboxilato (25 g, 0,13 mol) gota a gota durante 1 h a una suspensión en agitación de hidruro de litio y aluminio en tetrahidrofurano (150 ml) a 0°C. Después de que se completó el agregado, la mezcla de la reacción se calentó a reflujo durante 18 h adicionales. La mezcla se enfrió a 0°C y se la trató en secuencia con agua (10 g), luego 10% de hidróxido de sodio acuoso (10 g) y agua (30 g). La mezcla se filtró y el filtrado se secó sobre carbonato de potasio y se concentró bajo presión reducida. La destilación proporcionó (1-hidroximetil-ciclopropil)-metanol (8,8 g, 66% de rendimiento) como un aceite viscoso incoloro: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3,57 (4H, s), 3,26 (2H, s), 0,48 (4H, s).

Paso B: (1-Hidroximetil-ciclopropil)-metanol (4,08 g, 0,04 mol), N-hidroxiftalimida (6,53 g, 0,04 mol) y trifenilfosfina (10,50 g, 0,04 mol) se combinaron en tetrahidrofurano anhidro (100 ml) y se agitaron a 0°C durante 1,5 hora. Se agregó dietil azodicarboxilato (6,97 g, 0,04 mol) a 0°C y la mezcla de la reacción se agitó a temperatura ambiente toda la noche. La concentración repetida de la mezcla de la reacción desde cloroformo y la filtración del precipitado resultante (óxido

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de trifenilfosfina) dio el producto crudo que se purificó más por cromatografía de gel de sílice. La elución con hexano/acetato de etilo (3:2) proporcionó 2-(1-hidroximetil-ciclopropilmetoxi)-isoindol-1,3-diona (5,63 g, 57% de rendimiento) como un sólido blanco: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7,82-7,85 (2H, m), 7,74-7,78 (2H, m), 4,19 (2H, s), 3,72 (2H, s), 0,63 (4H, s).

Paso C: A una solución en agitación de 2-(1-hidroximetil-ciclopropilmetoxi)-isoindol-1,3-diona (5,63 g, 22,8 mmol) en diclorometano (60 ml) a 0°C se agregó metilhidrazina (1,1 g, 23,8). La mezcla de la reacción se agitó a temperatura ambiente toda la noche, se filtró y se concentró bajo presión reducida. La destilación dio 1-aminooximetil-ciclopropil-metanol (2,9 g, 71% de rendimiento) como un aceite incoloro: punto de ebullición 140°C a 20 mm Hg; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4,00 (br s, NH_2), 3,61 (2H, s), 3,43 (2H, s), 0,49 (4H, s); MS (APCI+) 117,9.



PREPARACIÓN 65

O-[3-(terc-Butil-dimetil-silaniloxi)-propil]-hidroxilamina

Paso A: Se agregó diisopropiletilamina (43 ml, 246 mmol) a una solución en agitación de N-hidroxiftalimida (20,6 g, 123 mmol)

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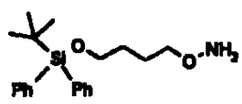
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en dimetilformamida (95 ml). Después de 5 minutos, se agregó 3-bromopropanol (11,5 ml, 127 mmol) y la mezcla de la reacción se celentó a 80°C durante 18 h. La solución enfriada se diluyó con acetato de etilo (700 ml) y se lavó con agua (4 x 500 ml) y solución salina saturada (2 x 500 ml), se secó sobre sulfato de sodio y se concentró en un aceite que se solidificó en reposo para dar 2-(3-hidroxi-propoxi)-isoindol-1,3-diona (17,5 g, 65% de rendimiento) como un aceite de color tostado: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7,81 (m, 2H), 7,74 (m, 2H), 4,36 (t, 2H, J=5,6 Hz), 3,92 (t, 2H; J=5,9 Hz), 1,98 (quinteto, 2H, J=5,9 Hz).

Paso B: A una solución de 2-(3-hidroxi-propoxi)-isoindol-1,3-diona (17,5 g, 79,1 mmol), e imidazol (5,92 g, 86,1 mmol) en diclorometano (200 ml) se agregó cloruro de terc-butildimetilsililo (13,2 g, 86,1 mmol). Después de 30 minutos, la reacción se transfirió a un embudo separador y se agitó con ácido clorhídrico acuoso diluido (400 ml). La capa orgánica se lavó con bicarbonato de sodio acuoso saturado, se secó sobre sulfato de magnesio y se concentró en vacío para dar 2-[3-(terc-butil-dimetilsilaniloxi)-propoxi]-isoindol-1,3-diona (26,3 g, 99% de rendimiento) como un líquido viscoso: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7,76 (m, 2H), 7,67 (m, 2H), 4,25 (t, 2H, J=5,9 Hz), 3,77 (t, 2H, J=6,0 Hz), 1,91 (quinteto, 2H, J=6,1 Hz) 0,82 (s, 9H), 0,00 (s, 6H).

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Paso C: Una solución de 2-[3-(terc-butil-dimetil-silaniloxi)-propoxi]-isoindol-1,3-diona (26,3 g, 78,3 mmol) en diclorometano (120 ml) se enfrió a 0°C y se la trató con metilhidrazina (16,1 g, 78,3 mmol). La mezcla de la reacción se agitó durante 30 minutos a 0°C y se filtró. El filtrado se concentró bajo presión reducida, se disolvió nuevamente en éter y se refrigeró (a 4°C) toda la noche. El material cristalino resultante se removió por filtración y el filtrado se concentró bajo presión reducida para dar O-[3-(terc-butil-dimetil-silaniloxi)-propil]-hidroxilamina (15,95 g, 99% de rendimiento) como un aceite incoloro: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4,69 (br s, 2 H), 3,74 (t, J=6,3 Hz, 2H), 3,67 (t, J=6,3 Hz, 2 H), 1,78 (quinteto, J=6,3 Hz, 2 H), 0,88 (s, 9 H), 0,00 (s, 6 H); MS (APCI+) 206,1. Análisis calculado/hallado para $C_9H_{23}NO_2Si$: C, 52,64/52,22; H, 11,29/10,94; N, 6,82/6,46.



PREPARACIÓN 66

O-[4-(terc-Butil-difenil-silaniloxi)-butil]-hidroxilamina

Paso A: A una solución de 1,4-butanodiol (5 g, 55 mol) en diclorometano (10 ml) que contiene diisopropiletilamina (10 ml) se agregó terc-butilclorodifenilsilano (5 ml, 18 mmol) gota a gota bajo una atmósfera de N_2 a 18°C durante 2 h. La

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solución resultante se agitó a temperatura ambiente durante 4 horas y se concentró bajo presión reducida. La purificación mediante cromatografía de columna con hexano/acetato de etilo (1/1) dio 4-(terc-butil-difenil-silaniloxi)-butan-1-ol (10,2 g, 85% de rendimiento) como un aceite de incoloro: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7,62-7,71 (4H, m), 7,32-7,43 (6H, m), 3,63-3,69 (4H, m), 1,83 (1H, br s), 1,59-1,71 (4H, m), 1,03 (9H, s).

Paso B: 4-(terc-Butil-difenil-silaniloxi)-butan-1-ol (10,0 g, 30,5 mmol), trifenilfosfina (8,0 g, 30 mmol) y N-hidroxiftalimida (4,97 g, 30,5 mmol) se combinaron en tetrahidrofurano anhidro (200 ml) a 0°C y la solución resultante se agitó a 0°C durante 1 hora. Se agregó dietil azodicarboxilato (5,31 g, 30,5 mmol) a 0°C, y la mezcla de la reacción se dejó calentar gradualmente a temperatura ambiente y se agitó toda la noche. La mezcla de la reacción se concentró bajo presión reducida y el residuo se disolvió en cloroformo. Sobrevino la precipitación y el sólido blanco se removió mediante filtración. El filtrado se concentró y se purificó con cromatografía de columna (hexano/acetato de etilo) (3/1)) para dar 2-[4-(terc-butil-difenil-silaniloxi)-butoxi]-isoindol-1,3-diona (11,06 g, 7% de rendimiento) como cristales incoloros. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7,84 (4H, s), 7,59 (4H, dd, J=7,6, 1,0 Hz), 7,39-7,43 (6H, m), 4,13 (2H, t,

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02

J=6,4 Hz), 3,68 (2H, t, J=5,8 Hz), 1,67-1,78 (4H, m), 0,95 (9H, s).

Paso C: Una solución de 2-[4-(terc-butil-difenil-silaniloxi)-butoxi]-isoindol-1,3-diona (11,1 g, 23,4 mmol) en diclorometano (100 ml) se trató con metilhidrazina. La mezcla de la reacción se agitó durante toda la noche y se filtró. El filtrado se concentró y se purificó por cromatografía de columna [hexano/acetato de etilo (3,5/1)] para dar O-[3-(terc-butil-difenil-silaniloxi)-butil]-hidroxilamina (7,2 g, 90% de rendimiento) como un aceite incoloro: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7,62-7,66 (4H, m), 7,33-7,42 (6H, m), 3,64-3,68 (4H), 1,54-1,70 (4H, m), 1,02 (9H, s); MS (APCI+) 344,2.



PREPARACIÓN 67

2-Aminooxi-2-metil-propan-1-ol

Paso A: A una solución en agitación de t-butil-N-hidroxicarbamato (2,38 g, 17,87 mmol) en etanol absoluto (50 ml) se agregó hidróxido de potasio (1,2 g, 21,45 mmol) y etil-2-bromoisobutirato (3,15 ml, 21,45 mmol). La mezcla de la reacción se calentó a reflujo durante 17 horas. Los sólidos se filtraron y el filtrado se concentró. El residuo logrado se repartió entre dietil éter y agua. Las capas acuosas se extrajeron con éter. Las capas orgánicas se recogieron y se

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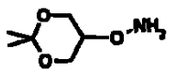
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secaron sobre Na_2SO_4, se filtraron y se concentraron en vacío, dando etil éster del ácido 2-Boc-aminooxi-2-metil-propiónico como un aceite claro (4,2 g, 95%). ^1H NMR (400 MHz, $CDCl_3$): δ 7,34 (bs, 1H), 4,16 (q, 2H, J=13,9, 6,6), 1,45 (s, 6H), 1,42 (s, 9H), 1,16 (t, 3H, J=7,1); MS (APCI-) 246,0.

Paso B: Etil éster del ácido 2-Boc-aminooxi-2-metil-propiónico (2,54 g, 10,27 mmol) se disolvió en THF recién destilado (100 ml), se enfrió a 0°C y se cargó con 2,0 M de solución de borohidruro de litio (10,3 ml, 20,54 mmol) en THF. El baño de hielo se removió y la reacción se calentó a reflujo. Después de 17 horas, la reacción se enfrió a 0°C y se enfrió con metanol y se concentró en vacío. El residuo logrado se repartió entre acetato de etilo y solución de hidróxido de sodio. Las capas orgánicas se lavaron dos vëces con 1 M de solución hidróxido de sodio, dos veces con solución de cloruro de sodio saturado, se recogieron y se secaron sobre Na_2SO_4, se filtraron y se concentraron en vacío, dando 2-Boc-aminooxi-2-metil-propan-1-ol (1,50 g, 71%) como un sólido blanco. ^1H NMR (400 MHz, $CDCl_3$): δ 6,84 (bs, 1H), 3,37 (s, 2H), 1,45 (s, 9H), 1,18 (s, 6H); MS ($APCI^-$) 204,0.

Paso C: 2-Boc-aminooxi-2-metil-propan-1-ol (0,21 g, 1,02 mmol) se disolvió en metanol (5 ml) y se cargó con gas de cloruro de hidrógeno anhidro durante 1 minuto. Después de agitar durante 1 hora, la mezcla de la reacción se concentró en vacío y al

residuo resultante se agregó dimetil éter, dando sólidos blancos. Los sólidos se lavaron varias veces con dietiléter y se secaron en vacío para dar 2-aminooxi-2-metil-propan-1-ol como la sal de cloruro de hidrógeno (0,091 g, 63%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3,61 (s, 2H), 1,16 (s, 2H); MS (APCI+) 105,9.



PREPARACIÓN 68

O-(2,2-Dimetil-[1,3]dioxan-5-il)-hidroxilamina

Paso A: El 2,2-dimetil-[1,3]dioxan-5-ol se preparó como se desribió previamente (Forbes, D.C. et al; *Síntesis*, 1998, 6, 879-882). ^{1}H NMR (400 MHz, DMSO-d_6): δ 4,91 (d, 1H, J=5,1), 3,70-3,75 (m, 2H), 3,41-3,46 (m, 3H), 1,30 (s, 3H), 1,24 (s, 3H); MS (APCI+) 132,9.

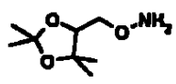
Paso B: A una solución en agitación de 2,2-dimetil-[1,3]dioxan-5-ol (1,50 g, 11,35. mmol), N-hidroxiftalimida (1,85 g, 11,35 mmol) y trifenilfosfina (2,98 g, 11,35 mmol) en tetrahidrofurano anhidro (30 ml) a 0°C se agregó dietil azodicarboxilato (2,3 ml, 14,74 mmol). La solución resultante se dejó calentar a temperatura ambiente. Después de agitar durante 3 horas, la mezcla se concentró en vacío y se cargó con cloroformo dando sólidos blancos. Los sólidos se filtraron

y el filtrado se recogió y concentró. El residuo se purificó mediante cromatografía de columna de sílice (4:1 hexanos/acetato de etilo) dando 2-(2,2-dimetil-[1,3]dioxan-5-iloxi)-isoindol-1,3-diona como cristales claros (1,74 g, 55% en 2 pasos): ^{1}H NMR (400 MHz, DMSO-d_6): δ 7,83 (s, 4H), 4,11-4,12 (m, 1H), 4,04-4,09 (m, 2H), 3,92-3,96 (m, 2H), 1,32 (s, 3H), 1,25 (s, 3H); MS (APCI+) 278,0.

Paso C: A una solución en agitación de 2-(2,2-dimetil-[1,3]dioxan-5-iloxi)-isoindol-1,3-diona (1,72 g, 6,20 mmol) en diclorometano (15 ml) a 0°C bajo nitrógeno se agregó metilhidrazina (0,36 ml, 6,82 mmol) y se dejó calentar a temperatura ambiente. Después de agitar durante dos horas la mezcla de la reacción se concentró en vacío y se cargó con dietil éter. Los sólidos se filtraron y el filtrado se recogió y se concentró para dar O-(2,2-dimetil-[1,3]dioxan-1-il)-hidroxilamina como un aceite amarillo (0,97 g, 100%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 5,98 (bs, 2H), 3,84-3,87 (m, 2H), 3,66-3,68 (m, 2H), 3,30-3,35 (m, 1H), 1,29 (s, 3H), 1,22 (s, 3H); MS (APCI+) 147,9.

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PREPARACIÓN 69

O-(2,2,5,5-Tetrametil-[1,3]dioxolan-4-ilmetil)-hidroxilamina

Paso A: A una solución en agitación de N-hidroxiftalimida (Aldrich, 1,63 g, 10,0 mmol) en etano anhidro (50 ml) se agregó 1-bromo-3-metil-but-2-eno (Aldrich, 1,4 ml, 12,0 mmol) e hidróxido de potasio (0,67 g, 12,0 mmol). Después de dejar que la reacción se agitara a 50°C durante 4 horas, se la concentró en vacío y luego se la disolvió en acetato de etilo y se la dividió en agua. La capa orgánica se lavó dos veces con agua, dos veces con solución de cloruro de sodio saturado, se recogió y se secó sobre Na_2SO_4, se filtró y se concentró en vacío, dando un sólido blanco. El sólido recogido se purificó mediante columna de sílice en 10% de metanol en diclorometano para dar 2-(3-metil-but-2-eniloxi)-isoindol-1,3-diona (0,53 g, 23%): ^{1}H NMR (400 MHz, DMSO-d_6): δ 7,81 (s, 4H), 5,38 (t, 1H, J=1,5), 4,57 (d, 2H, J=7,6), 1,67 (s, 3H), 1,62 (s, 3H); MS (APCI+) 232,0.

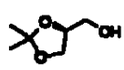
Paso B: 2-(3-Metil-but-2-eniloxi)-isoindol-1,3-diona se disolvió en una solución de t-butanol/THF/H_2O (10ml/3ml/1 ml) y se cargó con N-óxido de N-metilmorfolina (0,085 g, 0,73 mmol) y una cantidad catalítica de osmato de potasio dihidratado. Después de agitar durante 17 horas la reacción se diluyó con una solución saturada de metabisulfato de sodio y se

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particionó con acetato de etilo. La capa orgánica se lavó dos veces con una solución saturada de metabisulfato de sodio, dos veces con una solución saturada de cloruro de sodio, se recogió y se secó sobre Na_2SO_4, se filtró y se concentró en vacío dando 2-(2,3-dihidroxi-3-metil-butoxi)-isoindol-1,3-diona como un aceite claro, que se cargó con diclorometano (10 ml) 2,2-dimetoxipropano (0,12 ml, 0,75 mmol) y una cantidad catalítica de ácido p-toluenosulfónico. Después de agitar durante 17 horas, la reacción se concentró en vacío, y se repartió entre acetato de etilo y agua. La capa orgánica se lavó dos veces con agua, una vez con una solución saturada de cloruro de sodio, se recogió y se secó sobre Na_2SO_4, se filtró y se concentró en vacío, dando 2-(2,2,5,5-tetrametil-[1,3]dioxolan-4-ilmetoxi)-isoindol-1,3-diona como un sólido marrón claro (0m158 g, 7,11%): ^1H NMR (400 MHz, DMSO-d_6): δ 7,82 (s, 4H), 4,12-4,26 (m, 2H), 4,04-4,07 (m, 1H), 1,22 (s, 9H), 1,17 (s, 3H), 0,97 (s, 3H).

Paso C: 2-(2,2,5,5-Tetrametil-[1,3]dioxolan-4-ilmetoxi)-isoindol-1,3-diona (0,158 g, 0,52 mmol) se disolvió en diclorometano (3 ml), se enfrió a 0°C, y se cargó con metilhidrazina (30 µl, 0,57 mmol). El baño de hielo se removió y la reacción se dejó agitar a temperatura ambiente durante 1 hora. La mezcla de la reacción se diluyó con dietil éter y los

sólidos se filtraron y el filtrado se concentró en vacío para dar O-(2,2,5,5-tetrametil-[1,3]dioxolan-4-ilmetil)-hidroxilamina como un aceite amarillo (0,042 g, 46%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 6,06 (bs, 2H), 3,84-3,87 (m, 1H), 3,50-3,59 (m, 2H), 1,26 (s, 3H), 1,19 (s, 3H), 0,94 (s, 3H); MS (APCI+) 176,9.



PREPARACIÓN 70

(S)-(+)-(2,2-Dimetil-[1,3]dioxolan-4-il)-metanol

Paso A: A una suspensión de D-Manitol (1,82 g, 10,0 mmol) en tetrahidrofurano (21 ml) y dimetilformamida (9 ml) se agregó ácido p-toluenosulfónico monohidratado (0,02 g, 0,1 mmol), a temperatura ambiente, seguido por 2,2-dimetoxipropano (2,8 ml, 0,023 mol). La mezcla de la reacción se agitó durante 18 h a temperatura ambiente, luego se agregó 2,2-dimetoxipropano adicional (0,3 ml, 2,4 mmol). La suspensión se calentó a 40°C-45°C y se agitó durante 2 horas. Se agregó bicarbonato de sodio (1,8 g, 0,016 mol) para neutralizar el ácido y la mezcla se agitó durante 30 minutos. El exceso de Na_2CO_3 se filtró y se lavó con tetrahidrofurano (5 ml). El filtrado se concentró. Al aceite amarillo claro restante se agregó tolueno (15 ml) y la mezcla se agitó a 3°C-5°C hasta que se formó un sólido gelatinoso amarillo claro. El sólido se filtró y se lavó con

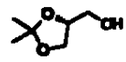
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hexano (2 x 5 ml). El producto se secó en vacío en un horno de vacío durante 18 h para dar 1,2:5,6-Di-O-isopropiliden-D-manitol (1,24 g, 47,3%) como un sólido blancuzco, punto de fusión 110°C-113°C.

Paso B: A una solución de 1,2:5,6-di-O-isopropiliden-D-manitol (50 g, 0,191 mol) en agua (700 ml), se agregó bicarbonato de sodio sólido (20 g). La solución resultante se agitó hasta que se disolvió todo el sólido, y luego se enfrió en un baño de hielo-agua. Se agregó lentamente peryodato de sodio sólido (81,5 g, 0,381 mol) a la solución porción por porción. Se observó la emisión de gas. La mezcla blanca se agitó a temperatura ambiente durante 2 horas. Se agregó cloruro de sodio sólido (30 g), y la mezcla se agitó durante 15 minutos. El sólido blanco se filtró. El filtrado se enfrió en un baño de hielo-agua. Se agregó lentamente borohidruro de sodio sólido. Se emitieron burbujas de gas. La mezcla se calentó a temperatura ambiente, y se agitó toda la noche. La mezcla turbia tornó a una solución clara. La solución acuosa se extrajo con diclorometano (3 X). La solución orgánica se lavó con solución salina, y secó sobre sulfato de magnesio. El solvente se removió en vacío para dar (S)-(+)-(2,2-dimetil-[1,3]dioxolan-4-il)-metanol como un aceite incoloro, que se secó bajo alto vacío a temperatura ambiente toda la noche, 34,82 g (60%); MS (APCI+) = 133 ($M^+ + 1$).

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PREPARACIÓN 71

(R)-(+)-(2,2-Dimetil-[1,3]dioxolan-4-il)-metanol

Paso A: A una solución de ácido L-ascórbico (83,9 g, 0,477 mol) en agua (600 ml) se agregó Pd/C (10%, 8,3 g). La mezcla fue sometida a hidrogenación en un hidrogenador Parr a 48 psi, a 18°C durante 62 horas. La mezcla de la reacción se filtró y el filtrado se concentró en vacío para dar γ-lactona L-gulónica (81,0 g, 96%) como un sólido blancuzco, después de agitar a 50°C en un horno de vacío durante 18 horas: punto de fusión 182°C-184°C.

Paso B: γ-Lactona L-gulónica (25,0 g, 140,3 mmol) se disolvió en una mezcla de tetrahidrofurano (140 ml) y dimetilformamida (200 ml). Se agregó ácido p-toluenosulfónico monohidratado (2,67 g, 14,0 mmol) y la mezcla de la reacción se enfrió a 0°C-5°C en un baño de hielo-agua. Se agregó 2,2-dimetoxipropano (22,4 ml, 182,4 mmol) gota a gota y la mezcla de la reacción se agitó a temperatura ambiente durante 18 horas. La mezcla se neutralizó con carbonato de sodio sólido (24,0 g) y se agitó durante 1 hora. El sólido se filtró y y se lavó con tetrahidrofurano. El THF se removió bajo vacío, y la DMF mediante destilación con alto vacío. El sólido naranja

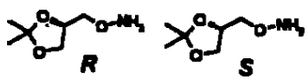
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resultante se trituró con tolueno (300 ml), se filtró y se lavó con tolueno (20 ml), y se secó en un horno de vacío a 40°C durante 3 días, para dar γ-lactona del ácido 5,6-isopropiliden-L-gulónico (28,9 g, 94%) como un sólido naranja pálido. punto de fusión 155°C-158°C; MS (APCI+)=219,0 (M^+ + 1).

Paso C: A una en agitación de 5,6-O-isopropiliden-L-gulono-1,4-lactona (15,16 g, 69,5 mmol) en agua (0,3 l), se agregó peryodato de sodio sólido en porciones pequeñas a 3°C-5°C. El pH de la mezcla se ajustó a 5,5 con 1N hidróxido de sodio acuoso. La suspensión se agitó durante 2 horas a temperatura ambiente y luego se saturó con cloruro de sodio (20,0 g) y se filtró. Al filtrado, a 3°C-5°C, se agregó borohidruro de sodio (10,5 g, 0,278 mol) en porciones pequeñas. La mezcla de la reacción se agitó durante 18 h a temperatura ambiente durante. Se agregó acetona (100 ml) para destruir el exceso de borohidruro de sodio, y la agitación se continuó durante 30 minutos. La acetona se removió bajo presión reducida y el residuo acuoso se extrajo con diclorometano (3 x 300 ml) y EtOAc (3 x 300 ml). Las capas orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron y se evaporaron para dar (R)-(+)-(2,2-dimetil-[1,3]dioxolan-4-il)-metanol (5,07 g, 55,7%) como un líquido claro incoloro: MS (APCI+) = 132,9 (M^++1).

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PREPARACIÓN 72

Preparación de (R)-O-(2,2-dimetil-[1,3]dioxolan-4-ilmetil)-hidroxilamina y (S)-O-(2,2-dimetil-[1,3]dioxolan-4-ilmetil)-hidroxilamina

(R)-O-(2,2-dimetil-[1,3]dioxolan-4-ilmetil)-hidroxilamina y (S)-O-(2,2-dimetil-[1,3]dioxolan-4-ilmetil)-hidroxilamina se prepararon desde (S)-(+)-(2,2-dimetil-[1,3]dioxolan-4-il)-metanol y (R)-(-)-(2,2-dimetil-[1,3]dioxolan-4-il)-metanol, respectivamente mediante el siguiente procedimiento:

Paso A: Un matraz con base circular de 3 L equipado con un agitador mecánico y un embudo adicional se cargó con N-hidroxiftalimida (68,0 g, 0,416 mol) y tetrahidrofurano (1,2 l) bajo una atmósfera de nitrógeno. A esta solución se agregó trifenilfosfina (109,2 g, 0,416 mol) y (R)- o (S)-(2,2-dimetil-[1,3]dioxolan-4-il)-metanol (55,0 g, 0,416 mol). La mezcla se enfrió a 3°C-5°C y se agregó dietil azodicarboxilato (85,2 ml, 0,541 mol) gota a gota, mientras se mantenía la temperatura interior por debajo de 15°C. La mezcla de la reacción se calentó a temperatura ambiente, y se agitó durante 18 horas. El tetrahidrofurano se evaporó bajo presión reducida. Al sólido naranja restante se agregó diclorometano (0,5 L) y la mezcla se agitó durante 1 h. El sólido blanco

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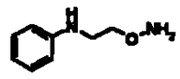
(Ph_3O) se filtró y se lavó con diclorometano (0,1 L). El solvente se removió y se agregó etanol (0,5 L) al sólido resultante. La mezcla se agitó durante 2 h a 3°C-5°C. El sólido blanco se filtró, se lavó con una cantidad pequeña de EtOH frío y se secó en vacío a 40°C para dar (S)- o (R)-2-(2,2-dimetil-[1,3]dioxolan-4-ilmetoxi)-isoindol-1,3-diona (112,5 g, 97%) como un sólido blanco: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1,33 (s, 3H), 1,99 (s, 3H), 3,69 (m, 1H), 4,15 (m, 2H), 4,30 (m, 1H), 4,48 (m, 1H), 7,59 (m, 2H), 7,84 (m, 2H); MS (APCI+) 278 (M^+ + 1).

Paso B: A una solución en agitación de (S)- o (R)-2-(2,2-dimetil-[1,3]dioxolan-4-ilmetoxi)-isoindol-1,3-diona (74,9 g, 0,27 mol) en diclorometano (480 ml) a 3°C-5°C se agregó metilhidrazina (15,8 ml, 0,29 mol) gota a gota. El color de la suspensión tornó de amarillo a blanco. El baño de enfriamiento se removió y la mezcla se agitó durante 2 horas a temperatura ambiente. La suspensión resultante se concentró sobre un evaporador giratorio. A un sólido blanco se agregó éter (0,5 L) y la mezcla resultante se agitó durante 1,5 h a temperatura ambiente. El precipitado blanco se filtró y se lavó con éter (0,2 L). El filtrado se concentró en un evaporador giratorio para dar (S)- o (R)-O-(2,2-dimetil-[1,3]dioxolan-4-ilmetil)-hidroxilamina (39,0 g, 98,3%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1,35

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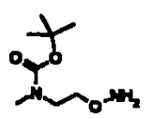
(s, 3H), 1,42 (s, 3H), 3,73 (m, 3H), 4,05 (m, 1H), 4,33 (m, 1H), 5,39 (m, 2H); MS (APCI+) 148,1 (M^+ + 1).



PREPARACIÓN 73

Clorhidrato de O-(2-Fenilamino-etil)-hidroxilamina

O-(2-Fenilamino-etil)-hidroxilamina se preparó desde 2-fenilamino-etanol mediante el procedimiento general de la Preparación 48 y se aisló como la sal de clorhidrato mediante la precipitación desde cloruro de hidrógeno etéreo. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7,12 (t, J=7,7 Hz, 2H), 6,72-6,61 (m, 3H), 4,16 (t, J=5,4 Hz, 2 H), 3,35 (t, J=5,4 Hz, 2 H); MS (APCI+) 153,1 (M^+ + 1).



PREPARACIÓN 74

terc-Butil éster del ácido (2-Aminooxi-etil)-metil-carbámico

Paso A: El terc-Butil éster del ácido (2-hidroxi-etil)-metil-carbámico se preparó como se describió previamente en: Mewshaw, R.E., et al, *J.Med.Chem.* 1999, 42, 2007.

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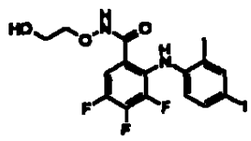
Paso B: Se agregó dietilazodicarboxilato gota a gota durante 45 minutos a una solución en agitación de terc-Butil éster del ácido (2-hidroxi-etil)-metil-carbámico (7,10 g, 40,5 mmol), N-hidroxiftalimida (7,17 g, 44,0 mmol) y trifenilfosfina (11,5 g, 43,8 mmol) en tetrahidrofurano (150 ml). La mezcla de la reacción resultante se agitó durante 22 h a temperatura ambiente y se concentró en vacío a un aceite espeso. Se agregó cloroformo (200 ml) y la solución resultante se enfrió efectuar la cristalización de dicarboxilato de dietil 1,2-hidrazina. El precipitado se filtró y el filtrado se concentró y se diluyó más cn hexanos. Se agregó un solo cristal de óxido de trifenilfosfina. Los cristales resultantes de óxido de trifenilfosfina se removieron mediante filtración y el filtrado se concentró en vacío y se sometió a cromatografía sobre gel de sílice para dar terc-butil éster del ácido [2-(1,3-dioxo-1,3-dihidro-isoindol-2-iloxi)-etil]-metil-carbámico (12,8 g, 98% de rendimiento) como un aceite incoloro: ^{1}H NMR (400 MHz, DMSO-d_6): δ 7,86 (bs, 4 H), 8,55 (bs, H), 4,24 (t, J=5,5 Hz, 2 H), 3,50 (br t, J=5,4 Hz, 2 H), 2,92 y 2,98 (br s, 3 H), 1,39 y 1,36 (br s, 9 H).

Paso C: Una solución terc-butil éster del ácido [2-(1,3-dioxo-1,3-dihidro-isoindol-2-iloxi)-etil]-metil-carbámico(4,50 g, 14,0 mmol) en diclorometano (40 ml) se trató con metilhidrazina (0,78 ml, 14,7 mmol) y la mezcla de la reacción

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se agitó durante 6 h a temperatura ambiente. Se agregó dietil éter (80 ml) y la solución heterogénea se dejó en reposo toda la noche. El precipitado se removió mediante filtración y se lavó con éter (80 ml). El filtrado se concentró más y el precipitado resultante y el segundo filtrado se concentró para dar terc-butil éster del ácido (2-aminooxi-etil)-metil-carbámico (2,83 g) como un aceite viscoso: ^{1}H NMR (400 MHz, DMSO-d_6): δ 3,73 (t, J=5,2 Hz, 2 H), 5,45 (br s, NH_2), 3,46 y 3,42 (br s, 2 H), 2,86 (br s, 3 H), 1,25 (br s, 9 H) ; MS (APCI+) 191,1.

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EJEMPLO 1

3,4,5-Trifluoro-N-(2-hidroxi-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

Paso A: A una solución compuesta por ácido 2-(4-yodo-2-metil-fenilamino)-3,4,5-trifluoro-benzoico (3,60 g, 8,84 mmol), O-(2-viniloxietil)hidroxilamina (1,09 g, 10,5 mol) y diisopropiletilamina (2,80 ml, 16,0 mmol) en diclorometano (50 ml) se agregó benzotriazol-1-il-oxi-tris-pirrolidino-fosfonio-hexafluorofosfato (5,26 g, 10,1 mmol). La solución resultante se agitó durante 90 minutos a temperatura ambiente. La mezcla de la reacción se diluyó con éter (100 ml) y se lavó con agua (3 x 50 ml) y solución salina saturada (50 ml). Los orgánicos se secaron sobre sulfato de magnesio anhidro y se concentraron en vacío. El residuo se purificó mediante cromatografía de gel de sílice para dar 2-(4-yodo-2-metil-fenilamino)-3,4,5-trifluoro-N-(2-viniloxietoxi) benzamida (3,17 g, 73%) como una espuma amarilla pálida.

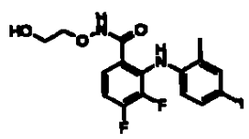
Paso B: Una solución de 2-(4-yodo-2-metil-fenilamino)-3,4,5-trifluoro-N-(2-viniloxietoxi) benzamida (3,00 g, 6,09 mmol) en etanol (80 ml) se trató con 1 M de ácido clorhídrico acuoso (16 ml, 16 mol). La solución resultante se agitó durante 2,5 h

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a temperatura ambiente. Se agregó agua (50 ml) y la suspensión se filtró. Los sólidos se lavaron con etanol-agua (1:1, 150 ml) y se recristalizaron desde metanol-acetona para dar N-(2-hidroxietoxi)-2-(4-yodo-2-metil-fenilamino)-3,4,5-trifluoro-benzamida (2,12 g, 75%): punto de fusión 205°C-207°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,85 (br s, 1 H), 8,13 (s, 1 H), 7,54 (dd, J=8,9, 8,7 Hz, 1 H), 7,47 (d, J=1,0 Hz, 1 H), 7,32 (d, J=8,5 Hz, 1 H), 6,41 (dd, J=8,1 5,0 Hz, 1 H), 4,69 (br s, 1 H), 3,79 (br s, 2 H), 3,52 (br s, 2 H), 2,20 (s, 3 H); MS (APCI+) 467,1; MS (APCI-)= 465,1. Análisis calculado/hallado para $C_{16}H_{14}F_3IN_2O_3$: C, 41,22/41,28; H, 3,03/2,91; N, 6,01/5,79.

Los Ejemplos 2-11 se prepararon mediante el procedimiento general del Ejemplo 1.



EJEMPLO 2

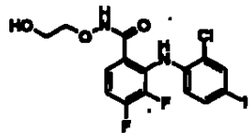
3,4-Difluoro-N-(2-hidroxi-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

Punto de fusión 181°C-183°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,87 (s, 1 H), 8,50 (s, 1 H), 7,49 (s, 1 H), 7,40 (dd, J=7,3, 6,6 Hz, 1 H), 7,35 (dd, J=8,3, 1,7 Hz, 1 H), 7,16 (dt, J=7,3 9,3

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Hz, 1 H), 6,46 (dd, J=8,5, 5,6 Hz, 1 H), 4,70 (br s, 1 H), 3,81 (br s, 2 H), 3,54 (br s, 2 H), 2,21 (s, 3 H); MS (APCI+) 449,1; MS (APCI-)= 447,1. Análisis calculado/hallado para $C_{16}H_{15}F_3IN_2O_3$: C, 42,88/42,94; H, 3,37/3,39; N, 6,25/6,05.



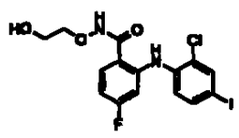
EJEMPLO 3

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-etoxi)-benzamida

Método A: Mediante el procedimiento general del Ejemplo 1: Punto de fusión 173°C-175°C; ^1H NMR (400 MHz, DMSO-d_6): δ 11,93 (br s, 1 H), 8,85 (br s, 1 H), 7,76 (d, J=1,7 Hz, 1 H), 7,48 (dd, J=8,6, 1,7 Hz, 1 H), 7,44 (dd, J=8,5, 6,2 Hz, 1 H), 7,25 (dt, J=8,5, 9,3 Hz, 1 H), 6,58 (dd, J= 8,5, 6,4 Hz, 1 H), 4,70 (br s, 1 H), 3,86 (br s, 2 H), 3,56 (br d, J=3,9 Hz, 2 H); MS (APCI+) 469,0; MS (APCI-)= 467,0. Análisis calculado/hallado para $C_{15}H_{12}ClF_2IN_2O_3$: C, 38,45/38,60; H, 2,58/2,53; N, 5,98/5,91; F, 8,11/8,08; I, 27,08/27,43.

Método B: A una solución de pentafluorofenil éster del ácido 2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-benzoico (10,0 g, 17,4 mmol) en dimetilformamida anhidra (36 ml) se agregó 2-

(aminooxi)-etanol (1,6 g, 20,8 mmol) y N,N-diisopropiletilamina (6,0 ml, 34,8 mmol). La solución resultante se agitó a temperatura ambiente durante 16 h. La mezcla de la reacción se concentró al 20% del volumen luego se diluyó con acetato de etilo (360 ml). La solución resultante se lavó con agua (6 x 60 ml) y solución salina (2 x 60 ml). Los orgánicos se secaron sobre sulfato de magnesio anhidro y se concentraron bajo presión reducida para dar un sólido blanco que se purificó sobre gel de sílice. La elución con acetato de etilo-metanol (9:1) dio 2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-etoxi)-benzamida (7,31 g, 90%) como un sólido blanco. La recristalización desde metanol dio un material analíticamente puro, idéntico en todos los aspectos al material preparado mediante el método A.

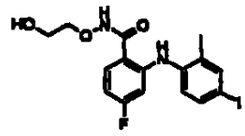


EJEMPLO 4

2-(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-etoxi)-benzamida

^{1}H NMR (400 MHz, DMSO-d_6): δ 11,88 (br s, 1 H), 9,81 (s, 1 H), 7,85 (d, J=2,0 Hz, 1 H), 7,64 (m, 1 H), 7,60 (dd, J=8,5, 1,9 Hz, 1 H), 7,31 (d, J=8,3 Hz, 1 H), 7,00 (dd, J=11,7, 2,5 Hz, 1

H), 6,75 (td, J= 8,5, 2,5 Hz, 1 H), 4,73 (br s, 1 H), 3,90 (t, J=4,6 Hz, 2 H), 3,60 (br t, J=4,2 Hz, 2 H); MS (APCI+) 451,0; MS (APCI-)= 449,0. Análisis calculado/hallado para $C_{15}H_{11}ClF_1IN_2O_3$: C, 39,98/40,07; H, 2,91/2,83; N, 6,22/6,11.



EJEMPLO 5

4-Fluoro-N-(2-hidroxi-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

^{1}H NMR (400 MHz, DMSO-d_6): δ 9,16 (br s, 1 H), 8,67 (s, 1 H), 7,60 (d, J=1,7 Hz, 1 H), 7,51 (dd, J=8,4, 1,7 Hz, 1 H), 7,37 (dd, J=7,8, 6,6 Hz, 1 H), 7,02 (d, J=8,3 Hz, 1 H), 6,59 (dd, J= 12,2, 2,4 Hz, 1 H), 6,41 (m, 1 H), 4,08 (t, J=4,2 Hz, 2 H), 3,80 (t, J=4,2 Hz, 2 H), 2,22 (s, 3H); MS (APCI+) 431,0; MS (APCI-)= 429,0.

EJEMPLO 6

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-hidroxi-etoxi)-benzamida

Rendimiento: 96%; punto de fusión: 183°C-184,5°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8,46 (s, 1 H), 7,73 (d, 1H, J=1,7 Hz), 7,58 (m, 1 H), 7,44 (dd, 1H, J=8,5, 2,0 Hz), 6,54 (dd, 1H, J=8,5,

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5,4 Hz), 4,70 (s ancho, 1 H), 3,84 (m, 2 H), 3,54 (s, 2H); ^{19}F-NMR (376 MHz; DMSO-d_6) δ -137,03 (d, 1F, J=20,2 Hz), -141,04 (s, 1F), -154,73 (s, 1F); MS (APCI+) 486,9 (M-1, 50); MS (APCI-)= 484,9 (100); IR (KBr) 3337 (O-H estiramiento), 1652 (C=O estiramiento), 1502 cm^{-1}. Análisis calculado/hallado para $C_{15}H_{11}ClF_3IN_2O_3$: C, 37,02/37,16; H, 2,28/2,29; N, 5,76/5,49.

EJEMPLO 7

5-Cloro-3,4-difluoro-N-(2-hidroxi-etoxi)-2-(4-yodo-fenilamino)-benzamida

Rendimiento: 21%; punto de fusión: 174°C-176°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,72 (s, 1H), 8,47 (s, 1 H), 7,53 (d, 1H, J=1,7 Hz), AB[7,43 (d, 2H, J=8,3 Hz), 6,63 (d, 2H, J=7,6 Hz)], 4,67 (s, 1 H), 3,74 (s, 2H), 3,49 (s, 2H); ^{19}F-NMR (376 MHz; DMSO-d_6) δ -134,59 (s, 1F), -139,07 (d, 1F, J=17,7 Hz); MS (APCI+) 469,0 (M+1, 100); MS (APCI-)= 467,0 (M-1, 40), 406,9 (100); IR (KBr) 1636 cm^{-1} (C=O estiramiento). Análisis calculado/hallado para $C_{15}H_{12}ClF_2IN_2O_3$: C, 38,45/38,61; H, 2,58/2,43; N, 5,98/5,94.

EJEMPLO 8

4-Fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-etoxi)-benzamida

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Rendimiento: 96%; punto de fusión: 117°C-119°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,83 (s, 1H), 9,62 (s, 1 H), 7,69 (d, 1H, J=10,5 Hz), 7,60 (m, 1H), 7,49 (d, 1H, J=8,6 Hz), 7,27 (m, 1H), 6,84 (d, 1H, J=11,2 Hz), 6,70 (m, 1H), 4,73 (s ancho, 1H), 3,90 (m, 2H), 3,60 (m, 2H); ^{19}F-NMR (376 MHz; DMSO-d_6) δ -106,74 (s, 1F), -124,58 (s, 1F); MS (APCI+) 435,0 (M+1, 100); MS (APCI-)= 433,0 (M-1, 82), 373,0 (100); IR (KBr) 1638 (C=O estiramiento), 1597 cm^{-1}. Análisis calculado/hallado para $C_{15}H_{13}F_2IN_2O_3$: C, 41,49/41,52; H, 3,02/2,97; N, 6,45/6,18.

EJEMPLO 9

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-etoxi)-benzamida

Método A: Mediante el procedimiento general del Ejemplo 32. Rendimiento: 54%; punto de fusión: 155°C-156°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,83 (s, 1H), 8,69 (s, 1 H), 7,56 (dd, 1H, J=11,0, 1,5 Hz), 7,36 (m, 2H), 7,19 (m, 1H), 6,65 (m, 1H), 3,82 (s, 2H), 3,55 (s, 2H); ^{19}F-NMR (376 MHz; DMSO-d_6) δ -128,18 (s, 1F), -144,16 (s, 1F); MS (APCI+) 453,0 (M+1, 100); MS (APCI-)= 451,0 (M-1, 100); IR (KBr) 3349 (O-H estiramiento), 1641 (C=O estiramiento), 1610 cm^{-1}. Análisis calculado/hallado para $C_{15}H_{12}F_3IN_2O_3$: C, 39,84/39,99; H, 2,67/2,81; N, 6,20/6,20.

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EJEMPLO 10

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-etoxi)-benzamida

Rendimiento: 96%; punto de fusión: 180°C-180,5°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,89 (s, 1H), 8,68 (s, 1 H), 7,59 (m, 2H), 7,34 (d, 1H, J=8,8 Hz), 6,72 (m, 1H), 4,70 (s ancho, 1H), 3,82 (m, 2H), 3,55 (s, 2H); ^{19}F-NMR (376 MHz; DMSO-d_6) δ -127,72 (s, 1F), -134,13 (s, 1F), -140,35 (d, 1F, J=27,7 Hz); MS (APCI+) 487,0 (M+1, 100); MS (APCI-)= 484,9 (M-1, 63), 424,9 (100); IR (KBr) 3333 (O-H estiramiento), 1643 (C=O estiramiento), 1609, 1490 cm^{-1}. Análisis calculado/hallado para $C_{15}H_{13}ClF_3IN_2O_3$: C, 37,02/37,30; H, 2,28/2,23; N, 5,76/5,69.

EJEMPLO 11

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-etoxi)-benzamida

Rendimiento: 100%; punto de fusión: 189°C-190°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,89 (s, 1H), 8,70 (s, 1 H), 7,69 (d, 1H, J=6,1 Hz), 7,57 (d, 1H, J=10,7 Hz), 7,34 (d, 1H, J=7,8 Hz), 6,73 (m, 1H), 4,70 (s ancho, 1H), 3,81 (s, 2H), 3,54 (s, 2H); ^{19}F-NMR (376 MHz; DMSO-d_6) δ -126,43 (s, 1F), -127,65 (s, 1F), -140,20 (d, 1F, J=17,7 Hz); MS (APCI+) 533,0 (95), 531,0 (M+1, 100); MS (APCI-)= 531,0 (40), 529,0 (M-1, 42), 470,9 (95), 468,9 (100); IR (KBr) 3341 (O-H estiramiento), 1647 (C=O

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estiramiento), 1606, 1509, 1484 cm^{-1}. Análisis calculado/hallado para $C_{15}H_{11}BrF_3IN_2O_3$: C, 33,93/33,89; H, 2,09/2,02; N, 5,27/5,13.

EJEMPLO 12

4,5-Difluoro-N-(2-hidroxi-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

A una solución de pentafluorofenil éster del ácido 4,5-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzoico (2,96 g, 0,33 mmol) en dimetilformamida a temperatura ambiente se agregó diisopropiletilamina (0,184 ml, 1,1 mmol). Después de agitar la reacción toda la noche, la mezcla de la reacción se concentró a la mitad del volumen. La solución se diluyó con éter (30 ml) luego se lavó con agua (4 x 10 ml) y solución salina (10 ml). La capa de éter se secó sobre sulfato de magnesio y la mezcla resultante se filtró. El solvente del filtrado se removió en vacío para obtener un sólido aceitoso. El sólido aceitoso se purificó mediante cromatografía rápida (35 g de gel de sílice), eluyendo con un gradiente de acetato de etilo en hexanos. El solvente se removió en vacío para obtener un sólido que se secó sobre una bomba de vacío toda la noche. La recristalización desde hexanos-acetona dio 4,5-difluoro-N-(2-hidroxi-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida como un sólido (0,107 g, 45% de rendimiento): punto de fusión: 151,2°C-152,5°C; ^1H NMR (400 MHz, $(CD_3)_2CO$): δ 9,22

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(br. S, 1H), 7,63 (m, 2H), 7,53 (dd, 1H, J=8,3, 1,95 Hz), 7,14 (d, 1H, J=8,3 Hz), 6,41 (m, 1H), 4,03 (t, 2H, J=4,4 Hz), 3,69 (t, 2H, J=4,88 Hz), 2,23 (s, 3H); ^{19}F-NMR (376 MHz; $(CD_3)_2CO$) δ -132,75, -152,61; MS 478,9 m/z (APCI+); 476,9 m/z (APCI-). Análisis calculado para $C_{16}H_{15}F_2IN_2O_3$: C, 42,88; H, 3,39; N, 6,25. Hallado: C, 42,79; H, 3,19; N, 6,02.

Los Ejemplos 13 a 20 se prepararon mediante el procedimiento general del Ejemplo 12.

EJEMPLO 13

5-Bromo-3,4-difluoro-N-(2-hidroxi-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

punto de fusión: 208,2°C-209,6°C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 8,62 (br. S, 1H), 7,79 (dd, 1H, J=7,08, 1,47 Hz), 7,55 (s, 1H), 7,42 (d, 1H, J=8,79 Hz), 6,65 (dd, 1H, J=8,30, 5,86 Hz), 4,02 (t, 2H, J=4,64 Hz), 3,67 (t, 2H, J=4,64 Hz), 2,32 (s, 3H); ^{19}F-NMR (376 MHz; $(CD_3)_2CO$) δ -126,85, -139,3 (d, J=15,16 Hz). Análisis calculado para $C_{16}H_{14}BrF_2IN_2O_3$: C, 36,46; H, 2,68; N, 5,31; F, 7,21; Br, 15,16; I, 24,08. Hallado: C, 36,67; H, 2,62; N, 5,23; F, 7,23; Br, 15,32; I, 23,3.

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EJEMPLO 14

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-etoxi)-benzamida

punto de fusión: 190,2°C-200,2°C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 11,11 (br s, 1H), 8,92 (br. s, 1H), 7,84 (dd, 1H, J=6,84, 2,2 Hz), 7,76 (d, 1H, J=1,95 Hz), 7,54 (dd, 1H, J=8,54, 6,59 Hz), 6,77 (dd, 1H, J=8,54, 6,59 Hz), 4,40 (t, 2H, J=4,39 Hz), 3,69 (t, 2H, J=4,89 Hz). ^{19}F-NMR (376 MHz; $(CD_3)_2CO$) δ -126,16, -137,47 (d, J=17,69 Hz); MS 546,9 m/z, 548,9 m/z (AP+); 544,9 m/z, 546,9 m/z (AP-). Análisis calculado para $C_{15}H_{11}BrClF_2IN_2O_3$: C, 32,91; H, 2,03; N, 5,12; F, 6,94; Br, 14,58; I, 23,18. Hallado: C, 32,94; H, 1,95; N, 5,30; F, 6,87; Br, 14,79; I, 22,91.

EJEMPLO 15

5-Cloro-3,4-difluoro-N-(2-hidroxi-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

punto de fusión: 199,1°C-200,8°C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 8,57 (br. S, 1H), 7,68 (dd, 1H, J=7,32, 2,2 Hz), 7,55 (s, 1H), 7,41 (dd, 1H, J=8,3, 1,71 Hz), 6,64 (dd, 1H, J=8,3, 5,86 Hz), 4,02 (t, 2H, J=4,63 Hz), 3,67 (t, 2H, J=4,88 Hz), 2,32 (s, 3H). ^{19}F-NMR (376 MHz; $(CD_3)_2CO$) δ -134,75, -139,56 (t, J=15,17 Hz); MS 483,0 m/z (AP+); 481,0 m/z (AP-). Análisis calculado para $C_{16}H_{14}ClF_2IN_2O_3$: C, 39,82; H, 2,92; N, 5,8; F, 7,87; Cl,

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7,35; I, 26,29. Hallado: C, 39,91; H, 2,92; N, 6,0; F, 7,91; Cl,7,39; I, 27,06.

EJEMPLO 16

5-Bromo-4-fluoro-N-(2-hidroxi-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

punto de fusión: 154,4°C-156,4°C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 9,42 (br. s, 1H), 7,86 (d, 1H, J=7,57 Hz), 7,66 (d, 1H, J=1,46 Hz), 7,56 (dd, 1H, J=8,3, 2,2 Hz), 7,16 (d, 1H, J=8,55 Hz), 6,8 (dd, 1H, J=11,72, 6,59 Hz), 4,04 (t, 2H, J=7,9, 4,4 Hz), 3,69 (t, 2 H, J?6,84, 4,64 Hz), 2,23 (s, 3H). ^{19}F-NMR (376 MHz; $(CD_3)_2CO$) δ -103,3; MS 508,9 m/z, 510,9 m/z (AP+); 506,9 m/z, 508,9 m/z (AP-). Análisis calculado para $C_{16}H_{15}BrFIN_2O_3$: C, 37,75; H, 2,97; N, 5,50. Hallado: C, 37,68; H, 2,7; N, 5,31.

EJEMPLO 17

2-(2-Cloro-4-yodo-fenilamino)-4,5-difluoro-N-(2-hidroxi-etoxi)-benzamida

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 11,01 (br s, 1H), 9,53 (br. s, 1H), 7,67 (br s., 1H), 7,59 (br. d, 1H, J=7,82 Hz), 7,32 (d, 1H, J=8,55 Hz), 7,26 (br. s, 1H), 3,7 (br. s, 2H). ^{19}F-NMR (376 MHz; $(CD_3)_2CO$) δ -132,54, -149,93; MS 469,0 (AP+); 467,0 (AP-).

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EJEMPLO 18

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-etoxi)-benzamida

punto de fusión: 189,6°C-190,6°C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 11,00 (br s, 1H), 9,39 (br. s, 1H), 7,65 (dd, 1H, J=11,23, 8,79 Hz), 7,59 (dd, 1H, J=10,26, 1,96 Hz), 7,51 (m, 1H), 7,31 (t, 1H, J=8,8 Hz), 7,13 (m, 1H), 4,02 (t, 2H, J=4,64 Hz), 3,69 (t, 2H, J=4,89 Hz); ^{19}F-NMR (376 MHz; $(CD_3)_2CO$) δ -125,9 (d, J=50,55 Hz), -132,74, -151,05; MS 453,0 m/z (AP+); 451,0 m/z (AP-). Análisis calculado para $C_{15}H_{12}F_3IN_2O_3$: C, 39,84; H, 2,67; N, 6,20. Hallado: C, 40,22; H, 2,62; N, 6,03.

EJEMPLO 19

5-Bromo-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-etoxi)-benzamida

punto de fusión: 173°C-175°C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 9,59 (br. s, 1H), 7,89 (d, 1H, J=7,57 Hz), 7,62 (dd, 1H, J=10,26, 1,95 Hz), 7,55 (m, 1H), 7,34 (t, 1H, J=8,64 Hz), 7,03 (d, 1H, J=11,48 Hz), 4,04 (d, 2H, J=4,39 Hz), 3,70 (d, 2H, J=4,64 Hz); ^{19}F-NMR (376 MHz; $(CD_3)_2CO$) δ -103,07, -124,7 (d, J=53,1 Hz); MS 412,8 m/z, 514,8 m/z (AP+); 410,9 m/z, 512,9 m/z (AP-). Análisis calculado para $C_{15}H_{12}BrF_2IN_2O_3$.0,17 $C_4H_8O_2$.0,13 C_6H_{14}: C, 36,66; H, 2,84; N, 5,19. Hallado: C, 36,65; H, 2,57; N, 5,16.

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EJEMPLO 20

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-etoxi)-benzamida

punto de fusión: 178°C-181°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12,00 (s, 1H), 8,80 (s, 1H), 7,76 (s, 1H), 7,66 (d, 1H, J=7,1), 7,47 (d, 1H, J=8,5), 6,66 (t, 1H, J=7,6), 4,70 (bs, 1H), 3,85 (m, 2H), 3,56 (m, 2H); MS(APCI+)= 502,9/504,9. Análisis calculado/hallado para $C_{15}H_{11}Cl_2F_2IN_2O_3$: C, 35,81/35,69; H, 2,20/2,25; N, 5,57/5,22; F, 7,55/7,72

Los Ejemplos 21-24 y 26-27 se prepararon mediante el método general del Ejemplo 38.

EJEMPLO 21

3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-etoxi)-benzamida

punto de fusión: 185°C-187°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,79 (s, 1H), 8,32 (s, 1H), 7,53 (m, 2H), 7,30 (d, 1H, J=8,5), 6,60-6,55 (m, 1H), 4,69 (bs, 1H), 3,80 (bs, 2H), 3,50 (bs, 2H); MS(APCI+)= 471,0. Análisis calculado/hallado para $C_{15}H_{11}F_4IN_2O_3$: C, 38,32/38,38; H, 2,36/2,15; N, 5,96/5,76; F, 16,16/15,87.

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EJEMPLO 22

2-(4-Bromo-2-fluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-etoxi)-benzamida

punto de fusión: 146,1°C-146,4°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,82 (1H, s), 8,71 (1H, s), 7,47 (1H, dd, J=11,1 Hz, 2,1 Hz), 7,30-7,40 (1H, m), 7,15-7,20 (2H, m), 6,76-6,81 (1H, m), 4,69 (1H, br s), 3,80 (2H, t, J≤4,0 Hz), 3,52 (2H, t, J≤4,0 Hz). Análisis calculado/hallado para $C_{15}H_{12}F_3BrN_2O_3$: C, 44,47/44,58; H, 2,99/2,88; N, 6,91/6,72; F, 14,07/14,01; Br, 19,72/19,60.

EJEMPLO 23

2-(4-Bromo-2-fluoro-fenilamino)-4,5-difluoro-N-(2-hidroxi-etoxi)-benzamida

punto de fusión: 190,8°C-192,5°C; ^{1}H NMR (400 MHz, Acetona-d_6): δ 9,40 (br s, 1H), 7,67 (1H, dd, J=11,48 Hz, 8,79 Hz), 7,48 (2H, m), 7,37 (1H, m), 7,12 (1H, m), 4,05 (2H, t, J=4,64 Hz), 3,71 (2H, t, J=4,64 Hz). Análisis calculado/hallado para $C_{15}H_{12}BrF_3N_2O_3$: C, 44,47/45,55; H, 2,99/2,98; N, 6,91/6,29.

EJEMPLO 24

2-(4-Cloro-2-fluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-etoxi)-benzamida

punto de fusión: 142,1°C-142,5°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,83 (1H, s), 8,72 (1H, s), 7,36-7,39 (2H, m), 7,16 (1H, dd,

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J=16,5 Hz, 9,4 Hz), 7,07 (1H, dd, J=8,5 Hz, 1,3 Hz), 6,82-6,88 (1H, m), 4,69 (1H, br s), 3,80 (2H, t, J=4,6 Hz), 3,52 (2H, t, J=4,6 Hz). Análisis calculado/hallado para $C_{15}H_{12}ClF_3N_2O_3$: C, 49,95/50,18; H, 3,53/3,21; N, 7,77/7,70; F, 15,80/15,70; Cl, 9,83/9,94.

EJEMPLO 25

3,4-Difluoro-2-(2-fluoro-fenilamino)-N-(2-hidroxi-etoxi)-benzamida

Preparada desde 3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-etoxi)-benzamida mediante el método general del Ejemplo 86. punto de fusión: 129,6°C-130,4°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,85 (1H, s), 8,72 (1H, s), 7,36-7,39 (1H, m), 6,82-7,18 (5H, m), 4,69 (1H, br s), 3,82 (2H, t, J=4,7 Hz), 3,53 (2H, t, J=4,7 Hz). Análisis calculado/hallado para $C_{15}H_{13}F_3N_2O_3$: C, 55,22/55,16; H, 4,02/3,97; N, 8,59/8,51; F, 17,47/17,15.

EJEMPLO 26

5-Cloro-2-(2,4-difluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-etoxi)-benzamida

punto de fusión: 161,6°C-162,4°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,89 (1H, s), 8,69 (1H, s), 7,56 (1H, dd, J=7,5 Hz, 1,9 Hz), 7,21-7,27 (1H, m), 6,94-7,06 (1H, m), 6,89-6,92 (1H, m), 4,69

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(1H, br s), 3,81 (2H, t, J=4,6 Hz), 3,53 (2H, t, J=4,6 Hz). Análisis calculado/hallado para $C_{15}H_{11}ClF_4N_2O_3$: C, 47,57/47,74; H, 2,93/2,83; N, 7,40/7,31; F, 20,07/19,76; Cl, 9,36/9,39.

EJEMPLO 27

2-(2,4-Difluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-etoxi)-benzamida

punto de fusión: 141,1°C-141,6°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,84 (1H, s), 8,73 (1H, s), 7,34-7,37 (1H, m), 7,11-7,27 (1H, m), 7,04-7,09 (1H, m), 6,89-6,99 (2H, m), 4,70 (1H, br s), 3,82 (2H, t, J=4,9 Hz), 3,53 (2H, t, J=4,8 Hz). Análisis calculado/hallado para $C_{15}H_{12}F_4N_2O_3$: C, 52,33/52,34; H, 3,51/3,39; N, 8,14/8,01; F, 22,07/21,93.

EJEMPLO 28

4-Fluoro-N-(3-hidroxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

Paso A: A una mezcla de ácido 4-fluoro-2-(4-yodo-2-metil-fenilamino)-benzoico (3,32 g, 8,95 mmol) en diclorometanoa temperatura ambiente se agregó diisopropiletilamina (2,82 ml, 16,2 mmol). A la solución resultante se agregó O-[3-(terc-butil-dimetil-silaniloxi)-propil]-hidroxilamina (2,19 g, 10,65 mmol) y PyBOP. Después de agitar durante 1,5 h, la solución se diluyó con éter (100 ml) y se lavó con agua (3x50 ml) y solución salina (50 ml), se secó sobre sulfato de magnesio y

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se filtró, y se concentró en vacío para obtener una goma. Cromatografía de la goma usando un gradiente de 100% de hexanos a 30% de acetato de etilo en hexanos durante 45 minutos. El solvente de las fracciones combinadas se removió en vacío para obtener una goma amarilla. La goma se secó sobre una bomba de vacío durante 18 h lo cual dio N-[3-terc-Butil-dimetil-silaniloxi)-propoxi]-4-fluoro-2-(4-yodo-2-metil-fenilamino)-benzamida como un sólido (4,06 g, 81% de rendimiento). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9,3 (br s, 1H), 9,0 (br s, 1H), 7,58 (s, 1H), 7,49 (dd, 1H, J=8,3, 1,95 Hz), 7,36 (br. t., 1H, J=5,71 Hz), 7,05 (d, 1H, J=8,3 Hz), 6,65 (dd, 1H, J=11,96, 2,44 Hz), 6,4 (br. t., J=7,1 Hz), 4,14 (t, 2H, J=5,61 Hz), 3,812 (t, 2H, J=5,62 Hz), 2,28 (s, 3H), 1,94 (p, 2H, J=5,86 Hz), 0,9 (s, 9H), 0,08 (s, 6H). ^{19}F-NMR (376 MHz, $CDCl_3$) δ -105,25. MS(AP+) 559,2 m/z, (AP-) 557,1 m/z.

Paso B: A una solución de N-[3-(terc-Butil-dimetil-silaniloxi)-propoxi]-4-fluoro-2-(4-yodo-2-metil-fenilamino)-benzamida (4,0 g, 7,27 mmol) en metanol (5 ml) a temperatura ambiente se agregó 5M H_2SO_4 en metanol (0,073 ml, 0,364 mmol). Después de agitar 1 h, a la reacción se le agregó 5 M H_2SO_4 en metanol adicional (0,035 ml, 0,182 mmol). Después de agitar 2 h, la reacción se ajustó a pH 7 usando $NaHCO_3$ (ac.) saturado (1,5 ml), seguido por el agregado de agua (35 ml). La capa acuosa se extrajo con acetato de etilo (1x20 ml, 2x10 ml). Los

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extractos se combinaron, se lavaron con solución salina, y se secaron sobre sulfato de magnesio. La mezcla resultante se filtró, y el solvente del filtrado se removió en vacío para obtener un aceite que se secó sobre una bomba de vacío durante el fin de semana. El aceite se purificó mediante cromatografía rápida, se eluyó con un gradiente de 100% de hexanos a 100% de acetato de etilo en 50 minutos. El solvente se removió en vacío de las fracciones combinadas para obtener un sólido que se secó sobre una bomba de vacío durante 6 h. El sólido se recristalizó en una mezcla de hexanos y acetato de etilo para obtener 4-fluoro-N-(3-hidroxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida como un sólido (2,4 g, 74% de rendimiento): punto de fusión 120,8°C-122,4°C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 10;91 (br s, 1H), 9,59 (br S, 1H), 9,68 (m, 2H), 7,57 (d, 1H, J=8,54 Hz), 7,18 (d, 1H, J=8,34 Hz), 6,72 (m, 1H), 6,53 (m, 1H), 4,12 (t, 2H, J=6,11 Hz), 3,71 (t, 2H, J=5,86 Hz), 2,26 (s, 3H), 1,86 (m, 2H). ^{19}F-NMR (376 MHz, $(CD_3)_2CO$) δ -108,4. MS 445,1 m/z (AP+), 443,1 m/z (AP-). Análisis calculado para $C_{17}H_{18}FIN_2O_3$: C, 45,96; H, 4,08; N, 6,31; F, 4,28; I, 28,57. Hallado: C, 45,78; H, 3,88; N, 6,14; F, 4,30; I, 28,27.

Los Ejemplos 29-33 se prepararon mediante el procedimiento general del ejemplo 28.

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EJEMPLO 29

5-Cloro-3,4-difluoro-N-(3-hidroxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

punto de fusión 155,2°C-156,6°C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 10,98 (br s, 1H), 8,70 (br S, 1H), 7,66 (dd, 1H, J=7,33, 1,95 Hz), 7,55 (s, 1H), 7,42 (dd, 1H, J=8,54, 1,95 Hz), 6,64 (dd, 1H, J=8,55, 6,11 Hz), 4,08 (t, 2H, J=6,11 Hz), 3,67 (t, 2H, J=6,10 Hz), 2,32 (s, 3H), 1,83 (m, 2H). ^{19}F-NMR (376 MHz, $(CD_3)_2CO$) δ -135,0, -139,63 (d, J=17,67 Hz). MS 497,1 m/z (AP+), 495,1 m/z (AP-). Análisis calculado para $C_{17}H_{16}ClF_2IN_2O_3$: C, 41,11; H, 3,25; N, 5,64; F, 7,65; Cl, 7,14; I, 25,55. Hallado: C, 41,09; H, 3,07; N, 5,46; F, 7,63; Cl, 7,24; I, 25,57.

EJEMPLO 30

2-(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(3-hidroxi-propoxi)-benzamida

punto de fusión 158,8°C-160,8°C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 10,90 (br s, 1H), 9,93 (br S, 1H), 7,84 (d, 1H, J=1,95 Hz), 7,72 (dd, 1H, J=8m55, 1,96 Hz), 7,65 (dd, 1H, J=8,55, 1,96 Hz), 7,39 (d, 1H, J=8,54 Hz), 7,05 (dd, 1H, J=11, 72, 2,44 Hz), 6,67 (td, 1H, J=8,55, 2,69 Hz), 4,13 (t, 2H, J=6,34 Hz), 3,71 (t, 2H, J=6,10 Hz), 1,86 (m, 2H). ^{19}F-NMR (376 MHz, $(CD_3)_2CO$) δ -108,0. MS 465,1 m/z (AP+), 463,1 m/z (AP-).

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Análisis calculado para $C_{16}H_{15}ClFIN_2O_3$: C, 41,36; H, 3,25; N, 6,03; F, 4,09; Cl, 7,63; I, 27,31. Hallado: C, 41,41; H, 3,13; N, 5,84; F, 4,10; Cl, 7,62; I, 27,41.

EJEMPLO 31

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-propoxi)-benzamida

punto de fusión 120°C-121°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,90 (bs, 1H), 8,91 (bs, 1H), 7,76 (bs, 2H), 7,47 (d, 1H, J=8,1), 7,67 (m, 1H), 4,48 (bs, 1H), 3,89 (bs 2H), 3,47 (bs, 2H), 1,73 (m, 2H). MS (APCI+), 560,8/562,8. Análisis calculado/hallado para $C_{16}H_{13}ClF_2IN_2O_3$: C, 34,22/34,45; H, 2,33/2,36; N, 4,99/4,91; F, 6,77/6,72.

EJEMPLO 32

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-propoxi)-benzamida

punto de fusión 151,8°C-152,4°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,74 (1H, s), 8,71 (1H, s), 7,56 (1H, d, J=11,0 Hz), 7,20-7,30 (2H, m), 7,16-7,22 (1H, m), 6,62-6,68 (1H, m), 4,46 (1H, br s), 3,83 (2H, t, J=5,6 Hz), 3,46 (2H, t, J=4,6 Hz), 1,67-1,70 (2H, m). Análisis calculado/hallado para $C_{16}H_{14}F_3IN_2O_3$: C, 41,22/41,27; H, 3,03/2,87; N, 6,01/5,92; F, 12,23/11,97; I, 27,22/27,44.

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EJEMPLO 33

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(4-hidroxi-propoxi)-benzamida

punto de fusión 131,4°C-131,9°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,71 (1H, s), 8,68 (1H, s), 7,54 (1H, d, J=11,0 Hz), 7,20-7,36 (2H, m), 7,14-7,18 (1H, m), 6,60-6,66 (1H, m), 4,38 (1H, br s), 3,74 (2H, t, J=6,1 Hz), 3,36 (2H, t, J=4,2 Hz), 1,41-1,55 (4H, m). Análisis calculado/hallado para $C_{17}H_{16}F_3IN_2O_3$: C, 42,52/42,91; H, 3,36/3,27; N, 5,83/5,58; F, 11,87/11,61; I, 26,43/26,67.

EJEMPLO 34

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-N-(2,3-dihidroxi-propoxi)-3,4-difluoro-benzamida

Paso A: A una solución en agitación de pentafluorofenil éster del ácido 5-cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-benzoico (5,80 g, 9,51 mmol) en tetrahidrofurano recién destilado (40 ml) se agregó O-(2,2-dimetil-[1,3]dioxolan-4-ilmetil)-hidroxilamina (1,54 g, 10,5 mmol) y diisopropilamina (1,8 ml, 10,5 mmol). Después de 20 horas, la mezcla se particionó entre acetato de etilo y agua. La capa orgánica se lavó dos veces con agua y dos veces con solución salina saturada. La capa orgánica se recogió, se secó sobre Na_2SO_4, se filtró y se concentró en vacío. El residuo se purificó mediante cristalización en acetato de etilo/hexanos dando 5-

cloro-2-(2-cloro-fenilamino)-N-(2,2-dimetil-[1,3]dioxolan-4-ilmetoxi)-3,4-difluoro-benzamida como un sólido blanco (3,7 g, 67,9%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9,82 (bs, 1H), 8,10 (bs, 1H), 7,68 (s, 1H), 7,47 (bs, 1H), 7,40-7,43 (m, 1H), 6,44-6,47 (m, 1H), 4,40 (bs, 1H), 3,97-4,20 (m, 3H), 3,77 (t, 1H, J=8,0 Hz), 1,37 (s, 3H). MS (APCI+)= 573,05/575,0.

Paso B: A una solución en agitación de 5-cloro-2-(2-cloro-4-yodo-fenilamino)-N-(2,2-dimetil-[1,3]dioxolan-4-ilmetoxi)-3,4-difluoro-benzamida (3,7 g, 6,45 mmol) en metanol (20 ml) y agua (2 ml) se agregó ácido p-toluenosulfónico (0,12 g, 0,65 mmol). Después de 20 horas la reacción se concentró en vacío. El residuo obtenido se particionó entre acetato de etilo y agua. La capa orgánica se lavó dos veces con una solución saturada de $NaHCO_3$ y dos veces con una solución salina saturada. Las capas orgánicas se recogieron, se secaron sobre Na_2SO_4, se filtraron y se concentraron en vacío. El residuo se purificó mediante cristalización con metanol/agua y los sólidos se secaron en un horno de vacío a 40°C para dar 5-cloro-2-(2-cloro-4-yodo-fenilamino)-N-(2,3-dihidroxi-propoxi)-3,4-difluoro-benzamida: punto de fusión = 152°C-154°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12,03 (s, 1H), 8,83 (s, 1H), 7,76 (s, 1H), 7,66 (d, 1H, J=6,8), 7,47 (d, 1H, J=8,5), 6,68 (t, 1H, J=6,6), 4,83 (bs, 1H), 4,60 (bs, 1H), 3,89-3,92 (m, 1H), 3,68-3,76 (m, 2H), 3,30 (2H, parcialmente oculto por HDO); MS

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(APCI+)= 533,0/535,0; Análisis calculado/hallado para $C_{16}H_{13}Cl_2F_2IN_2O_4$: C, 36,05/36,23; H, 2,46/2,40; N, 5,25/5,03; F, 7,13/7,14.

Los Ejemplos 35-37 se prepararon mediante el procedimiento general descripto en el Ejemplo 34.

EJEMPLO 35

5-Cloro-N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-benzamida

punto de fusión: 67°C-69°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7,51 (s, 1H), 7,46 (d, 1H, J=6,3), 7,38 (d, 1H, J=8,5), 6,44 (dd, 1H, J=8,3, 4,9), 3,94-3,98 (m, 2H), 3,89 (m, 1H), 3,74 (A de abx, 1H, J=11,5, 4,9), 2,30 (s, 3H); MS (APCI+)= 513,0/515,0; Análisis calculado/hallado para $C_{17}H_{16}ClF_2IN_2O_4$: C, 39,83/39,90; H, 3,15/3,23; N, 5,46/5,03; F, 7,41/7,20.

EJEMPLO 36

5-Cloro-N-(3,4-difluoro-butoxi)-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-benzamida

punto de fusión: 135°C-138°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,86 (bs, 1H), 8,55 (bs, 1H), 7,85 (s, 1H), 7,60 (d, 1H, J=7,1), 7,51 (s, 1H), 7,35 (d, 1H, J=8,5), 6,53 (dd, 1H, J=8,3, 5,4), 4,51-4,52 (m, 2H), 3,86-3,88 (m, 2H), 3,53 (bs,

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1H), 3,23-3,28 (cm, 1H), 2,20 (s, 3H), 1,73-1,77 (cm, 1H), 1,45-1,48 (cm, 1H); MS (APCI+)= 527,0; Análisis calculado/hallado para $C_{18}H_{18}ClF_2IN_2O_4$: C, 41,05/41,12; H, 3,44/3,41; N, 5,32/5,13; F, 7,21/6,83.

EJEMPLO 37

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-N-(3,4-dihidroxi-butoxi)-3,4-difluoro-benzamida

punto de fusión: 146°C-148°C; ^1H NMR (400 MHz, DMSO-d_6): δ 11,92 (s, 1H), 8,84 (s, 1H), 7,76 (s, 1H), 7,65 (d, 1H, J=7,1), 7,47 (d, 1H, J=8,8), 6,67 (dd, 1H, J=8,3, 6,3), 4,54-4,50 (m, 2H), 3,93 (t, 2H, J=6,3), 3,54 (t, 1H, J=4,2), 3,28-3,20 (m, 2H), 1,76 (cm, 1H), 1,52-1,47 (cm, 1H); MS (APCI+)= 547,0/549,0; Análisis calculado/hallado para $C_{17}H_{15}Cl_2F_2IN_2O_4$: C, 37,32/37,26; H, 2,76/2,62; N, 5,12/4,99; F, 6,94/7,07.

EJEMPLO 38

N-(2,2-Dimetil-[1,3]dioxolan-4-ilmetoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

A una solución en agitación de ácido 3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzoico (4,52 g, 11,5 mmol) en tetrahidrofurano recién destilado (20 ml) a -15°C se agregó ácido difenilfosfínico (2,85 ml, 14,95 mmol). La mezcla de la reacción resultante se agitó durante 30 minutos a -15°C. Se agregó N-metilmorfolina (1,26 ml, 11,5 mmol) y se continuó

agitando durante 90 monutos a -15°C. La reacción luego se cargó con O-(2,2-dimetil-[1,3]dioxolan-4-ilmetil)hidroxilamina (2,03 g, 13,8 mmol) y se la dejó agitar a -15°C durante 30 minutos. Se agregó N-metilmorfolina (1,9 ml, 17,25 mmol) y la reacción se dejó calentar a temperatura ambiente. Después de 17 horas, la mezcla se diluyó con acetato de etilo y se particionó dos veces con una solución saturada de $NaHCO_3$, luego dos veces con agua, y dos veces con solución salina saturada. Las capas orgánicas se recogieron, se secaron sobre sulfato de sodio, se filtraron y se concentraron en vacío. El residuo obtenido se purificó mediante cromatografía de columna de sílice en 3:1 hexanos/acetato de etilo. Las fracciones correspondientes se recogieron, se secaron en vacío, y se cristalizaron desde acetato de etilo/hexanos dando N-(2,2-dimetil-[1,3]dioxolan-4-ilmetoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida (4,12 g, 68,6%) como un sólido marrón claro: punto de fusión 114°C-115°C; ^1H NMR (400 MHz, DMSO-d_6): δ 11,89 (s, 1H), 8,62 (s, 1H), 7,53-7,55 (m, 1H), 7,31-7,37 (m, 2H), 7,17 (dd, 1H, J=16,9, 9,3), 6,60-6,65 (m, 1H), 4,22 (t, 1H, J=6,1), 3,96 (t, 1H, J=8,3), 3,76-3,77 (m, 2H), 3,63 (t, 1H, J=4,9), 1,26 (s, 3H), 1,21 (s, 3H); MS (APCI+)= 522,9; Análisis calculado/hallado para $C_{19}H_{18}F_3IN_2O_4$: C, 43,70/43,88; H, 3,47/3,43; N, 5,36/5,20; F, 10,91/10,87.

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EJEMPLO 39

N-(2,3-Dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida (Forma II del Compuesto A)

A una solución en agitación de N-(2,2-dimetil-[1,3]dioxolan-4-ilmetoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida (3,03 g, 5,81 mmol) en metanol (30 ml) y agua (3 ml) a temperatura ambiente se agregó ácido p-tolueno sulfónico (0,11 g, 0,581 mmol). Después de 18 horas, se agregaron otros 0,11 g de ácido p-tolueno sulfónico y 2 ml de agua. Después de 24 horas adicionales, la mezcla de la reacción se concentró en vacío. El residuo se particionó entre acetato de etilo y agua. La capa orgánica se lavó con una solución saturada de $NaHCO_3$ y dos veces con solución salina saturada. Las capas orgánicas se recogieron, se secaron sobre Na_2SO_4, se filtraron y se concentraron en vacío dando un sólido marrón claro, que se cristalizó desde acetato de etilo/hexanos para dar N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida como un sólido blanco. punto de fusión = 152°C-154°C; ^1H NMR (400 MHz, DMSO-d_6): δ 11,87 (s, 1H), 8,69 (s, 1H), 7,54 (dd, 1H, J=10,9, 1,5), 7,32-7,38 (m, 2H), 7,17 (dd, 1H, J=16,8, 9,0), 6,61-6,66 (cm, 1H), 4,82 (bs, 1H), 3,84-3,85 (m, 1H), 3,71-3,64 (cm, 2H), 3,33 (2H, parcialmente oculto por HDO); MS (APCI+)= 483,0; Análisis calculado/hallado para $C_{16}H_{14}F_3IN_2O_4$: C, 39,85/40,12; H, 2,93/2,84; N, 5,81/5,65; F, 11,82/11,47.

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Alternativamente, el sólido blanco crudo de N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida se suspendió en heptano-CH_2Cl_2 (1:1). La razón fue 6 ml del solvente por gramo del sólido. La suspensión se agitó a temperatura ambiente durante 30 minutos. El sólido se filtró, y se secó en un horno de vacío (a 20 mm Hg), a 45°C durante 18 horas, para dar cristales blancos, punto de fusión 131°C-132°C.

EJEMPLO 39A

N-(2,3-Dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida (Forma I del Compuesto A)

A una solución en agitación de N-(2,2-dimetil-[1,3]dioxolan-4-ilmetoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida (0,907 g, 1,74 mmol) en metanol (10 ml) y agua (1 ml) a temperatura ambiente se agregó ácido p-tolueno sulfónico (0,032 g, 0,17 mmol). Después de 18 horas, la mezcla de la reacción se concentró en vacío y el residuo obtenido se particionó entre acetato de etilo y agua. Las capas orgánicas se lavaron dos veces con agua y una vez con solución salina saturada. Las capas orgánicas se recogieron, se secaron sobre Na_2SO_4, se filtraron y se concentraron en vacío dando un sólido marrón claro, que se disolvió en etanol y se precipitó con agua para dar N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-

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fluoro-4-yodo-fenilamino)-benzamida como un sólido blanco 0,387 g). punto de fusión = 83°C-85°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,87 (s, 1H), 8,69 (s, 1H), 7,56 (d, 1H, J=11,0), 7,33-7,39 (m, 2H), 7,19 (dd, 1H, J=16,6, 9,0), 6,62-6,68 (cm, 1H), 4,82 (d, 1H, J=4,2), 4,58 (t, 1H, J=5,5), 3,84-3,87 (m, 1H), 3,66-3,72 (m, 2H), 3,3 (2H, parcialmente oculto por HDO); MS (APCI+)= 483,0; Análisis calculado/hallado para $C_{16}H_{14}F_3IN_2O_4$: C, 39,41/39,02; H, 3,02/2,93; N, 5,75/5,81; F, 11,69/11,68.

Alternativamente, el sólido crudo N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida se disolvió en una cantidad mínima de etanol en ebullición (95%). Se agregó agua a este solvente en ebullición hasta que fue ligeramente turbio. La mezcla se enfrió a temperatura ambiente y luego a 0°C durante 18 horas. El sólido formado se filtró y se secó en un horno de vacío (a 20 mmHg), a 45°C durante 18 horas, punto de fusión 81°C-84°C.

Más aún, el sólido blanco crudo N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida se disolvió en una cantidad mínima de acetato de etilo en ebullición y se agregó heptano a esta solución hasta que fue ligeramente turbia. La mezcla se enfrió a temperatura ambiente y luego a 0°C durante 18 horas. El sólido formado se filtró y se secó en un horno de vacío (a 20 mmHg), a 45°C durante 18 horas, punto de fusión 86°C.

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Los compuestos de los ejemplos 40-48 se prepararon mediante los procedimientos descriptos en los Ejemplos 38 y 39.

EJEMPLO 40

5-Bromo-N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

punto de fusión = 172°C-174°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,92 (s, 1H), 8,69 (s, 1H), 7,67 (d, 1H, J=6,8), 7,56 (d, 1H, J=10,7), 7,34 (d, 1H, J=8,3), 6,73 (cm, 1H), 4,81 (m, 1H), 4,58-4,57 (m, 1H), 3,86-3,84 (m, 1H), 3,70-3,67 (m, 2H), 3,30 (2H, parcialmente debajo de HDO); MS (APCI+)= 461,0; Análisis calculado/hallado para $C_{16}H_{13}BrF_3IN_2O_4$: C, 34,25/34,27; H, 2,34/2,22; N, 4,99/4,75.

EJEMPLO 41

5-Cloro-N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

punto de fusión = 152°C-155°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,91 (s, 1H), 8,66 (s, 1H), 7,58-7,55 (m, 2H), 7,34 (d, 1H, J=8,1 Hz), 6,72 (cm, 1H), 4,81 (d, 1H, J=4,1 Hz), 4,58 (t, 1H, J=5,9 Hz), 3,87-3,84 (m, 1H), 3,70-3,68 (m, 2H), 3,33 (2H, parcialmente debajo de HDO); MS (APCI+)= 517,0; Análisis calculado/hallado para $C_{16}H_{13}ClF_3IN_2O_4$: C, 37,20/36,88; H, 2,54/2,43; N, 5,42/5,14; F, 11,03/11,70.

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EJEMPLO 42

N-(2,3-Dihidroxi-propoxi)-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

punto de fusión = 173°C-175°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,86 (s, 1H), 9,59 (s, 1H), 7,69 (d, 1H, J=10,3), 7,58 (t, 1H, J=7,8), 7,49 (d, 1H, J=8,5), 7,27 (t, 1H, J=8,5), 6,82 (t, 1H, J=11,5), 6,69 (t, 1H, J=7,8), 3,94-3,92 (m, 1H), 3,78-3,71 (m, 2H), 3,4 (2H, debajo de HDO); MS (APCI+)= 465,0.

EJEMPLO 43

N-(2,3-Dihidroxi-propoxi)-3,4,5-trifluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

punto de fusión = 157°C-160°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,82 (s, 1H), 8,32 (s, 1H), 7,53-7,48 (m, 2H), 7,29 (d, 1H, J=8,3), 6,58-6,55 (m, 1H), 4,80 (d, 1H, J=3,0), 4,57 (t, 1H, J=5,9), 3,83-3,81 (m, 1H), 3,67-3,65 (m, 2H), 3,30 (2H, debajo de HDO); MS (APCI+)= 500,9. Análisis calculado/hallado para $C_{16}H_{13}F_4IN_2O_4$: C, 38,42/38,48; H, 2,62/2,54; N, 5,60/5,55; F, 15,19/14,96.

EJEMPLO 44

2-(4-Bromo-2-fluoro-fenilamino)-N-(2,3-dihidroxi-propoxi)-3,4-difluoro-benzamida

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Preparado en la forma de N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida (Ejemplo 39): punto de fusión 110°C-117°C. Análisis calculado/hallado para $C_{16}H_{14}BrF_3N_2O_4$: C, 44,16/43,86; H, 3,24/2,97; N, 6,44/6,13; F, 13,10/12,76; Br, 18,36/18,64.

EJEMPLO 45

2-(4-Cloro-2-fluoro-fenilamino)-N-(2,3-dihidroxi-propoxi)-3,4-difluoro-benzamida

punto de fusión = 114°C-114,9°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,87 (1H, s), 8,74 (1H, s), 7,38 (1H, dd, J=11,3, 2,3 Hz), 7,36 (1H, m), 7,07-7,20 (2H, m), 4,84-6,90 (1H, m), 4,83 (1H, br s), 4,59 (1H, br s), 3,84-3,87 (1H, m), 3,65-3,72 (2H, m), 3,20-3,40 (2H, m). Análisis calculado/hallado para $C_{16}H_{14}F_3ClN_2O_4$: C, 49,18/49,09; H, 3,61/3,56; N, 7,07/7,03; F, 14,59/14,45; Cl, 9,07/9,16.

EJEMPLO 46

N-(2,2-Dimetil-[1,3]dioxolan-5-iloxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

punto de fusión = 154°C-155°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,93 (s, 1H), 8,64 (s, 1H), 7,55 (dd, 1H, J=10,7, 1,7 Hz), 7,40 (t, 1H, J=7,1), 7,33 (d, 1H, J=8,3), 7,21-7,14 (m, 2H), 6,69-6,65 (m, 1H), 3,95 (A de AB, 2H, J=10,7), 3,80 (B de AB,

2H, J=12,2), 3,65 (bs, 1H), 1,33 (s, 3H), 1,25 (s, 3H); MS (APCI+)=523,1; Análisis calculado/hallado para $C_{19}H_{18}F_3IN_2O_4$: C, 43,70/43,76; H, 3,47/3,44; N, 5,36/5,21; F, 10,91/10,73.

EJEMPLO 47

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1-hidroximetil-etoxi)-benzamida

punto de fusión = 111°C-114°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,82 (bs, 1H), 8,64 (bs, 1H), 7,55 (dd, 1H, J=10,7, 1,9), 7,40 (t, 1H, J=7,3), 7,34-7,31 (m, 1H), 7,20 (dd, 1H, J=16,6, 9,3), 6,65-6,60 (m, 1H), 4,64 (bs, 2H), 3,75-3,72 (m, 1H), 3,48-3,44 (m, 4H); MS (APCI+)=482,9; Análisis calculado/hallado para $C_{19}H_{14}F_3IN_2O_4$: C, 39,85/39,93; H, 2,93/2,93; N, 5,81/5,51; F, 11,82/11,72.

EJEMPLO 48

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1-hidroximetil-etoxi)-benzamida

punto de fusión = 173°C-175°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,87 (s, 1H), 8,56 (s, 1H), 7,61 (d, 1H, J=6,3), 7,55 (d, 1H, J=9,3), 7,32 (d, 1H, J= 9,5), 6,69 (m, 1H), 4,61 (m, 2H), 3,73 (m, 1H), 3,48 (m, 4H); MS (APCI+)=516,9/518,9.

EJEMPLO 49

N-[(R)-2,3-Dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida (Forma I del Compuesto B)

Paso A: A una solución de ácido 3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzoico (39,3 g, 100,0 mmol) en tetrahidrofurano seco (500 ml, 0,2 M) bajo una atmósfera de nitrógeno, se agregó ácido (R)-O-(2,2-dimetil[1,3]dioxolan-4-ilmetil)-hidroxilamina (14,7 g, 100,0 mmol), seguida por N-metilmorfolina (27,5 ml, 0,25 mol). La solución de color naranja se enfrió con un baño de hielo. Se agregó cloruro difenilfosfínico (22,9 ml, 0,12 mol) gota a gota. Se formó algún sólido. La mezcla se calentó a temperatura ambiente y se agitó durante 18 horas. Se agregó agua para enfriar la reacción y se evaporó el tetrahidrofurano en vacío. El aceite restante se disolvió en acetato de etilo (500 ml), se lavó con una mezcla de solución salina saturada y bicarbonato de sodio saturado (1:1) dos veces. El acetato de etilo se removió y el sólido aceitoso crudo se purificó mediante cromatografía rápida (gel de sílice, hexano-acetona / 2:1) para dar N-((R)-2,2-dimetil-[1,3]dioxolan-4-ilmetoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida como un sólido blancuzco después de secar en un horno de vacío a 40°C durante 20 horas: 41,7 g (79,8%), punto de fusión 124°C-125°C. Las fracciones impuras se combinaron y se purificaron mediante una segunda

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cromatografía de columna usando las mismas condiciones para dar un segundo lote de 6,4 g (12,3%), punto de fusión 124°C-125°C, rendimiento total 48,1 g (92,1%). ^1H NMR (d^6-DMSO): δ 11,9 (s, br, 1H), 8,7 (s, br, 1H), 7,6 (d, 1H, J=10,99 Hz), 7,4 (m, 2H), 7,2 (m, 1H), 6,7 (m, 1H), 4,2 (m, 1H), 4,0 (t, 1H, J=8,3 Hz, J2=6,8 Hz), 3,8 (m, 2H), 3,7 (m, 1H), 1,3 (s, 3H), 1,2 (s, 3H); ^{19}F NMR (d^6-DMSO): δ -128,0, -133,1, -144,3; MS 523 (M^+ + 1).

Paso B: N-((R)-2,2-dimetil-[1,3]dioxolan-4-ilmetoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida (22,3 g, 42,7 mmol) se suspendió en metanol (223 ml, 10 ml/g) y se agregó una solución de pTsOH:H_2O (4,1 g 21,35 mmol) en agua (22,3 ml). La mezcla se agitó a temperatura ambiente durante 18 horas, durante las cuales todos los sólidos se disolvieron para dar una solución incolora, clara. La solución se concentró y se extrajo con acetato de etilo (2 x 300 ml). La solución orgánica se lavó con bicarbonato de sodio, se secó sobre $MgSO_4$. Después de la filtración, el filtrado se concentró y se evaporó conjuntamente con heptano para dar un sólido espumante. A este sólido se agregó hexano-CH_2Cl_2 (1:1, 100 ml) y la mezcla se agitó durante 30 minutos. Se formó un sólido blanco, que se filtró, se lavó con hexano. El sólido se recristalizó desde hexano-AcOEt para dar N-((R)-2,3-dihidroxi-

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propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida como cristales blancos, 13,57 g (65,9%), después de secar a 60°C en un horno de vacío durante 3 días. Se obtuvo una segunda cosecha de 5,05 g del otro líquido madre, después de la recristalización desde el mismo sistema de solventes. El rendimiento total fue de 18,62 g (90,4%): punto de fusión 89°C-90°C (Forma II del Compuesto B). Los cristales combinados se molieron con un conjunto de mortero y triturador para refinar el polvo, y se secaron a 60°C en un horno de vacío durante 3 días: punto de fusión 117°C-118°C (Forma I del Compuesto B); $[\alpha]$= -2,05° (c=1,12, metanol); Análisis: Calculado para $C_{16}H_{14}F_3I_1N_2O_4$: C, 39,85; H, 2,93; N, 5,81; F, 11,82; I, 26,32. Hallado: C, 39,95; H, 2,76; N, 5,72; F, 11,71; I 26,53. ^{1}NMR (400 MHz, DMSO-d_6): δ 11,87 (s, 1H), 8,69 (s, 1H), 7,54 (dd, 1H, J=10,9, 1,5), 7,32-7,38 (m, 2H), 7,17 (dd, 1H, J=16,8, 9,0), 6,61-6,6 (cm, 1H), 4,82 (bs, 1H), 4,58 (bs, 1H), 3,84-3,85 (m, 1H), 3,71-3,64 (cm, 2H), 3,33 (2H, parcialmente oculto por HDO).

EJEMPLO 49A

N-[(R)-2,3-Dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida (Forma II del Compuesto B)

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Paso A: A una solución de ácido 3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzoico (2,25 g, 5,10 mmol) en tetrahidrofurano seco bajo una atmósfera de nitrógeno, a 15°C, se agregó cloruro difenilfosfínico (1,26 ml, 6,63 mol) gota a gota. Después de agitar durante 20 minutos, se agregó N-metil morfolina (0,70 ml, 6,375 mmol) y la reacción se agitó otros 20 minutos. Se agregó (R)-O-(2,2-dimetil-[1,3]dioxolan-4-ilmetil)-hidroxilamina (0,748 g, 5,1 mmol) y la reacción se agitó durante 1 hora, en cuyo punto se agregó N-metil morfolina (0,7 ml, 6,37 mmol). La mezcla se calentó a temperatura ambiente y se agitó durante 12 horas. La reacción se concentró en vacío y luego se diluyó con EtOAc. La capa orgánica se lavó con $NaHCO_3$ saturado (2x), solución salina (1x), se secó sobre Na_2SO_4, se filtró y se concentró. El producto crudo se purificó sobre SiO_2 usando 4:1 hexano/EtOAc como eluyente para proveer 1,82 g (68%) de un sólido rojo amarronado.

Paso B: N-((R)-2,2-dimetil-[1,3]dioxolan-4-ilmetoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida (0,210 g, 0,40 mmol) se suspendió en 10:1 metanol/H_2O y se agregó pTsOH:H_2O (0,008 g, 0,04 mmol). La mezcla se agitó a temperatura ambiente durante 18 horas, durante las cuales todos los sólidos se disolvieron para dar una solución incolora, clara. La solución se concentró y se extrajo con

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acetato de etilo (2 x 300 ml). La solución orgánica se lavó con bicarbonato de sodio, se secó sobre $MgSO_4$. Después de la filtración, el filtrado se concentró y se evaporó conjuntamente con heptano para dar un sólido espumante. A este sólido se agregó hexano-CH_2Cl_2 (1:1, 100 ml) y la mezcla se agitó durante 30 minutos. Se formó un sólido blanco, que se filtró, se lavó con hexano. El sólido se recristalizó desde hexano-AcOEt para dar N-((R)-2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida como cristales blancos, 13,57 g (65,9%), después de secar a 60°C en un horno de vacío durante 3 días. Se obtuvo una segunda cosecha de 5,05 g del otro líquido madre, después de la recristalización desde el mismo sistema de solventes. El rendimiento total fue de 18,62 g (90,4%): punto de fusión 89°C-90°C (Forma II del Compuesto B). Los cristales combinados se molieron con un conjunto de mortero y triturador para refinar el polvo, y se secaron a 60°C en un horno de vacío durante 3 días: punto de fusión 117°C-118°C (Forma I del Compuesto B); $[\alpha]$= -2,05° (c=1,12, metanol); Análisis: Calculado para $C_{16}H_{14}F_3I_1N_2O_4$: C, 39,85; H, 2,93; N, 5,81; F, 11,82; I, 26,32. Hallado: C, 39,95; H, 2,76; N, 5,72; F, 11,71; I 26,53. ^{1}NMR (400 MHz, DMSO-d_6): δ 11,87 (s, 1H), 8,69 (s, 1H), 7,54 (dd, 1H, J=10,9, 1,5), 7,32-7,38 (m, 2H), 7,17 (dd, 1H, J=16,8, 9,0), 6,61-6,6 (cm, 1H), 4,82 (bs, 1H), 4,58

(bs, 1H), 3,84-3,85 (m, 1H), 3,71-3,64 (cm, 2H), 3,33 (2H, parcialmente oculto por HDO). La solución se diluyó con EtOAc. La solución orgánica se lavó con bicarbonato de sodio (2x), solución salina (1x) y se secó sobre Na_2SO_4. Después de la filtración, el filtrado se concentró, y se recristalizó desde EtOAc y heptano. Este sólido se lavó con heptano-CH_2Cl_2 (1:1) y se secó en vacío a 60°C para dar N-((R)-2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida como un sólido blanco (0,136 g, 70%). El producto se encoge a 90,8°C, se funde a 115°C-117°C. El análisis muestra C 40,92, H 3,16, N 5,41, F 11,30, I, 23,92 (6,75% de EtOAc, 0,96% de heptano).

EJEMPLO 50

N-[(S)-2,3-Dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida (Forma I del Compuesto C)

Preparada desde (S)-O-(2,2-dimetil-[1,3]dioxolan-4-ilmetil)-hidroxilamina y ácido 3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzoico mediante el procedimiento descripto anteriormente para N-[(R)-2,3-Dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida: punto de fusión 116°C-118°C (Forma II del Compuesto C); y punto de fusión 116°C-118°C (Forma I del Compuesto C); [α]= +1,77° (c=1,13, metanol); Análisis: Calculado para $C_{16}H_{14}F_3I_1N_2O_4$: C, 39,85; H,

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2,93; N, 5,81; F, 11,82; I, 26,32. Hallado: C, 40,01; H, 2,73; N, 5,84; F, 11,45; I, 26,42.

EJEMPLO 50A

N-[(S)-2,3-Dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida (Forma II del Compuesto C)

Preparada desde (S)-O-(2,2-dimetil-[1,3]dioxolan-4-ilmetil)-hidroxilamina y ácido 3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzoico mediante el procedimiento alternativo descripto anteriormente para N-[(R)-2,3-Dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida: punto de fusión 118°C-119°C.

EJEMPLO 51

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-benzamida-N-[(R)-2,3-dihidroxi-propoxi]-3,4-difluoro-benzamida

Preparada desde (R)-O-(2,2-dimetil-[1,3]dioxolan-4-ilmetil)-hidroxilamina y ácido 5-cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-benzoico mediante el procedimiento descripto para N-(2,3-Dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida: punto de fusión 155°C-156°C; [α]= -5,1° (c=3,5 mg/ml, etanol); ^{1}NMR (400 MHz, DMSO-d_6): δ 12,03 (s,

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1H), 8,83 (s, 1H), 7,76 (s, 1H), 7,66 (d, 1H, J=6,8 Hz), 7,47 (d, 1H, J=8,5 Hz), 6,68 (t, 1H, J=6,6 Hz), 4,83 (bs, 1H), 4,60 (bs, 1H), 3,89-3,92 (m, 1H), 3,68-3,76 (m, 2H), 3,30 (2H, parcialmente oculto por HDO); MS (APCI+)=533,0/535,0; Análisis calculado/hallado para $C_{16}H_{13}F_3Cl_2F_2IN_2O_4$: C, 36,05/36,04; H, 2,46/2,25; N, 5,25/5,10; F, 7,13/7,18; Cl, 13,30/13,50; I, 23,80, 24,02.

EJEMPLO 52

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-N-[(S)-2,3-dihidroxi-propoxi]-3,4-difluoro-benzamida

Paso A: Un solo matraz de base circular de 1 L equipado con una barra agitadora magnética se cargó con una solución de ácido 5-cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-benzoico (59,6 g, 135 mmol) en tetrahidrofurano seco (300 ml). La solución se enfrió a 0°C en un baño de hielo-acetona. A esta solución se agregó diisopropiletilamina (34,8 g, 270 mmol), (S)-O-(2,2-dimetil-[1,3]dioxolan-4-ilmetil)-hidroxilamina (29,7 g, 202 mmol), 1-hidroxibenzotriazol (30,93 g, 202 mmol) y hexafluorofosfato de benzotriazol-1-iloxi-tris(dimetilamino)fosfonio (BOP) (89,32g, 202 mmol). Después de 30 minutos, el baño de enfriamiento se removió, y la reacción se agitó a temperatura ambiente durante 18 horas. El solvente se evaporó en vacío, y el residuo se disolvió en dietil éter. La solución orgánica se lavó con 10% de hidróxido

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de sodio acuoso (3 x 500 ml) y solución salina, y se secó ($MgSO_4$). La solución se concentró para dar 5-cloro-2-(2-cloro-4-yodo-fenilamino)-N-((S)-2,2-dimetil-[1,3]dioxolan-4-ilmetoxi)-3,4-difluoro-benzamida (69,9 g) como un sólido amarillo pálido que se usó directamente en la siguiente reacción de hidrólisis.

Paso B: Un solo matraz de base circular de 3 L equipado con una barra agitadora magnética se cargó con una solución de 5-cloro-2-(2-cloro-4-yodo-fenilamino)-N-((S)-2,2-dimetil-[1,3]dioxolan-4-ilmetoxi)-3,4-difluoro-benzamdia (69,9 g, 122 mmol) en tetrahidrofurano (1,5 L). Se agregó 1N solución de ácido clorhídrico (500 ml) y la mezcla de la reacción se agitó a temperatura ambiente durante 18 horas. La mezcla de la reacción se concentró y se etrajo con acetato de etilo (3 x 800 ml). Los extractos orgánicos se lavaron con bicarbonato de sodio acuoso saturado (500 ml) y solución salina (500 ml) y se secaron ($MgSO_4$). El sólido amarillo pálido crudo se recristalizó desde acetato de etilo/hexano y se secó a 70°C en un horno de vacío para dar 5-cloro-2-(2-cloro-4-yodo-fenilamino)-N-((S)-2,3-dihidroxi-propoxi)-3,4-difluoro-benzamida (35 g, 54%) como cristales de color amarillo pálido: punto de fusión 153°C-154°C; $[\alpha]$= -3,36° (c=1,04, metanol); ^1H NMR (400 MHz, d^6-DMSO): δ 12,02 (s, 1H), 8,85 (s, 1H), 7,74 (s,

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1H), 7,64 (d, 1H), 7,45 (d, 1H), 6,66 (t, 1H), 4,82 (s, 1H), 4,58 (s, 1H), 3,88 (m, 2H), 3,74 (m, 3H); ^{19}F NMR (d^6-DMSO) δ -133,21 (s, 1F), -137,18 (s, 1F); MS (m/z): 534(68), 532(100), 483(28), 481(41), 441(51). Análisis calculado/hallado para $C_{16}H_{13}Cl_2F_2IN_2O_4$: C, 36,05/36,36; H, 2,46/2,38; N, 5,25/5,30; F, 7,13/7,15; Cl, 13,30/13,76; I, 23,80/23,83.

EJEMPLO 53

5-Cloro-N-[(2(R),3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

Preparada desde (R)-O-(2,2-dimetil-[1,3]dioxolan-4-ilmetil)-hidroxilamina y ácido 5-cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzoico mediante el procedimiento descripto anteriormente para N-[(R)-2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida: punto de fusión 142°C-143°C. ^1H NMR (400 MHz, DMSO-d_6): δ 11,91 (s, 1H), 8,66 (s, 1H), 7,58-7,55 (m, 2H), 7,34 (d, 1H, J=8,1 Hz), 6,72 (cm, 1H), 4,81 (d, 1H, J=4,1 Hz), 4,58 (t, 1H, J=5,9 Hz), 3,87-3,84 (m, 1H), 3,70-3,68 (m, 2H), 3,33 (2H, parcialmente debajo de HDO).

EJEMPLO 54

5-Cloro-N-[(2(S),3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

Preparada desde (S)-O-(2,2-dimetil-[1,3]dioxolan-4-ilmetil)-hidroxilamina y ácido 5-cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzoico mediante el procedimiento descripto anteriormente para N-[(R)-2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida: punto de fusión 157°C-158°C; [α]= +5,29° (c=1,02, metanol); ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,91 (s, 1H), 8,66 (s, 1H), 7,58-7,55 (m, 2H), 7,34 (d, 1H, J=8,1 Hz), 6,72 (cm, 1H), 4,81 (d, 1H, J=4,1 Hz), 4,58 (t, 1H, J=5,9 Hz), 3,87-3,84 (m, 1H), 3,70-3,68 (m, 2H), 3,33 (2H, parcialmente debajo de HDO). Análisis calculado/hallado para $C_{16}H_{13}ClF_3IN_2O_4$: C, 37,20/37,47; H, 2,54/2,57; N, 5,42/5,32; F, 11,03/11,09; Cl, 6,86/6,87; I, 24,50/24,80.

EJEMPLO 55

2-(4-Bromo-2-fluoro-fenilamino)-N-((R)-2,3-dihidroxi-propoxi)-3,4-difluoro-benzamida

Preparada desde N-[2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida (Ejemplo 39) con la siguiente excepción: Los orgánicos se secaron sobre sulfato de sodio y se concentraron para dar una espuma blanca. Ésta se calentó a 100°C bajo vacío (0,5 mm) durante 1 h para dar un vidrio: punto de fusión: 52°C (encogimiento), 70°C (fusión); [α]= -4,4° (c=6,8, etanol); ^{1}H NMR (400 MHz, CD_3OD): δ 7,40

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[cm, 1H]; 7,29 [dd, J=11,0, 2,2 Hz, 1H]; 7,16 [d, J=8,5 Hz, 1H]; 6,98 [dd, J=16,4, 9 Hz, 1H]; 6,73 [cm, 1H]; 3,94 [cm, 1H]; 3,55 [m, 2H]. Análisis calculado/hallado para $C_{16}H_{14}BrF_3BrN_2O_4$: C, 44,16/43,77; H, 3,24/3,36; N, 6,44/6,09; F, 13,10/12,64; Br, 18,36/18,24.

Los compuestos de los ejemplos 56-61 se prepararon mediante el procedimiento general del ejemplo 1.

EJEMPLO 56

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-viniloxi-etoxi)-benzamida

Rendimiento: 55%; punto de fusión 141,5°C-143,0°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12,01 (s, 1H), 8,84 (s, 1H), 7,77 (d, J=1,7 Hz, 1H), 7,51-7,42 (m, 2H), 7,27 (ddd, J=9,0, 8,8, 7,8 Hz, 1H), 6,59 (dd, J=14,2, 6,6 Hz, 1H), 4,19 (d, J=14,1 Hz, 1H), 4,06 (br s, 2 H), 3,98 (d, J=6,6 Hz, 1 H), 3,87 (br s, 2 H); ^{19}F NMR (DMSO-d_6) δ -132,4, -141,4; MS (APCI+): 495,1; MS (APCI-)=493,0. Análisis calculado/hallado para $C_{17}H_{14}ClF_2N_2O_3$ con 0,08 moles de C_6H_{14} residual: C, 41,86/41,90; H, 3,04/2,91; N, 5,95/5,72.

EJEMPLO 57

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2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-viniloxi-etoxi)-benzamida

Rendimiento: 25%; punto de fusión 115°C-116°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,96 (s, 1H), 8,42 (s, 1H), 7,73 (d, 1H, J=1,7 Hz), 7,59 (m, 1H), 7,44 (dd, 1H, J= 8,6, 1,7 Hz), 6,54 (m, 1H), 6,47 (dd, 1H, J= 14,2, 6,6 Hz), 4,15 (d, 1H, J=14,2 Hz), 4,02 (s, 2 H), 3,96 (dd, 1H, J=6,9, 1,7 Hz), 3,83 (s, 2 H); ^{19}F NMR (DMSO-d_6) δ -137,08 (d, 1F, J=20,0 Hz), -140,97 (s, 1F), -154,65 (s, 1F); MS ($APCI^+$): 513,0 (M+1, 100); MS ($APCI^-$) = 511,0 (M-1, 65), 424,9 (100); IR (KBr) 1647 (C=O estiramiento), 1621, 1488 cm^{-1}. Análisis calculado/hallado para $C_{17}H_{13}ClF_2IN_2O_3$: C, 39,83/40,04; H, 2,56/2,54; N, 5,46/5,32.

EJEMPLO 58

4-Fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-viniloxi-etoxi)-benzamida

Rendimiento: 44%; punto de fusión 103,5°C-104°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,90 (s, 1H), 9,62 (s, 1H), 7,69 (dd, 1H, J=10,5, 2,0 Hz), 7,60 (m, 1H), 7,49 (d, 1H, J= 8,3 Hz), 7,27 (m, 1H), 6,84 (d, 1H, J= 11,7 Hz), 6,70 (m, 1H), 6,52 (dd, 1H, J=14,4, 6,8 Hz), 4,20 (dd, 1H, J=14,4, 2,0 Hz), 4,09 (m, 2H); 3,98 (dd, 1H, J=6,8, 1,7 Hz), 3,90 (m, 2H); ^{19}F NMR (DMSO-d_6) δ -106,73 (s, 1F), -124,58 (s, 1F); MS ($APCI^+$): 461,0 (M+1, 100); MS ($APCI^-$) = 459,0 (M-1, 100); IR (KBr) 1641 (C=O

estiramiento), 1602 cm^{-1}. Análisis calculado/hallado para $C_{17}H_{15}F_2IN_2O_3$: C, 44,37/44,42; H, 3,29/3,28; N, 6,09/5,89.

EJEMPLO 59

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-viniloxi-etoxi)-benzamida

^1H NMR (400 MHz, DMSO-d_6): δ 11,89 (s, 1H), 8,67 (s, 1H), 7,57 (dd, J=11,0, 1,7 Hz, 1H), 7,41-7,39 (m, 2 H), 7,20 (m, 1H), 6,66 (m, 1 H), 6,46 (dd, J= 14,2, 6,8 Hz, 1 H), 4,17 (dd, J=14,2, 1,5 Hz, 1 H), 4,00 (br s, 2 H), 3,97 (dd, J=6,7, 1,8 Hz, 1 H), 3,84 (br s, 2 H); ^{19}F NMR (DMSO-d_6) δ -128,01 (s, 1F), -133,1 (s, 1F), -144,3 (d, 17,7 Hz, 1F). Análisis calculado/hallado para $C_{17}H_{14}F_3IN_2O_3$: C, 42,70/42,30; H, 2,95/2,92; N, 5,86/5,52.

EJEMPLO 60

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-viniloxi-etoxi)-benzamida

Rendimiento: 34%; punto de fusión 119°C-120°C; ^1H NMR (400 MHz, DMSO-d_6): δ 11,96 (s, 1H), 8,64 (s, 1H), 7,59 (m, 2H), 7,35 (d, 1H, J=8,3 Hz), 6,71 (m, 1H), 6,48 (dd, 1H, J= 14,4, 6,8 Hz), 4,17 (d, 1H, J=14,2), 3,98 (m, 3H), 3,84 (m, 2H); ^{19}F NMR (DMSO-d_6) δ -127,60 (s, 1F), -134,09 (d, 1F, J=15,2 Hz), -140,45 (d, 1F, J=17,7 Hz); MS (APCI$^-$) = 511,0 (M-1, 100); IR

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(KBr) 1646 (C=O estiramiento), 1608 cm^{-1}. Análisis calculado/hallado para $C_{17}H_{13}ClF_3IN_2O_3$: C, 39,83/39,78; H, 2,56/2,57; N, 5,46/5,36.

EJEMPLO 61

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-viniloxi-etoxi)-benzamida

Rendimiento: 39%; punto de fusión 128°C-130°C; ^1H NMR (400 MHz, DMSO-d_6): δ 11,95 (s, 1H), 8,67 (s, 1H), 7,69 (d, 1H, J=6,4 Hz), 7,57 (dd, 1H, J= 10,7, 1,7 Hz), 7,35 (d, 1H, J= 8,1 Hz), 6,72 (m, 1H), 6,48 (dd, 1H, J=14,4, 6,6 Hz), 4,17 (d, 1H, J=14,2 Hz), 3,98 (m, 3H), 3,83 (s, 2H); ^{19}F NMR (DMSO-d_6) δ -126,37 (s, 1F), -127,54 (s, 1F), -140,31 (d, 1F, J=17,7 Hz); MS ($APCI^+$): 558,9 (100), 556,9 (M+1, 98); MS ($APCI^-$) = 556,9 (31), 554,9 (M-1, 32), 468,9 (100); IR (KBr) 1644 (C=O estiramiento), 1607, 1515, 1490 cm^{-1}. Análisis calculado/hallado para $C_7H_{13}BrF_3IN_2O_3$: C, 36,65/36,71; H, 2,35/2,23; N, 5,03/4,97.

Los compuestos de los Ejemplos 62-64 se prepararon mediante el procedimiento general del ejemplo 12.

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EJEMPLO 62

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-1,1-dimetil-etoxi)-benzamida

punto de fusión 179°C-181°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,36 (s, 1H), 8,48 (s, 1H), 7,76 (d, 1H, J=6,8), 7,72 (s, 1H), 7,43 (d, 1H, J= 8,5), 6,59 (m, 1H), 4,55 (t, 1H, J= 6,4), 3,20 (d, 2H, J=5,9), 1,09 (s, 6H); MS (APCI$^+$)= 574,9/576,9. Análisis calculado/hallado para $C_{17}H_{15}ClF_2IN_2O_3$: C, 35,38/35,56; H, 2,63/2,53; N, 4,87/4,71; F, 6,60/6,68.

EJEMPLO 63

3,4-Difluoro-N-(2-hidroxi-1,1-dimetil-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

punto de fusión 175°C-176°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,29 (s, 1H), 8,15 (s, 1H), 7,46 (s, 1H), 7,41 (m, 1H), 7,32 (d, 1H, J= 8,3), 7,32 (q, 1H, J=16,4, 8,8), 6,38 (m, 1H), 4,59 (bs, 1H), 3,15 (d, 2H, J=4,9), 2,17 (s, 3H), 1,08 (s, 6H); MS (APCI$^+$)= 477,0. Análisis calculado/hallado para $C_{18}H_{19}F_2IN_2O_3$ (0,05eq de CH_2Cl_2): C, 45,12/44,73; H, 4,01/3,96; N, 5,83/5,54; F, 7,91/7,71.

EJEMPLO 64

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-2-metil-propoxi)-benzamida

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Rendimiento: 17%; punto de fusión 140°C-153°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,94 (s, 1H), 8,82 (s, 1H), 7,76 (d, 1H, J=1,5 Hz), 7,48 (dd, 1H, J= 8,5, 2,0 Hz), 7,42 (m, 1H), 7,25 (m, 1H), 6,57 (m, 1H), 4,58 (s, 1H), 3,63 (s, 2H), 1,12 (s, 6H); ^{19}F-NMR (376 MHz, DMSO-d_6) δ -132,53 (s, 1F), -141,45 (d, 1F); MS (APCI$^+$): 496,9 (M+1, 100); MS (APCI$^-$) 495,0, (M-1, 48), 406,9 (100); IR (KBr) 1637 cm^{-1} (C=O estiramiento). Análisis calculado/hallado para $C_{17}H_{16}ClF_2IN_2O_3$ con 0,03 mol de acetona residual: C, 41,18/41,57; H, 3,27/3,14; N, 5,62/5,31.

Los compuestos de los ejemplos 65-76 se prepararon mediante el procedimiento general del ejemplo 38.

EJEMPLO 65

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1,1-dimetil-etoxi)-benzamida

punto de fusión 182°C-183°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,25 (s, 1H), 8,38 (s, 1H), 7,54 (d, 1H, J=11,0), 7,39 (m, 1H), 7,31 (d, 1H, J= 8,1), 7,24 (dd, 1H, J=16,9, 9,5), 6,59-6,56 (m, 1H), 4,58 (m, 1H), 3,16 (d, 2H, J=6,3), 1,08 (s, 6H); MS (APCI$^+$): 481,0. Análisis calculado/hallado para $C_{17}H_{16}F_3IN_2O_3$ (+0,47 de $C_4H_8O_2$): C, 43,47/43,86; H, 3,82/3,40; N, 5,37/5,60.

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EJEMPLO 66

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-(2-hidroxi-1,1-dimetil-etoxi)-benzamida

punto de fusión 178°C-180°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,31 (s, 1H), 8,41 (s, 1H), 7,64 (d, 1H, J=7,1), 7,56 (d, 1H, J=11,0), 7,33 (d, 1H, J= 8,3), 6,69-6,65 (m, 1H), 4,57 (t, 1H, J=6,1), 3,19 (d, 2H, J=6,6); 1,10 (s, 6H); MS (APCI$^+$): 514,0/516,9. Análisis calculado/hallado para $C_{17}H_{15}ClF_3IN_2O_3$: C, 39,67/39,99; H, 2,94/2,74; N, 5,44/5,31; F, 11,07/11,05.

EJEMPLO 67

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-2-metil-propoxi)-benzamida

punto de fusión 156,7°C-156,9°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,85 (1H, s), 8,70 (1H, s), 7,55 (1H, dd, J=10,8 Hz, 1,9 Hz), 7,33-7,37 (2H, m), 7,17 (1H, dd, J=16,7 Hz, 9,4 Hz) 6,62-6,67 (1H, m), 4,57 (1H, br s), 3,58 (2H, s), 1,09 (s, 6H); MS (APCI$^+$): 514,0/516,9. Análisis calculado/hallado para $C_{17}H_{16}F_3IN_2O_3$: C, 42,52/42,48; H, 3,36/3,21; N, 5,83/5,67; F, 11,87/11,51; I, 26,43/26,38.

EJEMPLO 68

3,4-Difluoro-N-(2-hidroxi-3-metoxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

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punto de fusión 136,2°C-136,5°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,90 (1H, s), 8,49 (1H, s), 7,50 (1H, d, J=1,7 Hz), 7,34-7,41 (2H, m),7,14 (1H, dd, J=16,6 Hz, 9,3 Hz), 6,45 (1H, dd, J=8,4 Hz, 5,6 Hz), 4,97 (1H, s), 3,69-3,79 (3H, m), 3,25-3,31 (2H, m), 3,21 (3H, s), 2,21 (3H). Análisis calculado/hallado para $C_{18}H_{19}F_2IN_2O_3$: C, 43,92/44,14; H, 3,89/3,88; N, 5,69/5,59; F, 7,72/7,79; I, 25,78/25,89.

EJEMPLO 69

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-metoxi-propoxi)-benzamida

punto de fusión 139,5°C-140,1°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12,03 (1H, s), 8,83 (1H, s), 7,50-7,76 (2H, m), 7,47 (1H, dd, J=8,6 Hz, 1,5 Hz), 6,65-6,69 (1H, m), 4,98 (1H, s), 3,70-3,90 (3H, m), 3,31 (2H, m), 3,22 (3H, s). Análisis calculado/hallado para $C_{17}H_{15}ClF_2IN_2O_4$: C, 34,52/34,92; H, 2,56/2,54; N, 4,74/4,67; F, 6,42/6,48; I, 21,45/21,12.

EJEMPLO 70

3,4-Difluoro-N-(1-hidroximetil-ciclopropilmetoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida

punto de fusión 165,4°C-165,6°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,74 (1H, s), 8,49 (1H, s), 7,47 (1H, d, J=1,5 Hz), 7,31-7,36 (2H, m), 7,11 (1H, dd, J=16,5 Hz, 9,4 Hz), 6,43 (1H, dd, J=8,3

Hz, 5,6 Hz), 4,55 (1H, br s), 3,67 (2H, s), 3,33 (2H, s), 2,17 (3H, s), 0,36 (4H, J=4,9 Hz). Análisis calculado/hallado para $C_{19}H_{19}F_2IN_2O_3$: C, 46,74/46,87; H, 3,92/3,93; N, 5,74/5,99; F, 7,78/7,64; I, 25,99/25,84.

EJEMPLO 71

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(1-hidroximetil-ciclopropilmetoxi)-benzamida

punto de fusión 152,6°C-153,9°C; ^1H NMR (400 MHz, DMSO-d_6): δ 11,88 (1H, s), 8,81 (1H, s), 7,75 (1H, s), 7,69 (1H, d, J=6,6 Hz), 7,45 (1H, d, J=8,5 Hz), 6,63-6,67 (1H, m), 4,53 (1H, br s), 3,73 (2H, s), 3,33 (2H, s), 0,36 (4H, J=4,9 Hz). Análisis calculado/hallado para $C_{18}H_{15}BrClF_2IN_2O_3$: C, 36,79/37,21; H, 2,57/2,57; N, 4,77/4,64; F, 6,47/6,58; I, 21,60/21,78.

EJEMPLO 72

3,4-Difluoro-2-(4-yodo-2-metil-fenilamino)-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida

punto de fusión 175,2°C-175,5°C; ^1H NMR (400 MHz, DMSO-d_6): δ 12,00 (1H, s), 8,41 (1H, s), 7,47 (1H), 7,40 (1H, m), 7,33 (1H, d), 7,12 (1H, dd, J=16,6 Hz, 9,3 Hz), 6,54 (1H, br s), 6,44 (1H, dd, J=8,3 Hz, 5,3 Hz), 4,24 (1H, m), 3,83-3,98 (2H, s), 2,18 (3H, s). Análisis calculado/hallado para $C_{17}H_{14}F_5IN_2O_3$:

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C, 39,56/39,87; H, 2,73/2,66; N, 5,43/5,30; F, 18,40/18,32; I, 24,58/24,63.

EJEMPLO 73

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida

punto de fusión 186,9°C-187,3°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12,16 (1H, s), 8,77 (1H, s), 7,80 (1H, dd, J=7,0 Hz, 1,5 Hz), 7,75 (1H, d, J=1,7 Hz), 7,47 (1H, dd, J=8,6 Hz, 1,9 Hz), 6,66 (1H, dd, J=8,5 Hz, 5,9 Hz), 6,55 (1H, br s), 4,31 (1H, m), 3,92-4,07 (2H, m). Análisis calculado/hallado para $C_{16}H_{10}BrClF_5IN_2O_3$: C, 31,22/31,52; H, 1,64/1,60; N, 4,55/4,46; F, 15,43/15,39; I, 20,62/20,87.

EJEMPLO 74

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-[trans-(2-hidroximetil-ciclopropilmetoxi)]-benzamida

punto de fusión 128,5°C-128,7°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,71 (1H, s), 8,69 (1H, s), 7,55 (1H, dd, J=10,9 Hz, 1,8 Hz), 7,32-7,36 (2H, m), 7,17 (1H, dd, J=16,6 Hz, 9,3 Hz), 6,60-6,66 (1H, m), 4,43 (1H, t, J=5,6 Hz), 3,54-3,65 (2H, m), 3,14-3,34 (2H, m), 0,85-0,89 (2H, m), 0,34-0,41 (2H, m). Análisis calculado/hallado para $C_{18}H_{16}F_3IN_2O_3$: C, 43,92/44,23; H, 3,28/3,23; N, 5,69/5,54; F, 11,58/11,47; I, 25,78/25,58.

EJEMPLO 75

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-[trans-(2-hidroximetil-ciclopropilmetoxi)]-benzamida

punto de fusión 152,5°C-153,1°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,76 (1H, s), 8,65 (1H, s), 7,56 (1H, m), 7,52-7,53 (1H, m), 7,32 (1H, d, J=8,5 Hz), 6,66-6,72 (1H, m), 4,44-4,47 (1H, m), 3,54-3,62 (2H, m), 3,12-3,42 (2H, m), 0,81-0,89 (2H, m), 0,32-0,40 (2H, m). Análisis calculado/hallado para $C_{18}H_{15}ClF_3IN_2O_3$: C, 41,05/41,00; H, 2,87/2,96; N, 5,31/5,13; F, 10,82/10,48; I, 24,09/24,33.

EJEMPLO 76

N-(2,3-Dihidroxi-3-metil-butoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida

punto de fusión 180°C-183°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,85 (s, 1H), 8,69 (bs, 1H), 7,56 (d, 1H, J=10,7), 7,40 (m, 1H), 7,35 (d, 1H, J=9,0), 7,20 (dd, 1H, J=16,6, 8,3), 6,65 (m; 1H), 4,87 (bs, 1H), 4,31 (s, 1H), 4,07 (d, 1H, J=9,8), 3,65 (t, 1H, J=9,8), 3,44-3,41 (m, 1H), 1,05 (s, 3H), 0,97 (s, 3H); MS (APCI+)=511,1. Análisis calculado/hallado para $C_{18}H_{18}F_3IN_2O_4$ (+0,22 eq $C_4H_8O_2$): C, 42,82/43,20; H, 3,76/3,61; N, 5,29/5,15.

EJEMPLO 77

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2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-fenilamino-etoxi)-benzamida

El compuesto del título se preparó en la forma descripta para el ejemplo 1. Un sólido blanco: punto de fusión 157,8°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,3 (s, 1H), 7,70 (m, 2H), 7,44 (dd, dd, J=8,6 Hz, 1,95 Hz, 1H), 7,01 (t, J=8,1 Hz, 2H), 6,94 (t, J=9,2 Hz, 1H), 6,47 (m, 4H), 5,58 (br t, J=5,1 Hz, 1H), 3,91 (t, J=5,6 Hz, 2H), 3,19 (q, J=5,6 Hz, 2H); ^{19}F NMR (376 MHz, DMSO-d_6) δ -139,7 (s, 1F), -143,39 (d, J=20,2 Hz, 1F).

EJEMPLO 78

3,4-Difluoro-2-(4-yodo-2-metil-fenilamino)-N-(2-metilamino-etoxi)-benzamida

Paso A: A una solución de terc-butil éster del ácido (2-aminooxi-etil)-metil-carbámico (0,63 g, 3,31 mmol) y diisopropiletilamina (0,6 ml, 3,44 mmol) en dimetilformamida (10 ml) se agregó pentafluorofenil éster del ácido 3,4-difluoro-2-(4-yodo-metil-fenilamino)-benzoico (1,66 g, 2,99 mmol). La mezcla de la reacción resultante se agitó durante 5 horas a temperatura ambiente y se concentró bajo presión reducida. El residuo se diluyó con éter (100 ml), se lavó con agua (2 x 25 ml) y solución salina (2x 25 ml), se secó sobre sulfato de magnesio y se concentró en vacío. El residuo se purificó mediante cromatografía de gel de sílice. La elución

con diclorometano dio terc-butil éster del ácido [2-({1-[3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-fenil]-metanoil}-aminooxi)-etil]-metil-carbámico (1,05 g, 62%) como una espuma blanca: ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,85 y 11,80 (br s, 1H), 8,49 (br s, 1H), 7,50 (s, 1H), 7,39 (m, 1H), 7,35 (d, J=8,3 Hz, 1 H), 7,14 (m, 1H), 6,46 (dd, J=7,8, 5,9 Hz, 1H), 3,85 (br s, 2 H), 3,35 (br s, 2 H), 2,79 (br s, 3 H), 2,21 (s, 3 H), 1,36 y 1,33 (s, 9 H); ^{19}F-NMR (376 MHz, DMSO-d_6) δ -132,9, -143,3 (d, J=17,7 Hz); MS (APCI$^+$): 562,1.

Paso B: Se agregó ácido trifluoroacético (3,0 ml, 39 mmol) a una solución a 0°C de terc-butil éster del ácido [2-({1-[3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-fenil]-metoxi}-aminooxi)-etil]-metil-carbámico (0,75 g, 1,3 mmol) en diclorometano (12 ml). La solución resultante se agitó durante 1,5 h a 0°C y se diluyó con éter (50 ml). Se agregó agua (20 ml) y, con agitación vigorosa, el pH de la capa acuosa se ajustó a pH 8 con bicarbonato de sodio acuoso saturado. La mezcla heterogénea se agitó durante 30 minutos y el precipitado se removió mediante filtración y se lavó con agua-etanol (2:1) y acetona. El sólido (471 mg) se secó toda la noche en vacío y se trituró más con metanol caliente y se secó a 70°C bajo presión reducida para dar 3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-N-(2-metilamino-etoxi)-benzamida (272 mg) como un polvo blanco: punto de fusión 183°C-185°C; ^{1}H NMR (400

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MHz, DMSO-d_6): δ 10,33 (s, 1H), 7,69 (t, J=7,0 Hz, 1 H), 7,46 (d, J=1,7 Hz, 1 H), 7,33 (dd, J=8,6, 2,0 Hz, 1 H), 6,95 (app q, J=9,0 Hz, 1 H), 6,40 (t, J=7,8 Hz, 1 H), 3,87 (br t, J=4,4 Hz, 2 H), 2,82 (br s, 2 H), 2,47 (s, 3 H), 2,24 (s, 3 H); ^{19}F-NMR (376 MHz, DMSO-d_6) δ -137,7 (d, J=7,6 Hz), -143,3 (d, J=20,2 Hz). Análisis calculado/hallado para $C_{17}H_{18}F_2IN_3O_2$+0,07 $C_4H_{10}O$: C, 44,50/44,61; H, 4,01/3,97; N, 9,01/8,72.

EJEMPLO 79

Sal de clorhidrato de 3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-metilamino-etoxi)-benzamida

Paso A: Una solución de ácido 3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzoico (3,11 g, 7,91 mmol) en tetrahidrofurano (20 ml) se enfrió con un baño a -40°C y se trató con N-metilmorfolina (0,87 ml, 7,9 mmol). Se agregó cloruro difenilfosfínico (2,00 ml, 10,5 mmol) gota a gota durante 5 minutos y la mezcla de la reacción se agitó durante 90 minutos, durante cuyo tiempo la temperatura del baño de enfriamiento se calentó lentamente a 0°C. La mezcla de la reacción se enfrió nuevamente a -40°C y se agregó terc-butil éster del ácido (2-aminooxi-etil)-metil-carbámico (2,00 g, 10,5 mmol) como una solución en tetrahidrofurano (6 ml). Después de otros 10 minutos, se agregó N-metilmorfolina (1,33 ml, 12,1 mmol). La temperatura del baño de enfriamiento se

dejó calentar a temperatura ambiente durante 4 horas y la mezcla de la reacción se agitó nuevamente toda la noche. La reacción se diluyó con acetato de etilo (40 ml) y se lavó con cloruro de amonio acuoso saturado (2 x 10 ml). Los orgánicos se secaron sobre sulfato de magnesio, se concentraron y se purificiaron mediante cromatografía de gel de sílice. La elución con 35% de acetato de etilo-hexanos dio terc-butil éster [2-({1-[3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-fenil]-metanoil}-aminooxi)-etil]-metil-carbámico (3,28 g, 73% de rendimiento) como una espuma blancuzca: ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,84 y 11,75 (br s, 1H total), 8,66 (br s, 1H), 7,54 (dd, J=10,9, 1,6 Hz, 1 H), 7,36 (br t, J=8,8 Hz, 1 H), 7,33 (br d, J=8,8 Hz), 7,20 (m, 1H), 6,64 (m, 1H), 3,85 (t, J=5,2 Hz, 2 H), 3,34 (br s, 2 H), 2,81 y 2,79 (br s, 3 H total), 1,34 y 1,32 (s, 9 H total); ^{19}F-NMR (376 MHz, DMSO-d_6) δ -128,0 (d, J=32,9 Hz), -133,0, -144,2 (d, J=17,7 Hz); MS (APCI$^-$): 564,1.

Paso B: terc-Butil éster del ácido [2-({1-[3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-fenil]-metanoil}-aminooxi)-etil]-metil-carbámico (3,28 g, 5,80 mmol) se disolvió en una solución etérea de cloruro de hidrógeno (20 ml, 1,0 M en dietil éter). La solución resultante se agitó a temperatura ambiente durante 48 h, durante cuya precipitación se obtuvo un

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sólido blanco. Se agregaron hexanos (20 ml) y la mezcla de la reacción se agitó vigorosamente durante 20 minutos adicionales. La mezcla de la reacción se filtró, y la torta del filtro se rompió con una espátula. El sólido se lavó con hexanos (50 ml) y éter (20 ml) y se secó en vacío para lograr un polvo de color tostado, que fluye libremente (2,46 g, 85% de rendimiento). La recristalización desde acetonitrilo dio agujas incoloras: punto de fusión 173°C-176°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12,27 (s, 1H), 8,76 (s, 2 H), 8,64 (s, 1H), 7,55 (dd, J=11,0, 1,9 Hz, 1 H), 7,47 (dd, J=7,1, 6,3 Hz, 1 H), 7,33 (d, J=8,3 Hz, 1 H), 7,23 (dt, J=7,6, 9,2 Hz, 1 H), 6,64 (td, J=8,8, 4,2 Hz, 1 H), 4,05 (t, 4,9 Hz, 2 H), 3,11 (br s, 2 H), 2,56 (t, J=4,6 Hz, 3 H); ^{19}F-NMR (376 MHz, DMSO-d_6) δ -128,2 (t, J=10,1 Hz), -132,5 (d, J=20,2 Hz), -144,0 (d, 20,2 Hz). Análisis calculado/hallado para $C_{16}H_{16}F_3IN_2O_2Cl$: C, 38,31/38,20; H, 3,21/3,10; N, 8,38/8,34; F, 11,26/11,21; Cl, 7,07/7,05.

EJEMPLO 80

Clorhidrato de 3,4-Difluoro-2-(4-yodo-2-metil-fenilamino)-N-[2-(2,2,2-trifluoro-etilamino)-etoxi]-benzamida

Paso A: Se agregó dietilazodicarboxilato (3,60 ml, 22,9 mmol) gota a gota durante 30 minutos a una solución compuesta por O-[2-(2,2,2-trifluoro-etilamino)-etil]-hidroxilamina (3,19 g, 22,3 mmol, preparada como en J. Am. Chem. Soc., 1979, 101,

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4300), trifenilfosfina (6,05 g, 23,1 mmol) y N-hidroxiftalimida (3,65 g, 22,4 mmol). La mezcla de la reacción resultante se agitó a temperatura ambiente. Después de 20 h, la mezcla de la reacción se concentró y el residuo se disolvió en 60 ml de cloroformo caliente. Al enfriarlo, se obtuvo la cristalización de dicarboxilato de dietil 1,2-hidrazina. El precipitado se filtró y el filtrado se concentró y se diluyó más con éter. Se agregó un solo cristal de óxido de trifenilfosfina, iniciando una precipitación copiosa. El precipitado resultante se removió mediante filtración y el filtrado se concentró en vacío y se cromatografió sobre gel de sílice. La elución con hexanos-acetato de etilo (2:1) dio 2-[2-(2,2,2-trifluoro-etilamino)-etoxi]-isoindol-1,3-diona (4,05 g, 63% de rendimiento) como un aceite incoloro: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7,84-7,73 (m, 4H), 4,30 (t, J=4,8 Hz, 2H), 3,26 (q, J=9,5 Hz, 2H), 3,00 (t, J=4,9 Hz, 2H), 2,33 (br s, 1H); MS (APCI+)= 289,0.

Paso B: Se agregó diclorometano (5 ml) a 2-[2-(2,2,2-trifluoro-etilamino)-etoxi]-isoindol-1,3-diona (0,46 g, 1,6 mmol) y la solución resultante se enfrió a 0°C. Se agregó metilhidrazina (0,086 ml, 1,62 mmol) y la solución resultante se agitó a temperatura ambiente durante 1 h. Se agregó éter (20 ml) y el precipitado se filtró y el filtrado se concentró en vacío. Se agregó dimetilformamida (5 ml) y la solución

resultante se trató en secuencia con pentafluorofenil éster del ácido 3,4-difluoro-2-(4-yodo-2-metil-feniamino)-benzoico (0,847 g, 1,51 mmol) y diisopropiletilamina (0,60 ml, 3,4 mmol). La mezcla de la reacción resultante se agitó toda la noche, se diluyó con acetato de etilo y se lavó con agua (4x) y solución salina saturada, se secó sobre sulfato de magnesio y se concentró en vacío. La purificación mediante cromatografía de gel de sílice (hexanos-acetato de etilo, 1:1) dio 3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-N-[2-(2,2,2-trifluoro-etilamino)-etoxi]-benzamida (0,70 g, 83% de rendimiento) como una espuma cerosa: ^{1}H NMR (400 MHz, acetona-d_6): δ 10,98 (br s, 1H), 8,69 (br s, 1H), 7,52 (br s, 2H), 7,39 (dd, J=8,6, 2,0 Hz, 1H), 7,00 (m, 1H), 6,55 (dd, J=8,6, 6,4 Hz, 1H), 3,27 (q, J=10,0 Hz, 2H), 2,90 (br t, J=4,9 Hz, 2H), 2,82 (br s, 2H), 2,30 (s, 3H); ^{19}F-NMR (376 MHz, acetona-d_6) δ -73,1 (t, J=10,0 Hz, 3F), -133,8 (s, 1F), -143,2 (s, 1F); MS (APCI+)=530,0.

Paso C: La sal de clorhidrato se preparó mediante el tratamiento de una solución de 3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-N-[2-(2,2,2-trifluoro-etilamino)-etoxi]-benzamida (375 mg, 0,708 mmol) en éter (5 ml) con cloruro de hidrógeno etéreo (2 ml, 1,0 M en éter) y la precipitación mediante el agregado de hexanos (50 ml). El sólido resultante se secó en vacío a 75°C toda la noche para dar un polvo de color pajizo:

^{1}H NMR (400 MHz, acetona-d_6): δ 12,35 (br s, 1H), 8,84 (br s, 1H), 7,73 (br s, 1H), 7,54 (s, 1H), 7,40 (dd, J=8,4, 1,9 Hz, 1H), 7,00 (q aparente, J= 8,4 Hz, 1H), 6,58 (dd, J=8,4, 6,40 Hz, 1H), 4,43 (br s, 2H), 4,17 (br q, 2H), 3,59 (br s, 2H), 2,30 (s, 3H); ^{19}F-NMR (376 MHz, acetona-d_6) δ -68,39 (s, 3F), -133,07 (s, 1F), -143,20 (s, 1F); Análisis calculado/hallado para $C_{18}H_{17}F_5IN_3O_2$+0,86 HCl: C, 38,57/38,77; H, 3,21/3,04; N, 7,49/7,19; Cl, 5,44/5,66.

EJEMPLO 81

2-(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-etoxi)-N-metil-benzamida

Una solución de 2-(2-cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-etoxi)-benzamida (0,460 g, 1,02 mmol) en dimetilformamida (10 ml) se trató en secuencia con carbonato de potasio (0,61 g, 4,4 mmol) y yodometano (0,075 ml, 1,2 mmol). La mezcla de la reacción resultante se agitó 1 h a temperatura ambiente, se diluyó con exceso de agua y se extrajo con acetato de etilo. Los extractos orgánicos se lavaron con solución salina, se secaron sobre sulfato de magnesio y se concentraron en vacío. La cromatografía sobre gel de sílice dio un sólido blanco (200 mg). Otra purificación mediante cromatografía sobre gel de sílice de fase inversa de C_{18} (30% de agua-acetonitrilo) dio 2-(2-cloro-4-yodo-

fenilamino)-4-fluoro-N-(2-hidroxi-etoxi)-N-metil-benzamida (139 mg, 29% de rendimiento) como una espuma blanca. ^{1}H NMR (400 MHz, acetona-d_6): δ 8,45 (s, 1H), 7,79 (d, J= 2,0 Hz, 1H), 7,69 (dd, J=8,8, 6,6 Hz, 1H), 7,60 (dd, J=8,5, 2,0 Hz, 1H), 7,28 (d, J=8,5 Hz, 1H), 7,09 (dd, J=11,4, 2,3 Hz, 1H), 6,77 (td, J=8,6, 2,5 Hz, 1H), 3,90 (t, J=2 H), 3,85 (br m, OH), 3,58 (t, J=4,5 Hz, 2 H), 3,38 (s, 3H); ^{19}F-NMR (376 MHz, acetona-d_6) δ -109,8 (dd, J=10,1, 7,6 Hz); MS (APCI+)= 465,0.

EJEMPLO 82

2-({1-[3,4,5-trifluoro-2-(4-yodo-2-metil-fenilamino)-fenil]-metanoil}-aminooxi)-etil éster del ácido acético

A una solución a 0°C de 3,4,5-trifluoro-N-(2-hidroxi-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida (0,25 g, 0,536 mmol) en THF (10,72 ml) se agregó trietilamina (0,113 ml, 0,804 mmol). Después de 5 minutos, se agregó cloruro de acetilo (0,039 ml, 0,536 mmol) a la solución fría, que produjo inmediatamente un precipitado. Después de agitar durante 50 minutos de 0°C-5°C, la mezcla de la reacción se particionó entre agua (20 ml) y acetato de etilo (20 ml). La capa acuosa se extrajo con acetato de etilo (20 ml). Las capas orgánicas se combinaron y se secaron sobre sulfato de magnesio anhidro. La mezcla resultante se filtró y la torta de filtro se enjuagó

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completamente con acetato de etilo. El filtrado se concentró en vacío para obtener un aceite amarillo (0,1755 g). Se cromatografió el aceite crudo usando un gradiente de hexanos y acetato de etilo. Las fracciones se combinaron y el solvente se removió en vacío para obtener un sólido. El sólido se recristalizó en una mezcla de hexanos/acetona para obtener 0,0221 g (8%) de un sólido; ^{1}H NMR (400 MHz, acetona-d_6): δ 10,15 (br s, 1H), 8,49 (br s, 1H), 7,88 (t, J=0,9 Hz, 1H), 7,56 (s, 1H), 7,43 (d, J=8,3 Hz, 1H), 6,69 (dd, J=8,55, 5,86 Hz, 1H), 4,53 (br s, 2H), 4,19 (br s, 2H), 2,33 (s, 3H), 1,81 (br s, 3H); ^{19}F-NMR (376 MHz, acetona-d_6) δ -139,52 (br t, 1F), -146,62 (br q, 1F), -153,43 (br s, 1F). Análisis calculado/hallado para $C_{18}H_{16}F_3IN_2O_4$: C, 42,54/40,87; H, 3,17/2,98; N, 5,51/5,17.

EJEMPLO 83

[3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-fenil]-(4-hidroxi-isoxazolidin-2-il)-metanona

A una solución en agitación de pentafluorofenil éster del ácido 3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzoico (171 mg, 0,306 mmol) y cloruro de 4-hidroxitetrahidroisoxazol-2-io (BIONET, 58 mg, 0,46 mmol) en dimetilformamida (2 ml) se agregó 4-metilmorfolina (0,1 ml, 0,91 mmol). La mezcla de la reacción resultante se agitó a temperatura ambiente durante 3

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h. Se agregó acetato de etilo, la mezcla se lavó con agua (3 x 10 ml) y solución salina saturada (10 ml). Los extractos se secaron sobre sulfato de magnesio y se concentraron en vacío. La cromatografía (10% de metanol-diclorometano) dio un aceite de color tostado que se solidificó al estar en reposo. La recristalización desde acetona-éter dio [3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-fenil]-(4-hidroxi-isoxazolidin-2-il)-metanona (61 mg, 43% de rendimiento) como un polvo blanco: punto de fusión 122°C-124°C; ^{1}H NMR (400 MHz, acetona-d_6): δ 7,97 (br s, 1H), 7,51-7,45 (m, 2H), 7,38 (ddd, J=8,6, 1,7, 1,2 Hz, 1H), 7,12 (m, 1H), 6,68 (td, J=8,8, 5,2 Hz, 1H), 4,82 (m, 1H), 4,71 (br d, J=4,2 Hz, OH), 3,98 (dd, J=8,8, 4,2 Hz, 1H), 3,96-3,88 (m, 2H), 3,75 (dd, J=11,8, 0,9 Hz, 1H); ^{19}F-NMR (376 MHz, acetona-d_6) δ -30,5, -135,4, -144,4. Análisis calculado/hallado para $C_{16}H_{12}F_3IN_2O_3$: C, 41,40/41,52; H, 2,61/2,53; N, 6,03/6,05.

EJEMPLO 84

5-Bromo-N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-fenilamino)-benzamida

Una solución de 5-bromo-N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida (0,240 g, 0,429 mmol) y trietilamina (0,2 g, 1,98 mmol) en tetrahidrofurano (16 ml) se hidrogenó sobre Níquel de Raney

(0,2 g, enjuagado previamente con tetrahidrofurano) a 10 psig a temperatura ambiente durante un total de 7 horas. El catalizador se removió mediante filtración y el filtrado se concentró en vacío. El residuo obtenido se particionó entre acetato de etilo y agua. Los orgánicos se lavaron dos veces con agua, dos veces con solución salina saturada, se recogieron, se secaron sobre sulfato de sodio, se filtraron y se concentraron en vacío. La purificación mediante HPLC se realizó usando una columna de YMC 30x100 mm 5u (C18) en 0%-100% de acetonitrilo (3,0% de n-propanol)/100%-0% de agua (3,0% de n-propanol) a 30 ml/min. Las fracciones deseadas se recogieron, se concentraron y se secaron en un horno de vacío toda la noche a 50°C para dar 5-bromo-N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-fenilamino)-benzamida como un sólido blanco (0,054 g, 30%): punto de fusión 143,5°C-144,5°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,95 (bs, 1H), 8,74 (bs, 1H), 7,68 (d, 1H, J=6,1 Hz), 7,17 (t, 1H, J=9,8 Hz), 7,01-7,04 (m, 1H), 6,94 (m, 2H), 4,81 (m, 1H), 4,57 (m, 1H), 3,86 (m, 1H), 3,69-3,71 (m, 2H), 3,3 (2H, debajo de HDO); MS(APCI+)=435,0/437,0.

EJEMPLO 85

N-(2,3-Dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-fenilamino)-benzamida

Una solución de N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida (0,260 g, 0,539 mmol) y trietilamina (2,0 ml, 14,3 mmol) en tetrahidrofurano (14 ml) se hidrogenó sobre Níquel de Raney (0,2 g, húmedo) a 50 psig a temperatura ambiente durante 20 horas. El catalizador se removió mediante filtración y el filtrado se concentró en vacío. El residuo obtenido se particionó entre acetato de etilo y agua. Los orgánicos se lavaron dos veces con bicarbonato de sodio saturado, dos veces con agua, se recogieron, se secaron sobre sulfato de sodio, se filtraron y se concentraron en vacío. La purificación mediante HPLC se realizó usando una columna de YMC 30x100 mm 5u (C18) en 0%-100% de acetonitrilo (3,0% de n-propanol)/100%-0% de agua (3,0% de n-propanol) a 30 ml/min. Las fracciones deseadas se recogieron y se concentraron. El residuo obtenido se extrajo con acetato de etilo/agua. Las capas orgánicas se lavaron con una solución saturada de NaCl y se secaron en vacío para dar para dar N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-fenilamino)-benzamida como un sólido blanco (0,061 g, 31%): punto de fusión 113°C-115°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11,90 (s, 1H), 8,73 (s, 1H), 7,37 (m, 1H), 7,10-7,19 (m, 1H), 7,02 (t, 1H, J=7,4 Hz), 6,84-6,93 (m, 2H), 4,82 (m, 1H), 4,57-4,58 (m, 1H), 3,86-3,88 (m, 1H), 3,67-3,73 (m, 2H), 3,3 (2H, debajo de HDO); MS(APCI+)=357,1; Análisis calculado/hallado para $C_{16}H_{15}F_3N_2O_4$: C, 53,94/53,97; H, 4,24/4,37; N, 7,86/7,83.

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EJEMPLOS 86-97

Los ejemplos 86-97 se prepararon utilizando los métodos sintéticos combinatorios que se detallan a continuación, mediante la combinación de la alcoxiamina y el pentafluorofenil éster respectivos, preparados como se describió anteriormente. Procedimiento General:

Paso A: Un conjunto de tubos de 2 dram se cargó con la diarilamina de pentafluorofenil éster apropiada (0,12 mmol) como un sólido y se diluyó con 2 ml de N,N-dimetilformamida. Usando un distribuidor volumétrico, cada reacción se cargó con 0,2 gramos de resina de morfolina soportada por polímeros (comercialmente disponible en Novabiochem o preparada mediante el método de Booth y Hodges: J. Am. Chem. Soc., 1997, 119, 4842). Se prepararon las soluciones de los acetonuros de hiroxilamina en N,N-dimetilformamida (0,8 M, 1,6 ml) y se distribuyeron (0,1 mmo, 0,2 ml) en el tubo de reacción correspondiente. Las reacciones se sellaron con tapones recubiertos con teflon y se dejaron agitar en un agitador orbital durante 5 días a temperatura ambiente. Las 14 reacciones se cargaron con 0,2 gramos de tris(2-aminoetil)amina soportada por polímeros [Novabiochem; ver también: Booth, R.J.; Hodges, J.C., J.Am.Chem. Soc., 1997, 119, 4842], 0,1 gramo de metilisocianato soportado por polímeros [Novabiochem; ver también: Booth, R.J.; Hodges,

J.C., Am. Chem. Soc., 1997, 119, 4842], y 1 ml de diclorometano. Los recipientes de la reacción se resellaron y se dejaron agitar otras 6 horas a temperatura ambiente. Las reacciones se filtraron a través de un filtro de 3 A Specdisk y se enjuagaron con 6 ml de una solución de 10% de metanol/diclorometano y se concentraron a través de una corriente de nitrógeno.

Paso B: Las acetonuro benzamidas resultantes se cargaron con 2 ml de metanol, 0,05 ml de agua desionizada, 2 mligramos de ácido p-toluenosulfónico y 0,1 gramos de resina de glicerol. Las reacciones se sellaron con tapones recubiertos con teflon y se dejaron agitar durante 17 horas. Las reacciones se filtraron a través de un filtro de 3 A Specdisk y se lavaron con 6 ml de 50% de metanol en diclorometano y se concentraron a través de una corriente de nitrógeno. La purificación se realizó sobre todas las muestras usando una columna de SQ1600 Combi-Flash eluyendo con acetonitrilo/agua (0,05% de ácido trifluoroacético). Se realizó LC/MS usando una columna de CPI 120SE C18 (4,6 x 50 µm) eluyendo con acetonitrilo/agua (0,05% de ácido trifluoroacético).

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Ejemplo N°	Compuesto	Fórmula	Masa Exacta Hallada
86	2-(2-Cloro-4-yodo-fenilamino)-N-(2,3-dihidroxi-propoxi)-3,4-difluoro-benzamida	$C_{16}H_{14}ClF_2IN_2O_4$	499 (APCI +)
87	2-(2-Cloro-4-yodo-fenilamino)-N-(2,3-dihidroxi-propoxi)-3,4,5-trifluoro-benzamida	$C_{16}H_{13}ClF_3IN_2O_4$	517 (APCI +)
88	5-Bromo-2-(2-cloro-4-yodo-fenilamino)-N-(2,3-dihidroxi-propoxi)-3,4-difluoro-benzamida	$C_{16}H_{13}BrClF_2IN_2O_4$	577/579 (APCI +)
89	N-(2,3-Dihidroxi-propoxi)-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-benzamida	$C_{17}H_{17}F_2IN_2O_4$	479 (APCI +)
90	N-(2,3-Dihidroxi-propoxi)-3,4,5-trifluoro-2-(4-yodo-2-metil-fenilamino)-benzamida	$C_{17}H_{16}F_3IN_2O_4$	495 ($APCI^-$)
91	5-Bromo-N-(2,3-dihidroxi-	$C_{17}H_{16}BrF_2IN_2O_4$	557/559

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	propoxi)-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-benzamida		(APCI +)
92	2-(2-Cloro-4-yodo-fenilamino)-N-(3,4-dihidroxi-butoxi)-3,4-difluoro-benzamida	$C_{17}H_{16}ClF_2IN_2O_4$	513 (APCI +)
93	2-(2-Cloro-4-yodo-fenilamino)-N-(3,4-dihidroxi-butoxi)-3,4,5-trifluoro-benzamida	$C_{17}H_{15}ClF_3IN_2O_4$	531 (APCI +)
94	5-Bromo-2-(2-cloro-4-yodo-fenilamino)-N-(3,4-dihidroxi-butoxi)-3,4-difluoro-benzamida	$C_{17}H_{15}BrClF_2IN_2O_4$	591/593 (APCI +)
95	N-(3,4-Dihidroxi-butoxi)-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-benzamida	$C_{18}H_{19}F_2IN_2O_4$	493 (APCI +)
96	N-(3,4-Dihidroxi-butoxi)-3,4,5-trifluoro-2-(4-yodo-2-metil-fenilamino)-benzamida	$C_{18}H_{18}F_3IN_2O_4$	511 (APCI +)
97	5-Bromo-N-(3,4-dihidroxi-	$C_{18}H_{18}BrF_2IN_2O_4$	571/573

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	butoxi)-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-benzamida		(APCI +)

EJEMPLOS 98-235

Los ejemplos 98-235 se prepararon utilizando métodos sintéticos combinatorios, que se detallan a continuación, mediante la combinación de la alcoxiamina y el pentafluorofenil éster respectivos, preparados como se describió anteriormente. Procedimiento General: Tubos de 2 dram se cargaron cada uno con 100-110 mg de morfolina soportada por polímros (3,55 mmol N/g) empleando un distribuidor de resina volumétrico. [La resina de morfolinometilo soportada por polímeros está comercialmente disponible (Novabiochem) o puede prepararse mediante el método de Booth y Hodges: J. Am. Chem. Soc., 1997, 119, 4842]. Lo tubos apropiados se trataron en secuencia con una solución de 0,08 M de material de la alcoxiamina en DMF (0,6 ml, 0,048 mmol) y una solución de 0,12 M de material del pentafluorofenil éster en DMF (0,48 ml, 0,0576 mmol, 1,2 eq.) Los tubos se sellaron con tapones recubiertos con Teflon y se agitaron en un agitador orbital a temperatura ambiente. Después de 48 horas, las mezclas de las reacciones se trataron con tris(2-aminoetil)amina soportada por polímeros (100 mg,

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4,28 mmol/g) [Novabiochem; ver también: Booth, R.J.; Hodges, J.C., J.Am.Chem. Soc., 1997, 119, 4842], y diclorometano (1,0 ml). Los tubos se taparon nuevamente y se agitaron otras 6 horas. Los sólidos se removieron mediante filtración a través de un filtro de 3 A Specdisk y se lavaron con una solución de 10% de metanol-diclorometano (3 x 2 ml). Los filtrados se concentraron bajo una corriente de nitrógeno y se purificaron mdiante HPLC usando una columna de SQ1600 Combiflash eluyendo con acetonitrilo/agua (0,05% de ácido trifluoroacético). Se realizó LC/MS usando una columna de CPI 120SE C18 (0,0046 x 0,050 mm) eluyendo con acetonitrilo/agua (0,05% de ácido trifluoroacético).

Ejemplo N°	Compuesto	Fórmula	Masa Exacta Hallada
98	5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-propoxi)-benzamida	$C_{16}H_{13}BrClF_2IN_2O_3$	561/563 (M + 1)
99	2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-propoxi)-benzamida	$C_{16}H_{14}ClF_2IN_2O_3$	483 (M+1)
100	3,4,5-Trifluoro-N-(3-hidroxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida	$C_{17}H_{16}F_3IN_2O_3$	481 (M+1)
101	2-(2-cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(3-hidroxi-propoxi)-benzamida	$C_{16}H_{13}ClF_3IN_2O_3$	501 (M+1)
102	5-Bromo-3,4-difluoro-N-(3-hidroxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida	$C_{17}H_{16}BrF_2IN_2O_3$	541/543 (M+1)
103	3,4-Difluoro-N-(3-hidroxi-propoxi)-2-(4-	$C_{17}H_{17}F_2IN_2O_3$	463 (M+1)

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	yodo-2-metil-fenilamino)-benzamida		
104	2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-butoxi)-benzamida	$C_{17}H_{16}ClF_2IN_2O_3$	496,9 (M+1)
105	2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-hidroxi-butoxi)-benzamida	$C_{17}H_{15}ClF_3IN_2O_3$	514,9 (M+1)
106	3,4,4-Trifluoro-N-(2-hidroxi-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida	$C_{18}H_{18}F_3IN_2O_3$	494,9 (M+1)
107	5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-butoxi)-benzamida	$C_{17}H_{15}BrClF_2IN_2O_3$	574,8/576,8 (M+1)
108	5-Bromo-3,4-difluoro-N-(2-hidroxi-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida	$C_{18}H_{18}BrF_2IN_2O_3$	554,9/556,9 (M+1)
109	3,4-Difluoro-N-(2-hidroxi-butoxi)-2-(4-	$C_{18}H_{19}F_2IN_2O_3$	476,9 (M+1)

	yodo-2-metil-fenilamino)-benzamida		
110	5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-butoxi)-benzamida	$C_{17}H_{15}Cl_2F_2IN_2O_3$	530,8 (M+1)
111	5-Cloro-3,4-difluoro-N-(2-hidroxi-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida	$C_{18}H_{18}ClF_2IN_2O_3$	510,9 (M+1)
112	3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-butoxi)-benzamida	$C_{17}H_{16}F_3IN_2O_3$	481,1 (M+1)
113	5-Bromo-3,4-difluoro-2-(2-fluoro-2-metil-fenialmino)-N-(2-hidroxi-butoxi)-benzamida	$C_{17}H_{15}BrF_3IN_2O_3$	559,0/561,0 (M+1)
114	5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-butoxi)-benzamida	$C_{17}H_{15}ClF_3IN_2O_3$	515,1 (M+1)
115	4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-butoxi)-benzamida	$C_{17}H_{16}F_3IN_2O_3$	481,1 (M+1)

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116	5-Cloro-2-(2,4-difluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-butoxi)-benzamida	$C_{17}H_{15}ClF_4N_2O_3$	407,4 (M+1)
117	2-(2,4-Difluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-butoxi)-benzamida	$C_{17}H_{16}F_4N_2O_3$	373,5 (M+1)
118	2-(4-Bromo-2-fluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-butoxi)-benzamida	$C_{17}H_{16}BrF_3N_2O_3$	433,3/435,3 (M+1)
119	5-Cloro-3,4-difluoro-N-(2-hiroxi-1-metil-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida	$C_{17}H_{16}ClF_2IN_2O_3$	496,9 (M+1)
120	2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-1-metil-etoxi)-benzamida	$C_{16}H_{14}ClF_2IN_2O_3$	482,9 (M+1)
121	2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-hidroxi-1-metil-etoxi)-benzamida	$C_{16}H_{13}ClF_3IN_2O_3$	500,9 (M+1)

122	3,4,5-Trifluoro-N-(2-hidroxi-hidroxi-1-metil-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida	$C_{17}H_{16}F_3IN_2O_3$	480,9 (M+1)
123	5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-1-metil-etoxi)-benzamida	$C_{16}H_{13}BrClF_2IN_2O_3$	560,8/562,8 (M+1)
124	5-Bromo-3,4-difluoro-N-(2-hidroxi-1-metil-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida	$C_{17}H_{16}BrF_2IN_2O_3$	540,8/543,8 (M+1)
125	2-(4-Cloro-2-fluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-1-metil-etoxi)-benzamida	$C_{16}H_{14}ClF_3N_2O_3$	375,0 (M+1)
126	3,4-Difluoro-N-(2-hidroxi-1-metil-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida	$C_{17}H_{17}F_3IN_2O_3$	462,9 (M+1)
127	5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-1-metil-etoxi)-benzamida	$C_{16}H_{13}Cl_2F_2IN_2O_3$	516,8 (M+1)

128	3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1-metil-etoxi)-benzamida	$C_{16}H_{14}F_3IN_2O_3$	466,9 (M+1)
129	5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1-metil-etoxi)-benzamida	$C_{16}H_{13}BrF_3IN_2O_3$	545,0/547,0 (M+1)
130	5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1-metil-etoxi)-benzamida	$C_{16}H_{13}ClF_3IN_2O_3$	500,9 (M+1)
131	4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1-metil-etoxi)-benzamida	$C_{16}H_{14}F_3IN_2O_3$	466,9 (M+1)
132	5-Cloro-2-(2,4-difluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-1-metil-etoxi)-benzamida	$C_{16}H_{13}ClF_4N_2O_3$	393,4 (M+1)
133	2-(2,4-Difluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-1-metil-etoxi)-benzamida	$C_{16}H_{14}F_4N_2O_3$	359,4 (M+1)

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134	2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-metoxi-etoxi)-benzamida	$C_{16}H_{14}ClF_2IN_2O_3$	482,9 (M+1)
135	2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-metoxi-etoxi)-benzamida	$C_{16}H_{13}ClF_3IN_2O_3$	500,9 (M+1)
136	3,4-Difluoro-2-(4-yodo-2-metil-fenilamino)-N-(2-metoxi-etoxi)-benzamida	$C_{17}H_{17}F_2IN_2O_3$	462,9 (M+1)
137	5-Bromo-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-N-(2-metoxi-etoxi)-benzamida	$C_{17}H_{16}BrF_2IN_2O_3$	540,8/542,8 (M+1)
138	3,4,5-Trifluoro-2-(4-yodo-2-metil-fenilamino)-N-(2-metoxi-etoxi)-benzamida	$C_{17}H_{16}F_3IN_2O_3$	480,9 (M+1)
139	5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-metoxi-etoxi)-benzamida	$C_{16}H_{13}BrClF_2IN_2O_3$	560,8/562,8 (M+1)
140	5-Cloro-2-(2-cloro-4-	$C_{16}H_{13}Cl_2F_2IN_2O_3$	516,8 (M+1)

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	yodo-fenilamino)-3,4-difluoro-N-(2-metoxi-etoxi)-benzamida		
141	5-Cloro-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-N-(2-metoxi-etoxi)-benzamida	$C_{17}H_{16}ClF_2IN_2O_3$	496,9 (M+1)
142	5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-metoxi-etoxi)-benzamida	$C_{16}H_{13}ClF_3IN_2O_3$	501,1 (M+1)
143	2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-benzamida	$C_{20}H_{21}ClF_2IN_3O_4$	568,0 (M+1)
144	5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-benzamida	$C_{20}H_{20}BrClF_2IN_3O_4$	645,9/647,9 (M*1)
145	2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-hidroxi-3-morfolin-4-il-	$C_{20}H_{20}ClF_3IN_3O_4$	585,9 (M+1)

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	propoxi)benzamida		
146	3,4,5-Trifluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida	$C_{21}H_{23}F_3IN_3O_4$	566,0 (M+1)
147	5-Bromo-3,4-difluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida	$C_{21}H_{23}BrF_2IN_3O_4$	625,9/627,9 (M*1)
148	3,4-Difluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida	$C_{21}H_{24}F_3IN_3O_4$	548,0 (M+1)
149	5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-benzamida	$C_{20}H_{20}Cl_2F_2IN_3O_4$	601,9 (M+1)
150	5-Cloro-3,4-difluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-2-(4-yodo-2-	$C_{21}H_{23}ClF_2IN_3O_4$	582,0 (M+1)

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	metil-fenilamino)-benzamida		
151	3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-morfolin-4-il-propoxi)-benzamida	$C_{20}H_{21}F_3IN_3O_4$	551,9 (M+1)
152	5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-morfolin-4-il-propoxi)-benzamida	$C_{20}H_{20}ClF_3IN_3O_4$	585,8 (M+1)
153	4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-morfolin-4-il-propoxi)-benzamida	$C_{20}H_{21}F_3IN_3O_4$	551,9 (M+1)
154	5-Cloro-2-(2,4-difluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-benzamida	$C_{20}H_{20}ClF_4N_3O_4$	478,4 (M+1)
155	2-(4-Cloro-2-fluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-benzamida	$C_{20}H_{21}ClF_3N_3O_4$	460,0 (M+1)
156	2-(2-Cloro-4-yodo-	$C_{16}H_{14}ClF_2IN_2O_3$	482,9 (M+1)

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0393

	fenilamino)-3,4-difluro-N-(2-hidroxi-propoxi)-benzamida		
157	3,4,5-Trifluoro-N-(2-hidroxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida	$C_{17}H_{16}F_3IN_2O_3$	480,9 (M+1)
158	5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-propoxi)-benzamida	$C_{16}H_{13}BrClF_2IN_2O_3$	560,8/562,8 (M+1)
159	5-Bromo-3,4-difluoro-N-(2-hidroxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida	$C_{17}H_{16}BrF_2IN_2O_3$	540,8/542,8 (M+1)
160	2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-hidroxi-propoxi)-benzamida	$C_{16}H_{13}ClF_3IN_2O_3$	500,8 (M+1)
161	5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-propoxi)-benzamida	$C_{16}H_{13}Cl_2F_2IN_2O_3$	516,8 (M+1)
162	3,4-Difluoro-N-(2-	$C_{17}H_{17}F_2IN_2O_3$	462,9 (M+1)

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0394

	hidroxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida		
163	5-Cloro-3,4-difluoro-N-(2-hidroxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida	$C_{17}H_{16}ClF_2IN_2O_3$	496,9 (M+1)
164	3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-propoxi)-benzamida	$C_{16}H_{14}F_3IN_2O_3$	466,9 (M+1)
165	5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-propoxi)-benzamida	$C_{16}H_{13}ClF_3IN_2O_2$	500,8 (M+1)
166	5-Cloro-2-(2,4-difluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-propoxi)-benzamida	$C_{16}H_{13}ClF_4N_2O_3$	393,1 (M+1)
167	2-(2,4-Difluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-propoxi)-benzamida	$C_{16}H_{14}F_4N_2O_3$	359,4 (M+1)
168	2-(4-Cloro-2-fluoro-	$C_{16}H_{14}ClF_3N_2O_3$	375,1 (M+1)

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0385

	fenilamino)-3,4-difluoro-N-(2-hidroxi-propoxi)-benzamida		
169	4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-propoxi)-benzamida	$C_{16}H_{14}F_3IN_2O_3$	466,9 (M+1)
170	2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-hidroxi-2-metil-propoxi)-benzamida	$C_{17}H_{15}ClF_3IN_2O_3$	514,9 (M+1)
171	3,4,5-Trifluoro-N-(2-hidroxi-2-metil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida	$C_{18}H_{18}F_3IN_2O_3$	494,9 (M+1)
172	5-Bromo-3,4-difluoro-N-(2-hidroxi-2-metil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida	$C_{18}H_{18}BrF_2IN_2O_3$	554,9/556,9 (M+1)
173	5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-2-metil-propoxi)-benzamida	$C_{17}H_{15}BrClF_2IN_2O_3$	574,8/576,8 (M+1)

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0396

174	3,4-Difluoro-N-(2-hidroxi-2-metil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida	$C_{18}H_{19}F_2IN_2O_3$	477,0 (M+1)
175	5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-2-metil-propoxi)-benzamida	$C_{17}H_{15}Cl_2F_2IN_2O_3$	530,9 (M+1)
176	5-Cloro-3,4-difluoro-N-(2-hidroxi-2-metil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida	$C_{18}H_{18}ClF_2IN_2O_3$	510,9 (M+1)
177	3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-2-metil-propoxi)-benzamida	$C_{17}H_{16}F_3IN_2O_3$	481,1 (M+1)
178	5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-2-metil-propoxi)-benzamida	$C_{17}H_{15}BrF_3IN_2O_3$	559,0/561,0 (M+1)
179	5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-	$C_{17}H_{15}ClF_3IN_2O_3$	515,1 (M+1)

	fenilamino)-N-(2-hidroxi-2-metil-propoxi)-benzamida		
180	5-Cloro-2-(2,4-difluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-2-metil-propoxi)-benzamida	$C_{17}H_{15}ClF_4N_2O_3$	407,4 (M+1)
181	2-(2,4-Difluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-2-metil-propoxi)-benzamida	$C_{17}H_{16}F_4N_2O_3$	373,5 (M+1)
182	2-(4-Bromo-2-fluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-2-metil-propoxi)-benzamida	$C_{17}H_{16}BrF_3N_2O_3$	433,3/435,3 (M+1)
183	Cloro-4-yodo-fenilamino-3,4-difluoro-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida	$C_{22}H_{18}ClF_2IN_2O_4$	575,0 (M+1)
184	2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida	$C_{22}H_{17}ClF_3IN_2O_4$	592,9 (M+1)
185	3,4,5-Trifluoro-N-(2-	$C_{23}H_{20}F_3IN_2O_4$	573,0 (M+1)

	hidroxi-3-fenoxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida		
186	5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida	$C_{22}H_{17}BrClF_2INO_4$	652,8/654,8 (M +1)
187	5-Bromo-3,4-difluoro-N-(2-hidroxi-3-fenoxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida	$C_{23}H_{20}BrF_2IN_2O_4$	632,9/634,9 (M+1)
188	3,4-Difluoro-N-(2-hidroxi-3-fenoxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida	$C_{23}H_{21}F_2IN_2O_4$	555,0 (M+1)
189	5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida	$C_{23}H_{17}Cl_2F_2IN_2O_4$	608,9 (M+1)
190	5-Cloro-3,4-difluoro-N-(2-hidroxi-3-fenoxi-	$C_{23}H_{20}ClF_2IN_2O_4$	588,9 (M+1)

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	propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida		
191	3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida	$C_{23}H_{18}F_3IN_2O_4$	558,9 (M+1)
192	5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida	$C_{22}H_{17}ClF_3IN_2O_4$	592,8 (M+1)
193	4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida	$C_{22}H_{18}F_3IN_2O_4$	558,9 (M+1)
194	5-Cloro-2-(2,4-difluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida	$C_{22}H_{17}ClF_4N_2O_4$	485,4 (M+1)
195	2-(2,4-Difluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida	$C_{22}H_{18}F_4N_2O_4$	451,5 (M+1)

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196	2-(4-Cloro-2-fluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida	$C_{22}H_{18}ClF_3N_2O_4$	467,0 (M+1)
197	3,4-Difluoro-N-(3-hidroxi-2,2-dimetil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida	$C_{19}H_{21}F_2IN_2O_3$	491,0 (M+1)
198	2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(3-hidroxi-2,2-dimetil-propoxi)-benzamida	$C_{18}H_{17}ClF_3IN_2O_3$	528,9 (M+1)
199	3,4,5-Trifluoro-N-(3-hidroxi-2,2-dimetil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida	$C_{19}H_{20}F_3IN_2O_3$	508,9 (M+1)
200	5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-2,2-dimetil-propoxi)-benzamida	$C_{18}H_{17}Cl_2F_2IN_2O_3$	544,9 (M+1)

201	5-Cloro-3,4-difluoro-N-(3-hidroxi-2,2-dimetil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida	$C_{19}H_{20}ClF_2IN_2O_3$	524,9 (M+1)
202	3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-2,2-dimetil-propoxi)-benzamida	$C_{18}H_{18}F_3IN_2O_3$	495,1 (M+1)
203	5-Cloro-2-(2,4-difluoro-fenilamino)-3,4-difluoro-N-(3-hidroxi-2,2-dimetil-propoxi)-benzamida	$C_{18}H_{17}ClF_4N_2O_3$	421,4 (M+1)
204	3,4-Difluoro-2-(4-yodo-2-metil-fenilamino)-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida	$C_{19}H_{21}F_2IN_2O_4$	507 (M+1)
205	3,4,5-Trifluoro-2-(4-yodo-2-metil-fenilamino)-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida	$C_{19}H_{20}F_3IN_2O_4$	525 (M+1)
206	5-Bromo-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-N-[2-(2-	$C_{19}H_{20}BrF_2IN_2O_4$	585/587 (M+1)

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	metoxi-etoxi)-etoxi]-benzamida		
207	2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida	$C_{18}H_{18}ClF_2IN_2O_4$	527 (M+1)
208	2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida	$C_{18}H_{17}ClF_3IN_2O_4$	545 (M+1)
209	5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida	$C_{18}H_{17}BrClF_2IN_2O_4$	605/607 (M+1)
210	3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida	$C_{16}H_{10}F_7IN_2O_3$	539,1 (M+1)
211	5-Cloro-2-(2,4-difluoro-fenilamino)-3,4-difluoro-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida	$C_{16}H_{10}ClF_7N_2O_3$	447,4 (M+1)

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212	2-(2,4-Difluoro-fenilamino)-3,4-difluoro-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida	$C_{16}H_{11}F_7N_2O_3$	413,4 (M+1)
213	2-(4-Cloro-2-fluoro-fenilamino)-3,4-difluoro-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida	$C_{16}H_{11}ClF_6N_2O_3$	429,0 (M+1)
214	5-Cloro-2-(2,4-difluoro-fenilamino)-3,4-difluoro-N-(2-hidroximetil-ciclopropilmetoxi)-benzamida	$C_{18}H_{15}ClF_4N_2O_3$	419,4 (M+1)
215	2-(2,4-Difluoro-fenilamino)-3,4-difluoro-N-(2-hidroximetil-ciclopropilmetoxi)-benzamida	$C_{18}H_{16}F_4N_2O_3$	385,4 (M+1)
216	2-(4-Cloro-2-fluoro-fenilamino)-3,4-difluoro-N-(2-hidroximetil-ciclopropilmetoxi)-	$C_{18}H_{16}ClF_3N_2O_3$	401,0 (M+1)

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0404

	benzamida		
217	4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroximetil-ciclopropilmetoxi)-benzamida	$C_{18}H_{16}F_3IN_2O_3$	492,9 (M+1)
218	3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroximetil-ciclopropilmetoxi)-benzamida	$C_{18}H_{16}F_3N_2O_3$	493,5 (M+1)
219	3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroximetil-ciclopropilmetoxi)-benzamida	$C_{18}H_{15}F_4N_2O_3$	511,1 (M+1)
220	5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroximetil-ciclopropilmetoxi)-benzamida	$C_{18}H_{15}BrF_3IN_2O_3$	571,0/573,0 (M+1)
221	4,5-Difluoro-2-(2-fluoro-	$C_{18}H_{16}F_3IN_2O_3$	493,1 (M+1)

	4-yodo-fenilamino)-N-(1-hidroximetil-ciclopropilmetoxi)-benzamida		
222	2-(2,4-Difluoro-fenilamino)-3,4-difluoro-N-(1-hidroximetil-ciclopropilmetoxi)-benzamida	$C_{18}H_{16}F_4N_2O_3$	385,4 (M+1)
223	2-(4-Bromo-2-fluoro-fenilamino)-3,4-difluoro-N-(1-hidroximetil-ciclopropilmetoxi)-benzamida	$C_{18}H_{16}BrF_3N_2O_4$	445,3/447,3 (M+1)
224	2-(4-Cloro-2-fluoro-fenilamino)-3,4-difluoro-N-(1-hidroximetil-ciclopropilmetoxi)-benzamida	$C_{18}H_{16}ClF_3N_2O_3$	401,4 (M+1)
225	5-Cloro-2-(2,4-difluoro-fenilamino)-3,4-difluoro-N-(1-hidroximetil-ciclopropilmetoxi)-benzamida	$C_{18}H_{15}ClF_4N_2O_3$	419,1 (M+1)

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226	2-(2,4-Difluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-metoxi-propoxi)-benzamida	$C_{17}H_{16}F_4N_2O_4$	389,4 (M+1)
227	5-Cloro-2-(2,4-difluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-metoxi-propoxi)-benzamida	$C_{17}H_{15}ClF_4N_2O_4$	423,4 (M+1)
228	2-(4-Bromo-2-fluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-metoxi-propoxi)-benzamida	$C_{17}H_{16}BrF_3N_2O_4$	449,3/451,3 (M+1)
229	2-(4-Cloro-2-fluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-metoxi-propoxi)-benzamida	$C_{17}H_{16}ClF_3N_2O_4$	405,4 (M+1)
230	3,4,5-Trifluoro-2-(4-yodo-2-metil-fenilamino)-N-(2-fenilamino-etoxi)-benzamida	$C_{22}H_{19}F_3IN_3O_2$	542,0 (M+1)
231	5-Bromo-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-N-(2-fenilamino-etoxi)-	$C_{22}H_{19}BrF_2IN_3O_2$	574,0/576,0 (M+1)

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	benzamida		
232	2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-fenilamino-etoxi)-benzamida	$C_{21}H_{17}ClF_2IN_3O_2$	544,0 (M+1)
233	2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-fenilamino-etoxi)-benzamida	$C_{21}H_{16}ClF_3IN_3O_2$	562,0 (M+1)
234	3,4-Difluoro-2-(4-yodo-2-metil-fenilamino)-N-(2-fenilamino-etoxi)-benzamida	$C_{22}H_{20}F_2IN_3O_2$	524,0 (M+1)
235	5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-fenilamino-etoxi)-benzamida	$C_{21}H_{16}BrClF_2IN_3O_2$	622,0/624,0 (M+1)

EJEMPLO 236

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-((S)-3-hidroxi-2-metilamino-propoxi)-benzamida

Paso A: N-Boc-O-Bencil-L-Serina (8,86 g, 30,0 mmol) se disolvió en tetrahidrofurano (94 ml) y la solución resultante

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se enfrió con un baño de hielo a 0°C. Se agregó yoduro de metilo (dispersión acuosa al 60% en aceite mineral, 3,6 g, 90 mmol) en tres porciones durante 10 minutos. La mezcla de la reacción resultante se agitó bajo nitrógeno durante 76 g mientras la temperatura del baño de enfriamiento se mantenía a 0°C. La mezcla de la reacción se diluyó con acetato de etilo frío (0°C-5°C) (50 ml) y se agregó agua (1,5 ml) gota a gota durante 10 minutos. Se dejó calentar lentamente la temperatura del baño de enfriamiento hasta la temperatura ambiente durante toda la noche. La mezcla de la reacción se concentró en un aceite viscoso sobre un evaporador giratorio sin calentar. El residuo se particionó entre éter (100 ml) y agua (300 ml). La capa etérea se lavó nuevamente con bicarbonato de sodio acuoso saturado (150 ml). Las porciones acuosas combinadas se acidificaron a pH 3 usando ácido cítrico acuoso (2 M) y se extrajeron con acetato de etilo (3 x 150 ml). Los extractos combinados se secaron sobre sulfato de magnesio y se concentraron en un evaporador giratorio (sin calentar) para dar ácido (S)-3-benciloxi-2-(terc-butoxicarbonil-metil-amino)-propiónico como un aceite incoloro, viscoso (8,98 g).

Paso B: El ácido preparado en el Paso A (8,95 g, 28,9 mmol) se disolvió en metanol (50 ml) y diclorometano (50 ml). La solución resultante se enfrió a 0°C. Se agregó trimetilsilildiazometano (2,0 M en hexano, 26 ml) gota a gota

durante 1 h y la mezcla de la reacción resultante se agitó una hora más a 0°C. Se agregó una porción adicional de trimetilsilildiazometano (2,0 M en hexano, 3 ml) y la reacción se agitó otros 30 minutos a 0°C. La mezcla de la reacción se concentró en vacío, teniendo cuidado de no calentar la solución por encima de 20°C. El líquido residual se disolvió en tetrahidrofurano-metanol (3:1, 200 ml) y la solución resultante se enfrió a 0°C. Se agregó una solución de borohidruro de litio (2,0 M en tetrahidrofurano, 20 ml) gota a gota durante 30 minutos. La mezcla de la reacción se agitó 1 hora más a 0°C y 1 hora a temperatura ambiente. Se agregó una porción adicional de la solución de borohidruro de litio (20 ml) y la mezcla de la reacción se agitó toda la noche. Se agregó cuidadosamente agua agitando vigorosamente. Después de que se hubo asentado la emisión de gas, se agregó 50% de hidróxido de sodio acuoso (1 ml) y la agitación continuó durante 20 minutos. La mezcla de la reacción se concentró en vacío a ¼ del volumen y se diluyó con acetato de etilo (300 ml) y se lavó con agua (50 ml), cloruro de amonio acuoso saturado (50 ml) y solución salina (50 ml). Los extractos se secaron sobre sulfato de magnesio y se concentraron en vacío. La cromatografía del aceite residual (40% de acetato de etilo en hexanos) sobre gel de sílice proporcionó el producto terc-butil éster del ácido ((R)-1-benciloximetil-2-hidroxi-etil)-metil-carbámico (6,02 g, 68% desde N-Boc-O-Bencil serina) como

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un aceite incoloro: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7,39-7,28 (m, 5H), 4,55 (cuarteto AB, J=8,0 Hz, Δv=16,4 Hz, 2H), 4,13 (br s, 1H), 3,85-3,55 (cm, 4H), 2,86 (s, 3H), 1,45 (s, 9H); $[\alpha]_D$=+77 (metanol, c= 1 mg/ml); MS(APCI+)=296,2 (M+1, 10%), 222,1 (M+1-$C_4H_{10}O$, 60%), 196,1 (M+1-$C_5H_8O_2$, 100%).

Paso C, D: De acuerdo con el procedimiento de la Preparación 74, terc-butil éster del ácido ((R)-1-benciloximetil-2-hidroxi-etil)-metil-carbámico puede ser convertido en terc-butil éster del ácido ((S)-2-aminooxi-1-benciloximetil-etil)-metil-carbámico.

Paso E: El terc-butil éster del ácido [(S)-1-benciloximetil-2-({1-[3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-fenil]-metanoil}-aminooxi)-etil]-metil-carbámico se puede preparar desde terc-butil éster del ácido ((S)-2-aminooxi-1-benciloximetil-etil)-metil-carbámico y ácido 3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzoico mediante el procedimiento del Ejemplo 80, Paso A.

Paso F: El tratamiento del producto del Paso E con yodotrimetilsilano seguido por una elaboración con ácido clorhídrico acuoso proporciona 3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-((S)-3-hidroxi-2-metilamino-propoxi)-

benzamida, que se puede aislar como una sal farmacéuticamente aceptable.

EJEMPLO 237

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-((R)-3-hidroxi-2-metilamino-propoxi)-benzamida

Paso A: El tratamiento de terc-butil éster del ácido ((R)-1-benciloximetil-2-hidroxi-etil)-metil-carbámico con cloruro de terc-butildimetilsililo e imidazol en dimetilformamida da terc-butil éster del ácido [(S)-1-benciloximetil-2-(terc-butil-dimetil-silaniloxi)-etil]-metil-carbámico.

Paso B: La exposición del compuesto preparado en el Paso A a una atmósfera presurizada de hidrógeno en la presencia de paladio activado sobre carbón provee terc-butil éster del ácido [(S)-2-(terc-butil-1-dimetil-silaniloxi)-1-hidroximetil-etil]-metil-carbámico.

Paso C, D: El compuesto del paso B se puede convertir en terc-butil éster del ácido [(S)-1-aminooximetil-2-(terc-butil-dimetil-silaniloxi)-etil]-metil-carbámico mediante el procedimiento general de la Preparación 74.

Paso E: El terc-butil éster del ácido [(S)-2-(terc-butil-dimetil-silaniloxi)-1-({1-[3,4-difluoro-2-(2-fluoro-4-yodo-

fenilamino)-fenil]-metanoil}-aminooximetil)-etil]-metil-carbámico se puede preparar mediante el procedimiento del Ejemplo 80, Paso A.

Paso F: El tratamiento del producto del Paso E con yodotrimetilsilano seguido por una elaboración con fluoruro de tetrabutilamonio provee 3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-((R)-3-hidroxi-2-metilamino-propoxi)-benzamida, que se puede aislar como una sal farmacéuticamente aceptable.

EJEMPLO 238

(S)- y (R)-5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-2-metilamino-propoxi)-benzamida

(S)- y (R)-5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-2-metilamino-propoxi)-benzamida se pueden preparar desde el ácido 5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzoico por analogía con los ejemplos 236 y 237, respectivamente.

EJEMPLO 239

(S)- y (R)-5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-2-metilamino-propoxi)-benzamida

(S)- y (R)-5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-2-metilamino-propoxi)-benzamida se pueden

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preparar desde el ácido 5-cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-benzoico por analogía con los ejemplos 236 y 237, respectivamente.

EJEMPLO 240

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-metilamino)-propoxi)-benzamida

Paso A: N-(terc-butoxicarbonil)-N-metil-2,3-epoxipropilamina (disponible mediante el procedimiento de la bibliografía: Edwards, M.L.; Snyder, R.D.; Stemerick, D.M., J.Med. Chem. 1991, 34, 2414) se puede convertir en terc-butil éster del ácido (3-aminooxi-2-hidroxi-propil)-metil-carbámico mediante el procedimiento general del ejemplo 56.

Paso B, C: 3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-metilamino-propoxi)-benzamida se puede preparar desde terc-butil éster del ácido (3-aminooxi-2-hidroxi-propil)-metil-carbámico y ácido 3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzoico mediante el procedimiento general del ejemplo 236, pasos E y F.

EJEMPLO 241

Ensayo Celular para Medir la Inhibición de MEK

La evaluación de los compuestos como inhibidores de MEK se realizó en un ensayo que mide su capacidad de inhibir la fosforilación de la quinasa MAP (ERK) en células de carcinoma

de colon 26 (C26) murinas. Como ERK1 y ERK2 representan los únicos sustratos conocidos para MEK, la medición de la inhibición de la fosforilación de ERK en las células provee una lectura directa de la inhibición celular de MEK por los compuestos de la invención. En resumen, el ensayo consiste en tratar células C26 que crecen exponencialmente con concentraciones variadas del compuesto de ensayo (o el control vehículo) durante una hora a 37°C. Las células luego se enjuagan libres del compuesto/vehículo y se disuelven en una solución que contiene 70 mM NaCl, 50 mM fosfato de glicerol, 10 mM HEPES, pH 7,4, 1% de Triton X-100, 1 mM Na_3VO_4, 100 µM PMSF, 10 µM leupeptina y 10 µM pepstatina. Los sobrenadantes luego se someten a electroforesis de gel y Western blotting usando un anticuerpo principal que reconoce ERK1 y ERK2 fosforiladas doblemente. Para evaluar los niveles totales de MAPK, las manchas posteriormente se "pelaron" y se sondearon nuevamente con una mezcla de 1:1 de anticuerpos policlonales que reconocen ERK1 y ERK2 no fosforiladas.

Los datos de la inhibición generados por el protocolo precedente se revelan en la Tabla 1. Si se ensayaron varias concentraciones del inhibidor, los valores de IC_{50} (la concentración que da un 50% de inhibición) se determinaron gráficamente a partir de la curva de reacción a la dosis para

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el % de inhibición. De lo contrario, se informan los porcentajes de inhibición a concentraciones medidas.

Tabla 8. Inhibición Celular de la Fosforilación de ERK por Compuestos de la Invención

Compuesto del Ejemplo N°	IC_{50} (μM)	% de Inhibición a 0,1 μM	% de Inhibición a 1 μM	% de Inhibición a 10 μM
1	0,008			
2	0,003			
3	0,004			
4	0,002			
5	0,003			
6	0,005			
7	0,005			
8	0,0003			
9	0,00007			
10	0,0003			
11	0,002			
12	0,022			
13	0,002			
14	0,002			
15	0,001			

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16	0,02			
17	0,045			
18	0,002			
19	0,001			
20	0,003			
21	0,0018			
22	0,0077			
23	0,032			
24	0,026			
25	0,052			
26	0,24			
27	0,12			
28	0,12			
29	0,047			
30	0,13			
32	0,0044			
33	0,005			
34	0,001			
35	0,006			
36	0,053			
37	0,03			
38	1,00			
39	0,0004			
40	0,0014			

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0417

41	0,00073			
42	0,0027			
43	0,0018			
44	0,k003			
45	0,019			
46	0,582			
47	0,001			
48	0,0016			
49	0,00033			
50	0,00083			
51	0,0038			
52	0,0078			
53	0,0012			
54	0,0012			
55	0,0045			
58	0,06			
61	0,15			
62	0,018			
63	0,047			
64	0,013			
65	0,014			
66	0,002			
67	0,006			
68	0,024			

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69	0,06			
70	0,2			
71	0,12			
72	0,019			
73	0,08			
74	0,018			
75	0,042			
76	0,006			
77	0,24			
78	0,23			
79	0,02			
80	0,49			
81	0,234			
82	>1			
83	0,041			
85	0,054			
86	0,019			
87	0,025			
88	0,11			
89	0,012			
90	0,04			
91		89,4	98,9	
92		51,8	92,4	
93		4	79,1	

94	0,28			
95	0,19			
96		35	87,1	
97		30,1	91,9	
98	0,011			
99	0,018			
100	0,058			
101	0,225			
102	0,275			
103	0,487			
104	0,024			
105		3,3	71,3	
106		13,2	81,6	
107	0,076			
108		74	94,6	
109	0,038			
111		78	93,4	
112		95,2	95,5	
113		89,9	94,6	
114		90,5	97,3	
115		94,8	98,5	
116			62,8	75,8
117		0	66,7	86,9
118		74,6	95,6	

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~~420~~

119		87,4	97,9	
120	0,014			
121		46,9	85,5	
122		49,6	87,3	
123	0,021			
124		78	96,9	
125		9,1	89	
126	0,026			
127	0,025			
128	0,009			
129		100	100	
130	0,004			
131		78,7	91,3	
132			45,7	80,6
133		0	26,4	
134	0,37			
135		0	41,4	
136	0,25			
137	0,1			
138		0	19,6	
139	0,36			
140	0,45			
141		38	92,7	
142		31	91,4	

143	0,6			
145	0,1			
146		0	40,5	
147	0,1			
148	0,23			
149	0,17			
150		49	99,9	
151	0,041			
152		59,2	90,3	
153		13,9	89,5	
154			8,9	51
155		0	30,9	
156	0,011			
157		50,7	91,5	
159		88,4	100	
160		71,9	96,8	
161	0,015			
162	0,00785			
163		88,9	95,1	
164	0,003			
165	0,004			
166		0	31,9	88,7
167			80,5	89,2
168		48,8	89,5	

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169	0,014			
170		19	85,7	
171		35,6	94,6	
172		41,9	92,9	
173	0,3			
174	0,1			
175	0,18			
176		14,1	87,7	
177		91,6	95,7	
178		61,8	94,9	
179		90,4	99,3	
180			34	58,6
181			0	65,1
182		13,1	81,9	
183	0,053			
184		16,1	82,5	
185		6,2	71,9	
186	0,034			
187		13,8	83,3	
188	0,044			
190		51,5	94,6	
191	0,006			
192	0,007			
193	0,01			

425

194		0	0	
195		26,7	82,6	
196		10,2	82,8	
197	0,051			
198		0	43,5	
199	0,1			
200	0,3			
201	0,1			
202		59,7	94,6	
203			0	37,4
206	0,14			
207	0,212			
208	1,029			
210		79,7	99,2	
211			35	71,9
212			20,1	85,1
213		6,2	78,7	
214			15,4	38,2
215			11,7	84,8
216		41,2	87,6	
217		26,9	93,1	
218		87	96,9	
219		65,3	96,2	
220		35,4	88,8	

426

221		46	92,4	
222			9,6	55,6
223		5,2	56,7	
224		0	18,1	
225		0	8,7	36,9
226			41,5	84,1
227			24,2	63
228		48;6	92,4	
229		9,8	76,5	
230	0,051			
231	0,067			
232	0,022			
233	0,033			
234	0,054			
235	0,062			

EJEMPLO 242

Modelo de Rata con Edema de Planta de la Pata Inducido por Carrageenina (CFE)

Se administró a ratas Wistar reproducidas por cruza machos (135g-150g, Charles River Labs) con dosis vía oral de 10 mg/kg del vehículo o compuesto de ensayo una hora antes de la administración de una suspensión sonicada de carrageenina (1

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mg/0,1 ml de solución salina). La carrageenina se inyectó en la región subplantar de la pata posterior derecha. El volumen de la pata se determinó mediante pletismografía de mercurio inmediatamente después de la inyección y nuevamente cinco horas después de la inyección de carrageenina. Se determinó el porcentaje de inhibición del edema y se calculó ID40 mediante regresión lineal. Las diferencias en la hinchazón comparadas con los animales control se estimaron mediante un ANOVA de 1 vía, seguido por un ensayo de Dunnett.

EJEMPLO 243

Artritis Inducida por Colágeno en Ratones

La artritis inducida por colágeno de tipo II (CIA) en ratones es un modelo experimental de artritis que tiene numerosas características patológicas, inmunológicas, y genéticas en común con la artritis reumatoide. La enfermedad se induce mediante la inmunización de ratones DBA/1 con 100 µg de colágeno de tipo II, que es el principal componente de los cartílagos de las articulaciones, administrado en forma intradérmica en un coadyuvante completo de Freund. La susceptibilidad de la enfermedad es regulada por el lugar del gen MHC de la clase II, que es análoga a la asociación de la artritis reumatoide con HLA-DR4.

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Se desarrolla una artritis progresiva e inflamatoria en la mayor parte de los ratones inmunizados, caracterizada por aumentos en el ancho de la pata de hasta el 100%. Se administra un compuesto en ensayo a los ratones en una gama de cantidades, tales como 20, 60, 100 y 200 mg/kg de peso corporal/día. La duración del ensayo puede ser de varias semanas a algunos meses, tales como 40, 60 u 80 días. Se usa un índice de calificación clínica para evaluar el avance de la enfermedad desde el eritema y el edema (etapa 1), la distorción de la articulación (etapa 2), hasta la anquilosis de la articulación (etapa 3). La enfermedad es variable porque puede afectar una o todas las patas en un animal, lo cual deriva en una calificación posible total de 12 para cada ratón. La histopatología de una articulación artrítica revela sinovitis, formación de pannus, y erosiones del cartílago y el hueso. Todas las cepas de ratones que son susceptibles a la CIA reaccionan con altos anticuerpos al colágeno de tipo II, y hay una marcada respuesta celular a CII.

EJEMPLO 244

Artritis monoarticular inducida por SCW

La artritis se induce como lo describió Schwab, et al, *Infección e Inmunidad*, 59:4436-4442 (1991) con modificaciones menores. Las ratas reciben 6 µg de SWC sónico [en 10 µl de PBS

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de Dulbecco (DPBS)] mediante una inyección intraarticular en la articulación tibiotalar derecha el día 0. El día 21, se inicia el DTH con 100 µg de SCW (250 µl) administrados en forma intravenosa. Para los estudios de compuestos orales, las composiciones se suspenden en un vehículo (0,5% de hidroxipropil-metilcelulosa/0,2% de Tween 80), se sonorizan y se adminitran dos veces por día (10 ml/kg de volumen) comenzando 1 h antes de la reactivación con SCW. Los compuestos se administran en cantiddes de entre 10 y 500 mg/kg de peso corporal/día, tales como 20, 30, 60, 100, 200 y 300 mg/kg/día. Las mediciones de edema se obtienen determinando los volúmenes de referencia de la pata posterior sensibilizada antes de la reactivación el día 21, y comparándolos con los volúmenes en puntos de tiempo posteriores tales como el día 22, 23, 24 y 25. El volumen de la pata se determina mediante pletismografía de mercurio.

EJEMPLO 245

Modelo de transplante de oreja-corazón de Ratón

Fey, T.A. et al describen métodos para transplantar injertos cardíacos neonatales con el corazón abierto en el pabellón de la oreja de ratones y ratas (*J. Pharm. and Toxic. Meth.* 39:9-17 (1998)). Los compuestos se disuelven en soluciones que contienen combinaciones de etanol absoluto, 0,2% de

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hidroxipropil metil celulosa en agua, propilenglicol, cremophor y dextrosa, u otro solvente o vehículo para suspensión. Se administran a los ratones dosis orales o intraperitoneales una vez, dos veces o tres veces por día desde el día del transplante (día 0) hasta el día 13 o hasta que los injertos han sido rechazados. Las ratas son dosificadas una vez, dos veces o tres veces por día desde el día 0 hasta el día 13. Cada animal es anestesiado y se hace una incisión en la base la oreja del receptor, cortando solamente la epidermis y dermis dorsal. La incisión se abre y se extiende hacia abajo al cartílago paralelo a la cabeza, y es suficientemente ancha para acomodar el túnel apropiado para una rata o la herramienta de inserción para un ratón. Un ratón neonato o un cachorro de rata menor de 60 horas es anestisiado y descoyuntado en las cervicales. El corazón se remueve del pecho, se enjuaga con solución salina, se biseca longitudinalmente con un escalpelo y se enjuaga con solución salina estéril. El fragmento del corazón del donante se coloca en el túnel realizado con la herramienta de inserción y se extrae aire o fluido residual suavemente del túnel con ligera presión. No se requiere sutura, unión con adhesivos, vendaje o tratamiento con antibióticos.

Los implantes se examinan a un aumento de 10-20 veces con un microscopio de disección estereoscópico sin anestesia. Los

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receptores cuyos injertos no laten visiblemente se pueden anestesiar y evaluar la presencia de actividad eléctrica usando microelectrodos de guías subdérmicas de platino Grass E-2 colocados en el pabellón o directamente en el injerto y un tacógrafo. Los implantes se pueden examinar 1-4 veces por día durante 10, 20, 30 o más días. La capacidad de un compuesto en ensayo de mejorar los síntomas del rechazo de un transplante se puede comparar cn un compuesto control tal como ciclosporina, tacrolimus, o lefluonomida administrada oralmente.

EJEMPLO 246

La actividad analgésica de los compuestos de la presente invención se estimó mediante un ensayo con ratas. Se inyectaron ratas que pesaban de 175 g a 200 g con carrageenina (2% en una solución acuosa de cloruro de sodio al 0,9%, 100 µL de volumen de inyección) en la planta de la pata de un miembro trasero. Las ratas fueron colocadas sobre una placa de vidrio con iluminación de una lámpara halógena colocada directamente debajo de la pata inyectada. El tiempo (en segundos) desde el comienzo de la iluminación hasta que se retiró el miembro trasero del vidrio se midió y se calificó como Latencia de Retiro de la Pata (PWL). Las sustancias de droga se administraron mediante inyección por sonda oral 2½ después de la inyección de carrageenina en la planta de la pata. La PWL

se midió antes de la inyección de carrageenina, inmediatamente antes de la inyección de droga, y 1, 2 (y algunas veces 3) horas después de la inyección de droga.

La carrageenina (un polisacárido extraído de algas marinas) produce una inflamación estéril cuando se inyecta debajo de la piel. La inyección en la planta de la pata de la rata produce escaso o ningún comportamiento relacionado con el dolor pero induce una hiperalgesia (reacciones de comportamiento relacionado con el dolor de mayor intensidad que la esperada) a los estímulos térmicos o mecánicos. Esta hiperalgesia es máxima de 2 a 3 horas después de la inyección. El tratamiento de ratas con diversas drogas analgésicas reduce la hiperalgesia medida de esta manera y es un ensayo convencional para la detección de la actividad analgésica en ratas (Hargreaves K., Dubner R., Brown F., Flores C., Joris J., Método nuevo y sensible para medir la nocicepción térmica en la hiperalgesia cutánea. Dolor 1998;32:77-88 y Kayser V., Guilhaud G., Modificaciones locales y remotas de la sensibilidad nociceptiva durante la inflamación inducida por carrageenina en la rata. Dolor 1987;28:99-108). Las ratas no tratadas tuvieron una PWL de aproximadamente 10 segundos. La inyección de carrageenina redujo la PWL a aproximadamente 3 segundos durante por lo menos 4 horas, lo cual indicó hiperalgesia térmica. La inhibición de la reacción de

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hiperalgesia térmica a la carrageenina se determinó por la diferencia entre la PWL reducida antes de la droga y después del tratamiento con la droga, y se expresó como el porcentaje de inhibición de la reacción. La administración de inhibidores de MEK redujo independientemente de la dosis la hiperalgesia térmica (Tabla 9).

En la Tabla 9, las dosis se administraron por sonda oral (PO) y la inhibición de la reacción se midió 1 hora (1 h), 2 horas (2 h) o en algunos casos, 3 horas (3 h) después de la administración de la droga. La inhibición indica un efecto analgésico.

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TABLA 9

La Administración de inhibidores de MEK a Ratas Reduce la Hiperalgesia Térmica producida por Carrageenina Intraplantar

EJEMPLO N°	DOSIS (VÍA ORAL)	% de Inhibición (1 h)	% de Inhibición (2 h)	% de Inhibición (3 h)
9	30	103,0	114,4	65,2
	10	57,2	80,0	50,8
	3	38,1	44,3	26,1
34	10	39,6	61,5	
41	10	26,7	61,0	
55	10	36,8	60	22
54	10	49	52,9	29,6

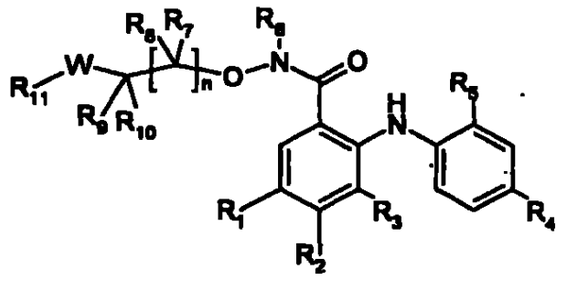
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REIVINDICACIONES

Habiendo descripto y determinado la naturaleza y alcance de la presente invención y la manera en que la misma ha de ser llevada a la práctica, se declara que lo que reivindica como invención y de propiedad exclusiva es:

1. Un compuesto caracterizado por la fórmula



I

en donde

R_1 es hidrógeno, halógeno, o nitro;

R_2 es hidrógeno o flúor;

R_3 es hidrógeno o flúor;

R_4 es hidrógeno, yodo, bromo, cloro, o flúor;

R_5 es hidrógeno, halógeno, hidroxi, alquilo de C_{1-8}, alcoxi de C_{1-8}, trifluorometilo, o ciano;

n es 1 a 5;

R_6, R_7, R_8, R_9, y R_{10} son independientemente hidrógeno, alquilo de C_{1-8}, cicloalquilo de C_{3-8}, hidroxi, alcoxi de C_{1-8}, perhaloalquilo (de C_{1-3}), hidroxialquilo (de C_{1-8}), alcoxi (de C_{1-5})alquilo (de C_{1-5}), [alquilo (de C_{1-4})]$_2$aminometilo,

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heterociclo (de C_{2-7})alquilo (de C_{1-5}), o ariloxialquilo (de C_{1-5}), o puede ser unido independientemente para completar un anillo cíclico de 3-10 miembros que contiene optativamente heteroátomos adicionales seleccionados del grupo formado por O, S, NH, y N-alquilo, en donde R_7 y R_8 se seleccionan independientemente para n>1;

R_a y R_b son independientemente hidrógeno o alquilo de C_{1-4};

W es O o NR_a;

R_{11} es hidrógeno, alquilo de C_{1-8}, alquenilo de C_{2-6}, cicloalquilo de C_{3-8}, hidroxialquilo (de C_{1-8}), alcoxi (de C_{1-5})alquilo (de C_{1-5}), fenilo, heteroarilo de C_{2-7}, alquilcarbonilo (de C_{1-8}), (fenil)carbonilo, (fenil)(alquilo de C_{1-3})carbonilo, o trifluoroalquilo (de C_{1-6});

en donde los grupos alquilo, alcoxi, cicloalquilo, heteroarilo, y fenilo se pueden sustituir optativamente con entre 1 y 5 sustituyentes seleccionados independientemente del grupo formado por hidroxi, amino, monoalquilamino, dialquilamino, halógeno, ciano, alcoxi (de C_{1-3}), COOR, $OCOR_a$, $CONR_aR_b$, NR_aCOR_b, SO, SO_2, SO_4 y $SO_2NR_aR_b$;

y sales farmacéuticamente aceptables;

siempre que cuando R_{11} es fenilo y n es 1, W no puede ser O;

además siempre que el compuesto no sea

5-bromo-N-(2-dietilamino-etoxi)-3,4-difluoro-(4-yodo-2-metil-fenilamino)-benzamida;

5-bromo-N-(2-dimetilamino-propoxi)-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-benzamida; o

5-bromo-2-(2-cloro-4-yodo-fenilamino)-N-(2-dimetilamino-etoxi)-3,4-difluoro-benzamida.

2. El compuesto de la reivindicación1, caracterizado porque R_1 es hidrógeno o halógeno.

3. El compuesto de la reivindicación 2, caracterizado porque el halógeno es flúor, bromo o cloro.

4. El compuesto de la reivindicación 1, caracterizado porque R_2 es flúor.

5. El compuesto de la reivindicación 1, caracterizado porque R_3 es flúor.

6. El compuesto de la reivindicación 1, caracterizado porque R_4 es yodo.

7. El compuesto de la reivindicación 1, caracterizado porque R_5 es flúor, cloro o metilo.

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8. El compuesto de la reivindicación 1, caracterizado porque n es 1 o 2.

9. El compuesto de la reivindicación 1, caracterizado porque R_6, R_7, R_8, R_9, R_{10} y R_{11} son hidrógeno.

10. El compuesto de la reivindicación 1, caracterizado porque R_6, R_7, R_8, R_9 y R_{10} son hidrógeno.

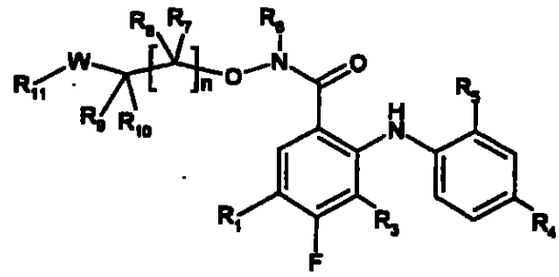
11. El compuesto de la reivindicación 1, caracterizado porque R_6, R_7, R_9, R_{10} y R_{11} son hidrógeno.

12. El compuesto de la reivindicación 1, caracterizado porque W es oxígeno.

13. El compuesto de la reivindicación 1, caracterizado porque W es NR_8 y R_8 es hidrógeno.

14. El compuesto de la reivindicación 1, carcterizado porque R_{11} es metilo o fenilo.

15. El compuesto de la reivindicación 1, caracterizado porque el compuesto tiene la fórmula



Ia

en donde

R_1 es hidrógeno o halógeno;

R_5 es hidrógeno, halógeno o alquilo de C_{1-8};

R_6, R_7, R_8, R_9, y R_{10} son independientemente hidrógeno, alquilo de C_{1-8}, hidroxi, alcoxi de C_{1-8}, perhaloalquilo (de C_{1-3}), heterociclo (de C_{2-7})alquilo (de C_{1-8}), o ariloxialquilo (de C_{1-5}), o puede ser unido independientemente para completar un anillo cíclico de 3-10 miembros que contiene optativamente heteroátomos adicionales seleccionados del grupo formado por O, S, NH, y N-alquilo, en donde R_7 y R_8 se seleccionan independientemente para n>1; y

R_{11} es hidrógeno, alquilo de C_{1-8}, alquenilo de C_{2-6}, alcoxi (de C_{1-5})alquilo (de C_{1-5}), fenilo, alquilcarbonilo (de C_{1-8}), o trifluoroalquilo (de C_{1-6}).

16. El compuesto de la reivindicación 15, caracterizado porque R_1 es hidrógeno.

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17. El compuesto de la reivindicación 15, caracterizado porque R_3 es hidrógeno.

18. El compuesto de la reivindicación 15, caracterizado porque R_3 es flúor.

19. El compuesto de la reivindicación 15, caracterizado porque R_4 es yodo.

20. El compuesto de la reivindicación 15, caracterizado porque R_5 es flúor, cloro o metilo.

21. El compuesto de la reivindicación 15, caracterizado porque n es 1 o 2.

22. El compuesto de la reivindicación 15, caracterizado porque R_6, R_7, R_8, R_9, R_{10} y R_{11} son hidrógeno.

23. El compuesto de la reivindicación 15, caracterizado porque R_6, R_7, R_8, R_9 y R_{10} son hidrógeno.

24. El compuesto de la reivindicación 15, caracterizado porque R_6, R_7, R_9, R_{10} y R_{11} son hidrógeno.

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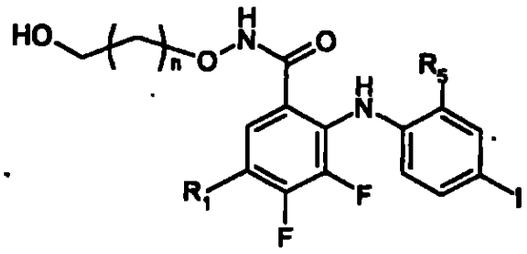
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25. El compuesto de la reivindicación 15, caracterizado porque W es oxígeno.

26. El compuesto de la reivindicación 15, caracterizado porque W es NR_a y R_a es hidrógeno.

27. El compuesto de la reivindicación 15, carcterizado porque R_{11} es metilo o fenilo.

28. El compuesto de la reivindicación 1, carcterizado porque el compuesto tiene la fórmula



II

en donde

R_1 es hidrógeno o halógeno;

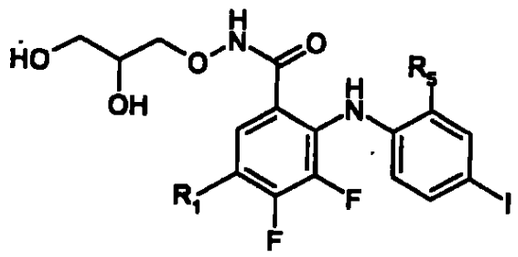
R_5 es flúor, cloro o metilo; y

n es 1 o 2.

29. Un compuesto de la Reivindicación 1, caracterizado porque el compuesto tiene la fórmula

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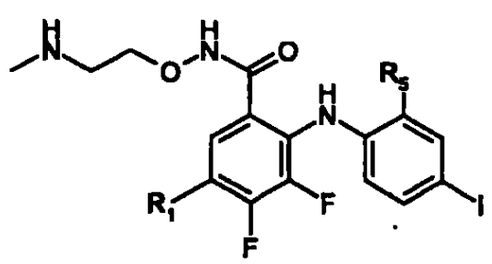
III

en donde

R_1 es hidrógeno o halógeno y

R_5 es flúor, cloro o metilo.

30. Un compuesto de la reivindicación 1, caracterizado porque el compuesto tiene la fórmula



IV

en donde

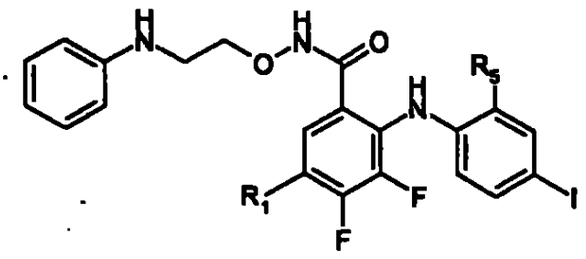
R_1 es hidrógeno o halógeno y

R_5 es flúor, cloro o metilo.

31. Un compuesto de la reivindicación 1, caracterizado porque el compuesto tiene la fórmula

943

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V

en donde

R_1 es hidrógeno o halógeno y

R_5 es flúor, cloro o metilo.

32. Una composición farmacéutica, caracterizada porque comprende un compuesto de la reivindicación 1 y un portador farmacéuticamente aceptable.

33. Un método de tratamiento de una enfermedad proliferativa en un paciente que lo necesita, caracterizado porque comprende administrar una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1.

34. Un método de la reivindicación 33, caracterizado porque la enfermedad proliferativa se selecciona del grupo formado por cáncer, restenosis, psoriasis y aterosclerosis.

35. Un método de tratamiento de la psoriasis en un paciente que lo necesita, caracterizado porque comprende administrar

una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1.

36. Un método de tratamiento del cáncer en un paciente que lo necesita, caracterizado porque comprende administrar una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1.

37. Un método de la reivindicación 36, caracterizado porque el cáncer está relacionado con MEK.

38. Un método de la reivindicación 36, caracterizado porque el cáncer es un cáncer de cerebro, mamas, pulmón, ovarios, páncreas, próstata, riñón, o colorectal.

39. Un método de tratamiento de la osteoartritis en un paciente que lo necesita, caracterizado porque comprende administrar una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1.

40. Un método de tratamiento de la artritis reumatoide en un paciente que lo necesita, caracterizado porque comprende administrar una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1.

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41. Un método de tratamiento de la insuficiencia cardíaca en un paciente que lo necesita, caracterizado porque comprende administrar una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1.

42. Un método de tratamiento del dolor crónico en un paciente que lo necesita, caracterizado porque comprende administrar una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1.

43. El método de la reivindicación 42, caracterizado porque el dolor crónico se selecciona del grupo formado por dolor neuropático, dolor idiopático, y dolor asociado con alcoholismo crónico, deficiencia vitamínica, uremia e hipotiroidismo.

44. El método de la reivindicación 42, caracterizado porque el dolor crónico está asociado con la inflamación.

45. El método de la reivindicación 42, caracterizado porque el dolor crónico está asociado con la artritis.

46. El método de la reivindicación 42, caracterizado porque el dolor crónico está asociado con el dolor postoperatorio.

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47. Un método de tratamiento del dolor neuropático en un paciente que lo necesita, caracterizado porque comprende administrar una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1.

48. El método de la reivindicación 47, caracterizado porque el dolor neuropático está asociado con una condición seleccionada del grupo formado por inflamación, dolor postoperatorio, dolor de miembro fantasma, dolor de quemadura, gota, neuralgia trigeminal, dolor herpético y postherpético agudo, causalgia, neuropatía diabética, avulsión del plexo, neuroma, vasculitis, infección viral, lesión por aplastamiento, lesión por constricción, lesión de tejidos, amputación de un miembro, dolor postoperatorio, dolor de artritis, lesión nerviosa entre el sistema nervioso periférico y el sistema nervioso central.

49. Un método para el tratamiento del cáncer en un paciente que lo necesita, caracterizado porque comprende administrar una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1 en combinación con terapia de radiación.

50. Un método para el tratamiento del cáncer en un paciente que lo necesita, caracterizado porque comprende administrar una cantidad terapéuticamente efectiva de un compuesto de la

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reivindicación 1 en combinación con por lo menos un agente quimioterapéutico.

51. Un método de la reivindicación 50, caracterizado porque el agente quimioterapéutico es un inhibidor mitótico.

52. Un método de la reivindicación 51, caracterizado porque el inhibidor mitótico se selecciona del grupo formado por paclitaxel, docetaxel, vincristina, vinblastina, vinorelbina y vinflunina.

53. Una Forma I cristalina de N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene por lo menos uno de los siguientes valores de 2θ medidos usando la radiación de CuK_α: 7,1, 19,2, o 32,1.

54. Una Forma I cristalina de N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 7,1, 19,2, y 32,1.

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55. Una Forma I cristalina de N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 7,1, 14,1, 15,3, 15,8, 16,9, 18,1, 19,2, 20,3, 21,4, 22,3, 23,4, 24,5, 25,5, 26,2, 26,8, 27,8, 28,3, 29,5, 32,1, 33,2, 33,6, 40,0, 42,9 y 44,1.

56. Una Forma I cristalina de N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 7,078, 14,123, 15,280, 15,836, 16,880 18,082, 19,162, 20,279, 21,360, 22,325, 23,400, 24,522, 25,480, 26,159, 26,801, 27,842, 28,280, 29,475, 32,118, 33,248, 33,645, 40,008, 42,885 y 44,095.

57. Una Forma II cristalina de N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 11,6, 12,6, o 24,9.

58. Una Forma II cristalina de N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 11,6, 12,6 y 24,9.

59. Una Forma II cristalina de N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 11,6, 12,6, 15,6, 17,3, 17,9, 20,3, 21,2, 22,1, 24,9, 25,9, 26,7, 27,8, 30,1, 30,9, 33,8, 35,4, 38,2, 39,3, 40,8, 41,6, 43,6, y 47,0.

60. Una Forma II cristalina de N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 11,582, 12,598, 15,622, 17,302, 17,886, 20,345, 21,140, 22,137, 24,855, 25,885, 26,699, 27,842, 30,059, 30,948, 33,799, 35,399, 38,242, 39,282, 40,755, 41,641, 43,570, y 46,958.

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61. Una Forma I cristalina de N-[(R)-2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 10,6, 13,7, 19,0 o 23,7.

62. Una Forma I cristalina de N-[(R)-2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 10,6, 13,7, 19,0 y 23,7.

63. Una Forma I cristalina de N-[(R)-2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 10,6, 13,7, 14,6, 17,3, 18,0, 18,2, 19,0, 19,3, 20,1, 21,0, 21,9, 22,4, 23,7, 24,0, 24,9, 26,3, 27,6, 28,0, 30,1, 32,1, 32,3, 32,9, 35,8, y 37,7.

64. Una Forma I cristalina de N-[(R)-2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la

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radiación de CuK_α: 10,560, 13,720, 14,619, 17,258, 17,958, 18,219, 18,998, 19,258, 20,142, 21,002, 21,940, 22,360, 23,680, 24,043, 24,919, 26,278, 27,603, 28,024, 30,100, 32,142, 32,298, 32,938, 35,841, y 37,660.

65. Una Forma II cristalina de N-[(R)-2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 5,5 o 19,6.

66. Una Forma II cristalina de N-[(R)-2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 5,5 y 19,6.

67. Una Forma II cristalina de N-[(R)-2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 5,5, 10,7, 16,5, 19,6, 22,0, 22,5, 23,6, 24,1, 25,0, 26,2, 27,6, 29,1, 30,5, 31,7, 33,3 y 39,0.

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68. Una Forma II cristalina de N-[(R)-2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 5,482, 10,721, 16,478, 19,523, 22,019, 22,478, 23,621, 24,100, 24,959, 26,181, 27,621, 29,081, 30,476, 31,698, 33,263 y 39,020.

69. Una Forma I cristalina de N-[(S)-2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 10,5, 13,7, 19,0 o 23,6.

70. Una Forma I cristalina de N-[(S)-2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 10,5, 13,7, 19,0 y 23,6.

71. Una Forma I cristalina de N-[(S)-2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la

radiación de CuK_α: 10,548, 13,703, 17,887, 18,958, 20,122, 21,950, 22,321, y 23,640, 24,803, 26,244, 27,570, 28,000, 29,566, 32,234, 32,769, 35,804, 37,641, 41,402, 41,956 y 44,600.

72. Una Forma I cristalina de N-[(S)-2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 10,548, 13,703, 17,887, 18,958, 20,122, 21,950, 22,321, y 23,640, 24,803, 26,244, 27,570, 28,000, 29,566, 32,234, 32,769, 35,804, 37,641, 41,402, 41,956 y 44,600.

73. Una Forma II cristalina de N-[(S)-2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 5,6 o 19,6.

74. Una Forma II cristalina de N-[(S)-2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que

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contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 5,6, y 19,6.

75. Una Forma II cristalina de N-[(S)-2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 5,6, 10,7, 16,5, 19,6, 20,9, 22,0, y 23,7, 24,2, 25,0, 26,2, 27,7, 28,0, 29,1, 31,7, 32,8, 33,3, 34,1, 42,0 y 42,3.

76. Una Forma II cristalina de N-[(S)-2,3-dihidroxi-propoxi]-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida que tiene una difracción de polvo de difracción de rayos X que contiene los siguientes valores de 2θ medidos usando la radiación de CuK_α: 5,550, 10,763, 16,485, 19,636, 20,922, 22,043, y 23,683, 24,153, 24,996, 26,236, 27,680, 28,037, 29,120, 31,718, 32,794, 33,314, 34,085, 41,999 y 42,278.

77. Un compuesto caracterizado porque se selecciona del grupo formado por:
5-Cloro-2-(2-cloro-4-yodo-fenilamino)-N-(2,3-dihidroxi-propoxi)-3,4-difluoro-benzamida;

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3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-etoxi)-benzamida;

N-(2,3-Dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida;

5-Cloro-N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida;

5-Cloro-N-((R)-2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida;

clorhidrato de 3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-metilamino-etoxi)-benzamida;

N-((R)-2,3-Dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida;

N-((S)-2,3-Dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida;

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-N-((S)-2,3-dihidroxi-propoxi)-3,4-difluoro-benzamida;

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-N-((R)-2,3-dihidroxi-propoxi)-3,4-difluoro-benzamida;

5-Cloro-N-((S)-2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida;

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1-hidroximetil-etoxi)-benzamida; y

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1-hidroximetil-etoxi)-benzamida.

78. Un compuesto caracterizado porque se selecciona del grupo formado por:

3,4,5-Trifluoro-N-(2-hidroxi-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

3,4-Difluoro-N-(2-hiroxi-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-etoxi)-benzamida;

2-(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-etoxi)-benzamida;

4-Fluoro-N-(2-hidroxi-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-hidroxi-etoxi)-benzamida;

5-Cloro-3,4-difluoro-N-(2-hidroxi-etoxi)-2-(4-yodo-fenilamino)-benzamida;

4-Fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-etoxi)-benzamida;

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-etoxi)-benzamida;

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-etoxi)-benzamida;

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-etoxi)-benzamida;

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4,5-Difluoro-N-(2-hidroxi-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

5-Bromo-3,4-difluoro-N-(2-hidroxi-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-etoxi)-benzamida;

5-Cloro-3,4-difluoro-N-(2-hidroxi-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

5-Bromo-4-fluoro-N-(2-hidroxi-etoxi)-2-(4-yodo-2-metil-fenilamio)-benzamida;

2-(2-Cloro-4-yodo-fenilamino)-4,5-difluoro-N-(2-hidroxi-etoxi)-benzamida;

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-etoxi)-benzamida;

5-Bromo-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-etoxi)-benzamida;

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-etoxi)-benzamida;

3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-etoxi)-benzamida;

2-(4-Bromo-2-fluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-etoxi)-benzamida;

2-(4-Bromo-2-fluoro-fenilamino)-4,5-difluoro-N-(2-hidroxi-etoxi)-benzamida;

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2-(4-Cloro-2-fluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-etoxi)-benzamida;

3,4-Difluoro-2-(2-fluoro-fenilamino)-N-(2-hidroxi-etoxi)-benzamida;

5-Cloro-2-(2,4-difluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-etoxi)-benzamida;

2-(2,4-Difluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-etoxi)-benzamida;

4-Fluoro-N-(3-hidroxi-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

5-Cloro-3,4-difluoro-N-(3-hidroxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

2-(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(3-hidroxi-propoxi)-benzamida;

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-propoxi)-benzamida;

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-propoxi)-benzamida;

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(4-hidroxi-butoxi)-benzamida;

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-N-(2,3-dihidroxi-propoxi)-benzamida;

5-Cloro-N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-benzamida;

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5-Cloro-N-(3,4-dihidroxi-butoxi)-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-benzamida;

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-N-(3,4-dihidroxi-butoxi)-3,4-difluoro-benzamida;

N-(2,3-Dimetil-1,3-dioxolan-4-ilmetoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida;

N-(2,3-Dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida;

5-Bromo-N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida;

5-Cloro-N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida;

N-(2,3-Dihidroxi-propoxi)-4-fluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida;

N-(2,3-Dihidroxi-propoxi)-3,4,5-trifluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida;

2-(4-Bromo-2-fluoro-fenilamino)-N-(2,3-dihidroxi-propoxi)-3,4-difluoro-benzamida;

2-(4-Cloro-2-fluoro-fenilamino)-N-(2,3-dihidroxi-propoxi)-3,4-difluoro-benzamida;

N-(2,2-Dimetil-1,3-dioxolan-5-iloxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida;

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1-hidroximetil-etoxi)-benzamida;

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5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1-hidroximetil-etoxi)-benzamida;

N-((R)-2,3-Dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida;

N-((S)-2,3-Dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida;

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-N-((R)-2,3-dihidroxi-propoxi)-3,4-difluoro-benzamida;

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-N-((S)-2,3-dihidroxi-propoxi)-3,4-difluoro-benzamida;

5-Cloro-N-((R)-2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida;

5-Cloro-N-((S)-2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida;

2-(4-Bromo-2-fluoro-fenilamino)-N-((R)-2,3-dihidroxi-propoxi)-3,4-difluoro-benzamida;

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-viniloxi-etoxi)-benzamida;

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-viniloxi-etoxi)-benzamida;

4-Fluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-viniloxi-etoxi)-benzamida;

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-viniloxi-etoxi)-benzamida;

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5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-viniloxi-etoxi)-benzamida;

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-viniloxi-etoxi)-benzamida;

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-1,1-dimetil-etoxi)-benzamida;

3,4-Difluoro-N-(2-hidroxi-1,1-dimetil-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-2-metil-propoxi)-benzamida;

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1,1-dimetil-etoxi)-benzamida;

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1,1-dimetil-etoxi)-benzamida;

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-2-metil-propoxi)-benzamida;

3,4-Difluoro-N-(2-hidroxi-3-metoxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-2-metoxi-propoxi)-benzamida;

3,4-Difluoro-N-(1-hiroximetil-ciclopropilmetoxi)-2-(4-yodo-2-meti-fenilamino)-benzamida;

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(1-hiroximetil-ciclopropilmetoxi)-benzamida;

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3,4-Difluoro-2-(4-yodo-2-metil-fenilamino)-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida;

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida;

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroximetil-ciclopropilmetoxi)-benzamida;

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroximetil-ciclopropilmetoxi)-benzamida;

N-(2,3-Dihidroxi-3-metil-butoxi)-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-benzamida;

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-fenilamino-etoxi)-benzamida;

3,4-Difluoro-2-(4-yodo-2-metil-fenilamino)-N-(2-metilamino-etoxi)-benzamida;

clorhidrato de 3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-metilamino-etoxi)-benzamida;

clorhidrato de 3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-N-[2-(2,2,2-trifluoro-etilamino)-etoxi]-benzamida;

2-(2-Cloro-4-yodo-fenilamino)-4-fluoro-N-(2-hidroxi-etoxi)-N-metil-benzamida;

2-[3,4,5-trifluoro-2-(4-yodo-2-metil-fenilamino)-benzoilaminooxi]-etil éster del ácido acético;

[3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-fenil]-(4-hidroxi-isoxazolidin-2-il)-metanona;

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5-Bromo-N-(2,3-dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-fenilamino)-benzamida;

N-(2,3-Dihidroxi-propoxi)-3,4-difluoro-2-(2-fluoro-fenilamino)-benzamida;

2-(2-Cloro-4-yodo-fenilamino)-N-(2,3-dihidroxi-propoxi)-3,4-difluoro-benzamida;

2-(2-Cloro-4-yodo-fenilamino)-N-(2,3-dihidroxi-propoxi)-3,4,5-trifluoro-benzamida;

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-N-(2,3-dihidroxi-propoxi)-3,4-difluoro-benzamida;

N-(2,3-Dihidroxi-propoxi)-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-benzamida;

N-(2,3-Dihidroxi-propoxi)-3,4,5-trifluoro-2-(4-yodo-2-metil-fenilamino)-benzamida;

5-Bromo-N-(2,3-Dihidroxi-propoxi)-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-benzamida;

2-(2-Cloro-4-yodo-fenilamino)-N-(3,4-dihidroxi-butoxi)-3,4-difluoro-benzamida;

2-(2-Cloro-4-yodo-fenilamino)-N-(3,4-dihidroxi-butoxi)-3,4,5-trifluoro-benzamida;

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-N-(3,4-dihidroxi-butoxi)-3,4-difluoro-benzamida;

N-(3,4-Dihidroxi-butoxi)-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-benzamida;

N-(3,4-Dihidroxi-butoxi)-3,4,5-trifluoro-2-(4-yodo-2-metil-fenilamino)-benzamida;

5-Bromo-N-(3,4-dihidroxi-butoxi)-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-benzamida;

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-propoxi)-benzamida;

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-propoxi)-benzamida;

3,4,5-Trifluoro-N-(3-hidroxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(3-hidroxi-propoxi)-benzamida;

5-Bromo-3,4-difluoro-N-(3-hidroxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

3,4-Difluoro-N-(3-hidroxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-butoxi)-benzamida;

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-hidroxi-butoxi)-benzamida;

3,4,5-Trifluoro-N-(2-hidroxi-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-butoxi)-benzamida;

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5-Bromo-3,4-difluoro-N-(2-hidroxi-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

3,4-Difluoro-N-(2-hidroxi-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-butoxi)-benzamida;

5-Cloro-3,4-difluoro-N-(2-hidroxi-butoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-butoxi)-benzamida;

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-butoxi)-benzamida;

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-butoxi)-benzamida;

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-butoxi)-benzamida;

5-Cloro-2-(2,4-difluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-butoxi)-benzamida;

2-(2,4-Difluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-butoxi)-benzamida;

2-(4-Bromo-2-fluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-butoxi)-benzamida;

5-Cloro-3,4-difluoro-N-(2-hidroxi-1-metil-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

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2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-1-metil-etoxi)-benzamida;

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-hidroxi-1-metil-etoxi)-benzamida;

3,4,5-Trifluoro-N-(2-hidroxi-1-metil-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-1-metil-etoxi)-benzamida;

5-Bromo-3,4-difluoro-N-(2-hidroxi-1-metil-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

2-(4-Cloro-2-fluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-1-metil-etoxi)-benzamida;

3,4-Difluoro-N-(2-hidroxi-1-metil-etoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-1-metil-etoxi)-benzamida;

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1-metil-etoxi)-benzamida;

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1-metil-etoxi)-benzamida;

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1-metil-etoxi)-benzamida;

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-1-metil-etoxi)-benzamida;

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5-Cloro-2-(2,4-difluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-1-metil-etoxi)-benzamida;

2-(2,4-Difluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-1-metil-etoxi)-benzamida;

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-metoxi-etoxi)-benzamida;

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-metoxi-etoxi)-benzamida;

3,4-Difluoro-2-(4-yodo-2-metil-fenilamino)-N-(2-metoxi-etoxi)-benzamida;

5-Bromo-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-N-(2-metoxi-etoxi)-benzamida;

3,4,5-Trifluoro-2-(4-yodo-2-metil-fenilamino)-N-(2-metoxi-etoxi)-benzamida;

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-metoxi-etoxi)-benzamida;

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-metoxi-etoxi)-benzamida;

5-Cloro-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-N-(2-metoxi-etoxi)-benzamida;

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-metoxi-etoxi)-benzamida;

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-benzamida;

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-benzamida;

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-benzamida;

3,4,5-Trifluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

5-Bromo-3,4-difluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

3,4-Difluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-benzamida;

5-Cloro-3,4-difluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-morfolin-4-il-propoxi)-benzamida;

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-morfolin-4-il-propoxi)-benzamida;

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-morfolin-4-il-propoxi)-benzamida;

5-Cloro-2-(2,4-difluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-benzamida;

2-(4-Cloro-2-fluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-morfolin-4-il-propoxi)-benzamida;

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-propoxi)-benzamida;

3,4,5-Trifluoro-N-(2-hidroxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-propoxi)-benzamida;

5-Bromo-3,4-difluoro-N-(2-hidroxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-hidroxi-propoxi)-benzamida;

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-propoxi)-benzamida;

3,4-Difluoro-N-(2-hidroxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

5-Cloro-3,4-difluoro-N-(2-hidroxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-propoxi)-benzamida;

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-propoxi)-benzamida;

5-Cloro-2-(2,4-difluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-propoxi)-benzamida;

2-(2,4-Difluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-propoxi)-benzamida;

2-(4-Cloro-2-fluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-propoxi)-benzamida;

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-propoxi)-benzamida;

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-hidroxi-2-metil-propoxi)-benzamida;

3,4,5-Trifluoro-N-(2-hidroxi-2-metil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

5-Bromo-3,4-difluoro-N-(2-hidroxi-2-metil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-2-metil-propoxi)-benzamida;

3,4-Difluoro-N-(2-hidroxi-2-metil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-2-metil-propoxi)-benzamida;

5-Cloro-3,4-difluoro-N-(2-hidroxi-2-metil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-2-metil-propoxi)-benzamida;

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-2-metil-propoxi)-benzamida;

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-2-metil-propoxi)-benzamida;

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5-Cloro-2-(2,4-difluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-2-metil-propoxi)-benzamida;

2-(2,4-Difluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-2-metil-propoxi)-benzamida;

2-(4-Bromo-2-fluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-2-metil-propoxi)-benzamida;

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida;

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida;

3,4,5-Trifluoro-N-(2-hidroxi-3-fenoxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

5-Bromo-2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida;

5-Bromo-2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida;

5-Bromo-3,4-difluoro-N-(2-hiroxi-3-fenoxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

3,4-Difluoro-N-(2-hidroxi-3-fenoxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida;

5-Cloro-3,4-difluoro-N-(2-hidroxi-3-fenoxi-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida;

5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-2-fenoxi-propoxi)-benzamida;

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida;

5-Cloro-2-(2,4-difluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida;

2-(2,4-Difluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida;

2-(4-Cloro-2-fluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-fenoxi-propoxi)-benzamida;

3,4-Difluoro-N-(3-hidroxi-2,2-dimetil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(3-hidroxi-2,2-dimetil-propoxi)-benzamida;

3,4,5-Trifluoro-N-(3-hidroxi-2,2-dimetil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-2,2-dimetil-propoxi)-benzamida;

5-Cloro-3,4-difluoro-N-(3-hidroxi-2,2-dimetil-propoxi)-2-(4-yodo-2-metil-fenilamino)-benzamida;

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-2,2-dimetil-propoxi)-benzamida;

5-Cloro-2-(2,4-difluoro-fenilamino)-3,4-difluoro-N-(3-hidroxi-2,2-dimetil-propoxi)-benzamida;

3,4-Difluoro-2-(4-yodo-2-metil-fenilamino)-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida;

3,4,5-Trifluoro-2-(4-yodo-2-metil-fenilamino)-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida;

5-Bromo-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida;

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida;

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida;

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-[2-(2-metoxi-etoxi)-etoxi]-benzamida;

3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida;

5-Cloro-2-(2,4-difluoro-fenilamino)-3,4-difluoro-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida;

2-(2,4-Difluoro-fenilamino)-3,4-difluoro-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida;

2-(4-Cloro-2-fluoro-fenilamino)-3,4-difluoro-N-(3,3,3-trifluoro-2-hidroxi-propoxi)-benzamida;

5-Cloro-2-(2,4-difluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-metil-ciclopropilmetoxi)-benzamida;

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2-(2,4-Difluoro-fenilamino)-3,4-difluoro-N-(2-hidroximetil)-ciclopropilmetoxi)-benzamida;

2-(4-Cloro-2-fluoro-fenilamino)-3,4-difluoro-N-(2-hidroximetil-ciclopropilmetoxi)-benzamida;

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroximetil-ciclopropilmetoxi)-benzamida;

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroximetil-ciclopropilmetoxi)-benzamida;

3,4,5-Trifluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroximetil-ciclopropilmetoxi)-benzamida;

5-Bromo-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroximetil-ciclopropilmetoxi)-benzamida;

4,5-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(1-hidroximetil-ciclopropilmetoxi)-benzamida;

2-(2,4-Difluoro-fenilamino)-3,4-difluoro-N-(1-hidroximetil-ciclopropilmetoxi)-benzamida;

2-(4-Bromo-2-fluoro-fenilamino)-3,4-difluoro-N-(1-hidroximetil-ciclopropilmetoxi)-benzamida;

2-(4-Cloro-2-fluoro-fenilamino)-3,4-difluoro-N-(1-hidroximetil-ciclopropilmetoxi)-benzamida;

5-Cloro-2-(2,4-difluoro-fenilamino)-3,4-difluoro-N-(1-hidroximetil-ciclopropilmetoxi)-benzamida;

2-(2,4-Difluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-metoxi-propoxi)-benzamida;

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5-Cloro-2-(2,4-difluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-metoxi-propoxi)-benzamida;

2-(4-Bromo-2-fluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-metoxi-propoxi)-benzamida;

2-(4-Cloro-2-fluoro-fenilamino)-3,4-difluoro-N-(2-hidroxi-3-metoxi-propoxi)-benzamida;

3,4,5-Trifluoro-2-(4-yodo-2-metil-fenilamino)-N-(2-fenilamino-etoxi)-benzamida;

5-Bromo-3,4-difluoro-2-(4-yodo-2-metil-fenilamino)-N-(2-fenilamino-etoxi)-benzamida;

2-(2-Cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-fenilamino-etoxi)-benzamida;

2-(2-Cloro-4-yodo-fenilamino)-3,4,5-trifluoro-N-(2-fenilamino-etoxi)-benzamida;

3,4-Difluoro-2-(4-yodo-2-metil-fenilamino)-N-(2-fenilamino-etoxi)-benzamida;

5-Bromo-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(2-fenilamino-etoxi)-benzamida;

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-((S)-3-hidroxi-2-metilamino-propoxi)-benzamida;

3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-((R)-3-hidroxi-2-metilamino-propoxi)-benzamida;

(S)-5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-2-metilamino-propoxi)-benzamida;

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(R)-5-Cloro-3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(3-hidroxi-2-metilamino-propoxi)-benzamida;
(S)-5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-2-metilamino-propoxi)-benzamida;
(R)-5-Cloro-2-(2-cloro-4-yodo-fenilamino)-3,4-difluoro-N-(3-hidroxi-2-metilamino-propoxi)-benzamida; y
3,4-Difluoro-2-(2-fluoro-4-yodo-fenilamino)-N-(2-hidroxi-3-metilamino-propoxi)-benzamida.

79. Una composición farmacéutica que comprende una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1 en combinación con por lo menos un agente quimioterapéutico.

80. Una composición farmacéutica tal como se describe en la Reivindicación 79, en la que el agente quimioterapéutico utilizado es un inhibidor mitótico.

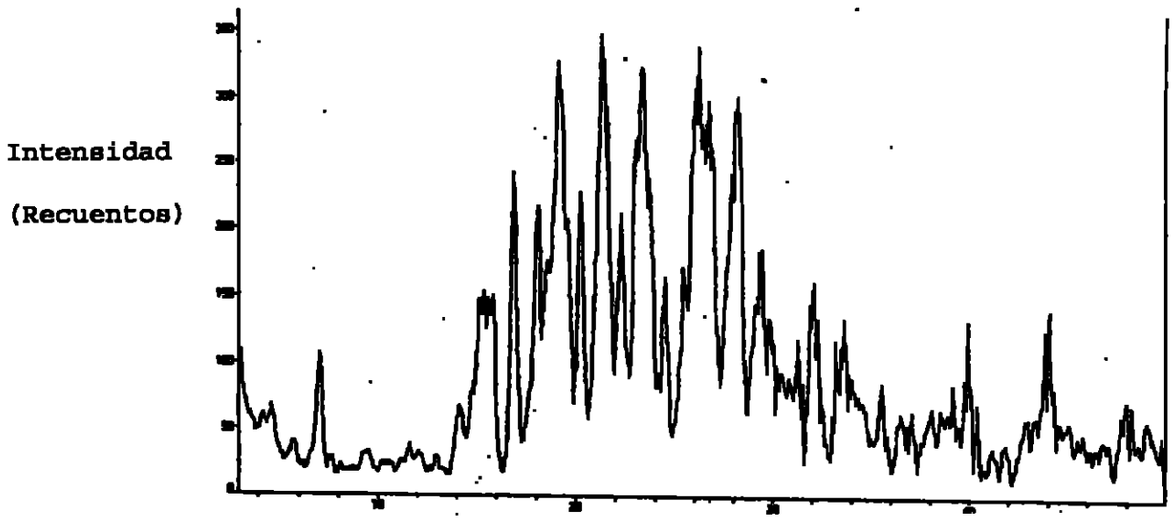
81. Una composición farmacéutica tal como se describe en la Reivindicación 80, en la que el inhibidor mitótico se selecciona del grupo formado por paclitaxel, docetaxel, vincristina, vinblastina, vinorelbina y vinflunina.

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RESUMEN DE LA INVENCIÓN

La presente invención se relaciona con ésteres oxigenados de derivados del ácido 4-yodofenilamino benzhidroxámico, con composiciones farmacéuticas y métodos de uso de ellos. La presente invención también se relaciona con formas cristalinas de ésteres oxigenados de derivados del ácido 4-yodofenilamino benzhidroxámico, con composiciones farmacéuticas y métodos de uso de ellos.

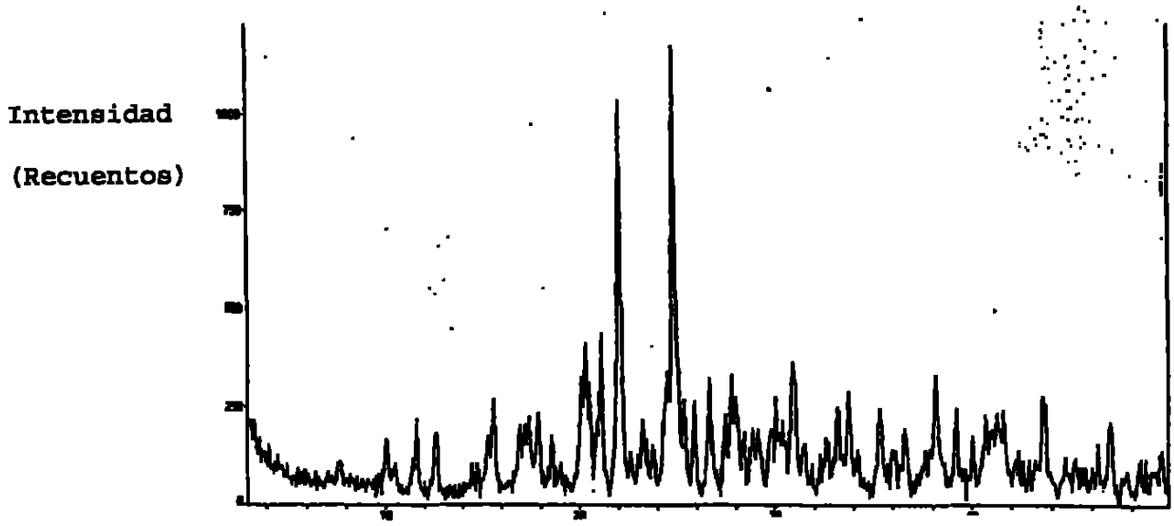
Fig - 1



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Fig - 2



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Fig - 3

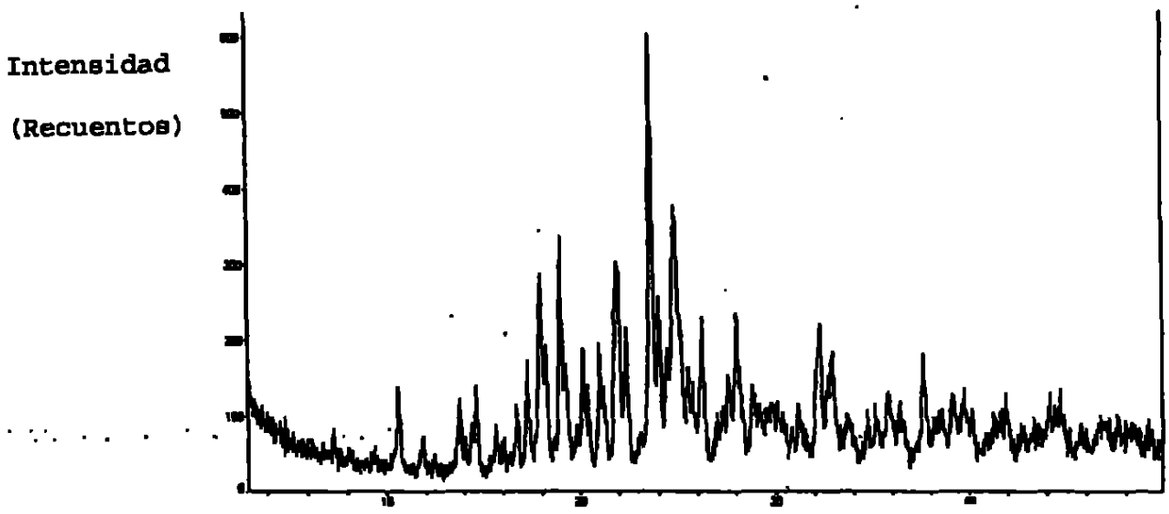


Fig - 4

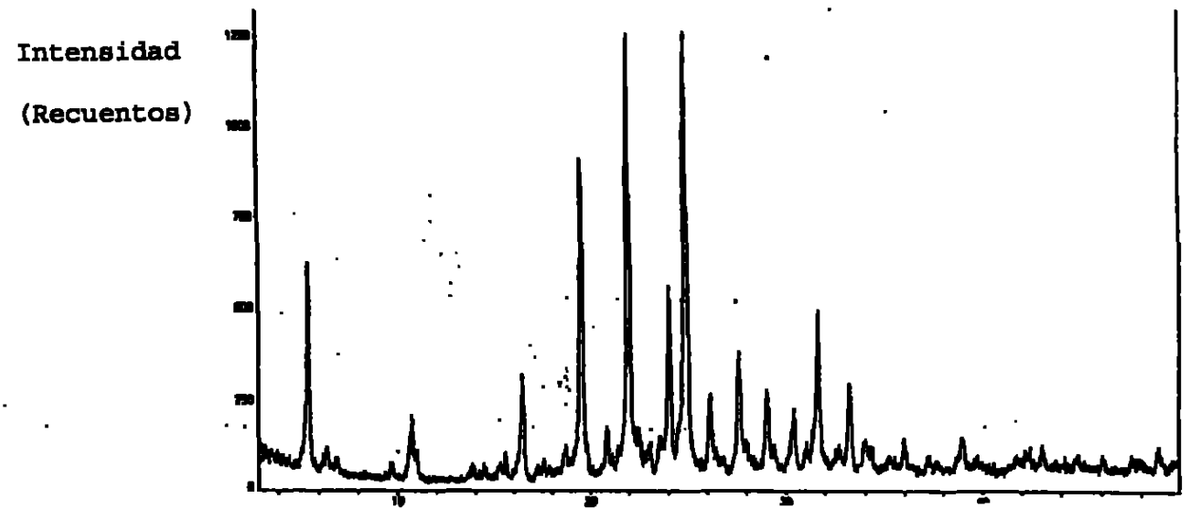


Fig - 5

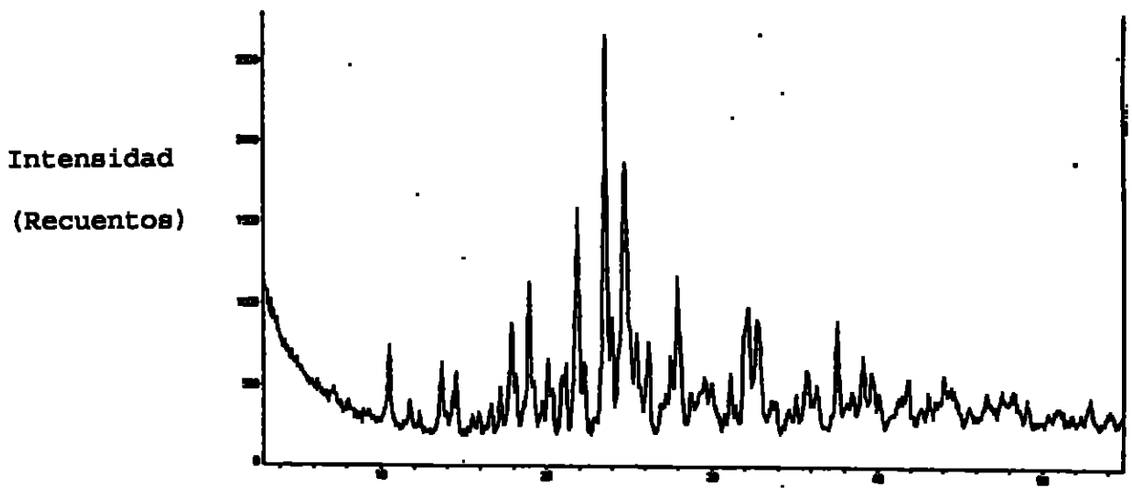
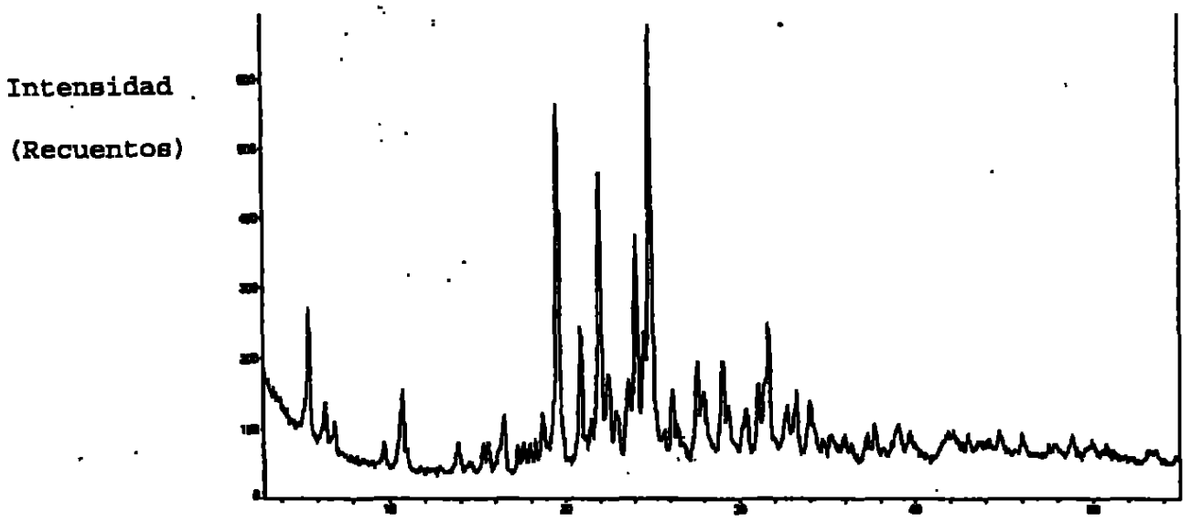


Fig - 6



=> Suzanne M. Harvey
Trevor Lau 6
German Castillo
Heather C. Anderson
Saul Lesser

A321 484
PCT

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:
MANSMANN, Ivo / Dr. TESCH Rudolf
Warner-Lambert Company
Legal Division
c/o Gödecke AG, Patente
Mooswaldallee 1
D-79090 Freiburg
ALLEMAGNE

Patentwesen
Eing.: 06. Juni 2002

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

	Date of mailing (day/month/year) 04/06/2002
Applicant's or agent's file reference A0000331-01-EMK	IMPORTANT NOTIFICATION

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US 01/22331	12/07/2001	19/07/2000

Applicant
WARNER-LAMBERT COMPANY et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	KENNEDY M B Tel. (+49-89) 2399 2828

Form PCT/IPEA/416 (July 1992) P2047j

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
A0000391-01-BHE		
International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US 01/ 22391	12/07/2001	19/07/2000
International Patent Classification (IPC) or national classification and IPC		
C07C259/10		
Applicant		
WARNER-LAMBERT COMPANY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 2 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
07/02/2002	30/05/2002
Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	DE BUNDEL K R J Tel. (+49-89) 2399 2828

Form PCT/IPEA/409 (cover sheet) (July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.PCT/ US 01/ 22331

I. Basis of the report

The basis of this international preliminary examination is the application as originally filed.

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(e) PCT); see also international search report).

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability

To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:

In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims, which have been the subject of an international search report, does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
A0000331-01S		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 01/ 22331	12/07/2001	19/07/2000
Applicant		
WARNER-LAMBERT COMPANY		

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.

[X] 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, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] Certain claims were found unsearchable (See Box I).

3. [X] Unity of invention is lacking (see Box II).

4. With regard to the title,

   [X] 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,

   [X] 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 III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATI NAL SEARCH REPORT

International Application No
PCT/US 01/22331 485

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C259/10 C07D295/088 A61K31/166 A61K31/5375

0485

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)
IPC 7 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BEILSTEIN 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 99 01426 A (DOHERTY ANNETTE MARIAN ;BARRETT STEPHEN DOUGLAS (US); BRIDGES ALEX) 14 January 1999 (1999-01-14) page 3, line 10 -page 5, line 8 examples 59-61,97,98	1-52,77, 78
X	WO 98 37881 A (BRIDGES ALEXANDER JAMES ;WARNER LAMBERT CO (US)) 3 September 1998 (1998-09-03) examples 59A-61A	1-52,77, 78
X	WO 00 40237 A (BRIDGES ALEXANDER JAMES ;DUDLEY DAVID THOMAS (US); GRACHECK STEPHE) 13 July 2000 (2000-07-13) examples 59A-61A	1-52,77, 78

-/—

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 February 2002	12/02/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	O'Sullivan, P

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATI NAL SEARCH REPORT

International Application No
PCT/US 01/22331 0486

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 37141 A (SEBOLT LEOPOLD JUDITH ;WARNER LAMBERT CO (US); GOWAN RICHARD CARLE) 29 June 2000 (2000-06-29) examples 59A-61A	1-52,77, 78
A	EP 0 316 630 A (WARNER LAMBERT CO) 24 May 1989 (1989-05-24) page 4, line 45 -page 5, line 56	1-52,77, 78

2

International Application No. PCT/US 01 22331

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-78 partially

   Compounds of the formula I (claim 1), corresponding uses,compositions and crystalline forms, where W = O.

2. Claims: 1-78 partially

   Compounds of the formula I, claim 1, corresponding uses and compositions where W = NRa.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/22331

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 33-52 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 dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [X] 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.

492 GTT

INTERNATI NAL SEARCH REPORT

Information on patent family members

International Application No PCT/US 01/22331

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9901426	A	14-01-1999	AU	8262798 A	25-01-1999
			BR	9810366 A	29-08-2000
			CN	1261877 T	02-08-2000
			EP	0993439 A1	19-04-2000
			HR	980368 A1	30-04-1999
			HU	0003731 A2	28-04-2001
			NO	996491 A	29-12-1999
			PL	337698 A1	28-08-2000
			TW	396149 B	01-07-2000
			WO	9901426 A1	14-01-1999
			ZA	9805728 A	27-01-1999
WO 9837881	A	03-09-1998	AU	5610398 A	18-09-1998
			WO	9837881 A1	03-09-1998
			US	6251943 B1	26-06-2001
			ZA	9801578 A	02-09-1998
WO 0040237	A	13-07-2000	AU	2203800 A	24-07-2000
			EP	1140067 A1	10-10-2001
			WO	0040237 A1	13-07-2000
WO 0037141	A	29-06-2000	AU	2203900 A	12-07-2000
			BR	9916839 A	09-10-2001
			CN	1333698 T	30-01-2002
			EP	1140291 A1	10-10-2001
			NO	20013099 A	20-08-2001
			WO	0037141 A1	29-06-2000
EP 0316630	A	24-05-1989	US	5155110 A	13-10-1992
			AU	2909289 A	23-05-1989
			EP	0316630 A1	24-05-1989
			WO	8903818 A1	05-05-1989
			ZA	8807696 A	27-06-1990

SUPERINTENDENCIA Y COMERCIO
Radicacion 03003336 00000000
Fecha (AMD): 2003-01-20 17:32:18 Folios 612
Tramite : 011 PCT-PATENT 370 FASE NACI 411 PRESENTAC
Dependencia 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

		USUARIO	RADICADOR
PATENTE DE INVENCIÓN	**MODELO DE UTILIDAD**	( )	(X)
- Indicación de que se solicita la concesión de una patente.		( )	(X)
- Datos de identificación del solicitante o de la persona que se presenta la solicitud		( )	(X)
- Descripción de la invención.		( )	(X)
- Dibujos de ser estos pertinentes.		( )	(X)
- Comprobante de Pago de las tasas establecidas			
COMPLETA	(X)	**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 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 de trazado		( )	( )
Comprobante de pago de las tasas establecidas.		( )	( )
COMPLETA	( )	**INCOMPLETA** ( )	( )

Edwar Navarro
Firma Responsable

20-01-2003
Fecha

494 0491

Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá, D.C.,

Doctor:
Carlos R. Olarte
Apoderado
Warner-Lambert Company

Oficio Nº 07238

ASUNTO:	**Radicación Nº**	03-03336
	Solicitud Internacional	PCT/US2001/22331
	Fecha inicio fase nacional	19/02/2003
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento el el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

☐ La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486).

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única Nº 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha, 05 SET. 2003.

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