CSA719400

Industria y Comercio
SUPERINTENDENCIA
PROPIEDAD INDUSTRIAL
Autoridad Nacional
Ministerio de Comercio, Industria y Turismo

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

PCT

SOLICITUD DE

PATENTE DE INVENCION
PCT ENTRADA EN FASE NACIONAL

21. EXPEDIENTE No. 08-30803

54. TITULO: **DERIVADOS DE FENIL- Y PIRIDIL-1,2,4-OXADIAZOLONA CON GRUPO FENILO, PROCEDIMIENTOS PARA SU PREPARACION Y SU USO COMO PRODUCTOS FARMACÉUTICOS**

52. CLASIFICACION INTERNACIONAL: **C07D 413/12, A61K 31/4245**

71. SOLICITANTE: **SANOFI-AVENTIS**

DOMICILIO: **174, Avenue de France, 75013 Paris, FRANCIA**

74. APODERADO: **DR. LUIS PATIÑO LEYVA**

42. BOGOTA, D.C., 28 MAR. 2008

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-030803- -00000-0000
Fecha: 2008-03-28 14:14:48 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 434

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

(1) **SOLICITUD DE:**

[X] Patente de Invención [ ] Patente de Modelo de Utilidad

[X] Capítulo I [ ] Capítulo II

SOLICITANTE (71)	Nombre: SANOFI-AVENTIS Dirección: 174, avenue de France 75013 Paris - FRANCIA Domicilio: 75013 Paris - FRANCIA Lugar de Constitución: FRANCIA Teléfono: Fax: E-mail:	C.C. [ ] NIT [ ] C.E. [ ] Otro [ ] Cual Número
(3) **REPRESENTANTE O APODERADO (74)**	Nombre: DR. LUIS PATIÑO LEYVA Dirección: Carrera 11A No. 94-76, Of. 308 Teléfono: 616 1948 Fax: 616 3976 E-mail: GUSTAVO_HOLLMANN@etb.com	IDENTIFICACIÓN C.C. [X] NIT [ ] C.E. [ ] Otro [ ] Cual Número 2.930.616 TPA 2698
(4) **INVENTOR (ES) (72)**	VER ANEXO # 1	

(5) **PCT (86)**

Solicitud Internacional No. PCT/EP2006/009298 Fecha 26/09/2006

Publicación Internacional No. WO 2007/039172 A1 Fecha 12/04/2007

(6) **Título (54)**

DERIVADOS DE FENIL- Y PIRIDIL-1,2,4-OXADIAZOLONA CON GRUPO FENILO, PROCEDIMIENTOS PARA SU PREPARACION Y SU USO COMO PRODUCTOS FARMACEUTICOS

(7) **Clasificación Internacional (51)** C07D 413/12; A61K 31/4245

(8) Prioridad	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
SI [X] NO [ ]	EP	29/09/2005	05021235.6

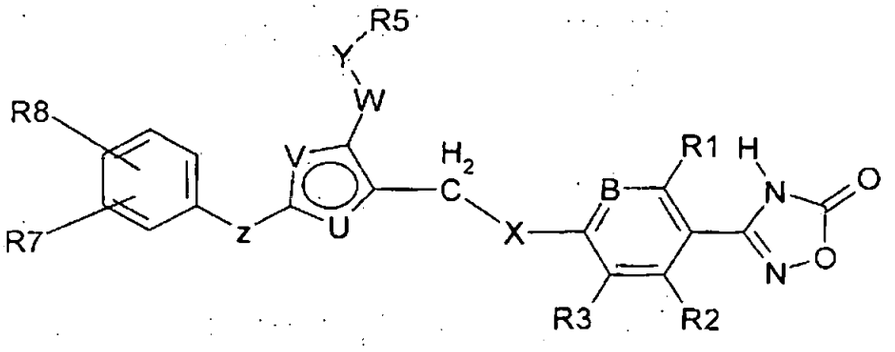
(9) **Comprobante de pago No.** 08-24,581 **Fecha** 26 de marzo de 2008

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

(10) **Anexos**

- [X] Comprobante de pago de la tasa de presentación de la solicitud.
- [X] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [X] Poderes, si fuere el caso, junto con la sustitución del mismo a mi favor
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [X] Copia de la solicitud internacional (Resumen, descripción, reivindicaciones, dibujos).
- [X] Traducción de la solicitud internacional al castellano (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [X] Arte final 12x12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [X] Otros **Tarjeta de Propietario, Extracto para la publicación y Forma PCT/IB/306**

(11) **FIGURA CARACTERISTICA:**



(12) **Solicito la concesión de la patente,**

28 MAR. 2008

NOMBRE: **DR. LUIS PATIÑO LEYVA**

FIRMA:

C.C. No. 2'930.616 Bogotá - TPA 2.698 C.S.J.

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página. - LPL/gcb - P20194

G. HOLLMANN RESTREPO
ABOGADOS LTDA.

ANEXO # 1

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174 Avenue de France
75013 Paris, FRANCIA

P2019497

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

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FECHA : MARZO 28 DE 2008

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Tra. 11 PATENTEIYII
Act. 411 PRESENTACION
Dep. 2020 NUECREACIONI
Eve: 378 FASENACIONALI
Folios: 434

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
GUILLMAN	CONSIGNACION	BANCO DE BOGOTA	062754307	4630722	26/03/2008	3,021,000.00

***** 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	501,000.00
		TOTAL : $	501,000.00

SON: QUINIENTOS UN MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Un poder xa poderio 5
P-2008-
Dr. Pedro

G.HOLLMANN RESTREPO
ABOGADOS LTDA

The undersigned SANOFI AVENTIS... .., acting on behalf of and representing of ..... , domiciled in 174 Avenue de France, 75013 PARIS, FRANCE, hereby

appoint(s) LUIS PATIÑO LEYVA and/or GUSTAVO HOLLMANN RESTREPO, domiciled in Bogotá D.C, Republic of Colombia , as our true and legal attorney with the necessary powers:

1) To apply to the administrative, judicial and police authorities of the Republic of Colombia, in any instance or appeal, for obtaining registration of patents, ~~utility models, industrial designs and models, commercial~~ ensigns and names, trademarks, slogans, health licenses, ~~copyrights and domain names~~ as well as their assignments, extensions, renewals and changes of name; 2) To prepare, apply for, obtain, execute and register contracts, licenses, authorizations and registrations of any kind; 3) To intervene as plaintiff or defendant, in any instance or appeal, before any judge, court, tribunal, corporation, public officer or authority, in any judicial, administrative or police action, such as: action dealing with commercial ensigns and names; oppositions against trademark registrations; caducity and nullity actions; recovery actions, actions arising from obtainment and working of license agreements; actions dealing with unfair competition; criminal actions; actions claiming indemnity for damages, complaints or remarks on all sort of industrial property matters; the performance of precautionary measures, and in any other similar action, measure or appeal related to intellectual property matters.

To this effect, I (we) hereby authorize him to file applications, make descriptions, protests, amendments, declarations, oppositions, cancellations, appeals and claims; to pay taxes, quotas and liens as provided by Law; to waive or abandon granted rights or rights in process of being granted, to receive all kind of documents and securities; to issue the respective releases and, in general, to take, before said authorities, pertinent steps to the above mentioned purposes and take all measures they may deem advisable to protect my (our) interests, with all other necessary legal faculties, and I (we) hereby declare as good and valid whatever the attorneys should do to my (our) benefit.

This power comprises the authority to ratify or confirm on my (our) behalf any action, as well as the faculty of receiving, desisting, transacting, compromising, substituting and revoking substitutions, taking notifications, and appointing judicial or extra-judicial attorneys.

Signed in Paris on this 14 day of December of 2006.

MERLIER Josiane, Director Patent Administration

G. HOLLMANN RESTREPO
ABOGADOS LTDA

Yo (nosotros) , obrando en nombre propio y representación de, con domicilio en , nombro(amos) a LUIS PATIÑO LEYVA y/o GUSTAVO HOLLMANN RESTREPO , con domicilio en Bogotá D.C., República de Colombia, apoderado verdadero y legal, con poder especial, amplio y suficiente:

1) Para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía en cualquier instancia o recurso, la obtención de patentes de invención, modelos de utilidad, dibujos y modelos industriales, registro de marcas, registro de lemas comerciales, depósito de nombres y enseñas comerciales, registros sanitarios, derechos de autor y nombres de dominio así como sus traspasos, prórrogas, renovaciones y cambios de nombre; 2) Elaborar, tramitar, solicitar, obtener, realizar, ejecutar y registrar contratos, licencias, autorizaciones y registros de cualesquiera clases; 3) Intervenir como demandante o como demandado en cualquier instancia y recurso y ante cualquier juez, entidad, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía, tales como acciones derivadas de nombre o enseña comerciales; acciones reivindicatorias; acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal, demandas penales y civiles; acciones de indemnización de perjuicios, reclamos, u observaciones a cualquier asunto sobre propiedad intelectual; al ejercicio de medidas cautelares y cualesquiera otras acciones, medidas o recursos similares relacionados con la propiedad intelectual.

A este efecto, lo facultamos para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la Ley; renunciar o desistir a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores dando al descargo respectivo, y en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomas todas las medidas que creyeren conducentes al resguardo de mis (nuestros) intereses, con todas las facultades necesarias, y por este documento desde ahora declaro(amos) válido y bueno todo cuanto los apoderados hicieren en mi (nuestro) beneficio.

Este poder comprende la facultad de ratificar, o confirmar en mi (nuestro) nombre lo actuado, así como la facultad de recibir, desistir, transigir, comprometer, sustituir y revocar sustituciones, recibir notificaciones y nombrar apoderados judiciales o extrajudiciales.

Firmado en Paris el de de

Je soussigné Me Hervé POMMERY
Notaire à Paris, certifie matériellement
la signature de Madame
Josiane MERLIER
apposée sur le présent document.
Cette certification ne comporte aucune
vérification de l'exactitude des faits et
actes mentionnés dans le présent document

Hervé POMMERY, Notaire Associé à PA

Esta copia coincide con el original que tuvo a la vista.
Bogotá, D.C.
10 MAR 2008
AGUSTIN MORALES RIVEIRA
NOTARIO CUARENTA Y UNO

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. *République française*

Le présent acte public

2. a été signé par Maître POMMERY

3. agissant en qualité de Notaire

4. est revêtu du sceau/timbre de son étude

Attesté

5. à PARIS

6. le 20/12/06

7. *par le Procureur général près la Cour d'appel de* PARIS

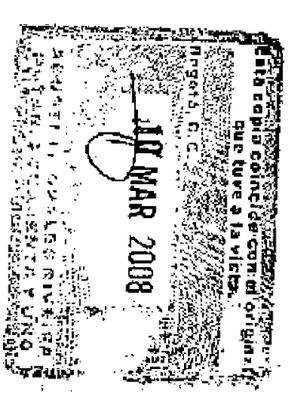
8. sous n° 17490

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Mme TEPLIER

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CERTIFICATION

COMPANIES

The undersigned Hervé POMMERY certifies: that the preceding signature(s) reading [illegible] (are) authentic; that the signer(s) at present fill(s) the position of Director of Patent administration he (they) is (are) empowered to grant this power; and that said company exists, accomplishes its social object and is organized in _____ in accordance with the Laws of FRANCE
All the foregoing facts are known to me, due to my having examined the respective documents to which I attest.

Signed in PARIS on this 19th day of February 2007.

CERTIFICACIÓN

SOCIEDADES

El(la) infrascrito(a)_____ certifica: que la(s) firma(s) que antecede(n) y dice(n) _____ es (son) auténtica(s); que el (los) signatario(s) desempeña(n) actualmente el cargo(s) de _____ de _____; que tiene(n) facultad para otorgar este poder; y que dicha compañía existe, cumple su objeto social y está organizada en _____ conforme a las Leyes de _____.
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Firmado en _____ el _____ de _____ de _____.

Hervé POMMERY
NOTAIRE

BAILLY POMMERY CAURO
NOTAIRES ASSOCIÉS D'UNE SCP
30, rue La Boétie - Paris - 8e

APOSTILLE
(Convention de La Haye du 5 octobre 1961)

1. *République française*
Le présent acte public
2. a été signé par Maître POMMERY
3. agissant en qualité de Notaire
4. est revêtu du sceau/timbre de son étude

Attesté
5. à PARIS
6. le 22/02/2007
7. *par le Procureur général près la Cour d'appel de* PARIS
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10 MAR 2008
AGUSTIN MORALES RIVEIRA
NOTARIO CUARENTA Y UNO

EDGAR HERMES PAIXÃO PARDO

Traductor oficial - Traducteur assermenté

Español - Francés
Français - Espagnol

Traducción oficial, parcial, de un documento que me fue presentado en lengua francesa, trabajo realizado en función de mi cargo de traductor oficial de esta ciudad de Santafé de Bogotá.

Contenido del documento:

PODER de SANOFI AVENTIS, 174, Avenue de France, 75013 París, Francia, para Luis Patiño Leyva y/o Gustavo Hollmann Restrepo.

Firma ilegible, Josiane Merlier.

El suscrito, Hervé Pommery, notario en París, autentico la firma de Josiane Merlier. Esta autenticación no implica aceptación del contenido del documento. Firma ilegible y sello de la notaría. París, 19 de febrero de 2007.

Apostillas. (Convención de La Haya del 5 de octubre de 1961)

1. República Francesa. El presente documento público. 2. Fue firmado por el señor Pommery. 3. Actuando en calidad de notario. 4. Lleva el sello de la notaría.

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5. En París, 6. El 20 de diciembre de 2006 y el 22 de febrero de 2007. 7. Por el Procurador General de la Corte de Apelaciones de París, 8. bajo los números **174190** y **173350**. 9. Sello de la Corte. 10. Firma ilegible.

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Edgar Pinzon

Bam

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DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

JEFE DE LEGALIZACIONES
BOGOTA D.C.

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

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International Bureau

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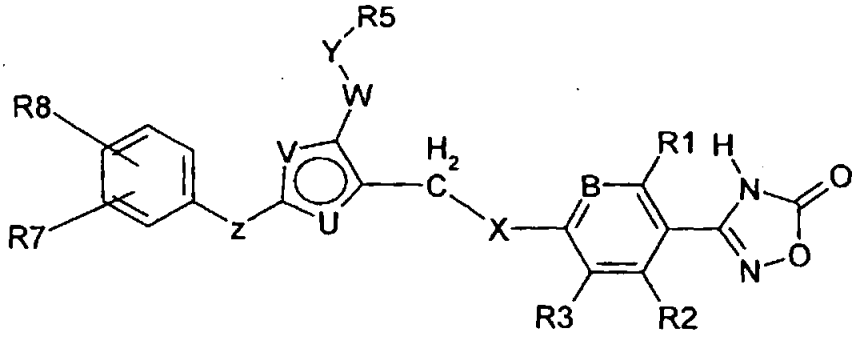
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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.

(54) Title: PHENYL- AND PYRIDYL-1, 2, 4 -OXADIAZOLONE DERIVATIVES WITH PHENYL GROUP, PROCESSES FOR THEIR PREPARATION AND THEIR USE AS PHARMACEUTICALS



(I)

(57) Abstract: The invention relates to phenyl-1,2,4-oxadiazolone derivatives with phenyl group and to their physiologically acceptable salts and physiologically functional derivatives showing PPARdelta agonist activity. What is described are compounds of the formula (I) in which the radicals are as defined, and their physiologically acceptable salts and processes for their preparations. The compounds are suitable for the treatment and/or prevention of disorders of fatty acid metabolism and glucose utilization disorders as well as of disorders in which insulin resistance is involved and demyelinating and other neurodegenerative disorders of the central and peripheral nervous system.

WO 2007/039172 A1

PHENYL- AND PYRIDYL-1,2,4-OXADIAZOLONE DERIVATIVES WITH PHENYL GROUP, PROCESSES FOR THEIR PREPARATION AND THEIR USE AS PHARMACEUTICALS

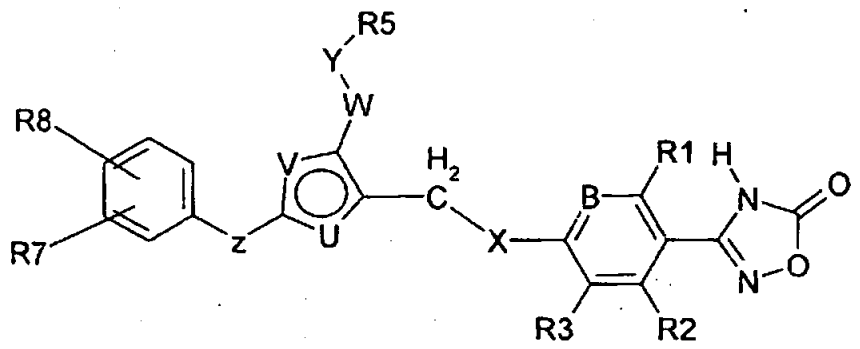
The invention relates to phenyl-1,2,4-oxadiazolone derivatives with phenyl group and to their physiologically acceptable salts and physiologically functional derivatives showing PPARdelta agonist activity.

PPARdelta agonists have been described in the prior art (e.g. WO 01/00603, WO 02/092590, WO2004/080943, WO2005/054213 and WO2005/097786). Compounds comprising an oxadiazolone feature as inhibitors of factor Xa were disclosed in DE 101 12 768 A1, oral hypoglycemic agents in WO 96/13264. From WO 97/40017 compounds having a phenyl group linked to heterocycles are known as modulators of molecules with phosphotyrosine recognition units. Benzene derivatives as inhibitors of squalene synthase and protein farnesyltransferase are described in WO96/34851.

The invention is based on the object of providing compounds, which permit therapeutically utilizable modulation of lipid and/or carbohydrate metabolism and are thus suitable for the prevention and/or treatment of diseases such as type 2 diabetes and atherosclerosis and the diverse sequelae thereof. Another purpose of the invention is to treat demyelinating and other neurodegenerative disorders of the central and peripheral nervous systems.

A series of compounds which modulate the activity of PPA receptors has been found. The compounds are suitable in particular for activating PPARdelta or PPARdelta and PPARalpha, however it being possible for the extent of the relative activation to vary depending on the compounds.

Compounds of the present invention are described by formula I:



formula I

wherein

B is C(R4) or N;

R1 is H, halogen, (C1-C8) alkyl, (C0-C4) alkylene-O-(C0-C4) alkylene-H, (C0-C2) alkylene-O-(C0-C2) alkylene-(C3-C6) cycloalkyl, SCH3, CN, wherein alkyl and alkylene are unsubstituted or mono, di- or trisubstitued by F;

R2,R3, R4 are independently
H, halogen, (C1-C8) alkyl, (C0-C4) alkylene-O-(C0-C4) alkylene-H, SCH3, CN, wherein alkyl and alkylene are unsubstituted or mono, di- or trisubstitued by F;

X is O, S, S(O), S(O)2, O-CH2, S-CH2, CH2-O, CH2-S;

one of U and V is N the other is S or O;

W is a bond, (C1-C8) alkylene, (C2-C8) alkenylene, (C0-C6) alkylene-(C3-C6) cycloalkylene, (C3-C6) cycloalkylene-(C1-C6) alkylene, wherein alkylene and alkenylene and cycloalkylene are unsubstituted or mono-, di- or trisubstituted by OH and F;

Y is a bond, O, S, S(O), S(O)2, N(R6) and

R5 is H, (C1-C8) alkyl, (C0-C4) alkylene-(C3-C13) cycloalkyl, (C0-C4) alkylene-(C6-C14) aryl, (C2-C8) alkenyl, (C0-C4) alkylene-(C3-C15) heterocycloalkyl, (C0-C4) alkylene-(C3-C15) heterocycloalkenyl, (C0-C4) alkylene-(C5-C15) heteroaryl, (C0-C4) alkylene-CO-(C1-C4) alkyl, (C0-C4) alkylene-CO-(C0-C4) alkylene-(C3-C13)cycloalkyl, (C0-C4) alkylene-CO-(C0-C4) alkylene-(C6-C10)aryl, (C0-C4) alkylene- CO-(C0-C4) alkylene- (C3-C15) heterocycloalkyl, (C0-C4) alkylene- CO-(C0-C4) alkylene- (C3-C15) heterocycloalkenyl, (C0-C4) alkylene- CO-(C0-C4) alkylene- (C5-C15) heteroaryl, SO2-(C1-C4)alkyl, SO2-(C0-C4) alkylene-(C3-C13)cycloalkyl, SO2-(C0-C4) alkylene-(C6-C10) aryl, SO2-(C0-C4) alkylene-(C3-C15) heterocycloalkyl, SO2-(C0-C4) alkylene-(C3-C15) heterocycloalkenyl, SO2-(C0-C4) alkylene-(C5-C15) heteroaryl, CO-O-(C0-C4) alkylene-(C6-C10) aryl, CO-O-(C1-C4) alkyl, CO-O-(C0-C4) alkylene-(C3-C13)cycloalkyl, CO-O-(C0-C4) alkylene-(C3-C15)heterocycloalkyl, CO-O-(C0-C4) alkylene-(C3-C15)heterocycloalkenyl, CO-O-(C0-C4) alkylene-(C5-C15)heteroaryl, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene- (C6-C10) aryl, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene-H, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene- (C3-C13)cycloalkyl, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene-(C3-C15) heterocycloalkyl, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene-(C3-C15) heterocycloalkenyl, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene-(C5-C15) heteroaryl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C6-C10)aryl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-H, SO2-N((C0-C4) alkylene-H)-(C0-C4)alkylene-(C3-C13)cycloalkyl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C15)heterocycloalkyl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C15)heterocycloalkenyl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C5-C15)heteroaryl wherein alkyl and alkylene are unsubstituted or mono-, di- or trisubstituted by F, S-(C1-C4) alkyl, SO-(C1-C4) alkyl, SO2-(C1-C4) alkyl, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene-H, N((C0-C4) alkylene-H)-(C0-C4) alkylene-H, CO-O(C1-C4) alkyl, (C1-C4) alkyl and O-(C0-C4) alkylene-H and wherein cycloalkyl, aryl,

heterocycloalkyl, heterocycloalkenyl and heteroaryl are unsubstituted or mono-, di- or trisubstituted by F, Cl, Br, CF3, (C1-C4) alkyl and (C0-C4)-alkylen-O-(C0-C4) alkylene-H,

with the proviso that,
if Y is S, S(O) or S(O)2 then
R5 is unequal SO2-(C1-C4)alkyl, SO2-(C0-C4)alkylene-(C3-C13)cycloalkyl, SO2-(C0-C4)alkylene-(C6C10)aryl, SO2-(C0-C4)alkylene-(C3-C15)heterocycloalkyl, SO2-(C0-C4)alkylene-(C3-C15)heterocycloalkenyl, SO2-(C0-C4)alkylene-(C5-C15)heteroaryl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C6-C10)aryl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-H, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C13)cycloalkyl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C15)heterocycloalkyl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C15)heterocycloalkenyl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C5-C15)heteroaryl;

with the proviso that,
if Y is a bond or O then
Z is unequal a bond;

or
Y is a bond,

with the proviso that
R5 is CN, (C1-C8) alkyl mono-, di- or trisubstituted by F, CO-(C1-C4) alkyl, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene-H, SO2-N((C0-C4) alkylene-H)-(C0-C4) alkylene-H, N((C0-C4) alkylene-H)-CO-(C0-C4) alkylene-H, (C1-C6) alkylene-(C3-C13) cycloalkyl, (C3-C15) heterocycloalkyl, (C3-C15) heterocycloalkenyl, (C5-C15) heteroaryl;

or

Y is O,

with the proviso that

R5 is (C1-C8) alkyl mono-, di- or trisubstituted by F, CO-(C1-C4) alkyl, CO-O-(C0-C4) alkylene-(C6-C10) aryl, CO-O-(C0-C4) alkylene-(C3-C13)cycloalkyl, CO-O-(C0-C4) alkylene-(C3-C15)heterocycloalkyl, CO-O-(C0-C4) alkylene-(C3-C15)heterocycloalkenyl, CO-O-(C0-C4) alkylene-(C5-C15)heteroaryl, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene-H, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene-(C6-C10) aryl, CO-N((C0-C4)alkylene-H)-(C0-C4) alkylene-(C3-C13)cycloalkyl, CO-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C15)heterocycloalkyl, CO-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C15)heterocycloalkenyl, CO-N((C0-C4)alkylene-H)-(C0-C4) alkylene-(C3-C13)cycloalkyl, CO-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C5-C15)heteroaryl, (C0-C4) alkylene-(C3-C13) cycloalkyl, (C0-C4) alkylene-(C3-C15) heterocycloalkyl, (C0-C4) alkylene-(C3-C15) heterocycloalkenyl, (C0-C4) alkylene-(C5-C15) heteroaryl, (C0-C4) alkylene-N((C0-C4) alkylene-H)-(C0-C4) alkylene-H, (C0-C4) alkylene-N((C0-C4) alkylene-H)-(C0-C4) alkylene-(C3-C13)cycloalkyl, (C0-C4) alkylene-N((C0-C4) alkylene-H)-(C0-C4) alkylene-(C6-C10)aryl, (C0-C4) alkylene-N((C0-C4) alkylene-H)-(C0-C4) alkylene-(C3-C15)heterocycloalkyl, (C0-C4) alkylene-N((C0-C4) alkylene-H)-(C0-C4) alkylene-(C3-C15)heterocycloalkenyl, (C0-C4) alkylene-N((C0-C4) alkylene-H)-(C0-C4) alkylene-(C5-C15)heteroaryl;

R6 is H, (C1-C8) alkyl, (C2-C8) alkenyl, (C0-C4) alkylene-(C3-C6) cycloalkyl , wherein alkyl and alkenyl are unsubstituted or mono-, di- or trisubstituted by F and O-(C0-C4)-alkylene-H;

R5 and R6 together with the nitrogen atom to which they are bonded (Y = N(R6)) form a (C3-C15)-heterocycloalkyl, a (C3-C15)-heterocycloalkenyl or a (C5-C15)-heteroaryl which can contain additionally 1 to 3 heteroatoms N, O, S in which further the heteroatoms can be oxidized and which is unsubstituted or mono-, di- or trisubstituted by halogen, CN, CF3, (C1-C4) alkyl, (C0-C4) alkylene-(C3-C6) cycloalkyl, (C0-C4) alkylene-O-(C0-C4) alkylene-H, (C0-C4) alkylene-O-(C0-C4) alkylene-(C3-C6) cycloalkyl, (C0-C4) alkylene-O-(C0-C4) alkylene-(C6-C10)aryl, (C0-C4)alkylene-O-(C0-C4)alkylene-(C3-C15) heterocycloalkyl, (C0-C4)alkylene-O-(C0-C4)alkylene-(C3-C15) heterocycloalkenyl, (C0-C4)alkylene-O-(C0-C4)alkylene-(C5-C15) heteroaryl, (C0-C4) alkylene-S-(C1-C4) alkyl, (C0-C4) alkylene-SO-(C1-C4) alkyl, (C0-C4) alkylene-SO2-(C1-C4) alkyl, (C0-C4) alkylene-CO-(C1-C4) alkyl, (C0-C4) alkylene-CO-(C6-C10)aryl, (C0-C4) alkylene-CO-(C3-C15)heterocycloalkyl, (C0-C4) alkylene-CO-(C3-C15)heterocycloalkenyl, (C0-C4) alkylene-CO-(C5-C15)heteroaryl, (C0-C4) alkylene-CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene-H, (C0-C4)alkylene-CO-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C6)cycloalkyl, (C0-C4)alkylene-CO-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C6-C10)aryl, (C0-C4)alkylene-CO-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C15)heterocycloalkyl, (C0-C4)alkylene-CO-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C15)heterocycloalkenyl, (C0-C4)alkylene-CO-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C5-C15)heteroaryl, (C0-C4) alkylene-N((C0-C4) alkylene-H)-CO-(C1-C4) alkyl, (C0-C4) alkylene-N((C0-C4) alkylene-H)-CO-(C0-C4) alkylene-(C3-C6) cycloalkyl, (C0-C4) alkylene-N((C0-C4) alkylene-H)-CO-(C0-C4) alkylene-(C6-C10)aryl, (C0-C4)alkylene-N((C0-C4) alkylene-H)-CO-(C0-C4)alkylene-(C3-C15)heterocycloalkyl, (C0-C4)alkylene-N((C0-C4) alkylene-H)-CO-(C0-C4)alkylene-(C3-C15)heterocycloalkenyl, (C0-C4)alkylene-N((C0-C4) alkylene-H)-CO-(C0-C4)alkylene-(C5-C15)heteroaryl, (C0-C4) alkylene-(C6-C14) aryl and (C0-C4) alkylene-(C3-C15) heterocycloalkyl, (C0-C4) alkylene-(C3-C15) heterocycloalkenyl, (C0-C4) alkylene-(C5-C15) heteroaryl whereby heteroaryl, heterocycloalkyl and heterocycloalkenyl can mono- or

disubstituted by oxo residue and where alkyl can be unsubstituted or mono-, di- or trisubstituted by F;

Z is a bond, (C1-C8) alkylene, (C2-C8) alkenylene, (C2-C8) alkylidene, (C1-C6) alkylene-O-(C1-C6) alkylene;

R7, R8 are independently selected from the group consisting of H, halogen, (C1-C8) alkyl, (C0-C4) alkylene-O-(C0-C4) alkylene-H, SCF3, SF5, S(O)2CF3, (C0-C4) alkylene-O-(C6-C12) aryl, (C0-C4) alkylene (C6-C12) aryl, NO2, wherein alkyl and alkylene are unsubstituted or mono-, di- or trisubstituted by F and aryl is unsubstituted or mono-, di- or trisubstituted by halogen, (C1-C4) alkyl or O-(C1-C4) alkyl ;

in all its stereoisomeric forms, enantiomeric forms and mixtures in any ratio, and its physiologically acceptable salts and tautomeric forms.

Another embodiment according to the invention are compounds of the formula I, wherein

R2,R3 are independently
H, halogen, (C1-C8) alkyl, (C0-C4) alkylene-O-(C0-C4) alkylene-H, SCH3, CN, wherein alkyl and alkylene are unsubstituted or mono, di- or trisubstitued by F;

R4 is H, (C1-C8) alkyl, (C0-C4) alkylene-O-(C0-C4) alkylene-H wherein alkyl and alkylene are unsubstituted or mono, di- or trisubstitued by F.

Another embodiment according to the invention are compounds of the formula I, wherein

B is C(R4) and
R4 is H.

Another embodiment according to the invention are compounds of the formula I, wherein

B is C(R4) and

R4 is H;

R1 is H, halogen, (C1-C8) alkyl, (C0-C4) alkylene-O-(C0-C4) alkylene-H, SCH3, CN, wherein alkyl and alkylene are unsubstituted or mono, bi- or trisubstitued by F;

R2,R3,R4 are independently
H, halogen, (C1-C8) alkyl, (C0-C4) alkylene-O-(C0-C4) alkylene-H, SCH3, CN, wherein alkyl and alkylene are unsubstituted or mono, bi- or trisubstitued by F;

X is O, S, S(O), S(O)2, O-CH2, S-CH2, CH2-O, CH2-S;

one of U and V is N the other is S or O;

W is a bond, (C1-C8) alkylene, (C2-C8) alkenylene, (C0-C6) alkylene-(C3-C6) cycloalkylene, (C3-C6) cycloalkylen-(C1-C6) alkylene, wherein alkylene and alkenylene and cycloalkylene are unsubstituted or mono-, di- or trisubstituted by OH and F;

Y is N(R6);

R5 is H, (C1-C8) alkyl, (C0-C4) alkylene-(C3-C13) cycloalkyl, (C0-C4) alkylene-(C6-C14) aryl, (C2-C8) alkenyl, (C0-C4) alkylene-(C3-C15) heterocycloalkyl, (C0-C4) alkylene-(C3-C15) heterocycloalkenyl, (C0-C4) alkylene-(C5-C15) heteroaryl, (C0-C4) alkylene-CO-(C1-C4)alkyl, (C0-C4) alkylene-CO-(C0-C4) alkylene-(C3-C13)cycloalkyl, (C0-C4) alkylene-CO-(C0-C4) alkylene-(C6-C10)aryl, (C0-C4) alkylene- CO-(C0-C4) alkylene- (C3-C15)

heterocycloalkyl, (C0-C4) alkylene- CO-(C0-C4) alkylene- (C3-C15) heterocycloalkenyl, (C0-C4) alkylene- CO-(C0-C4) alkylene- (C5-C15) heteroaryl, SO2-(C1-C4)alkyl, SO2-(C0-C4) alkylene-(C3-C13)cycloalkyl, SO2-(C0-C4) alkylene-(C6-C10) aryl, SO2-(C0-C4) alkylene-(C3-C15) heterocyclalkyl, SO2-(C0-C4) alkylene-(C3-C15) heterocycloalkenyl, SO2-(C0-C4) alkylene-(C5-C15) heteroaryl, CO-O-(C0-C4) alkylene-(C6-C10) aryl, CO-O-(C1-C4) alkyl, CO-O-(C0-C4) alkylene-(C3-C13)cycloalkyl, CO-O-(C0-C4) alkylene-(C3-C15)heterocycloalkyl, CO-O-(C0-C4) alkylene-(C3-C15)heterocycloalkenyl, CO-O-(C0-C4) alkylene-(C5-C15)heteroaryl, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene- (C6-C10) aryl, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene-H, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene- (C3-C13)cycloalkyl, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene-(C3-C15) heterocycloalkyl, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene-(C3-C15) heterocycloalkenyl, CO-N((C0-C4) alkylene-H)-(C0-C4) aikylene-(C5-C15) heteroaryl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C6-C10)aryl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-H, SO2-N((C0-C4) alkylene-H)-(C0-C4)alkylene-(C3-C13)cycloalkyl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C15)heterocycloalkyl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C15)heterocycloalkenyl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C5-C15)heteroaryl wherein alkyl and alkylene are unsubstituted or mono-, di- or trisubstituted by F, S-(C1-C4) alkyl, SO-(C1-C4) alkyl, SO2-(C1-C4) alkyl, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene-H, N((C0-C4) alkylene-H)-(C0-C4) alkylene-H, CO-O(C1-C4) alkyl, (C1-C4) alkyl and O-(C0-C4) alkylene-H and wherein cycloalkyl, aryl and heterocycloalkyl, heterocycloalkenyl and heteroaryl are unsubstituted or mono-, di- or trisubstituted by F, Cl, Br, CF3, (C1-C4) alkyl and (C0-C4)-alkylen-O-(C0-C4) alkylene-H;

R6 is H, (C1-C8) alkyl, (C2-C8) alkenyl, (C0-C4) alkylene-(C3-C6) cycloalkyl , wherein alkyl and alkenyl are unsubstituted or mono-, di- or trisubstituted by F and O-(C0-C4)-alkylene-H;

R5 and R6 together with the nitrogen atom to which they are bonded (Y = N(R6)) can form a (C3-C15)-heterocycloalkyl, a (C3-C15)-heterocycloalkenyl or a (C5-C15)-heteroaryl which can contain additionally 1 to 3 heteroatoms N, O, S and which is unsubstituted or mono-, di- or trisubstituted by halogen, CN, CF3, (C1-C4) alkyl, (C0-C4) alkylene-(C3-C6) cycloalkyl, (C0-C4) alkylene-O-(C0-C4) alkylene-H, (C0-C4) alkylene-O-(C0-C4) alkylene-(C3-C6) cycloalkyl, (C0-C4) alkylene-O-(C0-C4) alkylene-(C6-C10)aryl, (C0-C4)alkylene-O-(C0-C4)alkylene-(C3-C15) heterocycloalkyl, (C0-C4)alkylene-O-(C0-C4)alkylene-(C3-C15) heterocycloalkenyl, (C0-C4)alkylene-O-(C0-C4)alkylene-(C5-C15) heteroaryl, (C0-C4) alkylene-S-(C1-C4) alkyl, (C0-C4) alkylene-SO-(C1-C4) alkyl, (C0-C4) alkylene-SO2-(C1-C4) alkyl, (C0-C4) alkylene-CO-(C1-C4) alkyl, (C0-C4) alkylene-CO-(C6-C10)aryl, (C0-C4) alkylene-CO-(C3-C15)heterocycloalkyl, (C0-C4) alkylene-CO-(C3-C15)heterocycloalkenyl, (C0-C4) alkylene-CO-(C5-C15)heteroaryl, (C0-C4) alkylene-CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene-H, (C0-C4)alkylene-CO-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C6)cycloalkyl, (C0-C4)alkylene-CO-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C6-C10)aryl, (C0-C4)alkylene-CO-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C15)heterocycloalkyl, (C0-C4)alkylene-CO-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C15)heterocycloalkenyl, (C0-C4)alkylene-CO-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C5-C15)heteroaryl, (C0-C4) alkylene-N((C0-C4) alkylene-H)-CO-(C1-C4) alkyl, (C0-C4) alkylene-N((C0-C4) alkylene-H)-CO-(C0-C4) alkylene-(C3-C6) cycloalkyl, (C0-C4) alkylene-N((C0-C4) alkylene-H)-CO-(C0-C4) alkylene-(C6-C10)aryl, (C0-C4)alkylene-N((C0-C4) alkylene-H)-CO-(C0-C4)alkylene-(C3-C15)heterocycloalkyl, (C0-C4)alkylene-N((C0-C4) alkylene-H)-CO-(C0-C4)alkylene-(C3-C15)heterocycloalkenyl, (C0-C4)alkylene-N((C0-C4) alkylene-H)-CO-(C0-C4)alkylene-(C5-C15)heteroaryl, (C0-C4) alkylene-(C6-C14) aryl and (C0-C4) alkylene-(C3-C15) heterocycloalkyl, (C0-C4) alkylene-(C3-C15) heterocycloalkenyl, (C0-C4) alkylene-(C5-C15) heteroaryl whereby heteroaryl, heterocycloalkyl and heterocycloalkenyl can mono- or

disubstituted by oxo residue and where alkyl can be unsubstituted or mono-, di- or trisubstituted by F;

Z is a bond, (C1-C8) alkylene, (C2-C8) alkenylene, (C2-C8) alkylidene, (C1-C6) alkylene-O-(C1-C6) alkylene;

R7, R8 are independently selected from the group consisting of H, halogen, (C1-C8) alkyl, (C0-C4) alkylene-O-(C0-C4) alkylene-H, SCF3, SF5, S(O)2CF3, (C0-C4) alkylene-O-(C6-C12) aryl, (C0-C4) alkylene (C6-C12) aryl, NO2, wherein alkyl and alkylene are unsubstituted or mono-, di- or trisubstituted by F and aryl is unsubstituted or mono-, di- or trisubstituted by halogen, (C1-C4) alkyl or O-(C1-C4) alkyl .

Another embodiment according to the invention are compounds of the formula I, wherein

B is C(R4) and

R4 is H.

R1 is H, halogen, (C1-C8) alkyl, (C0-C4) alkylene-O-(C0-C4) alkylene-H, SCH3, CN, wherein alkyl and alkylene are unsubstituted or mono, bi- or trisubstitued by F;

R2,R3,R4 are independently
H, halogen, (C1-C8) alkyl, (C0-C4) alkylene-O-(C0-C4) alkylene-H, SCH3, CN, wherein alkyl and alkylene are unsubstituted or mono, bi- or trisubstitued by F;

X is O, S, S(O), S(O)2, O-CH2, S-CH2, CH2-O, CH2-S;

one of U and V is N the other is S or O;

W is a bond, (C1-C8) alkylene, (C2-C8) alkenylene, (C0-C6) alkylene-(C3-C6) cycloalkylene, (C3-C6) cycloalkylen-(C1-C6) alkylene, wherein alkylene and alkenylene and cycloalkylene are unsubstituted or mono-, di- or trisubstituted by OH and F;

Y is a bond, O, S, S(O), S(O)2 and

R5 is H, (C1-C8) alkyl, (C0-C4) alkylene-(C3-C13) cycloalkyl, (C0-C4) alkylene-(C6-C14) aryl, (C2-C8) alkenyl, (C0-C4) alkylene-(C3-C15) heterocycloalkyl, (C0-C4) alkylene-(C3-C15) heterocycloalkenyl, (C0-C4) alkylene-(C5-C15) heteroaryl, (C0-C4) alkylene-CO-(C1-C4)alkyl, (C0-C4) alkylene-CO-(C0-C4) alkylene-(C3-C13)cycloalkyl, (C0-C4) alkylene-CO-(C0-C4) alkylene-(C6-C10)aryl, (C0-C4) alkylene- CO-(C0-C4) alkylene- (C3-C15) heterocycloalkyl, (C0-C4) alkylene- CO-(C0-C4) alkylene- (C3-C15) heterocycloalkenyl, (C0-C4) alkylene- CO-(C0-C4) alkylene- (C5-C15) heteroaryl, SO2-(C1-C4)alkyl, SO2-(C0-C4) alkylene-(C3-C13)cycloalkyl, SO2-(C0-C4) alkylene-(C6-C10) aryl, SO2-(C0-C4) alkylene-(C3-C15) heterocycloalkyl, SO2-(C0-C4) alkylene-(C3-C15) heterocycloalkenyl, SO2-(C0-C4) alkylene-(C5-C15) heteroaryl, CO-O-(C0-C4) alkylene-(C6-C10) aryl, CO-O-(C1-C4) alkyl, CO-O-(C0-C4) alkylene-(C3-C13)cycloalkyl, CO-O-(C0-C4) alkylene-(C3-C15)heterocycloalkyl, CO-O-(C0-C4) alkylene-(C3-C15)heterocycloalkenyl, CO-O-(C0-C4) alkylene-(C5-C15)heteroaryl, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene- (C6-C10) aryl, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene-H, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene- (C3-C13)cycloalkyl, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene-(C3-C15) heterocycloalkyl, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene-(C3-C15) heterocycloalkenyl, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene-(C5-C15) heteroaryl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C6-C10)aryl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-H, SO2-N((C0-C4) alkylene-H)-(C0-C4)alkylene-(C3-C13)cycloalkyl, SO2-N((C0-C4)alkylene-

H)-(C0-C4)alkylene-(C3-C15)heterocycloalkyl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C15)heterocycloalkenyl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C5-C15)heteroaryl wherein alkyl and alkylene are unsubstituted or mono-, di- or trisubstituted by F, S-(C1-C4) alkyl, SO-(C1-C4) alkyl, SO2-(C1-C4) alkyl, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene-H, N((C0-C4) alkylene-H)-(C0-C4) alkylene-H, CO-O(C1-C4) alkyl, (C1-C4) alkyl and O-(C0-C4) alkylene-H and wherein cycloalkyl, aryl and heterocycloalkyl, heterocycloalkenyl and heteroaryl are unsubstituted or mono-, di- or trisubstituted by F, Cl, Br, CF3, (C1-C4) alkyl and (C0-C4)-alkylen-O-(C0-C4) alkylene-H;

with the proviso that,

if Y is S, S(O) or S(O)2 then

R5 is unequal SO2-(C1-C4)alkyl, SO2-(C0-C4)alkylene-(C3-C13)cycloalkyl, SO2-(C0-C4)alkylene-(C6C10)aryl, SO2-(C0-C4)alkylene-(C3-C15)heterocycloalkyl, SO2-(C0-C4)alkylene-(C3-C15)heterocycloalkenyl, SO2-(C0-C4)alkylene-(C5-C15)heteroaryl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C6-C10)aryl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-H, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C13)cycloalkyl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C15)heterocycloalkyl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C15)heterocycloalkenyl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C5-C15)heteroaryl;

with the proviso that, if Y is a bond or O then

Z is unequal a bond;

or

Y is a bond,

with the proviso that

R5 is CN, (C1-C8) alkyl mono-, di- or trisubstituted by F, CO-(C1-C4) alkyl, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene-H, SO2-N((C0-C4) alkylene-H)-(C0-C4) alkylene-H, N((C0-C4) alkylene-H)-CO-(C0-C4) alkylene-H, (C1-C6) alkylene- (C3-C13) cycloalkyl, (C3-C15) heterocycloalkyl, (C3-C15) heterocycloalkenyl, (C5-C15) heteroaryl;

or

Y is O,

with the proviso that

R5 is (C1-C8) alkyl mono-, di- or trisubstituted by F, CO-(C1-C4) alkyl, CO-O-(C0-C4) alkylene-(C6-C10) aryl, CO-O-(C0-C4) alkylene-(C3-C13)cycloalkyl, CO-O-(C0-C4) alkylene-(C3-C15)heterocycloalkyl, CO-O-(C0-C4) alkylene-(C3-C15)heterocycloalkenyl, CO-O-(C0-C4) alkylene-(C5-C15)heteroaryl, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene-H, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene-(C6-C10) aryl, CO-N((C0-C4)alkylene-H)-(C0-C4) alkylene-(C3-C13)cycloalkyl, CO-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C15)heterocycloalkyl, CO-N((C0-C4)alkylene-H)-(C0-C4) alkylene-(C3-C13)cycloalkyl, CO-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C15)heterocycloalkenyl, CO-N((C0-C4)alkylene-H)-(C0-C4) alkylene-(C3-C13)cycloalkyl, CO-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C5-C15)heteroaryl, (C0-C4) alkylene-(C3-C13) cycloalkyl, (C0-C4) alkylene-(C3-C15) heterocycloalkyl, (C0-C4) alkylene-(C3-C15) heterocycloalkenyl, (C0-C4) alkylene-(C5-C15) heteroaryl, (C0-C4) alkylene-N((C0-C4) alkylene-H)-(C0-C4) alkylene-H, (C0-C4) alkylene-N((C0-C4) alkylene-H)-(C0-C4) alkylene-(C3-C13)cycloalkyl, (C0-C4) alkylene-N((C0-C4) alkylene-H)-(C0-C4) alkylene-(C6-C10)aryl, (C0-C4) alkylene-N((C0-C4) alkylene-H)-(C0-C4) alkylene-(C3-C15)heterocycloalkyl, (C0-C4) alkylene-N((C0-C4) alkylene-H)-

(C0-C4) alkylene-(C3-C15)heterocycloalkenyl, (C0-C4) alkylene-N((C0-C4) alkylene-H)-(C0-C4) alkylene-(C5-C15)heteroaryl;

Z is a bond, (C1-C8) alkylene, (C2-C8) alkenylene, (C2-C8) alkylidene, (C1-C6) alkylene-O-(C1-C6) alkylene;

R7, R8 are independently selected from the group consisting of H, halogen, (C1-C8) alkyl, (C0-C4) alkylene-O-(C0-C4) alkylene-H, SCF3, SF5, S(O)2CF3, (C0-C4) alkylene-O-(C6-C12) aryl, (C0-C4) alkylene (C6-C12) aryl, NO2, wherein alkyl and alkylene are unsubstituted or mono-, di- or trisubstituted by F and aryl is unsubstituted or mono-, di- or trisubstituted by halogen, (C1-C4) alkyl or O-(C1-C4) alkyl.

Another embodiment according to the invention are compounds of the formula I wherein

R1 is halogen, (C1-C4) alkyl, (C0-C4) alkylene-O-(C0-C2) alkylene-H, O-(C0-C2) alkylene-(C3-C6) cycloalkyl, wherein alkyl and alkylene are unsubstituted or mono, di- or trisubstituted by F.

Another embodiment according to the invention are compounds of the formula I wherein

W is (C1-C3) alkylene;

Y is N(R6) and

R5 and R6 together with the nitrogen atom to which they are bonded (Y = N(R6)) form a (C3-C7)-heterocycloalkyl, a (C4-C7)-heterocycloalkenyl or a (C5-C8)-heteroaryl which can contain additionally 1 to 2 heteroatoms N, O, S and which is unsubstituted or mono- or disubstituted by F, CF3, (C1-C3) alkyl,

(C0-C3) alkylene-O-(C0-C3) alkylene-H, SO2-(C1-C3) alkyl, CO-(C1-C3) alkyl, CO-NH2, NH-CO-(C1-C3) alkyl, phenyl, (C5-C6) heteroaryl, (C3-C7) heterocycloalkyl and (C4-C7) heterocycloalkenyl, whereby heterocycloalkyl, heterocycloalkenyl and heteroaryl can be mono- or disubstituted by oxo residue

Another embodiment according to the invention are compounds of the formula I wherein

W is (C1-C3) alkylene;

Y is N(R6) and

R5 is H, (C1-C4) alkyl, (C0-C3) alkylene-(C3-C7) cycloalkyl, (C0-C3) alkylene-phenyl, (C0-C3) alkylene-(C3-C7) heterocycloalkyl, (C0-C4) alkylene-(C4-C7) heterocycloalkenyl, (C0-C3) alkylene-(C5-C6) heteroaryl, CO-(C0-C3) alkyl, CO-O-phenyl, wherein alkyl and alkylene can be mono-, di- or trisubstituted by F, S-(C1-C3) alkyl, SO-(C1-C3) alkyl, SO2-(C1-C3) alkyl, N((C0-C3) alkylene-H)-(C0-C3) alkylene-H, CO-O(C1-C3) alkyl and O-(C0-C3) alkylene-H and wherein cycloalkyl, phenyl, heterocycloalkyl, heterocycloalkenyl and heteroaryl are mono-, di- or trisubstituted by F and (C0-C4)-alkylen-O-(C0-C4) alkylene-H;

R6 is H, (C1-C3) alkyl or (C0-C3) alkylene-(C3-C6) cycloalkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted by O-(C0-C4)-alkylene-H; or

Y is S, S(O), S(O)2 and
R5 is (C1-C3) alkyl or (C0-C3) alkylene-(C3-C6) cycloalkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted by F; or

Y is O and
R5 is (C1-C4) alkyl mono-, di- or trisubstituted by F, CO-(C1-C3) alkyl, (C0-C3) alkylene-(C3-C6) cycloalkyl, (C0-C3) alkylene-(C3-C7) heterocycloalkyl, (C0-C3) alkylene-(C5-C8) heteroaryl; or
Z is –CH2-, -CH2-CH2-, -CH2-O-CH2-, -CH=CH-.

Another embodiment according to the invention are compounds of the formula I wherein

R1 is F, Cl, (C1-C4) alkyl, O-(C1-C4) alkyl, wherein alkyl and alkylene are unsubstituted or mono-, bi- or trisubstitued by F;

Another embodiment according to the invention are compounds of the formula I wherein

R1 is F, Cl, CH3 or OCH3.

Another embodiment according to the invention are compounds of the formula I wherein

V is N and U is O; or

V is N and U is S.

Another embodiment according to the invention are compounds of the formula I wherein

X is O or O-CH2.

Another embodiment according to the invention are compounds of the formula I wherein

X is O.

Another embodiment according to the invention are compounds of the formula I wherein

X is OCH2.

Another embodiment according to the invention are compounds of the formula I wherein

W is a bond or –CH2-.

Another embodiment according to the invention are compounds of the formula I wherein

R7 is in para-position.

Another embodiment according to the invention are compounds of the formula I wherein

R8 is H.

Another embodiment according to the invention are compounds of the formula I wherein

R1 is F or OCH3.

Another embodiment according to the invention are compounds of the formula I wherein

R1 is Cl or CH3.

Another embodiment according to the invention are compounds of the formula I wherein

R1 is Cl.

Another embodiment according to the invention are compounds of the formula I wherein

R1 is halogen, (C1-C4) alkyl, (C0-C4) alkylene-O-(C0-C2) alkylene-H, O-(C0-C2) alkylene-(C3-C6) cycloalkyl, wherein alkyl and alkylene are unsubstituted or mono, di- or trisubstituted by F;

W is (C1-C3) alkylene;

Y is N(R6) and

R5 and R6 together with the nitrogen atom to which they are bonded (Y = N(R6)) form a (C3-C7)-heterocycloalkyl, a (C4-C7)-heterocycloalkenyl or a (C5-C8)-heteroaryl which can contain additionally 1 to 2 heteroatoms N, O, S and which is unsubstituted or mono- or disubstituted by F, CF3, (C1-C3) alkyl, (C0-C3) alkylene-O-(C0-C3) alkylene-H, SO2-(C1-C3) alkyl, CO-(C1-C3) alkyl, CO-NH2, NH-CO-(C1-C3) alkyl, phenyl, (C5-C6) heteroaryl, (C3-C7) heterocycloalkyl and (C4-C7) heterocycloalkenyl, whereby heterocycloalkyl, heterocycloalkenyl and heteroaryl can be mono- or disubstituted by oxo residue;

Another embodiment according to the invention are compounds of the formula I wherein

R1 is halogen, (C1-C4) alkyl, (C0-C4) alkylene-O-(C0-C2) alkylene-H, O-(C0-C2) alkylene-(C3-C6) cycloalkyl, wherein alkyl and alkylene are unsubstituted or mono, di- or trisubstituted by F;

W is (C1-C3) alkylene;

Y is N(R6) and

R5 is H, (C1-C4) alkyl, (C0-C3) alkylene-(C3-C7) cycloalkyl, (C0-C3) alkylene-phenyl, (C0-C3) alkylene-(C3-C7) heterocycloalkyl, (C0-C4) alkylene-(C4-C7) heterocycloalkenyl, (C0-C3) alkylene-(C5-C6) heteroaryl, CO-(C0-C3) alkyl, CO-O-phenyl, wherein alkyl and alkylene can be mono-, di- or trisubstituted by F, S-(C1-C3) alkyl, SO-(C1-C3) alkyl, SO2-(C1-C3) alkyl, N((C0-C3) alkylene-H)-(C0-C3) alkylene-H, CO-O(C1-C3) alkyl and O-(C0-C3) alkylene-H and wherein

cycloalkyl, phenyl, heterocycloalkyl, heterocycloalkenyl and heteroaryl are mono-, di- or trisubstituted by F and (C0-C4)-alkylen-O-(C0-C4) alkylene-H;

R6 is H, (C1-C3) alkyl or (C0-C3) alkylene-(C3-C6) cycloalkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted by O-(C0-C4)-alkylene-H;

Y is S, S(O), S(O)2 and
R5 is (C1-C3) alkyl or (C0-C3) alkylene-(C3-C6) cycloalkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted by F;

Y is O and
R5 is (C1-C4) alkyl mono-, di- or trisubstituted by F, CO-(C1-C3) alkyl, (C0-C3) alkylene-(C3-C6) cycloalkyl, (C0-C3) alkylene-(C3-C7) heterocycloalkyl, (C0-C3) alkylene-(C5-C8) heteroaryl; or
Z is –CH2-, -CH2-CH2-, -CH2-O-CH2-, -CH=CH-.

Another embodiment according to the invention are compounds of the formula I wherein

R1 is halogen, (C1-C4) alkyl, (C0-C4) alkylene-O-(C0-C2) alkylene-H, O-(C0-C2) alkylene-(C3-C6) cycloalkyl, wherein alkyl and alkylene are unsubstituted or mono, di- or trisubstituted by F;

W is (C1-C3) alkylene;

Y is N(R6) and

R5 and R6 together with the nitrogen atom to which they are bonded (Y = N(R6)) form a (C3-C7)-heterocycloalkyl, a (C4-C7)-heterocycloalkenyl or a (C5-C8)-heteroaryl which can contain additionally 1 to 2 heteroatoms N, O, S and

which is unsubstituted or mono- or disubstituted by F, CF3, (C1-C3) alkyl, (C0-C3) alkylene-O-(C0-C3) alkylene-H, SO2-(C1-C3) alkyl, CO-(C1-C3) alkyl, CO-NH2, NH-CO-(C1-C3) alkyl, phenyl, (C5-C6) heteroaryl, (C3-C7) heterocycloalkyl and (C4-C7) heterocycloalkenyl, whereby heterocycloalkyl, heterocycloalkenyl and heteroaryl can be mono- or disubstituted by oxo residue;

W is (C1-C3) alkylene;

Y is N(R6) and

R5 is H, (C1-C4) alkyl, (C0-C3) alkylene-(C3-C7) cycloalkyl, (C0-C3) alkylene-phenyl, (C0-C3) alkylene-(C3-C7) heterocycloalkyl, (C0-C4) alkylene-(C4-C7) heterocycloalkenyl, (C0-C3) alkylene-(C5-C6) heteroaryl, CO-(C0-C3) alkyl, CO-O-phenyl, wherein alkyl and alkylene can be mono-, di- or trisubstituted by F, S-(C1-C3) alkyl, SO-(C1-C3) alkyl, SO2-(C1-C3) alkyl, N((C0-C3) alkylene-H)-(C0-C3) alkylene-H, CO-O(C1-C3) alkyl and O-(C0-C3) alkylene-H and wherein cycloalkyl, phenyl, heterocycloalkyl, heterocycloalkenyl and heteroaryl are mono-, di- or trisubstituted by F and (C0-C4)-alkylen-O-(C0-C4) alkylene-H;

R6 is H, (C1-C3) alkyl or (C0-C3) alkylene-(C3-C6) cycloalkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted by O-(C0-C4)-alkylene-H;

Y is S, S(O), S(O)2 and
R5 is (C1-C3) alkyl or (C0-C3) alkylene-(C3-C6) cycloalkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted by F;

Y is O and

R5 is (C1-C4) alkyl mono-, di- or trisubstituted by F, CO-(C1-C3) alkyl, (C0-C3) alkylene-(C3-C6) cycloalkyl, (C0-C3) alkylene-(C3-C7) heterocycloalkyl, (C0-C3) alkylene-(C5-C8) heteroaryl; or
Z is –CH2-, -CH2-CH2-, -CH2-O-CH2-, -CH=CH-.

Another embodiment according to the invention are compounds of the formula I where one or more substituents have the following meaning:

B is C(R4) and
R4 is H.

R1 is halogen, (C1-C8) alkyl, (C0-C4) alkylene-O-(C1-C4) alkylene-H, (C0-C2) alkylene-O-(C0-C2) alkylene-(C3-C6) cycloalkyl, wherein alkyl and alkylene are unsubstituted or mono, bi- or trisubstitued by F;

R2 is H;

R3 is H, F, Br;

R4 is H;

X is O, O-CH2;

U is S, O and
V is N
Or
U is N and
V is O;

W is a bond, (C1-C4) alkylene;

Y is N(R6) and

R5 is selected from the group consisting of (C1-C8) alkyl, (C0-C4) alkylene-(C3-C13) cycloalkyl, (C0-C4) alkylene-(C6-C12) aryl, (C0-C4) alkylene-(C3-C15) heterocycloalkyl, (C0-C4) alkylene-(C3-C15) heterocycloalkenyl, (C0-C4) alkylene-(C5-C15) heteroaryl, CO-(C0-C4) alkyl, CO-O-(C6-C10) aryl, wherein alkyl and alkylene can be mono-, di- or trisubstituted by F, S-(C1-C4) alkyl, SO-(C1-C4) alkyl, N((C0-C4) alkylene-H)-(C0-C4) alkylene-H, CO-O(C1-C4) alkyl and O-(C0-C4) alkylene-H and wherein cycloalkyl, aryl, heterocycloalkyl, heterocycloalkenyl and heteroaryl are mono-, di- or trisubstituted by F and (C0-C4)-alkylene-O-(C0-C4) alkylene-H;

Y is a bond and

R5 is (C1-C6) alkyl mono-, di- or trisubstituted by F;

Y is O and

R5 is (C1-C8) alkyl mono-, di- or trisubstituted by F, CO-(C1-C4) alkyl, (C0-C4) alkylene-(C3-C6) cycloalkyl, (C0-C4) alkylene-(C3-C15) heterocycloalkyl, (C0-C4) alkylene-(C3-C15) heterocycloalkenyl, (C0-C4) alkylene-(C5-C15) heteroaryl; or

Z is –CH2-, -CH2-CH2-, -CH2-O-CH2-, -CH=CH-.

R6 is H, (C1-C8) alkyl or (C0-C4) alkylene-(C3-C6) cycloalkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted by O-(C0-C4)-alkylene-H;

R5 and R6 together with the nitrogen atom to which they are bonded (Y = N(R6)) can form a (C3-C8)-heterocycloalkyl, a (C3-C10)-heterocycloalkenyl or a (C5-C8)-heteroaryl which can contain additionally 1 to 3 heteroatoms N, O, S and which is unsubstituted or mono-, di- or trisubstituted by F, CF3, (C1-C4) alkyl, (C0-C4) alkylene-O-(C0-C4) alkylene-H, SO2-(C1-C4) alkyl, CO-(C1-

C4) alkyl, CO-NH2, NH-CO-(C1-C4) alkyl, phenyl, (C5-C6) heteroaryl, (C3-C7) heterocycloalkyl and (C3-C7) heterocycloalkenyl, whereby heterocycloalkyl, heterocycloalkenyl and heteroaryl can mono- or disubstituted by oxo residue;

Z is a bond, (C1-C2) alkylene, (C2) alkenylene, (C1-C2) alkylene-O-(C1-C2) alkylene;

R7 is H, O-(C1-C4) alkyl, CF3;

R8 is H.,

Another embodiment according to the invention are compounds of the formula I where one or more substituents have the following meaning:

B is C(R4) and
R4 is H.

R1 is F, Cl, (C1-C4) alkyl, (C0-C4) alkylene-O-(C1-C4) alkylene-H, (C0-C2) alkylene-O-(C0-C2) alkylene-(C3-C6) cycloalkyl, wherein alkyl and alkylene are unsubstituted or mono, bi- or trisubstitued by F;

R2 is H;

R3 is H, F, Br;

R4 is H;

X is O, O-CH2;

U is S, O and
V is N

Or

U is N and

V is O;

W is a bond, (C1-C4) alkylene;

Y is N(R6) and

R5 is selected from the group consisting of (C1-C8) alkyl, (C0-C4) alkylene-(C3-C13) cycloalkyl, (C0-C4) alkylene-(C6-C12) aryl, (C0-C4) alkylene-(C3-C15) heterocycloalkyl, CO-(C0-C4) alkyl, CO-O-(C6-C10) aryl, wherein alkyl and alkylene can be mono-, di- or trisubstituted by S-(C1-C4) alkyl, SO-(C1-C4) alkyl, N((C0-C4) alkylene-H)-(C0-C4) alkylene-H and O-(C0-C4) alkylene-H and wherein aryl and heterocycloalkyl are mono-, di- or trisubstituted by F and (C0-C4)-alkylene-O-(C0-C4) alkylene-H;

Y is O and

R5 is (C1-C8) alkyl mono-, di- or trisubstituted by F, CO-(C1-C4) alkyl, (C0-C4) alkylene-(C3-C6) cycloalkyl; or

Z is –CH2-, -CH2-CH2-, -CH2-O-CH2-, -CH=CH-,

Y is S, S(O), S(O)2 and

R5 is (C1-C3) alkyl;

R6 is H, (C1-C8) alkyl or (C0-C4) alkylene-(C3-C6) cycloalkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted by O-(C0-C4)-alkylene-H;

R5 and R6 together with the nitrogen atom to which they are bonded (Y = N(R6)) can form a (C3-C8)-heterocycloalkyl or a (C3-C10)-heterocycloalkenyl which can contain additionally 1 to 3 heteroatoms N, O, S and which is unsubstituted or mono-, di- or trisubstituted by F, CF3, (C1-C4) alkyl, (C0-C4) alkylene-O-

(C0-C4) alkylene-H, SO2-(C1-C4) alkyl, CO-(C1-C4) alkyl, whereby heterocycloalkyl can mono- or disubstituted by oxo residue;

Z is a bond, (C1-C2) alkylene, (C2) alkenylene, (C1-C2) alkylene-O-(C1-C2) alkylene;

R7 is H, O-(C1-C4) alkyl, CF3;

R8 is H.

Another embodiment according to the invention are compounds of the formula I where one or more substituents have the following meaning:

R1 is halogen, (C1-C4) alkyl, OH, O-(C1-C3) alkyl, wherein alkyl is unsubstituted or mono, di- or trisubstitued by F;

R2 is H;

R3 is H, F;

B is C(R4) or N, and
R4 is H;

X is O;

one of U and V is N the other is S or O;

W is (C1-C3) alkylene;

Y is N(R6) and

R5 and R6 together with the nitrogen atom to which they are bonded (Y = N(R6)) form a (C3-C7)-heterocycloalkyl, a (C4-C7)-heterocycloalkenyl or a (C5-C8)-heteroaryl which can contain additionally 1 to 2 heteroatoms N, O, S and which is unsubstituted or mono- or disubstituted by F, CF3, (C1-C3) alkyl, (C0-C3) alkylene-O-(C0-C3) alkylene-H, SO2-(C1-C3) alkyl, CO-(C1-C3) alkyl, CO-NH2, NH-CO-(C1-C3) alkyl, phenyl, (C5-C6) heteroaryl, (C3-C7) heterocycloalkyl and (C4-C7) heterocycloalkenyl, whereby heterocycloalkyl, heterocycloalkenyl and heteroaryl can be mono- or disubstituted by oxo residue;

Y is N(R6) and

R5 is H, (C1-C4) alkyl, (C0-C3) alkylene-(C3-C7) cycloalkyl, (C0-C3) alkylene-phenyl, (C0-C3) alkylene-(C3-C7) heterocycloalkyl, (C0-C4) alkylene-(C4-C7) heterocycloalkenyl, (C0-C3) alkylene-(C5-C6) heteroaryl, CO-(C0-C3) alkyl, CO-O-phenyl, wherein alkyl and alkylene can be mono-, di- or trisubstituted by F, S-(C1-C3) alkyl, SO-(C1-C3) alkyl, SO2-(C1-C3) alkyl, N((C0-C3) alkylene-H)-(C0-C3) alkylene-H, CO-O(C1-C3) alkyl and O-(C0-C3) alkylene-H and wherein cycloalkyl, phenyl, heterocycloalkyl, heterocycloalkenyl and heteroaryl are mono-, di- or trisubstituted by F and (C0-C4)-alkylen-O-(C0-C4) alkylene-H;

R6 is H, (C1-C3) alkyl or (C0-C3) alkylene-(C3-C6) cycloalkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted by O-(C0-C4)-alkylene-H;

Y is S, S(O), S(O)2 and
R5 is (C1-C3) alkyl or (C0-C3) alkylene-(C3-C6) cycloalkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted by F;

Y is O and
R5 is (C1-C4) alkyl mono-, di- or trisubstituted by F, CO-(C1-C3) alkyl, (C0-C3) alkylene-(C3-C6) cycloalkyl, (C0-C3) alkylene-(C3-C7) heterocycloalkyl, (C0-C3) alkylene-(C5-C8) heteroaryl; or
Z is –CH2-, -CH2-CH2-, -CH2-O-CH2-, -CH=CH-.

Z is a bond, (C1-C2) alkylene, (C2) alkenylene, (C1-C2) alkylene-O-(C1-C2) alkylene;

R7 is H, halogen, (C1-C3) alkyl, O-(C1-C3) alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted by F;

R8 is H.

Another embodiment according to the invention are compounds of the formula I where one or more substituents have the following meaning:

R1 is F, OH, OCH3, OCHF2, OCH2CF3;

R2 is H;

R3 is H, F;

B is C(R4) or N, and
R4 is H;

X is O;

one of U and V is N the other is S or O;

W is CH2, CH2CH2CH2;

Y is N(R6) and

R5 and R6 together with the nitrogen atom to which they are bonded (Y = N(R6)) form a piperidine, pyrrolidine, azetidine, azepine, morpholine, thiomorpholine, thiomorpholine-S-oxide, thiomorpholine-S-dioxide, piperazine, piperazinone, iso-indoline, which is unsubstituted or mono- or disubstituted by F, CF3, (C1-C3) alkyl, O-(C1-C3) alkyl, OH, CH2OH, SO2CH3, COCH3, phenyl;

Y is S, S(O), S(O)2 and
R5 is CH3;

Z is a bond;

R7 is CF3;

R8 is H.

Another embodiment according to the invention are compounds of the formula I where one or more substituents have the following meaning:

R1 is H, F, Cl;

R2 is H;

R3 is H;

B is C(R4) or N, and
R4 is H;

X is O;

U is S, O and

V is N;

W is CH2;

Y is a bond or O;

Z is a bond;

R5 is (C1-C6) alkyl mono-, di- or trisubstituted by F;

R7 is in para-position and (C1-C4) alkyl, (C0-C4) alkylen-O-(C0-C4) alkylen-H, SF5, (C0-C4) alkylen-O-phenyl, wherein alkyl, alkylen and phenyl are mono-, di- or trisubstituted by F;

R8 is H.

Most preferred compounds are :

3-[2-Methoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl]-4H-[1,2,4]oxadiazol-5-one

3-[2-Chloro-4-[4-morpholin-4-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl]-4H-[1,2,4]oxadiazol-5-one

3-[2-Methoxy-4-[4-morpholin-4-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl]-4H-[1,2,4]oxadiazol-5-one

3-[4-[4-(4,4-Difluoro-piperidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl]-4H-[1,2,4]oxadiazol-5-one

3-{2-Methoxy-4-[4-(4-methyl-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{2-Methoxy-4-[4-pyrrolidin-1-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{4-[4-(4-Fluoro-piperidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{4-[4-Diethylaminomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{2-Methoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(3-trifluoromethyl-pyrrolidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{4-[4-{[Ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{4-[4-[([1,4]Dioxan-2-ylmethyl-methyl-amino)-methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{2-Methoxy-4-[4-(4-methoxy-piperidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{4-[4-(4-Ethyl-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one

Cyclopropyl-[5-[3-methoxy-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethyl]-carbamic acid phenyl ester

3-{4-[4-Cyclopropylaminomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{4-[4-(3-Azetidin-1-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{2-Fluoro-4-[2-(4-trifluorométhyl-phényl)-4-(4-trifluorométhyl-pipéridin-1-ylméthyl)-thiazol-5-ylméthoxy]-phényl}-4H-1,2,4-oxadiazol-5-one

3-{4-[4-(4,4-Difluoro-piperidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-fluoro-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{2-Fluoro-4-[4-[(2-hydroxy-ethyl)-methyl-amino]-methyl}-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{2-Fluoro-4-[4-(4-methyl-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{2-Fluoro-4-[4-morpholin-4-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{4-[4-(1,3-Dihydro-isoindol-2-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy}-2-fluoro-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{2-Fluoro-4-[4-[(4-fluoro-benzylamino)-methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{2-Fluoro-4-[4-(2-hydroxymethyl-pyrrolidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{2-Fluoro-4-[4-{[(furan-2-ylmethyl)-amino]-methyl}-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{2-Fluoro-4-[4-[(3-methylsulfanyl-propylamino)-methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

4-[5-{3-Fluoro-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethyl]-piperazin-2-one

3-{2-Fluoro-4-[4-[(4-methoxy-benzylamino)-methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy}-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{4-[4-[(1R,4R)-1-(2,5-Diaza-bicyclo[2.2.1]hept-2-yl)methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-fluoro-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{2-Fluoro-4-[4-(3-hydroxymethyl-piperidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{5-Bromo-2-methoxy-4-[4-piperidin-1-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{5-Fluoro-2-methoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

Acetic acid 5-[3-fluoro-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethyl ester

Acetic acid 5-[3-methoxy-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethyl ester

3-{2-Fluoro-4-[4-pyrrolidin-1-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-(2-Methoxy-4-{2-(4-trifluoromethyl-phenyl)-4-[(3,3,3-trifluoro-propylamino)-methyl]-thiazol-5-ylmethoxy}-phenyl)-4H-[1,2,4]oxadiazol-5-one

3-{4-[4-((1R,2R,4S)-Bicyclo[2.2.1]hept-2-ylaminomethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{2-Methoxy-4-[4-({[(S)-1-(tetrahydro-furan-2-yl)methyl]-amino}-methyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{2-Methoxy-4-[4-({[(R)-1-(tetrahydro-furan-2-yl)methyl]-amino}-methyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{4-[4-[(Cyclopropylmethyl-amino)-methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{4-[4-Cyclobutylaminomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{4-[4-(4-Methanesulfonyl-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{4-[4-{[Bis-(2-hydroxy-ethyl)-amino]-methyl}-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{4-[4-[(2-Methanesulfinyl-ethylamino)-methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{2-Methoxy-4-[4-thiomorpholin-4-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{4-[4-(1,1-Dioxo-1λ^6-thiomorpholin-4-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{2-Methyl-4-[4-propylaminomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{4-[4-[(2-Methoxy-ethylamino)-methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]- 2-methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{2-Methyl-4-[4-{[2-(1-methyl-pyrrolidin-2-yl)-ethylamino]-methyl}-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{2-Methyl-4-[4-[(2-pyrrolidin-1-yl-ethylamino)-methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy}-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{2-Methyl-4-[4-[(2-morpholin-4-yl-ethylamino)-methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{2-Methyl-4-[4-[(2-piperidin-1-yl-ethylamino)-methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{4-[4-[(2-Dimethylamino-ethylamino)-methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-(2-Chloro-4-{4-methyl-2-[2-(4-trifluoromethyl-phenyl)-ethyl]-oxazol-5-ylmethoxy}-phenyl)-4H-[1,2,4]oxadiazol-5-one

3-(2-Chloro-4-{4-methoxymethyl-2-[2-(4-methoxy-phenyl)-vinyl]-oxazol-5-ylmethoxy}-phenyl)- 4H-[1,2,4]oxadiazol-5-one

3-[4-(2-Benzyloxymethyl-4-methyl-oxazol-5-ylmethoxy)-2-chloro-phenyl]-4H-[1,2,4]oxadiazol-5-one

3-{2-Chloro-4-[2-(4-methoxy-benzyl)-4-methyl-oxazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-(2-Chloro-4-{4-methoxymethyl-2-[2-(4-trifluoromethyl-phenyl)-vinyl]-thiazol-5-ylmethoxy}-phenyl)-4H-[1,2,4]oxadiazol-5-one

3-[2-Chloro-4-[4-(2,2,2-trifluoro-ethoxymethyl)-2-(4-trifluoromethyl-phenyl)-oxazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{4-[4-{[Ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]- 2-methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{4-[4-Diethylaminomethyl-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2-methyl-phenyl}-4H- [1,2,4]oxadiazol-5-one

3-{4-[2-(4-Methoxy-phenyl)-4-pyrrolidin-1-ylmethyl-oxazol-5-ylmethoxy]-2-methyl-phenyl}- 4H-[1,2,4]oxadiazol-5-one

3-{4-[2-(4-Methoxy-phenyl)-4-morpholin-4-ylmethyl-oxazol-5-ylmethoxy]-2-methyl-phenyl}- 4H-[1,2,4]oxadiazol-5-one

3-{4-[4-{[Bis-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2- methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{4-[2-(4-Methoxy-phenyl)-4-piperidin-1-ylmethyl-oxazol-5-ylmethoxy]-2-methyl-phenyl}- 4H-[1,2,4]oxadiazol-5-one

3-{4-[2-(4-Methoxy-phenyl)-5-piperidin-1-ylmethyl-oxazol-4-ylmethoxy]-2-methyl-phenyl}- 4H-[1,2,4]oxadiazol-5-one

3-{4-[2-(4-Methoxy-phenyl)-5-pyrrolidin-1-ylmethyl-oxazol-4-ylmethoxy]-2-methyl-phenyl}- 4H-[1,2,4]oxadiazol-5-one

3-{4-[2-(4-Methoxy-phenyl)-5-morpholin-4-ylmethyl-oxazol-4-ylmethoxy]-2-methyl-phenyl}- 4H-[1,2,4]oxadiazol-5-one

3-{4-[5-{[Bis-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-4-ylmethoxy]-2- methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{2-Chloro-4-[2-(4-methoxy-phenyl)-4-morpholin-4-ylmethyl-oxazol-5-ylmethoxy]-phenyl}- 4H-[1,2,4]oxadiazol-5-one

3-{2-Chloro-4-[4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5- ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{4-[4-{[Bis-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2- chloro-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{2-Chloro-4-[4-piperidin-1-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{4-[4-(4-Acetyl-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]- 2-chloro-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{2-Chloro-4-[4-(4-methyl-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{2-Chloro-4-[4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{4-[4-{[Bis-(2-methoxy-ethyl)-amino]-methyl}-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-chloro-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{2-Chloro-4-[4-pyrrolidin-1-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-[2-Chloro-4-[4-diethylaminomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{2-Chloro-4-[4-(4,4-difluoro-piperidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{2-Chloro-4-[4-(4-phenyl-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{2-Chloro-4-[4-(2-morpholin-4-yl-ethoxymethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{2-Chloro-4-[4-(2-cyclohexyl-ethoxymethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{2-Chloro-4-[4-difluoromethyl-2-(4-methoxy-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{4-[4-(4-Hydroxy-piperidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-1,2,4-oxadiazol-5-one

3-{4-[4-(1,4-Dioxa-8-aza-spiro[4,5]dec-8-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-1,2,4-oxadiazol-5-one

3-{4-[4-(4,4-Dihydroxy-piperidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-1,2,4-oxadiazol-5-one

3-{2-Methoxy-4-[4-(1-oxo-1λ^4-thiomorpholin-4-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one

3-{2-Methoxy-4-[4-methylsulfanylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one

3-{4-[4-Methanesulfinylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-1,2,4-oxadiazol-5-one

3-{4-[4-Methanesulfonylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-1,2,4-oxadiazol-5-one

3-{4-[4-Aminomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-fluoro-phenyl}-4H-1,2,4-oxadiazol-5-one

N-[5-[3-Fluoro-4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethyl]-acetamide

3-{2-Difluoromethoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one

3-{2-Difluoromethoxy-5-fluoro-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one

3-{2-Isopropoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one

3-{2-Cyclopropylmethoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one

3-{2-(2,2,2-Trifluoro-ethoxy)-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one

3-{5-Fluoro-2-(2,2,2-trifluoro-ethoxy)-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one

3-{6-[4-Butyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methyl-pyridin-3-yl}-4H-[1,2,4]oxadiazol-5-one

3-{2-Methoxy-4-[4-(3-methylsulfanyl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one

3-{4-[4-(3-Methanesulfonyl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-1,2,4-oxadiazol-5-one

3-{2-Methoxy-4-[4-(3-thiomorpholin-4-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one

3-{2-Methoxy-4-[4-(3-perhydro-azepin-1-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one

3-{2-Methoxy-4-[4-(3-morpholin-4-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one

3-{2-Methoxy-4-[4-[3-(4-methyl-piperazin-1-yl)-propyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one

3-{2-Methoxy-4-[4-(3-piperidin-1-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy}-phenyl}-4H-1,2,4-oxadiazol-5-one

3-{2-Methoxy-4-[4-(3-pyrrolidin-1-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy}-phenyl}-4H-1,2,4-oxadiazol-5-one

3-{2-Fluoro-4-[4-(3-morpholin-4-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one

3-{2-Fluoro-4-[4-(3-pyrrolidin-1-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one

3-{4-[4-[3-(Benzyl-methyl-amino)-propyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-(2-Methoxy-4-{2-(4-trifluoromethyl-phenyl)-4-[3-(4-trifluoromethyl-piperidin-1-yl)-propyl]-thiazol-5-ylmethoxy}-phenyl)-4H-[1,2,4]oxadiazol-5-one.

This invention also encompasses all combinations of preferred aspects of the invention described herein.

As used herein, the term alkyl is to be understood in the broadest sense to mean saturated hydrocarbon residues which can be linear, i. e. straight-chain, or branched. If not otherwise defined alkyl has 1 to 8 carbon atoms. Examples of „-(C1-C8)-alkyl" are alkyl residues containing 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl or octyl, the n-isomers of all these residues, isopropyl, isobutyl, 1-methylbutyl, isopentyl, neopentyl, 2,2-dimethylbutyl, 2-methylpentyl, 3-methylpentyl, isohexyl, sec-butyl, tert-butyl or tert-pentyl. The term „-(C0-C8)-alkyl" is a hydrocarbon residue containing 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms, in which the term „-C0-alkyl" is a covalent bond. All these statements apply also to the term alkylene.

As used herein, the term alkenyl is to be understood in the broadest sense to mean hydrocarbon residues which has 1 to 4 double bonds and can be linear, i. e. straight-chain, or branched. If not otherwise defined alkenyl has 2 to 8 carbon atoms. Examples of „-(C2-C8)-alkenyl" are alkenyl residues containing 2, 3, 4, 5, 6, 7 or 8 carbon atoms are, for example vinyl, 1-propenyl, 2-propenyl (= allyl), 2-butenyl, 3-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 5-hexenyl or 1,3-pentadienyl. All these statements apply also to the term alkenylene.

As used herein, the term alkinyl is to be understood in the broadest sense to mean hydrocarbon residues, which has 1 to 4 triple bonds and can be linear, i. e. straight-chain, or branched. If not otherwise defined alkinyl has 2 to 8 carbon atoms. Examples of „-(C2-C8)-alkinyl" are alkinyl residues containing 2, 3, 4, 5, 6, 7 or 8 carbon atoms

are, for example ethynyl, 1-propynyl, 2-propynyl (= propargyl) or 2-butynyl. All these statements apply also to the term alkylidene.

All these statements also apply if an alkyl group occurs as a substituent on another residue, for example in an alkyloxy residue, an alkyloxycarbonyl residue or an arylalkyl residue.

If not otherwise defined, alkyl, alkylene, alkenyl, alkenylene, alkinyl and alkinylene are unsubstituted or mono, di- or trisubstituted independently of one another by suitable groups such as, for example: F, Cl, Br, I, CF3, NO2, CN, COOH, CO-O-(C0-C4) alkylene-(C6-C10) aryl, CO-O-(C1-C4) alkyl, CO-O-(C0-C4) alkylene-(C3-C13)cycloalkyl, CO-O-(C0-C4) alkylene-(C3-C15)heterocycle, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene- (C6-C10) aryl, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene-H, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene- (C3-C13)cycloalkyl, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene- (C3-C15) heterocycle, (C0-C4) alkylene-(C3-C6)cycloalkyl, (C0-C4) alkylene-(C6-C10)aryl, (C0-C4) alkylene-(C3-C15)heterocycle, (C2-C6)-alkenyl, (C2-C6)-alkinyl, O-(C0-C6)-alkyl, O-(C0-C4) alkylene-(C6-C10) aryl, O-(C0-C4) alkylene-(C3-C12)cycloalkyl, O-(C0-C4) alkylene-(C3-C15)heterocycle, O-CO-O-(C0-C4) alkylene-(C6-C10) aryl, O-CO-O-(C1-C4) alkyl, O-CO-O-(C0-C4) alkylene-(C3-C13)cycloalkyl, O-CO-O-(C0-C4) alkylene-(C3-C15)heterocycle, S-(C1-C4)alkyl, S-(C0-C4) alkylene-(C3-C13)cycloalkyl, S-(C0-C4) alkylene-(C6-C10) aryl, S-(C0-C4) alkylene-(C3-C15) heterocycle, SO-(C1-C4)alkyl, SO-(C0-C4) alkylene-(C3-C13)cycloalkyl, SO-(C0-C4) alkylene-(C6-C10) aryl, SO-(C0-C4) alkylene-(C3-C15) heterocycle, SO2-(C1-C4)alkyl, SO2-(C0-C4) alkylene-(C3-C13)cycloalkyl, SO2-(C0-C4) alkylene-(C6-C10) aryl, SO2-(C0-C4) alkylene-(C3-C15) heterocycle, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C6-C10)aryl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-H, SO2-N((C0-C4) alkylene-H)-(C0-C4)alkylene-(C3-C13)cycloalkyl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C15) heterocycle where the aryl ring or heterocyclic ring is unsubstituted or mono- or disubstituted by F, Cl, Br, OH, CF3, NO2, CN, OCF3, O-(C1-C6)-alkyl, (C1-C6)-alkyl, N((C0-C4)-alkylene-H)-(C0-C4)-alkylene-H; N((C0-C4)-alkylene-H)-(C0-C4)-alkylene-H, N((C0-C4) alkylene-H)-(C0-C4)alkylene-H)-(C1-C6)cycloalkyl, N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C6-C12)-aryl, N((C0-

C4)alkylene-H)-(C0-C4)alkylene-(C3-C15)heterocycle, N((C0-C4) alkylene-H)-CO-(C0-C4)alkylene-(C6-C12)-aryl, N((C0-C4)alkylene-H)-CO-(C0-C4)alkyl, N((C0-C4)alkylene-H)-CO-(C0-C4)alkylene-(C3-C13)cycloalkyl, N((C0-C4)alkylene-H)-CO-(C0-C4)alkylene-(C3-C15)heterocycle, N((C0-C4) alkylene-H)-CO-O-(C0-C4)alkylene-(C6-C12)-aryl, N((C0-C4)alkylene-H)-CO-O-(C0-C4)alkyl, N((C0-C4)alkylene-H)-CO-O-(C0-C4)alkylene-(C3-C13)cycloalkyl, N((C0-C4)alkylene-H)-CO-O-(C0-C4)alkylene-(C3-C15)heterocycle, N((C0-C4) alkylene-H)-CO-N((C0-C4)-alkylene-H)-(C0-C4)alkylene-(C6-C12)-aryl, N((C0-C4)alkylene-H)-CO-N((C0-C4)-alkylene-H)-(C0-C4)alkyl, N((C0-C4)alkylene-H)-CO-N((C0-C4)-alkylene-H)-(C0-C4)alkylene-(C3-C13)cycloalkyl, N((C0-C4)alkylene-H)-CO-N((C0-C4)-alkylene-H)-(C0-C4)alkylene-(C3-C15)heterocycle, where the aryl ring or heterocyclic ring is unsubstituted or mono- or disubstituted by F, Cl, Br, I, OH, CF3, NO2, CN, OCF3, O-(C1-C6)-alkyl, (C1-C6)-alkyl, N((C0-C4)-alkylene-H)-(C0-C4)-alkylene-H, SO2-CH3, COOH, COO-(C1-C6)-alkyl, SF5, CONH2.

The term cycloalkyl is to be understood to mean saturated hydrocarbon cycle containing from 3 to 13 carbon atoms in a mono- or bicyclic, fused, bridged or spirocyclic ring. Examples of (C3-C13)-cycloalkyl cyclic alkyl residues are cycloalkyl residues containing 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13 ring carbon atoms like cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl or cyclododecyl. The term cycloalkyl also includes bicyclic groups in which any of the above cycloalkyl ring is fused to a benzene ring, for example indane and 1,2,3,4-tetrahydronaphthalene.

The term cycloalkenyl is to be understood to mean unsaturated hydrocarbon cycle containing from 3 to 8 carbon atoms in a mono- or bicyclic , fused or bridged ring, wherein the one, two or three double bonds are not located within a cyclic alkyl group in such a manner that an aromatic system results. Examples of unsaturated cycloalkenyl groups are cyclopentenyl or cyclohexenyl, which can be bonded via any carbon atom. The term cycloalkenyl also includes bicyclic groups in which any of the above cycloalkenyl ring is fused to a benzene ring, for example 1,2-dihydronaphthalene, 1,4-dihydronaphthalene and 1H-indene.

If not otherwise defined cycloalkyl or cycloalkenyl are unsubstituted or mono, di- or trisubstituted independently of one another by suitable groups such as, for example: F, Cl, Br, I, CF3, NO2, CN, COOH, CO-O-(C0-C4) alkylene-(C6-C10) aryl, CO-O-(C1-C4) alkyl, CO-O-(C0-C4) alkylene-(C3-C13)cycloalkyl, CO-O-(C0-C4) alkylene-(C3-C15)heterocycle,, CO-N((C0-C4) alkylene-H)-(C1-C6)alkylene-H, CO-N((C0-C4) alkylene-H)-(C1-C6)cycloalkyl, CON((C0-C4) alkylene-H)-(C0-C4)alkylene-(C6-C12)-aryl, (C0-C4) alkylene-(C3-C6)cycloalkyl, (C3-C6)alkyl, (C2-C6)-alkenyl, (C2-C6)-alkinyl, (C0-C4) alkylene-(C6-C10)aryl, (C0-C4) alkylene-(C3-C15)heterocycle, O-(C0-C6)-alkyl, (C0-C4) alkylene-O-(C0-C4) alkyl, (C0-C4) alkylene-O-(C0-C4) alkylene-(C3-C13)cycloalkyl, (C0-C4) alkylene-O-(C0-C4) alkylene-(C6-C10)aryl, (C0-C4) alkylene-O-(C0-C4) alkylene-(C3-C15)heterocycle, O-CO-O-(C0-C4) alkylene-(C6-C10) aryl, O-CO-O-(C1-C4) alkyl, O-CO-O-(C0-C4) alkylene-(C3-C13)cycloalkyl, O-CO-O-(C0-C4) alkylene-(C3-C15)heterocycle, O-CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene- (C6-C10) aryl, O-CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene-H, O-CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene- (C3-C13)cycloalkyl, O-CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene- (C3-C15) heterocycle,S-(C1-C4)alkyl, S-(C0-C4) alkylene-(C3-C13)cycloalkyl, S-(C0-C4) alkylene-(C6-C10) aryl, S-(C0-C4) alkylene-(C3-C15) heterocycle, SO-(C1-C4)alkyl, SO-(C0-C4) alkylene-(C3-C13)cycloalkyl, SO-(C0-C4) alkylene-(C6-C10) aryl, SO-(C0-C4) alkylene-(C3-C15) heterocycle, SO2-(C1-C4)alkyl, SO2-(C0-C4) alkylene-(C3-C13)cycloalkyl, SO2-(C0-C4) alkylene-(C6-C10) aryl, SO2-(C0-C4) alkylene-(C3-C15) heterocycle, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C6-C10)aryl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-H, SO2-N((C0-C4) alkylene-H)-(C0-C4)alkylene-(C3-C13)cycloalkyl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C15)heterocycle, where the aryl ring or heterocyclic ring is unsubstituted or mono- or disubstituted by F, Cl, Br, OH, CF3, NO2, CN, OCF3, O-(C1-C6)-alkyl, (C1-C6)-alkyl, N((C0-C4)-alkylene-H)-(C0-C4)-alkylene-H; N((C0-C4)-alkylene-H)-(C0-C4)-alkylene-H, N((C0-C4) alkylene-H)-(C0-C4)alkylene-H)-(C1-C6)cycloalkyl, N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C6-C12)-aryl, N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C15)heterocycle, N((C0-C4) alkylene-H)-CO-(C0-C4)alkylene-(C6-C12)-aryl, N((C0-C4)alkylene-H)-CO-(C0-C4)alkyl, N((C0-C4)alkylene-H)-CO-(C0-C4)alkylene-(C3-C13)cycloalkyl, N((C0-C4)alkylene-H)-CO-(C0-C4)alkylene-(C3-C15)heterocycle, N((C0-C4) alkylene-H)-CO-O-(C0-

C4)alkylene-(C6-C12)-aryl, N((C0-C4)alkylene-H)-CO-O-(C0-C4)alkyl, N((C0-C4)alkylene-H)-CO-O-(C0-C4)alkylene-(C3-C13)cycloalkyl, N((C0-C4)alkylene-H)-CO-O-(C0-C4)alkylene-(C3-C15)heterocycle, N((C0-C4) alkylene-H)-CO-N((C0-C4)-alkylene-H)-(C0-C4)alkylene-(C6-C12)-aryl, N((C0-C4)alkylene-H)-CO-N((C0-C4)-alkylene-H)-(C0-C4)alkyl, N((C0-C4)alkylene-H)-CO-N((C0-C4)-alkylene-H)-(C0-C4)alkylene-(C3-C13)cycloalkyl, N((C0-C4)alkylene-H)-CO-N((C0-C4)-alkylene-H)-(C0-C4)alkylene-(C3-C15)heterocycle, where the aryl or heterocyclic ring is unsubstituted or mono- or disubstituted by F, Cl, Br, I, OH, CF3, NO2, CN, OCF3, O-(C1-C6)-alkyl, (C1-C6)-alkyl, N((C0-C4)-alkylene-H)-(C0-C4)-alkylene-H,SO2-CH3, COOH, COO-(C1-C6)-alkyl, SF5, CONH2.

The term "aryl" is understood to mean aromatic hydrocarbon ring containing from 6 to 14 carbon atoms in a mono- or bicyclic ring. Examples of (C6-C14)-aryl rings are phenyl, naphthyl, for example 1-naphthyl and 2-naphthyl, biphenylyl, for example 2-biphenylyl, 3-biphenylyl and 4-biphenylyl, anthryl or fluorenyl. Biphenylyl rings, naphthyl ring and, in particular, phenyl ring are further embodiments of aryl ring.

The terms heterocycle is understood to mean saturated (heterocycloalkyl), partly unsaturated (heterocycloalkenyl) or unsaturated (heteroaryl) hydrocarbon rings containing from 3 to 15 carbon atoms in a mono- or bicyclic , fused, bridged or spirocyclicring in which 1 to 5 carbon atoms of the 3 to 15 ring carbon atoms are replaced by heteroatoms such as nitrogen, oxygen or sulfur in which further the heteroatoms can be oxidized, for example N=O, S=O, SO2. Examples of heterocycles are acridinyl, azaindole (1H-pyrrolopyridinyl), azabenzimidazolyl, azaspirodecanyl, azepinyl, azetidinyl, aziridinyl, benzimidazolyl, benzofuranyl, dihydrobenzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydrochinolinyl, 4,5-dihydrooxazolinyl, dioxazolyl, dioxazinyl, 1,3-dioxolanyl, 1,3-dioxolenyl, 3,3-dioxo[1,3,4]oxathiazinyl, 6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]-tetrahydrofuranyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl

(benzimidazolyl), isothiazolyl, isothiazolidinyl, isothiazolinyl, isoxazolyl, isoxazolinyl, isoxazolidinyl, 2-isoxazolinyl, ketopiperazinyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2-oxa-thiepanyl, 1,2-oxathiolanyl, 1,4-oxazepanyl, 1,4-oxazepinyl, 1,2-oxazinyl, 1,3-oxazinyl, 1,4-oxazinyl, oxazolidinyl, oxazolinyl, oxazolyl, oxetanyl, oxocanyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolidinonyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydrothiophenyl, tetrazinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, 1,2-thiazinyl, 1,3-thiazinyl, 1,4-thiazinyl, 1,3-thiazolyl, thiazolyl, thiazolidinyl, thiazolinyl, thienyl, thietanyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiomorpholinyl, thiophenolyl, thiophenyl, thiopyranyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl; 1,2,3-triazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl.

The heterocyclic rings are unsubstituted or mono-, di- or trisubstituted by suitable groups such as, for example: F, Cl, Br, I, CF3, NO2, CN, COOH, CO-O-(C0-C4) alkylene-(C6-C10) aryl, CO-O-(C1-C4) alkyl, CO-O-(C0-C4) alkylene-(C3-C13) cycloalkyl, CO-O-(C0-C4) alkylene-(C3-C15)heterocycle, CO-N((C0-C4) alkylene-H)-(C1-C6)alkylene-H, CO-N((C0-C4) alkylene-H)-(C1-C6)cycloalkyl, CON((C0-C4) alkylene-H)-(C0-C4)alkylene-(C6-C12)-aryl, (C0-C4) alkylene-(C3-C6)cycloalkyl, (C3-C6) alkyl, (C2-C6)-alkenyl, (C2-C6)-alkinyl, (C0-C4) alkylene-(C6-C10) aryl, (C0-C4) alkylene-(C3-C15)heterocycle, O-(C0-C6)-alkyl, (C0-C4) alkylene-O-(C0-C4) alkyl, (C0-C4) alkylene-O-(C0-C4) alkylene-(C3-C13)cycloalkyl, (C0-C4) alkylene-O-(C0-C4) alkylene-(C6-C10)aryl, (C0-C4) alkylene-O-(C0-C4) alkylene-(C3-C15)heterocycle, O-CO-O-(C0-C4) alkylene-(C6-C10) aryl, O-CO-O-(C1-C4) alkyl, O-CO-O-(C0-C4) alkylene-(C3-C13)cycloalkyl, O-CO-O-(C0-C4) alkylene-(C3-C15)heterocycle, O-CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene- (C6-C10) aryl, O-CO-N((C0-C4) alkylene-H)-

(C0-C4) alkylene-H, O-CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene- (C3-C13)cycloalkyl, O-CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene- (C3-C15) heterocycle,S-(C1-C4)alkyl, S-(C0-C4) alkylene-(C3-C13)cycloalkyl, S-(C0-C4) alkylene-(C6-C10) aryl, S-(C0-C4) alkylene-(C3-C15) heterocycle, SO-(C1-C4)alkyl, SO-(C0-C4) alkylene-(C3-C13)cycloalkyl, SO-(C0-C4) alkylene-(C6-C10) aryl, SO-(C0-C4) alkylene-(C3-C15) heterocycle, SO2-(C1-C4)alkyl, SO2-(C0-C4) alkylene-(C3-C13)cycloalkyl, SO2-(C0-C4) alkylene-(C6-C10) aryl, SO2-(C0-C4) alkylene-(C3-C15) heterocycle, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C6-C10)aryl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-H, SO2-N((C0-C4) alkylene-H)-(C0-C4)alkylene-(C3-C13)cycloalkyl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C15)heterocycle, where the aryl ring or heterocyclic ring is unsubstituted or mono- or disubstituted by F, Cl, Br, OH, CF3, NO2, CN, OCF3, O-(C1-C6)-alkyl, (C1-C6)-alkyl, N((C0-C4)-alkylene-H)-(C0-C4)-alkylene-H,;
N((C0-C4)-alkylene-H)-(C0-C4)-alkylene-H, N((C0-C4) alkylene-H)-(C0-C4)alkylene-H)-(C1-C6)cycloalkyl, N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C6-C12)-aryl, N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C15)heterocycle, N((C0-C4) alkylene-H)-CO-(C0-C4)alkylene-(C6-C12)-aryl, N((C0-C4)alkylene-H)-CO-(C0-C4)alkyl, N((C0-C4)alkylene-H)-CO-(C0-C4)alkylene-(C3-C13)cycloalkyl, N((C0-C4)alkylene-H)-CO-(C0-C4)alkylene-(C3-C15)heterocycle, N((C0-C4) alkylene-H)-CO-O-(C0-C4)alkylene-(C6-C12)-aryl, N((C0-C4)alkylene-H)-CO-O-(C0-C4)alkyl, N((C0-C4)alkylene-H)-CO-O-(C0-C4)alkylene-(C3-C13)cycloalkyl, N((C0-C4)alkylene-H)-CO-O-(C0-C4)alkylene-(C3-C15)heterocycle, N((C0-C4) alkylene-H)-CO-N((C0-C4)-alkylene-H)-(C0-C4)alkylene-(C6-C12)-aryl, N((C0-C4)alkylene-H)-CO-N((C0-C4)-alkylene-H)-(C0-C4)alkyl, N((C0-C4)alkylene-H)-CO-N((C0-C4)-alkylene-H)-(C0-C4)alkylene-(C3-C13)cycloalkyl, N((C0-C4)alkylene-H)-CO-N((C0-C4)-alkylene-H)-(C0-C4)alkylene-(C3-C15)heterocycle, where the aryl or heterocyclic ring is unsubstituted or mono- or disubstituted by F, Cl, Br, I, OH, CF3, NO2, CN, OCF3, O-(C1-C6)-alkyl, (C1-C6)-alkyl, N((C0-C4)-alkylene-H)-(C0-C4)-alkylene-H,SO2-CH3, COOH, COO-(C1-C6)-alkyl, SF5, CONH2.

The term "R5 and R6 together with the nitrogen atom to which they are bonded (Y = N(R6)) can form a (C3-C9)-heterocycle which for example can contain additionally 1 to

3 heteroatoms" refer to structures of heterocycles which can be derived from compounds such as for example pyrrolidine, morpholine, thiomorpholine, piperidine, piperazine, azetidine, 2,3-dihydro-1H-isoindole, piperazin-2-one, azetidine, isoindoline, 2,5-diazabicyclo[2.2.1]heptane, thiomorpholine 1-oxide, thiomorpholine 1,1-dioxide, piperidin-4-one, piperidin-3-one, homopiperidine, homopiperazine, homomorpholine, 2,3,6,7-tetrahydro-(1H)-1,4-diazepin-5(4H)-one, 4-oxazolidine, azetidin-3-one, thiazolidine, thiazolidine 1-oxide, thiazolidine 1,1-dioxide, 4-imidazolidinone, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine, 1,4-diazabicyclo[4.3.0]nonane, 2-aza-5-oxabicyclo[2.2.1]heptane, 2-oxa-5-azabicyclo[2.2.1]heptane, diazabicyclo[4.4.0]decane, 4,5,6,7-tetrahydrothieno[3,2-c]pyridine, 4,5,6,7-tetrahydro-1H-imidazol[4,5-c]-pyridine, 4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine, 3,8-diaza-bicyclo[3.2.1]octane, octahydro-pyrrolo[3,4-c]pyrrole, 2,5-diazabicyclo[2.2.2]octane, 4-spiro-[3-(N-methyl-2-pyrrolidinone)]-piperidine, 2,8-diaza-spiro[5.5]undecane, 2,7-diaza-spiro[4.4]nonane, 3,9-diaza-spiro[5.5]undecane, 2,8-diaza-spiro[4.5]decane, 2,7-diaza-spiro[3.5]nonane, 2,9-diaza-spiro[5.5]undecane, 2,7-diaza-spiro[4.5]decane, 1-oxa-4,9-diaza-spiro[5.5]undecane, 1-oxa-4,8-diaza-spiro[5.5]undecane.

The term "oxo-residue" or "=O" refers to residues such as carbonyl (-CO-), nitroso (-N=O), sulfinyl (-SO-) or sulfonyl (-SO_2-).

Halogen is fluorine, chlorine, bromine or iodine.

Optically active carbon atoms present in the compounds of the formula I can independently of each other have R configuration or S configuration. The compounds of the formula I can be present in the form of pure enantiomers or pure diastereomers or in the form of mixtures of enantiomers and/or diastereomers, for example in the form of racemates. The present invention relates to pure enantiomers and mixtures of enantiomers as well as to pure diastereomers and mixtures of diastereomers. The invention comprises mixtures of two or of more than two stereoisomers of the formula I and it comprises all ratios of the stereoisomers in the mixtures. In case the compounds of the formula I can be present as E isomers or Z isomers (or cis isomers or trans

isomers) the invention relates both to pure E isomers and pure Z isomers and to E/Z mixtures in all ratios. The invention also comprises all tautomeric forms of the compounds of the formula I.

Diastereomers, including E/Z isomers, can be separated into the individual isomers, for example, by chromatography. Racemates can be separated into the two enantiomers by customary methods, for example by chromatography on chiral phases or by resolution, for example by crystallization of diastereomeric salts obtained with optically active acids or bases. Stereochemically uniform compounds of the formula I can also be obtained by employing stereochemically uniform starting materials or by using stereoselective reactions.

The compounds of the formula I may exist in the form of their racemates, racemic mixtures, pure enantiomers, diastereomers and mixtures of diastereomers as well in their tautomeric forms. The present invention encompasses all these isomeric and tautomeric forms of the compounds of the formula I. These isomeric forms can be obtained by known methods even if not specifically described in some cases.

Pharmaceutically acceptable salts are, because their solubility in water is greater than that of the initial or basic compounds, particularly suitable for medical applications. These salts must have a pharmaceutically acceptable anion or cation. Suitable pharmaceutically acceptable acid addition salts of the compounds of the invention are salts of inorganic acids such as hydrochloric acid, hydrobromic, phosphoric, metaphosphoric, nitric and sulfuric acid, and of organic acids such as, for example, acetic acid, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isethionic, lactic, lactobionic, maleic, malic, methanesulfonic, succinic, p-toluenesulfonic and tartaric acid. Suitable pharmaceutically acceptable basic salts are ammonium salts, alkali metal salts (such as sodium and potassium salts), alkaline earth metal salts (such as magnesium and calcium salts), and salts of trometamol (2-amino-2-hydroxymethyl-1,3-propanediol), diethanolamine, lysine or ethylenediamine.

Salts with a pharmaceutically unacceptable anion such as, for example, trifluoroacetate likewise belong within the framework of the invention as useful intermediates for the preparation or purification of pharmaceutically acceptable salts and/or for use in nontherapeutic, for example in vitro, applications.

The term "physiologically functional derivative" used herein refers to any physiologically tolerated derivative of a compound of the formula I of the invention, for example an ester, which on administration to a mammal such as, for example, a human is able to form (directly or indirectly) a compound of the formula I or an active metabolite thereof.

Physiologically functional derivatives also include prodrugs of the compounds of the invention, as described, for example, in H. Okada et al., Chem. Pharm. Bull. 1994, 42, 57-61. Such prodrugs can be metabolized in vivo to a compound of the invention. These prodrugs may themselves be active or not.

The compounds of the invention may also exist in various polymorphous forms, for example as amorphous and crystalline polymorphous forms. All polymorphous forms of the compounds of the invention belong within the framework of the invention and are a further aspect of the invention.

All references to "compound(s) of formula I" hereinafter refer to compound(s) of the formula I as described above, and their salts, solvates and physiologically functional derivatives as described herein.

Use

This invention relates further to the use of compounds of the formula I and their pharmaceutical compositions as PPAR ligands. The PPAR ligands of the invention are suitable as modulators of PPAR activity.

Peroxisome proliferator-activated receptors (PPAR) are transcription factors which can

be activated by ligands and belong to the class of nuclear hormone receptors. There are three PPAR isoforms, PPARalpha, PPARgamma and PPARdelta (identical to PPARbeta), which are encoded by different genes (Peroxisome proliferator-activated receptor (PPAR): structure, mechanisms of activation and diverse functions: Motojima K., Cell Struct Funct., 1993, 18(5), 267-77).

In humans, PPARgamma exists in three variants, PPARgamma$_1$, gamma$_2$, and gamma$_3$, which are the result of alternative use of promoters and differential mRNA splicing. Different PPARs have different tissue distribution and modulate different physiological functions. The PPARs play a key role in various aspects of the regulation of a large number of genes, the products of which genes are directly or indirectly crucially involved in lipid and carbohydrate metabolism. Thus, for example, the PPARalpha receptor plays an important part in the regulation of fatty acid catabolism or lipoprotein metabolism in the liver, while PPARgamma is crucially involved for example in regulating adipose cell differentiation. In addition, however, PPARs are also involved in the regulation of many other physiological processes, including those which are not directly connected with carbohydrate or lipid metabolism. The activity of different PPARs can be modulated by various fatty acids, fatty acid derivatives and synthetic compounds to varying extents. For relevant reviews about functions, physiological effects and pathophysiology, see: Berger, J. et al., Annu. Rev. Med., 2002, 53, 409-435; Wilson, T. et al., J. Med. Chem., 2000, 43 (4), 527-550; Kliewer, S. et al., Recent Prog Horm Res., 2001, 56, 239-63; Moller, D.E. and Berger, J.P., Int J Obes Relat Metab Disord., 2003, 27 Suppl 3, 17-21; Ram, V.J., Drugs Today, 2003, 39(8),609-32).

Among the three PPAR-isoforms the physiological functions of PPARdelta have long remained an enigma. The first proposed pharmacological role for PPARdelta has been the regulation of cholesterol homeostasis. It was shown that the somewhat selective PPARdelta ligand L-165041 raises plasma cholesterol in a diabetic animal model (Berger J. et al., J. Biol. Chem., 1999, 274, 6718-6725; Leibowitz M.D. et al., FEBS Lett., 2000, 473(3), 333-336). In obese, insulin resistant rhesus monkeys, the potent and selective PPARdelta ligand GW501516 raises HDL-cholesterol, decreases plasma

LDL-cholesterol, triglycerides and insulin levels (Oliver, W. et al., Proc. Natl. Acad. Sci., 2001, 98, 5306-5361). The dual PPARdelta/PPARalpha agonist YM-16638 significantly lowers plasma lipids in rhesus and cynomolgus monkeys (Goto, S. et al., Br. J. Pharm., 1996, 118, 174-178) and acts in a similar manner in two weeks clinical trials in healthy volunteers (Shimokawa, T. et al., Drug Dev. Res., 1996, 38, 86-92).

More recent publications underline that PPARdelta is an important target for the treatment of dyslipidemia, insulin resistance, type 2 diabetes, atherosclerosis and syndrom X (Wang,Y-X. et al., Cell, 2003, 113, 159-170; Luquet, S. et al., FASEB J., 2003, 17, 209-226 ; Tanaka, T. et al., PNAS, 2003, 100, 15924-15929 ; Holst, D. et al., BioChem. Biophys. Acta, 2003, 1633, 43-50; Dressel, U. et al., Mol. Endocrin., 2003, 17, 2477-2493 ; Lee, C.H. et al., Science, 2003, 302, 453-457).

Besides its actions as a regulator of the lipid-, glucose- and cholesterol-metabolism PPARdelta is known to play a role in embryonic development, implantation and bone formation (Lim, H. and Dey, S.K., Trends Endocrinol Metab., 2000, 11(4),137-42; Ding, N.Z. et al., Mol Reprod Dev., 2003, 66(3), 218-24; Mano, H. et al., J Biol Chem., 2000, 275(11), 8126-32).

Numerous publications demonstrate that PPARdelta is triggering proliferation and differentiation of keratinocytes which points to its role in skin disorders and wound healing (Di-Poi, N. et al., J Steroid Biochem Mol Biol., 2003, 85(2-5), 257-65; Tan, N.S. et al., Am J Clin Dermatol., 2003,4(8), 523-30; Wahli, W., Swiss Med Wkly., 2002, 132(7-8),83-91).

PPARdelta appears to be significantly expressed in the CNS; however much of its function there still remains undiscovered. Of singular interest however, is the discovery that PPARdelta was expressed in rodent oligodendrocytes, the major lipid producing cells of the CNS (J. Granneman, et al., J. Neurosci. Res., 1998, 51, 563-573). Moreover, it was also found that a PPARdelta selective agonist was found to significantly increase oligodendroglial myelin gene expression and myelin sheath diameter in mouse cultures (I. Saluja et al., Glia, 2001, 33, 194-204). Thus, PPARdelta activators may be of use for the treatment of demyelinating and

dysmyelinating diseases. The use of peroxisome proliferator activated receptor delta agonists for the treatment of MS and other demyelynating diseases can be shown as described in WO2005/097098.

Demyelinating conditions are manifested in loss of myelin - the multiple dense layers of lipids and protein which cover many nerve fibers. These layers are provided by oligodendroglia in the central nervous system (CNS), and Schwann cells in the peripheral nervous system (PNS). In patients with demyelinating conditions, demyelination may be irreversible; it is usually accompanied or followed by axonal degeneration, and often by cellular degeneration. Demyelination can occur as a result of neuronal damage or damage to the myelin itself - whether due to aberrant immune responses, local injury, ischemia, metabolic disorders, toxic agents, or viral infections (Prineas and McDonald, Demyelinating Diseases. In Greenfield's Neuropathology, 6.sup.th ed. (Edward Arnold: New York, 1997) 813-811, Beers and Berkow, eds., The Merck Manual of Diagnosis and Therapy, 17.sup.th ed. (Whitehouse Station, N.J.: Merck Research Laboratories, 1999) 1299, 1437, 1473-76, 1483).

Central demyelination (demyelination of the CNS) occurs in several conditions, often of uncertain etiology, that have come to be known as the primary demyelinating diseases. Of these, multiple sclerosis (MS) is the most prevalent. Other primary demyelinating diseases include adrenoleukodystrophy (ALD), adrenomyeloneuropathy, AIDS-vacuolar myelopathy, HTLV-associated myelopathy, Leber's hereditary optic atrophy, progressive multifocal leukoencephalopathy (PML), subacute sclerosing panencephalitis, Guillian-Barre syndrome and tropical spastic paraparesis. In addition, there are acute conditions in which demyelination can occur in the CNS, e.g., acute disseminated encephalomyelitis (ADEM) and acute viral encephalitis. Furthermore, acute transverse myelitis, a syndrome in which an acute spinal cord transection of unknown cause affects both gray and white matter in one or more adjacent thoracic segments, can also result in demyelination. Also, disorders in which myelin forming glial cells are damaged including spinal cord injuries, neuropathies and nerve injury.

The present invention relates to compounds of the formula I suitable for modulating the activity of PPARs, especially the activity of PPARdelta and PPARalpha. Depending on

the modulation profile, the compounds of the formula I are suitable for the treatment, control and prophylaxis of the indications described hereinafter, and for a number of other pharmaceutical applications connected thereto (see, for example, Berger, J., et al., Annu. Rev. Med., 2002, 53, 409-435; Wilson, T. et al., J. Med. Chem., 2000, 43(4), 527-550; Kliewer, S. et al., Recent Prog Horm Res., 2001, 56, 239-63; Fruchart, J.C. et al., 2001, Pharmacological Research, 44(5), 345-52; Kersten, S. et al., Nature, 2000, 405, 421-424; Torra, I.P. et al., Curr Opin Lipidol, 2001,12, 245-254).

Compounds of this type are particularly suitable for the treatment and/or prevention of:

1. - Disorders of fatty acid metabolism and glucose utilization disorders.
   - Disorders in which insulin resistance is involved

2. Diabetes mellitus, especially type 2 diabetes, including the prevention of the sequelae associated therewith.
   Particular aspects in this connection are
   - hyperglycemia,
   - improvement in insulin resistance,
   - improvement in glucose tolerance,
   - protection of the pancreatic ß cells
   - prevention of macro- and microvascular disorders

3. Dyslipidemias and their sequelae such as, for example, atherosclerosis, coronary heart disease, cerebrovascular disorders etc, especially those (but not restricted thereto) which are characterized by one or more of the following factors:
   - high plasma triglyceride concentrations, high postprandial plasma triglyceride concentrations,
   - low HDL cholesterol concentrations
   - low ApoA lipoprotein concentrations
   - high LDL cholesterol concentrations
   - small dense LDL cholesterol particles

- high ApoB lipoprotein concentrations

4. Various other conditions which may be associated with the metabolic syndrome, such as:
   - obesity (excess weight), including central obesity
   - thromboses, hypercoagulable and prothrombotic states (arterial and venous)
   - high blood pressure
   - heart failure such as, for example (but not restricted thereto), following myocardial infarction, hypertensive heart disease or cardiomyopathy

5. Disorders or conditions in which inflammatory reactions are involved:
   - atherosclerosis such as, for example (but not restricted thereto), coronary sclerosis including angina pectoris or myocardial infarction, stroke
   - vascular restenosis or reocclusion
   - chronic inflammatory bowel diseases such as, for example, Crohn's disease and ulcerative colitis
   - asthma
   - lupus erythematosus (LE) or inflammatory rheumatic disorders such as, for example, rheumatoid arthritis
   - other inflammatory states

6. Disorders of cell cycle or cell differentiation processes:
   - adipose cell tumors
   - lipomatous carcinomas such as, for example, liposarcomas
   - solid tumors and neoplasms such as, for example (but not restricted thereto), carcinomas of the gastrointestinal tract, of the liver, of the biliary tract and of the pancreas, endocrine tumors, carcinomas of the lungs, of the kidneys and the urinary tract, of the genital tract, prostate carcinomas etc
   - acute and chronic myeloproliferative disorders and lymphomas
   - angiogenesis

7. Demyelinating and other neurodegenerative disorders of the central and peripheral

nervous systems including:

- Alzheimer's disease
- multiple sclerosis
- Parkinson's disease
- adrenoleukodystrophy (ALD)
- adrenomyeloneuropathy
- AIDS-vacuolar myelopathy
- HTLV-associated myelopathy
- Leber's hereditary optic atrophy
- progressive multifocal leukoencephalopathy (PML)
- subacute sclerosing panencephalitis
- Guillian-Barre syndrome
- tropical spastic paraparesis
- acute disseminated encephalomyelitis (ADEM)
- acute viral encephalitis
- acute transverse myelitis
- spinal cord and brain trauma
- Charcot-Marie-Tooth disease

8. Skin disorders and/or disorders of wound healing processes:

- erythemato-squamous dermatoses such as, for example, psoriasis
- acne vulgaris
- other skin disorders and dermatological conditions which are modulated by PPAR
- eczemas and neurodermitis
- dermatitis such as, for example, seborrheic dermatitis or photodermatitis
- keratitis and keratoses such as, for example, seborrheic keratoses, senile keratoses, actinic keratosis, photo-induced keratoses or keratosis follicularis
- keloids and keloid prophylaxis
- warts, including condylomata or condylomata acuminata
- human papilloma viral (HPV) infections such as, for example, venereal papillomata, viral warts such as, for example, molluscum contagiosum,

leukoplakia
- papular dermatoses such as, for example, Lichen planus
- skin cancer such as, for example, basal-cell carcinomas, melanomas or cutaneous T-cell lymphomas
- localized benign epidermal tumors such as, for example, keratoderma, epidermal naevi
- chilblains
- wound healing

9. Other disorders
- high blood pressure
- pancreatitis
- syndrome X
- polycystic ovary syndrome (PCOS)
- asthma
- osteoarthritis
- lupus erythematosus (LE) or inflammatory rheumatic disorders such as, for example, rheumatoid arthritis
- vasculitis
- wasting (cachexia)
- gout
- ischemia/reperfusion syndrome
- acute respiratory distress syndrome (ARDS)

Formulations

The amount of a compound of formula I necessary to achieve the desired biological effect depends on a number of factors, for example the specific compound chosen, the intended use, the mode of administration and the clinical condition of the patient. The daily dose is generally in the range from 0.001 mg to 100 mg (typically from 0.01 mg to 50 mg) per day and per kilogram of bodyweight, for example 0.1-10 mg/kg/day. An intravenous dose may be, for example, in the range from 0.001 mg to 1.0 mg/kg, which

can suitably be administered as infusion of 10 ng to 100 ng per kilogram and per minute. Suitable infusion solutions for these purposes may contain, for example, from 0.1 ng to 10 mg, typically from 1 ng to 10 mg, per milliliter. Single doses may contain, for example, from 1 mg to 10 g of the active ingredient. Thus, ampules for injections may contain, for example, from 1 mg to 100 mg, and single-dose formulations which can be administered orally, such as, for example, capsules or tablets, may contain, for example, from 0.05 to 1000 mg, typically from 0.5 to 600 mg. For the therapy of the abovementioned conditions, the compounds of formula I may be used as the compound itself, but they are preferably in the form of a pharmaceutical composition with an acceptable carrier. The carrier must, of course, be acceptable in the sense that it is compatible with the other ingredients of the composition and is not harmful for the patient's health. The carrier may be a solid or a liquid or both and is preferably formulated with the compound as a single dose, for example as a tablet, which may contain from 0.05% to 95% by weight of the active ingredient. Other pharmaceutically active substances may likewise be present, including other compounds of formula I. The pharmaceutical compositions of the invention can be produced by one of the known pharmaceutical methods, which essentially consist of mixing the ingredients with pharmacologically acceptable carriers and/or excipients.

Pharmaceutical compositions of the invention are those suitable for oral, rectal, topical, peroral (for example sublingual) and parenteral (for example subcutaneous, intramuscular, intradermal or intravenous) administration, although the most suitable mode of administration depends in each individual case on the nature and severity of the condition to be treated and on the nature of the compound of formula I used in each case. Coated formulations and coated slow-release formulations also belong within the framework of the invention. Preference is given to acid- and gastric juice-resistant formulations. Suitable coatings resistant to gastric juice comprise cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methyl methacrylate.

Suitable pharmaceutical preparations for oral administration may be in the form of separate units such as, for example, capsules, cachets, suckable tablets or tablets,

each of which contain a defined amount of the compound of formula I; as powders or granules, as solution or suspension in an aqueous or nonaqueous liquid; or as an oil-in-water or water-in-oil emulsion. These compositions may, as already mentioned, be prepared by any suitable pharmaceutical method which includes a step in which the active ingredient and the carrier (which may consist of one or more additional ingredients) are brought into contact. The compositions are generally produced by uniform and homogeneous mixing of the active ingredient with a liquid and/or finely divided solid carrier, after which the product is shaped if necessary. Thus, for example, a tablet can be produced by compressing or molding a powder or granules of the compound, where appropriate with one or more additional ingredients. Compressed tablets can be produced by tableting the compound in free-flowing form such as, for example, a powder or granules, where appropriate mixed with a binder, glidant, inert diluent and/or one (or more) surface-active/dispersing agent(s) in a suitable machine. Molded tablets can be produced by molding the compound, which is in powder form and is moistened with an inert liquid diluent, in a suitable machine.

Pharmaceutical compositions which are suitable for peroral (sublingual) administration comprise suckable tablets which contain a compound of formula I with a flavoring, normally sucrose and gum arabic or tragacanth, and pastilles which comprise the compound in an inert base such as gelatin and glycerol or sucrose and gum arabic.

Pharmaceutical compositions suitable for parenteral administration comprise preferably sterile aqueous preparations of a compound of formula I, which are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also take place by subcutaneous, intramuscular or intradermal injection. These preparations can preferably be produced by mixing the compound with water and making the resulting solution sterile and isotonic with blood. Injectable compositions of the invention generally contain from 0.1 to 5% by weight of the active compound.

Pharmaceutical compositions suitable for rectal administration are preferably in the form of single-dose suppositories. These can be produced by mixing a compound of

the formula I with one or more conventional solid carriers, for example cocoa butter, and shaping the resulting mixture.

Pharmaceutical compositions suitable for topical use on the skin are preferably in the form of ointment, cream, lotion, paste, spray, aerosol or oil. Carriers which can be used are petrolatum, lanolin, polyethylene glycols, alcohols and combinations of two or more of these substances. The active ingredient is generally present in a concentration of from 0.1 to 15% by weight of the composition, for example from 0.5 to 2%.

Transdermal administration is also possible. Pharmaceutical compositions suitable for transdermal uses can be in the form of single plasters which are suitable for long-term close contact with the patient's epidermis. Such plasters suitably contain the active ingredient in an aqueous solution which is buffered where appropriate, dissolved and/or dispersed in an adhesive or dispersed in a polymer. A suitable active ingredient concentration is about 1% to 35%, preferably about 3% to 15%. A particular possibility is for the active ingredient to be released by electrotransport or iontophoresis as described, for example, in Pharmaceutical Research, 2(6): 368 (1986).

The compounds of the formula I are distinguished by favorable effects on metabolic disorders. They beneficially influence lipid and sugar metabolism, in particular they lower the triglyceride level and are suitable for the prevention and treatment of type II diabetes and atheriosclerosis and the diverse sequalae thereof.

Combinations with other medicaments

The compounds of the invention can be administered alone or in combination with one or more further pharmacologically active substances. In particular, the compounds of the invention can be administered in combination with active ingredients having a similar pharmacological action. For example, they can be administered in combination with active ingredients which have favorable effects on metabolic disturbances or disorders frequently associated therewith. Examples of such medicaments are

1. medicaments which lower blood glucose, antidiabetics,
2. active ingredients for the treatment of dyslipidemias,
3. antiatherosclerotic medicaments,
4. antiobesity agents,
5. antiinflammatory active ingredients
6. active ingredients for the treatment of malignant tumors
7. antithrombotic active ingredients
8. active ingredients for the treatment of high blood pressure
9. active ingredients for the treatment of heart failure and
10. active ingredients for the treatment and/or prevention of complications caused by diabetes or associated with diabetes.
11. active ingredients for the treatment of neurodegenerative diseases
12. active ingredients for the treatment of disorders of the central nervous system
13. active ingredients for the treatment of drug, nicotine and alcohol addiction
14. analgesics

They can be combined with the compounds of the invention of the formula I in particular for a synergistic enhancement of activity. Administration of the active ingredient combination can take place either by separate administration of the active ingredients to the patient or in the form of combination products in which a plurality of active ingredients are present in one pharmaceutical preparation.

Particularly suitable further active ingredients for the combination preparations are: All antidiabetics mentioned in the Rote Liste 2006, Chapter 12; all slimming agents/appetite supressants mentioned in the Rote Liste 2006, Chapter 1; all lipid-lowering agents mentioned in the Rote Liste 2006, Chapter 58. They can be combined with the compound of the formula I according to the invention in particular for a synergistic enhancement of activity. The active compound combination can be administered either by separate administration of the active compounds to the patient or in the form of combination preparations in which a plurality of active compounds are present in a pharmaceutical preparation. Most of the active compounds listed below

are disclosed in USP Dictionary of USAN and International Drug Names, US Pharmacopeia, Rockville 2001.

Antidiabetics include insulin and insulin derivatives, such as, for example, Lantus® (see www.lantus.com) or HMR 1964 or those descibed in WO2005005477 (Novo Nordisk), fast-acting insulins (see US 6,221,633), inhalable insulins, such as, for example, Exubera ® or oral insulins, such as, for example, IN-105 (Nobex) or Oral-lyn™ (Generex Biotechnology), GLP-1 derivatives, such as, for example, Exenatide, Liraglutide or those disclosed in WO 98/08871 or WO2005027978 by Novo Nordisk A/S, in WO 01/04156 by Zealand or in WO 00/34331 by Beaufour-Ipsen, pramlintide acetate (Symlin; Amylin Pharmaceuticals), and also orally effective hypoglycemic active ingredients.

The active compounds preferably include
sulfonylureas,
biguanidines,
meglitinides,
oxadiazolidinediones,
thiazolidinediones,
glucosidase inhibitors,
inhibitors of glycogen phosphorylase,
glucagon antagonists,
glucokinase activators,
inhibitors of fructose-1,6-bisphosphatase,
modulators of the glucose transporter 4 (GLUT4),
inhibitors of glutamine:fructose-6-phosphate amidotransferase (GFAT),
GLP-1 agonists,
potassium channel openers, such as, for example, those disclosed in WO 97/26265 and WO 99/03861 by Novo Nordisk A/S,
inhibitors of dipeptidylpeptidase IV (DPP-IV),
insulin sensitizers,

inhibitors of liver enzymes involved in the stimulation of gluconeogenesis and/or glycogenolysis,
modulators of glucose uptake, glucose transport and glucose backresorption,
inhibitors of 11ß-HSD1,
inhibitors of protein tyrosine phosphatase 1B (PTP1B),
modulators of the sodium/glucose cotransporter 1 or 2 (SGLT1, SGLT2),
compounds which alter lipid metabolism, such as antihyperlipidemic active ingredients and antilipidemic active ingredients,
compounds which reduce food intake or food absorption,
compounds which increase thermogenesis,
PPAR and RXR modulators and
active ingredients which act on the ATP-dependent potassium channel of the beta cells.

In one embodiment of the invention, the compound of the formula I is administered in combination with a HMGCoA reductase inhibitor, such as simvastatin, fluvastatin, pravastatin, lovastatin, atorvastatin, cerivastatin, rosuvastatin or L-659699.

In one embodiment of the invention, the compound of the formula I is administered in combination with a cholesterol resorption inhibitor, such as, for example, ezetimibe, tiqueside, pamaqueside, FM-VP4 (sitostanol/campesterol ascorbyl phosphate; Forbes Medi-Tech, WO2005042692), MD-0727 (Microbia Inc., WO2005021497) or with compounds as described in WO2002066464 (Kotobuki Pharmaceutical Co. Ltd.), WO2005062824 (Merck & Co.) or WO2005061451 and WO2005061452 (AstraZeneca AB).

In one embodiment of the invention, the compound of the formula I is administered in combination with a PPAR gamma agonist, such as, for example, rosiglitazone, pioglitazone, JTT-501, GI 262570, R-483 or CS-011 (rivoglitazone).

In one embodiment of the invention, the compound of the formula I is administered in combination with a PPAR alpha agonist, such as, for example, GW9578, GW-590735, K-111, LY-674, KRP-101 or DRF-10945.

In one embodiment of the invention, the compound of the formula I is administered in combination with a mixed PPAR alpha/gamma agonist, such as, for example, muraglitazar, tesaglitazar, naveglitazar, LY-510929, ONO-5129, E-3030 or as described in WO00/64888, WO00/64876, WO03/020269, WO2004075891, WO2004076402, WO2004075815, WO2004076447, WO2004076428, WO2004076401, WO2004076426, WO2004076427, WO2006018118, WO2006018115, and WO2006018116 or in J.P. Berger et al., TRENDS in Pharmacological Sciences 28(5), 244-251, 2005.

In one embodiment of the invention, the compound of the formula I is administered in combination with a PPAR delta agonist, such as, for example, GW-501516 or as described in WO2005097762, WO2005097786, WO2005097763, and WO2006029699.

In one embodiment of the invention, the compound of the formula I is administered in combination with metaglidasen or with MBX-2044 or other partial PPAR gamma agonists/antagonists.

In one embodiment of the invention, the compound of the formula I is administered in combination with a fibrate, such as, for example, fenofibrate, clofibrate or bezafibrate.

In one embodiment of the invention, the compound of the formula I is administered in combination with an MTP inhibitor, such as, for example, implitapide, BMS-201038, R-103757 or those described in WO2005085226.

In one embodiment of the invention, the compound of the formula I is administered in combination with a CETP inhibitor, such as, for example, torcetrapib or JTT-705.

In one embodiment of the invention, the compound of the formula I is administered in combination with a bile acid resorption inhibitor (see, for example, US 6,245,744, US 6,221,897 or WO00/61568), such as, for example, HMR 1741 or those described in DE 10 2005 033099.1 and DE 10 2005 033100.9.

In one embodiment of the invention, the compound of the formula I is administered in combination with a polymeric bile acid adsorber, such as, for example, cholestyramine or colesevelam.

In one embodiment of the invention, the compound of the formula I is administered in combination with an LDL receptor inducer (see US 6,342,512), such as, for example, HMR1171, HMR1586 or those described in WO2005097738.

In one embodiment, the compound of the formula I is administered in combination with Omacor® (omega-3 fatty acids; highly concentrated ethyl esters of eicosapentaenoic acid and docosahexaenoic acid).

In one embodiment of the invention, the compound of the formula I is administered in combination with an ACAT inhibitor, such as, for example, avasimibe.

In one embodiment of the invention, the compound of the formula I is administered in combination with an antioxidant, such as, for example, OPC-14117, probucol, tocopherol, ascorbic acid, ß-carotene or selenium.

In one embodiment of the invention, the compound of the formula I is administered in combination with a vitamin, such as, for example, vitamin B6 or vitamin B12.

In one embodiment of the invention, the compound of the formula I is administered in combination with a lipoprotein lipase modulator, such as, for example, ibrolipim (NO-1886).

In one embodiment of the invention, the compound of the formula I is administered in combination with an ATP-citrate lyase inhibitor, such as, for example, SB-204990.

In one embodiment of the invention, the compound of the formula I is administered in combination with a squalene synthetase inhibitor, such as, for example, BMS-188494 or as described in WO2005077907.

In one embodiment of the invention, the compound of the formula I is administered in combination with a lipoprotein(a) antagonist, such as, for example, gemcabene (CI-1027).

In one embodiment of the invention, the compound of the formula I is administered in combination with an HM74A receptor agonists, such as, for example, nicotinic acid.

In one embodiment of the invention, the compound of the formula I is administered in combination with a lipase inhibitor, such as, for example, orlistat or cetilistat (ATL-962).

In one embodiment of the invention, the compound of the formula I is administered in combination with insulin.

In one embodiment of the invention, the compound of the formula I is administered in combination with a sulfonylurea, such as, for example, tolbutamide, glibenclamide, glipizide or glimepiride.

In one embodiment of the invention, the compound of the formula I is administered in combination with a biguanide, such as, for example, metformin.

In another embodiment of the invention, the compound of the formula I is administered in combination with a meglitinide, such as, for example, repaglinide or nateglinide.

In one embodiment of the invention, the compound of the formula I is administered in combination with a thiazolidinedione, such as, for example, troglitazone, ciglitazone, pioglitazone, rosiglitazone or the compounds disclosed in WO 97/41097 by Dr.

Reddy's Research Foundation, in particular 5-[[4-[(3,4-dihydro-3-methyl-4-oxo-2-quinazolinylmethoxy]phenyl]methyl]-2,4-thiazolidinedione.

In one embodiment of the invention, the compound of the formula I is administered in combination with an α-glucosidase inhibitor, such as, for example, miglitol or acarbose.

In one embodiment of the invention, the compound of the formula I is administered in combination with an active ingredient which acts on the ATP-dependent potassium channel of the beta cells, such as, for example, tolbutamide, glibenclamide, glipizide, glimepiride or repaglinide.

In one embodiment of the invention, the compound of the formula I is administered in combination with more than one of the compounds mentioned above, for example in combination with a sulfonylurea and metformin, a sulfonylurea and acarbose, repaglinide and metformin, insulin and a sulfonylurea, insulin and metformin, insulin and troglitazone, insulin and lovastatin, etc.

In one embodiment of the invention, the compound of the formula I is administered in combination with an inhibitor of glycogen phosphorylase, such as, for example, PSN-357 or FR-258900 or those described in WO2003084922, WO2004007455, WO2005073229-31 or WO2005067932.

In one embodiment of the invention, the compound of the formula I is administered in combination with glucagon receptor antagonists, such as, for example, A-770077, NNC-25-2504 or such as in WO2004100875 or WO2005065680.

In one embodiment of the invention, the compound of the formula I is administered in combination with activators of glucokinase, such as, for example, RO-4389620, LY-2121260 (WO2004063179), PSN-105, PSN-110, GKA-50 or those described, for example, by Prosidion in WO2004072031, WO2004072066, WO 05103021 or WO 06016178, by Roche in WO 00058293, WO 00183465, WO 00183478, WO 00185706, WO 00185707, WO 01044216, GB 02385328, WO 02008209, WO 02014312, WO 0246173, WO 0248106, DE 10259786, WO 03095438, US 04067939 or WO

04052869, by Novo Nordisk in EP 1532980, WO 03055482, WO 04002481, WO 05049019, WO 05066145 or WO 05123132, by Merck/Banyu in WO 03080585, WO03097824, WO 04081001, WO 05063738 or WO 05090332, by Eli Lilly in WO 04063194, or by Astra Zeneca in WO 01020327, WO 03000262, WO 03000267, WO 03015774, WO 04045614, WO 04046139, WO 05044801, WO 05054200, WO 05054233, WO 05056530, WO 05080359, WO 05080360 or WO 05121110.

In one embodiment of the invention, the compound of the formula I is administered in combination with an inhibitor of gluconeogenesis, such as, for example, FR-225654.

In one embodiment of the invention, the compound of the formula I is administered in combination with inhibitors of fructose-1,6-bisphosphatase (FBPase), such as, for example, CS-917.

In one embodiment of the invention, the compound of the formula I is administered in combination with modulators of the glucose transporter 4 (GLUT4), such as, for example, KST-48 (D.-O. Lee et al.: Arzneim.-Forsch. Drug Res. 54 (12), 835 (2004)).

In one embodiment of the invention, the compound of the formula I is administered in combination with inhibitors of glutamine:fructose-6-phosphate amidotransferase (GFAT), as described, for example, in WO2004101528.

In one embodiment of the invention, the compound of the formula I is administered in combination with inhibitors of dipeptidylpeptidase IV (DPP-IV), such as, for example, vildagliptin (LAF-237), sitagliptin (MK-0431), saxagliptin ((BMS-477118), GSK-823093, PSN-9301, SYR-322, SYR-619, TA-6666, TS-021, GRC-8200, GW-825964X or as described in WO2003074500, WO2003106456, WO200450658, WO2005058901, WO2005012312, WO2005/012308, PCT/EP2005/007821, PCT/EP2005/008005, PCT/EP2005/008002, PCT/EP2005/008004, PCT/EP2005/008283, DE 10 2005 012874.2 or DE 10 2005 012873.4.

In one embodiment of the invention, the compound of the formula I is administered in combination with inhibitors of 11-beta-hydroxysteroid dehydrogenase-1 (11ß-HSD1), such as, for example, BVT-2733 or those described, for example, in WO200190090-94, WO200343999, WO2004112782, WO200344000, WO200344009, WO2004112779, WO2004113310, WO2004103980, WO2004112784, WO2003065983, WO2003104207, WO2003104208, WO2004106294, WO2004011410, WO2004033427, WO2004041264, WO2004037251, WO2004056744, WO2004065351, WO2004089367, WO2004089380, WO2004089470-71, WO2004089896, WO2005016877 or WO2005097759.

In one embodiment of the invention, the compound of the formula I is administered in combination with inhibitors of protein tyrosine phosphatase 1B (PTP1B), as described, for example, in WO200119830-31, WO200117516, WO2004506446, WO2005012295, PCT/EP2005/005311, PCT/EP2005/005321, PCT/EP2005/007151, PCT/EP2005/ or DE 10 2004 060542.4.

In one embodiment of the invention, the compound of the formula I is administered in combination with modulators of the sodium/glucose cotransporter 1 or 2 (SGLT1, SGLT2), such as, for example, KGA-2727, T-1095 and SGL-0010 or as described, for example, in WO2004007517, WO200452903, WO200452902, WO2005121161 , WO2005085237, JP2004359630 or by A. L. Handlon in Expert Opin. Ther. Patents (2005) 15(11), 1531-1540.

In one embodiment of the invention, the compound of the formula I is administered in combination with inhibitors of hormone-sensitive lipase (HSL), such as those described, for example, in WO01/17981, WO01/66531, WO2004035550, WO2005073199 or WO03/051842.

In one embodiment of the invention, the compound of the formula I is administered in combination with inhibitors of acetyl-CoA carboxylase (ACC) such as those described, for example, in WO199946262, WO200372197, WO2003072197 or WO2005044814.

In one embodiment of the invention, the compound of the formula I is administered in combination with an inhibitor of phosphoenolpyruvate carboxykinase (PEPCK), such as those described, for example, in WO2004074288.

In one embodiment of the invention, the compound of the formula I is administered in combination with an inhibitor of glycogen synthase kinase-3 beta (GSK-3 beta), such as those described, for example, in US2005222220, WO2004046117, WO2005085230, WO2005111018, WO2003078403, WO2004022544, WO2003106410, WO2005058908, US2005038023, WO2005009997, US2005026984, WO2005000836, WO2004106343, EP1460075, WO2004014910, WO2003076442, WO2005087727 or WO2004046117.

In one embodiment of the invention, the compound of the formula I is administered in combination with an inhibitor of protein kinase C beta (PKC beta), such as, for example, ruboxistaurin.

In one embodiment of the invention, the compound of the formula I is administered in combination with an endothelin-A receptor antagonist, such as, for example, avosentan (SPP-301).

In one embodiment of the invention, the compound of the formula I is administered in combination with inhibitors of "I-kappaB kinase" (IKK inhibitors), such as those described, for example, in WO2001000610, WO2001030774, WO2004022553 or WO2005097129.

In one embodiment of the invention, the compound of the formula I is administered in combination with modulators of the glucocorticoid receptor as described, for example, in WO2005090336.

In a further embodiment of the invention, the compound of the formula I is administered in combination with CART modulators (see "Cocaine-amphetamine-

regulated transcript influences energy metabolism, anxiety and gastric emptying in mice" Asakawa, A. et al.: Hormone and Metabolic Research (2001), 33(9), 554-558); NPY antagonists such as, for example, {4-[(4-aminoquinazolin-2-ylamino)methyl]-cyclohexylmethyl}naphthalene-1-sulfonamide hydrochloride (CGP 71683A);

peptide YY 3-36 (PYY3-36) or analogous compounds, such as, for example, CJC-1682 (PYY3-36 conjugated with human serum albumin via Cys34), CJC-1643 (derivative of PYY3-36 which conjugates in vivo to serum albumin) or those described in WO2005080424;

cannabinoid receptor 1 antagonists, such as, for example, rimonabant, SR147778 or those described, for example, in EP 0656354, WO 00/15609, WO 02/076949, WO2005080345, WO2005080328, WO2005080343, WO2005075450, WO2005080357, WO200170700, WO2003026647-48, WO200302776, WO2003040107, WO2003007887, WO2003027069, US6,509,367, WO200132663, WO2003086288, WO2003087037, WO2004048317, WO2004058145, WO2003084930, WO2003084943, WO2004058744, WO2004013120, WO2004029204, WO2004035566, WO2004058249, WO2004058255, WO2004058727, WO2004069838, US20040214837, US20040214855, US20040214856, WO2004096209, WO2004096763, WO2004096794, WO2005000809, WO2004099157, US20040266845, WO2004110453, WO2004108728, WO2004000817, WO2005000820, US20050009870, WO200500974, WO2004111033-34, WO200411038-39, WO2005016286, WO2005007111, WO2005007628, US20050054679, WO2005027837, WO2005028456, WO2005063761-62, WO2005061509 or WO2005077897;

MC4 agonists (for example [2-(3a-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(4-chlorophenyl)-2-oxoethyl]-1-amino-1,2,3,4-tetrahydro-naphthalene-2-carboxamide; (WO 01/91752)) or LB53280, LB53279, LB53278 or THIQ, MB243, RY764, CHIR-785, PT-141 or those described in WO2005060985, WO2005009950, WO2004087159, WO2004078717, WO2004078716, WO2004024720, US20050124652, WO2005051391, WO2004112793, WOUS20050222014, US20050176728, US20050164914, US20050124636, US20050130988, US20040167201, WO2004005324, WO2004037797, WO2005042516, WO2005040109, WO2005030797, US20040224901,

WO200501921, WO200509184, WO2005000339, EP1460069, WO2005047253, WO2005047251, EP1538159, WO2004072076, WO2004072077 or WO2006024390; orexin receptor antagonists (for example 1-(2-methylbenzoxazol-6-yl)-3-[1,5]naphthyridin-4-ylurea hydrochloride (SB-334867-A) or those described, for example, in WO200196302, WO200185693, WO2004085403 or WO2005075458); histamine H3 receptor agonists (for example 3-cyclohexyl-1-(4,4-dimethyl-1,4,6,7-tetrahydroimidazo[4,5-c]pyridin-5-yl)-propan-1-one oxalic acid salt (WO 00/63208) or those described in WO200064884, WO2005082893);
CRF antagonists (for example [2-methyl-9-(2,4,6-trimethylphenyl)-9H-1,3,9-triazafluoren-4-yl]dipropylamine (WO 00/66585));
CRF BP antagonists (for example urocortin);
urocortin agonists;
β3 agonists (such as, for example, 1-(4-chloro-3-methanesulfonylmethylphenyl)-2-[2-(2,3-dimethyl-1H-indol-6-yloxy)ethylamino]ethanol hydrochloride (WO 01/83451));
MSH (melanocyte-stimulating hormone) agonists;
MCH (melanin-concentrating hormone) receptor antagonists (such as, for example, NBI-845, A-761, A-665798, A-798, ATC-0175, T-226296, T-71, GW-803430 or those compounds described in WO2003/15769, WO2005085200, WO2005019240, WO2004011438, WO2004012648, WO2003015769, WO2004072025, WO2005070898, WO2005070925, WO2006018280, WO2006018279, WO2004039780, WO2003033476, WO2002006245, WO2002002744, WO2003004027 or FR2868780);
CCK-A agonists (such as, for example, {2-[4-(4-chloro-2,5-dimethoxyphenyl)-5-(2-cyclohexylethyl)-thiazol-2-ylcarbamoyl]-5,7-dimethylindol-1-yl}acetic acid trifluoroacetic acid salt (WO 99/15525), SR-146131 (WO 0244150) or SSR-125180);
serotonin reuptake inhibitors (for example dexfenfluramine);
mixed serotonin- and noradrenergic compounds (for example WO 00/71549);
5-HT receptor agonists, for example 1-(3-ethylbenzofuran-7-yl)piperazine oxalic acid salt (WO 01/09111);
5-HT2C receptor agonists (such as, for example, APD-356, BVT-933 or those described in WO200077010, WO20077001-02, WO2005019180, WO2003064423, WO200242304 or WO2005082859);

5-HT6 receptor antagonists, such as described, for example, in WO2005058858;
bombesin receptor agonists (BRS-3 agonists);
galanin receptor antagonists;
growth hormone (for example human growth hormone or AOD-9604);
growth hormone releasing compounds (tert-butyl 6-benzyloxy-1-(2-diisopropylamino-ethylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylate (WO 01/85695));
growth hormone secretagog receptor antagonists (ghrelin antagonists) such as, for example, A-778193 or those described in WO2005030734;
TRH agonists (see, for example, EP 0 462 884);
uncoupling protein 2 or 3 modulators;
leptin agonists (see for example Lee, Daniel W.; Leinung, Matthew C.; Rozhavskaya-Arena, Marina; Grasso, Patricia. Leptin agonists as a potential approach to the treatment of obesity. Drugs of the Future (2001), 26(9), 873-881);
DA agonists (bromocriptine or Doprexin);
lipase/amylase inhibitors (as described, for example, in WO 00/40569);
inhibitors of diacylglycerol O-acyltransferases (DGATs) such as described, for example, in US2004/0224997, WO2004094618, WO200058491, WO2005044250, WO2005072740, JP2005206492 or WO2005013907;
inhibitors of fatty acid synthase (FAS) such as, for example, C75 or those described in WO2004005277;
oxyntomodulin;
oleoyl-estrone

or thyroid hormone receptor agonists, such as, for example, KB-2115 or those described in WO20058279, WO200172692, WO200194293, WO2003084915, WO2004018421 or WO2005092316.

In one embodiment of the invention, the further active ingredient is leptin; see for example "Perspectives in the therapeutic use of leptin", Salvador, Javier; Gomez-Ambrosi, Javier; Fruhbeck, Gema, Expert Opinion on Pharmacotherapy (2001), 2(10), 1615-1622.

In one embodiment of the invention, the further active ingredient is dexamphetamine or amphetamine.

In one embodiment of the invention, the further active ingredient is fenfluramine or dexfenfluramine.

In another embodiment of the invention, the further active ingredient is sibutramine.

In one embodiment of the invention, the further active ingredient is mazindol or phentermine.

In one embodiment, the compounds of the formula I are administered in combination with bulking agents, preferably insoluble bulking agents (see, for example, carob/Caromax® (Zunft H J; et al., Carob pulp preparation for treatment of hypercholesterolemia, ADVANCES IN THERAPY (2001 Sep-Oct), 18(5), 230-6). Caromax is a carob-containing product from Nutrinova, Nutrition Specialties & Food Ingredients GmbH, Industriepark Höchst, 65926 Frankfurt/Main). Combination with Caromax® is possible in one preparation or by separate administration of compounds of the formula I and Caromax®. Caromax® can in this connection also be administered in the form of food products such as, for example, in bakery products or muesli bars.

In one embodiment of the invention, the compound of the formula I is administered in combination with PDE (phosphodiesterase) inhibitors, as described, for example, in WO2003/077949 or WO2005012485.

In one embodiment of the invention, the compound of the formula I is administered in combination with NAR-1 (nicotinic acid receptor) agonists as described, for example, in WO2004094429.

In one embodiment of the invention, the compound of the formula I is administered in combination with CB2 (cannabinoid receptor) agonists as described, for example, in US2005/143448.

In one embodiment of the invention, the compound of the formula I is administered in combination with histamine 1 agonists as described, for example, in WO2005101979.

In one embodiment of the invention, the compound of the formula I is administered in combination with bupropion, as described in WO2006017504.

In one embodiment of the invention, the compound of the formula I is administered in combination with opioid antagonists as described, for example, in WO2005107806 or WO2004094429.

In one embodiment of the invention, the compound of the formula I is administered in combination with neutral endopeptidase inhibitors as described, for example, in WO200202513, WO2002/06492, WO 2002040008, WO2002040022 or WO2002047670.

In one embodiment of the invention, the compound of the formula I is administered in combination with NPY inhibitors (neuropeptide Y) as described, for example, in WO2002047670.

In one embodiment of the invention, the compound of the formula I is administered in combination with sodium/hydrogen exchange inhibitors as described, for example, in WO2003092694.

In one embodiment of the invention, the compound of the formula I is administered in combination with modulators of the glucocorticoid receptor as described, for example, in WO2005090336.

In one embodiment of the invention, the compound of the formula I is administered in combination with nicotine receptor agonists as described, for example, in WO2004094429.

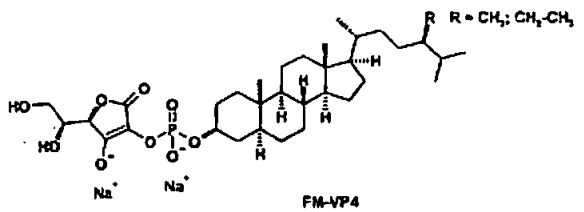
In one embodiment of the invention, the compound of the formula I is administered in combination with NRIs (norepinephrine reuptake inhibitors) as described, for example, in WO2002053140.

In one embodiment of the invention, the compound of the formula I is administered in combination with MOA (E-beta-methoxyacrylate), such as, for example, segeline, or as described, for example, in WO2002053140.

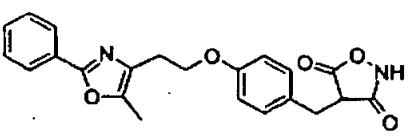
In one embodiment of the invention, the compound of the formula I is administered in combination with antithrombotic active ingredients, such as, for example, clopidrogel.

It is to be understood that each suitable combination of the compounds according to the invention with one or more of the compounds mentioned above and optionally one or more further pharmacologically active substances is meant to be included in the scope of the present invention.

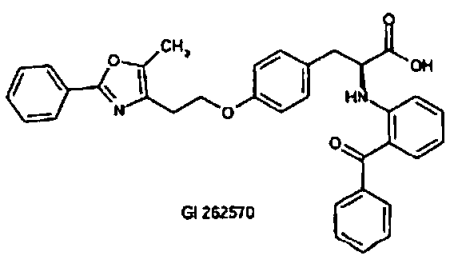
The formulae for some of the development codes mentioned above are given below.



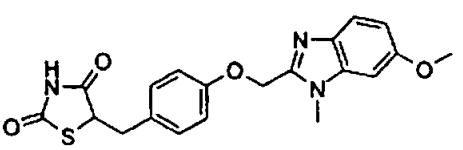
FM-VP4



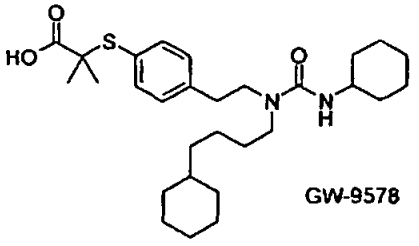
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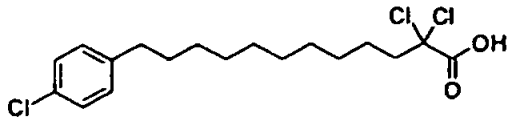
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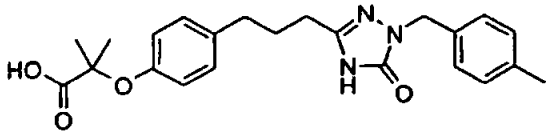
CS-011
Rivoglitazone



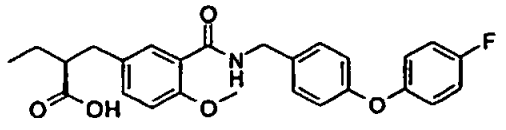
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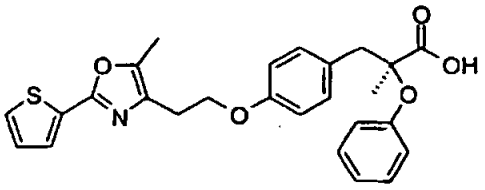
K-111



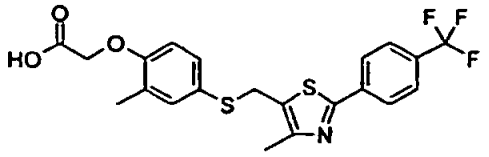
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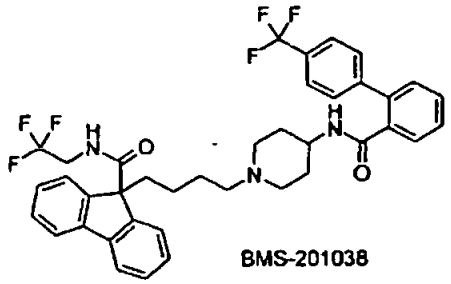
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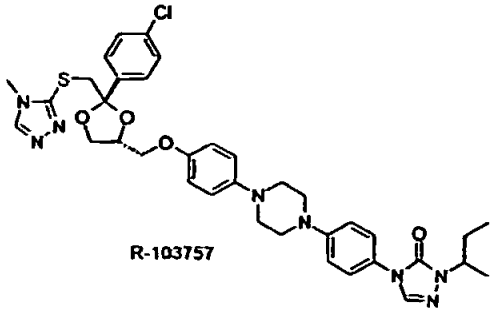
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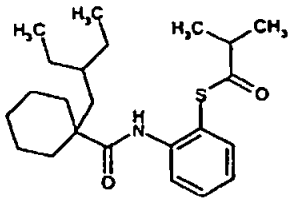
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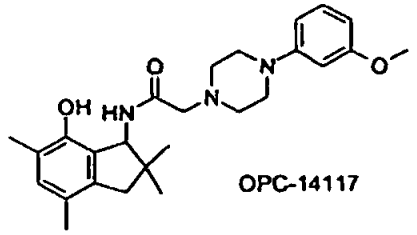
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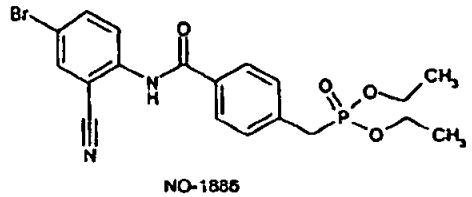
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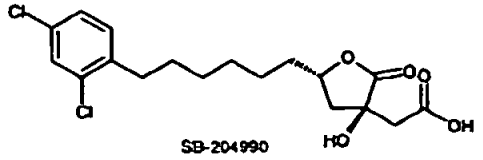
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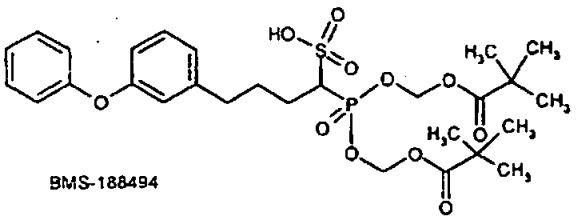
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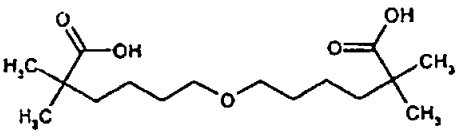
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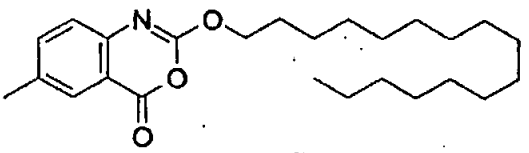
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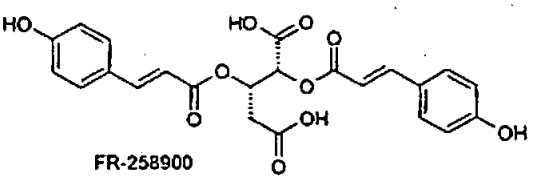
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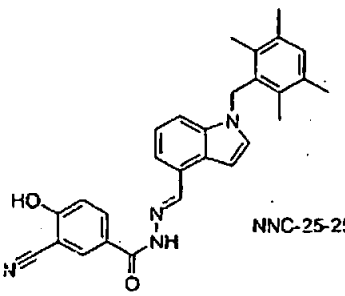
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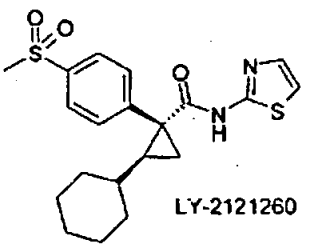
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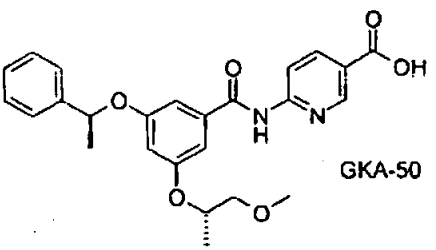
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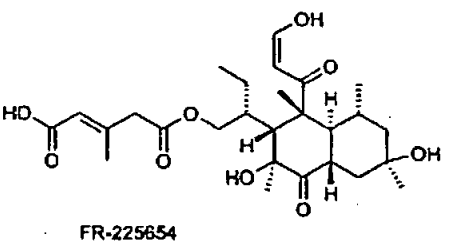
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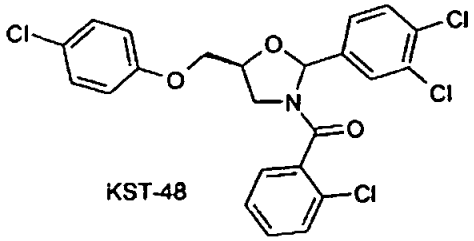
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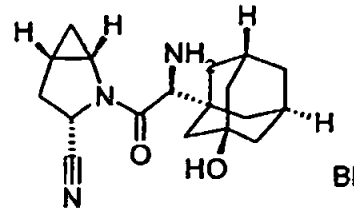
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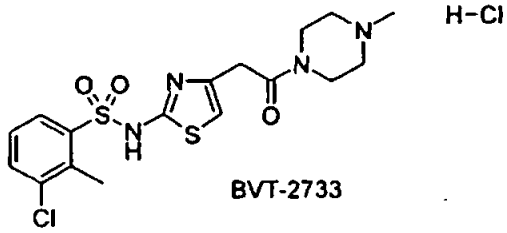
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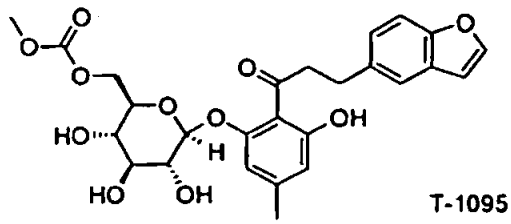
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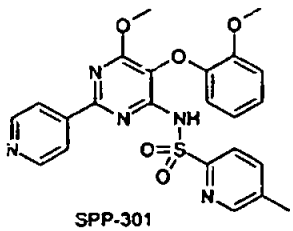
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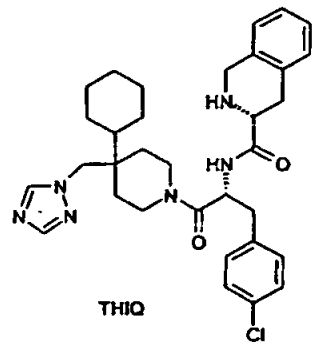
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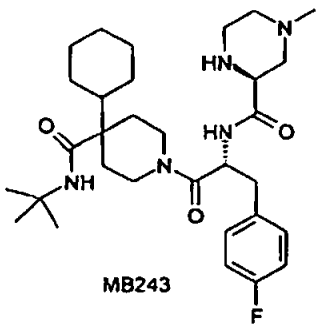
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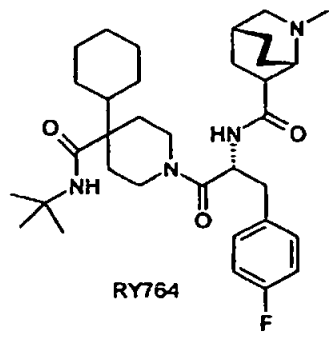
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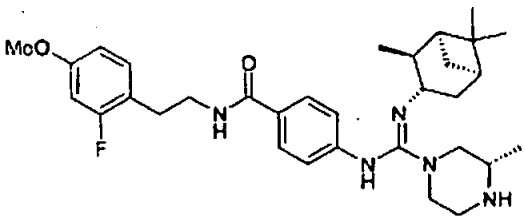
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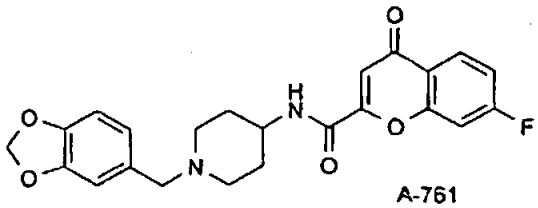
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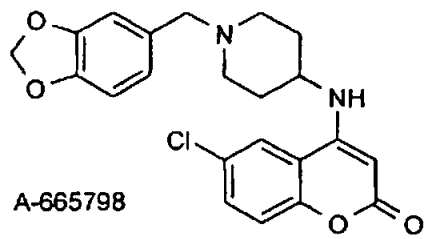
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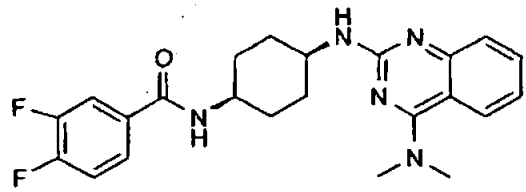
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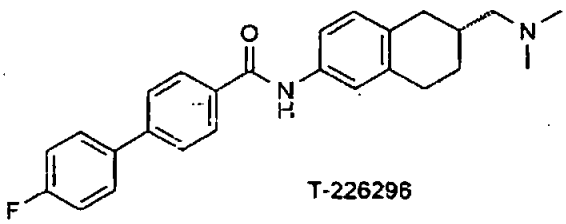
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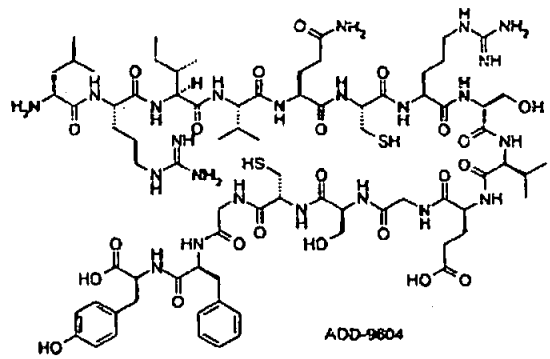
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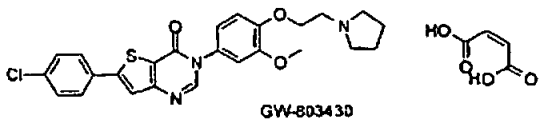
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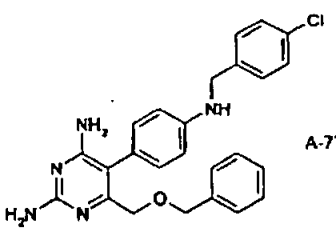
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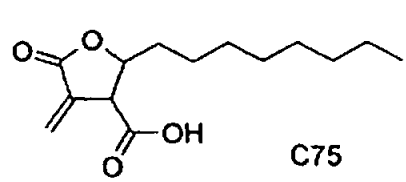
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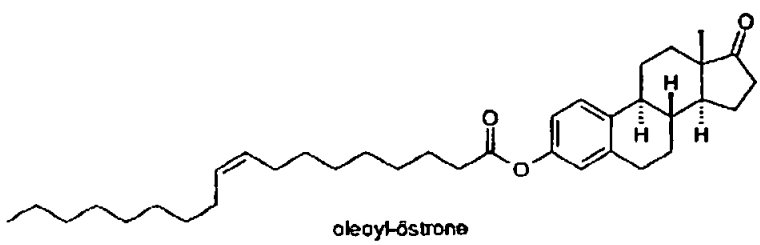
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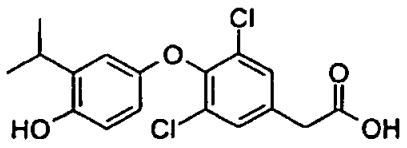
A-778193



C75



oleoyl-östrone



KB-2115

The activity of the compounds was tested as follows:

Determination of EC50 values of PPAR agonists in the cellular PPARalpha assay

Principle

The potency of substances which bind to human PPARalpha and activate it in an agonistic manner is analyzed using a stably transfected HEK cell line (HEK= human embryo kidney) which is referred to here as PPARalpha reporter cell line. It contains two genetic elements, a luciferase reporter element (pdeltaM-GAL4-Luc-Zeo) and a PPARalpha fusion protein (GR-GAL4-humanPPARalpha-LBD) which mediates expression of the luciferase reporter element depending on a PPARalpha ligand. The stably and constitutively expressed fusion protein GR-GAL4-humanPPARalpha-LBD binds in the cell nucleus of the PPARalpha reporter cell line via the GAL4 protein portion to the GAL4 DNA binding motifs 5'-upstream of the luciferase reporter element which is stably integrated in the genome of the cell line. There is only weak expression of the luciferase reporter gene in the absence of a PPARalpha ligand if fatty acid-depleted fetal calf serum (cs-FCS) is used in the assay. PPARalpha ligands bind and activate the PPARalpha fusion protein and thereby stimulate the expression of the luciferase reporter gene. The luciferase which is formed can be detected by means of chemiluminescence via an appropriate substrate.

Construction of the PPARalpha reporter cell line

The PPARalpha reporter cell line was prepared in two stages. Firstly, the luciferase reporter element was constructed and stably transfected into HEK cells. For this

purpose, five binding sites of the yeast transcription factor GAL4 (Accession # AF264724) were cloned in 5'-upstream of a 68 bp-long minimal MMTV promoter (Accession # V01175). The minimal MMTV promoter section contains a CCAAT box and a TATA element in order to enable efficient transcription by RNA polymerase II. The cloning and sequencing of the GAL4-MMTV construct took place in analogy to the description of Sambrook J. *et. al.* (Molecular cloning, Cold Spring Harbor Laboratory Press, 1989). Then the complete Photinus pyralis gene (Accession # M15077) was cloned in 3'-downstream of the GAL4-MMTV element. After sequencing, the luciferase reporter element consisting of five GAL4 binding sites, MMTV promoter and luciferase gene was recloned into a plasmid which confers zeocin resistance in order to obtain the plasmid pdeltaM-GAL4-Luc-Zeo. This vector was transfected into HEK cells in accordance with the statements in Ausubel, F.M. et al. (Current protocols in molecular biology, Vol. 1-3, John Wiley & Sons, Inc., 1995). Then zeocin-containing medium (0.5 mg/ml) was used to select a suitable stable cell clone which showed very low basal expression of the luceriferase gene.

In a second step, the PPARalpha fusion protein (GR-GAL4-humanPPARalpha-LBD was introduced into the stable cell clone described. For this purpose, initially the cDNA coding for the N-terminal 76 amino acids of the glucocorticoid receptor (Accession # P04150) was linked to the cDNA section coding for amino acids 1-147 of the yeast transcription factor GAL4 (Accession # P04386). The cDNA of the ligand-binding domain of the human PPARalpha receptor (amino acids S167-Y468; Accession # S74349) was cloned in at the 3'-end of this GR-GAL4 construct. The fusion construct prepared in this way (GR-GAL4-humanPPARalpha-LBD) was recloned into the plasmid pcDNA3 (Invitrogen) in order to enable constitutive expression therein by the cytomegalovirus promoter. This plasmid was linearized with a restriction endonuclease and stably transfected into the previously described cell clone containing the luciferase reporter element. The finished PPARalpha reporter cell line which contains a luciferase reporter element and constitutively expresses the PPARalpha fusion protein (GR-GAL4-human PPARalpha-LBD) was isolated by selection with zeocin (0.5 mg/ml) and G418 (0.5 mg/ml).

Assay procedure

The activity of PPARalpha agonists is determined in a 3-day assay, which is described below:

Day 1

The PPARalphareporter cell line is cultivated to 80% confluence in DMEM (# 41965-039, Invitrogen) which is mixed with the following additions: 10% cs-FCS (fetal calf serum; #SH-30068.03, Hyclone), 0.5 mg/ml zeocin (#R250-01, Invitrogen), 0.5 mg/ml G418 (#10136-027, Invitrogen), 1% penicillin-streptomycin solution (#15140-122, Invitrogen) and 2 mM L-glutamine (#25030-024, Invitrogen). The cultivation takes place in standard cell culture bottles (# 353612, Becton Dickinson) in a cell culture incubator at 37°C in the presence of 5% CO_2. The 80%-confluent cells are washed once with 15 ml of PBS (#14190-094, Invitrogen), treated with 3 ml of trypsin solution (#25300-054, Invitrogen) at 37°C for 2 min, taken up in 5 ml of the DMEM described and counted in a cell counter. After dilution to 500.000 cells/ml, 35,000 cells are seeded in each well of a 96 well microtiter plate with a clear plastic base (#3610, Corning Costar). The plates are incubated in the cell culture incubator at 37°C and 5% CO_2 for 24 h.

Day 2

PPARalpha agonists to be tested are dissolved in DMSO in a concentration of 10 mM. This stock solution is diluted in DMEM (#41965-039, Invitrogen) which is mixed with 5% cs-FCS (#SH-30068.03, Hyclone), 2 mM L-glutamine (#25030-024, Invitrogen) and the previously described antibiotics (zeocin, G418, penicillin and streptomycin).
Test substances are tested in 11 different concentrations in the range from 10 µM to 100 pM. More potent compounds are tested in concentration ranges from 1 µM to 10 pM or between 100 nM and 1 pM.
The medium of the PPARalpha reporter cell line seeded on day 1 is completely removed by aspiration, and the test substances diluted in medium are immediately added to the cells. The dilution and addition of the substances is carried out by a robot (Beckman FX). The final volume of the test substances diluted in medium is 100 µl per

well of a 96 well microtiter plate. The DMSO concentration in the assay is less than 0.1 % v/v in order to avoid cytotoxic effects of the solvent.
Each plate was charged with a standard PPARalpha agonist, which was likewise diluted in 11 different concentrations, in order to demonstrate the functioning of the assay in each individual plate. The assay plates are incubated in an incubator at 37°C and 5% CO_2 for 24 h.

Day 3

The PPARalpha reporter cells treated with the test substances are removed from the incubator, and the medium is aspirated off. The cells are lyzed by pipetting 50 µl of Bright Glo reagent (from Promega) into each well of a 96 well microtiter plate. After incubation at room temperature in the dark for 10 minutes, the microtiter plates are measured in the luminometer (Trilux from Wallac). The measuring time for each well of a microtiter plate is 1 sec.

Evaluation

The raw data from the luminometer are transferred into a Microsoft Excel file. Dose-effect plots and EC50 values of PPAR agonists are calculated using the XL.Fit program as specified by the manufacturer (IDBS).

The PPARalpha EC50 values for the compounds of Examples 1 to 112 in this assay are in the range from 5 nM to >10 µM. Compounds of the invention of the formula I activate the PPARalpha receptor.

Determination of EC50 values of PPAR agonists in the cellular PPARdelta assay

Principle

The potency of substances which bind to human PPARdelta and activate it in an agonistic manner is analyzed using a stably transfected HEK cell line (HEK= human embryo kidney) which is referred to here as PPARdelta reporter cell line. In analogy to

the assay described for PPARalpha, the PPARdelta reporter cell line also contains two genetic elements, a luciferase reporter element (pdeltaM-GAL4-Luc-Zeo) and a PPARdelta fusion protein (GR-GAL4-humanPPARdelta-LBD) which mediates expression of the luciferase reporter element depending on a PPARdelta ligand. The stably and constitutively expressed fusion protein GR-GAL4-humanPPARdelta-LBD binds in the cell nucleus of the PPARdelta reporter cell line via the GAL4 protein portion to the GAL4 DNA binding motifs 5'-upstream of the luciferase reporter element which is stably integrated in the genome of the cell line. There is only little expression of the luciferase reporter gene in the absence of a PPARdelta ligand if fatty acid-depleted fetal calf serum (cs-FCS) is used in the assay. PPARdelta ligands bind and activate the PPARdelta fusion protein and thereby stimulate expression of the luciferase reporter gene. The luciferase which is formed can be detected by means of chemiluminescence via an appropriate substrate.

Construction of the PPARdelta reporter cell line

The production of the stable PPARdelta reporter cell line is based on a stable HEK-cell clone which was stably transfected with a luciferase reporter element. This step was already described above in the section "construction of the PPARalpha reporter cell line". In a second step, the PPARdelta fusion protein (GR-GAL4-humanPPARdelta-LBD was stably introduced into this cell clone. For this purpose, the cDNA coding for the
N-terminal 76 amino acids of the glucocorticoid receptor (Accession # P04150) was linked to the cDNA section coding for amino acids 1-147 of the yeast transcription factor GAL4 (Accession # P04386). The cDNA of the ligand-binding domain of the human PPARdelta receptor (amino acids S139-Y441; Accession # L07592) was cloned in at the 3'-end of this GR-GAL4 construct. The fusion construct prepared in this way (GR-GAL4-humanPPARdelta-LBD) was recloned into the plasmid pcDNA3 (Invitrogen) in order to enable constitutive expression by the cytomegalovirus promoter. This plasmid was linearized with a restriction endonuclease and stably transfected into the previously described cell clone containing the luciferase reporter element. The resulting PPARdelta reporter cell line which contains a luciferase reporter

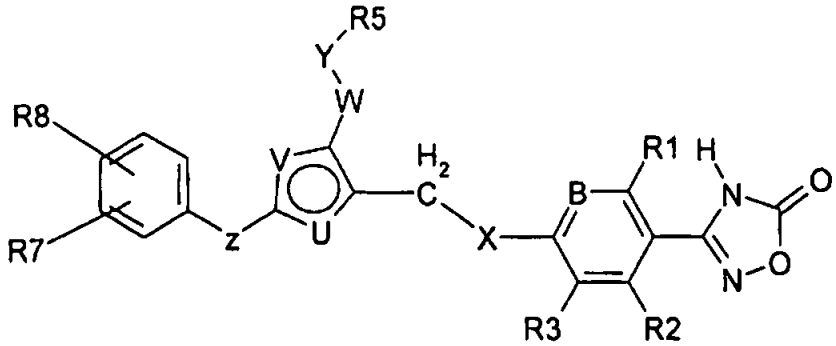
element and constitutively expresses the PPARdelta fusion protein (GR-GAL4-human PPARdelta-LBD) was isolated by selection with zeocin (0.5 mg/ml) and G418 (0.5 mg/ml).

Assay procedure and evaluation

The activity of PPARdelta agonists is determined in a 3-day assay in exact analogy to the procedure already described for the PPARalpha reporter cell line except that the PPARdelta reporter cell line and a specific PPARdelta agonist was used as a standard to control test efficacy.

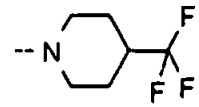
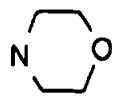
PPARdelta EC50 values in the range from 0.2 nM to >10 µM were measured for the PPAR agonists of Examples 1 to 112 described in this application. Compounds of the invention of the formula I activate the PPARdelta receptor.

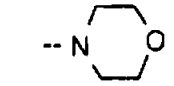
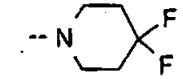
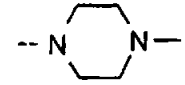
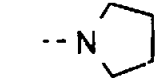
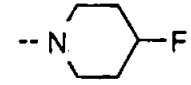
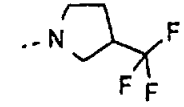
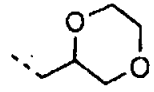
The examples given in Table I serve to illustrate the invention, but without limiting it.

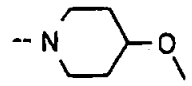
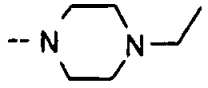
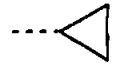
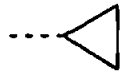
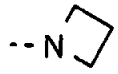
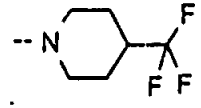
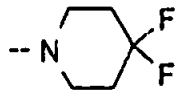
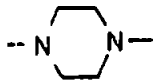


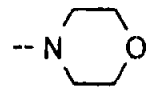
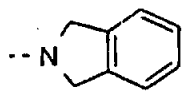
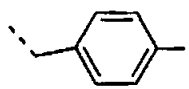
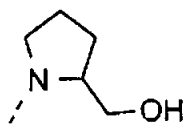
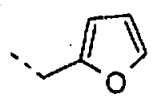
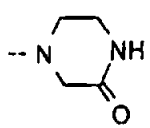
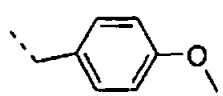
were R2 and R8 = H .
A dotted line means the point of attachment.

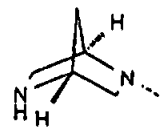
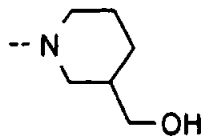
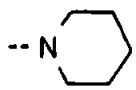
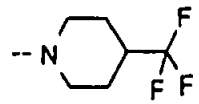
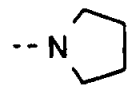
Table I

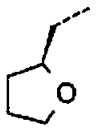
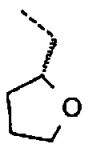
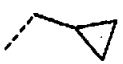
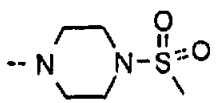
Example	Z	X	W	Y	R5	R6	U	V	R1	R3	R7	B
1	bond	O	-CH2-				S	N	-OCH3	H	p-CF3	CH
2	bond	O	-CH2-				S	N	Cl	H	p-CF3	CH

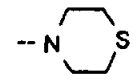
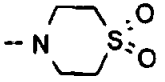
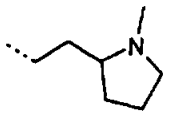
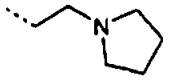
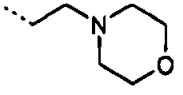
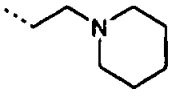
Example	Z	X	W	Y	R5	R6	U	V	R1	R3	R7	B
3	bond	O	-CH2-				S	N	-OCH3	H	p-CF3	CH
4	bond	O	-CH2-				S	N	-OCH3	H	p-CF3	CH
5	bond	O	-CH2-				S	N	-OCH3	H	p-CF3	CH
6	bond	O	-CH2-				S	N	-OCH3	H	p-CF3	CH
7	bond	O	-CH2-				S	N	-OCH3	H	p-CF3	CH
8	bond	O	-CH2-	N	-CH2CH3	-CH2CH3	S	N	-OCH3	H	p-CF3	CH
9	bond	O	-CH2CH2-				S	N	-OCH3	H	p-CF3	CH
10	bond	O	-CH2-	N	-(CH2)2OCH3	-CH2CH3	S	N	-OCH3	H	p-CF3	CH
11	bond	O	-CH2-	N		-CH3	S	N	-OCH3	H	p-CF3	CH

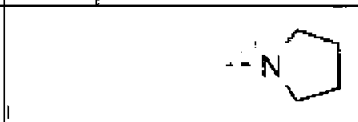
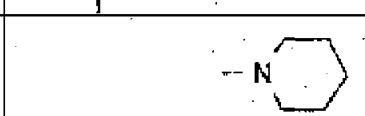
Example	Z	X	W	Y	R5	R6	U	V	R1	R3	R7	B
12	bond	O	-CH2-				S	N	-OCH3	H	p-CF3	CH
13	bond	O	-CH2-				S	N	-OCH3	H	p-CF3	CH
14	bond	O	-CH2-	N	-(CO)OPh		S	N	-OCH3	H	p-CF3	CH
15	bond	O	-CH2-	N		H	S	N	-OCH3	H	p-CF3	CH
16	bond	O	-(CH2)3-				S	N	-OCH3	H	p-CF3	CH
17	bond	O	-CH2-				S	N	F	H	p-CF3	CH
18	bond	O	-CH2-				S	N	F	H	p-CF3	CH
19	bond	O	-CH2-	N	-(CH2)2OH	-CH3	S	N	F	H	p-CF3	CH
20	bond	O	-CH2-				S	N	F	H	p-CF3	CH

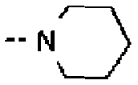
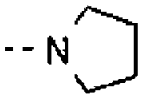
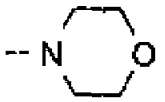
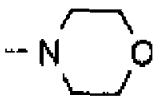
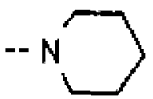
Example	Z	X	W	Y	R5	R6	U	V	R1	R3	R7	B
21	bond	O	-CH2-				S	N	F	H	p-CF3	CH
22	bond	O	-CH2-				S	N	F	H	p-CF3	CH
23	bond	O	-CH2-	N		H	S	N	F	H	p-CF3	CH
24	bond	O	-CH2-				S	N	F	H	p-CF3	CH
25	bond	O	-CH2-	N		H	S	N	F	H	p-CF3	CH
26	bond	O	-CH2-	N	-CH2CH2CH2SCH3	H	S	N	F	H	p-CF3	CH
27	bond	O	-CH2-				S	N	F	H	p-CF3	CH
28	bond	O	-CH2-	N		H	S	N	F	H	p-CF3	CH

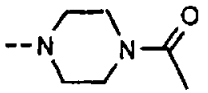
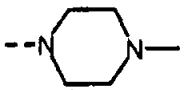
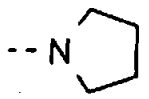
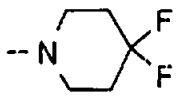
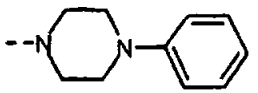
Example	Z	X	W	Y	R5	R6	U	V	R1	R3	R7	B
29	bond	O	-CH2-				S	N	F	H	p-CF3	CH
30	bond	O	-CH2-				S	N	F	H	p-CF3	CH
31	bond	O	-CH2-				S	N	-OCH3	Br	p-CF3	CH
32	bond	O	-CH2-				S	N	-OCH3	F	p-CF3	CH
33	bond	O	-CH2-	O	C(=O)CH3		S	N	F	H	p-CF3	CH
34	bond	O	-CH2-	O	C(=O)CH3		S	N	-OCH3	H	p-CF3	CH
35	bond	O	-CH2-				S	N	F	H	p-CF3	CH
36	bond	O	-CH2-	N	-CH2CH2CF3	H	S	N	-OCH3	H	p-CF3	CH

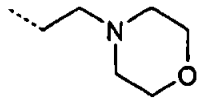
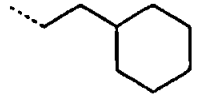
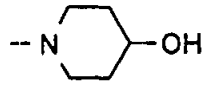
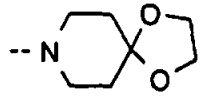
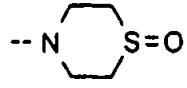
Example	Z	X	W	Y	R5	R6	U	V	R1	R3	R7	B
37	bond	O	-CH2-	N		H	S	N	-OCH3	H	p-CF3	CH
38	bond	O	-CH2-	N		H	S	N	-OCH3	H	p-CF3	CH
39	bond	O	-CH2-	N		H	S	N	-OCH3	H	p-CF3	CH
40	bond	O	-CH2-	N		H	S	N	-OCH3	H	p-CF3	CH
41	bond	O	-CH2-	N		H	S	N	-OCH3	H	p-CF3	CH
42	bond	O	-CH2-				S	N	-OCH3	H	p-CF3	CH
43	bond	O	-CH2-	N	-(CH2)2-OH	-(CH2)2-OH	S	N	-OCH3	H	p-CF3	CH
44	bond	O	-CH2-	N	-CH2CH2S(=O)CH3	H	S	N	-OCH3	H	p-CF3	CH

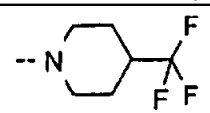
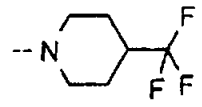
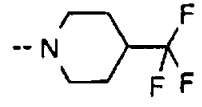
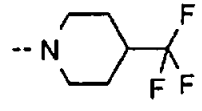
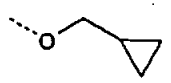
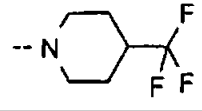
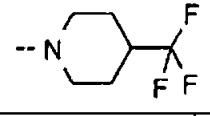
Example	Z	X	W	Y	R5	R6	U	V	R1	R3	R7	B
45	bond	O	-CH2-				S	N	-OCH3	H	p-CF3	CH
46	bond	O	-CH2-				S	N	-OCH3	H	p-CF3	CH
47	bond	O	-CH2-	N	-(CH2)2CH3	H	S	N	-CH3	H	p-CF3	CH
48	bond	O	-CH2-	N	-(CH2)2OCH3	H	S	N	-CH3	H	p-CF3	CH
49	bond	O	-CH2-	N		H	S	N	-CH3	H	p-CF3	CH
50	bond	O	-CH2-	N		H	S	N	-CH3	H	p-CF3	CH
51	bond	O	-CH2-	N		H	S	N	-CH3	H	p-CF3	CH
52	bond	O	-CH2-	N		H	S	N	-CH3	H	p-CF3	CH
53	bond	O	-CH2-	N	-(CH2)2N(CH3)2	H	S	N	-CH3	H	p-CF3	CH
54	-(CH2)2-	O	-CH2-	bond	H	-	O	N	-Cl	H	p-CF3	CH

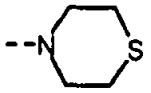
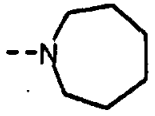
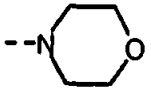
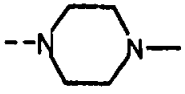
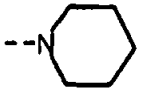
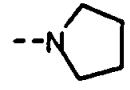
Example	Z	X	W	Y	R5	R6	U	V	R1	R3	R7	B
55	-CH=CH-	O	-CH2-	O	-CH3	-	O	N	-Cl	H	p-OCH3	CH
56	-CH2OCH2-	O	-CH2-	bond	H	-	O	N	-Cl	H	H	CH
57	-CH2-	O	-CH2-	bond	H	-	O	N	-Cl	H	p-OCH3	CH
58	-CH=CH-	O	-CH2-	O	-CH3	-	S	N	-Cl	H	p-CF3	CH
59	bond	O	-CH2-	O	-CH2CF3	-	O	N	-Cl	H	p-CF3	CH
60	bond	O	-CH2-	N	-(CH2)2OCH3	-CH2CH3	O	N	-CH3	H	p-OCH3	CH
61	bond	O	-CH2-	N	-CH2CH3	-CH2CH3	O	N	-CH3	H	p-OCH3	CH
62	bond	O	-CH2-				O	N	-CH3	H	p-OCH3	CH
63	bond	O	-CH2-				O	N	-CH3	H	p-OCH3	CH
64	bond	O	-CH2-	N	-(CH2)2OCH3	-(CH2)2OCH3	O	N	-CH3	H	p-OCH3	CH
65	bond	O	-CH2-				O	N	-CH3	H	p-OCH3	CH

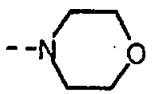
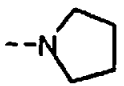
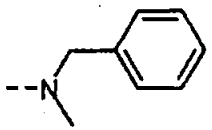
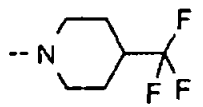
Example	Z	X	W	Y	R5	R6	U	V	R1	R3	R7	B
66	bond	O	-CH2-				N	O	-CH3	H	p-OCH3	CH
67	bond	O	-CH2-				N	O	-CH3	H	p-OCH3	CH
68	bond	O	-CH2-				N	O	-CH3	H	p-OCH3	CH
69	bond	O	-CH2-	N	-(CH2)2OCH3	-(CH2)2OCH3	N	O	-CH3	H	p-OCH3	CH
70	bond	O	-CH2-				O	N	Cl	H	p-OCH3	CH
71	bond	O	-CH2-	N	-(CH2)2OCH3	-CH2CH3	O	N	Cl	H	p-OCH3	CH
72	bond	O	-CH2-	N	-(CH2)2OCH3	-(CH2)2OCH3	O	N	Cl	H	p-OCH3	CH
73	bond	O	-CH2-				S	N	Cl	H	p-CF3	CH

Example	Z	X	W	Y	R5	R6	U	V	R1	R3	R7	B
74	bond	O	-CH2-				S	N	Cl	H	p-CF3	CH
75	bond	O	-CH2-				S	N	Cl	H	p-CF3	CH
76	bond	O	-CH2-	N	-(CH2)2OCH3	-CH2CH3	S	N	Cl	H	p-CF3	CH
77	bond	O	-CH2-	N	-(CH2)2OCH3	-(CH2)2OCH3	S	N	Cl	H	p-CF3	CH
78	bond	O	-CH2-				S	N	Cl	H	p-CF3	CH
79	bond	O	-CH2-	N	-CH2CH3	-CH2CH3	S	N	Cl	H	p-CF3	CH
80	bond	O	-CH2-				S	N	Cl	H	p-CF3	CH
81	bond	O	-CH2-				S	N	Cl	H	p-CF3	CH

Example	Z	X	W	Y	R5	R6	U	V	R1	R3	R7	B
82	bond	O	-CH2-	O		-	S	N	Cl	H	p-CF3	CH
83	bond	O	-CH2-	O		-	S	N	Cl	H	p-CF3	CH
84	bond	O	bond	bond	CHF2	-	S	N	Cl	H	p-OCH3	CH
85	bond	O	-CH2-				S	N	-OCH3	H	p-CF3	CH
86	bond	O	-CH2-				S	N	-OCH3	H	p-CF3	CH
87	bond	O	-CH2-				S	N	-OCH3	H	p-CF3	CH
88	bond	O	-CH2-				S	N	-OCH3	H	p-CF3	CH
89	bond	O	-CH2-	S	CH3	-	S	N	-OCH3	H	p-CF3	CH
90	bond	O	-CH2-	S(O)	CH3	-	S	N	-OCH3	H	p-CF3	CH
91	bond	O	-CH2-	S(O)2	CH3	-	S	N	-OCH3	H	p-CF3	CH

Example	Z	X	W	Y	R5	R6	U	V	R1	R3	R7	B
92	bond	O	-CH2-	N	H	H	S	N	F	H	p-CF3	CH
93	bond	O	-CH2-	N	-C(O)CH3	H	S	N	F	H	p-CF3	CH
94	bond	O	-CH2-				S	N	-OCHF2	H	p-CF3	CH
95	bond	O	-CH2-				S	N	-OCHF2	F	p-CF3	CH
96	bond	O	-CH2-				S	N	-OiPr	H	p-CF3	CH
97	bond	O	-CH2-				S	N		H	p-CF3	CH
98	bond	O	-CH2-				S	N	-OCH2CF3	H	p-CF3	CH
99	bond	O	-CH2-				S	N	- OCH2CF3	F	p-CF3	CH
100	bond	O	-(CH2)3-	bond	-CH3	-	S	N	-CH3	H	p-CF3	N

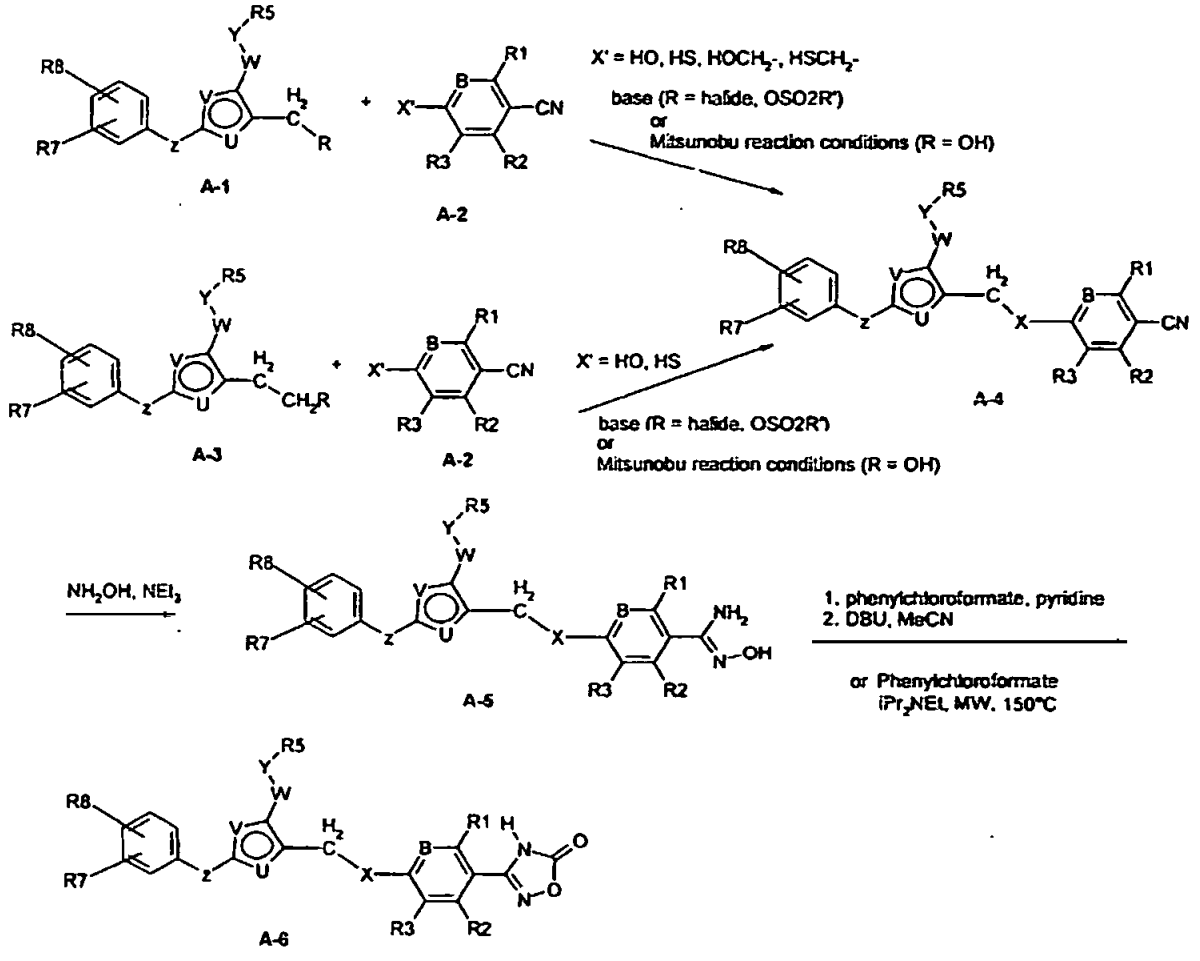
Example	Z	X	W	Y	R5	R6	U	V	R1	R3	R7	B
101	bond	O	-(CH2)3-	S	CH3	-	S	N	-OCH3	H	p-CF3	CH
102	bond	O	-(CH2)3-	S(O)2	CH3	-	S	N	-OCH3	H	p-CF3	CH
103	bond	O	-(CH2)3-				S	N	-OCH3	H	p-CF3	CH
104	bond	O	-(CH2)3-				S	N	-OCH3	H	p-CF3	CH
105	bond	O	-(CH2)3-				S	N	-OCH3	H	p-CF3	CH
106	bond	O	-(CH2)3-				S	N	-OCH3	H	p-CF3	CH
107	bond	O	-(CH2)3-				S	N	-OCH3	H	p-CF3	CH
108	bond	O	-(CH2)3-				S	N	-OCH3	H	p-CF3	CH

Example	Z	X	W	Y	R5	R6	U	V	R1	R3	R7	B
109	bond	O	-(CH2)3-				S	N	-F	H	p-CF3	CH
110	bond	O	-(CH2)3-				S	N	-F	H	p-CF3	CH
111	bond	O	-(CH2)3-				S	N	-OCH3	H	p-CF3	CH
112	bond	O	-(CH2)3-				S	N	-OCH3	H	p-CF3	CH

Processes

The compounds of the general formula I according to the invention can be obtained as outlined to the reaction schemes below:

Process A



A compound of general formula A-2 where X' is -OH, -SH, - CH2OH or -CH2SH and R1, R2, R3, B as defined above is either reacted with a compound of general formula A-1 where R is halide (I, Br, Cl) or a sulfonate (OSO_2CH_3, $OSO_2C_6H_4CH_3$) and R5, R7, R8, U, V, W, Y and Z are as defined above in the presence of a base as cesium

The potency of some of the described examples in the human GAL4 assays are indicated in the following table :

Example	PPARdelta EC50 (μM)	PPARalpha EC50 (μM)
1	0.056	0.830
9	0.056	0.729
15	0.153	>10
19	0.171	1.19
33	0.299	1.41
51	0.228	1.21
55	0.003	0.319
56	0.358	2.19
68	0.661	1.20
77	0.003	0.530
83	0.012	0.398
89	0.153	2.62
94	0.018	0.664
100	0.008	0.315
102	0.022	1.780
103	0.008	0.483

5

carbonate or sodium hydride in a solvent as dimethylformamide or with an alcohol of general formula A-1 where R = OH and R5, R7, R8, U, V, W, Y and Z are as defined above under Mitsunobu reaction conditions (triphenylphosphine, diethylazodicarboxylate for instance) in an apolar solvent as dichloromethane to give a compound of general formula A-4 where X= O, S, $-OCH_2-$ or $-SCH_2-$. This process can be applied to a compound of general formula A-3 where R is halide (I, Br, Cl) or a sulfonate (OSO_2CH_3, OSO_2PhCH_3) and R5, R7, R8, U, V, W, Y and Z are as defined above or with an alcohol of general formula A-3 where R = OH and R5, R7, R8, U, V, W, Y and Z are as defined above under reaction conditions as previously described to lead to a compound of general formula A-4 where X= $-CH_2O-$ or $-CH_2O-$.

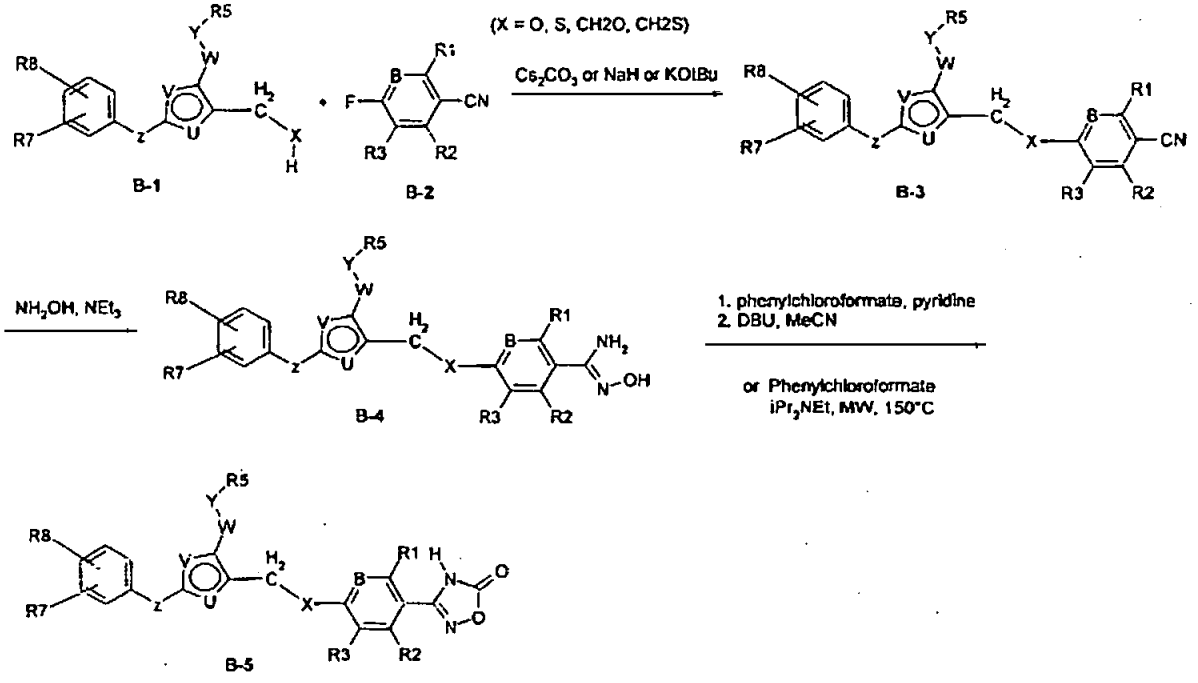
The compound of general formula A-4 is reacted with hydroxylamine hydrochloride in the presence of a base as triethylamine in a solvent as tetrahydrofuran and methanol to obtain a compound of general formula A-5. This reaction can be facilitated by heating the reaction mixture under microwave irradiation. This compound of general formula A-5 is converted to the product of general formula A-6 by reaction with phenylchloroformate in the presence of a base as pyridine or diisopropylethylamine followed by heating the reaction mixture with microwave irradiation to allow cyclization or alternatively isolating the resulting intermediate and treating it with a base as 1,8-diazabicyclo[5.4.0]undec-7-ene in a solvent as acetonitrile.

When R5 is H in the substrate A-5, the compound of general formula A-6 with R5= $C(=O)C_6H_5$ is formed which can be hydrolyzed with a hydroxide salt such as potassium hydroxide into a product of general formula A-6 where R5 is H.

Examples 54 – 59 were obtained according to process A.

Other compounds can be obtained accordingly or by known processes.

Process B

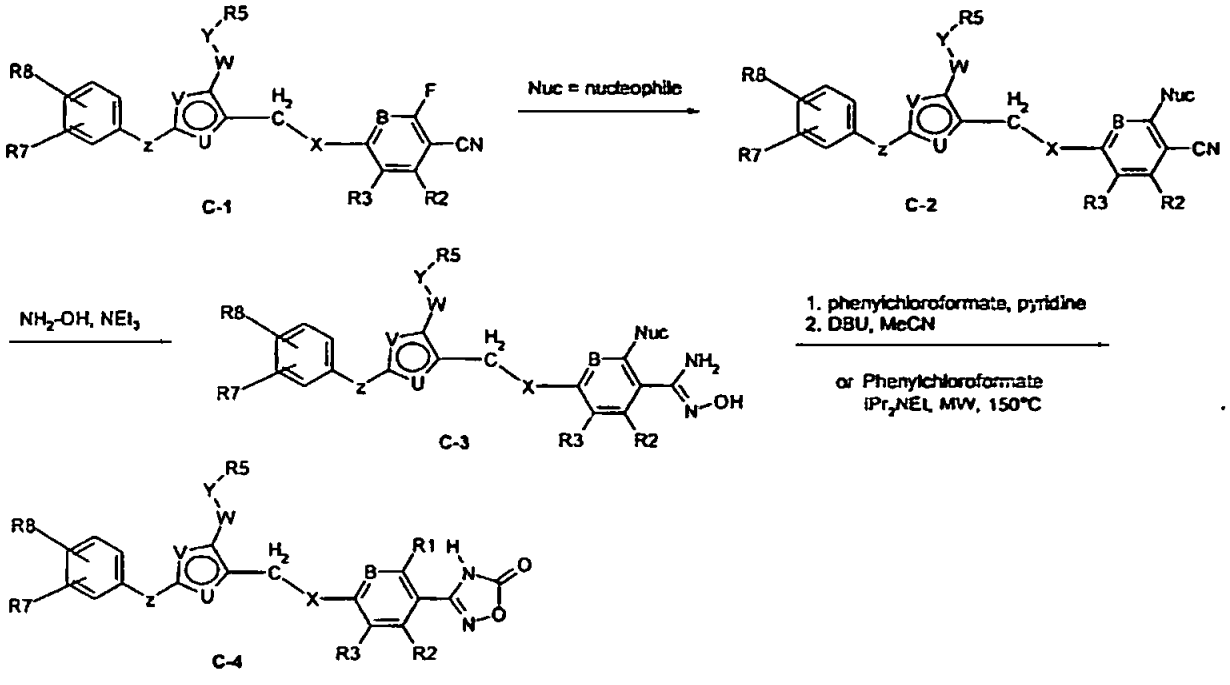


A compound of general formula B-1 where X is O, S, CH_2O or CH_2S and R5, R7, R8, U, V, W, Y and Z are as defined above is reacted with a fluoro-nitrile of general formula B-2 where B, R1, R2 and R3 are as defined above in the presence of a base such as cesium carbonate, sodium hydride or potassium tert-butoxide in a solvent such as dimethylformamide to give a compound of general formula B-3. This reaction can be performed by heating the reaction mixture at 60°C under microwave irradiation. As described in process A, compound B-3 is treated with hydroxylamine hydrochloride in the presence of a base such as triethylamine in a solvent as tetrahydrofuran and methanol to obtain a compound of general formula B-4. This reaction can be facilitated by heating the reaction mixture under microwave irradiation. Compound B-4 is converted to the product of general formula B-5 by reaction with phenylchloroformate in the presence of a base as pyridine or diisopropylethylamine followed by heating the reaction mixture under microwave irradiation to allow cyclization or alternatively isolating the resulting intermediate and treating it with a base as 1,8-diazabicyclo[5.4.0]undec-7-ene in a solvent as acetonitrile.

Examples 1 – 15, 94-98 and example 100 were obtained according to process B.

Other compounds can be obtained accordingly or by known processes.

Process C



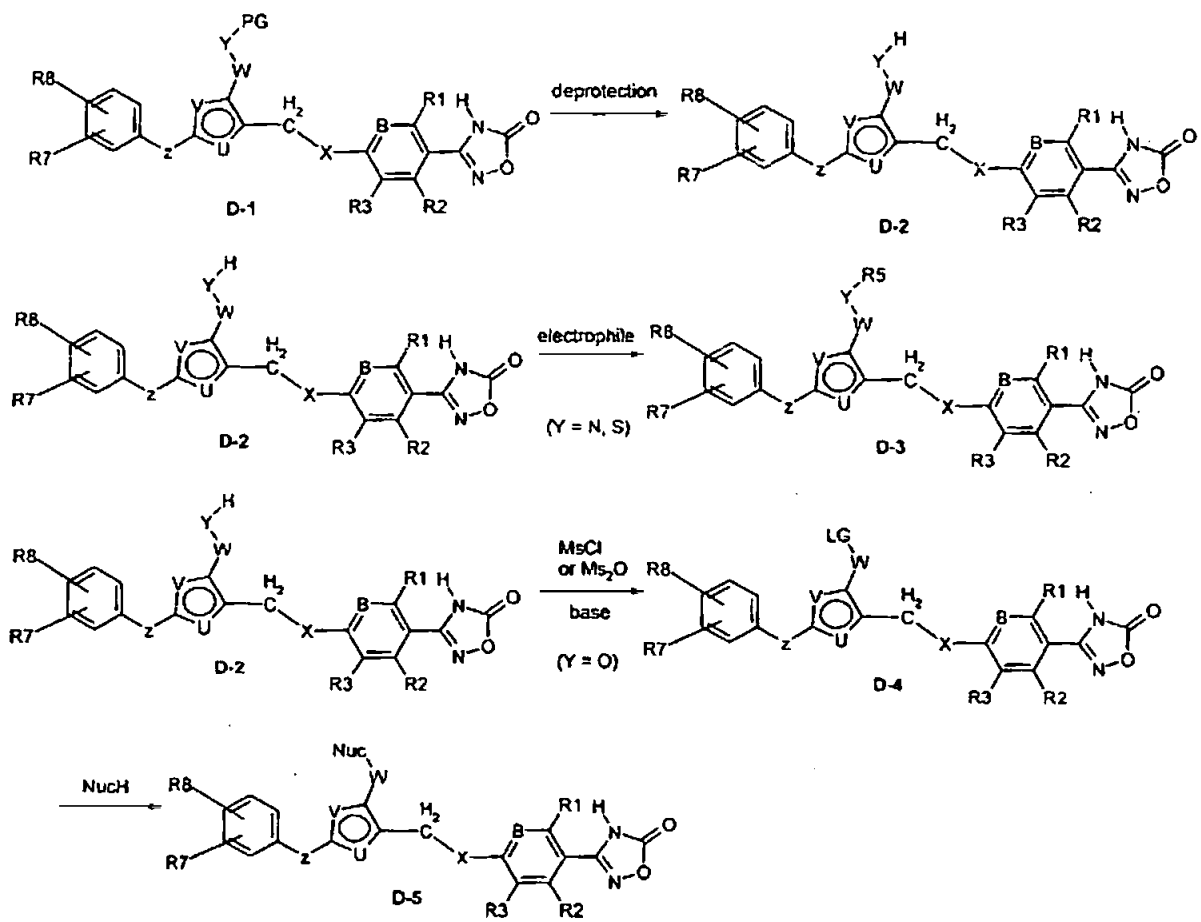
A compound of general formula C-1 where R1 = F and B, R2, R3, R5, R7, R8, U, V, W, Y and Z are as defined above is reacted with a nucleophile, e.g. sodium methylate, to obtain a compound of general formula C-2. A compound of general formula C-2 is reacted with hydroxylamine hydrochloride in the presence of a base as triethylamine in a solvent as tetrahydrofuran and methanol to obtain a compound of general formula C-3. This reaction can be facilitated by heating the reaction mixture under microwave irradiation. A compound of general formula C-3 is converted to the product of general formula C-4 by reaction with phenylchloroformate in the presence of a base as pyridine or diisopropylethylamine followed by heating the reaction mixture with microwave irradiation to allow cyclization or alternatively isolating the resulting intermediate and

treating it with a base as 1,8-diazabicyclo[5.4.0]undec-7-ene in a solvent as acetonitrile.

Example 99 was obtained according to process C.

Other compounds can be obtained accordingly or by known processes.

Process D:



A compound of general formula D-1 where PG is a protecting group and R1, R2, R3, R7, R8, B, U, V, W, Y and X are as defined above is deprotected under appropriate reaction conditions depending on Y and its protecting group according to methods known by the person skilled of the art to give the compound of general formula D-2. If

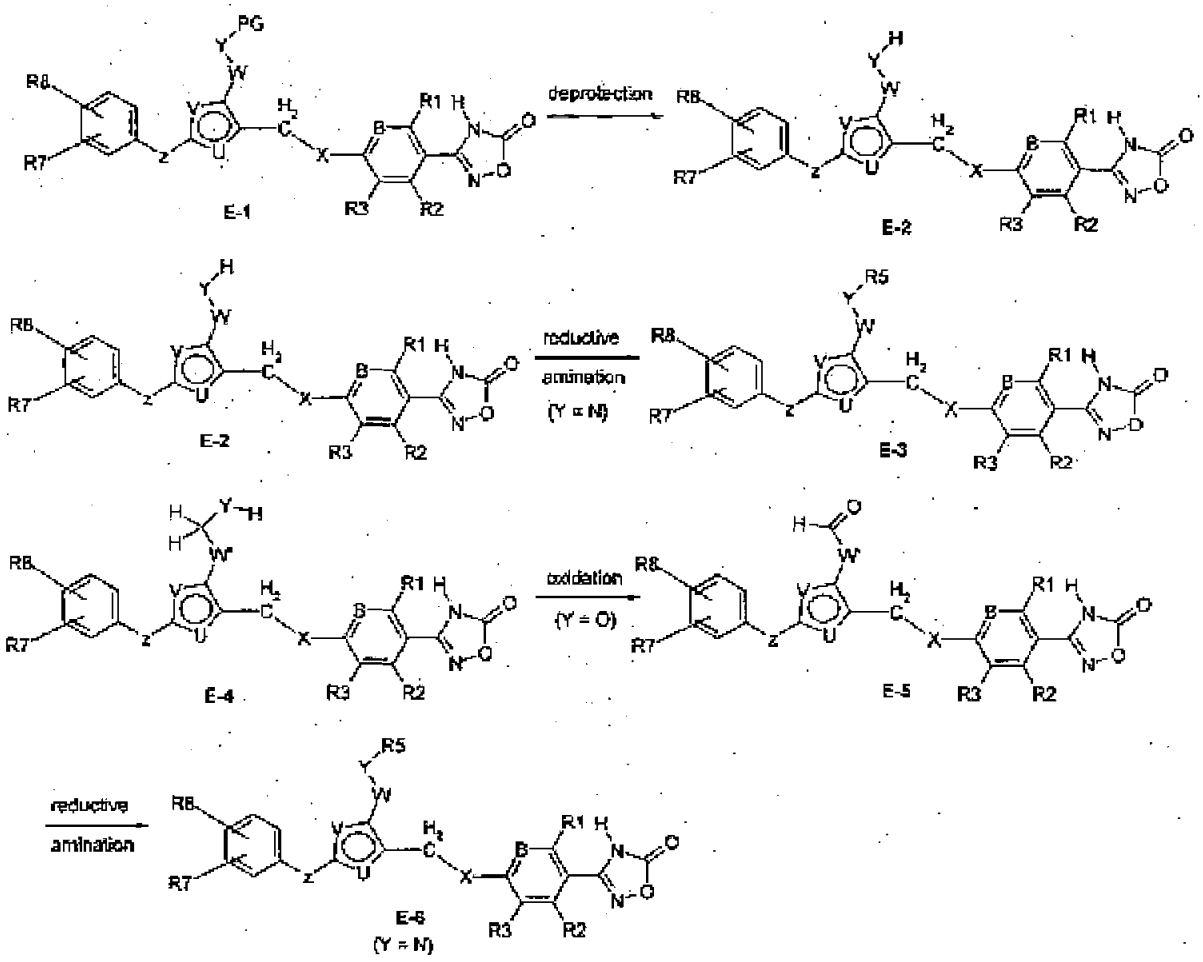
Y = N, the compound of formula D-2 can be reacted with an electrophile such as an alkyl halide or an acyl halide in the presence of a base such as diisopropyl ethyl amine in a polar solvent such dimethylformamide to obtain the compound of general formula D-3 where Y = N. If Y = S, the compound of formula D-2 can be reacted with an electrophile such as an alkyl halide or an acyl halide in the presence of a stronger base such as sodium methoxide in a polar solvent such dimethylformamide to obtain the compound of general formula D-3 where Y = S.

If Y = O, the alcohol of formula D-2 can be converted to an electrophile of general formula D-4 such as a halide (LG = Br, I, Cl) or as a sulfonate, for example mesylate (LG = OSO_2CH_3) by treatment with mesyl chloride or mesyl anhydride in the presence of a base as triethylamine in a polar solvant as dimethylformamide. The compound of general formula D-4 is reacted with a nucleophile, for example a primary or secondary amine or a sodium salt of a thiol or an alcohol, in a polar solvent such a dimethylformamide to obtain the compound of general formula D-5. This reaction can be facilitated by heating the reaction mixture under microwave irradiation.

Example 16, 42-46, 85-91, 101-112 were obtained according to process D.

Other compounds can be obtained accordingly or by known processes.

Process E:



A compound of general formula E-1 where PG is a protecting group and R1, R2, R3, R7, R8, B, U, V, W, Y and X are as defined above is deprotected under appropriate reaction conditions depending on Y and its protecting group according to methods known by the person skilled in the art to give the compound of general formula E-2. If Y = N, the amine of formula E-2 can be transformed into an amine of general formula E-3 by reductive amination following either a two-step procedure involving imine formation with an aldehyde and triethylamine in a solvent such as methanol then reduction by adding a reducing agent such as sodium borohydride, or a one-step

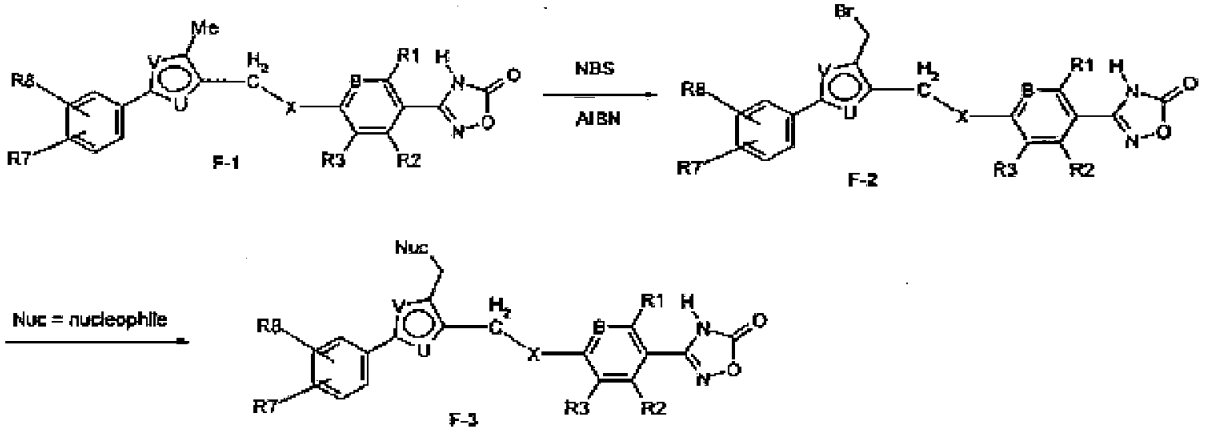
procedure using an aldehyde and a reducing agent such as sodium triacetoxyborohydride in a solvent as dichloromethane.

If Y = O and W = W'CH2 in E-2 where W' follows the definition of W previously cited, the corresponding primary alcohol of formula E-4 can be oxidized to an aldehyde of general formula E-5 with one of the methods known by the person skilled of the art such as treatment with Dess-Martin periodinane in a solvent as dichloromethane or dimethylformamide. The compound of general formula E-5 is converted into an amine of general formula E-6 by reductive amination following either a two-step procedure involving imine formation with a primary or secondary amine and triethylamine in a solvent such as methanol then reduction by adding a reducing agent such as sodium borohydride, or a one-step procedure using a primary or secondary amine and a reducing agent such as sodium triacetoxyborohydride in a solvent as dichloromethane.

Examples 35 – 41 and 47 - 53 were obtained according to process E.

Other compounds can be obtained accordingly or by known processes.

Process F :



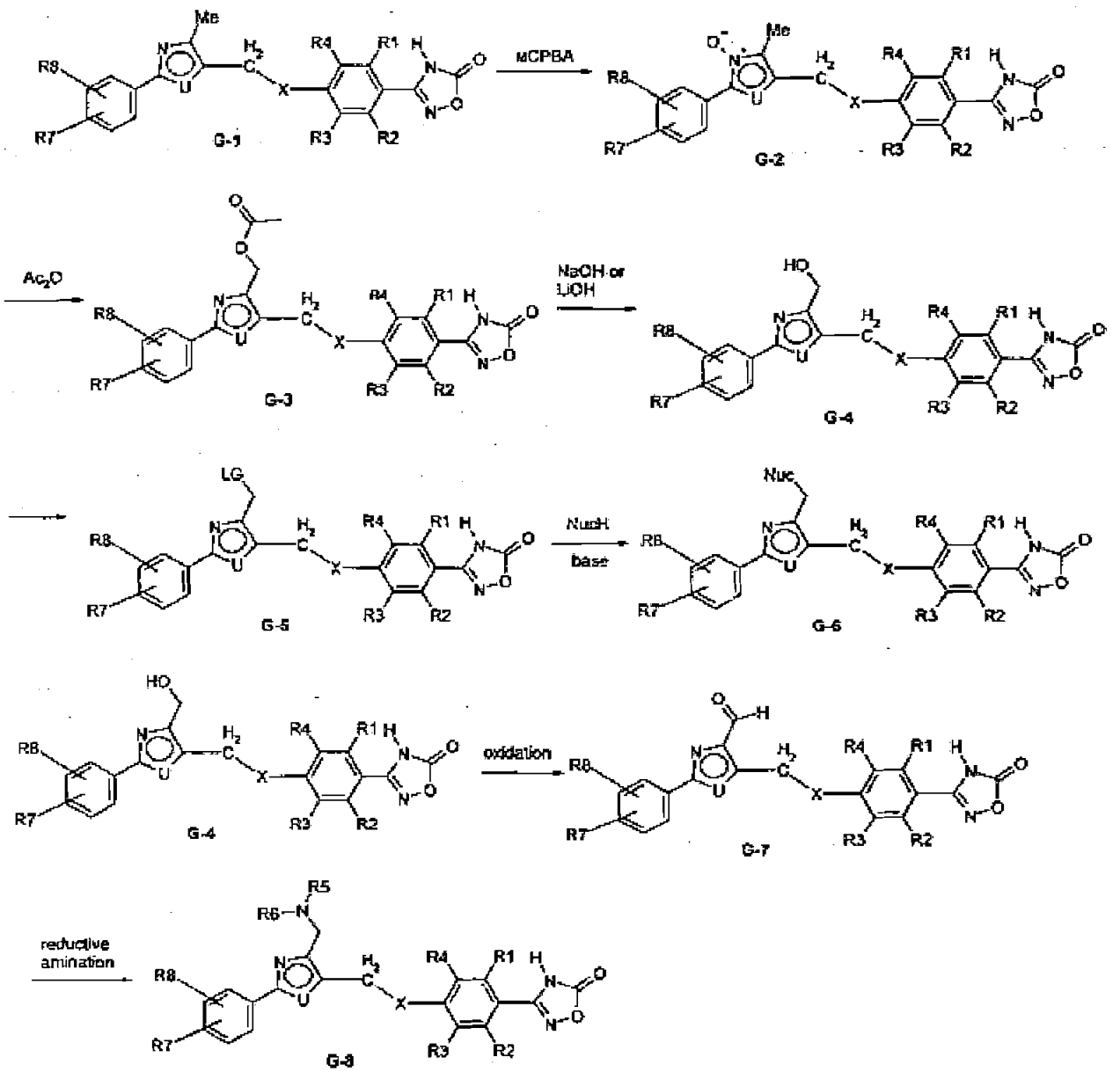
A compound of general formula F-1 where WYR5 = CH3 and R1, R2, R3, R7, R8, B, U, V and X are as defined above is reacted with N-bromosuccinimide or bromine in an inert solvent such as carbon tetrachloride (an inert polar co-solvent such as

hexafluoroisopropanol may be added to help solubilize the starting material) in the presence of a radical initiator such as AIBN or a peroxide to obtain the compound of general formula F-2. The resulting bromide of general formula F-2 is displaced with a nucleophile, for example a primary or secondary amine, in a polar solvent such a dimethylformamide to give a compound of general formula F-3.

Examples 17 – 32, 92-93 were obtained according to process F.

Other compounds can be obtained accordingly or by known processes.

Process G:



5

A compound of general formula G-1 where B=C(R4), WYR5 = CH3, V = N, X = O or OCH_2 and R1, R2, R3, R4, R7, R8 and U are as defined above is reacted with an oxidant such as meta-chloroperbenzoic acid MCPBA in a solvent such as dichloromethane (a polar co-solvent such as hexafluoroisopropanol may be added to

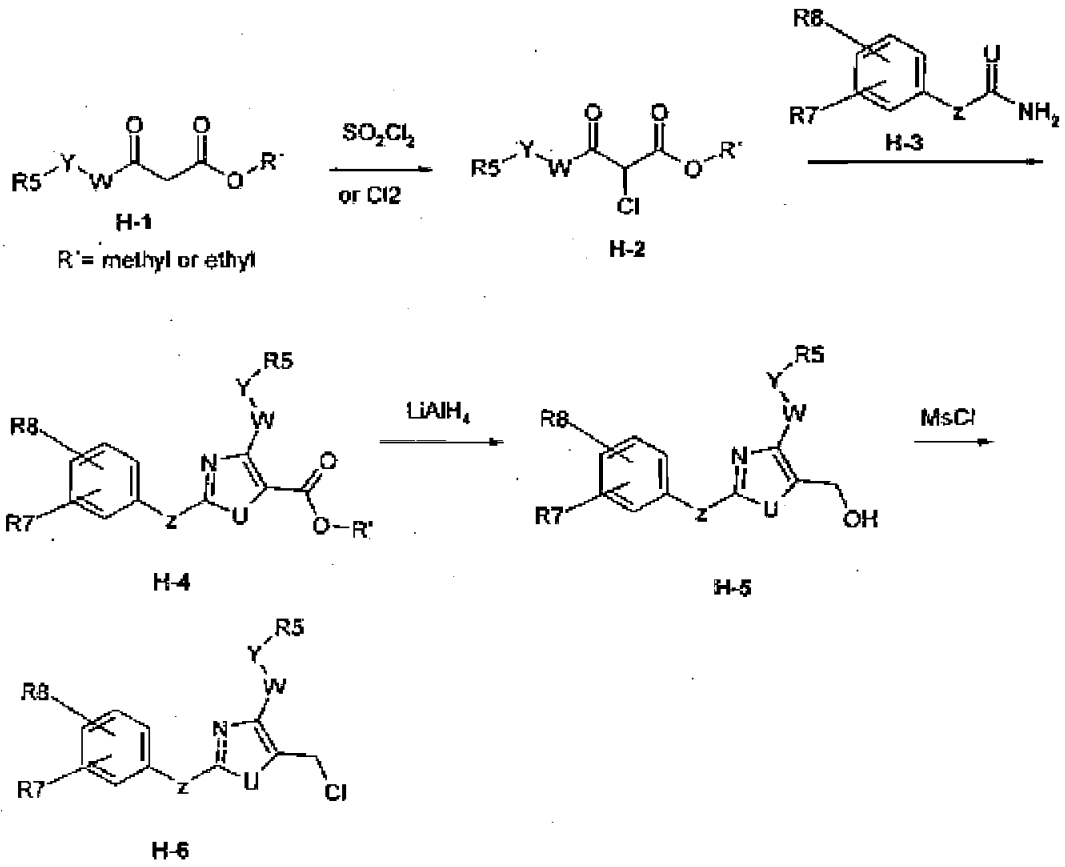
help solubilize the starting material) to give the N-oxide of general formula G-2. The compound of general formula G-2 is subjected to a Polonovsky-type rearrangement by heating it with acetic anhydride to lead to an acetate of general formula G-3. This acetate can be hydrolyzed to the corresponding alcohol of general formula G-4 with for instance lithium hydroxide in water and an organic solvent such as methanol or tetrahydrofuran. The alcohol of general formula G-4 can be converted to an electrophile of general formula G-5 such as a halide (LG = Br, I, Cl) or as a sulfonate, for example mesylate (LG = OSO_2CH_3) by treatment with mesyl chloride or mesyl anhydride in the presence of a base as triethylamine in a polar solvant as dimethylformamide. The compound of general formula G-5 is reacted with a nucleophile, for example a primary or secondary amine, to obtain the compound of general formula G-6.

Alternatively, the alcohol of general formula G-4 can be oxidized to an aldehyde of general formula G-7 with one of the methods known by the person skilled of the art such as treatment with manganese dioxide in a solvent as dichloromethane or dimethylformamide or with Dess-Martin periodinane. The compound of general formula G-7 is converted into an amine of general formula G-8 by reductive amination following either a two-step procedure involving imine formation with a primary or secondary amine and triethylamine in a solvent such as methanol then reduction by adding a reducing agent such as sodium borohydride, or a one-step procedure using a primary or secondary amine and a reducing agent such as sodium triacetoxyborohydride in a solvent as dichloromethane.

Examples 33 – 34 were obtained according to process G.

Other compounds can be obtained accordingly or by known processes.

Process H:

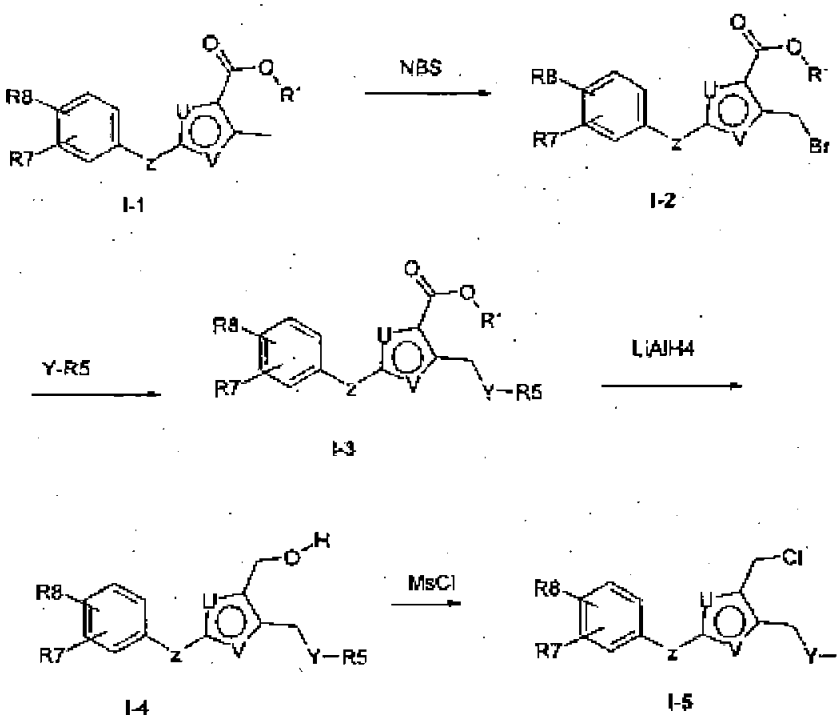


A 3-oxo-carboxylic acid methyl- or ethyl ester of general formula H-1 where R5, Y and W are as defined above is reacted with sulfuryl chloride or chlorine to yield the corresponding chloride of general formula H-2. This compound of general formula H-2 is reacted with a benzamide or thiobenzamide of general formula H-3, where U is S or O and R7, R8 and Z are as defined above to obtain a phenylthiazole or phenyloxazole ester of general formula H-4. The ester of general formula H-4 is reduced with a reducing agent, for example lithium aluminium hydride, to the alcohol of general formula H-5. The alcohol of general formula H-5 is reacted with methanesulfonyl chloride in the presence of a base as triethylamine in a solvent as dichloromethane to obtain the building block of general formula H-6, where R5, R7, R8, U, W, Y and Z are as defined above.

Other compounds can be obtained accordingly or by known processes.

Process I:

This process is used for synthesizing the building blocks I-4, which corresponds to general formula A-1 of process A, where R = OH , W is CH2 , R9 and R10 are H, Z is bond, (C2-C6) alkyl, -CH=CH-, -C≡C- and U, V, Y, R5, R7 and R8 are as defined and, I-5 which corresponds to general formula A-3 of process A, where R = Cl, W is CH2 , R9 and R10 are H, Z is bond, (C2-C6) alkyl, -CH=CH-, -C≡C- and U, V, Y, R5, R7 and R8 are as defined.



The oxazole or thiazole ester of general formula I-1 where Z is a bond, (C2-C6) alkyl, -CH=CH- or -C≡C- , W is CH2, Y is a bond, R5 is H and U, V, R7 and R8 are as defined, is brominated by the treatment with N-bromosuccinimide in refluxing tetrachloromethane in the presence of a radical initiator like AIBN to yield the brominated product of general formula I-2. In case Z is (C2-C6) alkyl, the carbon atom directly attached to the oxazole or thiazole ring is brominated as well. The brominated product of general formula I-2 is reacted with a nucleophile Y-R5 where Y is OH or Y is NH(R6) and R5 is as defined in a polar solvent like tetrahydrofuran in the presence of a base like DBU to obtain a compound of general formula I-3. In case the carbon atom directly attached to the oxazole or thiazole ring of the compound of general formula I-2

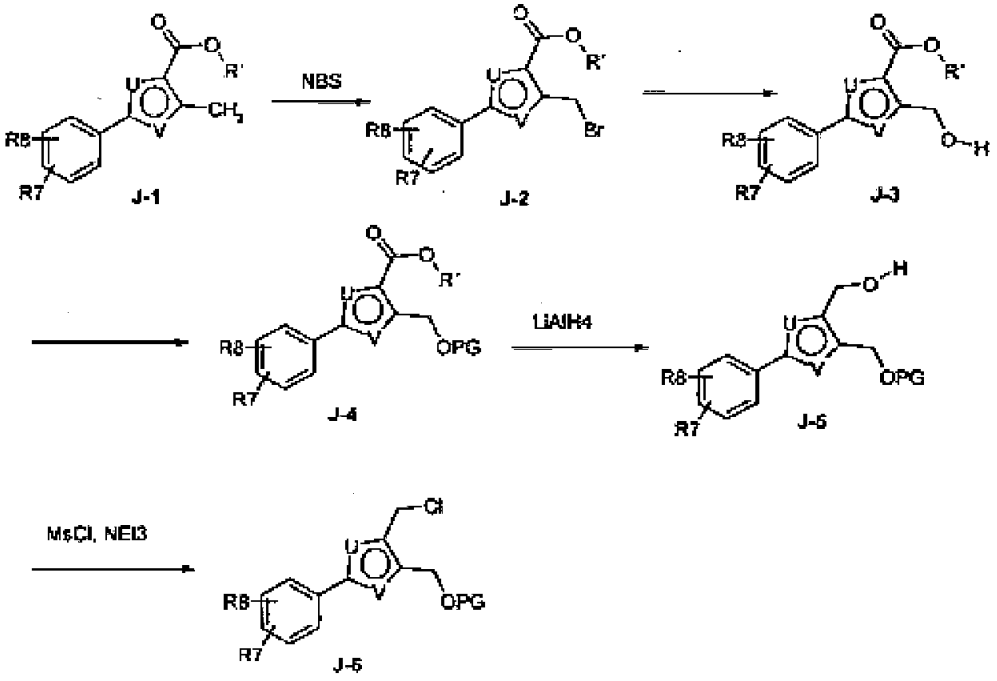
was brominated as well, this will eliminate under the reaction conditions to yield a double bond. In case Z is --CH2-CH2- the elimination takes place under the bromination conditions. The double bond can be hydrogenated with hydrogen in the presence of a palladium catalyst in a polar solvent as ethanol or methanol.

The ester of general formula I-3 is reduced with a reducing agent ,e.g. lithium aluminium hydride, to the alcohol of general formula I-4. The alcohol of general formula I-4 is reacted with methanesulfonyl chloride in the presence of a base as triethylamine in a solvent as dichloromethane to obtain the building block of general formula I-5.

Other compounds can be obtained accordingly or by known processes.

Process J:

This process is used for synthesizing the building blocks J-5 and J-6, which corresponds to general formula A-1 of process A, where R5 = PG (PG = protecting group) , Y = O, Z is a bond, W = -CH2 , R9 and R10 are H, R = -OH or –Cl and U, V, R7 and R8 are as defined above.



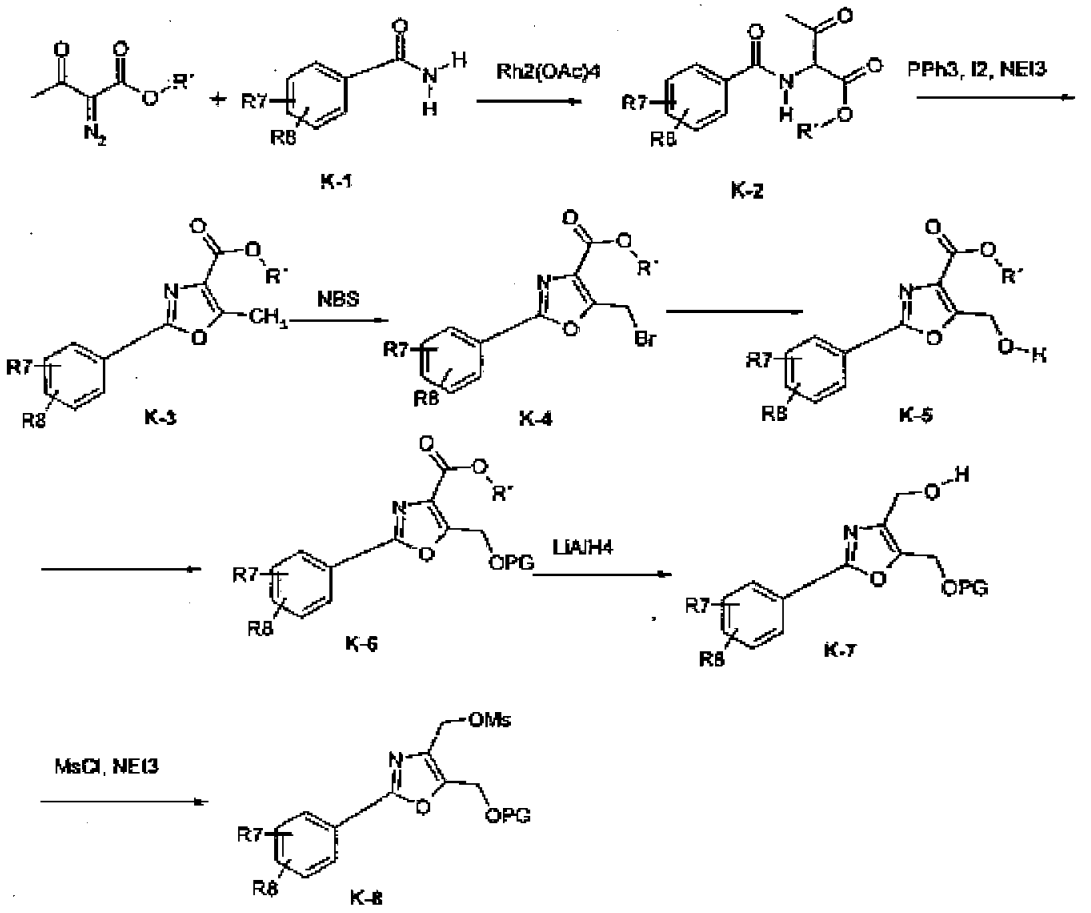
A compound of the general formula J-1 where R' is alkyl as methyl or ethyl, and U, V, R8 and R7 are as defined above is brominated upon treatment with N-bromosuccinimide in an apolar solvent as tetrachloromethane to obtain a compound of

general formula J-2. The bromide of general formula J-2 is converted into the alcohol of general formula J-3 upon treatment with silver trifluoroacetate in a solvent as dimethylformamide and subsequent heating of the resulting trifluoroacetate in a solvent as ethanol. The hydroxyl group of the compound of general formula J-2 is protected for example as a tetrahydropyranylether by treatment with 3,4-dihydro-2H-pyran in a solvent as dichloromethane in the presence of an acid as pyridinium para-toluenesulfonate to obtain a compound of general formula J-4. The ester of the compound of general formula J-4 is reduced with an agent as lithium aluminium hydride in a solvent as tetrahydrofuran to obtain the compound of general formula J-5, where R is OH. The hydroxyl group can be converted into a chlorine by treatment with methanesulfonylchloride in the presence of a base as triethylamine in a solvent as dichloromethane to obtain a compound of general formula J-6, where R is Cl.

Other compounds can be obtained accordingly or by known processes.

Process K:

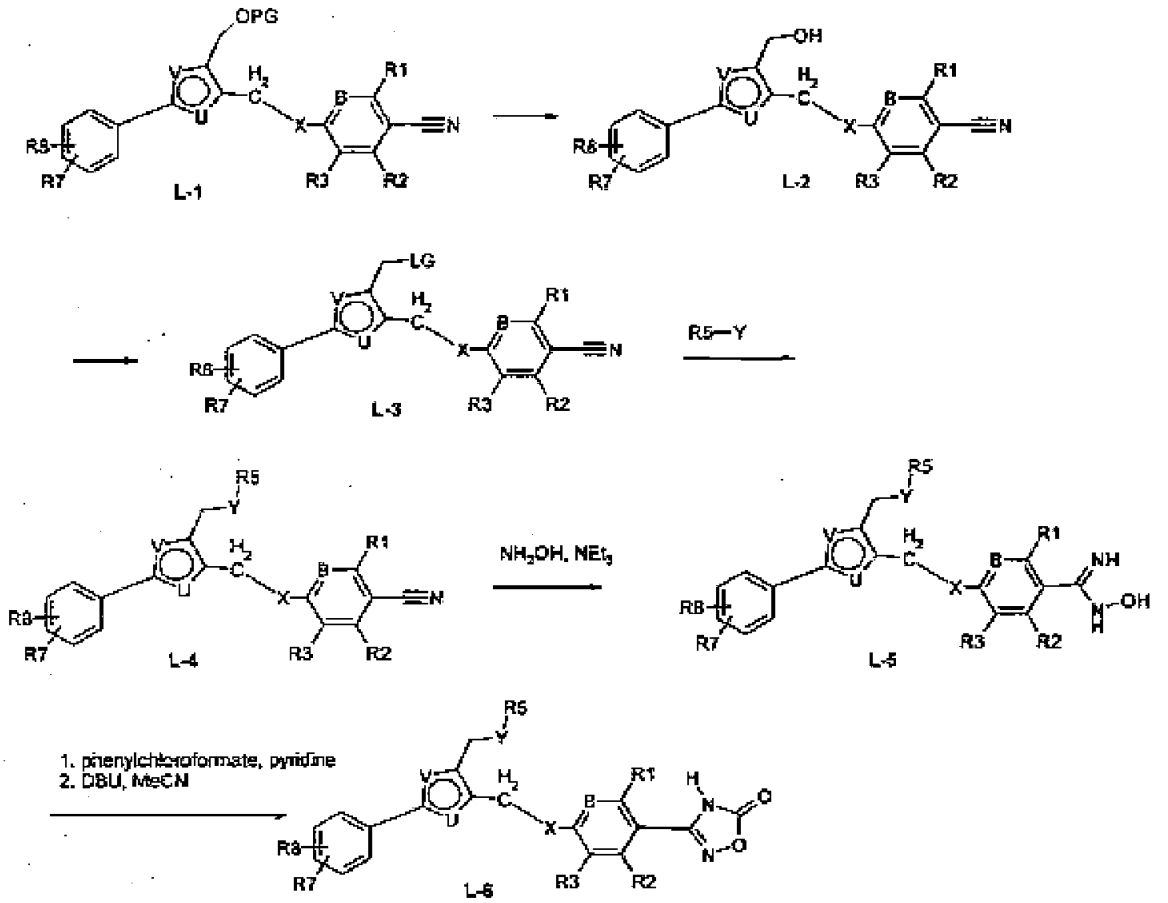
This process is used for synthesizing the building blocks K7 and K-8, which corresponds to general formula A-1 of process A, where R5 = PG (PG = protecting group) , Y = O, W = -CH2-, V is O and U is N, R = -OH or –OMs , R9 = H, R10 = H, Z is a bond R8 and R7 are as defined above.



Methyl 2-diazo-3-oxobutanoate (R´= Me) or Ethyl-2-diazo-3-oxobutanoate (R´= Et) is reacted with a benzamide of general formula K-1, where R8 and R7 are as defined above in the presence of dirhodium tetraacetate in an apolar solvent as 1,2-dichloroethane to obtain a compound of general formula K-2. The compound of general formula K-2 is cyclized to obtain a compound of general formula K-3 upon treatment with triphenylphosphine and iodine in an apolar solvent as dichloromethane. The compound of the general formula K-3 is brominated upon treatment with N-bromosuccinimide in an apolar solvent as tetrachloromethane to obtain a compound of general formula K-4. The bromide of general formula K-4 is converted into the alcohol of general formula K-5 upon treatment with silver trifluoroacetate in a solvent as dimethylformamide and subsequent heating of the resulting trifluoroacetate in a solvent as ethanol. The hydroxyl group of the compound of general formula K-5 is protected for example as a tetrahydropyranylether by treatment with 3,4-dihydro-2H-pyran in a solvent as dichloromethane in the presence of an acid as pyridinium para-

toluenesulfonate to obtain a compound of general formula K-6. The ester of the compound of general formula K-6 is reduced with a reducing agent as lithium aluminium hydride in a solvent as tetrahydrofuran to obtain the compound of general formula K-7. The hydroxyl group can be converted into a mesylate by treatment with methanesulfonylchloride in the presence of a base as triethylamine in a solvent as dichloromethane to obtain a compound of general formula K-8.

Process L



A compound of the general formula L-1 (which can be synthesized according to process A, where the substituent W-Y-R5 of building blocks A-1 is -CH2-OPG; synthesis of this building block is described in process J and K) where B, U, V, X, R1, R2, R3 , R4 , R7 and R8 are as defined and PG means a protecting group as for example a tetrahydropyranylether. The protecting group of the compound of the general formula L-1 is removed, in case PG is a tetrahydropyranylether for example by treatment with an acid in polar solvent as methanol to obtain a compound of general formula I-2. The hydroxyl group of the compound of general formula L-2 is converted into a leaving group (LG) for example a mesylate or chloride by treatment with methanesulfonylchloride in the presence of a base as triethylamine in a solvent as dichloromethane to obtain a compound of general formula L-3. The compound of

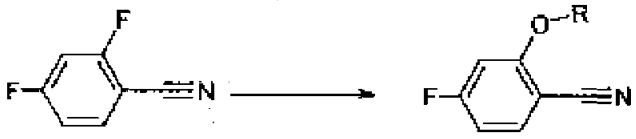
general formula L-3 is reacted with an nucleophile Y-R5 where Y is OH or Y is NH(R6) and R5 is as defined in a polar solvent like tetrahydrofuran in the presence of a base like DBU to obtain a compound of general formula L-4. The compound of the general formula L-4 is reacted with hydroxylamine hydrochloride in the presence of a base as triethylamine in a solvent as tetrahydrofuran and methanol to obtain a compound of the general formula L-5. A compound of the general formula L-5 is converted to the product of general formula L-6 by reaction with phenylchloroformate in the presence of a base as pyridine and treating this intermediate with a base as 1,8-diazabicyclo[5.4.0]undec-7-ene in a solvent as acetonitrile.

Examples 60 – 83 were obtained according to process L.

Other compounds can be obtained accordingly or by known processes.

Process M:

This process is used for synthesizing the building blocks M-2, which corresponds to general formula B-2 of process B, where B = C(R4), R1 = OR, R is (C1-C4) alkyl or (C0-C2) alkylene-(C3-C6)cycloalkyl wherein alkyl and alkylene are unsubstituted or mono, di- or trisubstitued by F, and where R2, R3 and R4 are H.



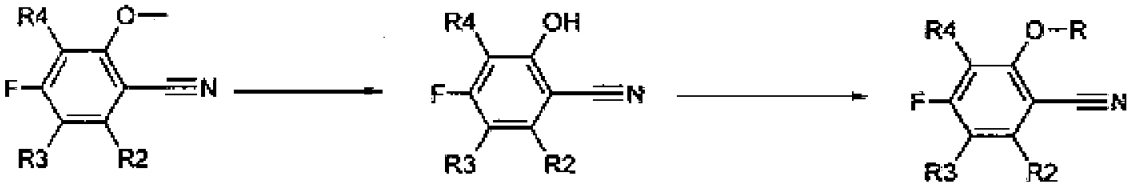
M-1 M-2

2,4-Difluoro-benzonitrile of formula M-1 is treated with an alcohol ROH in a solvent such as tetrahydrofuran in presence of a base such as potassium tert-butoxide at 0-5°C to give the ether of general formula M-2 where R is (C1-C4) alkyl or (C0-C2)alkylene-(C3-C6)cycloalkyl wherein alkyl and alkylene are unsubstituted or mono, di- or trisubstitued by F.

Other compounds can be obtained accordingly or by known processes.

Process N:

This process is used for synthesizing the building blocks N-3, which corresponds to general formula B-2 of process B, where B = C(R4), R1 = OR, R is (C1-C4)alkyl or (C0-C2)alkylene-(C3-C6)cycloalkyl wherein alkyl and alkylene are unsubstituted or mono, di- or trisubstitued by F, and where R2, R3 and R4 are as defined above.



N-1 N-2 N-3

The aryl methyl ether of general formula N-1 where R2, R3 and R4 are as defined above, is demethylated by the treatment with aluminium trichloride in refluxing dichloroethane to give the phenol of general formula N-2. The phenol of general formula N-2 is reacted with an electrophile RX where X is a leaving group such as halide or a sulfonate in a polar solvent like dimethylformamide in the presence of a base like potassium carbonate to obtain a compound of general formula N-3. When methyl chlorodifluororacetate is used as electrophile and the reaction mixture is heated to 60-120°C in a solvent such as dimethylformamide or dimethylacetamide, the compound of general formula N-3 where R is CHF2 is obtained.

Other compounds can be obtained accordingly or by known processes.

List of abbreviation:

Ac	acetyl
AIBN	2,2'-azobis(2-methylpropionitrile)
Bn	benzyl
iBu	isobutyl
tBu	tert-Butyl
BuLi	n-butyllithium
Bz	benzoyl
CI	Chemical ionization (MS)
Cy	cyclohexyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEAD	diethylazodicarboxylate
DCI	Direct chemical ionization (MS)
DCM	dichloromethane
DMAP	N,N-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
EE	ethyl acetate
eq	equivalents
EI	Electron impact ionization (MS)

ESI	electrospray-Ionization (MS)
FG	Functional group
F-TEDA	1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
Hal	halogen
HPLC	High performance liquid chromatography
LC-MS	liquid chromatography coupled with mass-spectroscopy
LG	Leaving Group
Me	methyl
MCPBA	Meta-chloroperbenzoic acid
MS	mass-spectroscopy
MsCl	Methanesulfonylchloride
MW	microwave
NBS	N-bromosuccinimide
NMR	Nuclear magnetic resonance
p	para
Pd/C	palladium on carbon
PG	Protecting Group
iPr	isopropyl
nPr	n-propyl

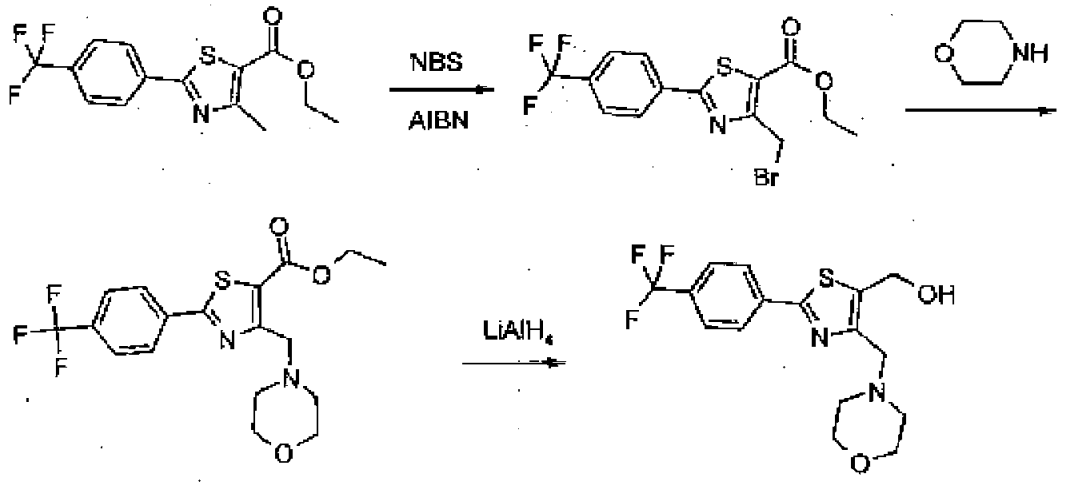
pTsOH	p-toluenesulfonic acid
Rf	retention factor (TLC)
tert	Tertiary
TLC	Thin layer chromatography
TMS	trimethylsilyl

Further compounds of the formula I can be prepared correspondingly or by known processes.

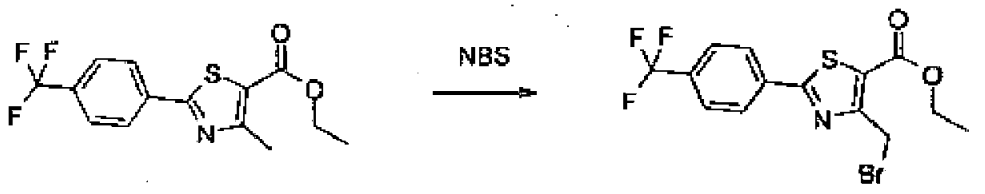
The experimental procedures for preparing the examples mentioned above are described below:

Building block synthesis according to process I:

2-(4-Trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-yl]-methanol

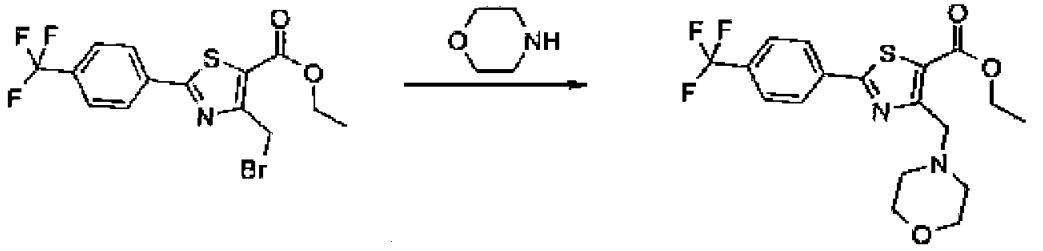


4-Bromomethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid ethyl ester[1]



To a solution of 1 g of 4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid ethyl ester in 8 mL of carbon tetrachloride was added portionwise 0.1 g of benzoyl peroxide and 0.56 g of NBS. The resulting mixture was heated to 80°C for 1.5 h. 0.1 g of NBS was added and the reaction mixture was heated to 80°C overnight. An additional 0.1 g of NBS was added and the reaction mixture was heated to 80°C for 2 h. It was then poured into water and extracted with dichloromethane. The organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (heptane 1/ toluene 1 followed by pure toluene) to give 1.02 g of 4-bromomethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid ethyl ester.
C14H11BrF3NO2S (394.21), MS(EI): 394 ($M+H^+$).

4-Morpholin-4-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid ethyl ester



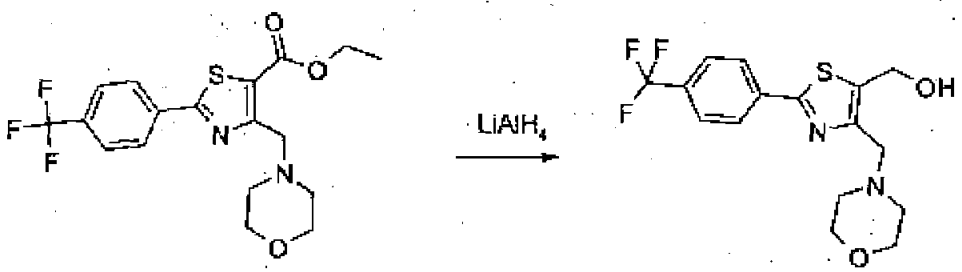
To a solution of 500 mg of 4-bromomethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid ethyl ester in 5 mL of acetonitrile was added 190 mg of potassium carbonate and 110.5 mg of morpholine. The resulting mixture was stirred at room temperature overnight. Water was added and the mixture was extracted with dichloromethane. The organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (gradient of dichloromethane/methanol from 100/0 to

[1] WO02067912

50/50) followed by washing of the collected solid with diisopropyl ether to give 355 mg of 4-morpholin-4-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid ethyl ester.

C18H19F3N2O3S (400.42), MS(EI): 400 (M^+).

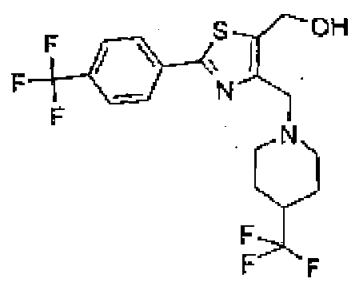
[4-Morpholin-4-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol



To a solution of 355 mg of 4-morpholin-4-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid ethyl ester in 1 mL of tetrahydrofuran was added 0.88 mL of a 1M solution of lithium aluminium hydride in tetrahydrofuran. The resulting mixture was stirred at room temperature for 1 h. Water was slowly added and the mixture was extracted with dichloromethane. The organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (gradient of dichloromethane/methanol from 100/0 to 90/10) to give 276 mg of [4-morpholin-4-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol.

C16H17F3N2O2S (358.39), MS(EI): 358 (M^+).

[2-(4-Trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-yl]-methanol

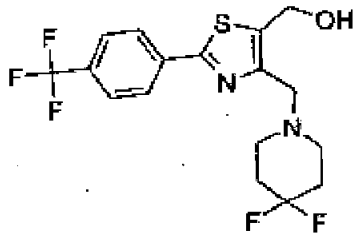


According to the method described for [4-morpholin-4-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol, [2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-

piperidin-1-ylmethyl)-thiazol-5-yl]-methanol was obtained from 4-bromomethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid ethyl ester and 4-trifluoromethyl-piperidine.

C18H18F6N2OS (424.41), MS(ESI): 425 ($M+H^+$).

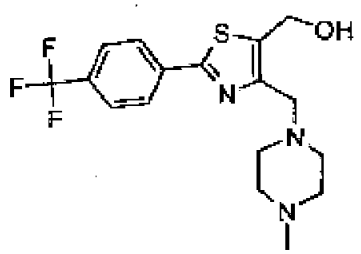
[4-(4,4-Difluoro-piperidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol



According to the method described for [4-morpholin-4-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol, 4-(4,4-difluoro-piperidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol was obtained from 4-bromomethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid ethyl ester and 4,4-difluoro-piperidine.

C17H17F5N2OS (392.39), MS(EI): 392 (M^+).

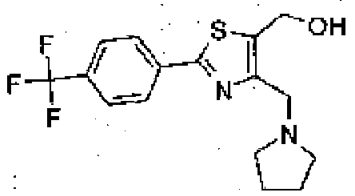
[4-(4-Methyl-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol



According to the method described for [4-morpholin-4-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol, [4-(4-methyl-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol was obtained from 4-bromomethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid ethyl ester and 1-methyl-piperazine.

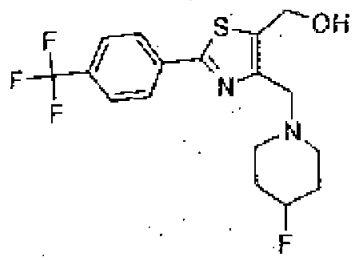
C17H20F3N3OS (371.43), MS(EI): 371 (M^+).

[4-Pyrrolidin-1-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol



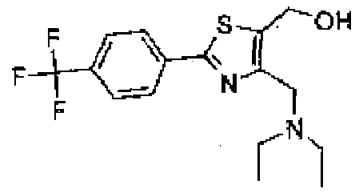
According to the method described for [4-morpholin-4-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol, [4-pyrrolidin-1-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol was obtained from 4-bromomethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid ethyl ester and pyrrolidine.
C16H17F3N2OS (342.38), MS(ESI): 343 ($M+H^+$).

[4-(4-Fluoro-piperidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol



According to the method described for [4-morpholin-4-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol, [4-(4-fluoro-piperidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol was obtained from 4-bromomethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid ethyl ester and 4-fluoro-piperidine.
C17H18F4N2OS (374.40), MS(ESI): 375 ($M+H^+$).

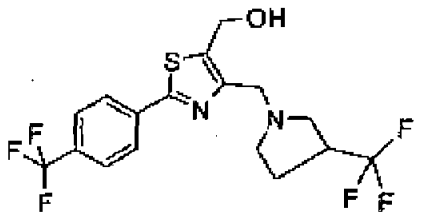
[4-Diethylaminomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol



According to the method described for [4-morpholin-4-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol, [4-diethylaminomethyl-2-(4-trifluoromethyl-phenyl)-

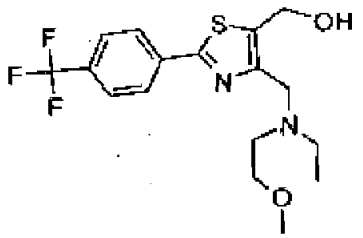
thiazol-5-yl]-methanol was obtained from 4-bromomethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid ethyl ester and diethylamine.
C16H19F3N2OS (344.40), MS(ESI): 345 ($M+H^+$).

[2-(4-Trifluoromethyl-phenyl)-4-(3-trifluoromethyl-pyrrolidin-1-ylmethyl)-thiazol-5-yl]-methanol



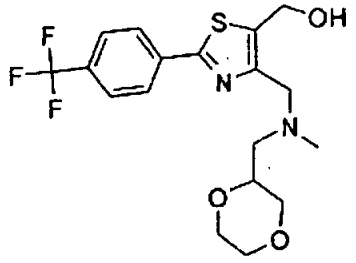
According to the method described for [4-morpholin-4-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol, racemic [2-(4-trifluoromethyl-phenyl)-4-(3-trifluoromethyl-pyrrolidin-1-ylmethyl)-thiazol-5-yl]-methanol was obtained from 4-bromomethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid ethyl ester and racemic 4-trifluoromethyl-pyrrolidine.
C17H16F6N2OS (410.38), MS(ESI): 411 ($M+H^+$).

[4-{[Ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol



According to the method described for [4-morpholin-4-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol, [4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol was obtained from 4-bromomethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid ethyl ester and ethyl-(2-methoxy-ethyl)-amine.
C17H21F3N2O2S (374.42), MS(ESI): 375 ($M+H^+$).

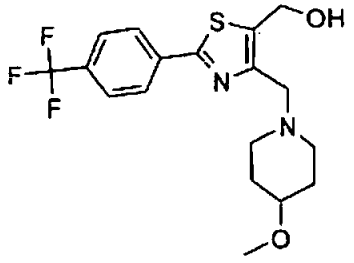
[4-[([1,4]Dioxan-2-ylmethyl-methyl-amino)-methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol



According to the method described for [4-morpholin-4-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol, racemic [4-[([1,4]dioxan-2-ylmethyl-methyl-amino)-methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol was obtained from 4-bromomethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid ethyl ester and racemic [1,4]dioxan-2-ylmethyl-methyl-amine.

$C_{18}H_{21}F_3N_2O_3S$ (402.43), MS(ESI): 403 ($M+H^+$).

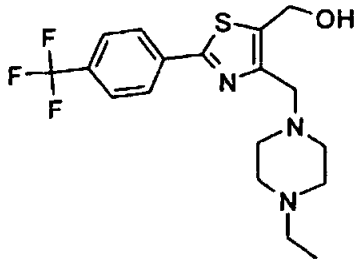
[4-(4-Methoxy-piperidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol



According to the method described for [4-Morpholin-4-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol, [4-(4-methoxy-piperidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol was obtained from 4-bromomethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid ethyl ester and 4-methoxy-piperidine.

$C_{18}H_{21}F_3N_2O_2S$ (386.44), MS(ESI): 387 ($M+H^+$).

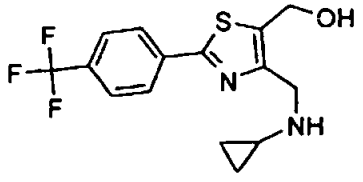
[4-(4-Ethyl-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol



According to the method described for [4-morpholin-4-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol, [4-(4-ethyl-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol was obtained from 4-bromomethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid ethyl ester and 1-piperazin-1-yl-ethanone. The amide function in the piperazine group is reduced to the corresponding amine in the reduction step. This building block could also be prepared starting from 4-ethyl-piperazine.

C18H22F3N3OS (385.45), MS(ESI): 386 ($M+H^+$).

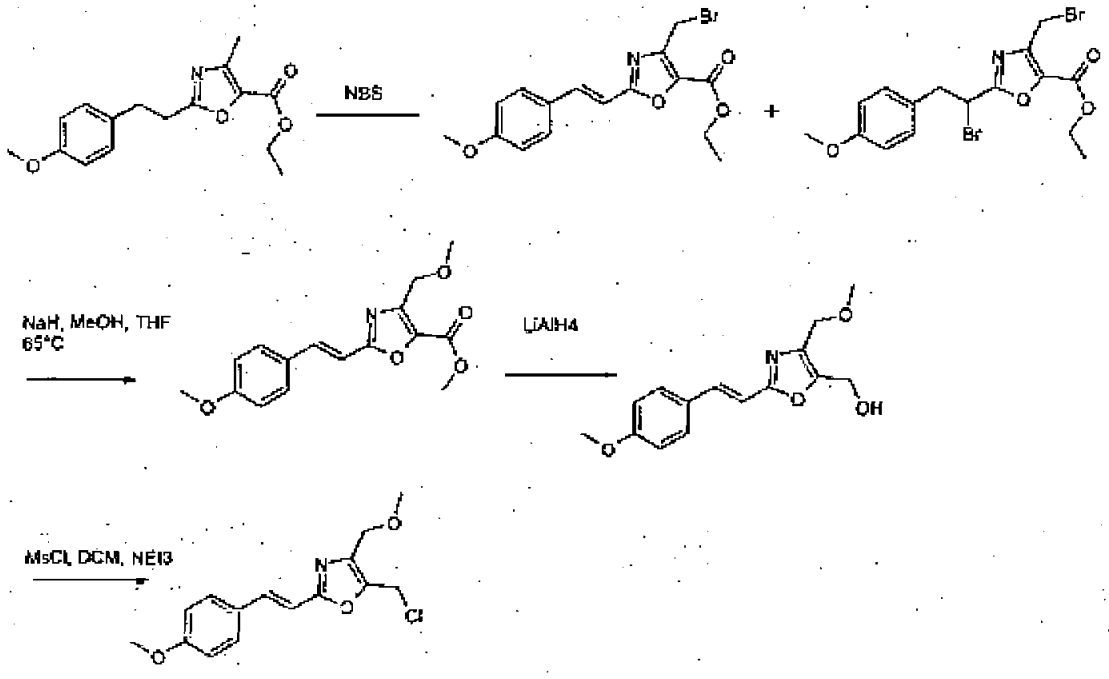
[4-Cyclopropylaminomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol



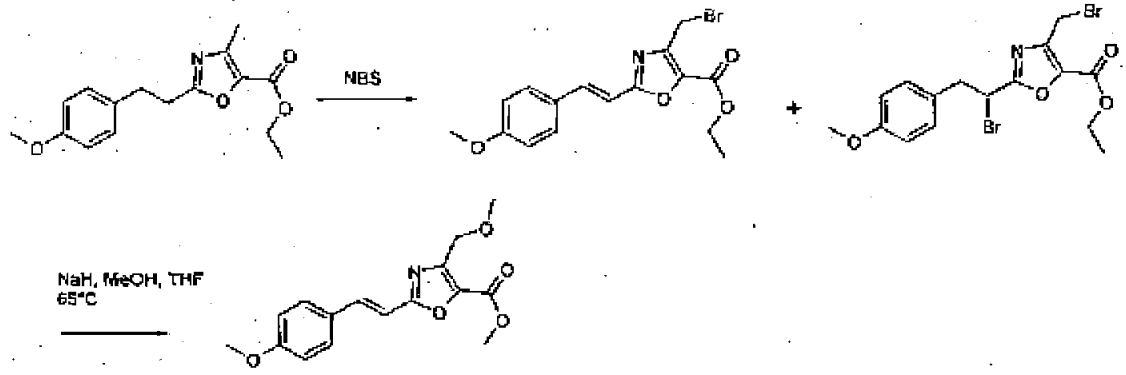
According to the method described for [4-morpholin-4-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol, [4-cyclopropylaminomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol was obtained from 4-bromomethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid ethyl ester and cyclopropylamine.

C15H15F3N2OS (328.36), MS(ESI): 329 ($M+H^+$).

5-Chloromethyl-4-methoxymethyl-2-[2-(4-methoxy-phenyl)-vinyl]-oxazole



4-Methoxymethyl-2-[2-(4-methoxy-phenyl)-vinyl]-oxazole-5-carboxylic acid methyl ester



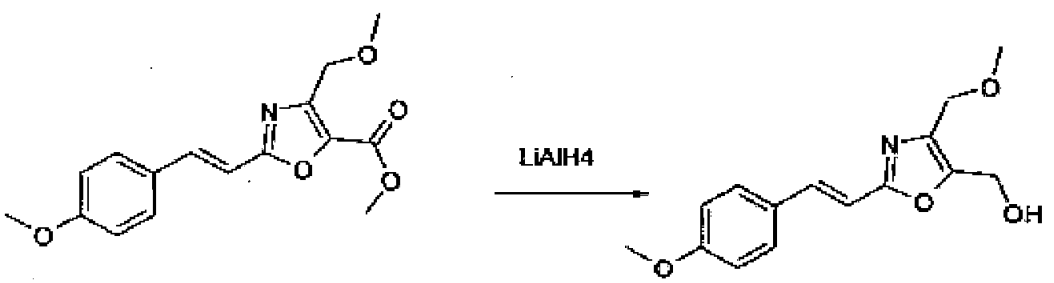
To a refluxing mixture of 6.40 g 2-[2-(4-methoxy-phenyl)-ethyl]-4-methyl-oxazole-5-carboxylic acid ethyl ester (synthesized according to the method described for 5-chloromethyl-4-methyl-2-[2-(4-trifluoromethyl-phenyl)-ethyl]-oxazole from 3-(4-methoxyphenyl)propionamide and 2-chloroacetoacetate) in 90 ml tetrachloromethane were added portionwise a mixture of 9.82 g N-bromosuccinimide and 3.63 g 2,2'-azobis(2-methylpropionitrile). The reaction mixture was heated under reflux for three hours. The cooled reaction mixture was filtered over a celite pad, the filtrate was evaporated in vacuo and the resulting residue was purified by chromatography on

silica gel with the eluent n-heptane : ethyl acetate = 15:1 => 5:1 to provide 11.0 g of a mixture of 4-bromomethyl-2-[2-(4-methoxy-phenyl)-vinyl]-oxazole-5-carboxylic acid ethyl ester and 2-[1-bromo-2-(4-methoxy-phenyl)-ethyl]-4-bromomethyl-oxazole-5-carboxylic acid ethyl ester.

This mixture was dissolved in a mixture of 50 ml methanol and 10 ml tetrahydrofuran. 1.87 g sodium hydride was added and the reaction mixture stirred at 65°C for one hour. The cooled reaction mixture was neutralized by the addition of acetic acid (pH ~ 6). The solvents were removed in vacuo, the residue was dissolved in 100 ml ethyl acetate and washed with 50 ml brine. The organic phase was dried over MgSO4. The solvent was removed in vacuo. The residue was purified by RP-HPLC to obtain 1.1 g 4-methoxymethyl-2-[2-(4-methoxy-phenyl)-vinyl]-oxazole-5-carboxylic acid methyl ester as an oil.

C16H17NO5 (303.32), MS(ESI): 304.2 ($M+H^+$).

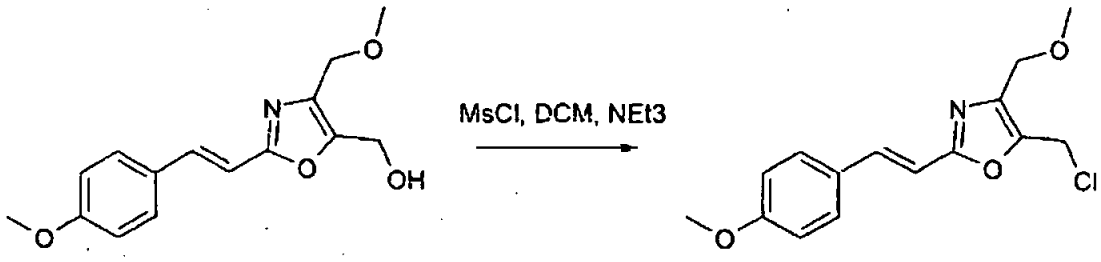
{4-Methoxymethyl-2-[2-(4-methoxy-phenyl)-vinyl]-oxazol-5-yl}-methanol



1.10 g 4-Methoxymethyl-2-[2-(4-methoxy-phenyl)-vinyl]-oxazole-5-carboxylic acid methyl ester were dissolved in 15 ml tetrahydrofuran and added to a ice cooled solution of 137 mg lithium aluminium hydride in 7 ml tetrahydrofuran. The reaction mixture was stirred at 0°C for one hour. Then 50 ml ethyl acetate and 20 ml saturated NH4Cl solution were added. The precipitate was filtered off through a celite pad and washed with ethyl acetate. The organic layer of the filtrate was separated. The aqueous layer of the filtrate was extracted two times with portions of 100 ml ethyl acetate. The combined organic layers were dried over MgSO4. The solvent was removed in vacuo and the residue purified by RP-HPLC to obtain to 420 mg {4-methoxymethyl-2-[2-(4-methoxy-phenyl)-vinyl]-oxazol-5-yl}-methanol as an oil.

C15H17NO4 (275.31), MS(ESI): 276.2.

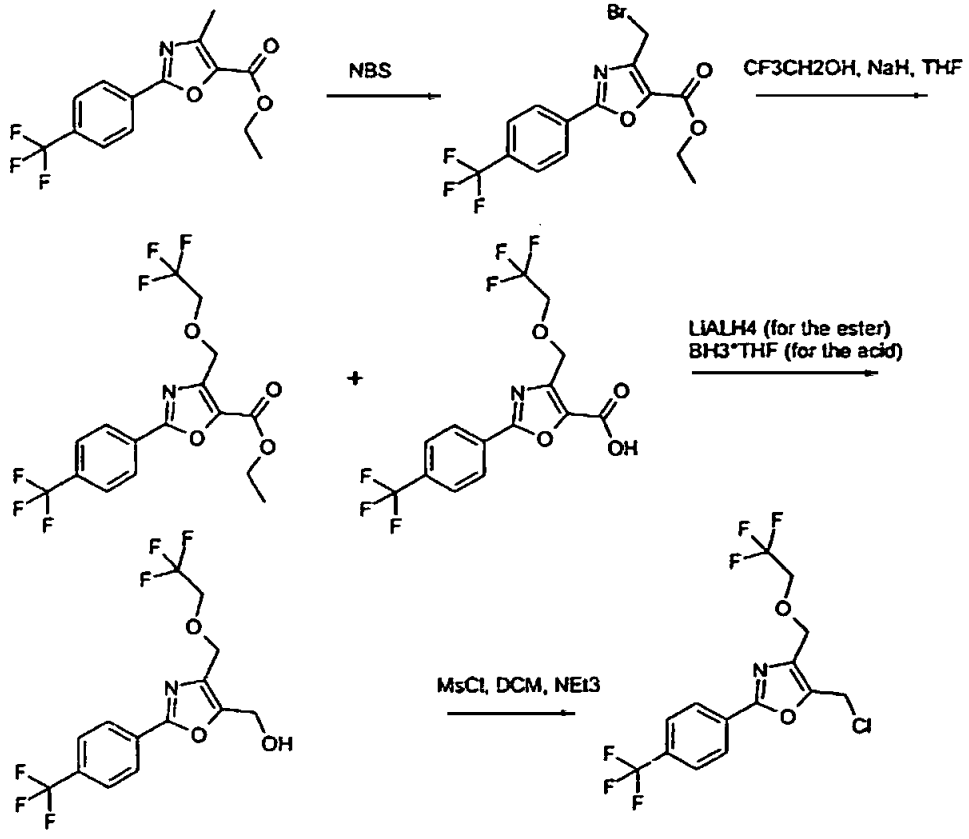
5-Chloromethyl-4-methoxymethyl-2-[2-(4-methoxy-phenyl)-vinyl]-oxazole



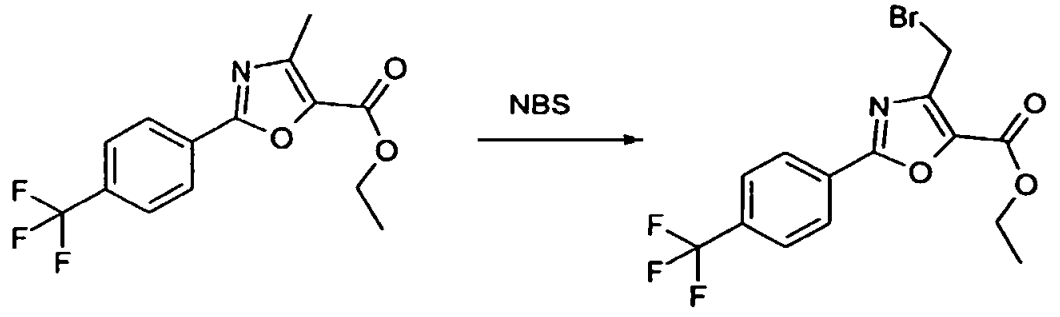
420 mg {4-Methoxymethyl-2-[2-(4-methoxy-phenyl)-vinyl]-oxazol-5-yl}-methanol were dissolved in 5 ml dichloromethane and cooled in an ice bath. 0.32 ml triethylamine were added, followed by the addition of 141 µl methanesulfonylchloride. The ice bath was removed and the resulting mixture stirred at room temperature over night. 50 ml dichloromethane were added and the reaction mixture was then washed with water and brine, dried over MgSO4 and the solvent removed in vacuo to obtain 491 mg 5-chloromethyl-4-methoxymethyl-2-[2-(4-methoxy-phenyl)-vinyl]-oxazole as an oil which was used without further purification.

C15H16ClNO3 (293.75), Rf(ethyl acetate:n-heptane = 1:1) = 0.44.

5-Chloromethyl-4-(2,2,2-trifluoro-ethoxymethyl)-2-(4-trifluoromethyl-phenyl)-oxazole



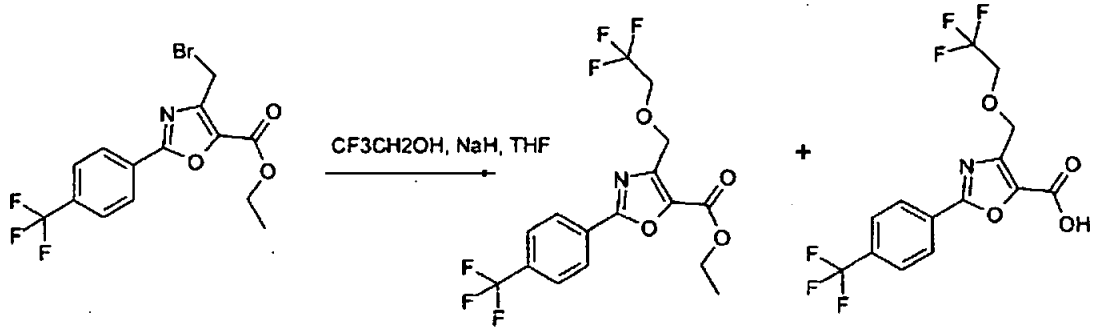
4-Bromomethyl-2-(4-trifluoromethyl-phenyl)-oxazole-5-carboxylic acid ethyl ester



To a refluxing mixture of 21.5 g 4-methyl-2-(4-trifluoromethyl-phenyl)-oxazole-5-carboxylic acid ethyl ester (synthesized according to the method described for 5-chloromethyl-4-methyl-2-[2-(4-trifluoromethyl-phenyl)-ethyl]-oxazole from 4-trifluoromethyl-benzamide and 2-chloroacetoacetate) in 180 ml tetrachloro-methane were added portionwise a mixture of 15.4 g N-bromosuccinimide and 4.73 g 2,2'-azobis(2-methylpropionitrile). The reaction mixture was heated under reflux for five hours. The cooled reaction mixture was filtered over a celite pad, the filtrate was evaporated in vacuo and the resulting residue was purified by chromatography on

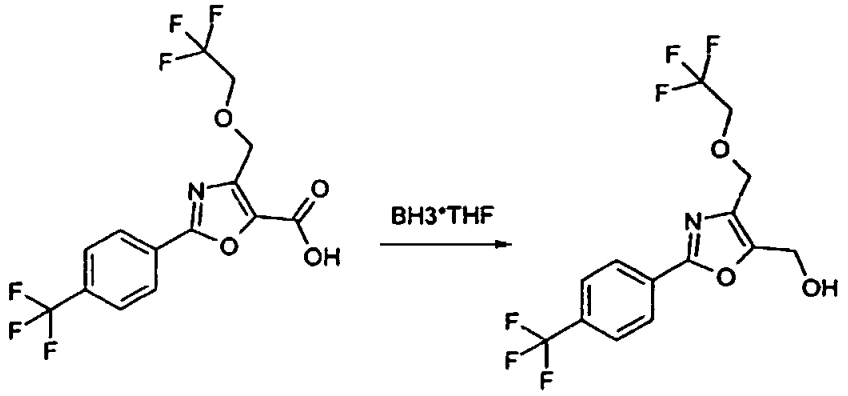
silica gel with the eluent petroleum benzene : dichloromethane = 7 : 3 to provide 18.5 g 4-bromomethyl-2-(4-trifluoromethyl-phenyl)-oxazole-5-carboxylic acid ethyl ester. C14H11BrF3NO3 (378.15), MS(ESI): 378.3, 380.3 ($M+H^+$).

4-(2,2,2-Trifluoro-ethoxymethyl)-2-(4-trifluoromethyl-phenyl)-oxazole-5-carboxylic acid ethyl ester and 4-(2,2,2-Trifluoro-ethoxymethyl)-2-(4-trifluoromethyl-phenyl)-oxazole-5-carboxylic acid



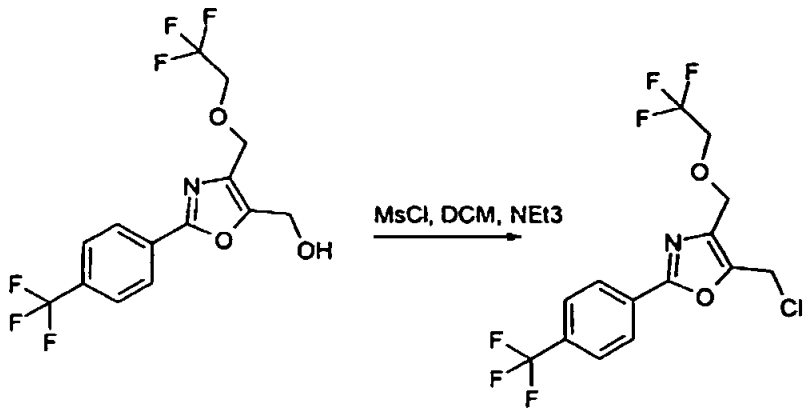
4.0 g 4-Bromomethyl-2-(4-trifluoromethyl-phenyl)-oxazole-5-carboxylic acid ethyl ester is dissolved in a mixture of 20 ml tetrahydrofuran and 50 ml 2,2,2-trifluoroethanol. 635 mg sodium hydride were added and the reaction mixture stirred at 60°C for three hours. The cooled reaction mixture was neutralized by the addition of acetic acid (pH ~ 6). The solvents were removed in vacuo, the residue was dissolved in 250 ml ethyl acetate and washed with 100 ml brine. The organic phase was dried over MgSO4. The solvent was removed in vacuo. The residue was purified by RP-HPLC to obtain 1.0 g 4-(2,2,2-trifluoro-ethoxymethyl)-2-(4-trifluoromethyl-phenyl)-oxazole-5-carboxylic acid C14H9F6NO4 (369.22), MS(ESI): 369.9 (M+H+). and 830 mg 4-(2,2,2-trifluoro-ethoxymethyl)-2-(4-trifluoromethyl-phenyl)-oxazole-5-carboxylic acid ethyl ester. C16H13F6NO4 (397.28), MS(ESI): 398.0 (M+H+).

[4-(2,2,2-Trifluoro-ethoxymethyl)-2-(4-trifluoromethyl-phenyl)-oxazol-5-yl]-methanol



1.0 g 4-(2,2,2-Trifluoro-ethoxymethyl)-2-(4-trifluoromethyl-phenyl)-oxazole-5-carboxylic acid were dissolved in 30 ml tetrahydrofuran. At 0-5°C 6.6 ml of a one molar solution of borane tetrahydrofuran complex were added. The reaction mixture was stirred at room temperature for three hours and at 60°C for one hour. The cooled reaction mixture was diluted by addition of 100 ml ethyl acetate and washed with 50 ml water. The organic phase was dried over MgSO4 then the solvent was removed in vacuo. The residue was purified by RP-HPLC to obtain 422 mg [4-(2,2,2-trifluoro-ethoxymethyl)-2-(4-trifluoromethyl-phenyl)-oxazol-5-yl]-methanol.
C14H11F6NO3 (355.24), MS(ESI): 356.0 (M+H+).

5-Chloromethyl-4-(2,2,2-trifluoro-ethoxymethyl)-2-(4-trifluoromethyl-phenyl)-oxazole



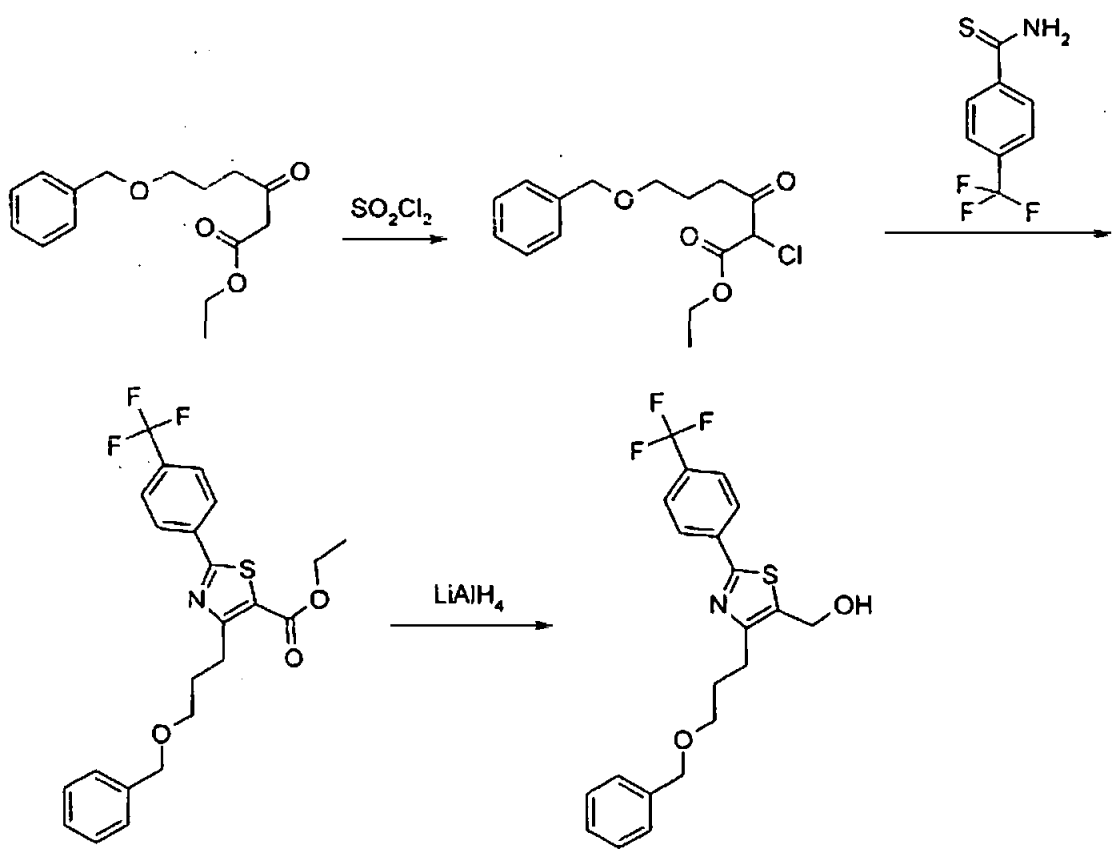
422 mg [4-(2,2,2-Trifluoro-ethoxymethyl)-2-(4-trifluoromethyl-phenyl)-oxazol-5-yl]-methanol were dissolved in 5 ml dichloromethane and cooled in an ice bath. 247 µl triethylamine were added, followed by the addition of 110 µl methanesulfonylchloride. The ice bath was removed and the resulting mixture stirred at room temperature over

night. 50 ml dichloromethane were added and the reaction mixture was then washed with water and brine, dried over MgSO4 and the solvent removed in vacuo to obtain 509 mg 5-chloromethyl-4-(2,2,2-trifluoro-ethoxymethyl)-2-(4-trifluoromethyl-phenyl)-oxazole as an oil which was used without further purification.

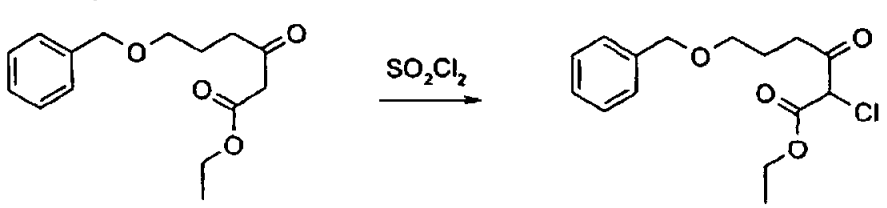
C14H10ClF6NO2 (373.68), MS(ESI): 373.9 (M+H+).

Building block synthesis according to process H:

[4-(3-Benzyloxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol

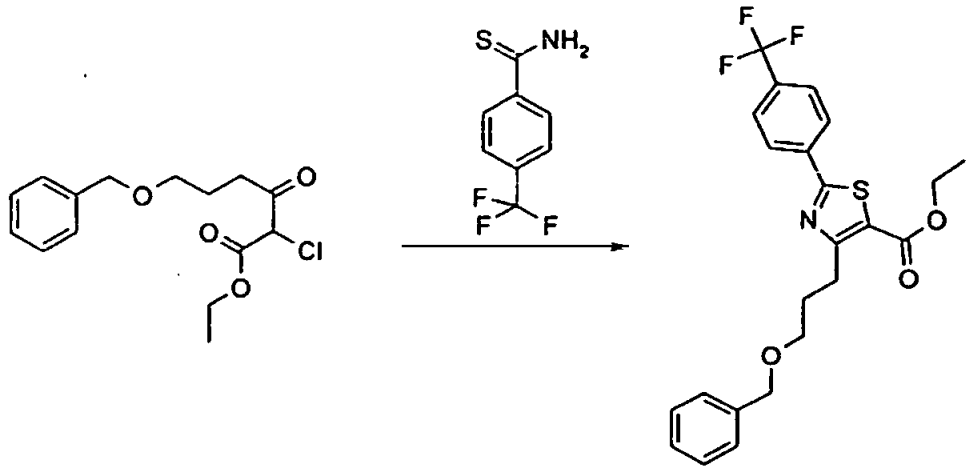


6-Benzyloxy-2-chloro-3-oxo-hexanoic acid ethyl ester



To a solution of 1 g of 6-benzyloxy-3-oxo-hexanoic acid ethyl ester[2] in 10 ml of anhydrous dichloromethane at 0°C was dropwise added 0.307 ml of sulfurylchloride. The reaction mixture was stirred at room temperature for 30 minutes at 0°C and 1h at room temperature. The reaction mixture was poured onto 20 ml of water and extracted twice with portions of 100 ml of dichloromethane. The combined organic extracts were washed with water, dried over magnesium sulfate, filtered and concentrated under reduced pressure to provide 1.15 g of 6-benzyloxy-2-chloro-3-oxo-hexanoic acid ethyl ester which was used in the next step without further purification.

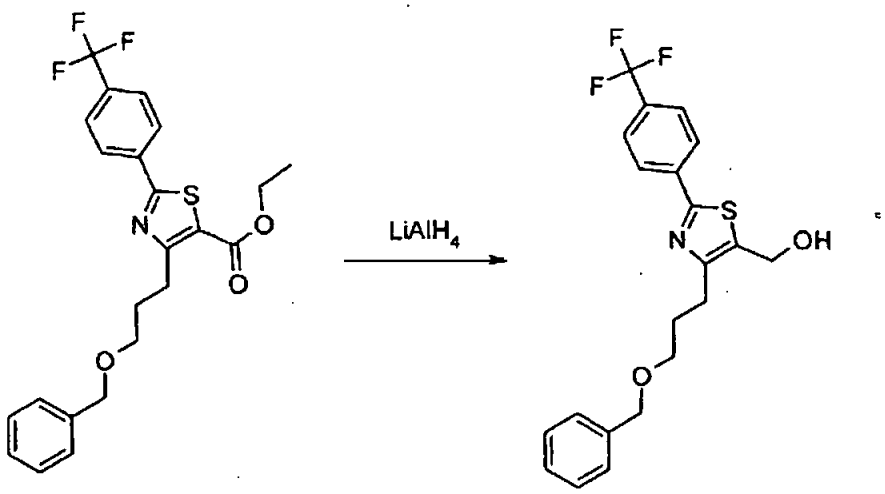
4-(3-Benzyloxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid ethyl ester



To a solution of 1.15 g of 6-benzyloxy-2-chloro-3-oxo-hexanoic acid ethyl ester in 10 ml of ethanol was added 0.932 g of 4-(trifluoromethyl)thiobenzamide. The reaction mixture was refluxed overnight. The solvent was removed under reduced pressure. The resulting residue was taken into ethyl acetate, washed with water. The aqueous layer was separated and extracted wih ethyl acetate. The combined organic extracts were washed with water, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (heptane 90/ethyl acetate 10) to give 1.15 g of 4-(3-benzyloxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid ethyl ester as a colorless liquid. C23H22F3NO3S (449.49), MS(ESI): 450 ($M+H^+$).

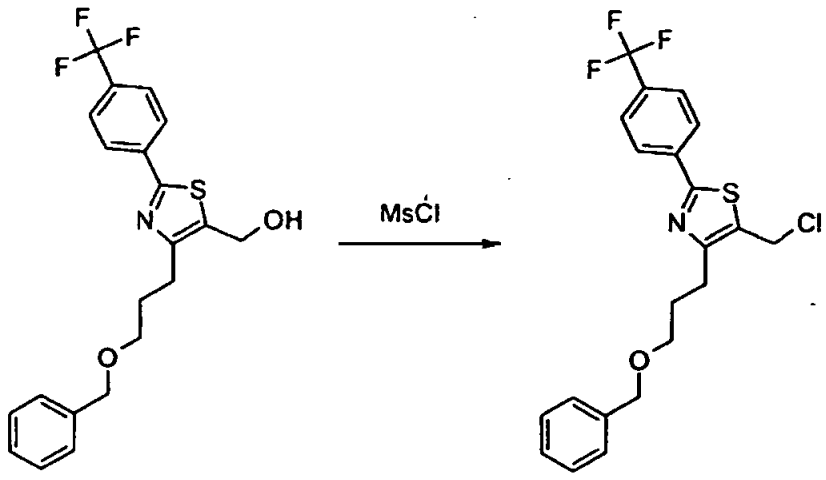
[2] Paulvannan, K.; Stille, J.R. *J. Org. Chem.*, 1994, *59*, 1613-1620.

[4-(3-Benzyloxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol



To a solution of 2.76 g of 4-(3-benzyloxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid ethyl ester in 50 mL of tetrahydrofuran was added 6.14 mL of a 1M solution of lithium aluminium hydride in tetrahydrofuran. The resulting mixture was stirred at room temperature for 1 h. Ethyl acetate was added followed by a saturated aqueous solution of ammonium chloride. The aqueous layer was separated and extracted three times wih ethyl acetate. The combined organic extracts were washed with water, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (heptane 70/ ethyl acetate 30) to give 1.69 g of [4-(3-benzyloxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol as a white solid.
C21H20F3NO2S (407.45), MS(ESI): 408 ($M+H^+$).

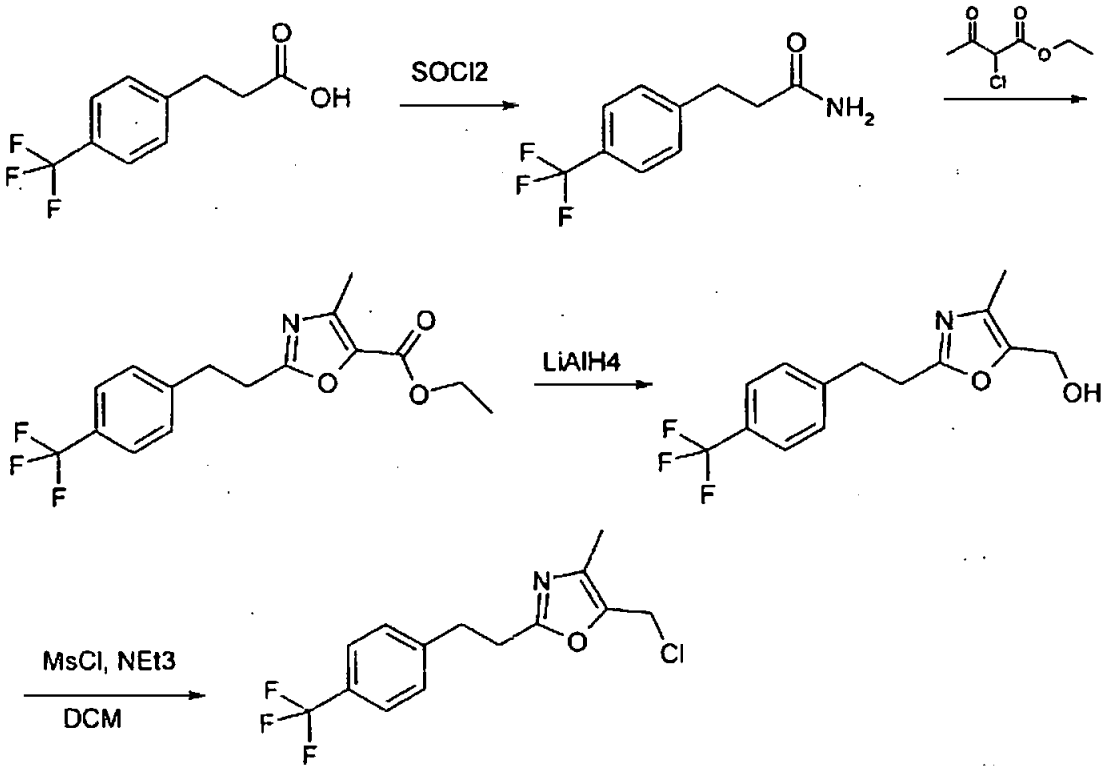
4-(3-Benzyloxy-propyl)-5-chloromethyl-2-(4-trifluoromethyl-phenyl)-thiazole



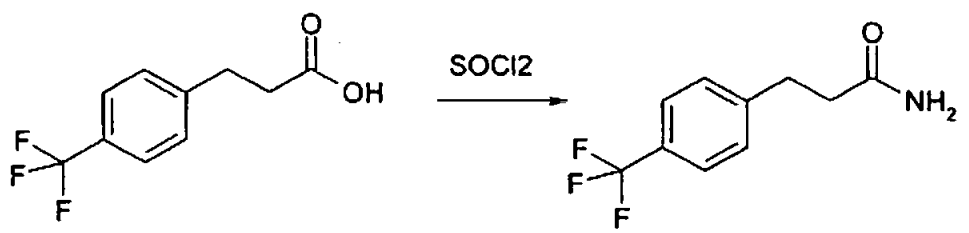
To a solution of 1.5 g of [4-(3-benzyloxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol in 15 mL of dichloromethane was added 1.026 mL of triethylamine and 0.484 mL of methanesulfonyl chloride. The resulting mixture was stirred at room temperature for 2 h. The mixture was then diluted with dichloromethane and water was added. The aqueous layer was separated and extracted three times wih dichloromethane. The combined organic extracts were washed with water, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (heptane 90/ ethyl acetate 10) to give 0.84 g of 4-(3-benzyloxy-propyl)-5-chloromethyl-2-(4-trifluoromethyl-phenyl)-thiazole as a yellow oil.

C21H19ClF3NOS (425.90), MS(EI): 425 (M^+).

5-Chloromethyl-4-methyl-2-[2-(4-trifluoromethyl-phenyl)-ethyl]-oxazole



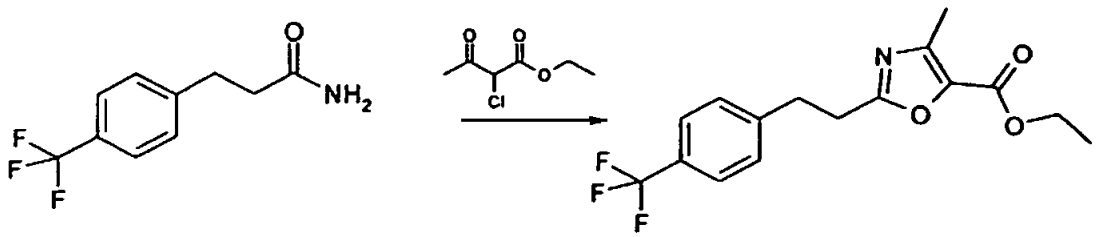
3-(4-Trifluoromethyl-phenyl)-propionamide



20.0 g 4-(Trifluoromethyl)hydrocinnamic acid were heated under reflux in 150 ml thionyl chloride for three hours. The thionyl chloride was removed in vacuo and the residue dissolved in 150 ml tetrahydrofuran and added dropwise to a stirred solution of concentrated ammonia in water. The reaction mixture was stirred at room temperature. After 15 minutes the organic layer was separated and the aqueous layer was extracted two times with portions of 100 ml ethyl acetate. The combined organic layers were

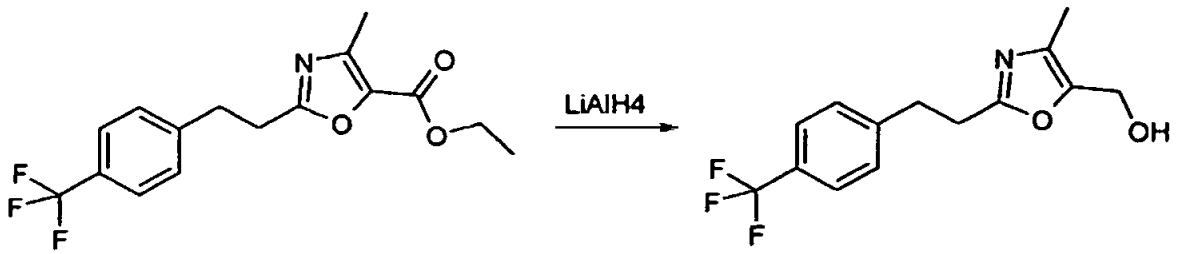
dried over MgSO4. The solvent was removed in vacuo to obtain 18.6 g 3-(4-trifluoromethyl-phenyl)-propionamide as white solid.
C10H10F3NO (217,19), MS(ESI): 218.1.

4-Methyl-2-[2-(4-trifluoromethyl-phenyl)-ethyl]-oxazole-5-carboxylic acid ethyl ester



18.6 g 3-(4-Trifluoromethyl-phenyl)-propionamide and 42.8 ml ethyl 2-chloroacetoacetate were mixed and stirred at 150 °C for eight hours. Excess ethyl 2-chloroacetoacetate was removed in vacuo (oil pump) and the residue purified by chromatography on silica gel with the eluent petroleum benzene : ethyl acetate = 3 : 1 to obtain 13.75 g 4-methyl-2-[2-(4-trifluoromethyl-phenyl)-ethyl]-oxazole-5-carboxylic acid ethyl ester as an oil.
C16H16F3NO3 (327,31), MS(ESI): 328.2.

{4-Methyl-2-[2-(4-trifluoromethyl-phenyl)-ethyl]-oxazol-5-yl}-methanol

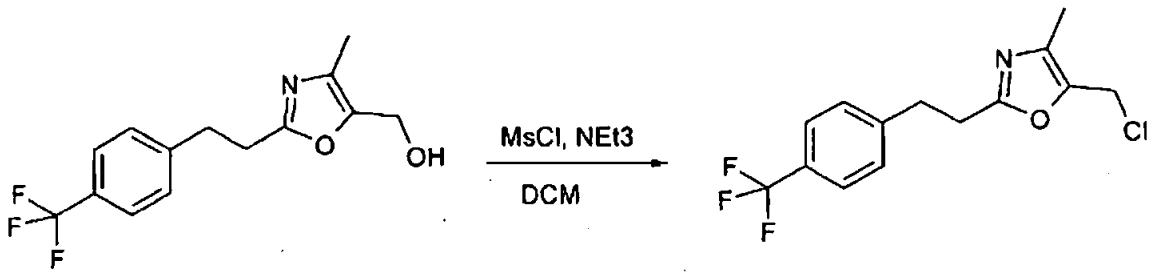


9.70 g 4-Methyl-2-[2-(4-trifluoromethyl-phenyl)-ethyl]-oxazole-5-carboxylic acid ethyl ester were dissolved in 20 ml tetrahydrofuran and added to a ice cooled solution of 1.13 g lithium aluminium hydride in 10 ml tetrahydrofuran. The reaction mixture was stirred at 0°C for one hour. Then 100 ml ethyl acetate and 50 ml saturated NH4Cl solution were added. The precipitate was filtered off through a celite pad and washed with ethyl acetate. The organic layer of the filtrate was separated. The aqueous layer of the filtrate was extracted two times with portions of 100 ml ethyl acetate. The

combined organic layers were dried over MgSO4. The solvent was removed in vacuo and the residue purified by chromatography on silica gel with the eluent petroleum benzene : ethyl acetate = 1 : 1 to obtain to 4.20 g {4-methyl-2-[2-(4-trifluoromethyl-phenyl)-ethyl]-oxazol-5-yl}-methanol a yellow solid.

C14H14F3NO2 (285,27), MS(ESI): 286.2.

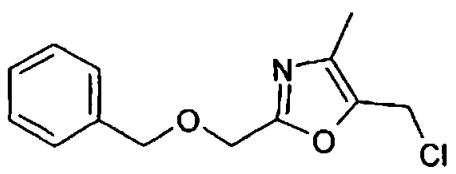
5-Chloromethyl-4-methyl-2-[2-(4-trifluoromethyl-phenyl)-ethyl]-oxazole



4.20 g {4-Methyl-2-[2-(4-trifluoromethyl-phenyl)-ethyl]-oxazol-5-yl}-methanol were dissolved in 20 ml dichloromethane and cooled in an ice bath. 3.10 ml triethylamine were added, followed by the addition of 1.37 ml methanesulfonylchloride. The ice bath was removed and the resulting mixture stirred at room temperature over night. The reaction mixture was then washed with water and brine, dried over MgSO4 and the solvent removed in vacuo to obtain 4.0 g 5-chloromethyl-4-methyl-2-[2-(4-trifluoromethyl-phenyl)-ethyl]-oxazole as an oil which was used without further purification.

C14H13ClF3NO (303.71), MS(ESI): 304.1 ($M+H^+$), Rf(ethyl acetate:n-heptane = 1:1) = 0.52.

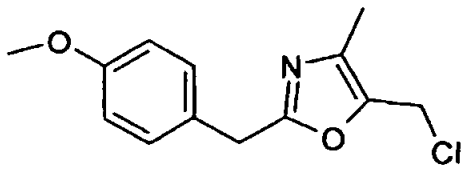
2-Benzyloxymethyl-5-chloromethyl-4-methyl-oxazole



According to the method described for 5-chloromethyl-4-methyl-2-[2-(4-trifluoromethyl-phenyl)-ethyl]-oxazole, 2-benzyloxymethyl-5-chloromethyl-4-methyl-oxazole was obtained from benzyloxaacetic acid and ethyl 2-chloroacetoacetate.

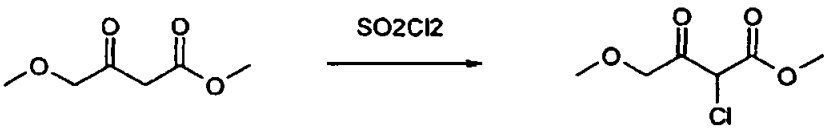
C13H14ClNO2 (251.72), Rf (n-heptane:ethyl acetate = 1:1) = 0.51.

5-Chloromethyl-2-(4-methoxy-benzyl)-4-methyl-oxazole



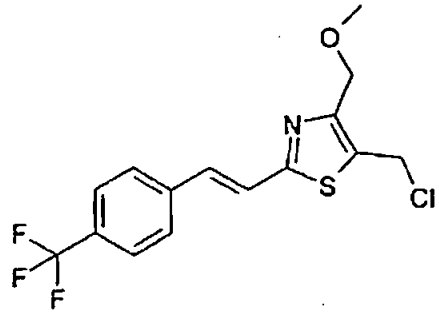
According to the method described for 5-chloromethyl-4-methyl-2-[2-(4-trifluoromethyl-phenyl)-ethyl]-oxazole, 5-chloromethyl-2-(4-methoxy-benzyl)-4-methyl-oxazole was obtained from 4-methoxyphenylacetamide and ethyl 2-chloroacetoacetate.
C13H14ClNO2 (251.72), MS(ESI): 252.1 ($M+H^+$), Rf (n-heptane:ethyl acetate = 1:1) = 0.49.

2-Chloro-4-methoxy-3-oxo-butyric acid methyl ester



46.0 g Methyl 4-methoxyacetoacetate were dissolved in 500 ml dichloromethane. 28.1 ml Sulfuryl chloride were added in one portion. The reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure, the resulting residue was dissolved in 300 ml ethyl acetate and washed with 100 ml water and 100 ml brine. The organic layer was dried over MgSO4 and the solvent removed under reduced pressure. The resulting residue was purified by chromatography on silica gel with the eluent n-heptane:ethyl acetate = 5:1 => 2:1 to obtain 45.0g 2-chloro-4-methoxy-3-oxo-butyric acid methyl ester as a yellow oil.
C6H9ClO4 (180.59), MS(ESI): 181.2 ($M+H^+$), Rf(n-heptane : ethyl acetate = 2:1) = 0.31.

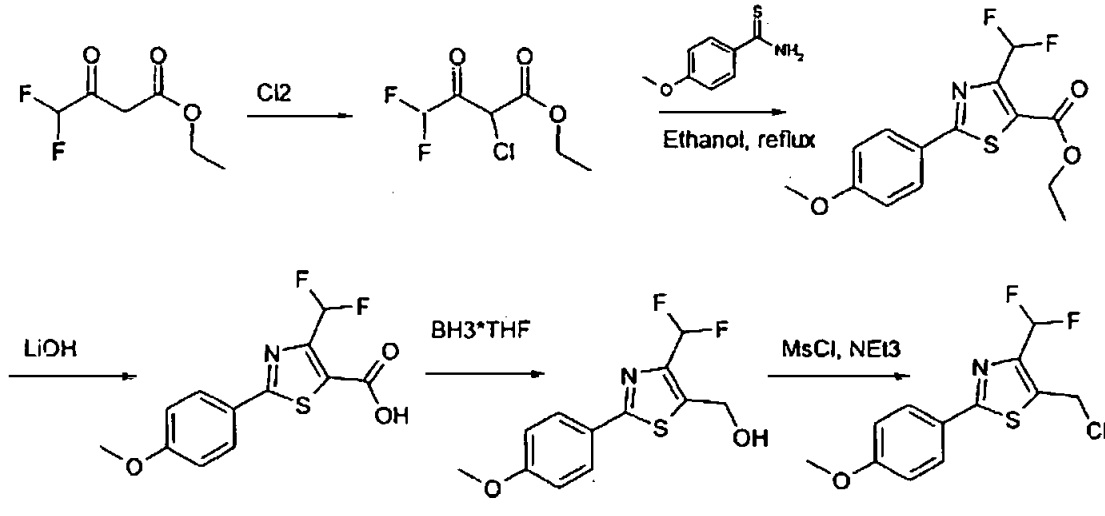
5-Chloromethyl-4-methoxymethyl-2-[2-(4-trifluoromethyl-phenyl)-vinyl]-thiazole



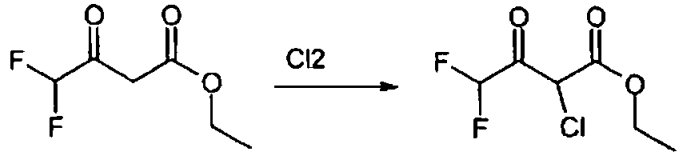
According to the method described for 5-chloromethyl-4-methyl-2-[2-(4-trifluoromethyl-phenyl)-ethyl]-oxazole, 5-chloromethyl-4-methoxymethyl-2-[2-(4-trifluoromethyl-phenyl)-vinyl]-thiazole was obtained from 4-(trifluoromethyl)cinnamide and 2-chloro-4-methoxy-3-oxo-butyric acid methyl ester.

C15H13ClF3NOS (347.79), MS(ESI): 348.0 ($M+H^+$).

5-Chloromethyl-4-difluoromethyl-2-(4-methoxy-phenyl)-thiazole



2-Chloro-4,4-difluoro-3-oxo-butyric acid ethyl ester

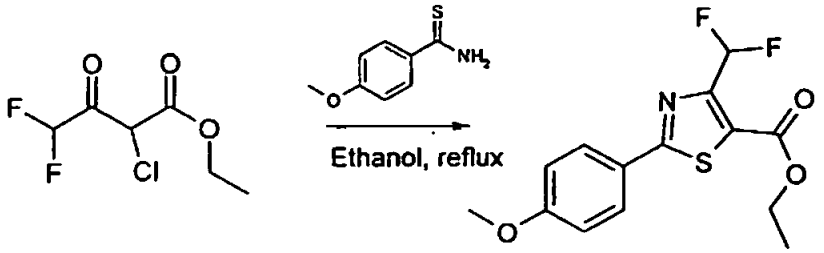


Chlorine was bubbled through 10.0 g ethyl 4,4-difluoroacetoacetate for fifteen minutes at room temperature. Then argon was bubbled through. 11.67 g 2-Chloro-4,4-difluoro-

3-oxo-butyric acid ethyl ester were obtained as crude material which was used without further purification.

C6H7ClF2O3 (200.57), MS(ESI): 200.95 ($M+H^+$), Rf(n-heptane : ethyl acetate = 1:1) = 0.10.

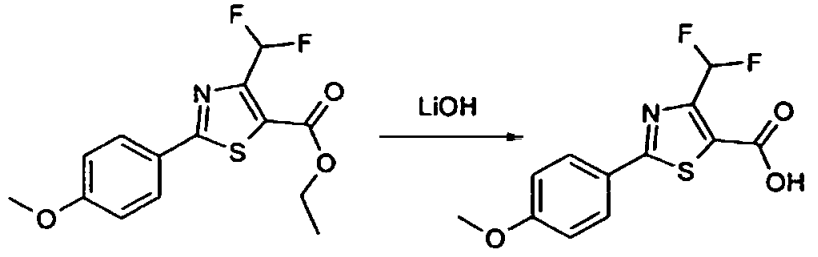
4-Difluoromethyl-2-(4-methoxy-phenyl)-thiazole-5-carboxylic acid ethyl ester



8.84 g 4-Methoxythiobenzamide were dissolved in 100 ml ethanol and warmed to 50°C. Then 10.59 g 2-chloro-4,4-difluoro-3-oxo-butyric acid ethyl ester were added and the reaction mixture stirred under reflux for three hours. The cooled reaction mixture was evaporated in vacuo and the residue purified by chromatograph on silica gel with the eluent ethyl acetate / petroleum benzene = 1 : 4 to obtain 7.04 g 4-difluoromethyl-2-(4-methoxy-phenyl)-thiazole-5-carboxylic acid ethyl ester as pale yellow solid.

C14H13F2NO3S (313.33), MS(ESI): 313.95 ($M+H^+$).

4-Difluoromethyl-2-(4-methoxy-phenyl)-thiazole-5-carboxylic acid

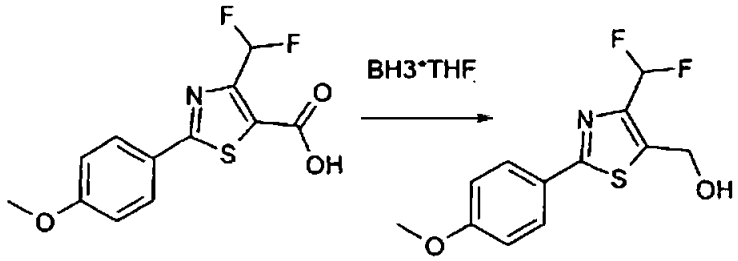


3.0 g 4-Difluoromethyl-2-(4-methoxy-phenyl)-thiazole-5-carboxylic acid ethyl ester were dissolved in 90 ml tetrahydrofuran. A solution of 2.29 g lithium hydroxide dissolved in 30 ml water was added and the reaction mixture stirred at room temperature overnight. Concentrated acetic acid were added until a pH of ~ 6 was attained, then the tetrahydrofuran was removed in vacuo. The residual aqueous phase was extracted thrre time with portions of 100 ml ethyl acetate. The combined organic layers were dried over MgSO4. Then the solvent was removed in vacuo to obtain 2.73

g 4-difluoromethyl-2-(4-methoxy-phenyl)-thiazole-5-carboxylic acid as pale yellow solid.

C12H9F2NO3S (285.27), MS(ESI): 285.90 ($M+H^+$).

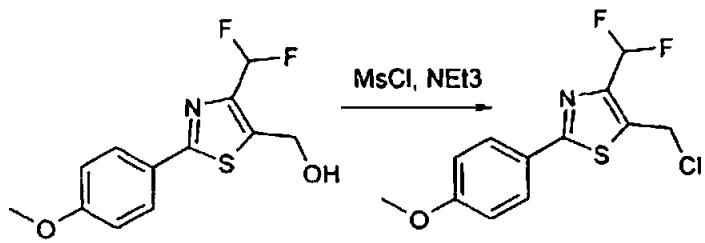
[4-Difluoromethyl-2-(4-methoxy-phenyl)-thiazol-5-yl]-methanol



2.73 g 4-Difluoromethyl-2-(4-methoxy-phenyl)-thiazole-5-carboxylic acid were dissolved in 30 ml tetrahydrofuran. 23 ml of a one molar solution of borane tetrahydrofuran complex were added and the reaction mixture stirred at 40°C for three hours. The cooled reaction mixture was poured on ice water and extracted three times with portions of 100 ml ethyl acetate. The combined organic layers were dried over MgSO4. Then the solvent was removed in vacuo to obtain 2.70 g [4-difluoromethyl-2-(4-methoxy-phenyl)-thiazol-5-yl]-methanol.

C12H11F2NO2S (271.29), MS(ESI): 272.0 ($M+H^+$).

5-Chloromethyl-4-difluoromethyl-2-(4-methoxy-phenyl)-thiazole

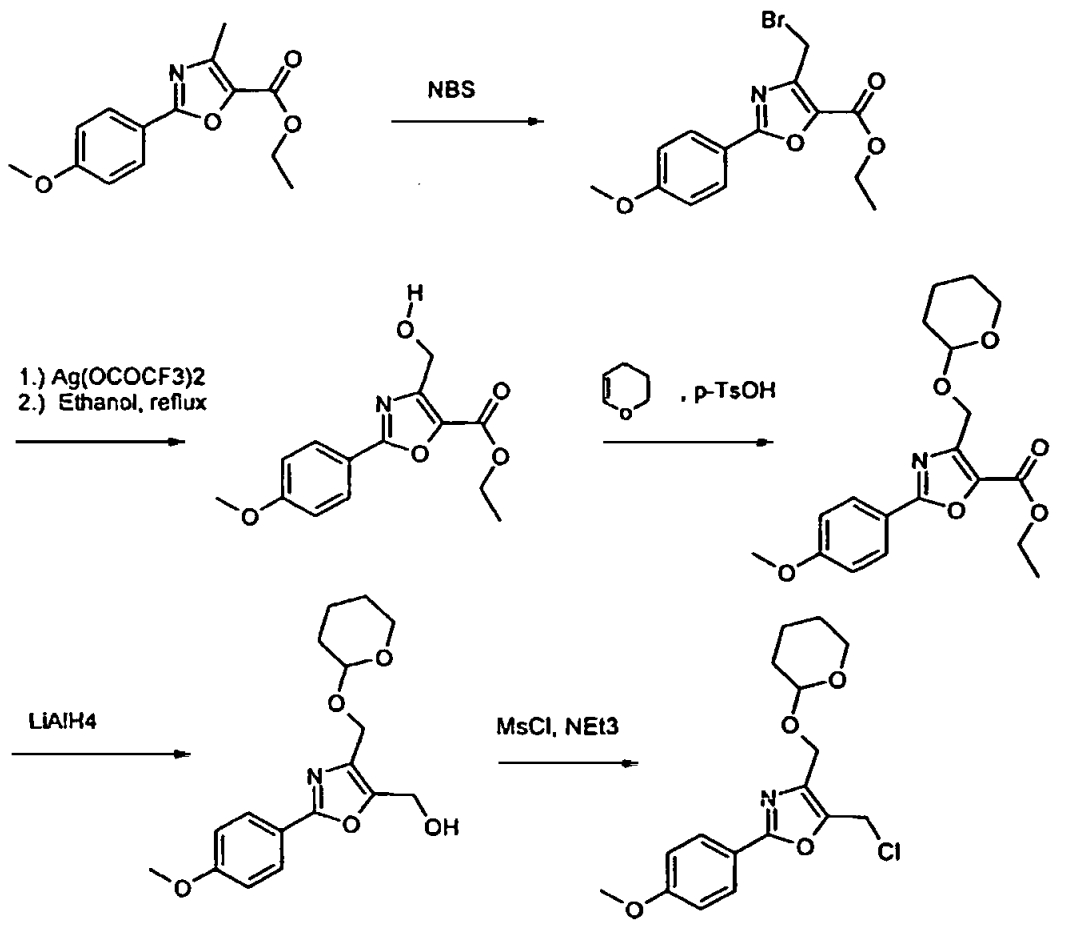


2.70 g [4-Difluoromethyl-2-(4-methoxy-phenyl)-thiazol-5-yl]-methanol were dissolved in 15 ml dichloromethane and cooled in an ice bath. 2.07 ml triethylamine were added, followed by the addition of 0.92 ml methanesulfonylchloride. The ice bath was removed and the resulting mixture stirred at room temperature over night. Then 2.07 ml triethylamine and 0.92 ml methanesulfonylchloride were added again and the reaction mixture stirred at room temperature for additional four hours. The reaction mixture was then washed with water and brine, dried over MgSO4 and the solvent removed in

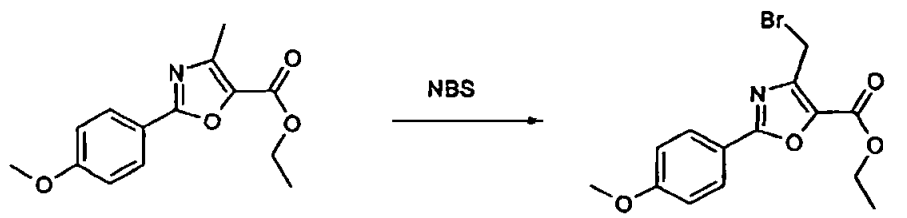
vacuo to obtain 3.0 g crude 5-chloromethyl-4-difluoromethyl-2-(4-methoxy-phenyl)-thiazole as an oil which was used without further purification.
C12H10ClF2NOS (289.73), MS(ESI): 289.9 ($M+H^+$), Rf(ethyl acetate:n-heptane = 1:1) = 0.76.

Building block synthesis according to process J:

[2-(4-Methoxy-phenyl)-4-(tetrahydro-pyran-2-yloxymethyl)-oxazol-5-yl]-methanol and 5-chloromethyl-2-(4-methoxy-phenyl)-4-(tetrahydro-pyran-2-yloxymethyl)-oxazole

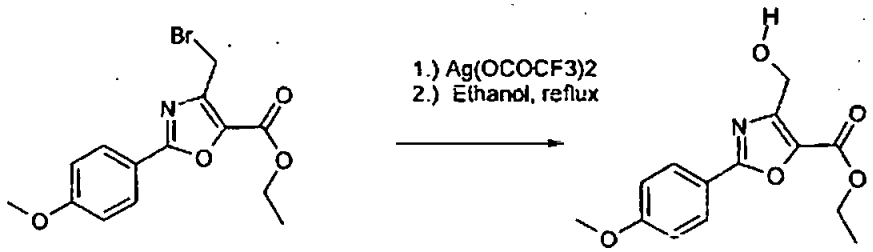


4-Bromomethyl-2-(4-methoxy-phenyl)-oxazole-5-carboxylic acid ethyl ester



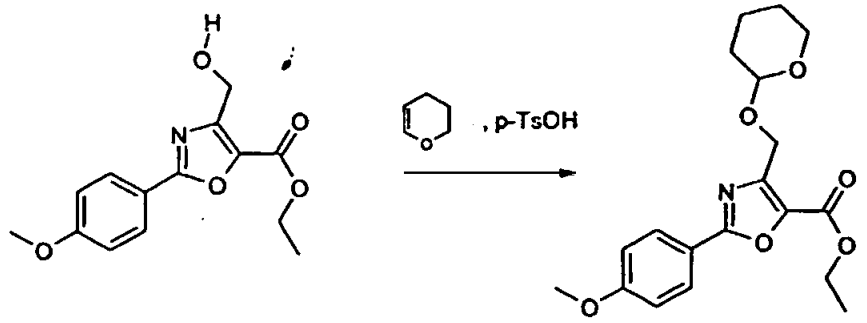
To a boiling solution of 23.5 g 2-(4-methoxy-phenyl)-4-methyl-oxazole-5-carboxylic acid ethyl ester in 250 ml tetrachloro-methane were added portionwise a mixture of 5.92 g 2,2'-azobis(2-methylpropionitrile) and 19.3 g N-bromosuccinimde. The reaction mixture was refluxed for seven hours. The cooled reaction mixture was filtered over a celite pad and the solvent removed in vacuo to obtain 30.7 g of crude 4-bromomethyl-2-(4-methoxy-phenyl)-oxazole-5-carboxylic acid ethyl ester. The material was used without further purification in the next step.
C14H14BrNO4 (340.18), MS(ESI): 340.0 and 342.0 ($M+H^+$), Rf(ethyl acetate:n-heptane = 7:3) = 0.43).

4-Hydroxymethyl-2-(4-methoxy-phenyl)-oxazole-5-carboxylic acid ethyl ester



30.7 g of crude 4-Bromomethyl-2-(4-methoxy-phenyl)-oxazole-5-carboxylic acid ethyl ester were dissolved in 170 ml dry dimethylformamide. 29.95 g Silver trifluoroacetate were added and the mixture was stirred at room temperature overnight. 100 ml brine was added and the mixture was stirred for one hour. The reaction mixture was filtered through a pad of celite, the solvent removed in vacuo and the resulting residue dissolved in 200 ml ethanol. The mixture was heated to reflux for three hours. Then the solvent was removed in vacuo and the residue dissolved in water and extracted five times with ethyl acetate. The combined organic layers were dried over MgSO4, the solvent removed in vacuo and the residue purified by flash chromatography on silica gel (eluting with n-heptane:ethyl acetate = 5:1 => ethylacetate) to obtain 17.8 g 4-hydroxymethyl-2-(4-methoxy-phenyl)-oxazole-5-carboxylic acid ethyl ester as a solid.
C14H15NO5 (277.28), MS(ESI): 278.1 ($M+H^+$), Rf(ethyl acetate:n-heptane = 1:2) = 0.11.

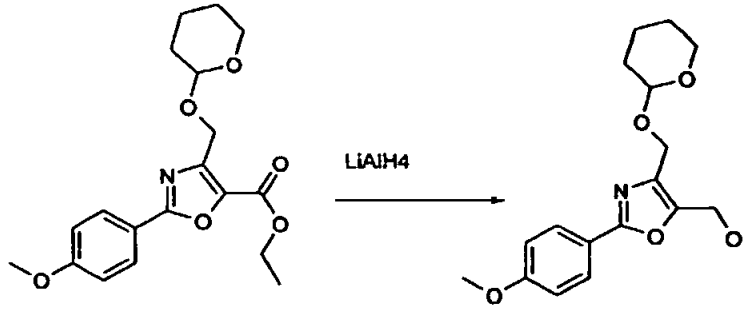
2-(4-Methoxy-phenyl)-4-(tetrahydro-pyran-2-yloxymethyl)-oxazole-5-carboxylic acid ethyl ester



10.0 g 4-Hydroxymethyl-2-(4-methoxy-phenyl)-oxazole-5-carboxylic acid ethyl ester were dissolved in 85 ml dichloromethane. 4.0 ml 3,4-dihydro-2H-pyran and 1.85 mg pyridinium p-toluenesulfonate were added and the reaction mixture stirred at room temperature overnight. The solvent was removed in vacuo and the residue purified by flash chromatography on silica gel (eluting with n-heptane:ethyl acetate = 4:1 => 1:1) to obtain 12.3 g 2-(4-methoxy-phenyl)-4-(tetrahydro-pyran-2-yloxymethyl)-oxazole-5-carboxylic acid ethyl ester as an oil.

C19H23NO6 (361.40), MS(ESI): 362.2 ($M+H^+$), 278.2 (M-THP+H^+), Rf(ethyl acetate:n-heptane = 1:1) = 0.56.

[2-(4-Methoxy-phenyl)-4-(tetrahydro-pyran-2-yloxymethyl)-oxazol-5-yl]-methanol

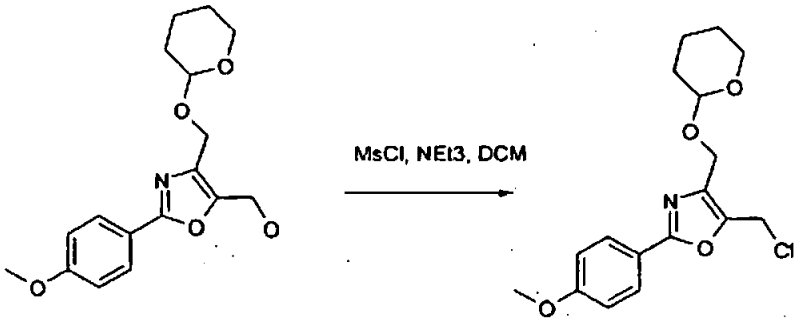


To a cooled suspension of 2.73 g lithium aluminium hydride in 180 ml tetrahydrofuran a solution of 12.3 g 2-(4-methoxy-phenyl)-4-(tetrahydro-pyran-2-yloxymethyl)-oxazole-5-carboxylic acid ethyl ester in 120 ml tetrahydrofuran were added at 0°C. The ice bath was removed and the reaction mixture stirred at room temperature for one hour. The reaction mixture was cooled in an ice bath again and 100 ml ethyl acetate were added followed by the addition of 300 ml methyl-tert-butyl ether. Then a solution of 10.92 g sodium hydroxide in 12.3 ml water was added. Solid precipitate was filtered off through

a plug of celite. The filtrate was dried over MgSO4 and then the solvent was removed in vacuo to obtain 11.8 g [2-(4-methoxy-phenyl)-4-(tetrahydro-pyran-2-yloxymethyl)-oxazol-5-yl]-methanol as a solid.

C17H21NO5 (319.36), MS(ESI): 320.2 ($M+H^+$), Rf(ethyl acetate:n-heptane = 1:1) = 0.18.

5-Chloromethyl-2-(4-methoxy-phenyl)-4-(tetrahydro-pyran-2-yloxymethyl)-oxazole

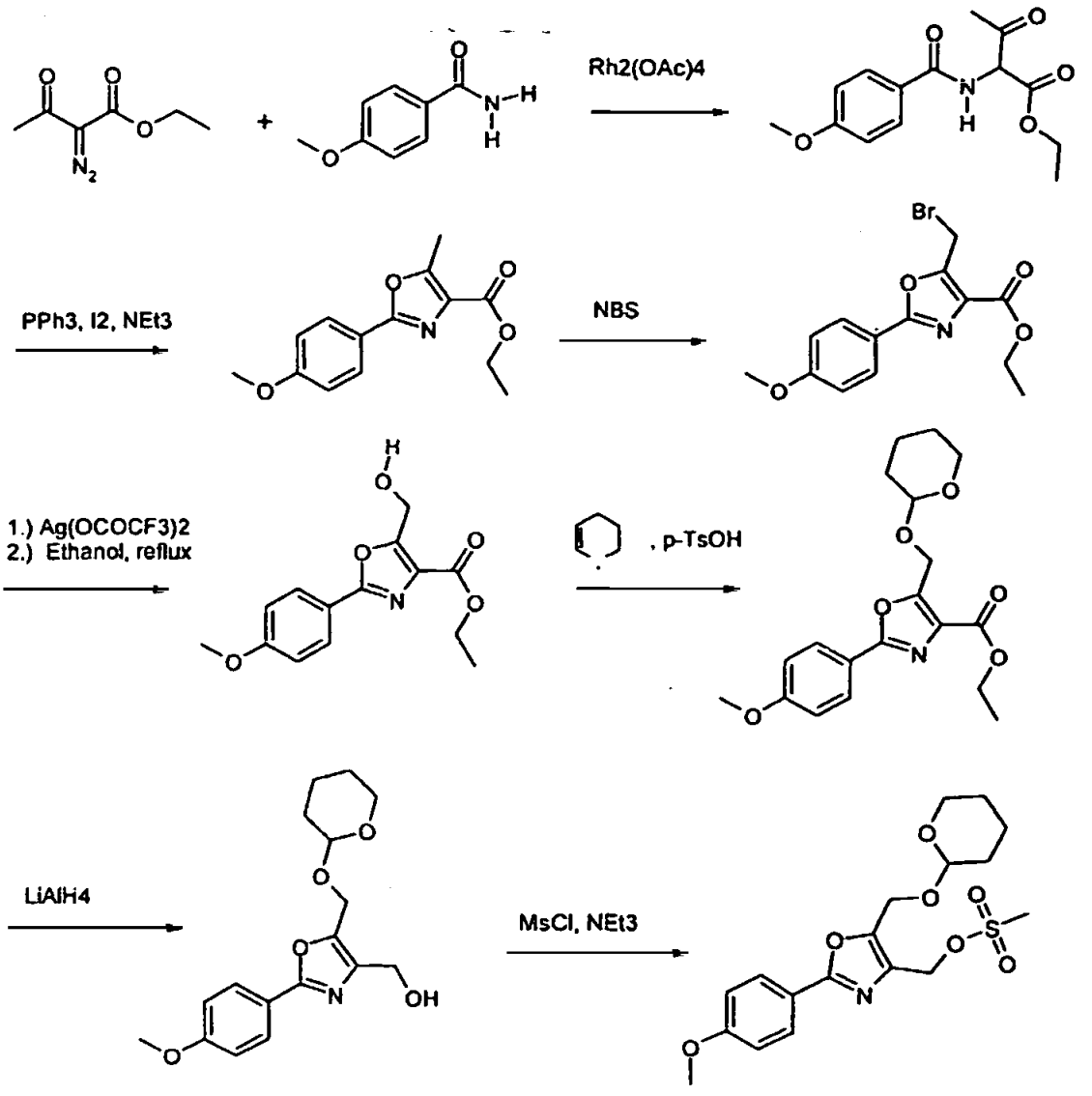


2.0 g [2-(4-Methoxy-phenyl)-4-(tetrahydro-pyran-2-yloxymethyl)-oxazol-5-yl]-methanol were dissolved in 30 ml dichloromethane and cooled in an ice bath. 0.88 ml triethylamine were added, followed by the addition of 0.49 ml methanesulfonylchloride. The ice bath was removed and the resulting mixture stirred at room temperature over night. The reaction mixture was then washed with water and brine, dried over MgSO4 and the solvent removed in vacuo to obtain 2.5 g of 5-chloromethyl-2-(4-methoxy-phenyl)-4-(tetrahydro-pyran-2-yloxymethyl)-oxazole as an oil which was used without further purification.

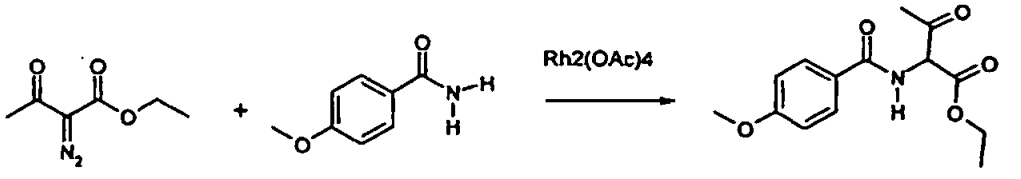
C17H20ClNO4 (337.81), MS(ESI): 338.2 ($M+H^+$), Rf(ethyl acetate:n-heptane = 1:1) = 0.42.

Building block synthesis according to process K:

[2-(4-Methoxy-phenyl)-5-(tetrahydro-pyran-2-yloxymethyl)-oxazol-4-yl]-methanol and methanesulfonic acid 2-(4-methoxy-phenyl)-5-(tetrahydro-pyran-2-yloxymethyl)-oxazol-4- ylmethyl ester



2-(4-Methoxy-benzoylamino)-3-oxo-butyric acid ethyl ester



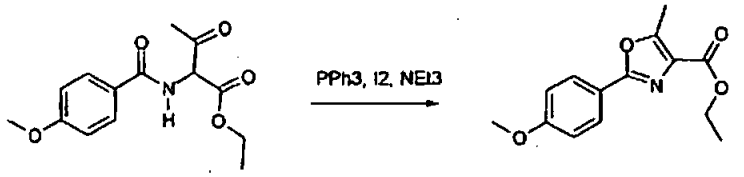
A solution of 12.1 g ethyl-2-diazo-3-oxobutanoate[3] in 100 ml 1,2-dichloroethane was added dropwise over 5 hours to a boiling solution of 9.0 g 4-methoxybenzamide and 1.05 g rhodium(II) acetate dimer in 200 ml dry 1,2-dichloroethane. The mixture was

[3] J.Chem.Soc., Perkin Trans. 1, 1998, 591-600.

refluxed for thirty minutes, allowed to cool, evaporated in vacuo and purified by flash chromatography on silica gel to obtain 11.3 g 2-(4-methoxy-benzoylamino)-3-oxo-butyric acid ethyl ester.

C14H17NO5 (279.30), MS(ESI): 280.2 ($M+H^+$), Rf(ethyl acetate:n-heptane = 1:1) = 0.32.

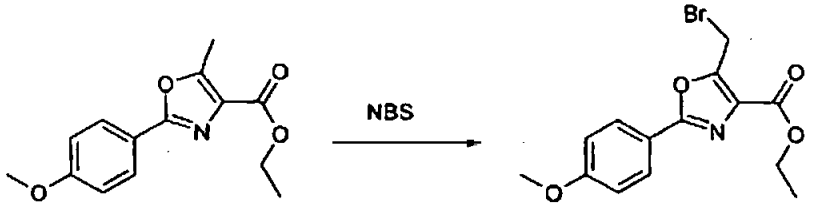
2-(4-Methoxy-phenyl)-5-methyl-oxazole-4-carboxylic acid ethyl ester



23.2 ml Triethylamine and a solution of 11.3 g 2-(4-methoxy-benzoylamino)-3-oxo-butyric acid ethyl ester in 200 ml dichloromethane were added sequentially to a stirred solution of 20.5 g iodine and 21.2 g triphenylphosphine in 500 ml dry dichloromethane. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated in vacuo and the resulting residue purified by flash chromatography on silica gel to obtain 6.0 g 2-(4-methoxy-phenyl)-5-methyl-oxazole-4-carboxylic acid ethyl ester as pale yellow solid.

C14H15NO4 (261.28), MS(ESI): 262.2 ($M+H^+$), Rf(ethyl acetate:n-heptane = 2:1) = 0.31.

5-Bromomethyl-2-(4-methoxy-phenyl)-oxazole-4-carboxylic acid ethyl ester

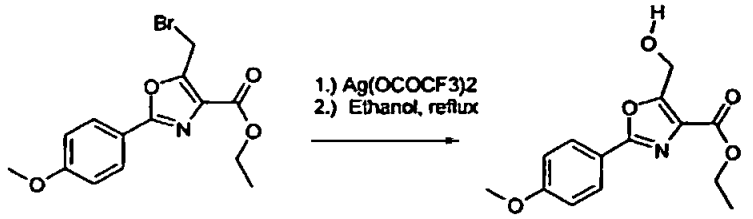


To a boiling solution of 6.0 g 2-(4-methoxy-phenyl)-5-methyl-oxazole-4-carboxylic acid ethyl ester in 100 ml tetrachloro-methane were added portionwise a mixture of 1.51 g 2,2'-azobis(2-methylpropionitrile) and 4.9 g N-bromosuccinimde. The reaction mixture was refluxed for three hours. The cooled reaction mixture was filtered over a celite pad and the solvent removed in vacuo to obtain 10.6 g of crude 5-bromomethyl-2-(4-methoxy-phenyl)-oxazole-4-carboxylic acid ethyl ester, which contains to some extend

the dibrominated byproduct. The material was used without further purification in the next step.

C14H14BrNO4 (340.18), MS(ESI): 340.0 and 342.0 ($M+H^+$), Rf(ethyl acetate:n-heptane = 2:1) = 0.27).

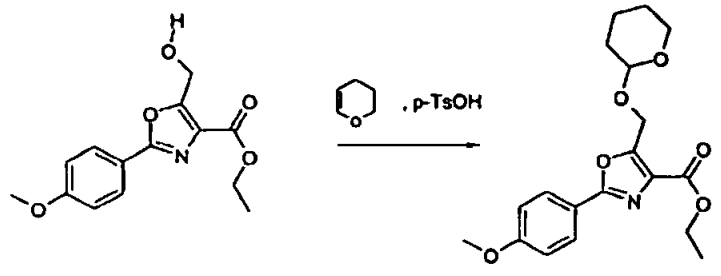
5-Hydroxymethyl-2-(4-methoxy-phenyl)-oxazole-4-carboxylic acid ethyl ester



8.0 g 5-Bromomethyl-2-(4-methoxy-phenyl)-oxazole-4-carboxylic acid ethyl ester were dissolved in 50 ml dry dimethylformamide. 7.8 g Silver trifluoroacetate were added and the mixture was stirred at room temperature for two hours. 30 ml brine were added and the mixture was stirred for two hours. The reaction mixture was filtered through a pad of celite, the solvent removed in vacuo and the resulting residue dissolved in 200 ml ethanol. The mixture was heated to reflux for three hours. Then the solvent was removed in vacuo and the residue dissolved in water and extracted five times with ethyl acetate. The combined organic layers were dried over MgSO4, the solvent removed in vacuo and the residue purified by flash chromatography on silica gel (eluting with n-heptane:ethyl acetate = 2:3 => ethylacetate) to obtain 4.8 g 5-hydroxymethyl-2-(4-methoxy-phenyl)-oxazole-4-carboxylic acid ethyl ester as a solid.

C14H15NO5 (277.28), MS(ESI): 278.1 ($M+H^+$), Rf(ethyl acetate:n-heptane = 1:2) = 0.09.

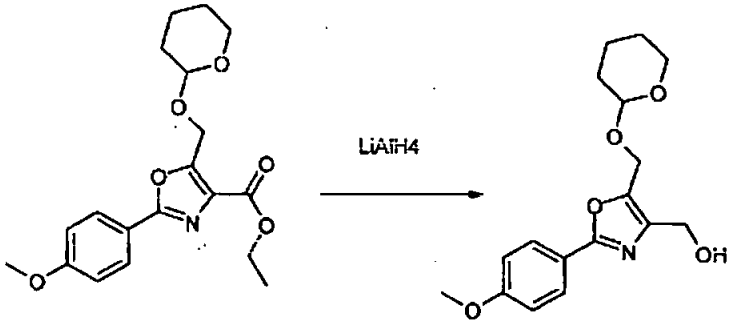
2-(4-Methoxy-phenyl)-5-(tetrahydro-pyran-2-yloxymethyl)-oxazole-4-carboxylic acid ethyl ester



4.8 g 5-Hydroxymethyl-2-(4-methoxy-phenyl)-oxazole-4-carboxylic acid ethyl ester were dissolved in 75 ml dichloromethane. 1.9 ml 3,4-dihydro-2H-pyran and 870 mg pyridinium p-toluenesulfonate were added and the reaction mixture stirred at room temperature over night. The solvent was removed in vacuo and the residue purified by flash chromatography on silica gel (eluting with n-heptane:ethyl acetate = 3:1 => 1:1) to obtain 5.3 g 2-(4-methoxy-phenyl)-5-(tetrahydro-pyran-2-yloxymethyl)-oxazole-4-carboxylic acid ethyl ester.

C19H23NO6 (361.40), MS(ESI): 362.2 ($M+H^+$), 278.1 ($M-THP+H^+$).

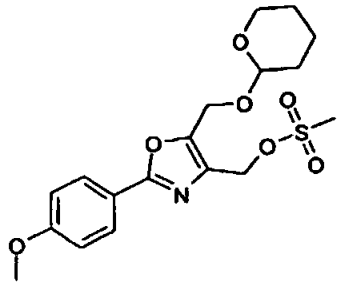
[2-(4-Methoxy-phenyl)-5-(tetrahydro-pyran-2-yloxymethyl)-oxazol-4-yl]-methanol



5.3 g 2-(4-Methoxy-phenyl)-5-(tetrahydro-pyran-2-yloxymethyl)-oxazole-4-carboxylic acid ethyl ester were dissolved in 100 ml tetrahydrofuran and cooled in an ice bath. 21.8 ml of a one molar solution of lithium aluminium hydride in tetrahydrofuran were added. The cooling bath was removed and the reaction mixture stirred at room temperature for thirty minutes. The reaction mixture was cooled in an ice bath again and sequentially added 6 ml water, 12 ml 15% NaOH and 18 ml water. After being stirred for one hour at room temperature the reaction mixture was filtered over a pad of celite and washed with ethyl acetate. The filtrate was dried over MgSO4 and the solvent was removed in vacuo and the residue purified by flash chromatography on silica gel (eluting with n-heptane:ethyl acetate = 6:4 => 9:1 => ethyl acetate) to obtain 3.0 g [2-(4-methoxy-phenyl)-5-(tetrahydro-pyran-2-yloxymethyl)-oxazol-4-yl]-methanol.

C17H21NO5 (319.36), MS(ESI): 320.2 ($M+H^+$).

Methanesulfonic acid 2-(4-methoxy-phenyl)-5-(tetrahydro-pyran-2-yloxymethyl)-oxazol-4- ylmethyl ester

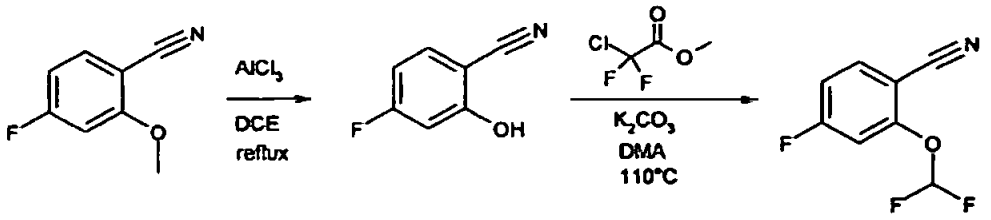


0,44 g [2-(4-Methoxy-phenyl)-5-(tetrahydro-pyran-2-yloxymethyl)-oxazol-4-yl]-methanol were dissolved in 30 ml dichloromethane and cooled in an ice bath. 0.29 ml triethylamine were added, followed by the addition of 0.13 ml methanesulfonylchloride. The reaction mixture was stirred at 0°C for one hour then the ice bath was removed and the resulting mixture stirred at room temperature for an additional hour. The reaction mixture was then washed with water and brine, dried over MgSO4 and the solvent removed in vacuo to obtain 0,55 mg of methanesulfonic acid 2-(4-methoxy-phenyl)-5-(tetrahydro-pyran-2-yloxymethyl)-oxazol-4- ylmethyl ester as an oil which was used without further purification.

C18H23NO7S (397.45), MS(ESI): 398.2 ($M+H^+$).

Building block synthesis according to process N:

2-Difluoromethoxy-4-fluoro-benzonitrile



4-Fluoro-2-methoxy-benzonitrile was prepared according to a previous publication:[4] To a solution of 1 g of 4-fluoro-2-methoxy-benzonitrile in 15 mL of dichloroethane was added 1.1 g of aluminium trichloride. The resulting mixture was refluxed for 1 day then poured slowly into water and extracted with ethyl acetate. The organic extracts were

[4] JP9143139

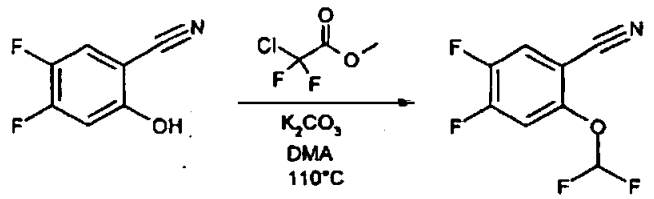
washed twice with 10% aqueous solution of sodium hydroxide. The combined basic layers were washed twice with ethyl acetate, acidified with concentrated aqueous solution of hydrochloric acid and extracted three times with ethyl acetate. The combined organic extracts were washed with water, with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure to give 0.78 g of 4-fluoro-2-hydroxy-benzonitrile as a white solid.

C7H4FNO (137.11), MS(ESI): 138.17 ($M+H^+$).

To a solution of 4.6 g of 4-fluoro-2-hydroxy-benzonitrile in 15 mL of anhydrous dimethylacetamide were added 6.8 g of methyl chlorodifluororacetate and 6.5 g of potassium carbonate. The resulting mixture was degassed by bubbling argon through it and heated to 110°C for 2h then an additional 6.5 g of methyl chlorodifluororacetate and 6.5 g of potassium carbonate were added. The resulting mixture was heated to 110°C for another hour then concentrated under reduced pressure. The residue was taken into ethyl acetate, washed twice with a molar aqueous solution of sodium hydroxide, with water and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (gradient from heptane 100 to heptane 80/ ehtyl acetate 20) to give 4.78 g of 2-difluoromethoxy-4-fluoro-benzonitrile as a yellowish liquid.

C8H4F3NO (187.12), MS(ESI): 188.0 ($M+H^+$).

2-Difluoromethoxy-4,5-difluoro-benzonitrile



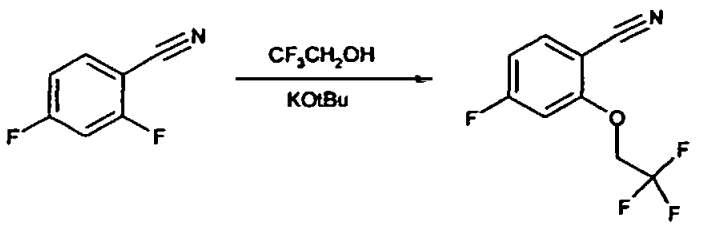
To a solution of 1 g of commercially available 4,5-difluoro-2-hydroxy-benzonitrile in 5 mL of anhydrous dimethylacetamide were added 1.3 g of methyl chlorodifluororacetate and 1.28 g of potassium carbonate. The resulting mixture was degassed by bubbling argon through it and heated to 110°C for 1.5h then concentrated under reduced pressure. The residue was taken into ethyl acetate, washed twice with a molar aqueous solution of sodium hydroxide, with water and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was

purified by column chromatography on silica gel (gradient from heptane 100 to heptane 80/ ehtyl acetate 20) to give 0.42 g of 2-difluoromethoxy-4,5-difluoro-benzonitrile as a yellowish liquid.

C8H3F4NO (205.11), MS(EI): 205 (M^+).

Building block synthesis according to process M:

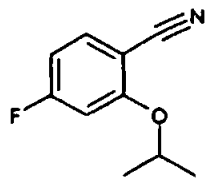
4-Fluoro-2-(2,2,2-trifluoro-ethoxy)-benzonitrile



To a solution of 359 mg of trifluoroethanol in 3 mL of anhydrous tetrahydrofuran at 5°C was slowly added 3.6 mL of a molar solution of potassium tert-butoxide in tert-butanol. The resulting solution was stirred for 30 minutes at 5°C and slowly added to a solution of 500 mg of 2,4-difluoro-benzonitrile in 3 mL of anhydrous tetrahydrofuran at 5°C. The resulting mixture was stirred for 1h at 5°C, then poured into water and extracted with ethyl acetate. The organic extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (gradient from heptane 100 to heptane 90/ ethyl acetate 10) to give 640 mg of 4-fluoro-2-(2,2,2-trifluoro-ethoxy)-benzonitrile as a white solid.

C9H5F4NO (219.14), MS(ESI): 220 ($M+H^+$).

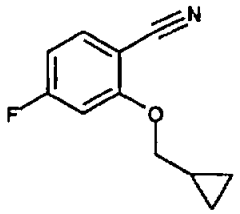
4-Fluoro-2-isopropoxy-benzonitrile



According to the method described for 4-fluoro-2-(2,2,2-trifluoro-ethoxy)-benzonitrile, 4-fluoro-2-isopropoxy-benzonitrile was obtained from 2,4-difluoro-benzonitrile and isopropanol.

C10H10FNO (179.20), MS(ESI): 180 ($M+H^+$).

2-Cyclopropylmethoxy-4-fluoro-benzonitrile



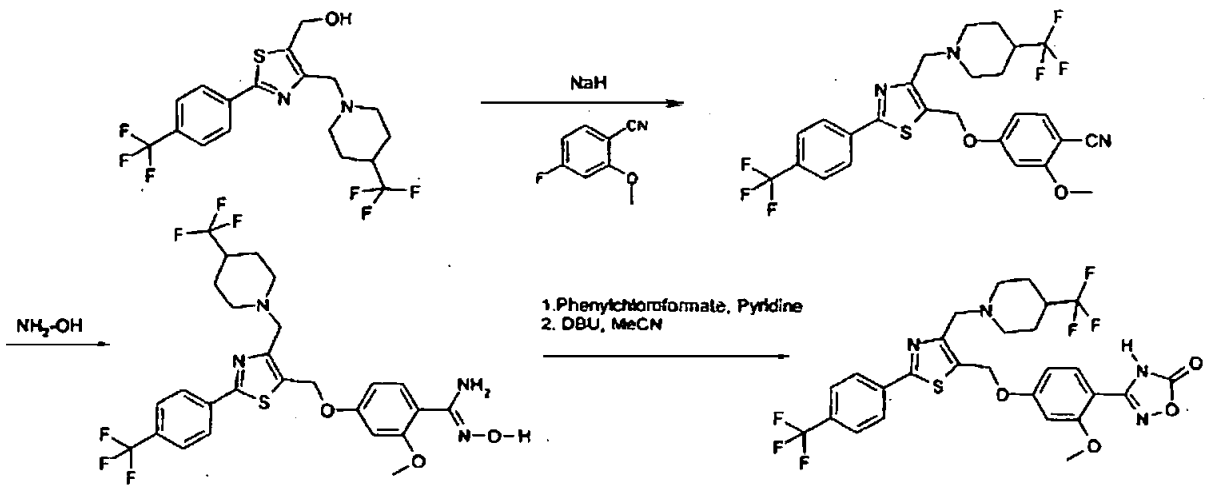
According to the method described for 4-fluoro-2-(2,2,2-trifluoro-ethoxy)-benzonitrile, 2-cyclopropylmethoxy-4-fluoro-benzonitrile was obtained from 2,4-difluoro-benzonitrile and cyclopropylmethanol.

C11H10FNO (191.21), MS(EI): 205 (M^+).

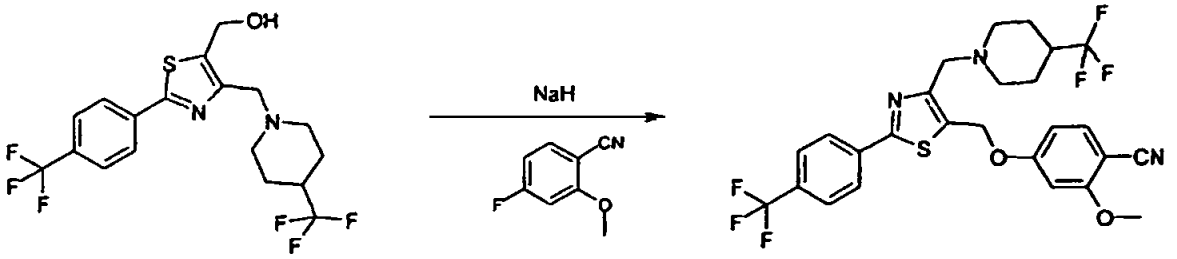
The following examples were prepared according to process B:

Example 1

3-{2-Methoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one



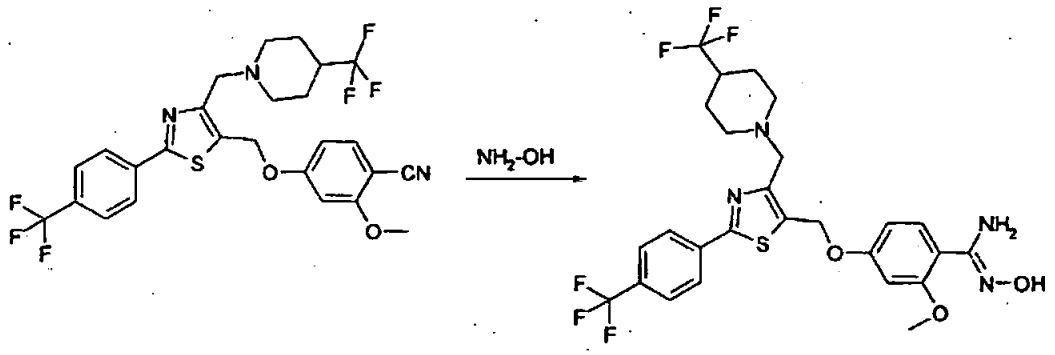
2-Methoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-benzonitrile



To a solution of 474 mg of [2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-yl]-methanol in 2.9 mL of dimethylformamide was added 60 mg of sodium hydride. The resulting mixture was stirred for 30 minutes at 0°C then 208 mg of 4-fluoro-2-methoxybenzonitrile was added. After stirring for 30 minutes at 0°C, the temperature was allowed to warm up to room temperature and the reaction mixture was stirred for 30 minutes. The solvent was removed under reduced pressure and dichloromethane/water was added to the residue. The organic layer was separated and the aqueous layer extracted three times with dichloromethane. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (dichloromethane 95/ methanol 5) to give 279 mg of 2-methoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-benzonitrile.

C26H23F6N3O2S (555.55), MS(ESI): 556 ($M+H^+$).

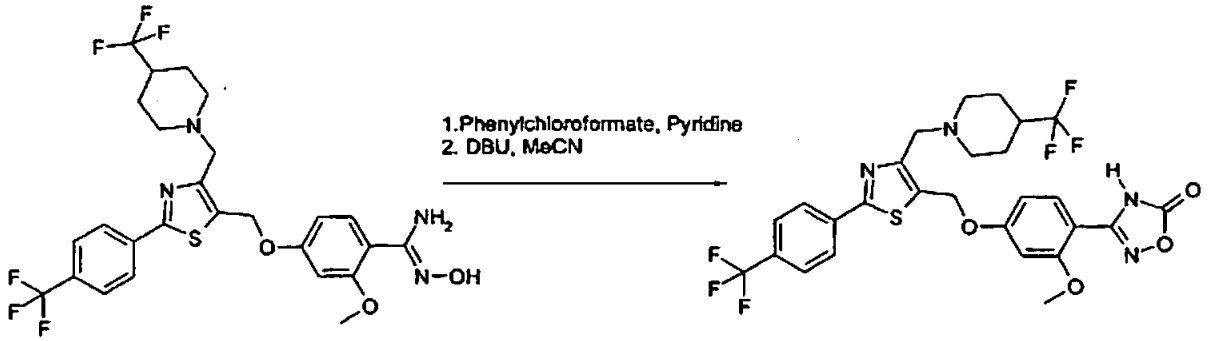
N-hydroxy-2-methoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-benzamidine



To a solution of 279 mg of 2-methoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-benzonitrile in 3 mL of tetrahydrofuran and 1.5 mL of methanol was added 333 mg of hydroxylamine hydrochloride followed by 0.69 mL of triethylamine. The resulting mixture was heated to 60°C overnight. After allowing it to cool down to room temperature, the mixture was poured into water and extracted with dichloromethane. The organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (gradient from dichloromethane 100 to dichloromethane 95/ methanol 5) to give 154 mg of *N*-hydroxy-2-methoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-benzamidine.

C26H26F6N4O3S (588.58), MS(ESI): 589 (M^++H).

3-{2-Methoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one



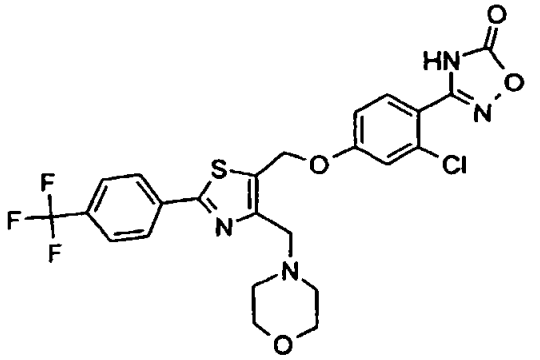
To a solution of 150 mg of *N*-hydroxy-2-methoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-benzamidine in 5 mL of

anhydrous dichloromethane at 0°C were dropwise added 50 µL of pyridine followed by 40 µL of phenylchloroformate. The resulting mixture was stirred at room temperature for 1 h then water and dichloromethane were added. The aqueous layer was separated and extracted with dichloromethane. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. To a solution of the resulting residue in 2.7 mL of acetonitrile was added 60 µL of 1,8-diazabicyclo[5.4.0]undec-7-ene. The mixture was stirred at room temperature overnight. The solvent was removed under vacuo. The resulting residue was taken into tetrahydrofuran/ethyl acetate 50/50, washed with water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (gradient from dichloromethane 100 to dichloromethane 90/ methanol 10) to give 105 mg of 3-{2-methoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one.

C27H24F6N4O4S (614.57), MS (EI): 614 (M^+).

Example 2

3-{2-Chloro-4-[4-morpholin-4-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

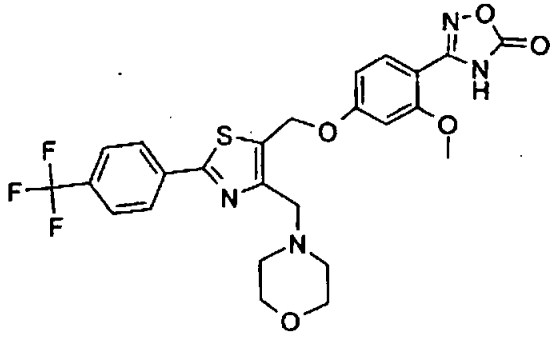


According to the method described in Example 1, 3-{2-chloro-4-[4-morpholin-4-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from [4-morpholin-4-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol and commercially available 2-chloro-4-fluoro-benzonitrile.

C24H20ClF3N4O4S (552.96), MS(EI): 552 (M^+).

Example 3

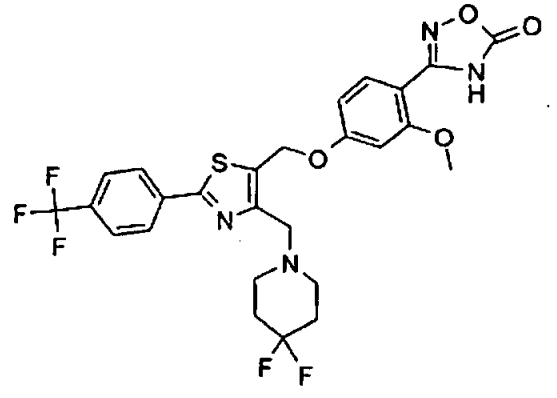
3-{2-Methoxy-4-[4-morpholin-4-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one



According to the method described in Example 1, 3-{2-methoxy-4-[4-morpholin-4-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from [4-morpholin-4-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol and commercially available 4-fluoro-2-methoxybenzonitrile. C25H23F3N4O5S (548.54), MS(ESI): 549 ($M+H^+$).

Example 4

3-{4-[4-(4,4-Difluoro-piperidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one

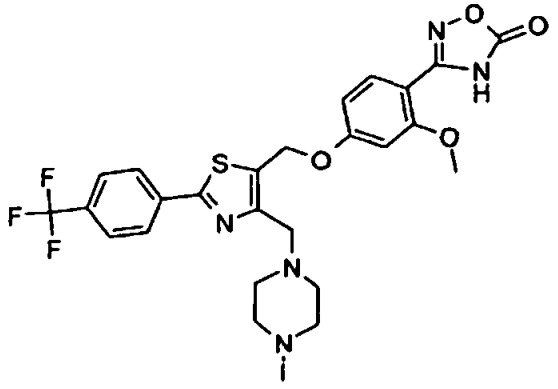


According to the method described in Example 1, 3-{4-[4-(4,4-difluoro-piperidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 4-(4,4-difluoro-piperidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol and commercially available 4-fluoro-2-methoxybenzonitrile.

C26H23F5N4O4S (582.55); MS(ESI): 583 ($M+H^+$).

Example 5

3-{2-Methoxy-4-[4-(4-methyl-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

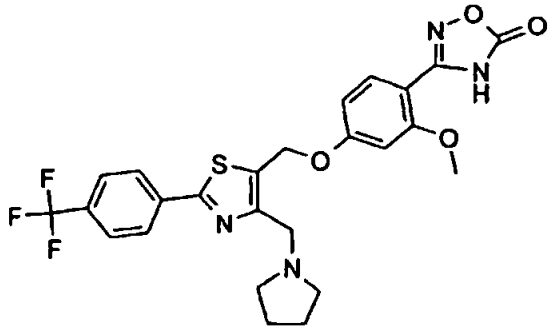


According to the method described in Example 1, 3-{2-methoxy-4-[4-(4-methyl-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from [4-(4-methyl-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol and commercially available 4-fluoro-2-methoxybenzonitrile.

C26H26F3N5O4S (561.59), MS(ESI): 562 ($M+H^+$).

Example 6

3-{2-Methoxy-4-[4-pyrrolidin-1-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

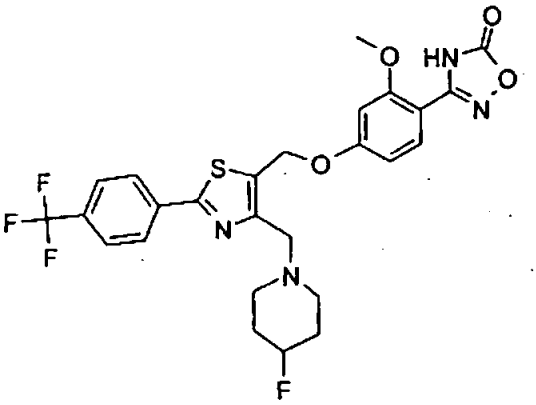


According to the method described in Example 1, 3-{2-methoxy-4-[4-pyrrolidin-1-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-

5-one was obtained from [4-pyrrolidin-1-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol and commercially available 4-fluoro-2-methoxybenzonitrile.
C25H23F3N4O4S (532.54), MS(ESI): 533 ($M+H^+$).

Example 7

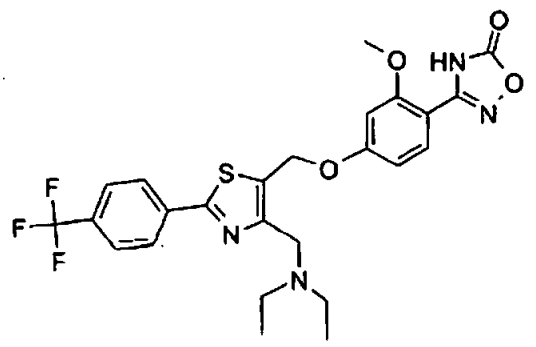
3-{4-[4-(4-Fluoro-piperidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one



According to the method described in Example 1, 3-{4-[4-(4-fluoro-piperidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from [4-(4-fluoro-piperidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol and commercially available 4-fluoro-2-methoxybenzonitrile.
C26H24F4N4O4S (564.56), MS(ESI): 565 ($M+H^+$).

Example 8

3-{4-[4-Diethylaminomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one

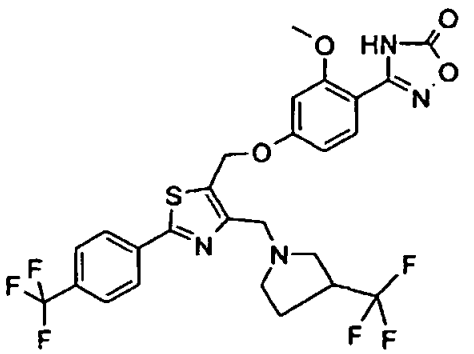


According to the method described in Example 1, 3-{4-[4-diethylaminomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from [4-diethylaminomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol and commercially available 4-fluoro-2-methoxybenzonitrile.

C25H25F3N4O4S (534.56), MS(ESI): 535 ($M+H^+$).

Example 9

3-{2-Methoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(3-trifluoromethyl-pyrrolidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

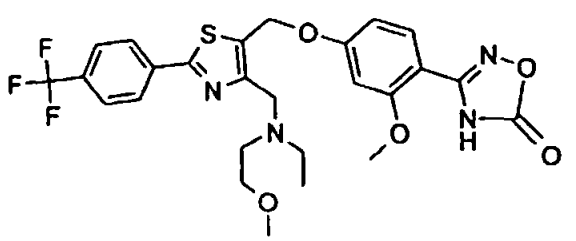


According to the method described in Example 1, racemic 3-{2-methoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(3-trifluoromethyl-pyrrolidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from racemic [2-(4-trifluoromethyl-phenyl)-4-(3-trifluoromethyl-pyrrolidin-1-ylmethyl)-thiazol-5-yl]-methanol and commercially available 4-fluoro-2-methoxybenzonitrile.

C26H22F6N4O4S (600.54), MS(ESI): 601 ($M+H^+$).

Example 10

3-{4-[4-{[Ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one

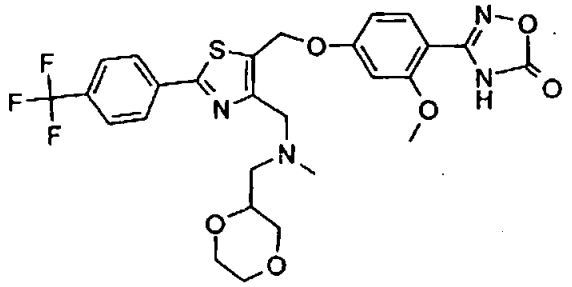


According to the method described in Example 1, 3-{4-[4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from [4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol and commercially available 4-fluoro-2-methoxybenzonitrile.

C26H27F3N4O5S (564.59), MS(CI): 565 ($M+H^+$).

Example 11

3-{4-[4-[([1,4]Dioxan-2-ylmethyl-methyl-amino)-methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one

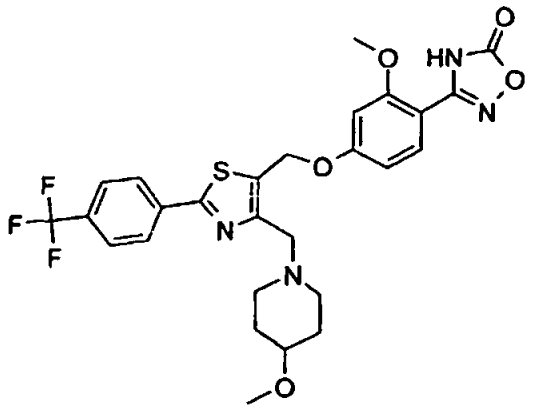


According to the method described in Example 1, racemic 3-{4-[4-[([1,4]dioxan-2-ylmethyl-methyl-amino)-methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from racemic [4-[([1,4]dioxan-2-ylmethyl-methyl-amino)-methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol and commercially available 4-fluoro-2-methoxybenzonitrile.

C27H27F3N4O6S (592.60), MS(ESI): 593 ($M+H^+$).

Example 12

3-{2-Methoxy-4-[4-(4-methoxy-piperidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

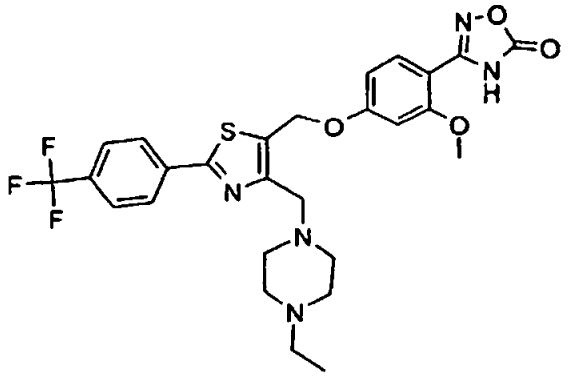


According to the method described in Example 1, 3-{2-methoxy-4-[4-(4-methoxy-piperidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from [4-(4-methoxy-piperidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol and commercially available 4-fluoro-2-methoxybenzonitrile.

C27H27F3N4O5S (576.60), MS(ESI): 577 ($M+H^+$).

Example 13

3-{4-[4-(4-Ethyl-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one

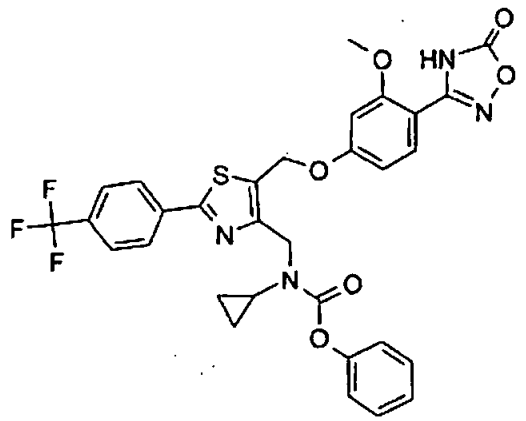


According to the method described in Example 1, 3-{4-[4-(4-ethyl-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from [4-(4-ethyl-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol and commercially available 4-fluoro-2-methoxybenzonitrile.

C27H28F3N5O4S (575.61), MS(ESI): 576 ($M+H^+$).

Example 14

Cyclopropyl-[5-[3-methoxy-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethyl]-carbamic acid phenyl ester

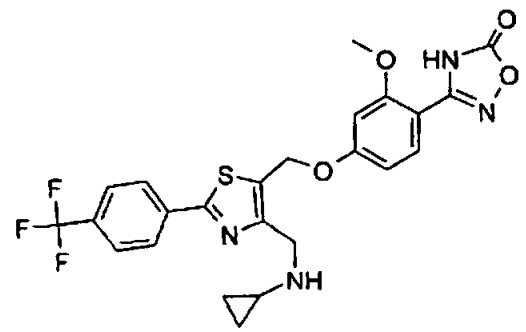


According to the method described in Example 1, cyclopropyl-[5-[3-methoxy-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethyl]-carbamic acid phenyl ester was obtained from [4-cyclopropylaminomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol and commercially available 4-fluoro-2-methoxybenzonitrile. During the formation of the oxadiazolone ring, the secondary cyclopropylamine reacted with phenyl chloroformate to give the cited phenyl carbamate.

C31H25F3N4O6S (638.63), MS(CI): 639 ($M+H^+$).

Example 15

3-[4-[4-Cyclopropylaminomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl]-4H-[1,2,4]oxadiazol-5-one



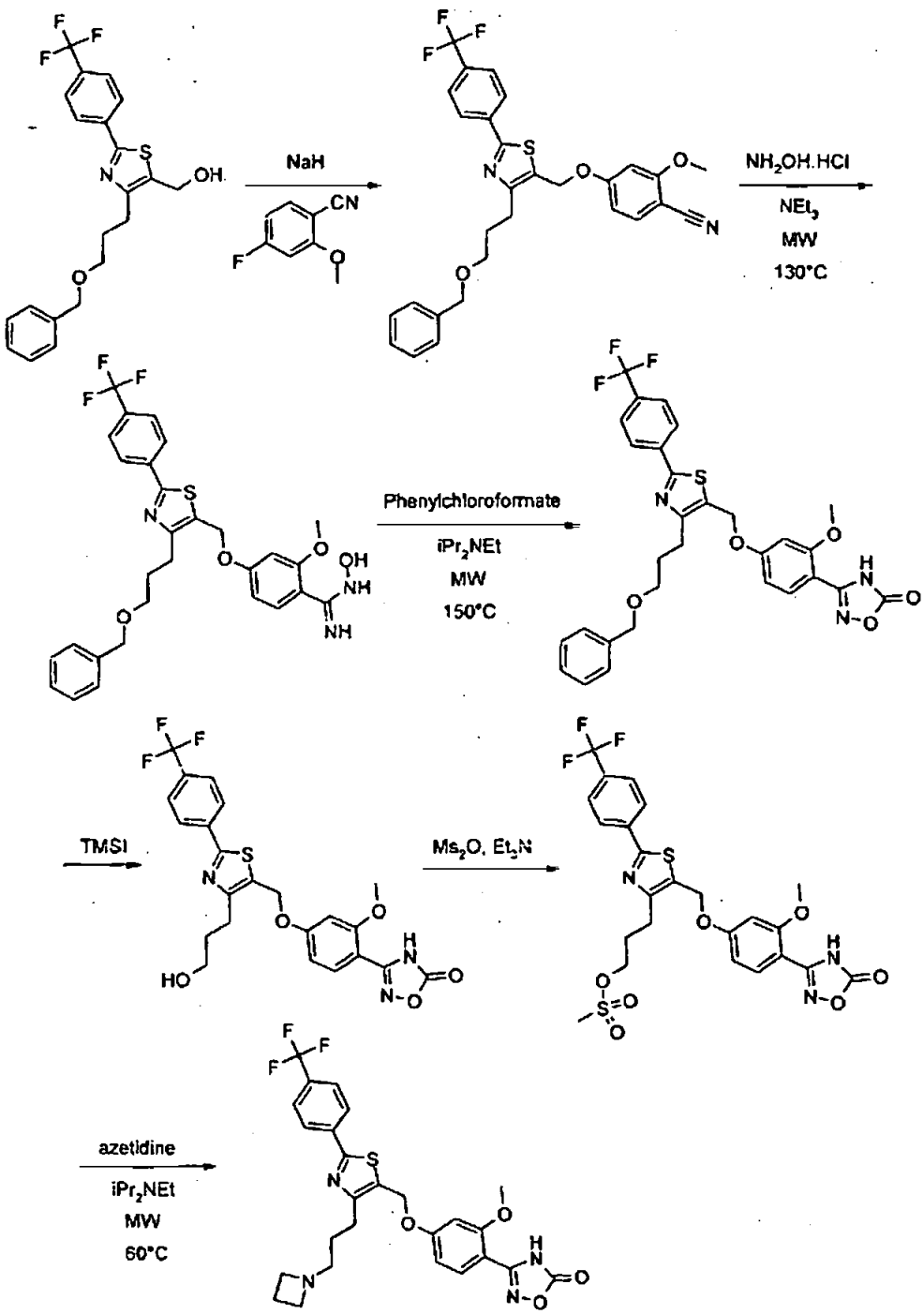
To a solution of 32.6 mg of cyclopropyl-[5-[3-methoxy-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethyl]-carbamic acid phenyl ester in 2 mL of ethylene glycol was added 2 mL of a saturated solution of potassium hydroxide in water. The resulting mixture was stirred in a sealed tube under microwave irradiation for 25 minutes to 100°C, then 10 additional minutes to 120°C and finally 15 more minutes to 140°C. It was then extracted with dichloromethane. The organic extracts were washed water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (gradient from dichloromethane 100 to dichloromethane 90/ methanol 10) to give 9.5 mg of 3-{4-[4-cyclopropylaminomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one.

C24H21F3N4O4S (518.52), MS(ESI): 519 ($M+H^+$).

The following examples were prepared according to process D, whereby the first two reaction steps were performed according to process B:

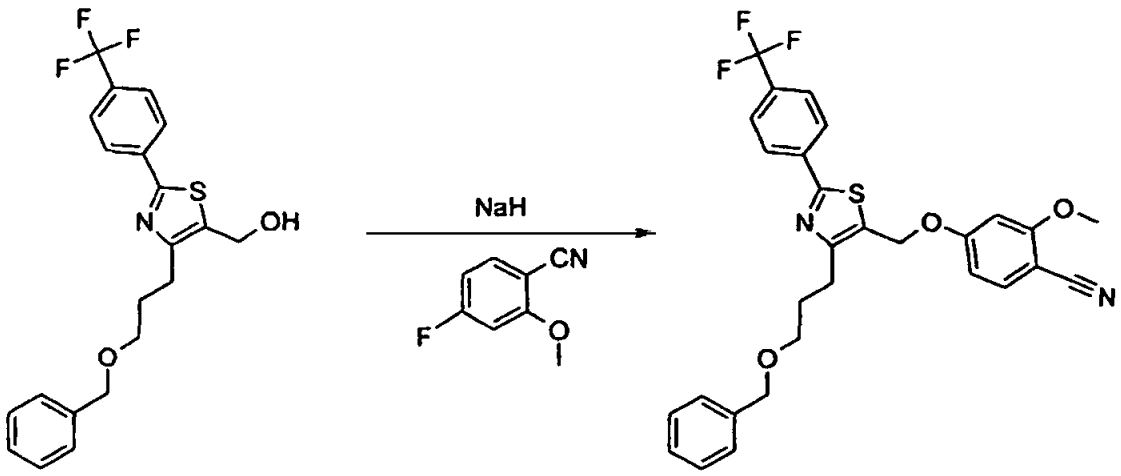
Example 16

3-{4-[4-(3-Azetidin-1-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one


NaH
NH2OH.HCl
NEt3
MW
130°C
Phenylchloroformate
iPr2NEt
MW
150°C
TMSI
Ms2O, Et3N
azetidine
iPr2NEt
MW
60°C

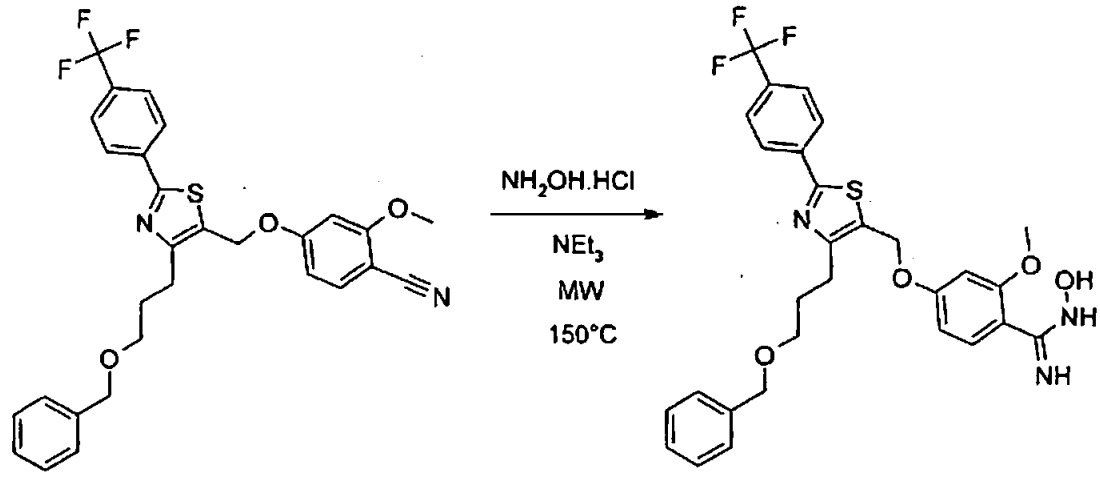
5

4-[4-(3-Benzyloxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-benzonitrile



To a solution of 1.34 g of [4-(3-benzyloxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol in 20 mL of dimethylformamide at 0°C was added 158 mg of a 60% suspension of sodium hydride in mineral oil. The resulting mixture was stirred for 10 minutes at 0°C then 497 mg of 4-fluoro-2-methoxybenzonitrile were added. After stirring for 30 minutes at 0°C, the temperature was allowed to warm up to room temperature and the reaction mixture was stirred until completion. The solvent was removed under reduced pressure and dichloromethane/water were added to the residue. The organic layer was separated and the aqueous layer extracted three times with dichloromethane. The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give 1.82 g of crude product as a yellow oil. A 1/1 solution of heptane/ diisopropyl ether was added to the residue and the solidified product was filtered off to provide a first crop of 1.26 g of desired product. The mother liquor was concentrated and purified by column chromatography on silica gel (heptane 60/ ethyl acetate 40) to give an additional 110 mg. The two fractions were combined to obtain 1.37 g of 4-[4-(3-benzyloxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-benzonitrile.
C29H25F3N2O3S (538.59), MS(ESI): 539 ($M+H^+$).

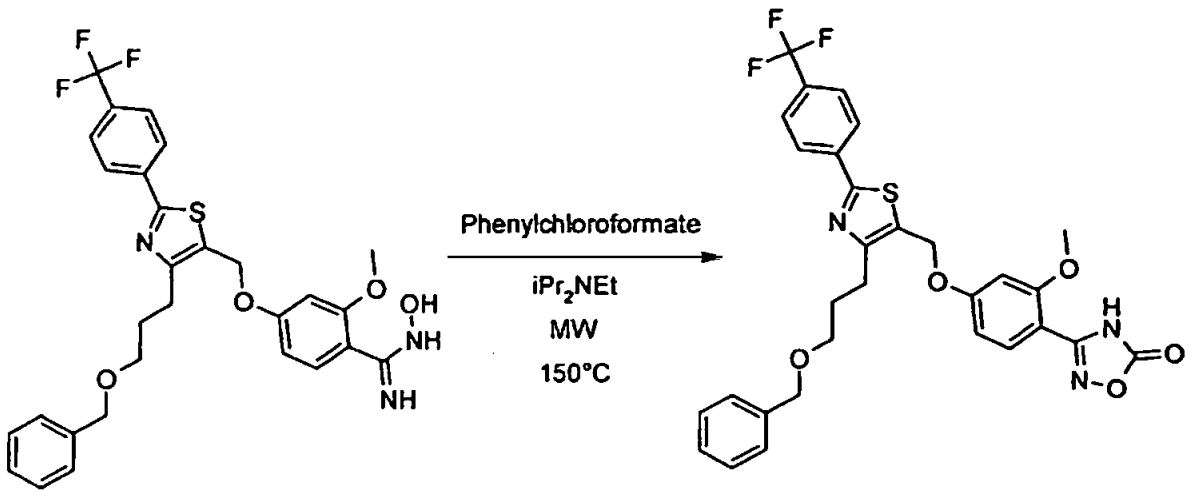
4-[4-(3-Benzyloxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxyl-*N*-hydroxy-2-methoxy-benzamidine



To a solution of 300 mg of 4-[4-(3-benzyloxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-benzonitrile in 1.8 mL of tetrahydrofuran and 2 mL of methanol was added 387 mg of hydroxylamine hydrochloride followed by 0.62 mL of triethylamine. The resulting mixture was heated to 150°C under microwave irradiation for 10 minutes. After allowing it to cool down to room temperature, the mixture was concentrated under reduced pressure and dichloromethane/water were added to the residue. The organic layer was separated and the aqueous layer extracted three times with dichloromethane. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (heptane 50/ ethyl acetate 50) to give 162 mg of 4-[4-(3-benzyloxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-*N*-hydroxy-2-methoxy-benzamidine.

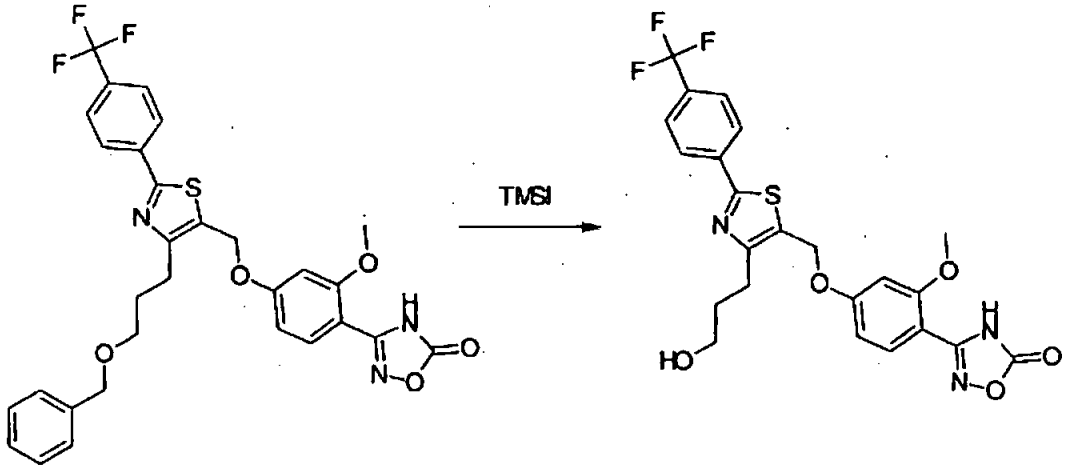
C29H28F3N3O4S (571.62), MS(ESI): 572 ($M+H^+$).

3-{4-[4-(3-Benzyloxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one



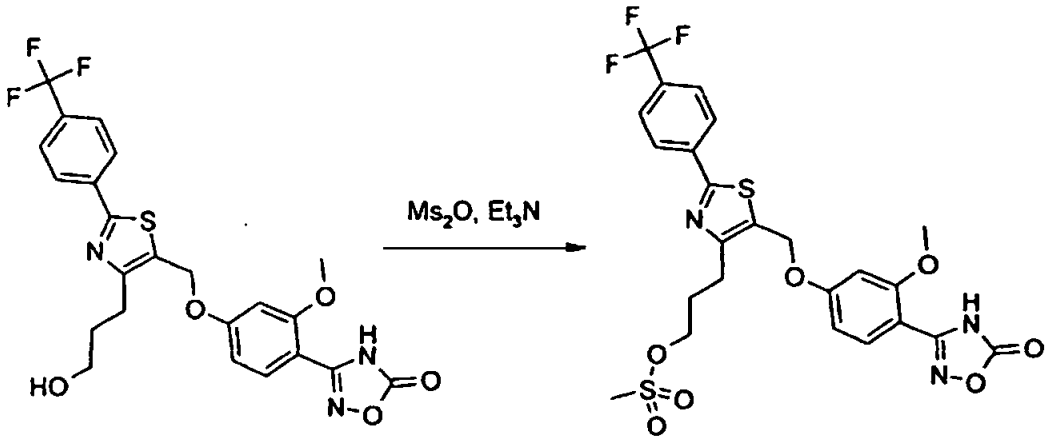
To a solution of 1.05 g of 4-[4-(3-benzyloxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-*N*-hydroxy-2-methoxy-benzamidine in 5 mL of tetrahydrofuran were added 254 µL of phenyl chloroformate and 607 µL of diisopropylethylamine. The resulting mixture was heated to 150°C under microwave irradiation for 20 minutes. After allowing it to cool down to room temperature, the mixture was concentrated under reduced pressure and dichloromethane/water were added to the residue. The organic layer was separated and the aqueous layer extracted three times with dichloromethane. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Diisopropyl ether was added to the residue and the solid was collected by filtration and washed with diisopropyl ether to give 558 mg of 3-{4-[4-(3-benzyloxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one.
C30H26F3N3O5S (597.62), MS(ESI): 598 ($M+H^+$).

3-{4-[4-(3-Hydroxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one



118 mg of 3-{4-[4-(3-benzyloxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one were dissolved in 14 mL of dichloromethane by heating and allowing to cool down to room temperature. To the resulting solution was added 144 µL of iodotrimethylsilane. The resulting mixture was stirred at room temperature for 6.5 h and 6 mL of methanol were added followed by a saturated aqueous solution of sodium bicarbonate. The mixture was stirred for 1 h, filtered and concentrated under reduced pressure. Dichloromethane/water were added to the residue. The organic layer was separated and the aqueous layer extracted three times with dichloromethane. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (dichloromethane 90/ methanol 10) to give 40 mg of 3-{4-[4-(3-hydroxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one.
$C_{23}H_{20}F_3N_3O_5S$ (507.49), MS(ESI): 508 ($M+H^+$).

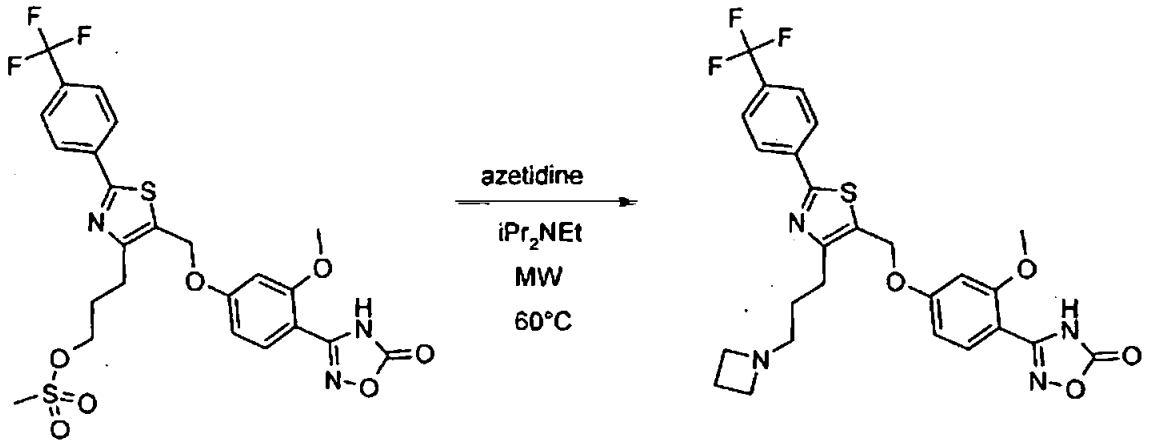
Methanesulfonic acid 3-[5-[3-methoxy-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazol-4-yl]-propyl ester



To a solution of 300 mg of 3-{4-[4-(3-hydroxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one in 15 mL of dichloromethane was added 1.2 mL of triethylamine and 217 mg of methanesulfonic anhydride. The resulting mixture was stirred at room temperature for 1 hour. A saturated aqueous solution of ammonium chloride was added. The organic layer was separated and the aqueous layer extracted three times with dichloromethane. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give 228 mg of methanesulfonic acid 3-[5-[3-methoxy-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazol-4-yl]-propyl ester which was used in the next step without further purification.

C24H22F3N3O7S2 (585.58), MS(ESI): 586 ($M+H^+$).

3-{4-[4-(3-Azetidin-1-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one

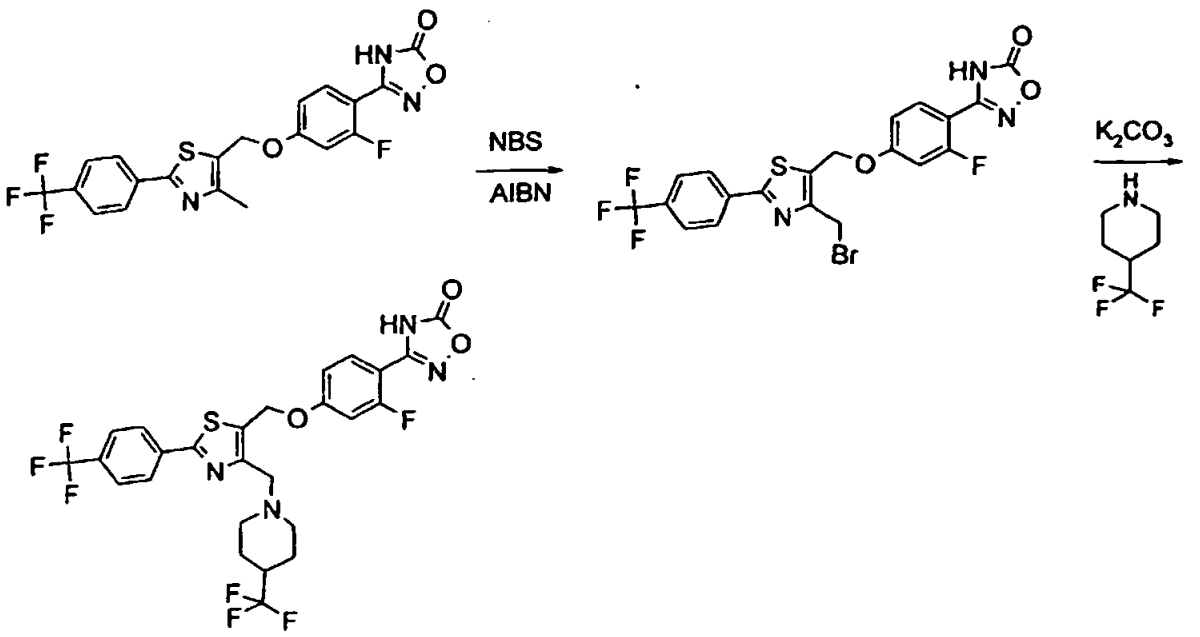


To a suspension of 130 mg of methanesulfonic acid 3-[5-[3-methoxy-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazol-4-yl]-propyl ester in 7 mL of acetonitrile was added 25 µL of azetidine and 57 mg of diisopropylethyl amine. The resulting mixture was heated in a sealed tube to 60°C under microwave irradiation for 30 minutes and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (gradient from dichloromethane 100 to dichloromethane 90/ methanol 10/water 1/acetic acid 1) followed by a 2g SCX Waters column with gradient CH2Cl2/MeOH 30/70 to 7N NH3 in MeOH and another column chromatography on silica gel (eluting with dichloromethane 90/ methanol 10) to give 3.5 mg of 3-{4-[4-(3-azetidin-1-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one. C26H25F3N4O4S (546.57), MS(ESI): 547 ($M+H^+$).

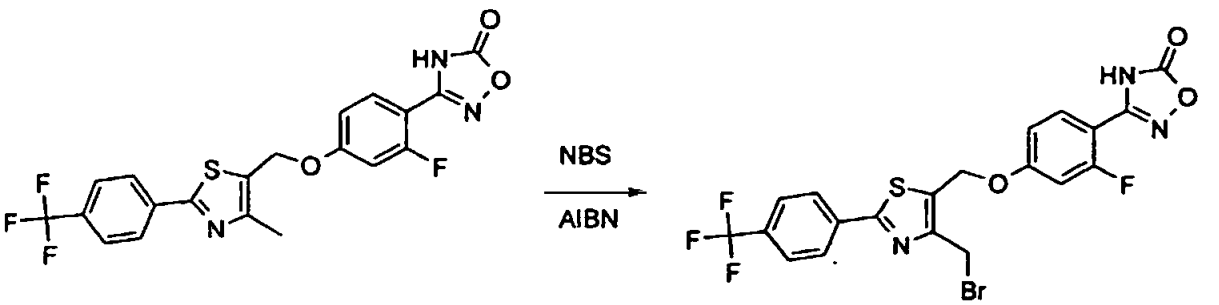
The following examples were prepared according to process F:

Example 17

3-{2-Fluoro-4-[2-(4-trifluorométhyl-phényl)-4-(4-trifluorométhyl-pipéridin-1-ylméthyl)-thiazol-5-ylméthoxy]-phényl}-4H-1,2,4-oxadiazol-5-one



3-{4-[4-Bromomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-fluoro-phenyl}-



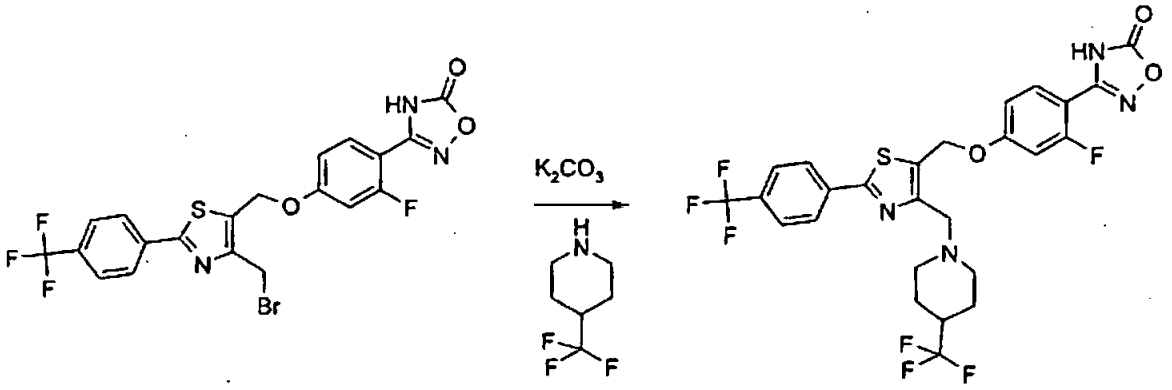
4H-[1,2,4]oxadiazol-5-one

To a mixture of 100 mg of 3-{2-fluoro-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-ylmethoxy]-phenyl}-4H- [1,2,4]oxadiazole-5-one[5] in 3 mL of carbon tetrachloride and 2 mL of hexafluoroisopropanol at reflux was added 100 mg of N-bromosuccinimide and

[5] Example 1 from application WO2005/097786

10 mg of AIBN. The resulting mixture was refluxed for 1 h. It was then poured into water and extracted with dichlomethane. The organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The solid was taken into dichloromethane, precipitated by adding diisopropyl ether, filtered and washed with diisopropyl ether. The white solid was purified by column chromatography on silica gel (gradient of dichloromethane/methanol from 100/0 to 80/20) to give 59 mg of 3-{4-[4-bromomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-fluoro-phenyl}-4H-[1,2,4]oxadiazol-5-one as a white solid.
C20H12BrF4N3O3S (530.29), MS(CI): 530 ($M+H^+$).

3-{2-Fluoro-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

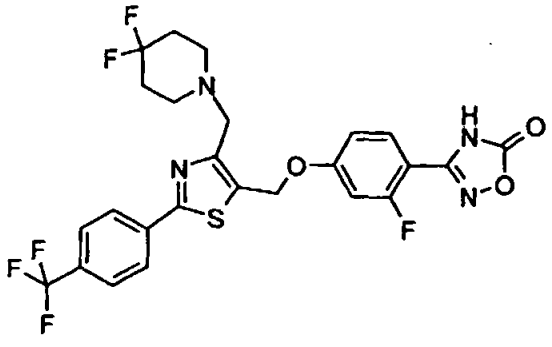


To a mixture of 136 mg of 3-{4-[4-bromomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-fluoro-phenyl}-4H-[1,2,4]oxadiazol-5-one in 17 mL of acetonitrile was added 48.6 mg of 4-trifluoropiperidine hydrochloride and 70 mg of potassium carbonate. The resulting mixture was stirred overnight and then concentrated under reduced pressure. It was then taken into dichloromethane and washed with water. The aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (dichloromethane 98/methanol 2) to give 51.6 mg of 3-{2-fluoro-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one as a white solid.

C26H21F7N4O3S (602.53), MS(ESI): 603 ($M+H^+$).

Example 18

3-{4-[4-(4,4-Difluoro-piperidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-fluoro-phenyl}-4H-[1,2,4]oxadiazol-5-one

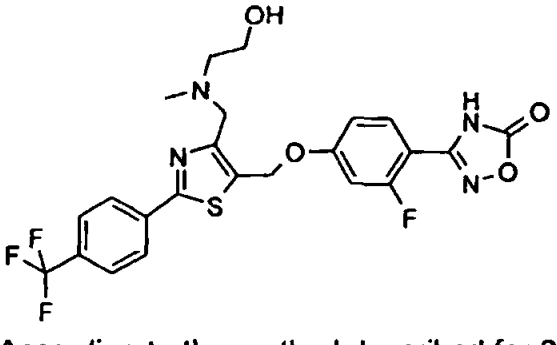


According to the method described for 3-{2-fluoro-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one, 3-{4-[4-butyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2,6-difluoro-phenyl}-4*H*-[1,2,4]oxadiazol-5-one was obtained from 3-{2-fluoro-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazole-5-one and 4,4-difluoro-piperidine hydrochloride.

C25H20F6N4O3S (570.51), MS(ESI): 571 ($M+H^+$).

Example 19

3-{2-Fluoro-4-[4-{[(2-hydroxy-ethyl)-methyl-amino]-methyl}-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

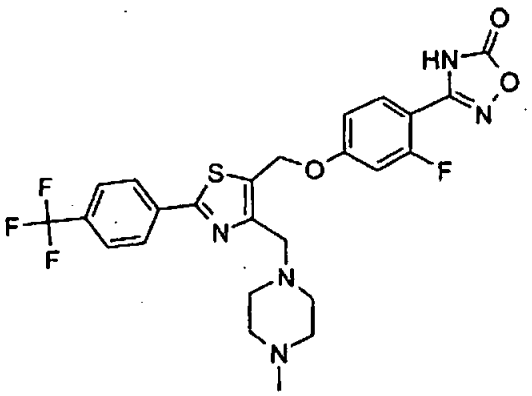


According to the method described for 3-{2-fluoro-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one, 3-{2-fluoro-4-[4-{[(2-hydroxy-ethyl)-methyl-amino]-methyl}-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 3-

{2-fluoro-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazole-5-one and 2-methylaminoethanol.
C23H20F4N4O4S (524.49), MS(ESI): 525 ($M+H^+$).

Example 20

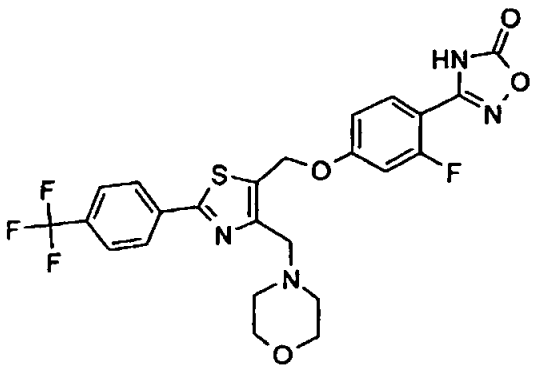
3-{2-Fluoro-4-[4-(4-methyl-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one



According to the method described for 3-{2-fluoro-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one, 3-{2-fluoro-4-[4-(4-methyl-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 3-{2-fluoro-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazole-5-one and 4-methyl-piperazine.
C25H23F4N5O3S (549.55), MS(ESI): 550 ($M+H^+$).

Example 21

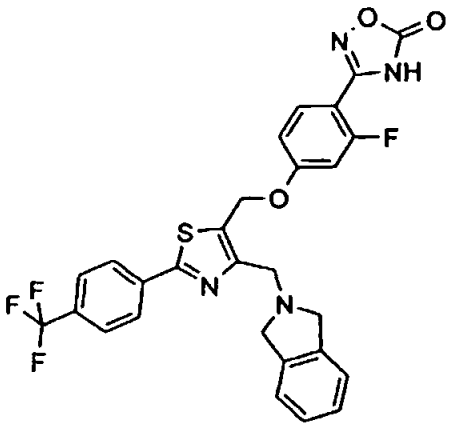
3-{2-Fluoro-4-[4-morpholin-4-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one



According to the method described for 3-{2-fluoro-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one, 3-{2-fluoro-4-[4-morpholin-4-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 3-{2-fluoro-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazole-5-one and morpholine.
C24H20F4N4O4S (536.50), MS(ESI): 537 ($M+H^+$).

Example 22

3-{4-[4-(1,3-Dihydro-isoindol-2-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-fluoro-phenyl}-4H-[1,2,4]oxadiazol-5-one

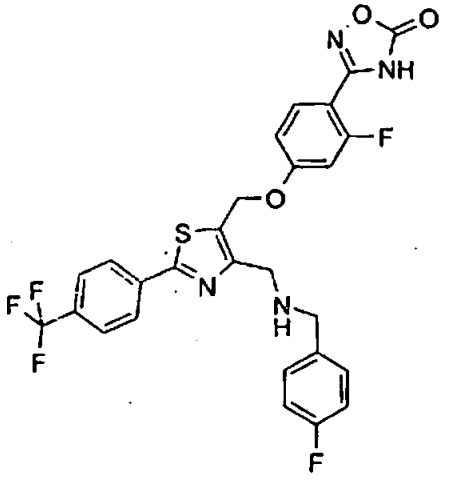


According to the method described for 3-{2-fluoro-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one, 3-{4-[4-(1,3-dihydro-isoindol-2-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-fluoro-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 3-{2-fluoro-

4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazole-5-one and 2,3-dihydro-1H-isoindole.
$C_{28}H_{20}F_4N_4O_3S$ (568.55), MS(ESI): 569 ($M+H^+$).

Example 23

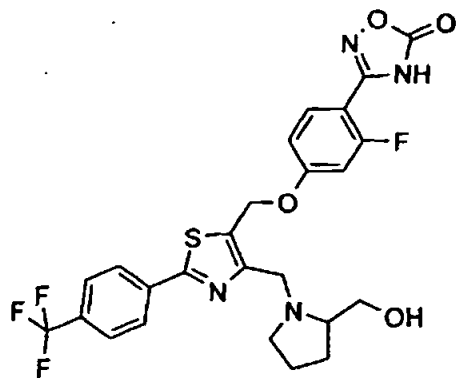
3-{2-Fluoro-4-[4-[(4-fluoro-benzylamino)-methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one



According to the method described for 3-{2-fluoro-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one, 3-{2-fluoro-4-[4-[(4-fluoro-benzylamino)-methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 3-{2-fluoro-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazole-5-one and 4-fluoro-benzylamine.
$C_{27}H_{19}F_5N_4O_3S$ (574.53), MS(ESI): 575 ($M+H^+$).

Example 24

3-{2-Fluoro-4-[4-(2-hydroxymethyl-pyrrolidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one



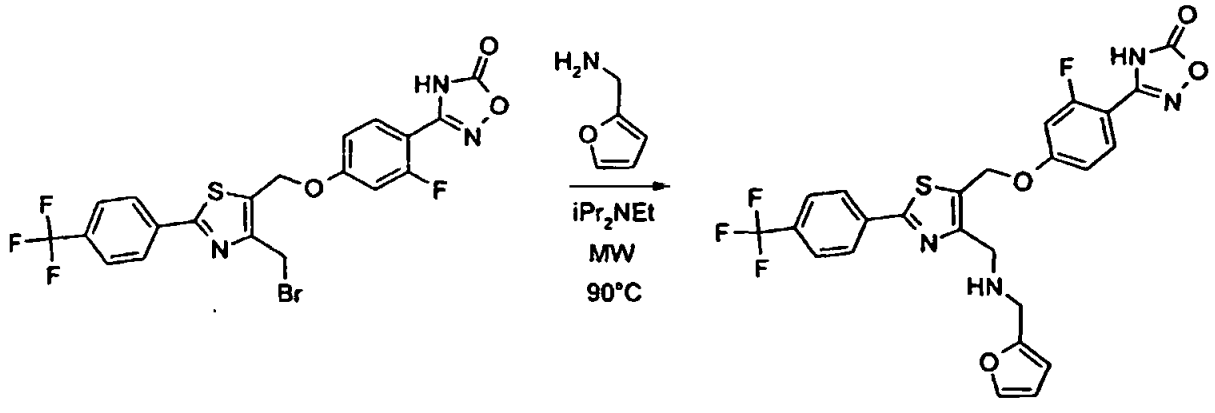
According to the method described for 3-{2-fluoro-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one, racemic 3-{2-fluoro-4-[4-(2-hydroxymethyl-pyrrolidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 3-{2-fluoro-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazole-5-one and racemic 2-hydroxymethyl-pyrrolidine.

$C_{25}H_{22}F_4N_4O_4S$ (550.53), MS(ESI): 551 ($M+H^+$).

Example 25

3-{2-Fluoro-4-[4-[[(furan-2-ylmethyl)-amino]-methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

To a solution of 50 mg of 3-{4-[4-bromomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-



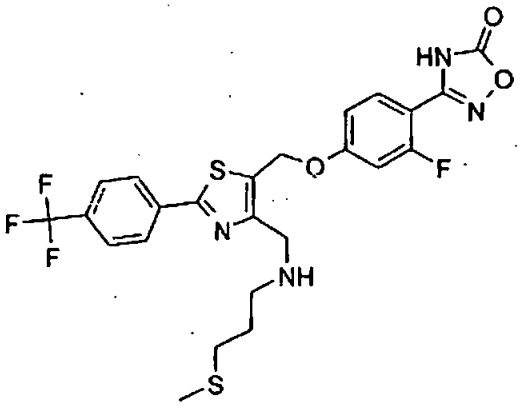
ylmethoxy]-2-fluoro-phenyl}-4H-[1,2,4]oxadiazol-5-one in 2.5 mL of acetonitrile was added 12 mg of furfurylamine and 25 mg of diisopropylethyl amine. The resulting mixture was heated in a sealed tube to 90°C under microwave irradiation for 5 minutes and then concentrated under reduced pressure. The residue was purified by column

chromatography on silica gel (gradient from dichloromethane 100 to dichloromethane 90/ methanol 10/water 1/acetic acid 1) followed by washings with diisopropyl ether to give 18 mg of 3-{2-fluoro-4-[4-{[(furan-2-ylmethyl)-amino]-methyl}-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one.

C25H18F4N4O4S (546.50), MS(ESI): 547 ($M+H^+$).

Example 26

3-{2-Fluoro-4-[4-[(3-methylsulfanyl-propylamino)-methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

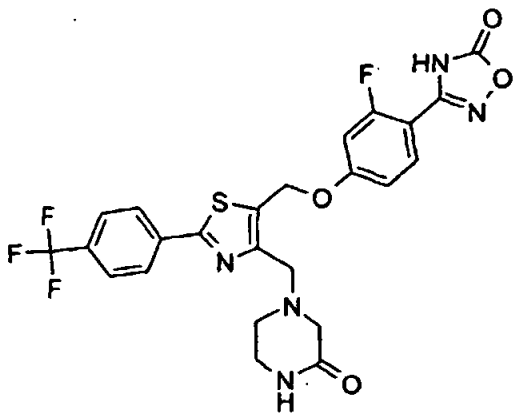


According to the method described for 3-{2-fluoro-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one, 3-{2-fluoro-4-[4-[(3-methylsulfanyl-propylamino)-methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 3-{2-fluoro-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazole-5-one and 3-methylsulfanyl-propylamine.

C24H22F4N4O3S2 (554.59),MS(ESI): 555 ($M+H^+$).

Example 27

4-[5-[3-Fluoro-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethyl]-piperazin-2-one

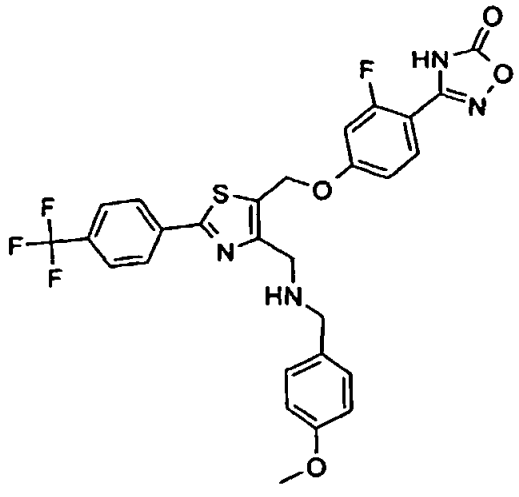


According to the method described for 3-{2-fluoro-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one, 4-[5-[3-fluoro-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethyl]-piperazin-2-one was obtained from 3-{2-fluoro-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazole-5-one and piperazin-2-one.

C24H19F4N5O4S (549.50), MS(ESI): 550 ($M+H^+$).

Example 28

3-{2-Fluoro-4-[4-[(4-methoxy-benzylamino)-methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

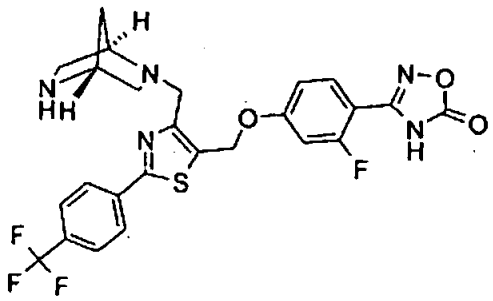


According to the method described for 3-{2-fluoro-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one, 3-{2-fluoro-4-[4-[(4-methoxy-benzylamino)-methyl]-2-(4-trifluoromethyl-phenyl)-

thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 3-{2-fluoro-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazole-5-one and 4-methoxy-benzylamine.
C28H22F4N4O4S (586.56), MS(ESI): 587 ($M+H^+$).

Example 29

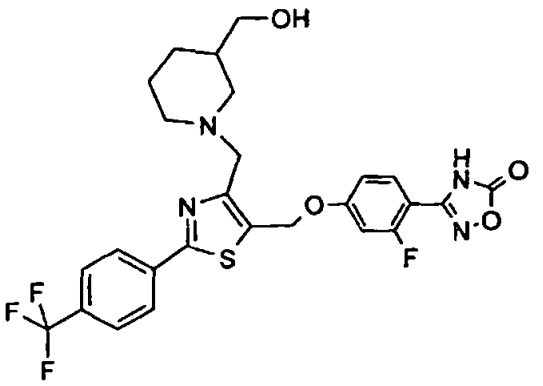
3-{4-[4-[(1R,4R)-1-(2,5-Diaza-bicyclo[2.2.1]hept-2-yl)methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-fluoro-phenyl}-4H-[1,2,4]oxadiazol-5-one



According to the method described for 3-{2-fluoro-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one, 3-{4-[4-[(1R,4R)-1-(2,5-diaza-bicyclo[2.2.1]hept-2-yl)methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-fluoro-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 3-{2-fluoro-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazole-5-one and (1R,4R)-2,5-diaza-bicyclo[2.2.1]heptane.
C25H21F4N5O3S (547.53), MS(ESI): 548 ($M+H^+$).

Example 30

3-{2-Fluoro-4-[4-(3-hydroxymethyl-piperidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

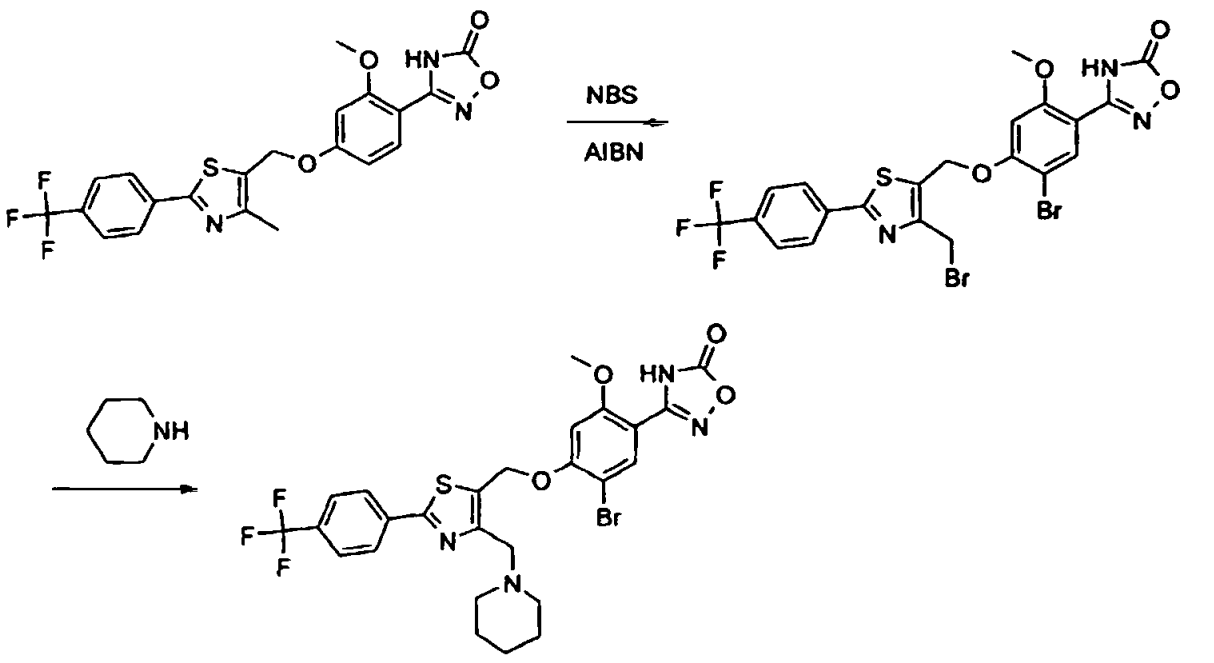


According to the method described for 3-{2-fluoro-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one, racemic 3-{2-fluoro-4-[4-(3-hydroxymethyl-piperidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 3-{2-fluoro-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazole-5-one and racemic 3-hydroxymethyl-piperidine.

$C_{26}H_{24}F_4N_4O_4S$ (564.56), MS(ESI): 565 ($M+H^+$).

Example 31

<u>3-{5-Bromo-2-methoxy-4-[4-piperidin-1-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one</u>

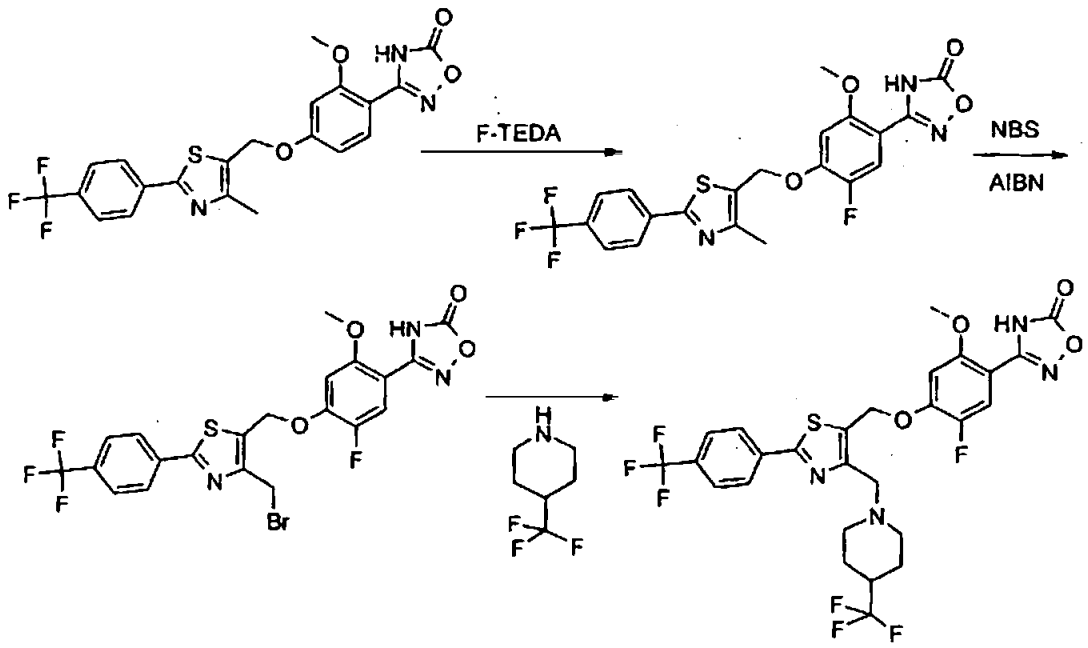


According to the method described for 3-{2-fluoro-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one, 3-{5-bromo-2-methoxy-4-[4-piperidin-1-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 3-{2-methoxy-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one[6] and piperidine. During the bromination step on 3-{2-methoxy-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one, 3-{5-bromo-4-[4-bromomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained. It was then converted to the cited product upon reaction with piperidine.

C26H24BrF3N4O4S (625.46), MS(ESI): 625 ($M+H^+$).

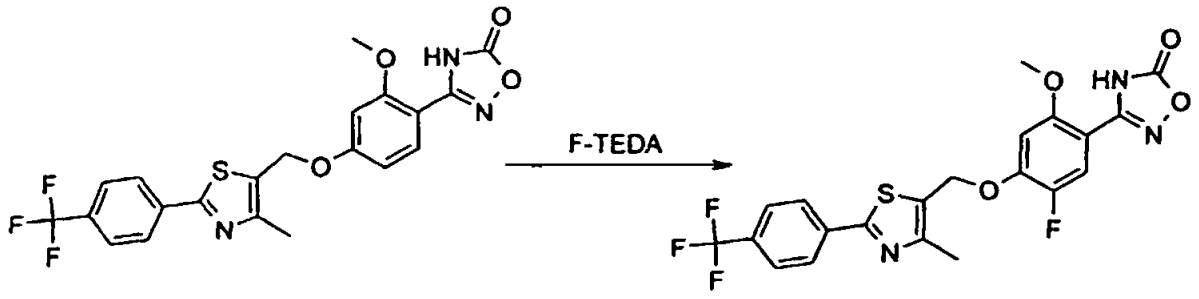
Example 32

3-{5-Fluoro-2-methoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one



[6] Example 11 from application WO2005/097786

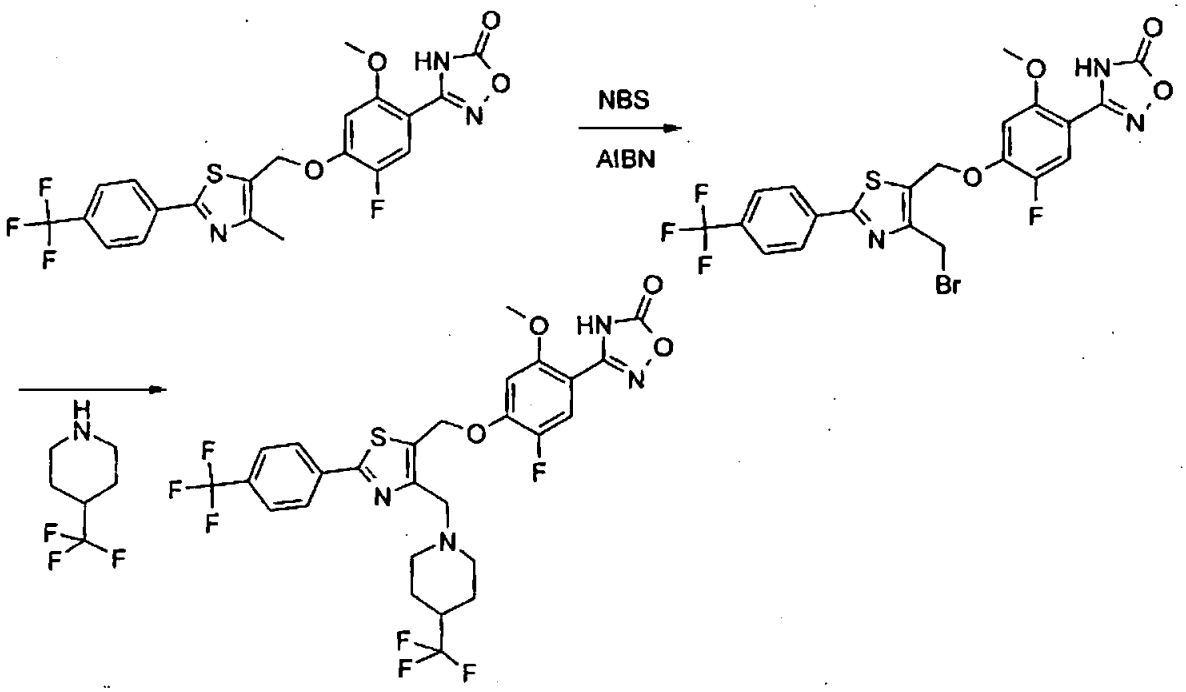
3-{5-Fluoro-2-methoxy-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one



To a solution of 1.13 g of 3-{2-methoxy-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one in 40 mL of trifluoroacetic acid was added 738 mg of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (F-TEDA). The resulting mixture was heated to 70°C for 6 h then poured into water and extracted with dichloromethane. The organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (gradient from dichloromethane 100 to dichloromethane 80/ methanol 20) to give 164 mg of a 1/1 mixture of 3-{5-fluoro-2-methoxy-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one and starting material which was used in the next step without further purification.

C21H15F4N3O4S (481.42), MS(ESI): 482 ($M+H^+$).

3-{5-Fluoro-2-methoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

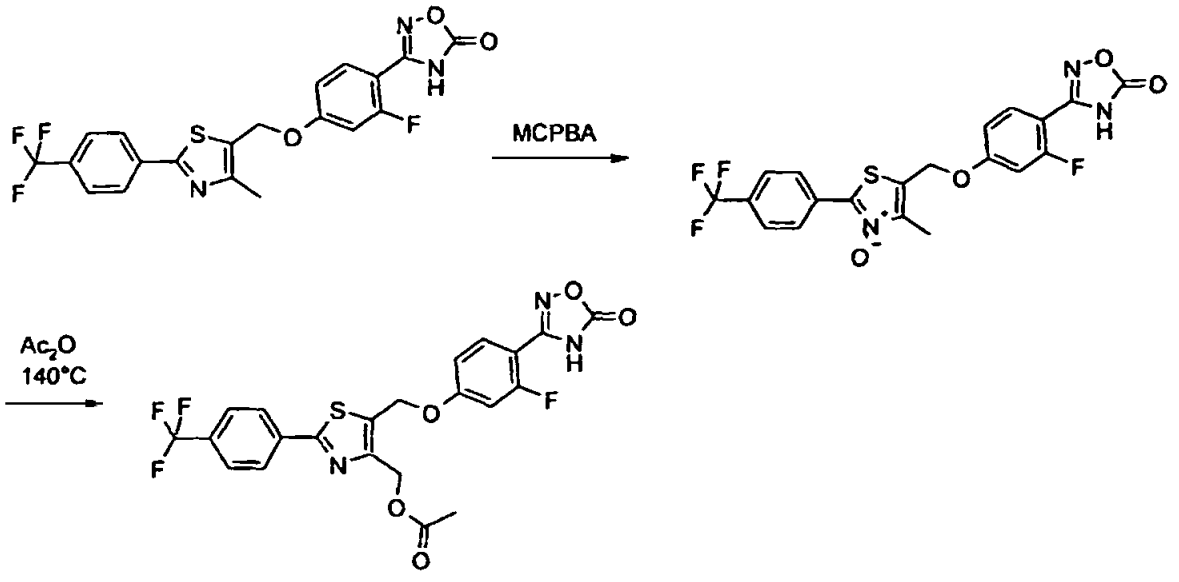


According to the method described for 3-{2-fluoro-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one, 3-{5-fluoro-2-methoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 3-{5-fluoro-2-methoxy-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one and 4-trifluoromethyl-piperidine. C27H23F7N4O4S (632.55), MS(ESI): 633 ($M+H^+$).

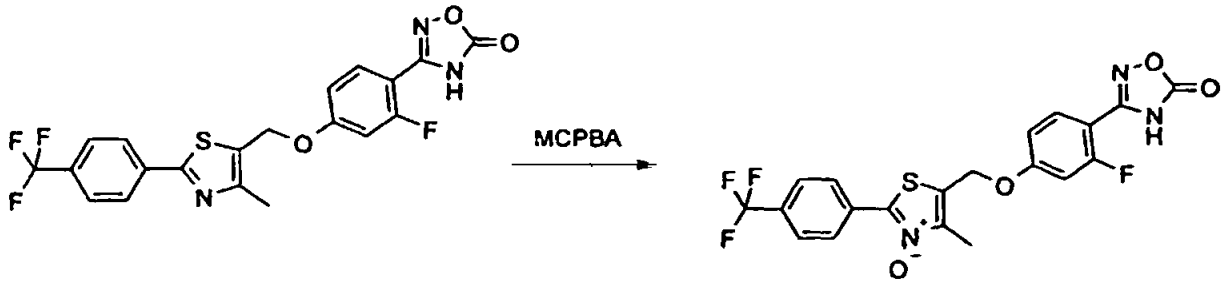
The following examples were prepared according to process G:

Example 33

Acetic acid 5-[3-fluoro-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethyl ester



3-{2-Fluoro-4-[4-methyl-3-oxy-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

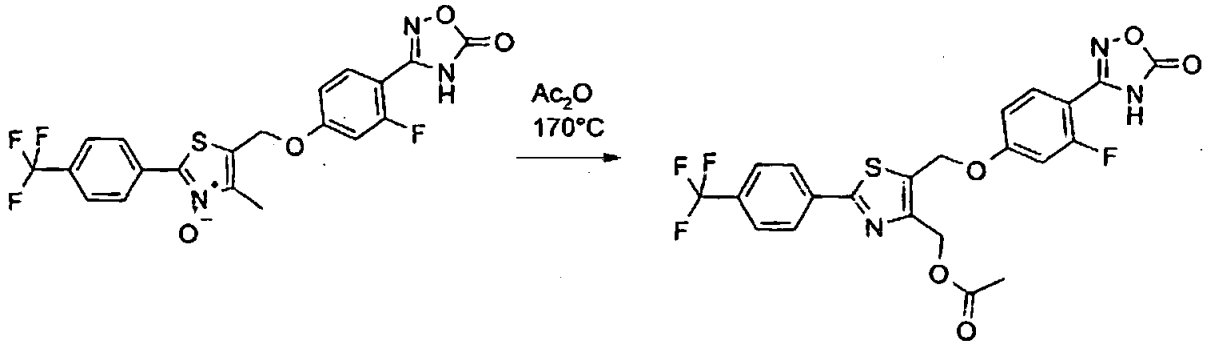


1 g of 3-{2-fluoro-4-[4-methyl-3-oxy-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one were dissolved in 23 mL of hexafluoroisopropanol. To the resulting solution was added 2.1 g of MCPBA (70% pure). The resulting mixture was heated to 50°C for 6 h and stirred at room temperature overnight. The precipitate is filtered. The filtrate is concentrated under reduced pressure and 8 mL of ethyl acetate was added to the residue. The solid was filtered and washed with ethyl acetate to give 0.48 g of a first crop of desired product as a white solid. The filtrate was concentrated and recrystalized in methanol to provide an additional 0.19 g of desired

product as a white solid. The mother liquor was concentrated and purified by column chromatography on silica gel (heptane 1/ ethyl acetate 3 then dichloromethane 95/ methanol 5). The crops were combined to give 0.67 g of 3-{2-fluoro-4-[4-methyl-3-oxy-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one as a white solid.

C20H13F4N3O4S (467.40), MS(ESI): 468 ($M+H^+$).

Acetic acid 5-[3-fluoro-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethyl ester

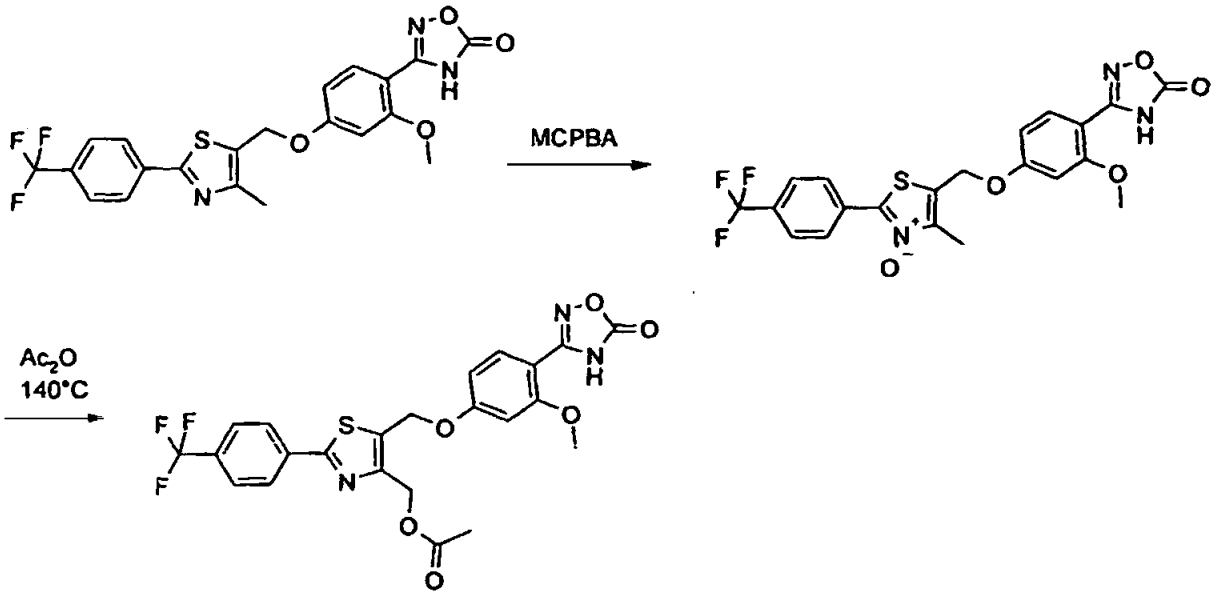


A mixture of 470 mg of 3-{2-fluoro-4-[4-methyl-3-oxy-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one in 5 mL of acetic anhydride was heated to 170°C for 18 minutes. The mixture was poured into water/ethyl acetate. The organic layer was separated and the aqueous layer extracted three times with ethyl acetate. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (gradient from heptane 4/ ethyl acetate 1 to heptane 1/ ethyl acetate 1) to give 180 mg of acetic acid 5-[3-fluoro-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethyl ester as a beige solid.

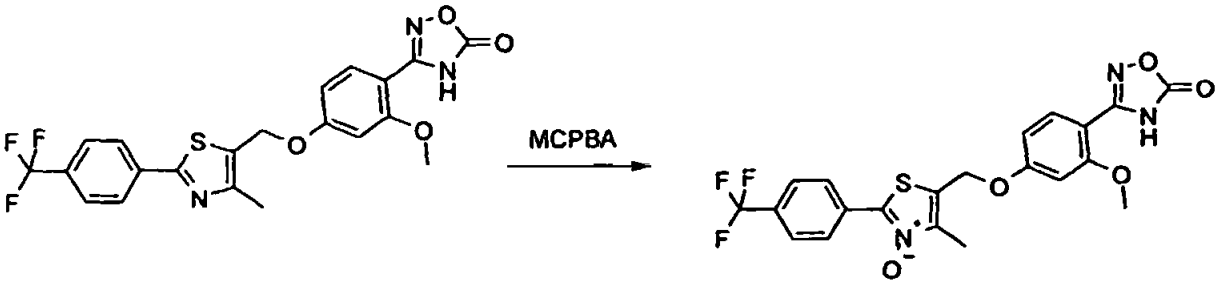
C22H15F4N3O5S (509.43), MS(ESI): 510 ($M+H^+$).

Example 34

Acetic acid 5-[3-methoxy-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethyl ester



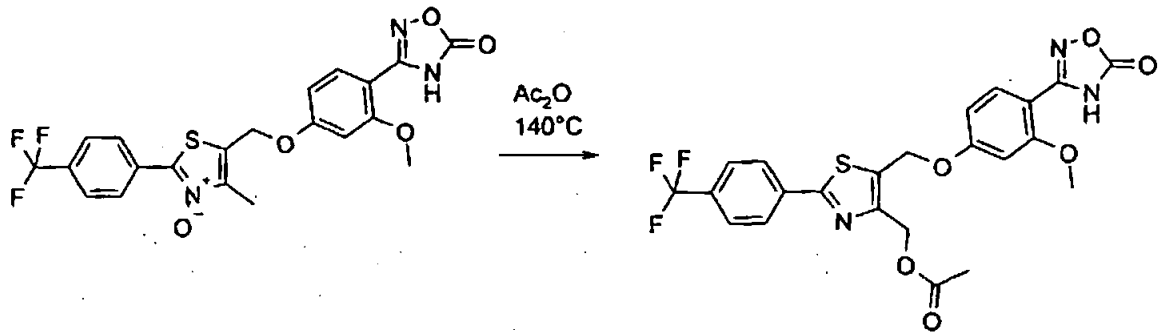
3-{2-Methoxy-4-[4-methyl-3-oxy-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one



7.55 g of 3-{2-methoxy-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one were dissolved by adding 210 mL of hexafluoroisopropanol followed by 2.5 mL of dichloromethane. To the resulting solution was added 16.3 g of MCPBA (70% pure). The resulting mixture was heated to 50°C for 5 h and slowly stirred at room temperature over the weekend. The precipitate is filtered and washed with 3 mL of hexafluoroisopropanol. The filtrate is concentrated under reduced pressure and 250 mL of ethyl acetate was added to the residue. The resulting suspension was stirred at room temperature for 3 h then filtered and washed with a

mixture of hexane and diisopropyl ether to give 4.77 g of 3-{2-methoxy-4-[4-methyl-3-oxy-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one as a white solid which was used in the next step without further purification.
C21H16F3N3O5S (479.43), MS(ESI): 480 ($M+H^+$).

Acetic acid 5-[3-methoxy-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-

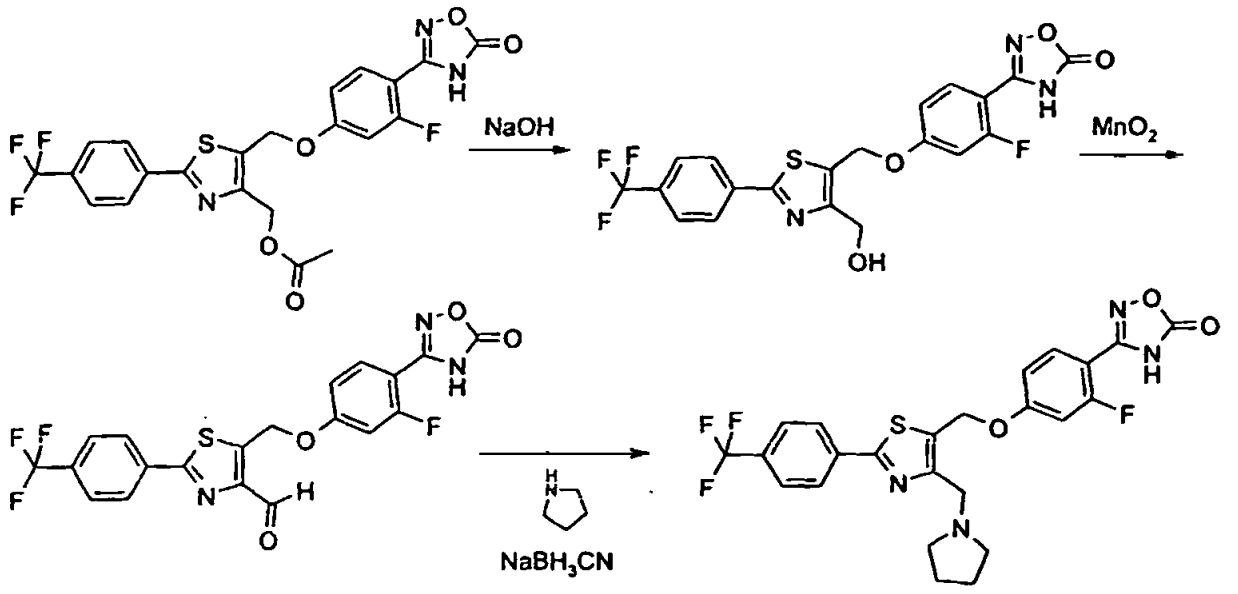


2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethyl ester

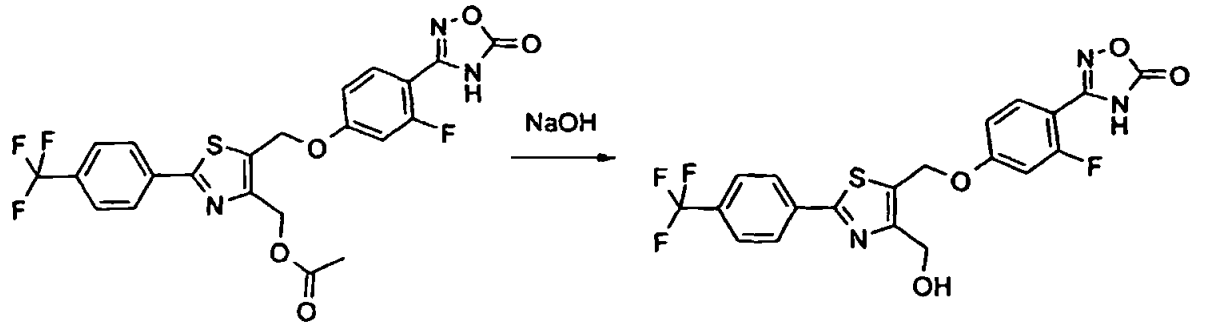
A suspension of 0.4 g of 3-{2-methoxy-4-[4-methyl-3-oxy-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one in 15 mL of acetic anhydride was heated to 140°C for 1.5 h. The mixture was allowed to cool down to room temperature. 20 mL of Toluene was added and the mixture was concentrated under reduced pressure to give 0.5 g of acetic acid 5-[3-methoxy-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethyl ester which was used in the next step without further purification.
C21H16F3N3O5S (479.43), MS(ESI): 478 ($M-H^+$).

The following examples were prepared according to process E:

3-{2-Fluoro-4-[4-pyrrolidin-1-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one



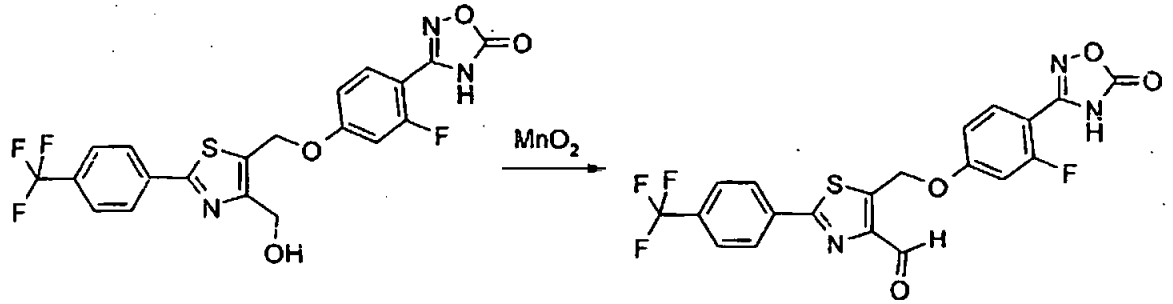
3-{2-Fluoro-4-[4-hydroxymethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one



To a suspension of 150 mg of acetic acid 5-[3-fluoro-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethyl ester in 5 mL of methanol at 0°C was dropwise added 0.29 mL of a 1 molar aqueous

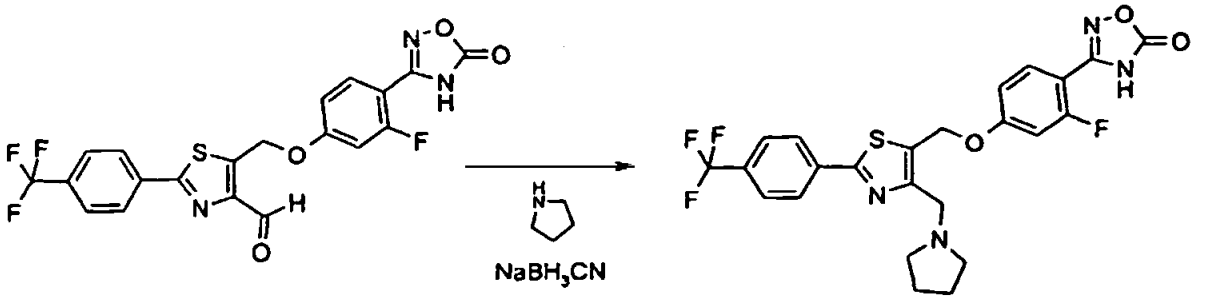
solution of sodium hydroxide. After stirring for 15 minutes at 10°C, the reaction mixture was concentrated under reduced pressure. Ethyl acetate/a 1 molar aqueous solution of sodium hydrogenophosphate was added. The organic layer was separated and the aqueous layer extracted three times with ethyl acetate. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give 110 mg of 3-{2-fluoro-4-[4-hydroxymethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one as a yellowish solid.
C20H13F4N3O4S (467.40), MS(ESI): 468 ($M+H^+$).

5-[3-Fluoro-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazole-4-carbaldehyde



To a mixture of 20 mg of 3-{2-fluoro-4-[4-hydroxymethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one in 10 mL of chloroform was added 23 mg of manganese dioxide. After stirring at room temperature overnight, the reaction mixture was filtered through celite and washed with dichloromethane/methanol. The filtrate was concentrated under reduced pressure to give 200 mg of 5-[3-fluoro-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazole-4-carbaldehyde as a beige solid.
C20H11F4N3O4S (465.39), MS(CI): 483 ($M+NH4^+$).

3-{2-Fluoro-4-[4-pyrrolidin-1-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

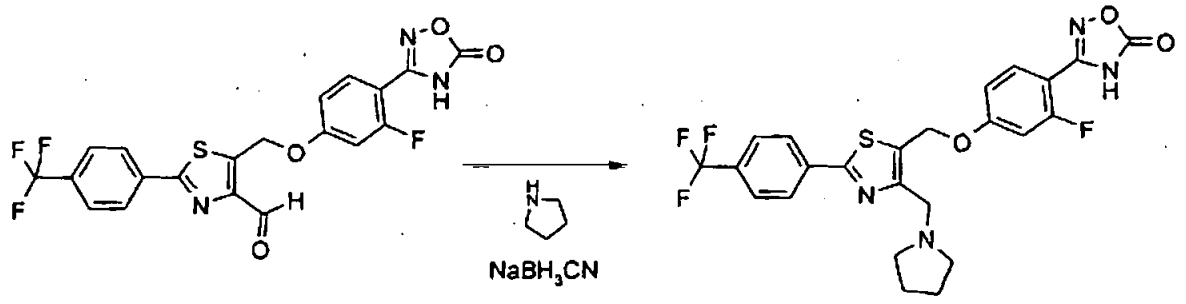


To a suspension of 50 mg of 5-[3-fluoro-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazole-4-carbaldehyde in 2 mL of methanol was added 0.03 mL of pyrrolidine. The resulting solution was stirred at room temperature for 1.5 h then 13.5 mg of sodium cyanoborohydride was added. After stirring at room temperature for 4 h, the reaction mixture was concentrated under reduced pressure. Ethyl acetate/water was added to the residue. The organic layer was separated and the aqueous layer extracted three times with ethyl acetate. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (dichloromethane 80/ methanol 20) to give 9 mg of 3-{2-fluoro-4-[4-pyrrolidin-1-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one as a beige solid.
C24H20F4N4O3S (520.51), MS(ESI): 521 ($M+H^+$).

Example 36

3-(2-Methoxy-4-{2-(4-trifluoromethyl-phenyl)-4-[(3,3,3-trifluoro-propylamino)-methyl]-thiazol-5-ylmethoxy}-phenyl)-4H-[1,2,4]oxadiazol-5-one

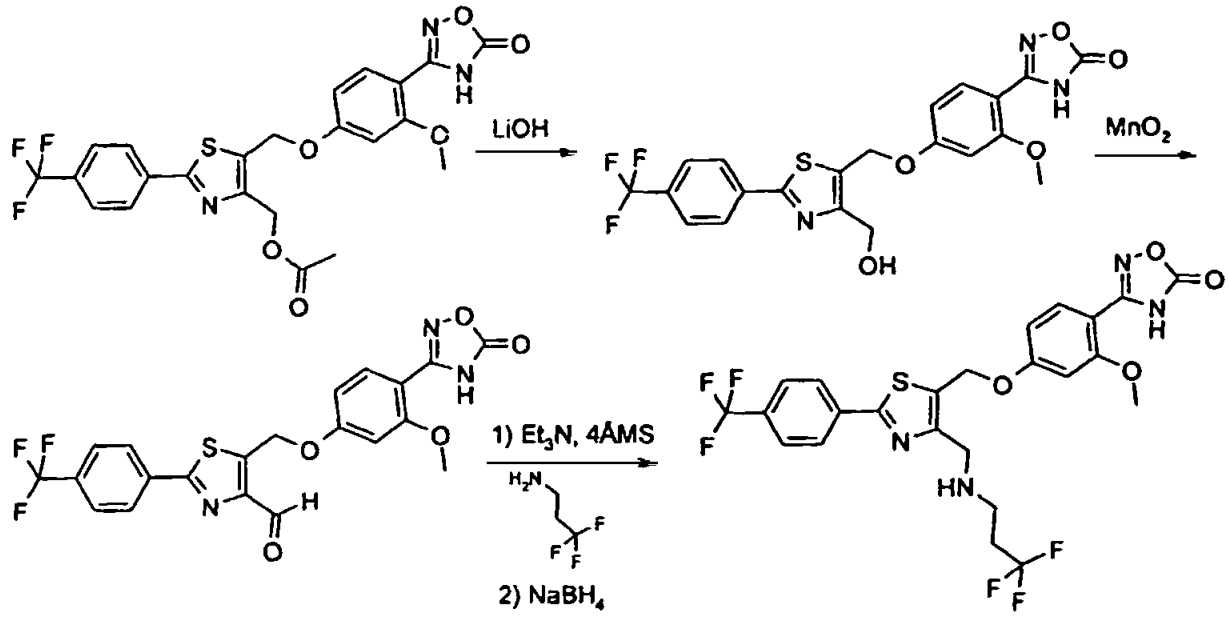
3-{2-Fluoro-4-[4-pyrrolidin-1-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one



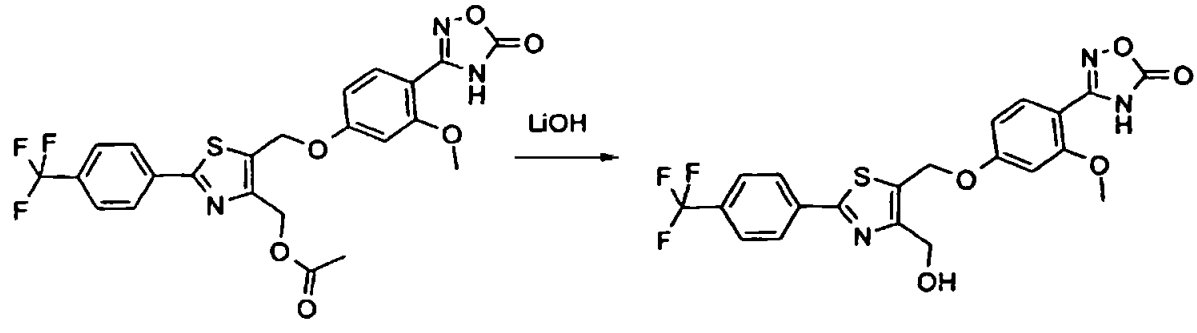
To a suspension of 50 mg of 5-[3-fluoro-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazole-4-carbaldehyde in 2 mL of methanol was added 0.03 mL of pyrrolidine. The resulting solution was stirred at room temperature for 1.5 h then 13.5 mg of sodium cyanoborohydride was added. After stirring at room temperature for 4 h, the reaction mixture was concentrated under reduced pressure. Ethyl acetate/water was added to the residue. The organic layer was separated and the aqueous layer extracted three times with ethyl acetate. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (dichloromethane 80/ methanol 20) to give 9 mg of 3-{2-fluoro-4-[4-pyrrolidin-1-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one as a beige solid.
C24H20F4N4O3S (520.51), MS(ESI): 521 ($M+H^+$).

Example 36

3-(2-Methoxy-4-{2-(4-trifluoromethyl-phenyl)-4-[(3,3,3-trifluoro-propylamino)-methyl]-thiazol-5-ylmethoxy}-phenyl)-4H-[1,2,4]oxadiazol-5-one



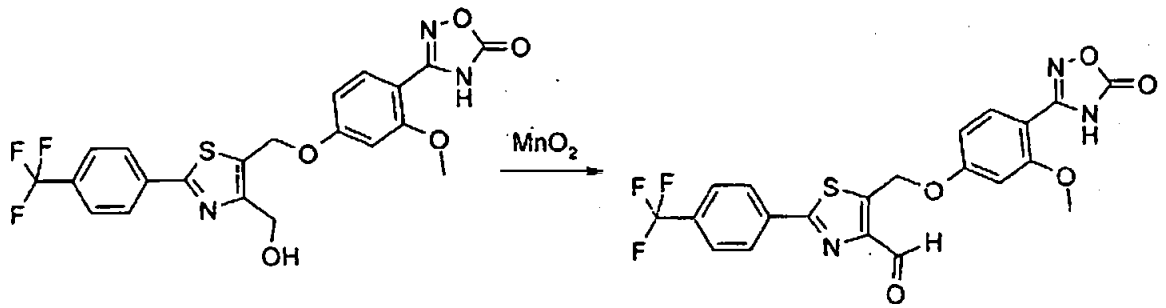
3-{4-[4-Hydroxymethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one



To a suspension of 0.5 g of acetic acid 5-[3-methoxy-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethyl ester in 5 mL of methanol at 0°C was added 0.22 g of lithium hydroxide. The resulting solution was stirred for 45 minutes at 0°C then it was allowed to warm up to room temperature. The solvent was partly removed under reduced pressure and ethyl acetate/ 1 molar aqueous solution of KH2PO4 was added. The organic layer was separated and the aqueous layer extracted three times with ethyl acetate. The

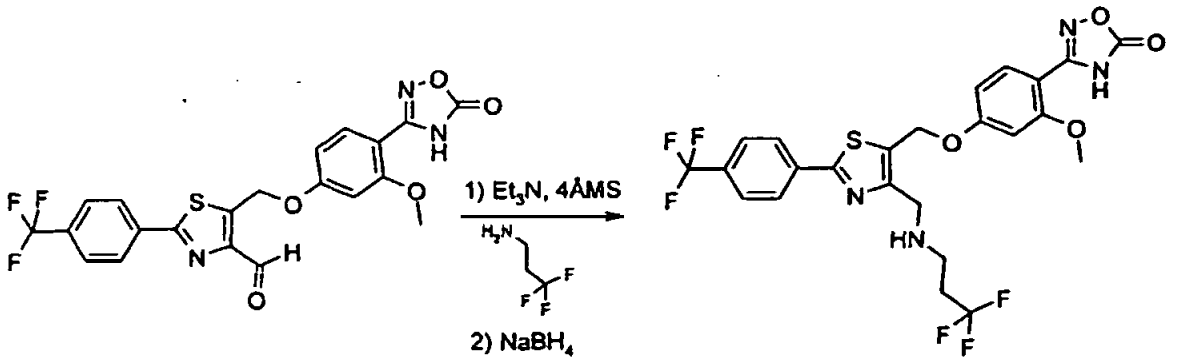
combined organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. 40 mL of Ethyl acetate was added to the residue and, after stirring for 30 minutes, the resulting solid was collected by filtration to give 225 mg of 3-{4-[4-hydroxymethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one as a beige solid. C21H16F3N3O5S (479.44), MS(ESI): 480 ($M+H^+$).

5-[3-Methoxy-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazole-4-carbaldehyde



50 mg of 3-{4-[4-hydroxymethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one were dissolved in 2 mL of dimethylformamide by heating to 60°C and 2 mL of dichloromethane was added. To the resulting solution was added 90 mg of manganese dioxide. The reaction mixture was heated to 60°C overnight. 5 mL of dimethylformamide was added. The hot mixture was filtered through celite and washed with dichloromethane/methanol. The filtrate was concentrated under reduced pressure to give 30 mg of 5-[3-methoxy-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazole-4-carbaldehyde which was used in the next step without further purification. C21H14F3N3O5S (477.42), MS(ESI): 478 ($M+H^+$).

3-(2-Methoxy-4-{2-(4-trifluoromethyl-phenyl)-4-[(3,3,3-trifluoro-propylamino)-methyl]-thiazol-5-ylmethoxy}-phenyl)-4H-[1,2,4]oxadiazol-5-one

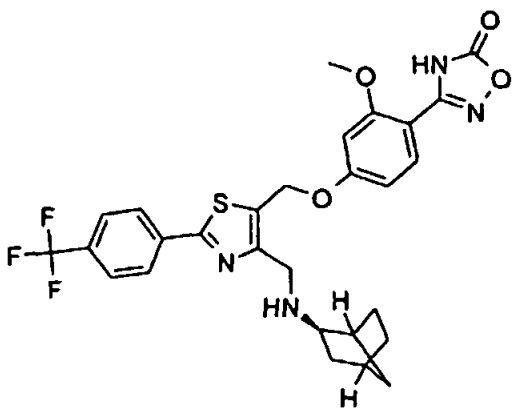


To a suspension of 30 mg of 5-[3-methoxy-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazole-4-carbaldehyde in 1.5 mL of methanol were added 0.018 mL of triethylamine, 10 mg of 3,3,3-trifluoro-propylamine hydrochloride and 0.5 g of 4Å powdered molecular sieves. The resulting mixture was stirred at room temperature for 1 h then 2.4 mg of sodium borohydride was added. After stirring at room temperature for 45 minutes, the reaction mixture was concentrated under reduced pressure. The crude product was purified by preparative thin layer chromatography on silica gel (dichloromethane 90/ methanol 10/ water 1/ acetic acid 1) followed by azeotropal removal of traces of acetic acid with cyclohexane to give 6.5 mg of 3-(2-methoxy-4-{2-(4-trifluoromethyl-phenyl)-4-[(3,3,3-trifluoro-propylamino)-methyl]-thiazol-5-ylmethoxy}-phenyl)-4H-[1,2,4]oxadiazol-5-one as a white solid.

C24H20F6N4O4S (574.50), MS(ESI): 575 ($M+H^+$).

Example 37

3-{4-[4-((1R,2R,4S)-Bicyclo[2.2.1]hept-2-ylaminomethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one

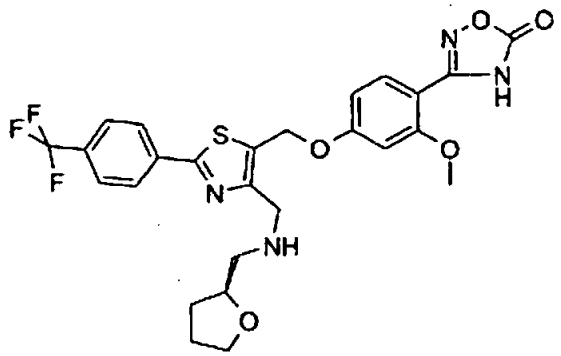


According to the method described for 3-(2-methoxy-4-{2-(4-trifluoromethyl-phenyl)-4-[(3,3,3-trifluoro-propylamino)-methyl]-thiazol-5-ylmethoxy}-phenyl)-4H-[1,2,4]oxadiazol-5-one, 3-{4-[4-((1R,2R,4S)-bicyclo[2.2.1]hept-2-ylaminomethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 5-[3-methoxy-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazole-4-carbaldehyde and exo-2-aminonorbornane.

$C_{28}H_{27}F_3N_4O_4S$ (572.61), MS(ESI): 573 ($M+H^+$).

Example 38

3-{2-Methoxy-4-[4-({[(S)-1-(tetrahydro-furan-2-yl)methyl]-amino}-methyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

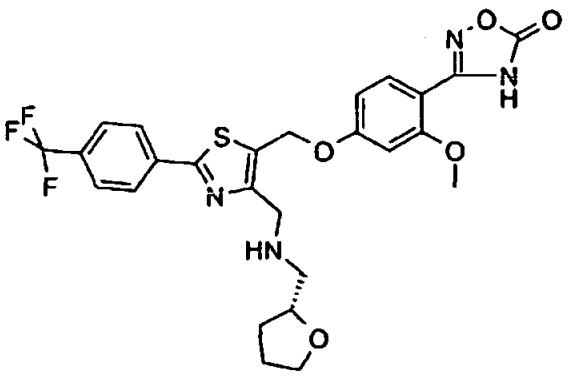


According to the method described for 3-(2-methoxy-4-{2-(4-trifluoromethyl-phenyl)-4-[(3,3,3-trifluoro-propylamino)-methyl]-thiazol-5-ylmethoxy}-phenyl)-4H-[1,2,4]oxadiazol-5-one, 3-{2-methoxy-4-[4-({[(S)-1-(tetrahydro-furan-2-yl)methyl]-amino}-methyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 5-[3-methoxy-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazole-4-carbaldehyde and (S)-(+)-tetrahydrofurfuryl amine.

$C_{26}H_{25}F_3N_4O_5S$ (562.57), MS(ESI): 563 ($M+H^+$).

Example 39

3-{2-Methoxy-4-[4-({[(R)-1-(tetrahydro-furan-2-yl)methyl]-amino}-methyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

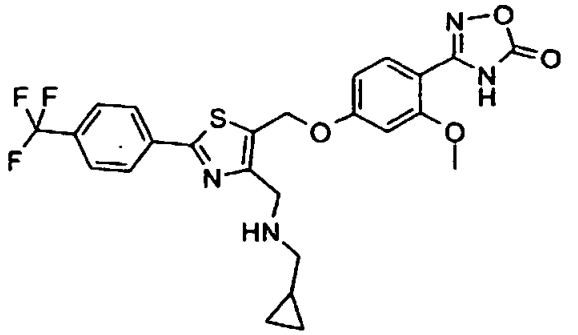


According to the method described for 3-(2-methoxy-4-{2-(4-trifluoromethyl-phenyl)-4-[(3,3,3-trifluoro-propylamino)-methyl]-thiazol-5-ylmethoxy}-phenyl)-4H-[1,2,4]oxadiazol-5-one, 3-{2-methoxy-4-[4-({[(R)-1-(tetrahydro-furan-2-yl)methyl]-amino}-methyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 5-[3-methoxy-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazole-4-carbaldehyde and (R)-(-)-tetrahydrofurfuryl amine.

C26H25F3N4O5S (562.57), MS(ESI): 563 ($M+H^+$).

Example 40

3-{4-[4-[(Cyclopropylmethyl-amino)-methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one

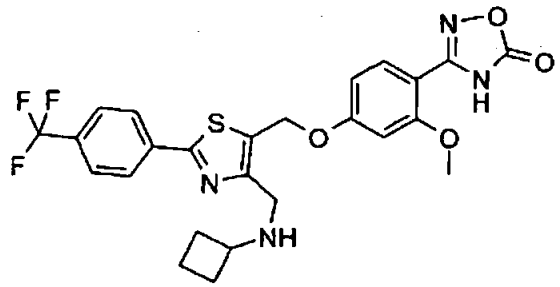


According to the method described for 3-(2-methoxy-4-{2-(4-trifluoromethyl-phenyl)-4-[(3,3,3-trifluoro-propylamino)-methyl]-thiazol-5-ylmethoxy}-phenyl)-4H-[1,2,4]oxadiazol-5-one, 3-{4-[4-[(cyclopropylmethyl-amino)-methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 5-[3-methoxy-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazole-4-carbaldehyde and cyclopropylmethyl amine.

C25H23F3N4O4S (532.54), MS(ESI): 533 ($M+H^+$).

Example 41

3-{4-[4-Cyclobutylaminomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one

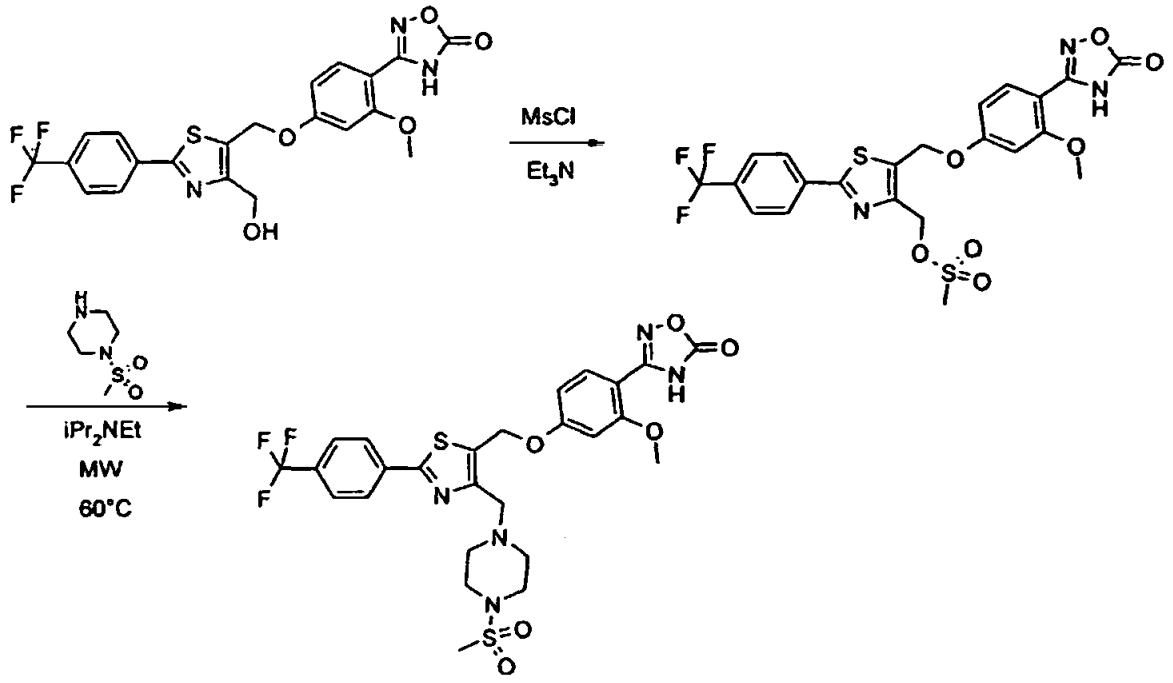


According to the method described for 3-(2-methoxy-4-{2-(4-trifluoromethyl-phenyl)-4-[(3,3,3-trifluoro-propylamino)-methyl]-thiazol-5-ylmethoxy}-phenyl)-4H-[1,2,4]oxadiazol-5-one, 3-{4-[4-cyclobutylaminomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 5-[3-methoxy-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazole-4-carbaldehyde and cyclobutylamine.
C25H23F3N4O4S (532.54), MS(ESI): 533 ($M+H^+$).

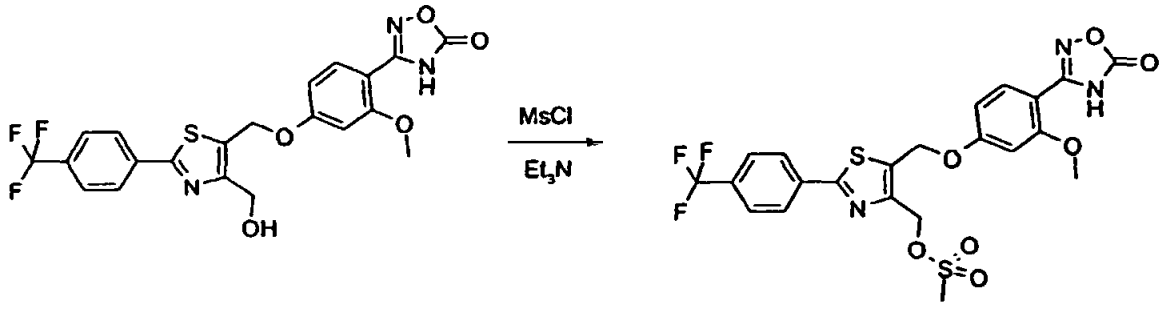
The following examples were prepared according to process D:

Example 42

3-{4-[4-(4-Methanesulfonyl-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one



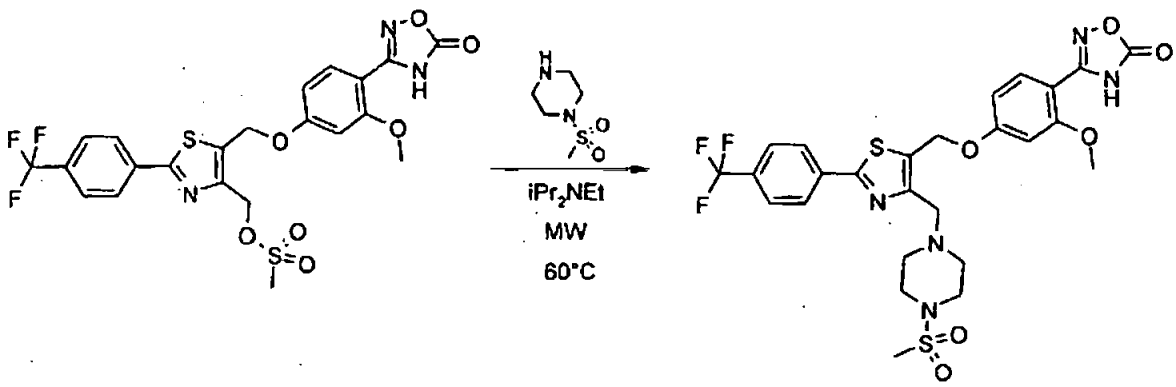
Methanesulfonic acid 5-[3-methoxy-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethyl ester



To a solution of 400 mg of 3-{4-[4-hydroxymethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one in 8 mL of dimethylformamide was added 0.42 mL of triethylamine followed by dropwise addition of 0.1 mL of methanesulfonyl chloride. The resulting mixture was stirred at room temperature for 45 minutes then concentrated under reduced pressure to give 830 mg of crude methanesulfonic acid 5-[3-methoxy-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethyl ester which was used in the next step without further purification.

C22H18F3N3O7S2 (557.52), MS(ESI): 558 ($M+H^+$).

3-{4-[4-(4-Methanesulfonyl-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one

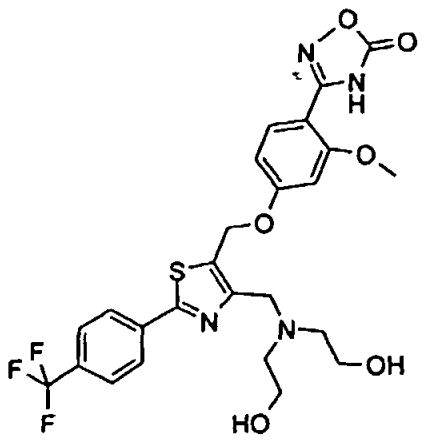


To a solution of 50 mg of methanesulfonic acid 5-[3-methoxy-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethyl ester in 2 mL of dimehtylformamide was added 80 µL of diisopropylethyl amine and 19.2 mg of 1-methylsulfonylpiperazine. The resulting mixture was heated in a sealed tube to 90°C under microwave irradiation for 5 minutes and then concentrated under reduced pressure. The residue was purified by chromatography on a SCX Waters column with gradient CH2Cl2/MeOH 30/70 to 7N NH3 in MeOH followed by recrystalization in dichloromethane 9/ methanol 1 to give 6.7 mg of 3-{4-[4-(4-methanesulfonyl-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one.

C26H26F3N5O6S2 (625.65), MS(ESI): 626.

Example 43

3-{4-[4-{[Bis-(2-hydroxy-ethyl)-amino]-methyl}-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one

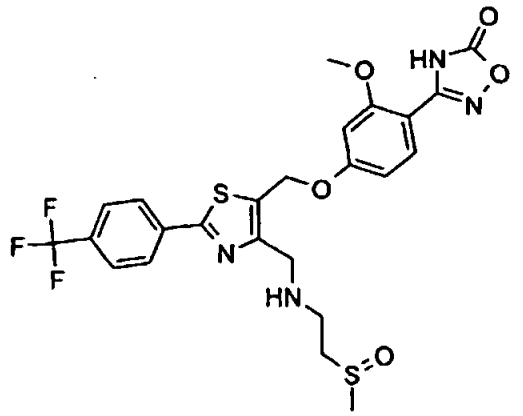


According to the method described for 3-{4-[4-(4-methanesulfonyl-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one, 3-{4-[4-{[bis-(2-hydroxy-ethyl)-amino]-methyl}-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from methanesulfonic acid 5-[3-methoxy-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethyl ester and diethanolamine.

C25H25F3N4O6S (566.55), MS(ESI): 567.

Example 44

3-{4-[4-[(2-Methanesulfinyl-ethylamino)-methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one



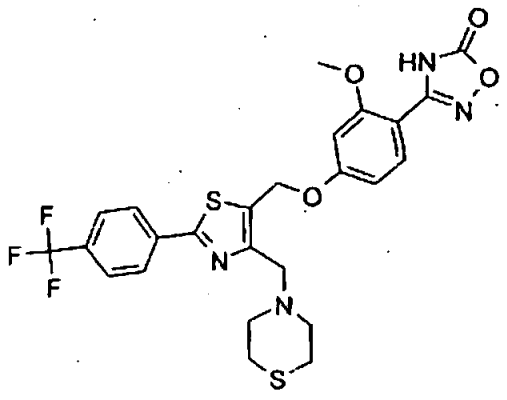
According to the method described for 3-{4-[4-(4-methanesulfonyl-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one, 3-{4-[4-[(2-methanesulfinyl-ethylamino)-methyl]-2-(4-

trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from methanesulfonic acid 5-[3-methoxy-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethyl ester and 2-methanesulfinyl-ethylamine.

C24H23F3N4O5S2 (568.59), MS(ESI): 569.

Example 45

3-{2-Methoxy-4-[4-thiomorpholin-4-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

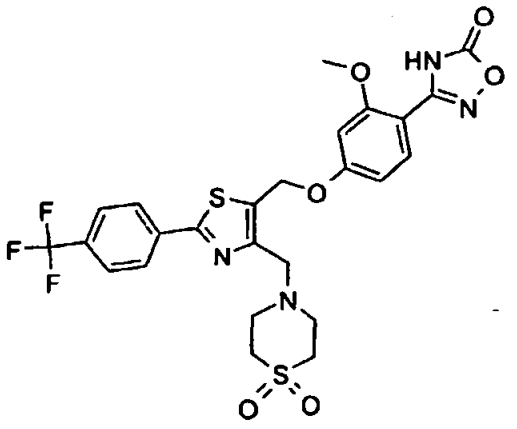


According to the method described for 3-{4-[4-(4-methanesulfonyl-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one, 3-{2-methoxy-4-[4-thiomorpholin-4-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from methanesulfonic acid 5-[3-methoxy-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethyl ester and thiomorpholine.

C25H23F3N4O4S2 (564.61), MS(ESI): 565.

Example 46

3-{4-[4-(1,1-Dioxo-1λ^6-thiomorpholin-4-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one



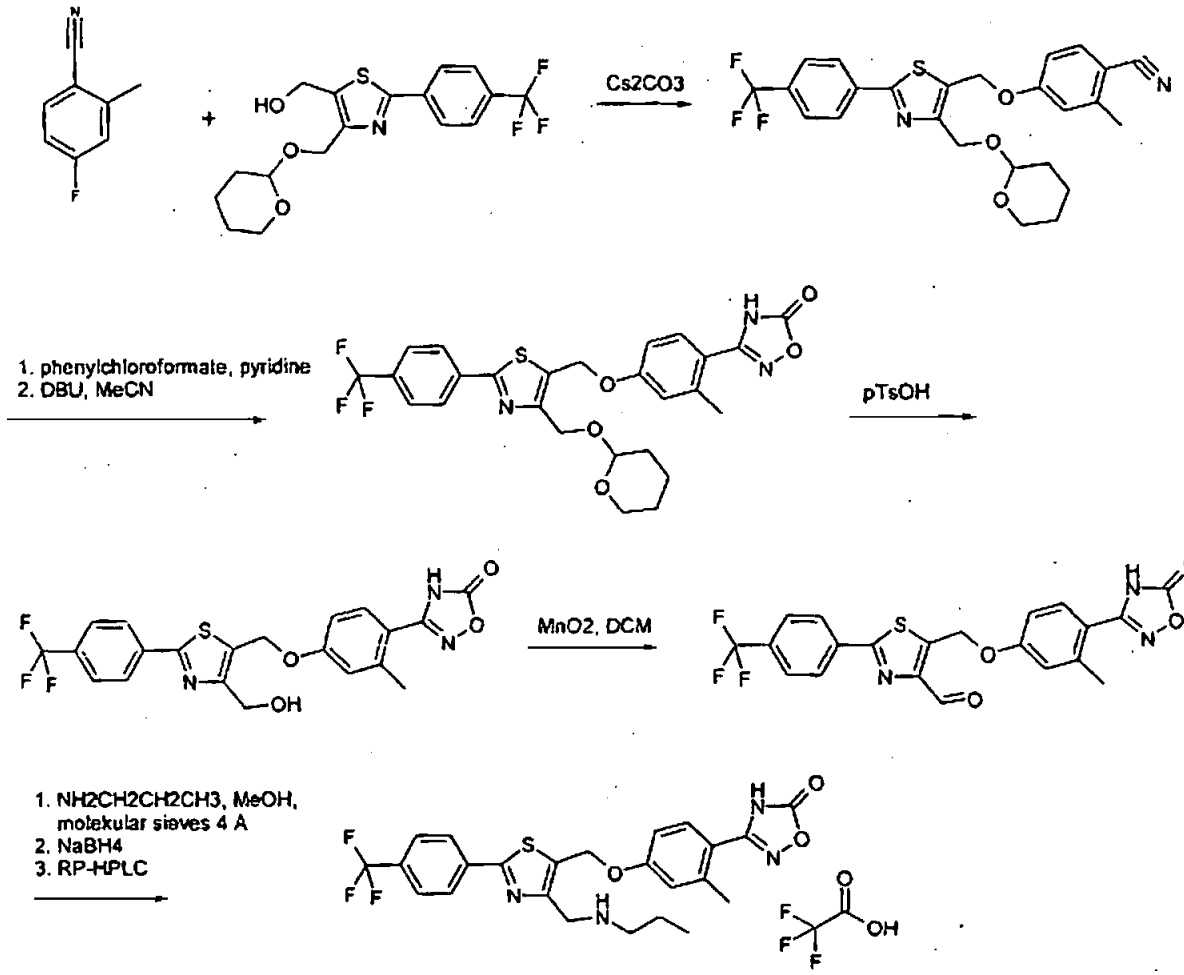
50 mg of 3-{2-Methoxy-4-[4-thiomorpholin-4-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one were suspended in 3 mL of a 2N solution of hydrochloric acid in ether and 3 mL of methanol were added. The resulting solution was concentrated under reduced pressure. To a suspension of the resulting hydrochloride in 1.5 mL of acetonitrile and 0.5 mL of water was added 108 mg of Oxone® (potassium peroxymonosulfate). The resulting mixture was stirred at room temperature for 1 hour then poured into dichloromethane/water. The organic layer was separated, washed with a saturated aqueous solution of Na2S2O3, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by preparative thin layer chromatography on silica gel (dichloromethane 95/ acetone 5) to give 4.5 mg of 3-{4-[4-(1,1-dioxo-1λ^6-thiomorpholin-4-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one.

C25H23F3N4O6S2 (596.60), MS(ESI): 597.

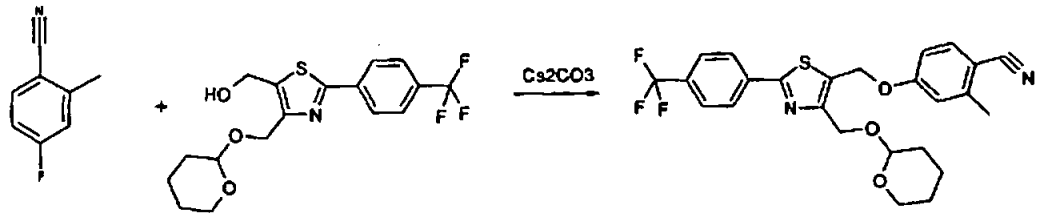
The following examples were prepared according to process E, whereby the first two reaction steps were performed according to process B:

Example 47

3-[2-Methyl-4-[4-propylaminomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl]-4H-[1,2,4]oxadiazol-5-one



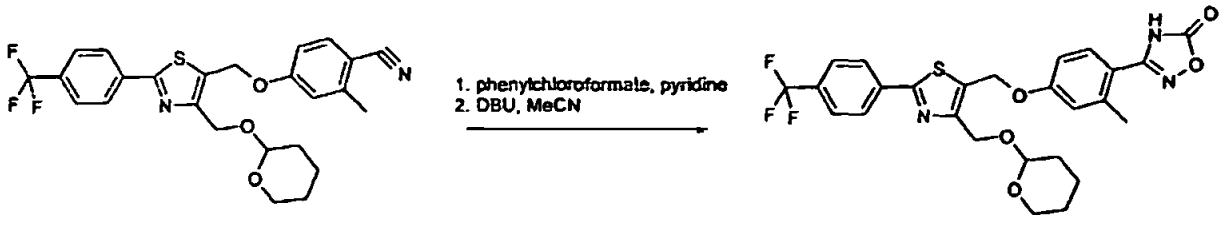
5 2-Methyl-4-[4-(tetrahydro-pyran-2-yloxymethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-benzonitrile



To a stirred solution of 1.09 g 4-fluoro-2-methylbenzonitrile in 50 ml dimethylformamide were given 3.0 g [4-(tetrahydro-pyran-2-yloxymethyl)-2-(4-trifluoromethyl-phenyl)-

thiazol-5-yl]- methanol[7] and 2.62 g cesium carbonate. The reaction mixture was stirred at room temperature overnight. 250 ml ethyl acetate were added and the mixture washed five times with portions of 50 ml water and brine. The organic layer was dried over MgSO4, then the solvent was removed in vacuo. The residue was purified by silica gel chromatography with the eluent n-heptane : ethyl acetate = 15: 1 => 2 : 1 to obtain 1.5 g 2-methyl-4-[4-(tetrahydro-pyran-2-yloxymethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5- ylmethoxy]-benzonitrile as pale yellow solid.
C25H23F3N2O3S (488.53), MS(ESI): 489.2, 405.2 , Rf(n-heptane : ethyl acetate = 2: 1) = 0.36.

3-{2-Methyl-4-[4-(tetrahydro-pyran-2-yloxymethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5- ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

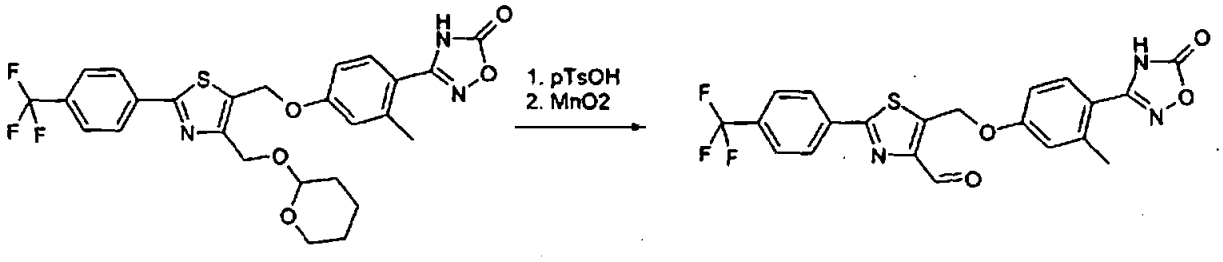


1.5 g 2-Methyl-4-[4-(tetrahydro-pyran-2-yloxymethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5- ylmethoxy]-benzonitrile were dissolved in a mixture of 10 ml tetrahydrofuran and 10 ml methanol. 2.12 g hydroxylamine hydrochloride were added followed by the addition of 5.08 ml triethylamine. The reaction mixture was stirred at 65°C overnight. The solvents were removed in vacuo and the resulting residue poured into water and extracted five times with ethylacetate. The combined organic extracts were washed with brine, dried over MgSO4 and the solvent was evaporated in vacuo. The residue was dissolved in 10 ml dichloromethane. 0.32 ml pyridine and 0.49 ml phenylchloroformate were added and the mixture stirred at room temperature for fifteen minutes. The mixture was diluted by the addition of 50 ml acetonitrile and 2.28 ml 1,8-diazabicyclo[5.4.0]undec-7-ene were added. The mixture was stirred at room temperature for thirty minutes. The mixture was evaporated in vacuo and the resulting crude material was purified by silica gel chromatography with the eluent n-heptane :

7 WO 2002067912, WO 2002059098

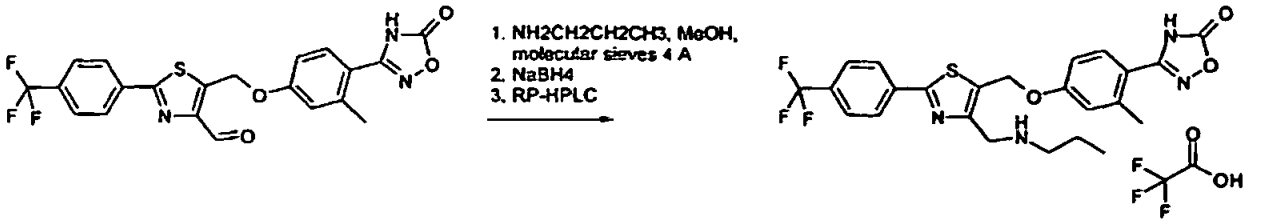
ethyl acetate = 4: 1 => ethyl acetate => ethyl acetate : methanol = 4:1 to obtain 1.05 g 3-{2-methyl-4-[4-(tetrahydro-pyran-2-yloxymethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5- ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one as pale yellow solid.
C26H24F3N3O5S (547.56), MS(ESI): 464.2.

5-[3-Methyl-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazole-4-carbaldehyde



1.05 g 3-{2-Methyl-4-[4-(tetrahydro-pyran-2-yloxymethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5- ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one was suspended in 80 ml methanol. 66.0 mg p-Toiuenesulfonic acid were added and the reaction mixture warmed to 60°C until the reaction mixture became a clear solutution. The cooled reaction mixture was evaporated in vacuo. The residue was dissolved in a mixture of 10 ml dimethylformamide and 40 ml dichloromethane. 3.76 g Manganese (IV) oxide on activated charcoil were added and the reaction mixture heated to reflux for two hours. The cooled reaction mixture was filtered through a celite pad. The filtrate was evaporated in vacuo to obtain 670 mg crude 5-[3-methyl-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4- trifluoromethyl-phenyl)-thiazole-4-carbaldehyde which was used without further purification.
C21H14F3N3O4S (461.42), MS(ESI):462.0, Rf(ethyl acetate : methanol = 19: 1) = 0.52.

3-{2-Methyl-4-[4-propylaminomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

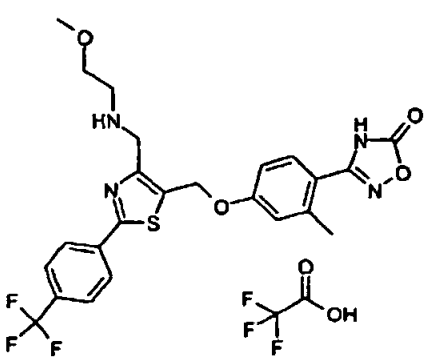


100 mg 5-[3-Methyl-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazole-4-carbaldehyde and 12.8 mg propylamine were suspended in 3 ml methanol. 30.0 µl triethylamine were added upon the reaction mixture became a clear solution. 400 mg molecular sieves four angstrom were added and the reaction mixture stirred at room temperature for two hours. Then 8.2 mg sodium borohydride were added and the reaction mixture stirred at room temperature for thirty minutes. The reaction mixture was filtered through a celite pad. The filtrate was evaporated in vacuo and then evaporated in vacuo. The residue was purified by RP-HPLC to obtain 45.7 mg 3-{2-methyl-4-[4-propylaminomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]- phenyl}-4H-[1,2,4]oxadiazol-5-one as its trifluoroacetate salt.

C24H23F3N4O3S.C2HF3O2(618.56), MS(ESI):505.1.

Example 48

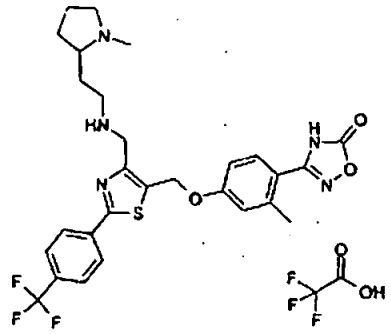
3-{4-[4-[(2-Methoxy-ethylamino)-methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]- 2-methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one



According to the method described for 3-{2-methyl-4-[4-propylaminomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]- phenyl}-4H-[1,2,4]oxadiazol-5-one in example 47, 3-{4-[4-[(2-methoxy-ethylamino)-methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]- 2-methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 5-[3-Methyl-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazole-4-carbaldehyde and 2-methoxyethylamine. The compound was obtained as its trifluoroacetate salt.
C24H23F3N4O4S.C2HF3O2 (634.56), MS(ESI):521.1.

Example 49

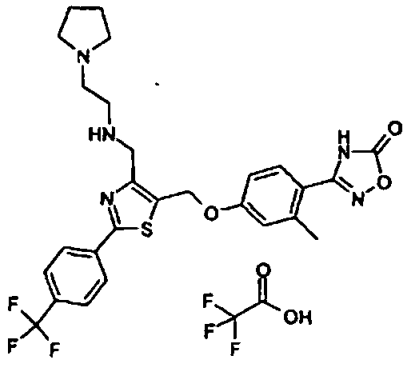
3-{2-Methyl-4-[4-{[2-(1-methyl-pyrrolidin-2-yl)-ethylamino]-methyl}-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one



According to the method described for 3-{2-methyl-4-[4-propylaminomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]- phenyl}-4H-[1,2,4]oxadiazol-5-one in example 47, 3-{2-methyl-4-[4-{[2-(1-methyl-pyrrolidin-2-yl)-ethylamino]-methyl}-2-(4-trifluoromethyl- phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 5-[3-methyl-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4- trifluoromethyl-phenyl)-thiazole-4-carbaldehyde and 2-(2-aminoethyl)-1-methylpyrrolidine. The compound was obtained as its trifluoroacetate salt.
C24H23F3N4O3S.C2HF3O2 (618.56), MS(ESI):574.2.

Example 50

3-{2-Methyl-4-[4-[(2-pyrrolidin-1-yl-ethylamino)-methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

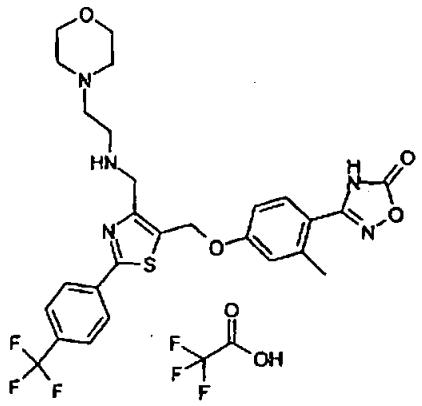


According to the method described for 3-{2-methyl-4-[4-propylaminomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]- phenyl}-4H-[1,2,4]oxadiazol-5-one in example 47, 3-{2-methyl-4-[4-[(2-pyrrolidin-1-yl-ethylamino)-methyl]-2-(4-trifluoromethyl-phenyl)- thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 5-[3-methyl-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4- trifluoromethyl-phenyl)-thiazole-4-carbaldehyde and N-(2-aminoethyl)pyrrolidine. The compound was obtained as its trifluoroacetate salt.

C27H28F3N5O3S.2C2HF3O2 (787.66), MS(ESI):560.2.

Example 51

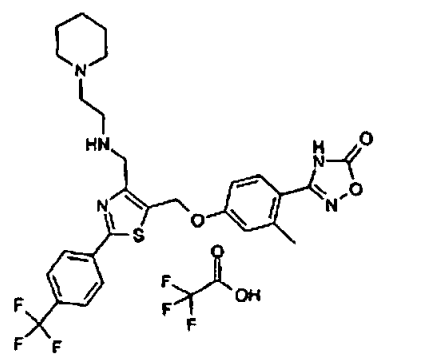
3-{2-Methyl-4-[4-[(2-morpholin-4-yl-ethylamino)-methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one



According to the method described for 3-{2-methyl-4-[4-propylaminomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]- phenyl}-4H-[1,2,4]oxadiazol-5-one in example 47, 3-{2-methyl-4-[4-[(2-morpholin-4-yl-ethylamino)-methyl]-2-(4-trifluoromethyl-phenyl)- thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 5-[3-methyl-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4- trifluoromethyl-phenyl)-thiazole-4-carbaldehyde and N-(2-aminoethyl)-morpholine. The compound was obtained as its trifluoroacetate salt. C27H28F3N5O4S.C2HF3O2 (803.66), MS(ESI):576.2.

Example 52

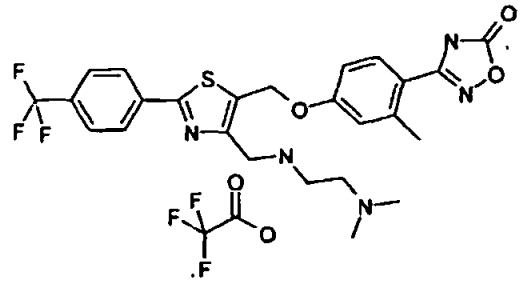
3-{2-Methyl-4-[4-[(2-piperidin-1-yl-ethylamino)-methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one



According to the method described for 3-{2-methyl-4-[4-propylaminomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]- phenyl}-4H-[1,2,4]oxadiazol-5-one in example 47, 3-{2-methyl-4-[4-[(2-piperidin-1-yl-ethylamino)-methyl]-2-(4-trifluoromethyl-phenyl)- thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 5-[3-methyl-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4- trifluoromethyl-phenyl)-thiazole-4-carbaldehyde and 1-(2-aminoethyl)piperidine. The compound was obtained as its trifluoroacetate salt. C28H30F3N5O3S.C2HF3O2 (801.69), MS(ESI):574.2.

Example 53

3-{4-[4-[(2-Dimethylamino-ethylamino)-methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one

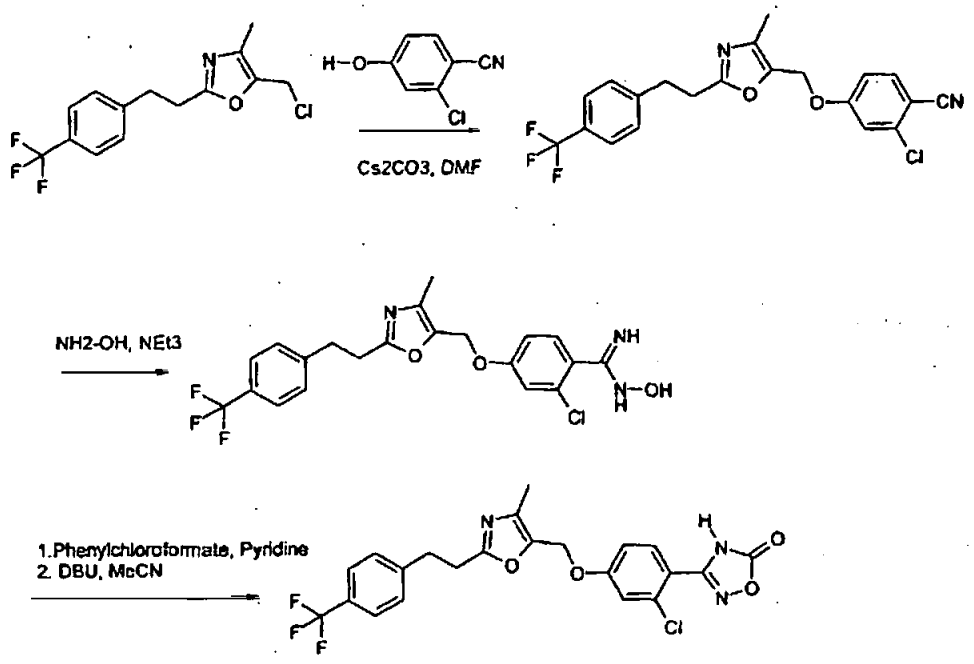


According to the method described for 3-{2-methyl-4-[4-propylaminomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]- phenyl}-4H-[1,2,4]oxadiazol-5-one in example 47, 3-{4-[4-[(2-dimethylamino-ethylamino)-methyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5- ylmethoxy]-2-methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 5-[3-methyl-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4- trifluoromethyl-phenyl)-thiazole-4-carbaldehyde and N,N-dimethylethylenediamine. The compound was obtained as its trifluoroacetate salt. C25H26F3N5O3S.C2HF3O2 (761.63), MS(ESI):534.2.

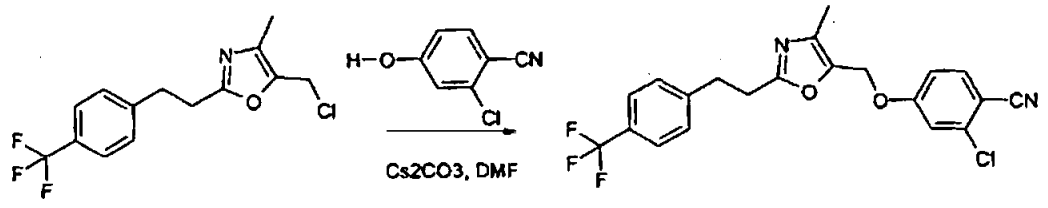
The following examples were prepared according to process A:

Example 54

3-(2-Chloro-4-{4-methyl-2-[2-(4-trifluoromethyl-phenyl)-ethyl]-oxazol-5-ylmethoxy}-phenyl)-4H-[1,2,4]oxadiazol-5-one

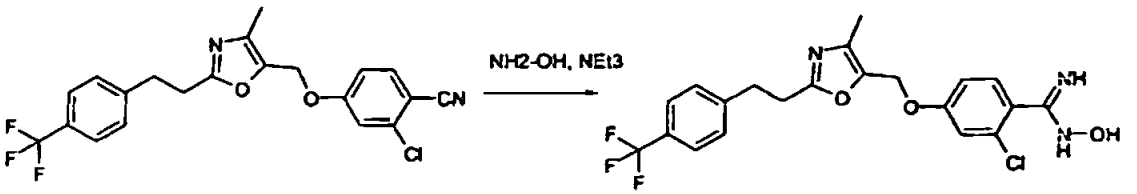


2-Chloro-4-{4-methyl-2-[2-(4-trifluoromethyl-phenyl)-ethyl]-oxazol-5-ylmethoxy}-benzonitrile



To a solution of 2.63 g 2-chloro-4-hydroxy-benzonitrile in 25 ml dimethylformamide were added 4.0 g 5-chloromethyl-4-methyl-2-[2-(4-trifluoromethyl-phenyl)-ethyl]-oxazole and 8.58 g cesium carbonate. The mixture was stirred at room temperature overnight. Then 150 ml of ethyl acetate were added, the mixture washed with 40ml water and brine and then dried over MgSO4. The solvent was removed in vacuo. The resulting crude material was purified by RP-HPLC to obtain 3.0 g 2-chloro-4-{4-methyl-2-[2-(4-trifluoromethyl-phenyl)-ethyl]-oxazol-5-ylmethoxy}-benzonitrile.
C21H16ClF3N2O2 (420.82), MS(ESI): 421.1 ($M+H^+$).

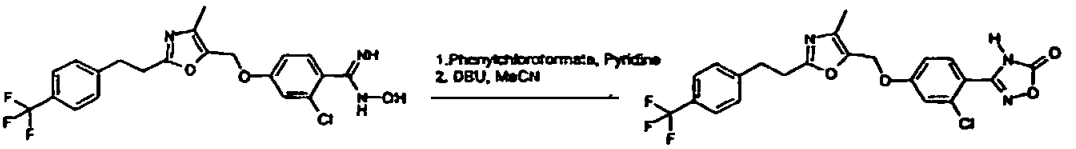
2-Chloro-N-hydroxy-4-{4-methyl-2-[2-(4-trifluoromethyl-phenyl)-ethyl]-oxazol-5-ylmethoxy}-benzamidine



3.0 g 2-Chloro-4-{4-methyl-2-[2-(4-trifluoromethyl-phenyl)-ethyl]-oxazol-5-ylmethoxy}-benzonitrile were dissolved in a mixture of 20 ml tetrahydrofuran and 20 ml methanol. 9.91 g hydroxylamine hydrochloride were added followed by the addition of 19.9 ml triethylamine. The reaction mixture was stirred at 65°C overnight. The solvents were removed in vacuo and the resulting residue poured into water and extracted five times with ethylacetate. The combined organic extracts were washed with brine, dried over MgSO4 and the solvent was evaporated in vacuo to obtain 4.4 g crude 2-chloro-N-hydroxy-4-{4-methyl-2-[2-(4-trifluoromethyl-phenyl)-ethyl]-oxazol-5-ylmethoxy}-benzamidine which was used without further purification.

C21H19ClF3N3O3 (453.85), MS(ESI): 454.2 ($M+H^+$).

3-(2-Chloro-4-{4-methyl-2-[2-(4-trifluoromethyl-phenyl)-ethyl]-oxazol-5-ylmethoxy}-phenyl)-4H-[1,2,4]oxadiazol-5-one

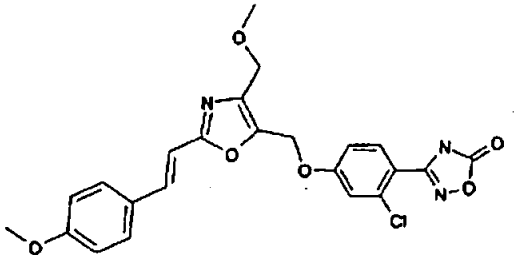


4.4 g crude 2-Chloro-N-hydroxy-4-{4-methyl-2-[2-(4-trifluoromethyl-phenyl)-ethyl]-oxazol-5-ylmethoxy}-benzamidine were dissolved in 20 ml dichloromethane. 0.94 ml pyridine and 1.46 ml phenylchloroformate were added and the mixture stirred at room temperature for ten minutes. The mixture was diluted by the addition of 40 ml acetonitrile and 7.25 ml 1,8-diazabicyclo[5.4.0]undec-7-ene were added. The mixture was stirred at room temperature for 10 minutes. The mixture was evaporated in vacuo and the resulting crude material was purified by reversed phase HPLC to obtain 460 mg 3-(2-chloro-4-{4-methyl-2-[2-(4-trifluoromethyl-phenyl)-ethyl]-oxazol-5-ylmethoxy}-phenyl)-4H-[1,2,4]oxadiazol-5-one.

C22H17ClF3N3O4 (479.85), MS(ESI): 479.98 ($M+H^+$).

Example 55

3-(2-Chloro-4-{4-methoxymethyl-2-[2-(4-methoxy-phenyl)-vinyl]-oxazol-5-ylmethoxy}-phenyl)- 4H-[1,2,4]oxadiazol-5-one

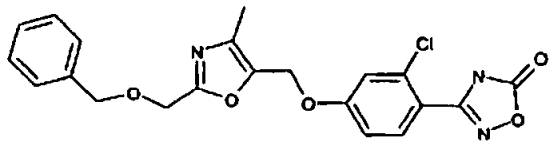


According to the method described for 3-(2-chloro-4-{4-methyl-2-[2-(4-trifluoromethyl-phenyl)-ethyl]-oxazol-5-ylmethoxy}- phenyl)-4H-[1,2,4]oxadiazol-5-one in example 54, 3-(2-chloro-4-{4-methoxymethyl-2-[2-(4-methoxy-phenyl)-vinyl]-oxazol-5-ylmethoxy}-phenyl)- 4H-[1,2,4]oxadiazol-5-one was obtained from 5-chloromethyl-4-methoxymethyl-2-[2-(4-methoxy-phenyl)-vinyl]-oxazole and 2-chloro-4-hydroxy-benzonitrile.

$C_{23}H_{20}ClN_3O_6$ (469.88), MS(ESI): 470.0 ($M+H^+$).

Example 56

3-[4-(2-Benzyloxymethyl-4-methyl-oxazol-5-ylmethoxy)-2-chloro-phenyl]-4H-[1,2,4]oxadiazol-5-one

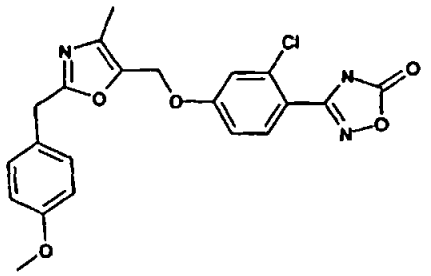


According to the method described for 3-(2-chloro-4-{4-methyl-2-[2-(4-trifluoromethyl-phenyl)-ethyl]-oxazol-5-ylmethoxy}- phenyl)-4H-[1,2,4]oxadiazol-5-one in example 54, 3-[4-(2-benzyloxymethyl-4-methyl-oxazol-5-ylmethoxy)-2-chloro-phenyl]-4H-[1,2,4]oxadiazol-5-one was obtained from 2-benzyloxymethyl-5-chloromethyl-4-methyl-oxazole and 2-chloro-4-hydroxy-benzonitrile.

$C_{21}H_{18}ClN_3O_5$ (427.85), MS(ESI): 428.4 ($M+H^+$).

Example 57

3-{2-Chloro-4-[2-(4-methoxy-benzyl)-4-methyl-oxazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

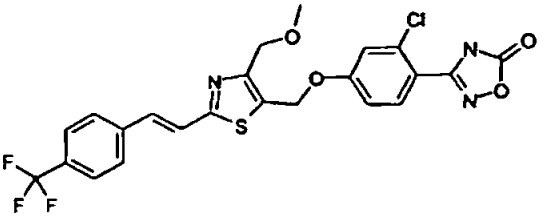


According to the method described for 3-(2-chloro-4-{4-methyl-2-[2-(4-trifluoromethyl-phenyl)-ethyl]-oxazol-5-ylmethoxy}- phenyl)-4H-[1,2,4]oxadiazol-5-one in example 54, 3-{2-chloro-4-[2-(4-methoxy-benzyl)-4-methyl-oxazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 5-chloromethyl-2-(4-methoxy-benzyl)-4-methyl-oxazole and 2-chloro-4-hydroxy-benzonitrile.

C21H18ClN3O5 (427.85), MS(ESI): 428.2 ($M+H^+$).

Example 58

3-{2-Chloro-4-{4-methoxymethyl-2-[2-(4-trifluoromethyl-phenyl)-vinyl]-thiazol-5-ylmethoxy}-phenyl)-4H-[1,2,4]oxadiazol-5-one

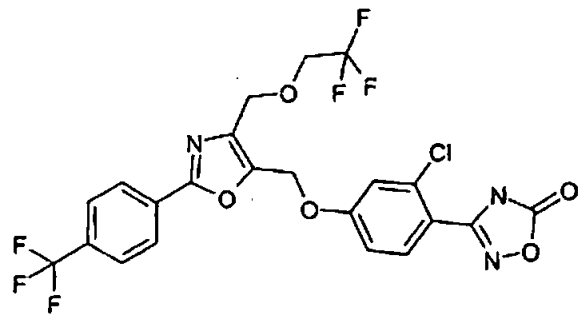


According to the method described for 3-(2-chloro-4-{4-methyl-2-[2-(4-trifluoromethyl-phenyl)-ethyl]-oxazol-5-ylmethoxy}- phenyl)-4H-[1,2,4]oxadiazol-5-one in example 54, 3-(2-chloro-4-{4-methoxymethyl-2-[2-(4-trifluoromethyl-phenyl)-vinyl]-thiazol-5-ylmethoxy}-phenyl)-4H-[1,2,4]oxadiazol-5-one was obtained from 5-chloromethyl-4-methoxymethyl-2-[2-(4-trifluoromethyl-phenyl)-vinyl]-thiazole and 2-chloro-4-hydroxy-benzonitrile.

C23H17ClF3N3O4S (523.92), MS(ESI): 524.0 ($M+H^+$).

Example 59

3-{2-Chloro-4-[4-(2,2,2-trifluoro-ethoxymethyl)-2-(4-trifluoromethyl-phenyl)-oxazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one



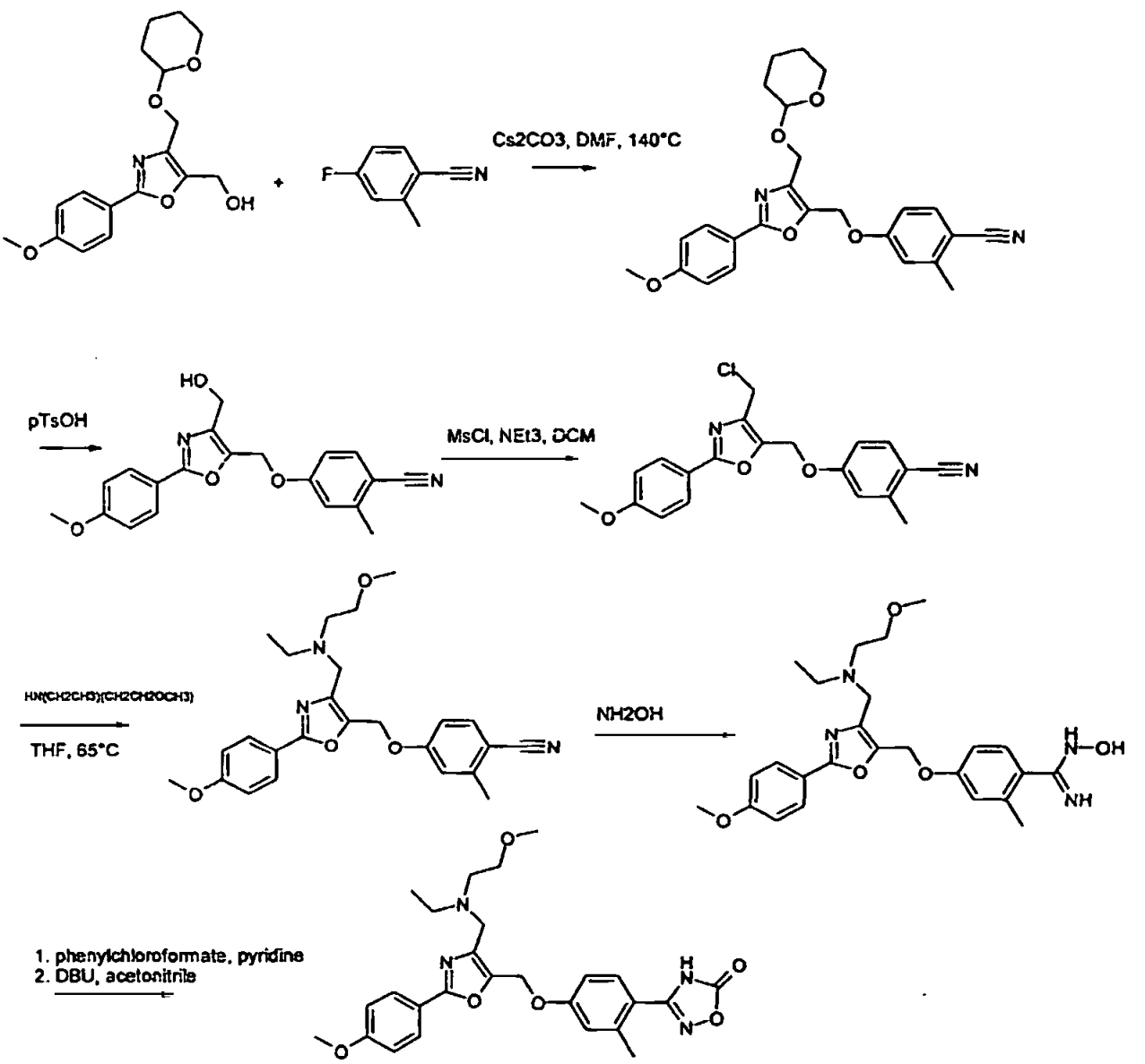
According to the method described for 3-(2-chloro-4-{4-methyl-2-[2-(4-trifluoromethyl-phenyl)-ethyl]-oxazol-5-ylmethoxy}- phenyl)-4H-[1,2,4]oxadiazol-5-one in example 54, 3-{2-chloro-4-[4-(2,2,2-trifluoro-ethoxymethyl)-2-(4-trifluoromethyl-phenyl)-oxazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 5-chloromethyl-4-(2,2,2-trifluoro-ethoxymethyl)-2-(4-trifluoromethyl-phenyl)-oxazole and 2-chloro-4-hydroxy-benzonitrile.

$C_{22}H_{14}ClF_6N_3O_5$ (549.82), MS(ESI): 550.2 ($M+H^+$).

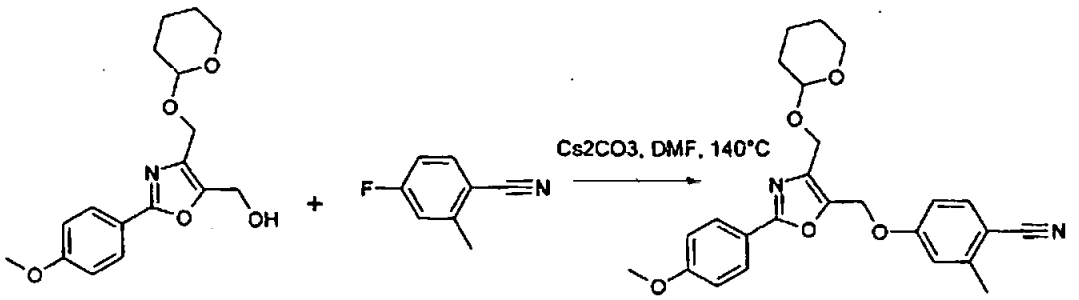
The following examples were prepared according to process L, whereby the first reaction step was performed according to general process B [B1 + B2 => B3]:

Example 60

3-{4-[4-{[Ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]- 2-methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one

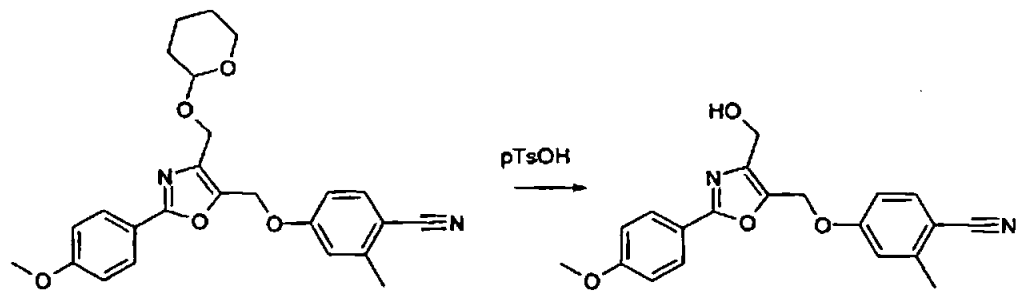


4-[2-(4-Methoxy-phenyl)-4-(tetrahydro-pyran-2-yloxymethyl)-oxazol-5-ylmethoxy]-2-methyl- benzonitrile



To a solution of 3.2 g 4-fluoro-2-methylbenzonitrile in 50 ml dimethylformamide 5.0g [2-(4-methoxy-phenyl)-4-(tetrahydro-pyran-2-yloxymethyl)-oxazol-5-yl]-methanol were added followed by the addition of 10.2 g cesium carbonate. The reaction mixture was stirred at 140°C overnight. The cooled reaction mixture was diluted with 200 ml ethyl acetate and washed five times with portions of 50 ml water and brine. The organic phase was dried over MgSO4 and the solvent was evaporated in vacuo.The residue was purified by chromatography on silica gel with the eluent n-heptane:ethyl acetate = 5:1 => 2:1 to obtain 5.96 g 4-[2-(4-Methoxy-phenyl)-4-(tetrahydro-pyran-2-yloxymethyl)-oxazol-5-ylmethoxy]-2-methyl- benzonitrile as an oil.
C25H26N2O5 (434.50), MS(ESI): 435.2 ($M+H^+$), Rf(n-heptane:ethyl acetate = 1:1) = 0.42.

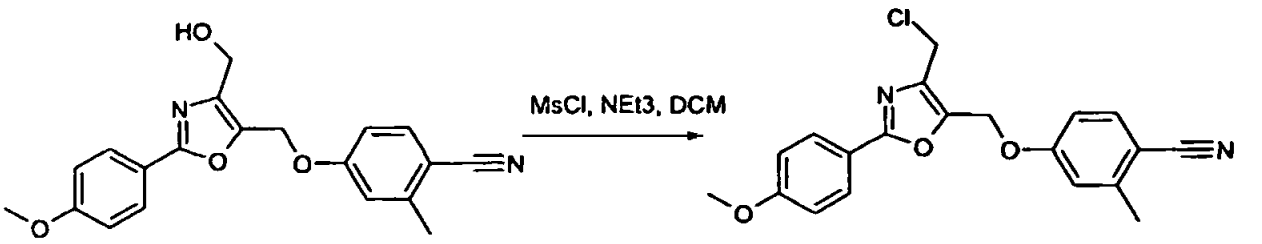
4-[4-Hydroxymethyl-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2-methyl-benzonitrile



5.96 g 4-[2-(4-Methoxy-phenyl)-4-(tetrahydro-pyran-2-yloxymethyl)-oxazol-5-ylmethoxy]-2-methyl- benzonitrile were dissolved in 100 ml methanol. 522 mg p-toluenesulfonic acid monohydrate were added and the reaction mixture stirred at room temperature for one hour. The solvent was removed in vacuo . The residue was dissolved in 150 ml ethyl acetate and washed with 80 ml saturated NaHCO3 solution

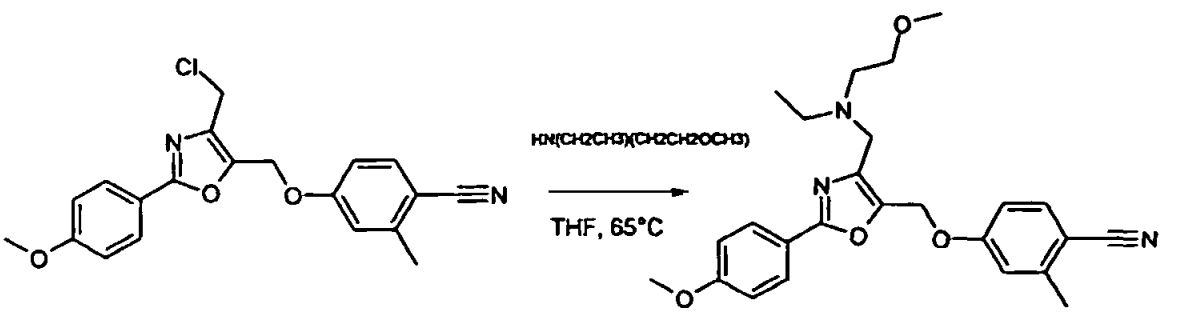
and brine. The organic phase was dried over MgSO4 and the solvent was evaporated in vacuo to obtain 4.1 g 4-[4-hydroxymethyl-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2-methyl-benzonitrile as pale yellow solid.
C20H18N2O4 (350.38), MS(ESI): 351.2 ($M+H^+$).

4-[4-Chloromethyl-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2-methyl-benzonitrile



4.1 g 4-[4-Hydroxymethyl-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2-methyl-benzonitrile were dissolved in 90 ml dichloromethane and cooled in an ice bath. 2.44 ml triethylamine were added, followed by the addition of 1.08 ml methanesulfonylchloride. The ice bath was removed and the resulting mixture stirred at room temperature over night. The reaction mixture was then washed with water and brine, dried over MgSO4 and the solvent removed in vacuo to obtain 2.5 g of 5-chloromethyl-2-(4-methoxy-phenyl)-4-(tetrahydro-pyran-2-yloxymethyl)-oxazole as an oil which was used without further purification.
C20H17ClN2O3 (368.82), MS(ESI): 369.1 ($M+H^+$), Rf(ethyl acetate:n-heptane = 1:1) = 0.59.

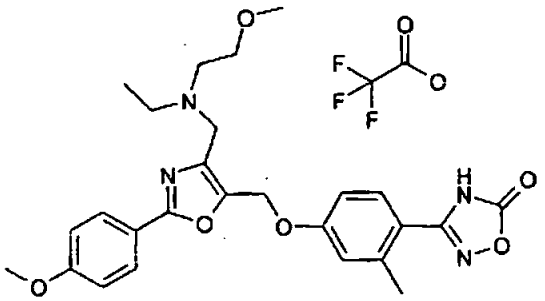
4-[4-{[Ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2- methyl-benzonitrile



200 mg 5-chloromethyl-2-(4-methoxy-phenyl)-4-(tetrahydro-pyran-2-yloxymethyl)-oxazole and 224 mg N-(2-methoxyethyl)ethylamine were dissolved in 5 ml tetrahydrofuran and stirred at 60°C for six hours. The cooled reaction mixture was diluted with 50 ml ethyl acetate and washed with portions of 20 ml water and brine, then dried over MgSO4. The solvent was removed in vacuo to obtain 158 mg 4-[4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2-methyl-benzonitrile as an oil.

C25H29N3O4 (435.53), MS(ESI): 436.3 (M+H+).

3-{4-[4-{[Ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]- 2-methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one

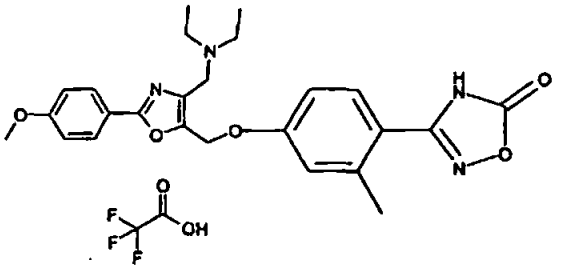


According to the method described for 3-(2-chloro-4-{4-methyl-2-[2-(4-trifluoromethyl-phenyl)-ethyl]-oxazol-5-ylmethoxy}- phenyl)-4H-[1,2,4]oxadiazol-5-one in example 54, 3-{4-[4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]- 2-methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 4-[4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2-methyl-benzonitrile. The compound was obtained as its trifluoro-acetate salt.

C26H30N4O6.C2HF3O2 (608.57), MS(ESI): 495.1 ($M+H^+$).

Example 61

3-{4-[4-Diethylaminomethyl-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2-methyl-phenyl}-4H- [1,2,4]oxadiazol-5-one

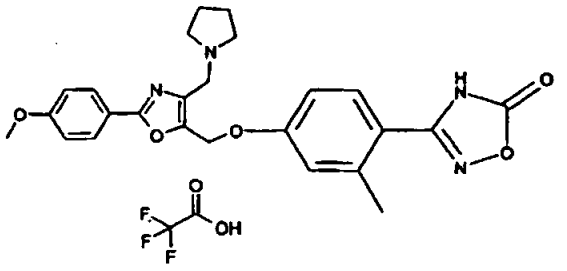


According to the method described for 3-{4-[4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2-methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one in example 60, 3-{4-[4-diethylaminomethyl-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2-methyl-phenyl}-4H- [1,2,4]oxadiazol-5-one was obtained from 5-chloromethyl-2-(4-methoxy-phenyl)-4-(tetrahydro-pyran-2-yloxymethyl)-oxazole and diethylamine. The compound was obtained as its trifluoro-acetate salt.

C25H28N4O5.C2HF3O2 (578.55), MS(ESI): 465.1 ($M+H^+$).

Example 62

3-{4-[2-(4-Methoxy-phenyl)-4-pyrrolidin-1-ylmethyl-oxazol-5-ylmethoxy]-2-methyl-phenyl}- 4H-[1,2,4]oxadiazol-5-one



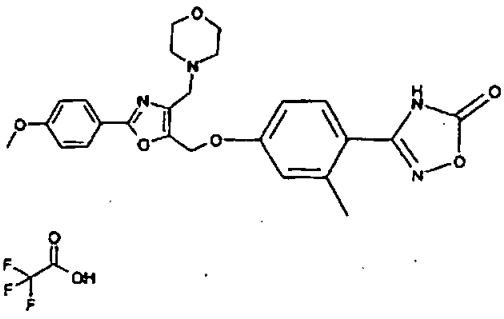
According to the method described for 3-{4-[4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2-methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one in example 60, 3-{4-[2-(4-methoxy-phenyl)-4-pyrrolidin-1-ylmethyl-oxazol-5-ylmethoxy]-2-methyl-phenyl}- 4H-[1,2,4]oxadiazol-5-one was obtained from 5-chloromethyl-2-(4-methoxy-phenyl)-4-(tetrahydro-pyran-2-

yloxymethyl)-oxazole and pyrrolidine. The compound was obtained as its trifluoro-acetate salt.

C25H26N4O5.C2HF3O2 (576.53), MS(ESI): 463.2 ($M+H^+$).

Example 63

3-{4-[2-(4-Methoxy-phenyl)-4-morpholin-4-ylmethyl-oxazol-5-ylmethoxy]-2-methyl-phenyl}- 4H-[1,2,4]oxadiazol-5-one

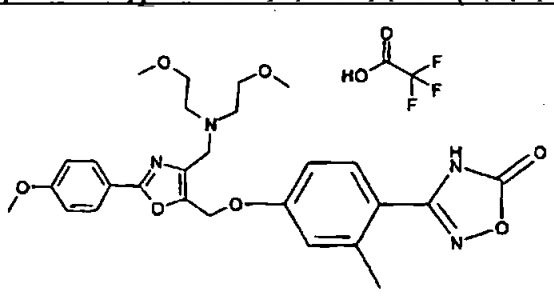


According to the method described for 3-{4-[4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2-methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one in example 60, 3-{4-[2-(4-methoxy-phenyl)-4-morpholin-4-ylmethyl-oxazol-5-ylmethoxy]-2-methyl-phenyl}- 4H-[1,2,4]oxadiazol-5-one was obtained from 5-chloromethyl-2-(4-methoxy-phenyl)-4-(tetrahydro-pyran-2-yloxymethyl)-oxazole and morpholine. The compound was obtained as its trifluoro-acetate salt.

C25H26N4O6.C2HF3O2 (592.53), MS(ESI): 479.3 ($M+H^+$).

Example 64

3-{4-[4-{[Bis-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2- methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one



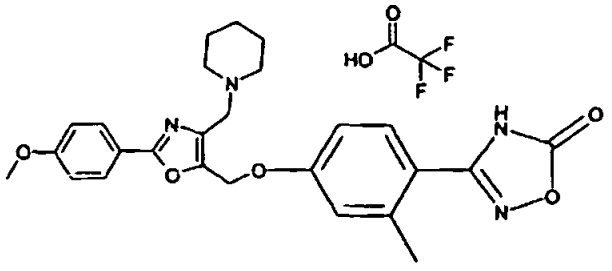
According to the method described for 3-{4-[4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2-methyl-phenyl}-4H-

[1,2,4]oxadiazol-5-one in example 60, 3-{4-[4-{[bis-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2- methyl-phenyl}-4H-[1,2,4]oxadiazol-5-onewas obtained from 5-chloromethyl-2-(4-methoxy-phenyl)-4-(tetrahydro-pyran-2-yloxymethyl)-oxazole and bis-(2-methoxy-ethyl)-amine. The compound was obtained as its trifluoro-acetate salt.

C27H32N4O7.C2HF3O2 (638.60), MS(ESI): 525.1 ($M+H^+$).

Example 65

3-{4-[2-(4-Methoxy-phenyl)-4-piperidin-1-ylmethyl-oxazol-5-ylmethoxy]-2-methyl-phenyl}- 4H-[1,2,4]oxadiazol-5-one

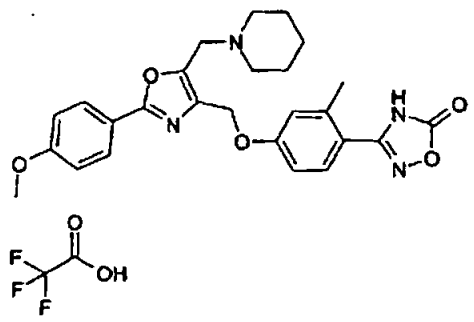


According to the method described for 3-{4-[4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2-methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one in example 60, 3-{4-[2-(4-methoxy-phenyl)-4-piperidin-1-ylmethyl-oxazol-5-ylmethoxy]-2-methyl-phenyl}- 4H-[1,2,4]oxadiazol-5-one was obtained from 5-chloromethyl-2-(4-methoxy-phenyl)-4-(tetrahydro-pyran-2-yloxymethyl)-oxazole and piperidine. The compound was obtained as its trifluoro-acetate salt.

C26H28N4O5.C2HF3O2 (590.56), MS(ESI): 477.2 ($M+H^+$).

Example 66

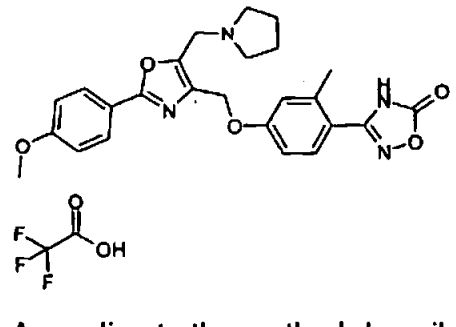
3-{4-[2-(4-Methoxy-phenyl)-5-piperidin-1-ylmethyl-oxazol-4-ylmethoxy]-2-methyl-phenyl}- 4H-[1,2,4]oxadiazol-5-one



According to the method described for 3-{4-[4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2-methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one in example 60, 3-{4-[2-(4-methoxy-phenyl)-5-piperidin-1-ylmethyl-oxazol-4-ylmethoxy]-2-methyl-phenyl}- 4H-[1,2,4]oxadiazol-5-one was obtained from methanesulfonic acid 2-(4-methoxy-phenyl)-5-(tetrahydro-pyran-2-yloxymethyl)-oxazol-4- ylmethyl ester, 4-fluoro-2-methylbenzonitrile and piperidine. The compound was obtained as its trifluoro-acetate salt.
C26H28N4O5.C2HF3O2 (590.56), MS(ESI): 477.3 ($M+H^+$).

Example 67

3-{4-[2-(4-Methoxy-phenyl)-5-pyrrolidin-1-ylmethyl-oxazol-4-ylmethoxy]-2-methyl-phenyl}- 4H-[1,2,4]oxadiazol-5-one

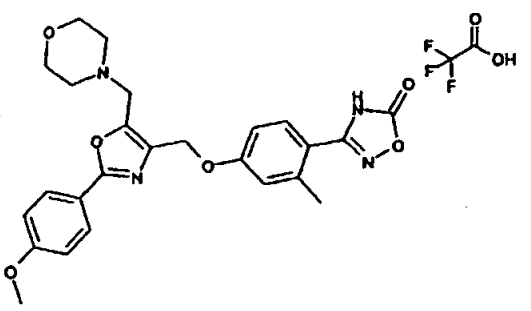


According to the method described for 3-{4-[4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2-methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one in example 60, 3-{4-[2-(4-methoxy-phenyl)-5-pyrrolidin-1-ylmethyl-oxazol-4-ylmethoxy]-2-methyl-phenyl}- 4H-[1,2,4]oxadiazol-5-one was obtained from methanesulfonic acid 2-(4-methoxy-phenyl)-5-(tetrahydro-pyran-2-

yloxymethyl)-oxazol-4- ylmethyl ester, 4-fluoro-2-methylbenzonitrile and pyrrolidine. The compound was obtained as its trifluoro-acetate salt.
C25H26N4O5.C2HF3O2 (576.53), MS(ESI): 463.3 ($M+H^+$).

Example 68

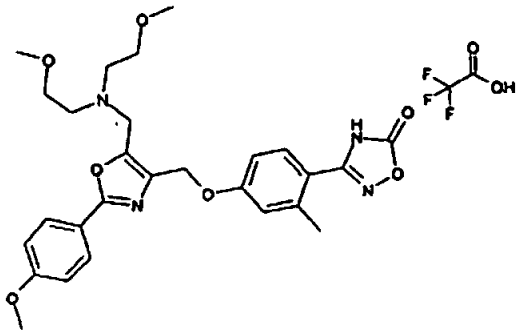
3-{4-[2-(4-Methoxy-phenyl)-5-morpholin-4-ylmethyl-oxazol-4-ylmethoxy]-2-methyl-phenyl}- 4H-[1,2,4]oxadiazol-5-one



According to the method described for 3-{4-[4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2-methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one in example 60, 3-{4-[2-(4-methoxy-phenyl)-5-morpholin-4-ylmethyl-oxazol-4-ylmethoxy]-2-methyl-phenyl}- 4H-[1,2,4]oxadiazol-5-onewas obtained from methanesulfonic acid 2-(4-methoxy-phenyl)-5-(tetrahydro-pyran-2-yloxymethyl)-oxazol-4- ylmethyl ester, 4-fluoro-2-methylbenzonitrile and morpholine. The compound was obtained as its trifluoro-acetate salt.
C25H26N4O6.C2HF3O2 (592.53), MS(ESI): 479.2 ($M+H^+$).

Example 69

3-{4-[5-{[Bis-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-4-ylmethoxy]-2- methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one

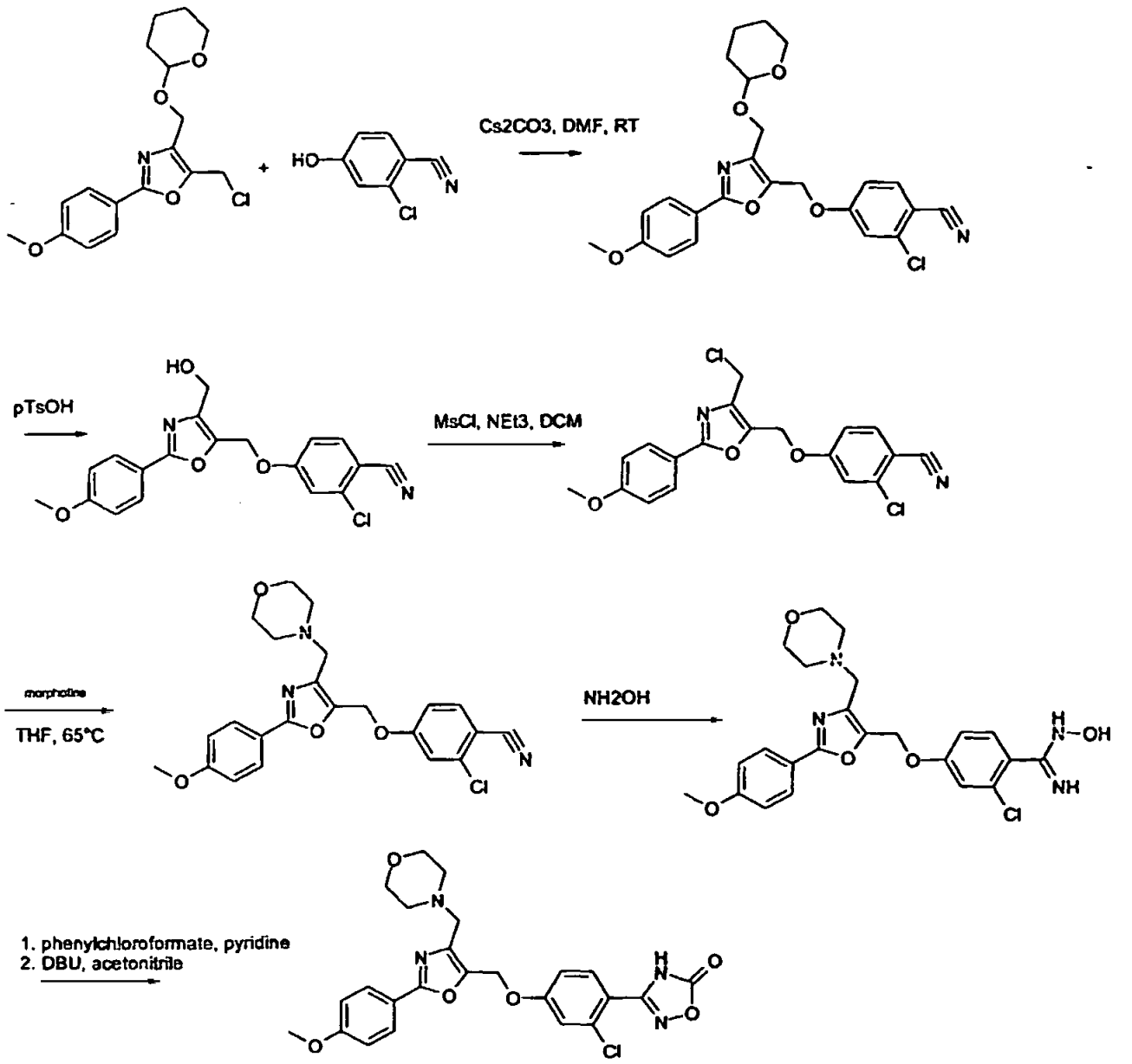


According to the method described for 3-{4-[4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2-methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one in example 60, 3-{4-[5-{[bis-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-4-ylmethoxy]-2- methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from methanesulfonic acid 2-(4-methoxy-phenyl)-5-(tetrahydro-pyran-2-yloxymethyl)-oxazol-4- ylmethyl ester, 4-fluoro-2-methylbenzonitrile and bis-(2-methoxy-ethyl)-amine.
C27H32N4O7 (524.57), MS(ESI): 525.2 ($M+H^+$).

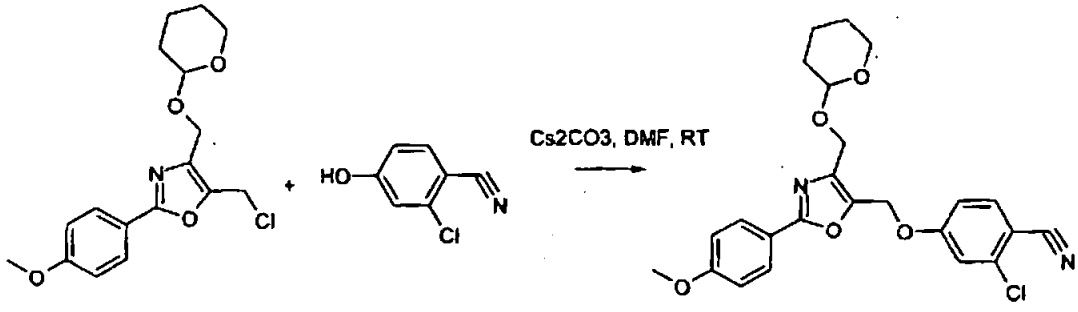
The following examples were prepared according to process L, whereby the first reaction step was performed according to general process A [A1 + A2 => A3]:

Example 70

3-{2-Chloro-4-[2-(4-methoxy-phenyl)-4-morpholin-4-ylmethyl-oxazol-5-ylmethoxy]-phenyl}- 4H-[1,2,4]oxadiazol-5-one


Cs2CO3, DMF, RT
pTsOH
MsCl, NEt3, DCM
morpholine
THF, 65°C
NH2OH
1. phenylchloroformate, pyridine
2. DBU, acetonitrile

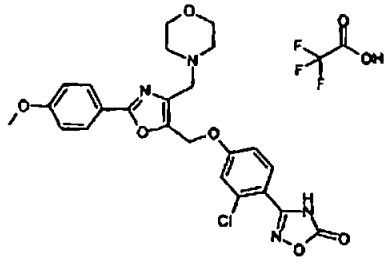
2-Chloro-4-[2-(4-methoxy-phenyl)-4-(tetrahydro-pyran-2-yloxymethyl)-oxazol-5-ylmethoxy]- benzonitrile



2.5 g 5-Chloromethyl-2-(4-methoxy-phenyl)-4-(tetrahydro-pyran-2-yloxymethyl)-oxazole and 1.48 g 2-chloro-4-hydroxybenzonitrile were dissolved in 20 ml dimethylformamide. 4.82 g Cesium carbonate were added and the reaction mixture stirred at room temperature overnight. The reaction mixture was diluted with 200 ml ethyl acetate and washed five times with portions of 50 ml water and brine. The organic phase was dried over MgSO4 and the solvent was evaporated in vacuo to obtain 4.0 g crude 2-chloro-4-[2-(4-methoxy-phenyl)-4-(tetrahydro-pyran-2-yloxymethyl)-oxazol-5-ylmethoxy]- benzonitrile. This material was used without further purification.

C24H23ClN2O5 (454.91), MS(ESI): 455.2 ($M+H^+$).

3-{2-Chloro-4-[2-(4-methoxy-phenyl)-4-morpholin-4-ylmethyl-oxazol-5-ylmethoxy]-phenyl}- 4H-[1,2,4]oxadiazol-5-one

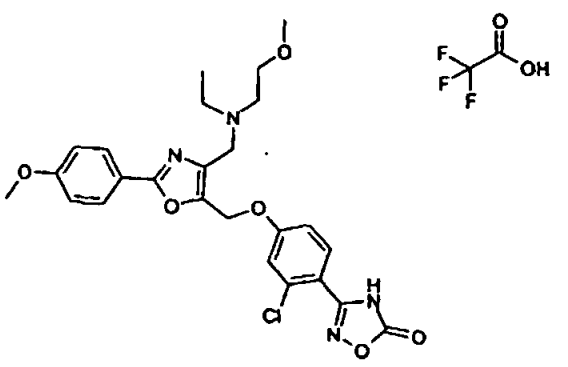


According to the method described for 3-{4-[4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2-methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one in example 60, 3-{2-chloro-4-[2-(4-methoxy-phenyl)-4-morpholin-4-ylmethyl-oxazol-5-ylmethoxy]-phenyl}- 4H-[1,2,4]oxadiazol-5-one was obtained from 2-chloro-4-[2-(4-methoxy-phenyl)-4-(tetrahydro-pyran-2-yloxymethyl)-

oxazol-5-ylmethoxy]- benzonitrile and morpholine. The compound was obtained as its trifluoro-acetate salt.
C24H23ClN4O6.C2HF3O2 (612.95), MS(ESI): 499.2 ($M+H^+$).

Example 71

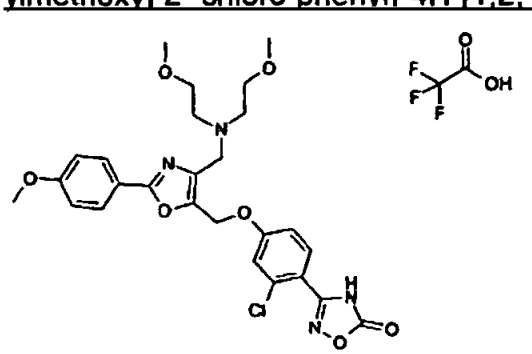
3-{2-Chloro-4-[4-[[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5- ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one



According to the method described for 3-{4-[4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2-methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one in example 60, 3-{2-chloro-4-[4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5- ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 2-chloro-4-[2-(4-methoxy-phenyl)-4-(tetrahydro-pyran-2-yloxymethyl)-oxazol-5-ylmethoxy]- benzonitrile and ethyl-(2-methoxy-ethyl)-amine. The compound was obtained as its trifluoro-acetate salt.
C25H27ClN4O6.C2HF3O2 (628.99), MS(ESI): 515.2 ($M+H^+$).

Example 72

3-{4-[4-{[Bis-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2- chloro-phenyl}-4H-[1,2,4]oxadiazol-5-one

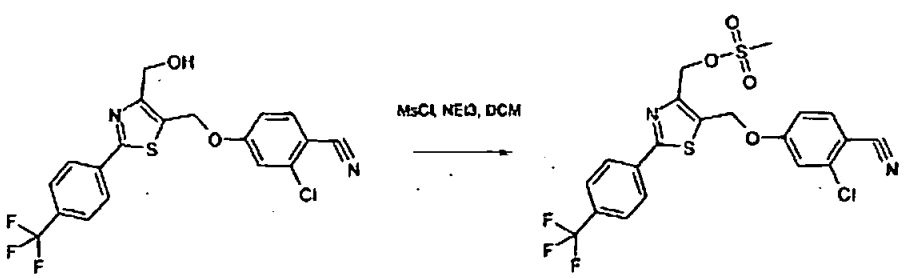


According to the method described for 3-{4-[4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2-methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one in example 60, 3-{4-[4-{[bis-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2- chloro-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 2-chloro-4-[2-(4-methoxy-phenyl)-4-(tetrahydro-pyran-2-yloxymethyl)-oxazol-5-ylmethoxy]- benzonitrile and bis-(2-methoxy-ethyl)-amine. The compound was obtained as its trifluoro-acetate salt.
$C_{26}H_{29}ClN_4O_7.C_2HF_3O_2$ (659.02), MS(ESI): 545.3 ($M+H^+$).

Example 73

3-[2-Chloro-4-[4-piperidin-1-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl]-4H-[1,2,4]oxadiazol-5-one

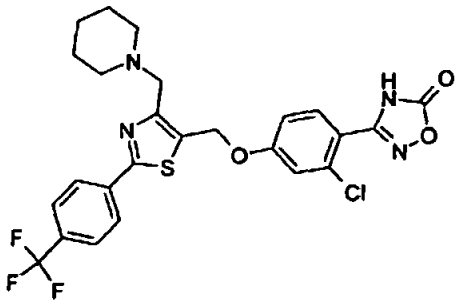
Methanesulfonic acid 5-(3-chloro-4-cyano-phenoxymethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethyl ester



2.0g 2-Chloro-4-[4-hydroxymethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-benzonitrile [obtained from 5-chloromethyl-4-(tetrahydro-pyran-2-yloxymethyl)-2-(4-trifluoromethyl-phenyl)- thiazole[8] and 2-chloro-4-hydroxybenzonitrile according to the method described in example 70] were suspended in 50 ml dichloromethane. At 0°C 0.44 ml methanesulfonyl chloride and 0.98 ml triethylamine were added and the reaction mixture was stirred at 0°C for one hour. The reaction mixture was diluted with 150 ml ethyl acetate and washed with 50 ml water and brine. The organic phase was dried over MgSO4, then the solvent was evaporated in vacuo to obtain 2.5 g methanesulfonic acid 5-(3-chloro-4-cyano-phenoxymethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethyl ester as a pale yellow solid.
$C_{20}H_{14}ClF_3N_2O_4S_2$ (502.92), MS(ESI): 503.1 ($M+H^+$).

8 WO 2002067912, WO 2002059098

3-{2-Chloro-4-[4-piperidin-1-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxyl-phenyl}-4H-[1,2,4]oxadiazol-5-one

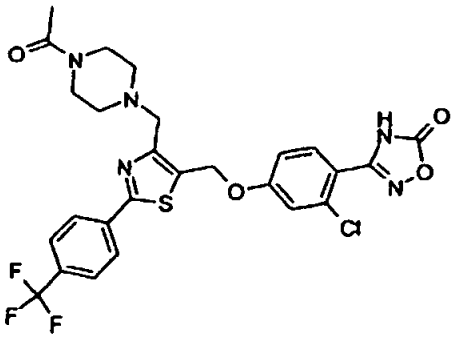


According to the method described for 3-{4-[4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2-methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one in example 60, 3-{2-chloro-4-[4-piperidin-1-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]- phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from methanesulfonic acid 5-(3-chloro-4-cyano-phenoxymethyl)-2-(4-trifluoromethyl-phenyl)- thiazol-4-ylmethyl ester and piperidine.

C25H22ClF3N4O3S (550.99), MS(ESI): 551.1 ($M+H^+$).

Example 74

3-{4-[4-(4-Acetyl-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxyl- 2-chloro-phenyl}-4H-[1,2,4]oxadiazol-5-one

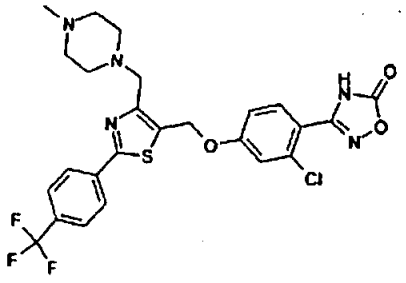


According to the method described for 3-{4-[4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2-methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one in example 60, 3-{4-[4-(4-acetyl-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]- 2-chloro-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from methanesulfonic acid 5-(3-chloro-4-cyano-phenoxymethyl)-2-(4-trifluoromethyl-phenyl)- thiazol-4-ylmethyl ester and 4-acetylpiperazine.

C26H23ClF3N5O4S (594.02), MS(ESI): 594.2 ($M+H^+$).

Example 75

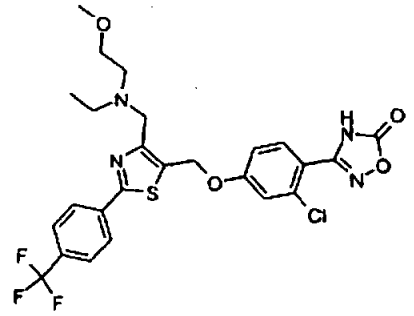
3-{2-Chloro-4-[4-(4-methyl-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one



According to the method described for 3-{4-[4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2-methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one in example 60, 3-{2-chloro-4-[4-(4-methyl-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5- ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from methanesulfonic acid 5-(3-chloro-4-cyano-phenoxymethyl)-2-(4-trifluoromethyl-phenyl)- thiazol-4-ylmethyl ester and 4-methyl-piperazine. C25H23ClF3N5O3S (566.01), MS(ESI): 566.2 (M+H+).

Example 76

3-{2-Chloro-4-[4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

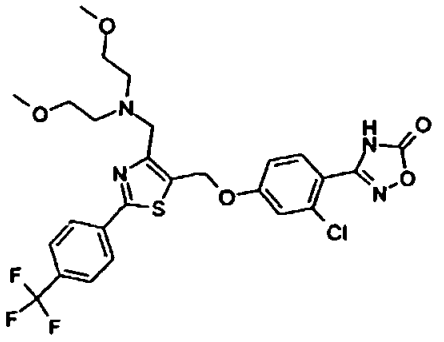


According to the method described for 3-{4-[4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2-methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one in example 60, 3-{2-chloro-4-[4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-trifluoromethyl-phenyl)- thiazol-5-ylmethoxy]-phenyl}-4H-

[1,2,4]oxadiazol-5-one was obtained from methanesulfonic acid 5-(3-chloro-4-cyano-phenoxymethyl)-2-(4-trifluoromethyl-phenyl)- thiazol-4-ylmethyl ester and N-(2-methoxyethyl)ethylamine.
C25H24ClF3N4O4S (569.01), MS(ESI): 569.1 ($M+H^+$).

Example 77

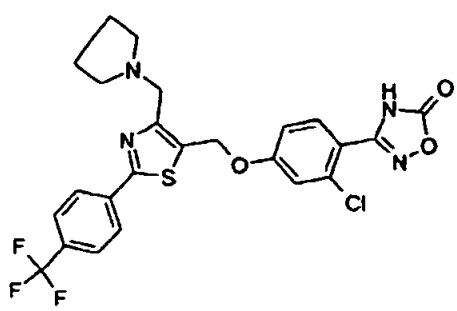
3-{4-[4-{[Bis-(2-methoxy-ethyl)-amino]-methyl}-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-chloro-phenyl}-4H-[1,2,4]oxadiazol-5-one



According to the method described for 3-{4-[4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2-methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one in example 60, 3-{4-[4-{[bis-(2-methoxy-ethyl)-amino]-methyl}-2-(4-trifluoromethyl-phenyl)-thiazol-5- ylmethoxy]-2-chloro-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from methanesulfonic acid 5-(3-chloro-4-cyano-phenoxymethyl)-2-(4-trifluoromethyl-phenyl)- thiazol-4-ylmethyl ester and bis-(2-methoxy-ethyl)-amine.
C26H26ClF3N4O5S (599.03), MS(ESI): 599.2 ($M+H^+$).

Example 78

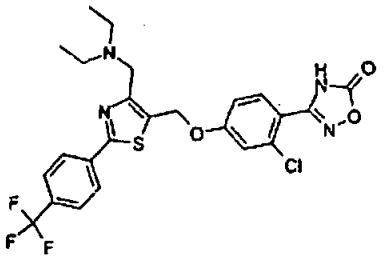
3-{2-Chloro-4-[4-pyrrolidin-1-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one



According to the method described for 3-{4-[4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2-methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one in example 60, 3-{2-chloro-4-[4-pyrrolidin-1-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]- phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from methanesulfonic acid 5-(3-chloro-4-cyano-phenoxymethyl)-2-(4-trifluoromethyl-phenyl)- thiazol-4-ylmethyl ester and pyrrolidine.
$C_{24}H_{20}ClF_3N_4O_3S$ (536.96), MS(ESI): 537.2 ($M+H^+$).

Example 79

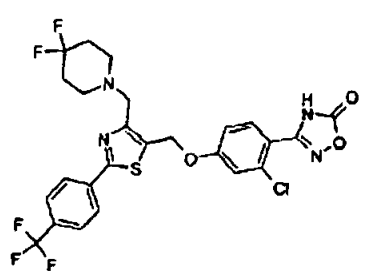
3-{2-Chloro-4-[4-diethylaminomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one



According to the method described for 3-{4-[4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2-methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one in example 60, 3-{2-chloro-4-[4-diethylaminomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]- phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from methanesulfonic acid 5-(3-chloro-4-cyano-phenoxymethyl)-2-(4-trifluoromethyl-phenyl)- thiazol-4-ylmethyl ester and diethylamine.
$C_{24}H_{22}ClF_3N_4O_3S$ (538.98), MS(ESI): 539.1 ($M+H^+$).

Example 80

3-{2-Chloro-4-[4-(4,4-difluoro-piperidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

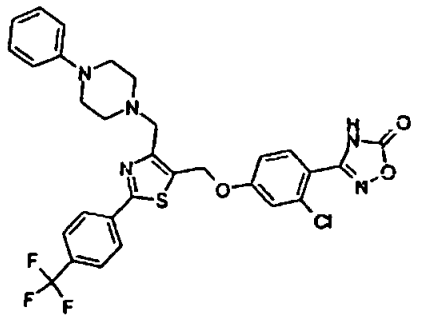


According to the method described for 3-{4-[4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2-methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one in example 60, 3-{2-chloro-4-[4-(4,4-difluoro-piperidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol- 5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from methanesulfonic acid 5-(3-chloro-4-cyano-phenoxymethyl)-2-(4-trifluoromethyl-phenyl)- thiazol-4-ylmethyl ester and 4,4-difluoro-piperidine.

C25H20ClF5N4O3S (586.97), MS(ESI): 587.1 ($M+H^+$).

Example 81

3-{2-Chloro-4-[4-(4-phenyl-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one



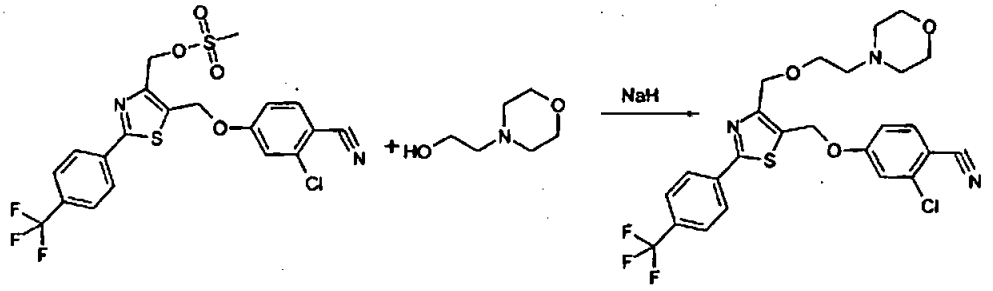
According to the method described for 3-{4-[4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2-methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one in example 60, 3-{2-chloro-4-[4-(4-phenyl-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5- ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from methanesulfonic acid 5-(3-chloro-4-cyano-phenoxymethyl)-2-(4-trifluoromethyl-phenyl)- thiazol-4-ylmethyl ester and 4-phenyl-piperidine.

C30H25ClF3N5O3S (628.08), MS(ESI): 628.1 ($M+H^+$).

Example 82

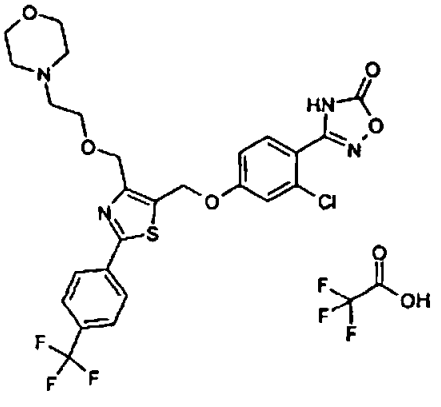
3-[2-Chloro-4-[4-(2-morpholin-4-yl-ethoxymethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl]-4H-[1,2,4]oxadiazol-5-one

2-Chloro-4-[4-(2-morpholin-4-yl-ethoxymethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-benzonitrile



120 mg Methanesulfonic acid 5-(3-chloro-4-cyano-phenoxymethyl)-2-(4-trifluoromethyl-phenyl)- thiazol-4-ylmethyl ester was dissolved in 5 ml N-(2-hydroxyethyl)morpholine. 10 mg sodium hydride were added and the reaction mixture stirred at 50°C for one hour. 10 ml water was added and the reaction mixture extracted 50 ml ethyl acetate. The organic layer was separated and washed twice with 20 ml brine. The organic layer was dried over MgSO4 and the solvent was then removed in vacuo. The residue was purified by RP-HPLC to obtain 40 mg 2-chloro-4-[4-(2-morpholin-4-yl-ethoxymethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5- ylmethoxy]-benzonitrile as its trifluoro-acetate salt. C25H23ClF3N3O3S.C2HF3O2 (652.02), MS(ESI): 538.2 ($M+H^+$).

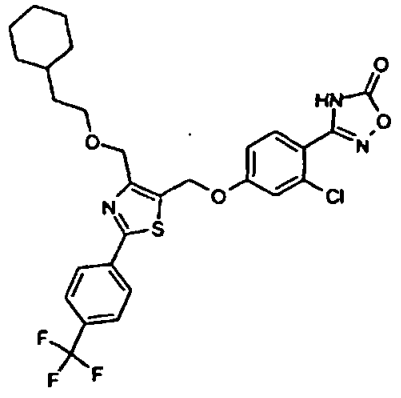
3-[2-Chloro-4-[4-(2-morpholin-4-yl-ethoxymethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl]-4H-[1,2,4]oxadiazol-5-one



According to the method described for 3-{4-[4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2-methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one in example 60, 3-{2-chloro-4-[4-(2-morpholin-4-yl-ethoxymethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5- ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 2-chloro-4-[4-(2-morpholin-4-yl-ethoxymethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5- ylmethoxy]-benzonitrile. The compound was obtained as its trifluoro-acetate salt. C26H24ClF3N4O5S.C2HF3O2 (711.04), MS(ESI): 597.3 ($M+H^+$).

Example 83

3-{2-Chloro-4-[4-(2-cyclohexyl-ethoxymethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one

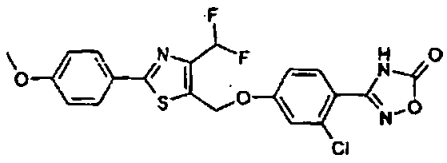


According to the method described for 3-{2-chloro-4-[4-(2-morpholin-4-yl-ethoxymethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one in example 82 and 3-{4-[4-{[ethyl-(2-methoxy-ethyl)-amino]-methyl}-2-(4-methoxy-phenyl)-oxazol-5-ylmethoxy]-2-methyl-phenyl}-4H-[1,2,4]oxadiazol-5-one in example 60, 3-{2-chloro-4-[4-(2-cyclohexyl-ethoxymethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5- ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from methanesulfonic acid 5-(3-chloro-4-cyano-phenoxymethyl)-2-(4-trifluoromethyl-phenyl)- thiazol-4-ylmethyl ester and 2-cyclohexylethanol. C28H27ClF3N3O4S (594.06), MS(ESI): 594.3 ($M+H^+$).

The following example was obtained according to process A:

Example 84

3-{2-Chloro-4-[4-difluoromethyl-2-(4-methoxy-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one



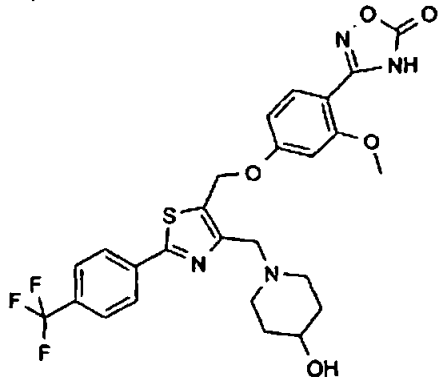
According to the method described for 3-(2-chloro-4-{4-methyl-2-[2-(4-trifluoromethyl-phenyl)-ethyl]-oxazol-5-ylmethoxy}- phenyl)-4H-[1,2,4]oxadiazol-5-one in example 54, 3-{2-chloro-4-[4-difluoromethyl-2-(4-methoxy-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 5-chloromethyl-4-difluoromethyl-2-(4-methoxy-phenyl)-thiazole and 2-Chloro-4-hydroxy-benzonitrile.

C20H14ClF2N3O4S (465.87), MS(ESI): 466.0 ($M+H^+$).

The following examples were prepared according to process D:

Example 85

3-{4-[4-(4-Hydroxy-piperidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-1,2,4-oxadiazol-5-one

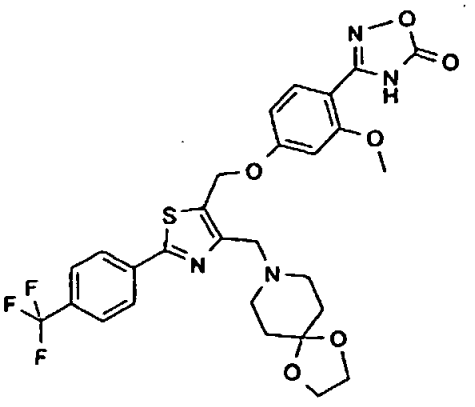


According to the method described for 3-{4-[4-(4-methanesulfonyl-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one, 3-{4-[4-(4-hydroxy-piperidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-1,2,4-oxadiazol-5-one was obtained from methanesulfonic acid 5-[3-methoxy-4-(5-oxo-4,5-dihydro-

[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethyl ester and 4-hydroxy-piperidine.
C26H25F3N4O5S (562.57), MS(ESI): 563 ($M+H^+$).

Example 86

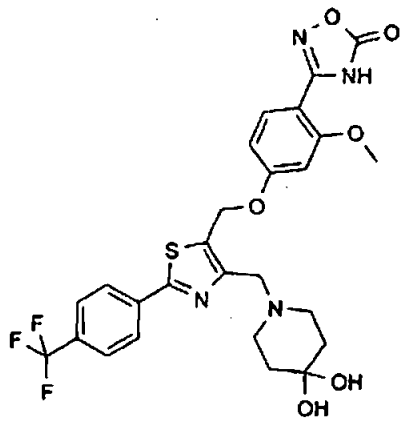
3-{4-[4-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-1,2,4-oxadiazol-5-one



According to the method described for 3-{4-[4-(4-methanesulfonyl-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one, 3-{4-[4-(1,4-dioxa-8-aza-spiro[4.5]dec-8-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-1,2,4-oxadiazol-5-one was obtained from methanesulfonic acid 5-[3-methoxy-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethyl ester and 1,4-dioxa-8-aza-spiro[4.5]decane.
C28H27F3N4O6S (604.61), MS(ESI): 605 ($M+H^+$).

Example 87

3-{4-[4-(4,4-Dihydroxy-piperidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-1,2,4-oxadiazol-5-one

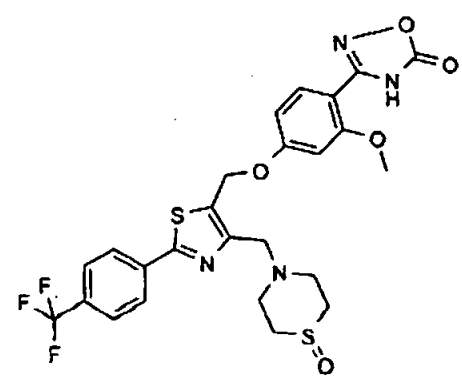


To a suspension of 10 mg of 3-{4-[4-(1,4-dioxa-8-aza-spiro[4.5]dec-8-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-1,2,4-oxadiazol-5-one in 2 mL of dioxane was added 0.5 mL of a 6N aqueous solution of hydrochloric acid. The resulting mixture was heated to 50°C for 2h and then poured into a saturated aqueous solution of sodium hydrogenocarbonate and extracted with ethyl acetate. The organic extracts were washed with water, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was recrystallized in acetonitrile to give 6 mg of 3-{4-[4-(4,4-dihydroxy-piperidin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-1,2,4-oxadiazol-5-one as yellowish solid.

C26H25F3N4O6S (578.57), MS(ESI): 579 ($M+H^+$).

Example 88

3-{2-Methoxy-4-[4-(1-oxo-1λ^4-thiomorpholin-4-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one



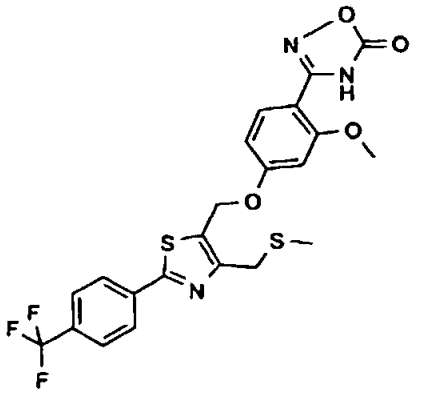
To a solution of 80 mg of 3-{2-methoxy-4-[4-thiomorpholin-4-ylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one in 1 mL

of methanol was added 2 mL of a 2N solution of hydrochloric acid in diethylether. The resulting mixture was concentrated under reduced pressure. To a solution of the residue in 1 mL of acetonitrile were added 1 mL of water and 88 mg of Oxone®. The resulting mixture was stirred at room temperature for 1h, then poured into water and extracted with dichloromethane. The organic extracts were washed with water, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (gradient of methanol in dichloromethane) to give 10.5 mg of 3-{2-methoxy-4-[4-(1-oxo-1λ^4-thiomorpholin-4-ylmethyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one as white solid.

C25H23F3N4O5S2 (580.61), MS(ESI): 581 ($M+H^+$).

Example 89

3-{2-Methoxy-4-[4-methylsulfanylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one

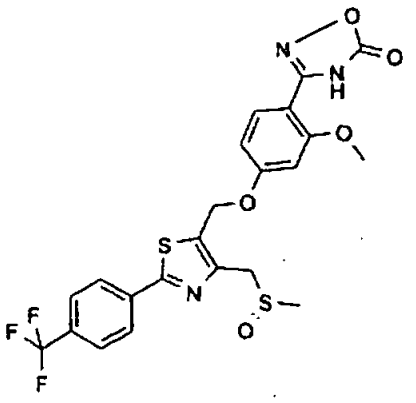


To a solution of 200 mg of methanesulfonic acid 5-[3-methoxy-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethyl ester in 5 mL of dimethylformamide was added 50.3 mg of sodium methoxide. The resulting mixture was heated in a sealed tube to 90°C under microwave irradiation for 5 minutes and concentrated under reduced pressure. The residue was taken into ethyl acetate, washed with water and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (gradient of acetone in

dichloromethane) to give 55 mg of 3-{2-methoxy-4-[4-methylsulfanylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one. C22H18F3N3O4S2 (509.53), MS(ESI): 510 ($M+H^+$).

Example 90

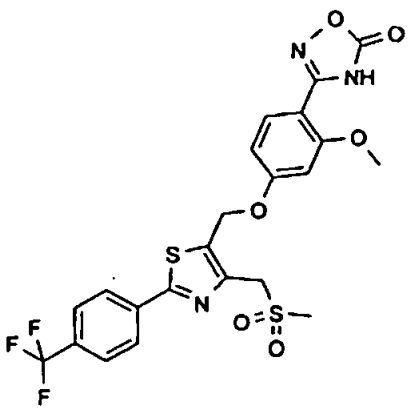
3-{4-[4-Methanesulfinylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-1,2,4-oxadiazol-5-one



To a solution of 32 mg of 3-{2-methoxy-4-[4-methylsulfanylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one in 4 mL of dimethylformamide was added 15 mg of metachloroperbenzoic acid. The resulting mixture was stirred for 45 min at room temperature, then poured into water and extracted with dichloromethane. The organic extracts were washed with a saturated aqueous solution if sodium bicarbonate and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (gradient of methanol in dichloromethane) to give 25 mg of 3-{4-[4-methanesulfinylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-1,2,4-oxadiazol-5-one as a white solid which was further purified by trituration with diisopropyl ether. C22H18F3N3O5S2 (525.53), MS(ESI): 526 ($M+H^+$).

Example 91

3-{4-[4-Methanesulfonylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-1,2,4-oxadiazol-5-one

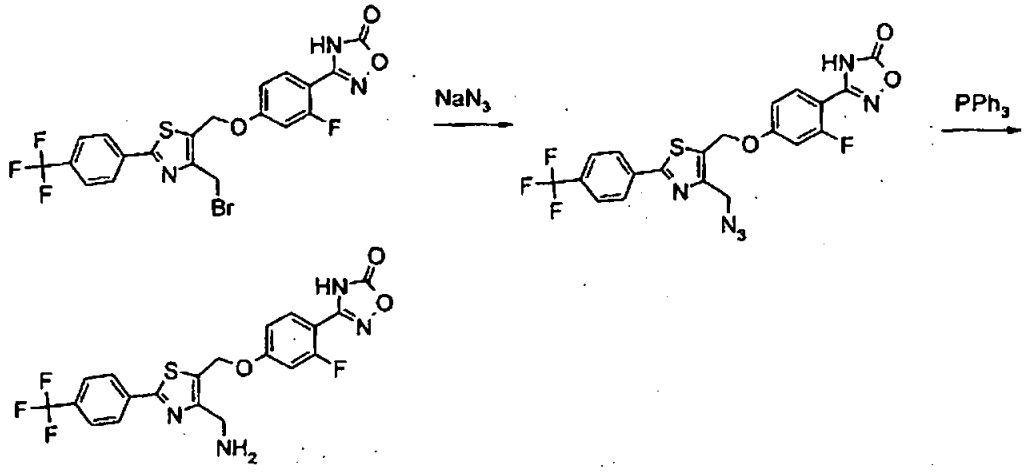


To a suspension of 35 mg of 3-{2-methoxy-4-[4-methylsulfanylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one in 4 mL of acetonitrile was added 1 mL of water and 84 mg of Oxone®. The resulting mixture was stirred overnight at room temperature, then poured into water and extracted with dichloromethane. The organic extracts were washed with a saturated aqueous solution if sodium bicarbonate and concentrated under reduced pressure. The crude product was triturated with dichloromethane/ methanol/tetrahydrofuran/acetone to give 26 mg of 3-{4-[4-methanesulfonylmethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-1,2,4-oxadiazol-5-one as a white solid.
C22H18F3N3O6S2 (541.53), MS(ESI): 542 ($M+H^+$).

The following examples were prepared according to process F:

Example 92

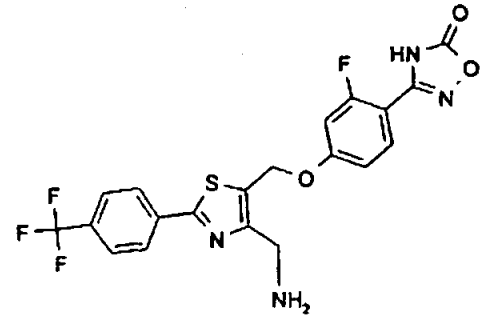
3-{4-[4-Aminomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-fluoro-phenyl}-4H-1,2,4-oxadiazol-5-one



3-{4-[4-Azidomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-fluoro-phenyl}-4H-1,2,4-oxadiazol-5-one

To a solution of 126 mg of 3-{4-[4-bromomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-fluoro-phenyl}-4H-[1,2,4]oxadiazol-5-one in 1.3 mL of dimethylformamide was added 43.5 mg of sodium azide. The resulting solution was stirred for 5h and then concentrated under reduced pressure to give 118mg of 3-{4-[4-azidomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-fluoro-phenyl}-4H-1,2,4-oxadiazol-5-one which was used in the next step without further purification.

3-{4-[4-Aminomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-fluoro-phenyl}-4H-1,2,4-oxadiazol-5-one



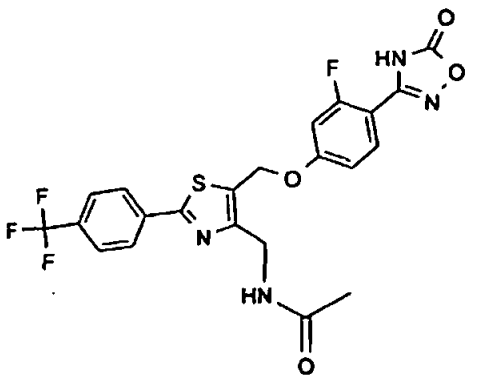
To a mixture of 118 mg of 3-{4-[4-azidomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-fluoro-phenyl}-4H-1,2,4-oxadiazol-5-one in 0.25 mL of

dimethylformamide and 0.022 mL of water was added 31 mg of triphenylphosphine. The resulting mixture was stirred for 20h at room temperature and then concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (gradient from dichloromethane 100 to dichloromethane 90/ methanol 10/water 1/acetic acid 1) followed by chromatography on a SCX Waters column with gradient CH2Cl2/MeOH 30/70 to 7N NH3 in MeOH to give 5.5 mg of 3-{4-[4-aminomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-fluoro-phenyl}-4H-1,2,4-oxadiazol-5-one.

C20H14F4N4O3S (466.42), MS(ESI): 467 ($M+H^+$).

Example 93

N-[5-[3-Fluoro-4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethyl]-acetamide



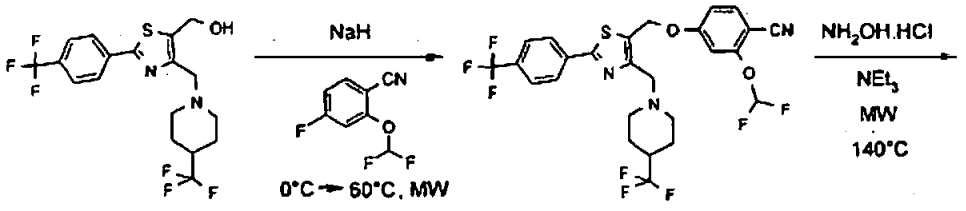
To a suspension of 53.3 mg of 3-{4-[4-aminomethyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-fluoro-phenyl}-4H-1,2,4-oxadiazol-5-one in 1 mL of dichloromethane was added 27 mg of pyridine and 19 mg of acetic anhydride. The resulting mixture was stirred for 1.5h at room temperature and then a drop of pyridine and acetic anhydride were added. After stirring for 25 minutes at room temperature, it was poured into water and extracted with dichloromethane. The organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (gradient from dichloromethane 100 to dichloromethane 90/ methanol 10/water 1/acetic acid 1) to give 6.2 mg of N-[5-[3-fluoro-4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-phenoxymethyl]-2-(4-trifluoromethyl-phenyl)-thiazol-4-ylmethyl]-acetamide.

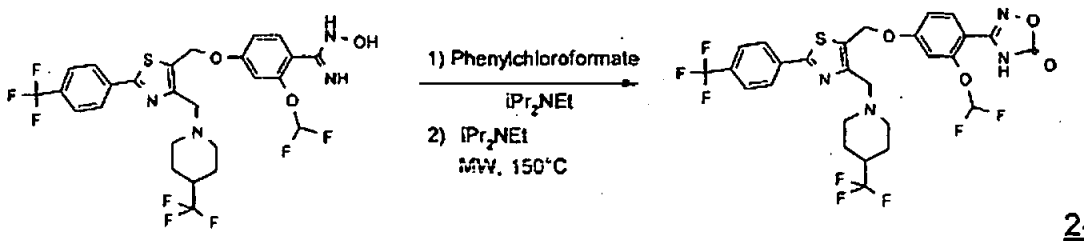
C22H16F4N4O4S (508.45), MS(ESI): 509 ($M+H^+$).

The following examples were prepared according B:

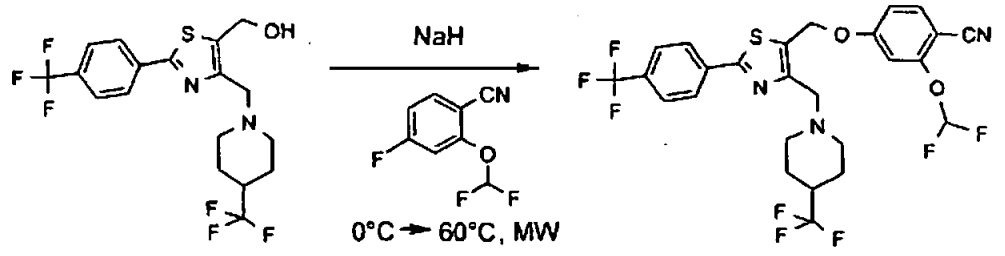
Example 94

3-[2-Difluoromethoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl]-4H-1,2,4-oxadiazol-5-one





2-Difluoromethoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-benzonitrile

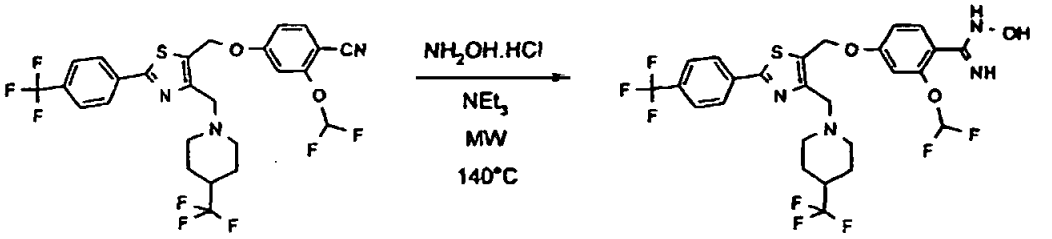


To a solution of 3 g of [2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-yl]-methanol in 12 mL of dimethylformamide at 5°C was added 319 mg of a 55% suspension of sodium hydride in mineral oil. The resulting mixture was stirred for 30 minutes at 5°C. 4.7 mL of the resulting solution was slowly added to a solution 319 mg of 2-difluoromethoxy-4-fluoro-benzonitrile in 1.2 mL of dimethylformamide at 5°C. The resulting mixture was stirred at 5°C allowing the temperature to warm up to room temperature. It was then heated in a sealed tube to 60°C under microwave irradiation for 15 minutes. After allowing it to cool down to room temperature, the mixture was poured into water and extracted with dichloromethane. The organic extracts were dried over magnesium sulfate, filtered and concentrated

under reduced pressure. The crude product was purified by column chromatography on silica gel (gradient from heptane 100 to heptane 50/ ethyl acetate 50) to give 0.83 g of 2-difluoromethoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-benzonitrile.

C26H22F8N3O2S (592.54), MS(ESI): ($M+H^+$) 593.1 ($M+H^+$).

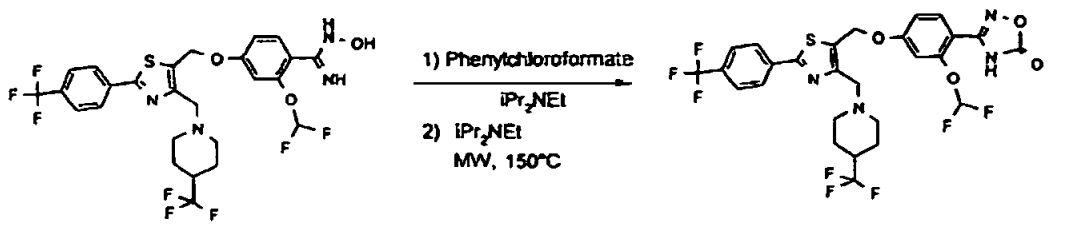
2-Difluoromethoxy-N-hydroxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-benzamidine



To a solution of 830 mg of 2-difluoromethoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-benzonitrile in 13 mL of methanol was added 5.7 mL of triethylamine followed by 430 mg of hydroxylamine hydrochloride. The resulting mixture was heated in a sealed tube to 140°C under microwave irradiation for 30 minutes. After allowing it to cool down to room temperature, the mixture was poured into water and extracted with dichloromethane. The organic extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (gradient from heptane 100 to heptane 60/ ethyl acetate 40) to give 480 mg of 2-difluoromethoxy-N-hydroxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-benzamidine.

C26H24F8N4O3S (624.56), MS(ESI): 625.0 ($M+H^+$).

3-[2-Difluoromethoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl]-4H-1,2,4-oxadiazol-5-one

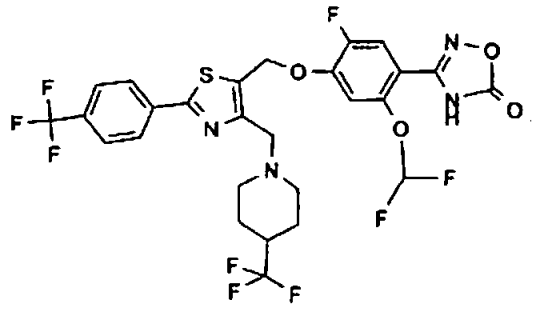


To a solution of 475 mg of 2-difluoromethoxy-N-hydroxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-benzamidine in 7.8 mL of tetrahydrofuran at 0°C was added 1.8 mL of diisopropylethylamine followed by 0.1 mL of phenyl chloroformate. The resulting mixture was stirred for 5 minutes at 0°C then poured into water and extracted with dichloromethane. The organic extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was dissolved 7.8 mL of tetrahydrofuran and 0.33 mL of diisopropylethylamine. The resulting solution was heated in a sealed tube to 150°C under microwave irradiation for 15 minutes. After allowing it to cool down to room temperature, the mixture was poured into water and extracted with dichloromethane. The organic extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (diisopropryl ether 100 followed by a gradient from dichloromethane 100 to dichloromethane 90/ methanol 10) followed by another column chromatography on silica gel (gradient from dichloromethane 100 to dichloromethane 90/ tetrahydrofuran 10) to give 70 mg of 3-{2-difluoromethoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one.

C27H22F8N4O4S (650.55), MS(ESI): 651.2 ($M+H^+$).

Example 95

3-{2-Difluoromethoxy-5-fluoro-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one



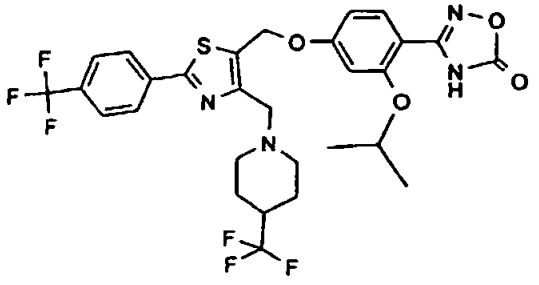
According to the method described for 3-{2-difluoromethoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one, 3-{2-difluoromethoxy-5-fluoro-4-[2-(4-trifluoromethyl-phenyl)-4-

(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one was obtained from [2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-yl]-methanol and 2-difluoromethoxy-4,5-difluoro-benzonitrile.

C27H21F9N4O4S (668.54), MS(ESI): 669.9 ($M+H^+$).

Example 96

3-{2-Isopropoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one

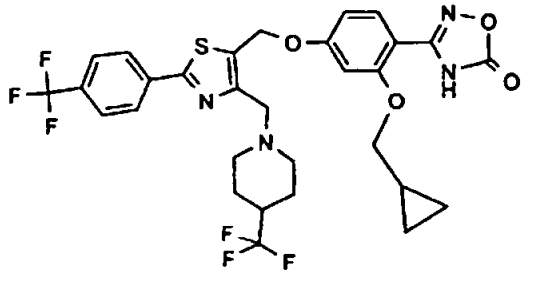


According to the method described for 3-{2-difluoromethoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one, 3-{2-isopropoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one was obtained from [2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-yl]-methanol and 4-fluoro-2-isopropoxy-benzonitrile.

C29H28F6N4O4S (642.63), MS(ESI): 643.0 ($M+H^+$).

Example 97

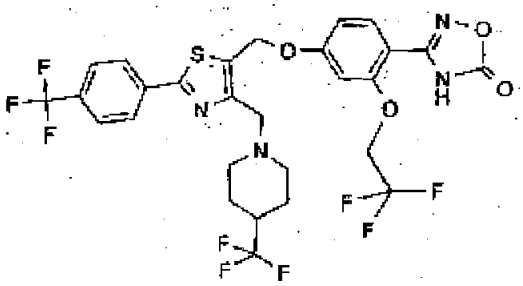
3-{2-Cyclopropylmethoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one



According to the method described for 3-{2-difluoromethoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one, 3-{2-cyclopropylmethoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one was obtained from [2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-yl]-methanol and 2-cyclopropylmethoxy-4-fluoro-benzonitrile. $C_{30}H_{28}F_6N_4O_4S$ (654.64), MS(ESI): 656.1 ($M+H^+$).

Example 98

3-[2-(2,2,2-Trifluoro-ethoxy)-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one

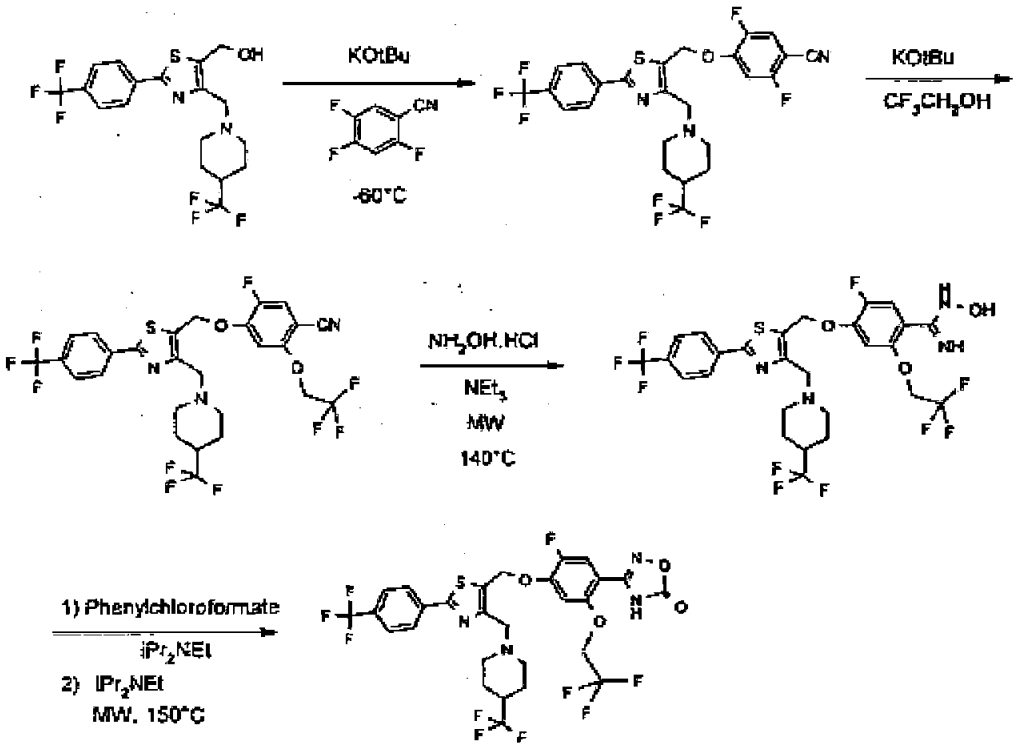


According to the method described for 3-{2-difluoromethoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one, 3-{2-(2,2,2-trifluoro-ethoxy)-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one was obtained from [2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-yl]-methanol and 4-fluoro-2-(2,2,2-trifluoro-ethoxy)-benzonitrile. $C_{28}H_{23}F_9N_4O_4S$ (682.57), MS(ESI): 683.1 ($M+H^+$).

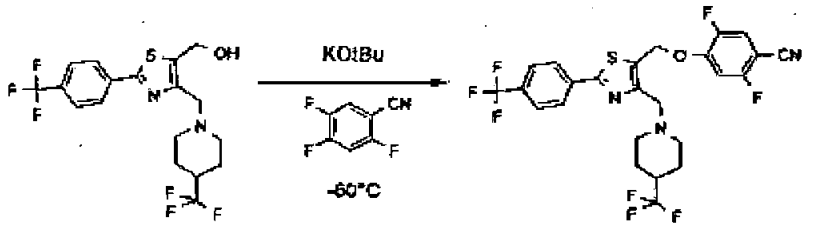
The following example was prepared according to process C:

Example 99

3-[5-Fluoro-2-(2,2,2-trifluoro-ethoxy)-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one



2,5-Difluoro-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-benzonitrile

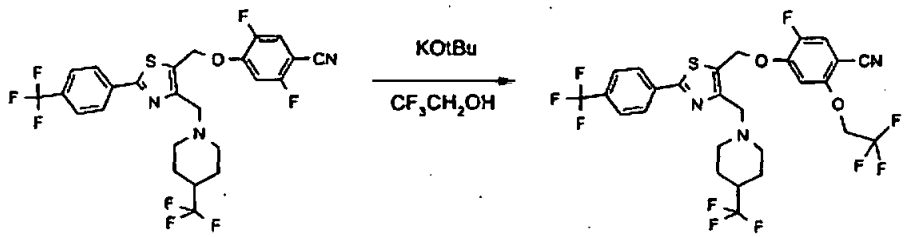


To a solution of 800 mg of [2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-yl]-methanol in 4 mL of tetrahydrofuran at 5°C was slowly added 2.13 mL of a molar solution of potassium tert-butoxide in tert-butanol. After stirring at 5°C for 30 minutes, the resulting solution was slowly added to a solution of 296 mg of 2,4,5-trifluoro-benzonitrile in 1 mL of tetrahydrofuran at -60°C. The resulting mixture was stirred for 1h at -60°C then stirred overnight allowing the temperature to warm up to room temperature. It was then poured into water and extracted with dichloromethane. The organic extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was recrystallized from methanol and washed with diisopropyl ether to give 890 mg of 2,5-difluoro-4-[2-(4-

trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-benzonitrile.

C25H19F8N3OS (561.50), MS(ESI): 563.1 ($M+H^+$).

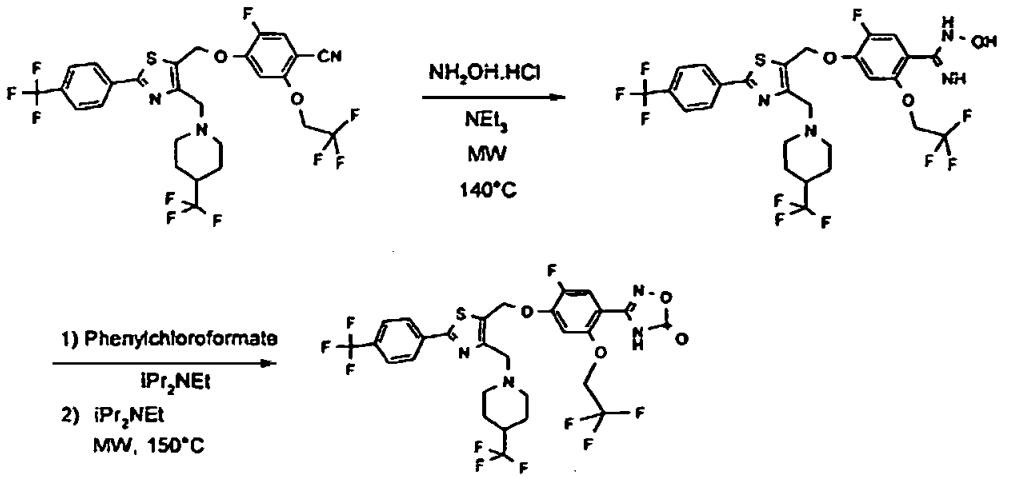
5-Fluoro-2-(2,2,2-trifluoro-ethoxy)-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-benzonitrile



To a solution of 190 mg of trifluoroethanol in 1.16 mL of tetrahydrofuran at 5°C was slowly added 2.2 mL of a molar solution of potassium tert-butoxide in tert-butanol. After stirring at 5°C for 30 minutes, the resulting solution was slowly added to a solution of 890 mg of 2,5-difluoro-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-benzonitrile in 3.1 mL of tetrahydrofuran at -60°C. The resulting mixture was stirred overnight allowing the temperature to warm up to room temperature. It was then poured into water and extracted with dichloromethane. The organic extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was triturated with diisopropyl ether and filtered to give 410 mg of 5-fluoro-2-(2,2,2-trifluoro-ethoxy)-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-benzonitrile as a white solid.

C27H21F10N3O2S (641.54), MS(ESI): 642.1 ($M+H^+$).

3-{5-Fluoro-2-(2,2,2-trifluoro-ethoxy)-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one



According to the method described for 3-{2-difluoromethoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one, 3-{5-fluoro-2-(2,2,2-trifluoro-ethoxy)-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one was obtained from 5-fluoro-2-(2,2,2-trifluoro-ethoxy)-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-benzonitrile.

C28H22F10N4O4S (700.56), MS(ESI): 701.9 ($M+H^+$).

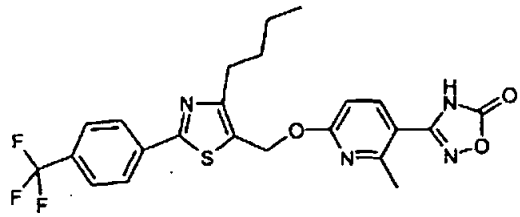
3-{5-fluoro-2-(2,2,2-trifluoro-ethoxy)-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one can also be prepared according to the method described for 3-{2-difluoromethoxy-4-[2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one by starting from [2-(4-trifluoromethyl-phenyl)-4-(4-trifluoromethyl-piperidin-1-ylmethyl)-thiazol-5-yl]-methanol and 4,5-difluoro-2-(2,2,2-trifluoro-ethoxy)-benzonitrile.[9]

The following example was prepared according to process B:

[9] WO2005/111003

Example 100

3-{6-[4-Butyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methyl-pyridin-3-yl}-4H-[1,2,4]oxadiazol-5-one



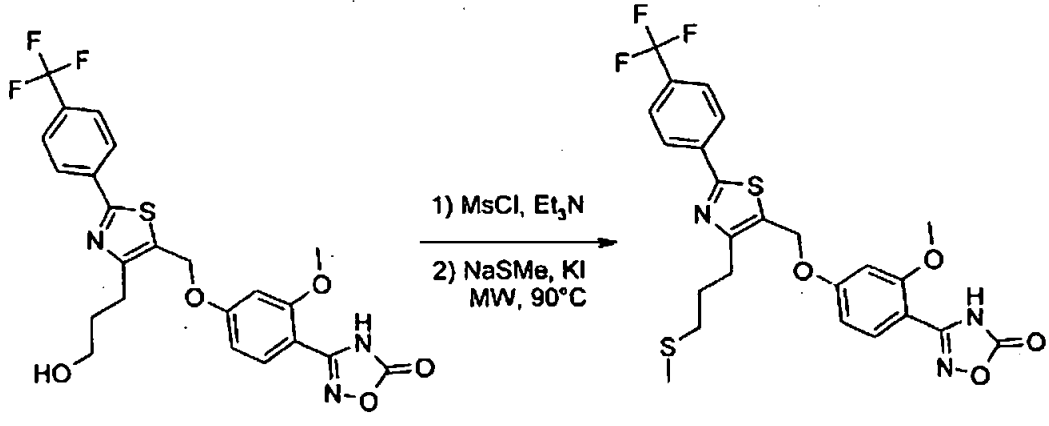
According to the method described in Example 1, 3-{6-[4-Butyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methyl-pyridin-3-yl}-4H-[1,2,4]oxadiazol-5-one was obtained from [4-Butyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol[10] and commercially available 6-Fluoro-2-methyl-nicotinonitrile.

C23H21F3N4O3S (490.51), MS(ESI): 491 ($M+H^+$).

The following examples were prepared according to process D:

Example 101

3-{2-Methoxy-4-[4-(3-methylsulfanyl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one



To a solution of 100 mg of 3-{4-[4-(3-hydroxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one in 1 mL of dimethylformamide at 0°C were added 0.077 mL of triethylamine and 0.015 mL of methanesulfonyl chloride. The resulting mixture was stirred at 0°C for 30 minutes and

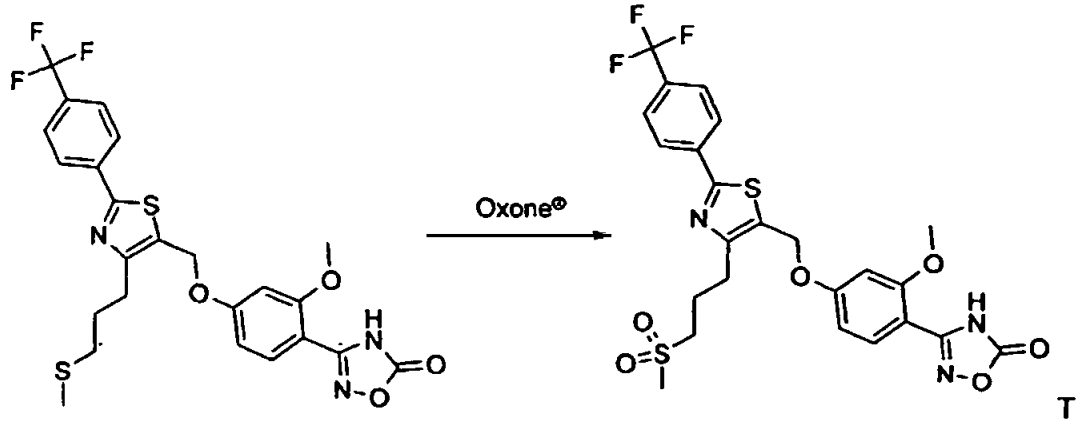
[10] EP1586573

then concentrated under reduced pressure. The product was dissolved in 3 mL of dimethylformamide. To the resulting solution were added 5.5 mg of sodium methanethiolate and 13 mg of potassium iodide. The reaction mixture was heated for 10 minutes to 90°C under microwave irradiation in a sealed tube. It was then concentrated under reduced pressure, taken into dichloromethane, washed with water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give 20 mg of 3-{2-methoxy-4-[4-(3-methylsulfanyl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one.

C24H22F3N3O4S2 (537.58), MS(ESI): 538 ($M+H^+$).

Example 102

3-{4-[4-(3-Methanesulfonyl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-1,2,4-oxadiazol-5-one

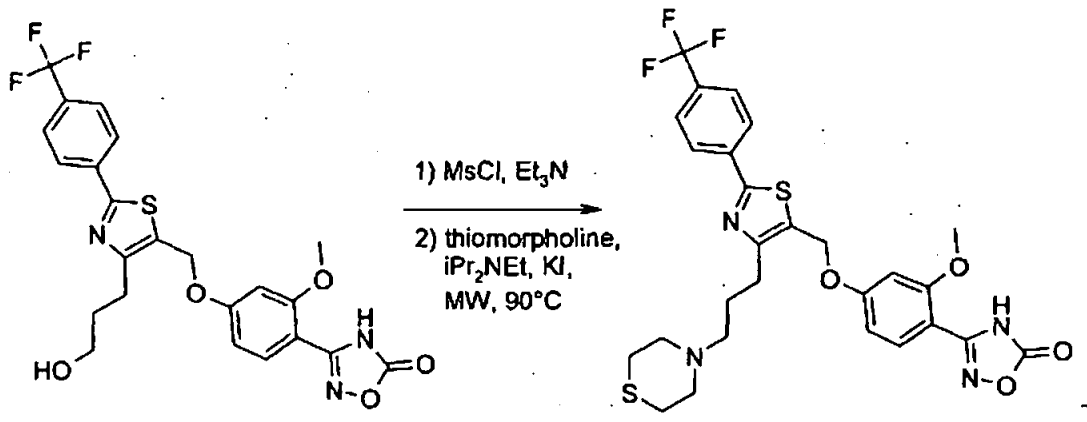


To a suspension of 60 mg of methoxy-4-[4-(3-methylsulfanyl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one in 2 mL of acetonitrile and 0.5 mL of water was added 230 mg of Oxone® (potassium peroxymonosulfate). The resulting mixture was stirred at room temperature for 3 hour then poured into ethyl acetate/water. The organic layer was separated, washed with a saturated aqueous solution of Na2S2O3, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was triturated with 1 mL of acetonitrile and filtered to give 16 mg of 3-{4-[4-(3-methanesulfonyl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-1,2,4-oxadiazol-5-one as beige solid.

C24H22F3N3O6S2 (569.58), MS(ESI): 570 ($M+H^+$).

Example 103

3-{2-Methoxy-4-[4-(3-thiomorpholin-4-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one

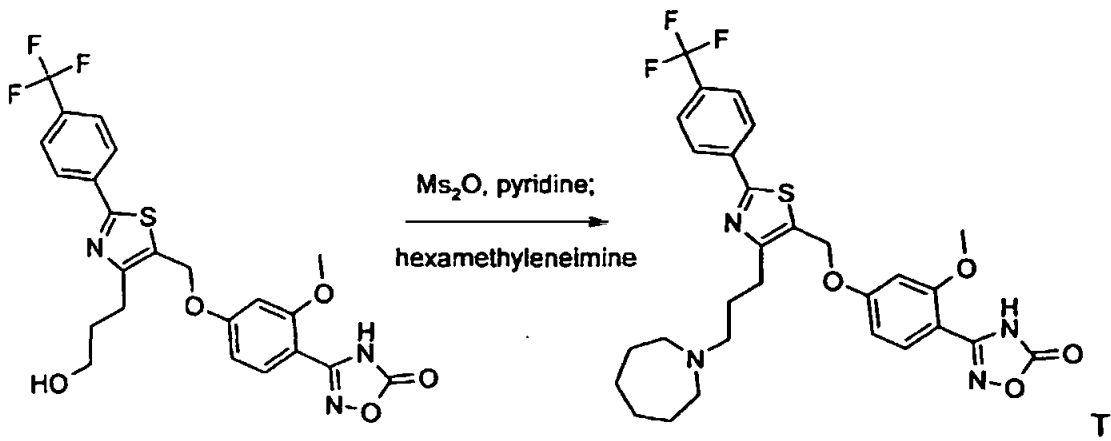


To a solution of 50 mg of 3-{4-[4-(3-hydroxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one in 1.5 mL of dimethylformamide at 0°C were added 0.015 mL of triethylamine and 0.008 mL of methanesulfonyl chloride. The resulting mixture was stirred at 0°C for 30 minutes and then concentrated under reduced pressure, taken into dichloromethane, washed with water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was dissolved in 4 mL of dimethylformamide. To the resulting solution were added 0.012 mL of thiomorpholine, 0.017 mL of diisopropylethyl amine and 29 mg of potassium iodide. The reaction mixture was heated to 90°C for 10 minutes under microwave irradiation in a sealed tube. It was then concentrated under reduced pressure, taken into dichloromethane, washed with water, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (gradient of methanol in dichloromethane), triturated in acetonitrile and filtered to give 5.3 mg of 3-{2-methoxy-4-[4-(3-thiomorpholin-4-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one.

C27H27F3N4O4S2 (592.66), MS(ESI): 593 ($M+H^+$).

Example 104

3-{2-Methoxy-4-[4-(3-perhydro-azepin-1-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one

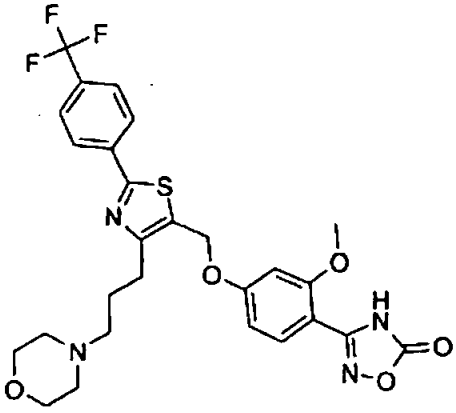


To a mixture of 150 mg of 3-{4-[4-(3-hydroxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one in 6 mL of acetonitrile were added 0.100 mL of pyridine and 0.200 mL of methanesulfonic anhydride. The resulting mixture was stirred at room temperature for 5 hour then 0.250 mL of hexamethyleneimine was added. The mixture was stirred at room temperature overnight and then concentrated under reduced pressure. The residue was purified by preparative HPLC on normal phase coupled to MS (gradient of methanol 5 in dichloromethane containing NH4OH), then precipitated from dichloromethane/pentane to give 26 mg of 3-{2-methoxy-4-[4-(3-perhydro-azepin-1-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one as a white solid.

C29H31F3N4O4S (588.65), MS(ESI): 589 ($M+H^+$).

Example 105

3-{2-Methoxy-4-[4-(3-morpholin-4-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one

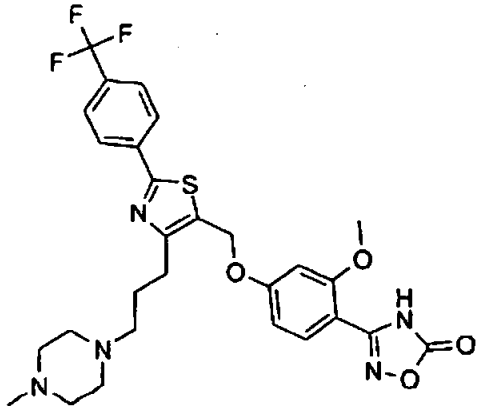


According to the method described 3-{2-methoxy-4-[4-(3-perhydro-azepin-1-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one, 3-{2-methoxy-4-[4-(3-morpholin-4-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one was obtained from 3-{4-[4-(3-hydroxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one and morpholine.

$C_{27}H_{27}F_3N_4O_5S$ (576.60), MS(ESI): 577 ($M+H^+$).

Example 106

3-{2-Methoxy-4-[4-[3-(4-methyl-piperazin-1-yl)-propyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one



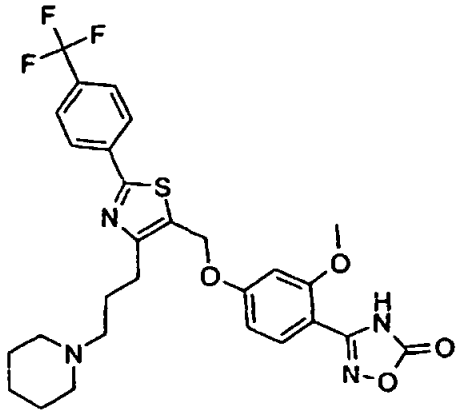
According to the method described 3-{2-methoxy-4-[4-(3-perhydro-azepin-1-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one, 3-

{2-methoxy-4-[4-[3-(4-methyl-piperazin-1-yl)-propyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one was obtained from 3-{4-[4-(3-hydroxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one and 1-methylpiperazine.

C28H30F3N5O4S (589.64), MS(ESI): 590 ($M+H^+$).

Example 107

3-{2-Methoxy-4-[4-(3-piperidin-1-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one

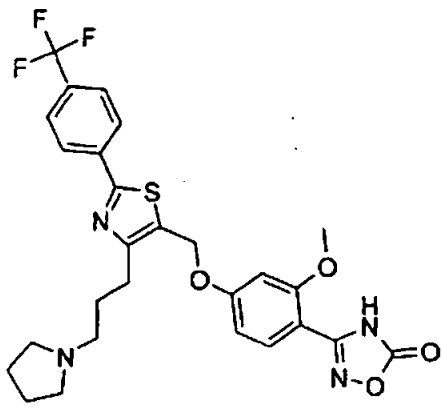


According to the method described 3-{2-methoxy-4-[4-(3-perhydro-azepin-1-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one, 3-{2-methoxy-4-[4-(3-piperidin-1-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one was obtained from 3-{4-[4-(3-hydroxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one and piperidine.

C28H29F3N4O4S (574.63), MS(ESI): 575 ($M+H^+$).

Example 108

3-[2-Methoxy-4-[4-(3-pyrrolidin-1-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl]-4H-1,2,4-oxadiazol-5-one



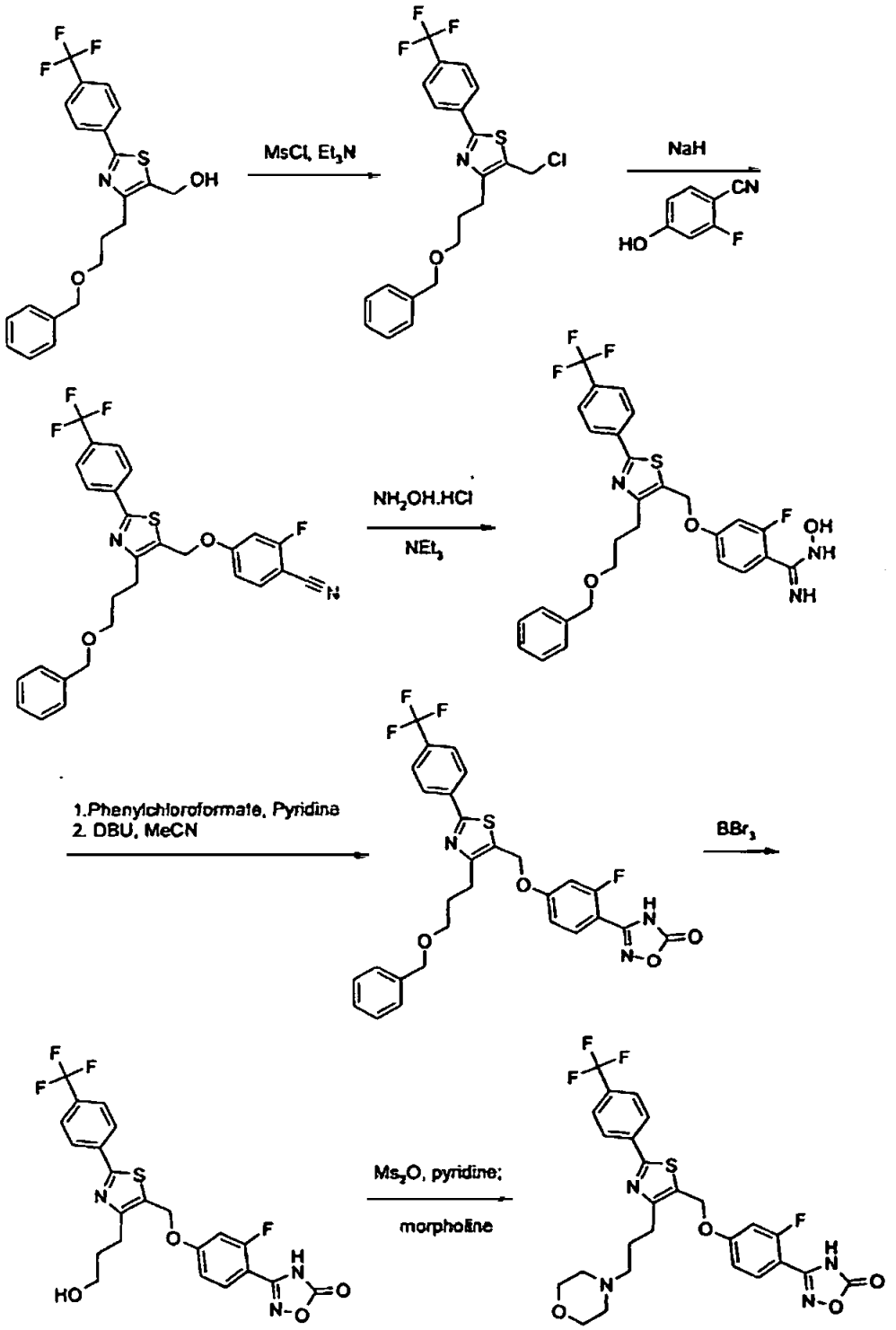
According to the method described 3-[2-methoxy-4-[4-(3-perhydro-azepin-1-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl]-4H-1,2,4-oxadiazol-5-one, 3-[2-methoxy-4-[4-(3-pyrrolidin-1-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl]-4H-1,2,4-oxadiazol-5-one was obtained from 3-[4-[4-(3-hydroxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl]-4H-[1,2,4]oxadiazol-5-one and pyrrolidine.

$C_{27}H_{27}F_3N_4O_4S$ (560.60), MS(ESI): 561 ($M+H^+$).

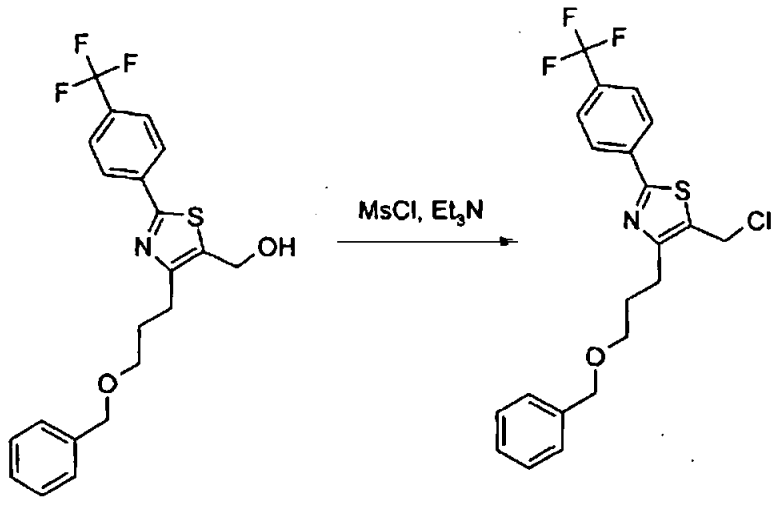
The following examples were prepared according to process D, whereby the first two reaction steps were performed according to process B:

Example 109

3-[2-Fluoro-4-[4-(3-morpholin-4-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl]-4H-1,2,4-oxadiazol-5-one


MsCl, Et3N
NaH
NH2OH.HCl
NEt3
1.Phenylchloroformate, Pyridine
2. DBU, MeCN
BBr3
Ms2O, pyridine;
morpholine

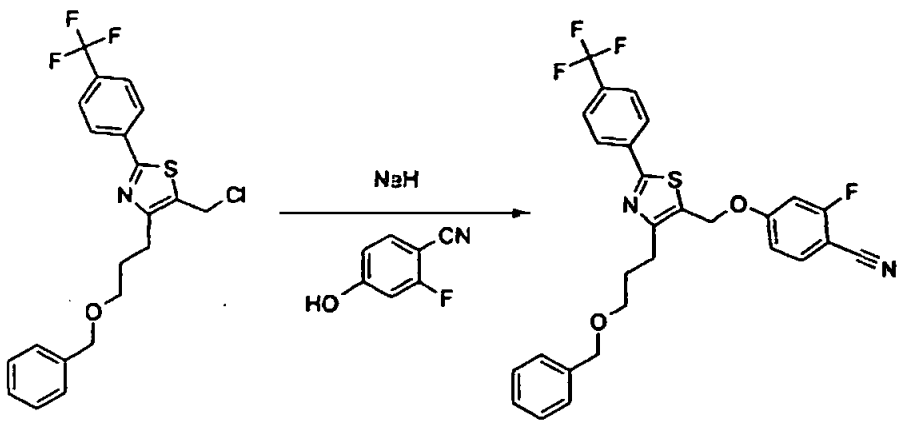
4-(3-Benzyloxy-propyl)-5-chloromethyl-2-(4-trifluoromethyl-phenyl)-thiazole



To a stirred solution of 1.5g of {4-[3-(benzyloxy)propyl]-2-[4-(trifluoromethyl)phenyl]-1,3-thiazol-5-yl} methanol in 15 mL of dichloromethane were added 0.484g of methanesulfonylchloride and 1.03 mL of triethylamine. The solution was stirred for 2h at room temperature. The mixture was diluted with dichloromethane and poured into water. The aqueous layer was separated and extracted three times with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure to give 1.65 g of crude product as a yellow oil. Purification by column chromatography on silica gel (heptane 90/ ethyl acetate 10) gave 0.840 g of 4-(3-benzyloxy-propyl)-5-chloromethyl-2-(4-trifluoromethyl-phenyl)-thiazole.

C21H19ClF3NOS (425.90), MS(ESI): 426 ($M+H^+$).

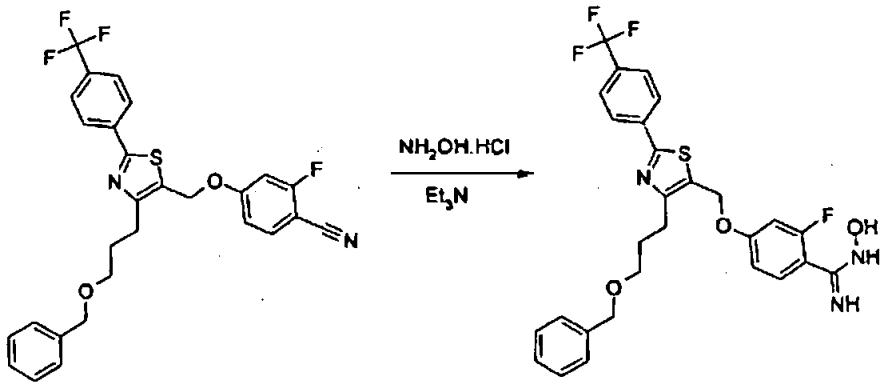
4-[4-(3-Benzyloxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-fluoro-benzonitrile



To a stirred solution of 0.82 g of 4-(3-benzyloxy-propyl)-5-chloromethyl-2-(4-trifluoromethyl-phenyl)-thiazole in 12 mL of DMF at 0°C was added 0.1 g NaH 55 %. The reaction mixture was stirred at 0°C for 10min then 2-0.264 g of fluoro-4-hydroxybenzonitrile was added at this temperature. The reaction mixture was stirred at 0°C for 1h30, allowed to warm up to room temperature and then stirred for 4h at room temperature. The solvent was removed and the resulting residue was taken up into dichloromethane then water was added. After decantation and separation, the aqueous layer was extracted three times with dichloromethane. The combined organic layers were washed with water, dried over magnesium sulfate, filtered and concentrated under reduced pressure to give 0.91 g of crude product as a yellow oil. Purification by column chromatography on silica gel (heptane 1/ ether 1) gave 840 mg of 4-[4-(3-benzyloxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-fluoro-benzonitrile as a white foam.

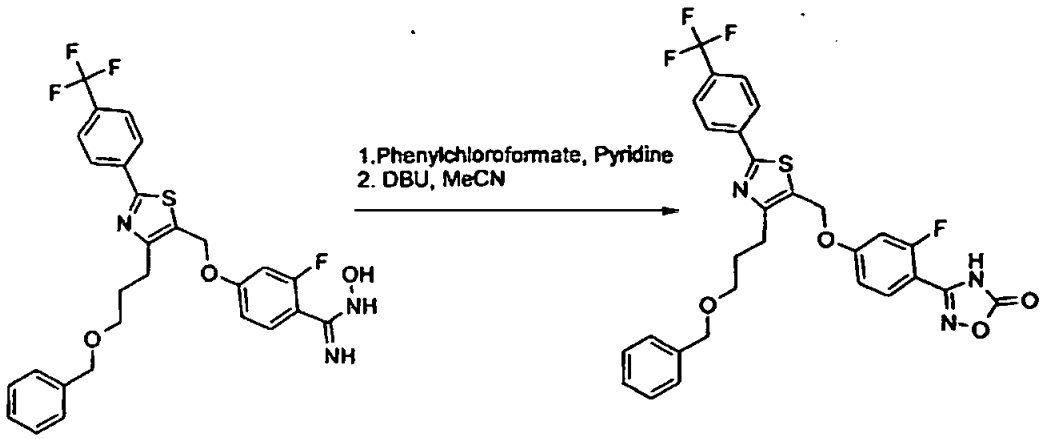
$C_{28}H_{22}F_4N_2O_2S$ (526.56), MS(ESI): 527 ($M+H^+$).

4-[4-(3-Benzyloxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-fluoro-N-hydroxy-benzamidine



To a stirred solution of 0.84 g of 4-[4-(3-benzyloxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-fluoro-benzonitrile in 5 mL of tetrahydrofuran and 5.6 mL of methanol were added 1.14 g of hydroxylamine hydrochloride followed by 1.8 mL of triethylamine. The reaction mixture was stirred at reflux temperature for 2h and then at room temperature overnight. The reaction mixture was refluxed for an additional 2h and then concentrated under reduced pressure. The residue was taken up into dichloromethane then water was added. The aqueous layer was separated and extracted three times with dichloromethane. The combined organic layers were washed with water, dried over magnesium sulfate, filtered and concentrated under reduced pressure to give 0.840 g of crude product as a yellow gum. Precipitation in heptane afforded 620 mg of 4-[4-(3-benzyloxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-fluoro-N-hydroxy-benzamidine as a beige powder. C28H25F4N3O3S (559.59), MS(ESI): 560 ($M+H^+$).

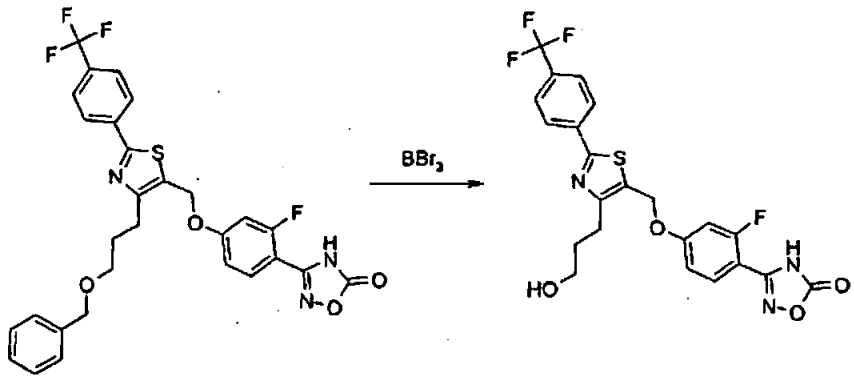
3-[4-[4-(3-Benzyloxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-fluoro-phenyl]-4H-[1,2,4]oxadiazol-5-one



To a stirred suspension of 0.62 g of 4-[4-(3-benzyloxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-fluoro-N-hydroxy-benzamidine in 17 mL of dichloromethane at 0°C, under argon, were added 0.23mL of pyridine and 154 µL of phenyl chloroformate. The reaction mixture was stirred for 10 min at 0°C followed by 1h at room temperature. The reaction mixture was concentrated under reduced pressure and the resulting residue was taken up into 10 mL of acetonitrile under argon and 0.165 mL of 1,4-diazabicyclo[5.4.0]undec-7-ene (DBU) was added. The reaction mixture was stirred at room temperature overnight then warmed to 40°C for 2h. The reaction mixture was concentrated under reduced pressure. The residue was taken up into dichloromethane and a 1M aqueous solution of NaH2PO4 was added. The aqueous layer was separated and extracted three times with dichloromethane. The combined organic layers were washed with water, dried over magnesium sulfate, filtered and concentrated under reduced pressure to give 770 mg of crude product as a yellow powder. Purification by column chromatography on silica gel (heptane 1/ ethyl acetate 1) gave 150 mg followed by column washing with 100 % MeOH gave 320 mg of the title compound. In total, 470 mg of 3-[4-[4-(3-benzyloxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-fluoro-phenyl]-4H-[1,2,4]oxadiazol-5-one as white powder was obtained.

C29H23F4N3O4S (585.58), MS(ESI): 586 ($M+H^+$).

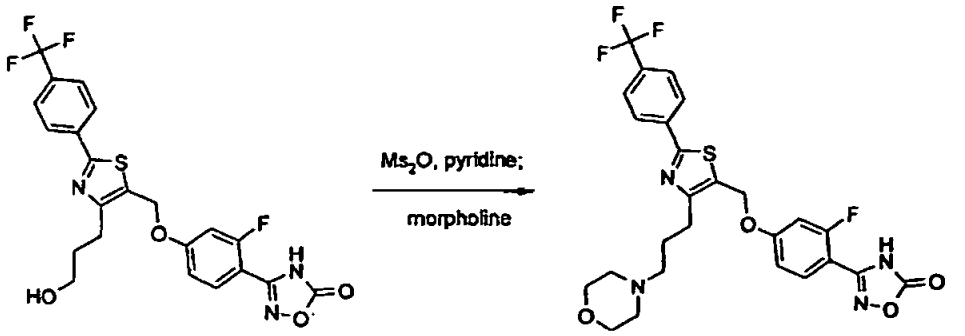
3-{2-Fluoro-4-[4-(3-hydroxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one



To a stirred solution of 100 mg of 3-{4-[4-(3-benzyloxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-fluoro-phenyl}-4H-[1,2,4]oxadiazol-5-one in 3 mL of dichloromethane at –70°C was added 0.34 mL of a 1M solution of boron tribromide in dichloromethane. After 1h at –60°C, TLC monitoring (dichloromethane / acetone 8 / 2) showed remaining starting material so 1 mL of a 1M solution of boron tribromide in dichloromethane was added. After 10 min, the reaction mixture was poured into 30mL of methanol and was neutralised with 5 mL of a saturated aqueous solution of NaHCO3. The suspension was filtered and the filtrate was concentrated under reduced pressure. The residue was was taken up into dichloromethane then water added. The aqueous layer was separated and extracted three times with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure to give 60 mg of crude product. Purification by column chromatography on silica gel (dichloromethane 1/ acetone 1) gave 13 mg of a first batch of the title compound (purity > 95%) and 50 mg of a second batch of the title compound (purity > 90%). The second batch was repurified by column chromatography on silica gel (dichloromethane 90/methanol 10). A total of 48 mg of 3-{2-fluoro-4-[4-(3-hydroxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained.

C22H17F4N3O4S (495.46), MS(ESI): 496 ($M+H^+$).

3-{2-Fluoro-4-[4-(3-morpholin-4-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one

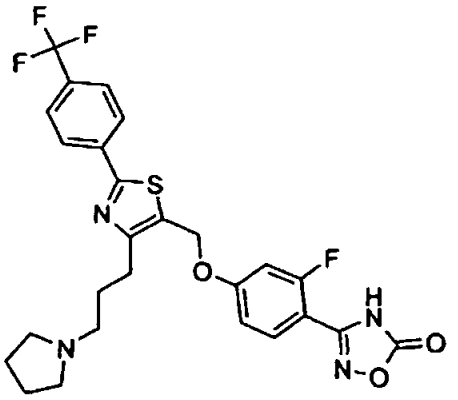


According to the method described 3-{2-methoxy-4-[4-(3-perhydro-azepin-1-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one, 3-{2-fluoro-4-[4-(3-morpholin-4-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one was obtained from 3-{2-fluoro-4-[4-(3-hydroxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one and morpholine.

C26H24F4N4O4S (564.56), MS(ESI): 565 ($M+H^+$).

Example 110

3-{2-Fluoro-4-[4-(3-pyrrolidin-1-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one



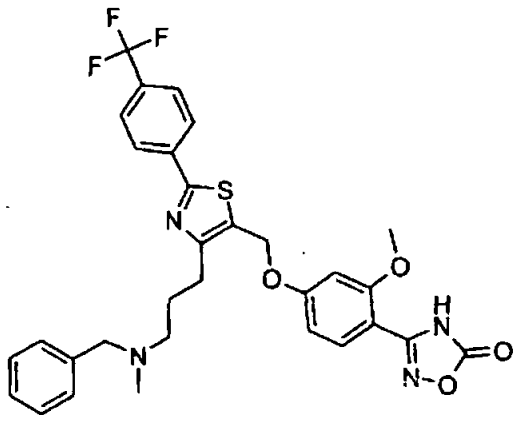
According to the method described 3-{2-methoxy-4-[4-(3-perhydro-azepin-1-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one, 3-{2-fluoro-4-[4-(3-pyrrolidin-1-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one was obtained from 3-{2-fluoro-4-[4-(3-

hydroxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one and pyrrolidine.

C26H24F4N4O3S (548.56), MS(ESI): 549 ($M+H^+$).

Example 111

3-{4-[4-[3-(Benzyl-methyl-amino)-propyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one

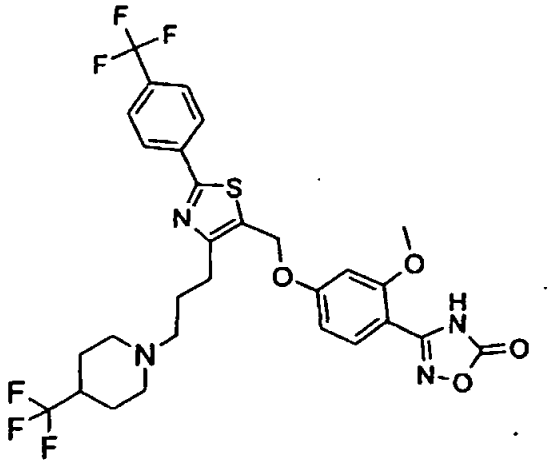


According to the method described 3-{2-methoxy-4-[4-(3-perhydro-azepin-1-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one, 3-{4-[4-[3-(benzyl-methyl-amino)-propyl]-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 3-{4-[4-(3-hydroxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one and benzyl-methyl-amine.

C31H29F3N4O4S (610.66), MS(ESI): 611 ($M+H^+$).

Example 112

3-(2-Methoxy-4-{2-(4-trifluoromethyl-phenyl)-4-[3-(4-trifluoromethyl-piperidin-1-yl)-propyl]-thiazol-5-ylmethoxy}-phenyl)-4H-[1,2,4]oxadiazol-5-one

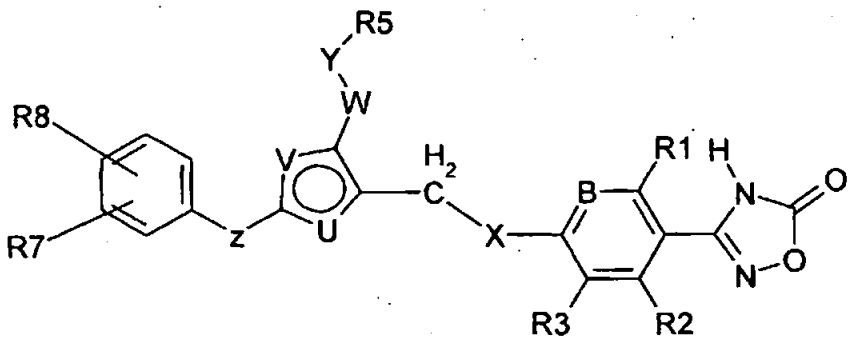


According to the method described for 3-{2-methoxy-4-[4-(3-perhydro-azepin-1-yl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-4H-1,2,4-oxadiazol-5-one, 3-(2-methoxy-4-{2-(4-trifluoromethyl-phenyl)-4-[3-(4-trifluoromethyl-piperidin-1-yl)-propyl]-thiazol-5-ylmethoxy}-phenyl)-4H-[1,2,4]oxadiazol-5-one was obtained from 3-{4-[4-(3-hydroxy-propyl)-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-methoxy-phenyl}-4H-[1,2,4]oxadiazol-5-one and 4-trifluoromethyl-piperidine.

$C_{29}H_{28}F_6N_4O_4S$ (642.63), MS(ESI): 643 ($M+H^+$).

Claims

1. Compounds of formula I:



formula I

wherein

B is C(R4) or N;

R1 is H, halogen, (C1-C8) alkyl, (C0-C4) alkylene-O-(C0-C4) alkylene-H, (C0-C2) alkylene-O-(C0-C2) alkylene-(C3-C6) cycloalkyl, SCH3, CN, wherein alkyl and alkylene are unsubstituted or mono, bi- or trisubstitued by F;

R2,R3,R4 are independently
H, halogen, (C1-C8) alkyl, (C0-C4) alkylene-O-(C0-C4) alkylene-H, SCH3, CN, wherein alkyl and alkylene are unsubstituted or mono, bi- or trisubstitued by F;

X is O, S, S(O), S(O)2, O-CH2, S-CH2, CH2-O, CH2-S;

one of U and V is N the other is S or O;

W is a bond, (C1-C8) alkylene, (C2-C8) alkenylene, (C0-C6) alkylene-(C3-C6) cycloalkylene, (C3-C6) cycloalkylene-(C1-C6) alkylene, wherein alkylene and alkenylene and cycloalkylene are unsubstituted or mono-, di- or trisubstituted by OH and F;

Y is a bond, O, S, S(O), S(O)2, N(R6) and

R5 is H, (C1-C8) alkyl, (C0-C4) alkylene-(C3-C13) cycloalkyl, (C0-C4) alkylene-(C6-C14) aryl, (C2-C8) alkenyl, (C0-C4) alkylene-(C3-C15) heterocycloalkyl, (C0-C4) alkylene-(C3-C15) heterocycloalkenyl, (C0-C4) alkylene-(C5-C15) heteroaryl, (C0-C4) alkylene-CO-(C1-C4) alkyl, (C0-C4) alkylene-CO-(C0-C4) alkylene-(C3-C13)cycloalkyl, (C0-C4) alkylene-CO-(C0-C4) alkylene-(C6-C10)aryl, (C0-C4) alkylene- CO-(C0-C4) alkylene- (C3-C15) heterocycloalkyl, (C0-C4) alkylene- CO-(C0-C4) alkylene- (C3-C15) heterocycloalkenyl, (C0-C4) alkylene- CO-(C0-C4) alkylene- (C5-C15) heteroaryl, SO2-(C1-C4)alkyl, SO2-(C0-C4) alkylene-(C3-C13)cycloalkyl, SO2-(C0-C4) alkylene-(C6-C10) aryl, SO2-(C0-C4) alkylene-(C3-C15) heterocycloalkyl, SO2-(C0-C4) alkylene-(C3-C15) heterocycloalkenyl, SO2-(C0-C4) alkylene-(C5-C15) heteroaryl, CO-O-(C0-C4) alkylene-(C6-C10) aryl, CO-O-(C1-C4) alkyl, CO-O-(C0-C4) alkylene-(C3-C13)cycloalkyl, CO-O-(C0-C4) alkylene-(C3-C15)heterocycloalkyl, CO-O-(C0-C4) alkylene-(C3-C15)heterocycloalkenyl, CO-O-(C0-C4) alkylene-(C5-C15)heteroaryl, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene- (C6-C10) aryl, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene-H, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene- (C3-C13)cycloalkyl, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene-(C3-C15) heterocycloalkyl, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene-(C3-C15) heterocycloalkenyl, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene-(C5-C15) heteroaryl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C6-C10)aryl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-H, SO2-N((C0-C4) alkylene-H)-(C0-C4)alkylene-(C3-C13)cycloalkyl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C15)heterocycloalkyl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C15)heterocycloalkenyl, SO2-N((C0-C4)alkylene-H)-

(C0-C4)alkylene-(C5-C15)heteroaryl wherein alkyl and alkylene are unsubstituted or mono-, di- or trisubstituted by F, S-(C1-C4) alkyl, SO-(C1-C4) alkyl, SO2-(C1-C4) alkyl, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene-H, N((C0-C4) alkylene-H)-(C0-C4) alkylene-H, CO-O(C1-C4) alkyl, (C1-C4) alkyl and O-(C0-C4) alkylene-H and wherein cycloalkyl, aryl, heterocycloalkyl, heterocycloalkenyl and heteroaryl are unsubstituted or mono-, di- or trisubstituted by F, Cl, Br, CF3, (C1-C4) alkyl and (C0-C4)-alkylen-O-(C0-C4) alkylene-H,

with the proviso that,
if Y is S, S(O) or S(O)2 then
R5 is unequal SO2-(C1-C4)alkyl, SO2-(C0-C4)alkylene-(C3-C13)cycloalkyl, SO2-(C0-C4)alkylene-(C6C10)aryl, SO2-(C0-C4)alkylene-(C3-C15)heterocycloalkyl, SO2-(C0-C4)alkylene-(C3-C15)heterocycloalkenyl, SO2-(C0-C4)alkylene-(C5-C15)heteroaryl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C6-C10)aryl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-H, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C13)cycloalkyl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C15)heterocycloalkyl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C15)heterocycloalkenyl, SO2-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C5-C15)heteroaryl;

with the proviso that,
if Y is a bond or O then
Z is unequal a bond or

or

Y is a bond,
with the proviso that

R5 is CN, (C1-C8) alkyl mono-, di- or trisubstituted by F, CO-(C1-C4) alkyl, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene-H, SO2-N((C0-C4) alkylene-H)-(C0-C4) alkylene-H, N((C0-C4) alkylene-H)-CO-(C0-C4) alkylene-H, (C1-C6) alkylene- (C3-C13) cycloalkyl, (C3-C15) heterocycloalkyl, (C3-C15) heterocycloalkenyl, (C5-C15) heteroaryl;

or

Y is O,

with the proviso that

R5 is (C1-C8) alkyl mono-, di- or trisubstituted by F, CO-(C1-C4) alkyl, CO-O-(C0-C4) alkylene-(C6-C10) aryl, CO-O-(C0-C4) alkylene-(C3-C13)cycloalkyl, CO-O-(C0-C4) alkylene-(C3-C15)heterocycloalkyl, CO-O-(C0-C4) alkylene-(C3-C15)heterocycloalkenyl, CO-O-(C0-C4) alkylene-(C5-C15)heteroaryl, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene-H, CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene-(C6-C10) aryl, CO-N((C0-C4)alkylene-H)-(C0-C4) alkylene-(C3-C13)cycloalkyl, CO-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C15)heterocycloalkyl, CO-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C15)heterocycloalkenyl, CO-N((C0-C4)alkylene-H)-(C0-C4) alkylene-(C3-C13)cycloalkyl, CO-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C5-C15)heteroaryl, (C0-C4) alkylene-(C3-C13) cycloalkyl, (C0-C4) alkylene-(C3-C15) heterocycloalkyl, (C0-C4) alkylene-(C3-C15) heterocycloalkenyl, (C0-C4) alkylene-(C5-C15) heteroaryl, (C0-C4) alkylene-N((C0-C4) alkylene-H)-(C0-C4) alkylene-H, (C0-C4) alkylene-N((C0-C4) alkylene-H)-(C0-C4) alkylene-(C3-C13)cycloalkyl, (C0-C4) alkylene-N((C0-C4) alkylene-H)-(C0-C4) alkylene-(C6-C10)aryl, (C0-C4) alkylene-N((C0-C4) alkylene-H)-(C0-C4) alkylene-(C3-C15)heterocycloalkyl, (C0-C4) alkylene-N((C0-C4) alkylene-H)-

(C0-C4) alkylene-(C3-C15)heterocycloalkenyl, (C0-C4) alkylene-N((C0-C4) alkylene-H)-(C0-C4) alkylene-(C5-C15)heteroaryl;

R6 is H, (C1-C8) alkyl, (C2-C8) alkenyl, (C0-C4) alkylene-(C3-C6) cycloalkyl , wherein alkyl and alkenyl are unsubstituted or mono-, di- or trisubstituted by F and O-(C0-C4)-alkylene-H;

R5 and R6 together with the nitrogen atom to which they are bonded (Y = N(R6)) form a (C3-C15)-heterocycloalkyl, a (C3-C15)-heterocycloalkenyl or a (C5-C15)-heteroaryl which can contain additionally 1 to 3 heteroatoms N, O, S in which further the heteroatoms can be oxidized and which is unsubstituted or mono-, di- or trisubstituted by halogen, CN, CF3, (C1-C4) alkyl, (C0-C4) alkylene-(C3-C6) cycloalkyl, (C0-C4) alkylene-O-(C0-C4) alkylene-H, (C0-C4) alkylene-O-(C0-C4) alkylene-(C3-C6) cycloalkyl, (C0-C4) alkylene-O-(C0-C4) alkylene-(C6-C10)aryl, (C0-C4)alkylene-O-(C0-C4)alkylene-(C3-C15) heterocycloalkyl, (C0-C4)alkylene-O-(C0-C4)alkylene-(C3-C15) heterocycloalkenyl, (C0-C4)alkylene-O-(C0-C4)alkylene-(C5-C15) heteroaryl, (C0-C4) alkylene-S-(C1-C4) alkyl, (C0-C4) alkylene-SO-(C1-C4) alkyl, (C0-C4) alkylene-SO2-(C1-C4) alkyl, (C0-C4) alkylene-CO-(C1-C4) alkyl, (C0-C4) alkylene-CO-(C6-C10)aryl, (C0-C4) alkylene-CO-(C3-C15)heterocycloalkyl, (C0-C4) alkylene-CO-(C3-C15)heterocycloalkenyl, (C0-C4) alkylene-CO-(C5-C15)heteroaryl, (C0-C4) alkylene-CO-N((C0-C4) alkylene-H)-(C0-C4) alkylene-H, (C0-C4)alkylene-CO-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C6)cycloalkyl, (C0-C4)alkylene-CO-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C6-C10)aryl, (C0-C4)alkylene-CO-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C15)heterocycloalkyl, (C0-C4)alkylene-CO-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C3-C15)heterocycloalkenyl, (C0-C4)alkylene-CO-N((C0-C4)alkylene-H)-(C0-C4)alkylene-(C5-C15)heteroaryl, (C0-C4) alkylene-N((C0-C4) alkylene-H)-CO-(C1-C4) alkyl, (C0-C4) alkylene-N((C0-C4) alkylene-H)-CO-(C0-C4) alkylene-(C3-C6) cycloalkyl, (C0-C4) alkylene-N((C0-C4) alkylene-H)-CO-(C0-C4) alkylene-(C6-C10)aryl, (C0-C4)alkylene-N((C0-C4) alkylene-H)-CO-(C0-C4)alkylene-(C3-

C15)heterocycloalkyl, (C0-C4)alkylene-N((C0-C4) alkylene-H)-CO-(C0-C4)alkylene-(C3-C15)heterocycloalkenyl, (C0-C4)alkylene-N((C0-C4) alkylene-H)-CO-(C0-C4)alkylene-(C5-C15)heteroaryl, (C0-C4) alkylene-(C6-C14) aryl and (C0-C4) alkylene-(C3-C15) heterocycloalkyl, (C0-C4) alkylene-(C3-C15) heterocycloalkenyl, (C0-C4) alkylene-(C5-C15) heteroaryl whereby heteroaryl, heterocycloalkyl and heterocycloalkenyl can mono- or disubstituted by oxo residue and where alkyl can be unsubstituted or mono-, di- or trisubstituted by F;

Z is a bond, (C1-C8) alkylene, (C2-C8) alkenylene, (C2-C8) alkylidene, (C1-C6) alkylene-O-(C1-C6) alkylene;

R7, R8 are independently selected from the group consisting of H, halogen, (C1-C8) alkyl, (C0-C4) alkylene-O-(C0-C4) alkylene-H, SCF3, SF5, S(O)2CF3, (C0-C4) alkylene-O-(C6-C12) aryl, (C0-C4) alkylene (C6-C12) aryl, NO2, wherein alkyl and alkylene are unsubstituted or mono-, di- or trisubstituted by F and aryl is unsubstituted or mono-, di- or trisubstituted by halogen, (C1-C4) alkyl or O-(C1-C4) alkyl ;

-

in all its stereoisomeric forms, enantiomeric forms and mixtures in any ratio, and its physiologically acceptable salts and tautomeric forms.

2. Compounds of the formula I as claimed in claim 1, wherein

R2,R3 are independently
H, halogen, (C1-C8) alkyl, (C0-C4) alkylene-O-(C0-C4) alkylene-H, SCH3, CN, wherein alkyl and alkylene are unsubstituted or mono, di- or trisubstitued by F;

R4 is H, (C1-C8) alkyl, (C0-C4) alkylene-O-(C0-C4) alkylene-H wherein alkyl and alkylene are unsubstituted or mono, di- or trisubstitued by F.

3. Compounds of the formula I as claimed in claim 1 or 2, wherein

B is C(R4) and
R4 is H.

4. Compounds of the formula I as claimed in claims 1 to 3, wherein

R1 is halogen, (C1-C4) alkyl, (C0-C4) alkylene-O-(C0-C2) alkylene-H, O-(C0-C2) alkylene-(C3-C6) cycloalkyl, wherein alkyl and alkylene are unsubstituted or mono, di- or trisubstituted by F.

5. Compounds of the formula as claimed in claims 1 to 4, wherein

W is (C1-C3) alkylene;

Y is N(R6) and

R5 and R6 together with the nitrogen atom to which they are bonded (Y = N(R6)) form a (C3-C7)-heterocycloalkyl, a (C4-C7)-heterocycloalkenyl or a (C5-C8)-heteroaryl which can contain additionally 1 to 2 heteroatoms N, O, S and which is unsubstituted or mono- or disubstituted by F, CF3, (C1-C3) alkyl, (C0-C3) alkylene-O-(C0-C3) alkylene-H, SO2-(C1-C3) alkyl, CO-(C1-C3) alkyl, CO-NH2, NH-CO-(C1-C3) alkyl, phenyl, (C5-C6) heteroaryl, (C3-C7) heterocycloalkyl and (C4-C7) heterocycloalkenyl, whereby heterocycloalkyl, heterocycloalkenyl and heteroaryl can be mono- or disubstituted by oxo residue

6. Compounds of the formula I as claimed in claims 1 to 5, wherein

W is (C1-C3) alkylene;

Y is N(R6) and

R5 is H, (C1-C4) alkyl, (C0-C3) alkylene-(C3-C7) cycloalkyl, (C0-C3) alkylene-phenyl, (C0-C3) alkylene-(C3-C7) heterocycloalkyl, (C0-C4) alkylene-(C4-C7) heterocycloalkenyl, (C0-C3) alkylene-(C5-C6) heteroaryl, CO-(C0-C3) alkyl, CO-O-phenyl, wherein alkyl and alkylene can be mono-, di- or trisubstituted by F, S-(C1-C3) alkyl, SO-(C1-C3) alkyl, SO2-(C1-C3) alkyl, N((C0-C3) alkylene-H)-(C0-C3) alkylene-H, CO-O(C1-C3) alkyl and O-(C0-C3) alkylene-H and wherein cycloalkyl, phenyl, heterocycloalkyl, heterocycloalkenyl and heteroaryl are mono-, di- or trisubstituted by F and (C0-C4)-alkylen-O-(C0-C4) alkylene-H;

R6 is H, (C1-C3) alkyl or (C0-C3) alkylene-(C3-C6) cycloalkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted by O-(C0-C4)-alkylene-H; or

Y is S, S(O), S(O)2 and
R5 is (C1-C3) alkyl or (C0-C3) alkylene-(C3-C6) cycloalkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted by F; or

Y is O and
R5 is (C1-C4) alkyl mono-, di- or trisubstituted by F, CO-(C1-C3) alkyl, (C0-C3) alkylene-(C3-C6) cycloalkyl, (C0-C3) alkylene-(C3-C7) heterocycloalkyl, (C0-C3) alkylene-(C5-C8) heteroaryl; or
Z is –CH2-, -CH2-CH2-, -CH2-O-CH2-, -CH=CH-.

7. Compounds of the formula I as claimed in claims 1 to 6, wherein
V is N and U is O; or
V is N and U is S.

8. Compounds of the formula I as claimed in claims 1 to 7, wherein
X is O or O-CH2.

9. Compounds of the formula I as claimed in claims 1 to 8, wherein
W is a bond or –CH2-.

10. Compounds of the formula I as claimed in claims 1 to 9, wherein
R7 is in para-position.

11. Compounds of the formula I as claimed in claims 1 to 10, wherein
R8 is H.

12. Compounds of the formula I as claimed in claims 1 to 11, wherein

R1 is halogen, (C1-C4) alkyl, (C0-C4) alkylene-O-(C0-C2) alkylene-H, O-(C0-C2) alkylene-(C3-C6) cycloalkyl, wherein alkyl and alkylene are unsubstituted or mono, di- or trisubstituted by F;

W is (C1-C3) alkylene;

Y is N(R6) and

R5 and R6 together with the nitrogen atom to which they are bonded (Y = N(R6)) form a (C3-C7)-heterocycloalkyl, a (C4-C7)-heterocycloalkenyl or a (C5-C8)-heteroaryl which can contain additionally 1 to 2 heteroatoms N, O, S and which is unsubstituted or mono- or disubstituted by F, CF3, (C1-C3) alkyl, (C0-C3) alkylene-O-(C0-C3) alkylene-H, SO2-(C1-C3) alkyl, CO-(C1-C3)

alkyl, CO-NH2, NH-CO-(C1-C3) alkyl, phenyl, (C5-C6) heteroaryl, (C3-C7) heterocycloalkyl and (C4-C7) heterocycloalkenyl, whereby heterocycloalkyl, heterocycloalkenyl and heteroaryl can be mono- or disubstituted by oxo residue;

W is (C1-C3) alkylene;

Y is N(R6) and

R5 is H, (C1-C4) alkyl, (C0-C3) alkylene-(C3-C7) cycloalkyl, (C0-C3) alkylene-phenyl, (C0-C3) alkylene-(C3-C7) heterocycloalkyl, (C0-C4) alkylene-(C4-C7) heterocycloalkenyl, (C0-C3) alkylene-(C5-C6) heteroaryl, CO-(C0-C3) alkyl, CO-O-phenyl, wherein alkyl and alkylene can be mono-, di- or trisubstituted by F, S-(C1-C3) alkyl, SO-(C1-C3) alkyl, SO2-(C1-C3) alkyl, N((C0-C3) alkylene-H)-(C0-C3) alkylene-H, CO-O(C1-C3) alkyl and O-(C0-C3) alkylene-H and wherein cycloalkyl, phenyl, heterocycloalkyl, heterocycloalkenyl and heteroaryl are mono-, di- or trisubstituted by F and (C0-C4)-alkylen-O-(C0-C4) alkylene-H;

R6 is H, (C1-C3) alkyl or (C0-C3) alkylene-(C3-C6) cycloalkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted by O-(C0-C4)-alkylene-H;

Y is S, S(O), S(O)2 and
R5 is (C1-C3) alkyl or (C0-C3) alkylene-(C3-C6) cycloalkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted by F;

Y is O and

R5 is (C1-C4) alkyl mono-, di- or trisubstituted by F, CO-(C1-C3) alkyl, (C0-C3) alkylene-(C3-C6) cycloalkyl, (C0-C3) alkylene-(C3-C7) heterocycloalkyl, (C0-C3) alkylene-(C5-C8) heteroaryl; or
Z is –CH2-, -CH2-CH2-, -CH2-O-CH2-, -CH=CH-.

13. Compounds of the formual I as claimed in claims 1 to 12, wherein

B is C(R4) and
R4 is H.

R1 is F, Cl, (C1-C4) alkyl, (C0-C4) alkylene-O-(C1-C4) alkylene-H, (C0-C2) alkylene-O-(C0-C2) alkylene-(C3-C6) cycloalkyl, wherein alkyl and alkylene are unsubstituted or mono, bi- or trisubstitued by F;

R2 is H;

R3 is H, F, Br;

R4 is H;

X is O, O-CH2;

U is S, O and
V is N
Or
U is N and
V is O;

W is a bond, (C1-C4) alkylene;

Y is N(R6) and

R5 is selected from the group consisting of (C1-C8) alkyl, (C0-C4) alkylene-(C3-C13) cycloalkyl, (C0-C4) alkylene-(C6-C12) aryl, (C0-C4) alkylene-(C3-C15) heterocycloalkyl CO-(C0-C4) alkyl, CO-O-(C6-C10) aryl, wherein alkyl and alkylene can be mono-, di- or trisubstituted by S-(C1-C4) alkyl, SO-(C1-C4) alkyl, N((C0-C4) alkylene-H)-(C0-C4) alkylene-H and O-(C0-C4) alkylene-H and wherein aryl and heterocycloalkyl, are mono-, di- or trisubstituted by F and (C0-C4)-alkylene-O-(C0-C4) alkylene-H;

Y is O and

R5 is (C1-C8) alkyl mono-, di- or trisubstituted by F, CO-(C1-C4) alkyl, (C0-C4) alkylene-(C3-C6) cycloalkyl; or

Z is –CH2-, -CH2-CH2-, -CH2-O-CH2-, -CH=CH-;

Y is S, S(O), S(O)2 and

R5 is (C1-C3) alkyl;

R6 is H, (C1-C8) alkyl or (C0-C4) alkylene-(C3-C6) cycloalkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted by O-(C0-C4)-alkylene-H;

R5 and R6 together with the nitrogen atom to which they are bonded (Y = N(R6)) can form a (C3-C8)-heterocycloalkyl, a (C3-C10)-heterocycloalkenyl which can contain additionally 1 to 3 heteroatoms N, O, S and which is unsubstituted or mono-, di- or trisubstituted by F, CF3, (C1-C4) alkyl, (C0-C4) alkylene-O-(C0-C4) alkylene-H, SO2-(C1-C4) alkyl, CO-(C1-C4) alkyl, whereby heterocycloalkyl can mono- or disubstituted by oxo residue;

Z is a bond, (C1-C2) alkylene, (C2) alkenylene, (C1-C2) alkylene-O-(C1-C2) alkylene;

R7 is H, O-(C1-C4) alkyl, CF3;

R8 is H.

14 Compounds of the formula I as claimed in claims 1 to 13, wherein:

R1 is halogen, (C1-C4) alkyl, OH, O-(C1-C3) alkyl, wherein alkyl is unsubstituted or mono, di- or trisubstitued by F;

R2 is H;

R3 is H, F;

B is C(R4) or N, and

R4 is H;

X is O;

one of U and V is N the other is S or O;

W is (C1-C3) alkylene;

Y is N(R6) and

R5 and R6 together with the nitrogen atom to which they are bonded (Y = N(R6)) form a (C3-C7)-heterocycloalkyl, a (C4-C7)-heterocycloalkenyl or a (C5-C8)-heteroaryl which can contain additionally 1 to 2 heteroatoms N, O, S and which is unsubstituted or mono- or disubstituted by F, CF3, (C1-C3) alkyl, (C0-C3) alkylene-O-(C0-C3) alkylene-H, SO2-(C1-C3) alkyl, CO-(C1-C3) alkyl, CO-NH2, NH-CO-(C1-C3) alkyl, phenyl, (C5-C6) heteroaryl, (C3-C7) heterocycloalkyl and (C4-C7) heterocycloalkenyl, whereby heterocycloalkyl, heterocycloalkenyl and heteroaryl can be mono- or disubstituted by oxo residue;

Y is N(R6) and

R5 is H, (C1-C4) alkyl, (C0-C3) alkylene-(C3-C7) cycloalkyl, (C0-C3) alkylene-phenyl, (C0-C3) alkylene-(C3-C7) heterocycloalkyl, (C0-C4) alkylene-(C4-C7) heterocycloalkenyl, (C0-C3) alkylene-(C5-C6) heteroaryl, CO-(C0-C3) alkyl, CO-O-phenyl, wherein alkyl and alkylene can be mono-, di- or trisubstituted by F, S-(C1-C3) alkyl, SO-(C1-C3) alkyl, SO2-(C1-C3) alkyl, N((C0-C3) alkylene-H)-(C0-C3) alkylene-H, CO-O(C1-C3) alkyl and O-(C0-C3) alkylene-H and wherein cycloalkyl, phenyl, heterocycloalkyl, heterocycloalkenyl and heteroaryl are mono-, di- or trisubstituted by F and (C0-C4)-alkylen-O-(C0-C4) alkylene-H;

R6 is H, (C1-C3) alkyl or (C0-C3) alkylene-(C3-C6) cycloalkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted by O-(C0-C4)-alkylene-H;

Y is S, S(O), S(O)2 and
R5 is (C1-C3) alkyl or (C0-C3) alkylene-(C3-C6) cycloalkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted by F;

Y is O and
R5 is (C1-C4) alkyl mono-, di- or trisubstituted by F, CO-(C1-C3) alkyl, (C0-C3) alkylene-(C3-C6) cycloalkyl, (C0-C3) alkylene-(C3-C7) heterocycloalkyl, (C0-C3) alkylene-(C5-C8) heteroaryl; or
Z is –CH2-, -CH2-CH2-, -CH2-O-CH2-, -CH=CH-.

Z is a bond, (C1-C2) alkylene, (C2) alkenylene, (C1-C2) alkylene-O-(C1-C2) alkylene;

R7 is H, halogen, (C1-C3) alkyl, O-(C1-C3) alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted by F;

R8 is H.

15. Compounds of the formula I as claimed in claims 1 to 14, wherein:

R1 is F, OH, OCH3, OCHF2, OCH2CF3;

R2 is H;

R3 is H, F;

B is C(R4) or N, and

R4 is H;

X is O;

one of U and V is N the other is S or O;

W is CH2, CH2CH2CH2;

Y is N(R6) and

R5 and R6 together with the nitrogen atom to which they are bonded (Y = N(R6)) form a piperidine, pyrrolidine, azetidine, azepine, morpholine, thiomorpholine, thiomorpholine-S-oxide, thiomorpholine-S-dioxide, piperazine, piperazinone, iso-indoline, which is unsubstituted or mono- or disubstituted by F, CF3, (C1-C3) alkyl, O-(C1-C3) alkyl, OH, CH2OH, SO2CH3, COCH3, phenyl;

Y is S, S(O), S(O)2 and

R5 is CH3;

Z is a bond;

R7 is CF3;

R8 is H.

16. Compounds of the formula I as claimed in claims 1 to 15, wherein:

R1 is H, F, Cl;

R2 is H;

R3 is H;

B is C(R4) or N, and
R4 is H;

X is O;

U is S, O and
V is N;

W is CH2;

Y is a bond or O;

Z is a bond;

R5 is (C1-C6) alkyl mono-, di- or trisubstituted by F;

R7 is in para-position and (C1-C4) alkyl, (C0-C4) alkylen-O-(C0-C4) alkylen-H, SF5, (C0-C4) alkylen-O-phenyl, wherein alkyl, alkylen and phenyl are mono-, di- or trisubstituted by F;

R8 is H.

17. A pharmaceutical comprising one or more compounds of the formula I as claimed in one or more of claims 1 to 16.

18. A pharmaceutical comprising one or more compounds of the formula I as claimed in one or more of claims 1 to 16 and one or more active substances which have favorable effects on metabolic disturbances or disorders frequently associated therewith.

19. A pharmaceutical comprising one or more compounds of the formula I as claimed in one or more of claims 1 to 16 and one or more antidiabetics.

20. A pharmaceutical comprising one or more compounds of the formula I as claimed in one or more of claims 1 to 16 and one or more lipid modulators.

21. The use of the compounds of the formula I as claimed in one or more of claims 1 to 16 for the treatment and/or prevention of disorders of fatty acid metabolism and glucose utilization disorders.

22. The use of the compounds of the formula I as claimed in one or more of claims 1 to 16 for the treatment and/or prevention of disorders in which insulin resistance is involved.

23. The use of the compounds of the formula I as claimed in one or more of claims 1 to 16 for the treatment and/or prevention of diabetes mellitus including the prevention of the squelae associated therewith.

24. The use of the compounds of the formula I as claimed in one or more of claims 1 to 16 for the treatment and/or prevention of dyslipidemias and their squelae.

25. The use of the compounds of the formula I as claimed in one or more of claims 1 to 16 for the treatment and/or prevention of conditions, which may be associated with the metabolic syndrome.

26. The use of the compounds of the formula I as claimed in one or more of claims 1 to 16 for the treatment and/or prevention of demyelinating and other neurodegenerative disorders of the central and peripheral nervous system.

27. The use of compounds as claimed in one or more of claims 1 to 16 in combination with at least one further active compound for the treatment of disorders of fatty acid metabolism and glucose utilization disorders.

28. The use of compounds as claimed in one or more of claims 1 to 16 in combination with at least one further active compound for the treatment of disorders in which insulin resistance is involved.

29. A process for preparing a pharmaceutical comprising one or more of the compounds as claimed in one or more of claims 1 to 16, which comprises mixing the active compound with a pharmaceutically suitable carrier and bringing this mixture into a form suitable for administration.

156

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/009298

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/12 A61K31/4245

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2005/097762 A (AVENTIS PHARMACEUTICALS INC; MCGARRY, DANIEL, G; CHANDROSS, KAREN; MER) 20 October 2005 (2005-10-20) the whole document	1-29
P,X	EP 1 586 573 A (AVENTIS PHARMA DEUTSCHLAND GMBH) 19 October 2005 (2005-10-19) the whole document	1-29
P,X	& WO 2005/097786 A (AVENTIS PHARMA GMBH [DE]; KEIL STEFANIE [DE]; WENDLER WOLFGANG [DE]; G) 20 October 2005 (2005-10-20) cited in the application	1
A	US 5 641 796 A (DOMINIANNI ET AL) 24 June 1997 (1997-06-24) the whole document	1-16,25

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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"P" document published prior to the international filing date but later than the priority date claimed

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"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
22 February 2007	06/03/2007

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/009298

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 424 330 A (NIPPON CHEMIPHAR CO., LTD) 2 June 2004 (2004-06-02) the whole document	1-29
A	US 6 710 063 B1 (CHAO ESTHER YU-HSUAN ET AL) 23 March 2004 (2004-03-23) the whole document	1-29
A	KULKARNI S S ET AL: "Three-Dimensional Quantitative Structure Activity Relationship (3-D-QSAR) of Antihyperglycemic Agents" BIOORGANIC & MEDICINAL CHEMISTRY, ELSEVIER SCIENCE LTD, GB, vol. 7, 1999, pages 1475-1485, XP002345584 ISSN: 0968-0896 the whole document	1-29
A	WO 00/78313 A (MERCK & CO., INC; DESAI, RANJIT, C; SAHOO, SOUYMA, P; BERGMAN, JEFFREY) 28 December 2000 (2000-12-28) the whole document	1-29
A	WO 96/13264 A (LILLY CO ELI [US]; DOMINIANNI SAMUEL JAMES [US]; FITCH LORA LOUISE [US) 9 May 1996 (1996-05-09) cited in the application the whole document	1-29

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/009298

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 21-28
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 21-28 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2006/009298

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
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			CA	2561738	A1	20-10-2005
			EP	1735303	A2	27-12-2006
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2006/009298

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DERIVADOS DE FENIL- Y PIRIDIL-1,2,4-OXADIAZOLONA CON GRUPO FENILO, PROCEDIMIENTOS PARA SU PREPARACIÓN Y SU USO COMO PRODUCTOS FARMACÉUTICOS

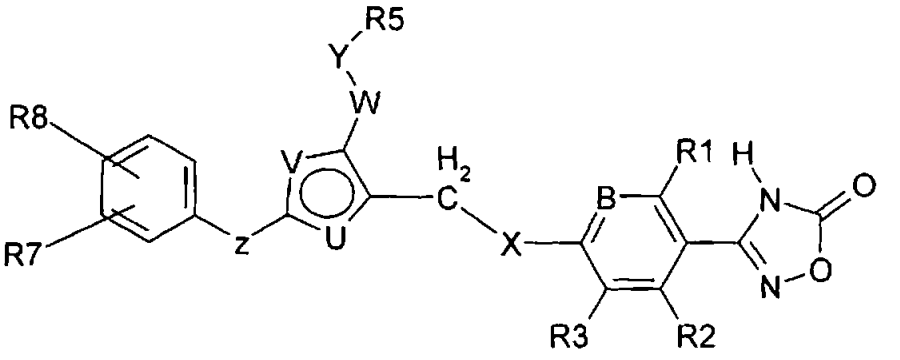
La invención se refiere a derivados de fenil-1,2,4-oxadiazolona con grupo fenilo y a sus sales fisiológicamente aceptables y derivados fisiológicamente funcionales que muestran actividad agonista de PPARdelta.

Los agonistas de PPARdelta se han descrito en la técnica anterior (p. ej., WO 01/00603, WO 02/092590, WO2004/080943, WO2005/054213 y WO2005/097786). Los compuestos que comprenden una característica de oxadiazolona como inhibidores del factor Xa fueron descritos en el documento DE 10112768 A1, y los agentes hipoglucémicos orales en el documento WO 96/13264. A partir del documento WO 97/40017, los compuestos que tienen un grupo fenilo unido a heterociclos se conocen como moduladores de moléculas con unidades de reconocimiento de fosfotirosina. Los derivados de benceno como inhibidores de escualeno sintasa y proteína farnesiltransferasa se describen en el documento WO96/34851.

La invención se basa en el objeto de proveer compuestos que permitan una modulación terapéuticamente utilizable del metabolismo de lípidos y/o carbohidratos y que sean, por lo tanto, adecuados para la prevención y/o el tratamiento de enfermedades tales como la diabetes de tipo 2 y la aterosclerosis y sus diversas secuelas. Otro propósito de la invención es tratar el trastorno de desmielinización y otros trastornos neurodegenerativos de los sistemas nerviosos central y periférico.

Se ha encontrado una serie de compuestos que modulan la actividad de los receptores de PPA. Los compuestos son adecuados en particular para activar PPARdelta o PPARdelta y PPARalfa, siendo posible, no obstante, para el grado de activación relativa, variar dependiendo de los compuestos.

Los compuestos de la presente invención se describen con la fórmula I:



fórmula I

en la que

B es C(R4) o N;

R1 es H, halógeno, alquilo (C1-C8), alquilen (C0-C4)-O-alquilen (C0-C4)-H, alquilen (C0-C2) -O-alquilen (C0-C2)-cicloalquilo (C3-C6), SCH3, CN, en el que alquilo y alquileno no están sustituidos o están mono, di o trisustituidos con F;

R2, R3, R4 son independientemente

H, halógeno; alquilo (C1-C8), alquilen (C0-C4)-O-alquilen (C0-C4)-H, SCH3, CN, en los que alquilo y alquileno no están sustituidos o están mono, di o trisustituidos con F;

X es O, S, S(O), S(O)2, O-CH2, S-CH2, CH2-O, CH2-S;

uno de U y V es N, el otro es S u O;

W es un enlace, alquileno (C1-C8), alquenileno (C2-C8), alquilen (C0-C6)-cicloalquileno (C3-C6), cicloalquilen (C3-C6) alquileno (C1-C6), en el que alquileno y alquenileno no están sustituidos o están mono, di o trisustituidos con OH y F;

Y es un enlace, O, S, S(O), S(O)2, N(R6) y

R5 es H, alquilo (C1-C8), alquilen (C0-C4)-cicloalquilo (C3-C13), alquilen (C0-C4)-arilo (C6-C14), alquenilo (C2-C8), alquilen (C0-C4)-heterocicloalquilo (C3-C15), alquilen (C0-C4)-heterocicloalquenilo (C3-C15), alquilen (C0-C4)-heteroarilo (C5-C15), alquilen (C0-C4)-CO-alquilo (C1-C4), alquilen (C0-C4)-CO-alquilen (C0-C4)-cicloalquilo (C3-C13), alquilen (C0-C4)-CO-alquilen (C0-C4)-arilo (C6-C10), alquilen (C0-C4)- CO-alquilen (C0-C4)-heterocicloalquilo

(C3-C15), alquilen (C0-C4)- CO-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), alquilen (C0-C4)-CO-alquilen (C0-C4)-heteroarilo (C5-C15), SO2-alquilo (C1-C4), SO2-alquilen (C0-C4)-cicloalquilo (C3-C13), SO2-alquilen (C0-C4)-arilo (C6-C10), SO2-alquilen (C0-C4)-heterocicloalquilo (C3-C15), SO2-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), SO2-alquilen (C0-C4)-heteroarilo (C5-C15), CO-O-alquilen (C0-C4)-arilo (C6-C10), CO-O-alquilo (C1-C4), CO-O-alquilen (C0-C4)-cicloalquilo (C3-C13), CO-O-alquileno (C0-C4)-heterocicloalquilo (C3-C15), CO-O-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), CO-O-alquilen (C0-C4)-heteroarilo (C5-C15), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-arilo (C6-C10), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-cicloalquilo (C3-C13), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)- heterocicloalquilo (C3-C15), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heteroarilo (C5-C15), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-arilo (C6-C10), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-cicloalquilo (C3-C13), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquilo (C3-C15), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heteroarilo (C5-C15) en el que alquilo y alquileno no están sustituidos o están mono, di o trisustituidos con F, S-alquilo (C1-C4), SO-alquilo (C1-C4), SO2-alquilo (C1-C4), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, CO-O alquilo (C1-C4), alquilo (C1-C4) y O-alquilen (C0-C4)-H y en los que cicloalquilo, arilo, heterocicloalquilo, heterocicloalquenilo y heteroarilo no están sustituidos o están mono, di o trisustituidos con F, Cl, Br, CF3, alquilo (C1-C4) y alquilen (C0-C4)-O-alquilen (C0-C4)-H,

con la salvedad que,

si Y es S, S(O) o S(O)2, entonces

R5 no es igual SO2-alquilo (C1-C4), SO2-alquilen (C0-C4)-cicloalquilo (C3-C13), SO2-alquilen (C0-C4)-arilo (C6C10), SO2-alquilen (C0-C4)-heterocicloalquilo (C3-C15), SO2-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), SO2-alquilen (C0-C4)-heteroarilo (C5-C15), SO2-N(alquilen (C0-C4)-H)-

alquilen (C0-C4)-arilo (C6-C10), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-cicloalquilo (C3-C13), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquilo (C3-C15), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heteroarilo (C5-C15);

con la salvedad que,

si Y es un enlace u O, entonces

Z no es igual un enlace;

o

Y es un enlace,

con la salvedad que

R5 es CN, alquilo (C1-C8) mono, di o trisustituido con F, CO-alquilo (C1-C4), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, N(alquilen (C0-C4)-H)-CO-alquilen (C0-C4)-H, alquilen (C1-C6)-cicloalquilo (C3-C13), heterocicloalquilo (C3-C15), heterocicloalquenilo (C3-C15), heteroarilo (C5-C15);

o

Y es O,

con la salvedad que

R5 es alquilo (C1-C8) mono, di o trisustituido con F, CO-alquilo (C1-C4), CO-O-alquilen (C0-C4)-arilo (C6-C10), CO-O-alquilen (C0-C4)-cicloalquilo (C3-C13), CO-O-alquilen (C0-C4)-heterocicloalquilo (C3-C15), CO-O-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), CO-O-alquilen (C0-C4)-heteroarilo (C5-C15), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-arilo (C6-C10), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-cicloalquilo (C3-C13), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquilo (C3-C15), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4) -cicloalquilo (C3-C13), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heteroarilo (C5-C15), alquilen (C0-C4) cicloalquilo (C3-C13), alquilen (C0-C4) heterocicloalquilo (C3-C15), alquilen (C0-C4) heterocicloalquenilo (C3-C15), alquilen (C0-C4)-heteroarilo (C5-C15), alquilen (C0-C4)-N(alquilen (C0-C4)-H)-

alquilen (C0-C4)-H, alquilen (C0-C4)-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-cicloalquilo (C3-C13), alquilen (C0-C4)-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-arilo (C6-C10), alquilen (C0-C4)-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquilo (C3-C15), alquilen (C0-C4)-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), alquilen (C0-C4)-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heteroarilo (C5-C15);

R6 es H, alquilo (C1-C8), alquenilo (C2-C8), alquilen (C0-C4)-cicloalquilo (C3-C6), en el que alquilo y alquenilo no están sustituidos o están mono, di o trisustituidos con F y O-alquilen (C0-C4)-H;

R5 y R6 junto con el átomo de nitrógeno al que están unidos (Y = N(R6)) forman un heterocicloalquilo (C3-C15), un heterocicloalquenilo (C3-C15) o un heteroarilo (C5-C15) que puede adicionalmente contener 1 a 3 heteroátomos N, O, S en el que además se pueden oxidar heteroátomos y que puede no estar sustituido o estar mono, di o trisustituido con halógeno, CN, CF3, alquilo (C1-C4), alquilen (C0-C4)-cicloalquilo (C3-C6), alquilen (C0-C4)-O-alquilen (C0-C4)-H, alquilen (C0-C4)-O-alquilen (C0-C4)-cicloalquilo (C3-C6), alquilen (C0-C4)-O-alquilen (C0-C4)-arilo (C6-C10), alquilen (C0-C4)-O-alquilen (C0-C4)-heterocicloalquilo (C3-C15), alquilen (C0-C4)-O-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), alquilen (C0-C4)-O-alquilen (C0-C4)-heteroarilo (C5-C15), alquilen (C0-C4)-S-alquilo (C1-C4), alquilen (C0-C4)-SO-alquilo (C1-C4), alquilen (C0-C4)-SO2-alquilo (C1-C4), alquilen (C0-C4)-CO-alquilo (C1-C4), alquilen (C0-C4)-CO-arilo (C6-C10), alquilen (C0-C4)-CO-heterocicloalquilo (C3-C15), alquilen (C0-C4)-CO-heterocicloalquenilo (C3-C15), alquilen (C0-C4)-CO-heteroarilo (C5-C15), alquilen (C0-C4)-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, alquilen (C0-C4)-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-cicloalquilo (C3-C6), alquilen (C0-C4)-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-arilo (C6-C10), alquilen (C0-C4)-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquilo (C3-C15), alquilen (C0-C4)-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), alquilen (C0-C4)-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heteroarilo (C5-C15), alquilen (C0-C4)-N(alquilen (C0-C4)-H)-CO-alquilo (C1-C4), alquilen (C0-C4)-

N(alquilen (C0-C4)-H)-CO-alquilen (C0-C4)-cicloalquilo (C3-C6), alquilen (C0-C4)-N(alquilen (C0-C4)-H)-CO-alquilen (C0-C4)-arilo (C6-C10), alquilen (C0-C4)-N(alquilen (C0-C4)-H)-CO-alquilen (C0-C4)-heterocicloalquilo (C3-C15), alquilen (C0-C4)-N(alquilen (C0-C4)-H)-CO-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), alquilen (C0-C4)-N(alquilen (C0-C4)-H)-CO-alquilen (C0-C4)-heteroarilo (C5-C15), alquilen (C0-C4)-arilo (C6-C14) y alquilen (C0-C4) heterocicloalquilo (C3-C15), alquilen (C0-C4)-heterocicloalquenilo (C3-C15), alquilen (C0-C4)-heteroarilo (C5-C15) en los que heteroarilo, heterocicloalquilo y heterocicloalquenilo pueden estar mono o disustituidos con residuo oxo y en los que alquilo puede no estar sustituido o estar mono, di o trisustituido con F;

Z es un enlace, alquileno (C1-C8), alquenileno (C2-C8), alquilideno (C2-C8), alquilen (C1-C6)-O-alquileno (C1-C6);

R7, R8 se seleccionan independientemente entre el grupo que consiste en H, halógeno, alquilo (C1-C8), alquilen (C0-C4)-O-alquilen (C0-C4)-H, SCF3, SF5, S(O)2CF3, alquilen (C0-C4)-O-arilo (C6-C12), alquilen (C0-C4)-arilo (C6-C12), NO2, en los que alquilo y alquileno no están sustituidos o están mono, di o trisustituidos con F y arilo no está sustituido o está mono, di o trisustituido con halógeno, alquilo (C1-C4) u O-alquilo (C1-C4);

en todas sus formas estereoisoméricas, formas enantioméricas y mezclas en cualquier relación, y sus sales farmacéuticamente aceptables y formas tautoméricas.

Otra realización según la invención consiste en compuestos de la fórmula I, en la que

R2, R3 son independientemente

H, halógeno, alquilo (C1-C8), alquilen (C0-C4)-O-alquilen (C0-C4)-H, SCH3, CN, en los que alquilo y alquileno no están sustituidos o están mono, di o trisustituidos con F;

R4 es H, alquilo (C1-C8), alquilen (C0-C4)-O-alquilen (C0-C4)-H, en el que alquilo y alquileno no están sustituidos o están mono, di o trisustituidos con F.

Otra realización según la invención consiste en compuestos de la fórmula I, en la que

B es C(R4) y

R4 es H.

Otra realización según la invención consiste en compuestos de la fórmula I, en la que

B es C(R4) y

R4 es H;

R1 es H, halógeno, alquilo (C1-C8), alquilen (C0-C4)-O-alquilen (C0-C4)-H, SCH3, CN, en el que alquilo y alquileno no están sustituidos o están mono, bi o trisustituidos con F;

R2, R3, R4 son independientemente

H, halógeno, alquilo (C1-C8), alquilen (C0-C4)-O-alquilen (C0-C4)-H, SCH3, CN, en el que alquilo y alquileno no están sustituidos o están mono, bi o trisustituidos con F;

X es O, S, S(O), S(O)2, O-CH2, S-CH2, CH2-O, CH2-S;

uno de U y V es N, el otro es S u O;

W es un enlace, alquileno (C1-C8), alquenileno (C2-C8),

alquilen (C0-C6)-cicloalquileno (C3-C6), cicloalquilen (C3-C6)-alquileno (C1-C6), en el que alquileno y alquenileno y cicloalquileno no están sustituidos o están mono, di o trisustituidos con OH y F;

Y es N(R6);

R5 es H, alquilo (C1-C8), alquilen (C0-C4)-cicloalquilo (C3-C13), alquilen (C0-C4)-arilo (C6-C14), alquenilo (C2-C8), alquilen (C0-C4)-heterocicloalquilo (C3-C15), alquilen (C0-C4)-heterocicloalquenilo (C3-C15), alquilen (C0-C4)-heteroarilo (C5-C15), alquilen (C0-C4)-CO-alquilo (C1-C4), alquilen (C0-C4)-CO-alquilen (C0-C4)-cicloalquilo (C3-C13), alquilen (C0-C4)-CO-alquilen (C0-C4)-arilo (C6-C10), alquilen (C0-C4)-CO-alquilen (C0-C4)-heterocicloalquilo (C3-C15), alquilen (C0-C4)-CO-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), alquilen (C0-C4)- CO-alquilen (C0-C4)-heteroarilo (C5-C15), SO2-alquilo (C1-C4), SO2-alquilen (C0-C4)-cicloalquilo (C3-C13), SO2-alquilen (C0-C4)-arilo (C6-C10), SO2-alquilen (C0-C4)-heterocicloalquilo (C3-C15), SO2-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), SO2-alquilen (C0-C4)-heteroarilo (C5-C15), CO-O-alquilen (C0-C4)-arilo (C6-C10), CO-O-alquilo (C1-C4), CO-O-alquilen

(C0-C4)-cicloalquilo (C3-C13), CO-O-alquilen (C0-C4)-heterocicloalquilo (C3-C15), CO-O-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), CO-O-alquilen (C0-C4)-heteroarilo (C5-C15), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-arilo (C6-C10), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-cicloalquilo (C3-C13), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquilo (C3-C15), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heteroarilo (C5-C15), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-arilo (C6-C10), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-cicloalquilo (C3-C13), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquilo (C3-C15), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heteroarilo (C5-C15) en el que alquilo y alquileno no están sustituidos o están mono, di o trisustituidos con F, S-alquilo (C1-C4), SO-alquilo (C1-C4), SO2-alquilo (C1-C4), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, CO-O alquilo (C1-C4), alquilo (C1-C4) y O-alquilen (C0-C4)-H y en los que cicloalquilo, arilo y heterocicloalquilo, heterocicloalquenilo y heteroarilo no están sustituidos o están mono, di o trisustituidos con F, Cl, Br, CF3, alquilo (C1-C4) y alquilen (C0-C4)-O-alquilen (C0-C4)-H;

R6 es H, alquilo (C1-C8), alquenilo (C2-C8), alquilen (C0-C4)-cicloalquilo (C3-C6), en el que alquilo y alquenilo no están sustituidos o están mono, di o trisustituidos con F y O-alquilen (C0-C4)-H;

R5 y R6 junto con el átomo de nitrógeno al que están unidos (Y = N(R6)) pueden formar un heterocicloalquilo (C3-C15), un heterocicloalquenilo (C3-C15) o un heteroarilo (C5-C15) que puede contener adicionalmente 1 a 3 heteroátomos N, O, S y que no está sustituido o está mono, di o trisustituido con halógeno, CN, CF3, alquilo (C1-C4), alquilen (C0-C4)-cicloalquilo (C3-C6), alquilen (C0-C4)-O-alquilen (C0-C4)-H, alquilen (C0-C4)-O-alquilen (C0-C4)-cicloalquilo (C3-C6), alquilen (C0-C4)-O-alquilen (C0-C4)-arilo (C6-C10), alquilen (C0-C4)-O-alquilen (C0-C4)-heterocicloalquilo (C3-C15), alquilen (C0-C4)-O-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), alquilen (C0-C4)-O-

alquilen (C0-C4)-heteroarilo (C5-C15), alquilen (C0-C4)-S-alquilo (C1-C4), alquilen (C0-C4)-SO-alquilo (C1-C4), alquilen (C0-C4)-SO2-alquilo (C1-C4), alquilen (C0-C4)-CO-alquilo (C1-C4), alquilen (C0-C4)-CO-arilo (C6-C10), alquilen (C0-C4)-CO-heterocicloalquilo (C3-C15), alquilen (C0-C4)-CO-heterocicloalquenilo (C3-C15), alquilen (C0-C4)-CO-heteroarilo (C5-C15), alquilen (C0-C4)-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, alquilen (C0-C4)-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-cicloalquilo (C3-C6), alquilen (C0-C4)-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-arilo (C6-C10), alquilen (C0-C4)-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquilo (C3-C15), alquilen (C0-C4)-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), alquilen (C0-C4)-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heteroarilo (C5-C15), alquilen (C0-C4)-N(alquilen (C0-C4)-H)-CO-alquilo (C1-C4), alquilen (C0-C4) -N(alquilen (C0-C4)-H)-CO-alquilen (C0-C4)-cicloalquilo (C3-C6), alquilen (C0-C4)-N(alquilen (C0-C4)-H)-CO-alquilen (C0-C4)-arilo (C6-C10), alquilen (C0-C4)-N(alquilen (C0-C4)-H)-CO-alquilen (C0-C4)-heterocicloalquilo (C3-C15), alquilen (C0-C4)-N(alquilen (C0-C4)-H)-CO-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), alquilen (C0-C4)-N(alquilen (C0-C4)-H)-CO-alquilen (C0-C4)-heteroarilo (C5-C15), alquilen (C0-C4)-arilo (C6-C14) y alquilen (C0-C4)-heterocicloalquilo (C3-C15), alquilen (C0-C4)-heterocicloalquenilo (C3-C15), alquilen (C0-C4)-heteroarilo (C5-C15) en los que heteroarilo, heterocicloalquilo y heterocicloalquenilo pueden estar mono o disustituidos con un residuo oxo y en los que alquilo puede no estar sustituido o estar mono, di o trisustituido con F;

Z es un enlace, alquileno (C1-C8), alquenileno (C2-C8), alquilideno (C2-C8), alquilen (C1-C6)-O-alquileno (C1-C6);

R7, R8 se seleccionan independientemente entre el grupo que consiste en H, halógeno, alquilo (C1-C8), alquilen (C0-C4)-O-alquilen (C0-C4)-H, SCF3, SF5, S(O)2CF3, alquilen (C0-C4)-O-arilo (C6-C12), alquilen (C0-C4)-arilo (C6-C12), NO2, en los que alquilo y alquileno no están sustituidos o están mono, di o trisustituidos con F y arilo no está sustituido o está mono, di o trisustituido con halógeno, alquilo (C1-C4) u O-alquilo (C1-C4);

Otra realización según la invención consiste en compuestos de la

fórmula I, en la que

B es C(R4) y

R4 es H.

R1 es H, halógeno, alquilo (C1-C8), alquilen (C0-C4)-O-alquilen (C0-C4)-H, SCH3, CN, en el que alquilo y alquileno no están sustituidos o están mono, bi o trisustituidos con F;

R2, R3, R4 son independientemente

H, halógeno, alquilo (C1-C8), alquilen (C0-C4)-O-alquilen (C0-C4)-H, SCH3, CN, en los que alquilo y alquileno no están sustituidos o están mono, bi o trisustituidos con F;

X es O, S, S(O), S(O)2, O-CH2, S-CH2, CH2-O, CH2-S;

uno de U y V es N, el otro es S u O;

W es un enlace, alquileno (C1-C8), alquenileno (C2-C8), alquilen (C0-C6)-cicloalquileno (C3-C6), cicloalquilen (C3-C6)-alquileno (C1-C6), en los que alquileno y alquenileno y cicloalquileno no están sustituidos o están mono, di o trisustituidos con OH y F;

Y es un enlace, O, S, S(O), S(O)2 y

R5 es H, alquilo (C1-C8), alquilen (C0-C4)-cicloalquilo (C3-C13), alquilen (C0-C4)-arilo (C6-C14), alquenilo (C2-C8), alquilen (C0-C4)-heterocicloalquilo (C3-C15), alquilen (C0-C4)-heterocicloalquenilo (C3-C15), alquilen (C0-C4)-heteroarilo (C5-C15), alquilen (C0-C4)-CO-alquilo (C1-C4), alquilen (C0-C4)-CO-alquilen (C0-C4) cicloalquilo-(C3-C13), alquilen (C0-C4)-CO-alquilen (C0-C4)-arilo (C6-C10), alquilen (C0-C4)-CO-alquilen (C0-C4)-heterocicloalquilo (C3-C15), alquilen (C0-C4)-CO-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), alquilen (C0-C4)- CO-alquilen (C0-C4)-heteroarilo (C5-C15), SO2-alquilo (C1-C4), SO2-alquilen (C0-C4)-cicloalquilo (C3-C13), SO2-alquilen (C0-C4)-arilo (C6-C10), SO2-alquilen (C0-C4)-heterocicloalquilo (C3-C15), SO2-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), SO2-alquilen (C0-C4)-heteroarilo (C5-C15), CO-O-alquilen (C0-C4)-arilo (C6-C10), CO-O-alquilo (C1-C4), CO-O-alquilen (C0-C4)-cicloalquilo (C3-C13), CO-O-alquilen (C0-C4)-heterocicloalquilo (C3-C15), CO-O-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), CO-O-alquilen (C0-C4)-heteroarilo (C5-C15), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-arilo

(C6-C10), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-cicloalquilo (C3-C13), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquilo (C3-C15), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heteroarilo (C5-C15), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-arilo (C6-C10), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-cicloalquilo (C3-C13), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquilo (C3-C15), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heteroarilo (C5-C15) en el que alquilo y alquileno no están sustituidos o están mono, di o trisustituidos con F, S-alquilo (C1-C4), SO-alquilo (C1-C4), SO2-alquilo (C1-C4), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, CO-O alquilo (C1-C4), alquilo (C1-C4) y O-alquilen (C0-C4)-H y en los que cicloalquilo, arilo y heterocicloalquilo, heterocicloalquenilo y heteroarilo no están sustituidos o están mono, di o trisustituidos con F, Cl, Br, CF3, alquilo (C1-C4) y alquilen (C0-C4)-O-alquilen (C0-C4)-H;

con la salvedad que,

si Y es S, S(O) o S(O)2, entonces

R5 no es igual SO2-alquilo (C1-C4), SO2-alquilen (C0-C4)-cicloalquilo (C3-C13), SO2-alquilen (C0-C4)-arilo (C6C10), SO2-alquilen (C0-C4)-heterocicloalquilo (C3-C15), SO2-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), SO2-alquilen (C0-C4)-heteroarilo (C5-C15), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-arilo (C6-C10), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-cicloalquilo (C3-C13), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquilo (C3-C15), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heteroarilo (C5-C15);

con la salvedad que, si Y es un enlace u O entonces

Z no es igual un enlace;

o

Y es un enlace,

con la salvedad que

R5 es CN, alquilo (C1-C8) mono, di o trisustituido con F, CO-alquilo (C1-C4), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, N(alquilen (C0-C4)-H)-CO-alquilen (C0-C4)-H, alquilen (C1-C6)-cicloalquilo (C3-C13), heterocicloalquilo (C3-C15), heterocicloalquenilo (C3-C15), heteroarilo (C5-C15);

o

Y es O,

con la salvedad que

R5 es alquilo (C1-C8) mono, di o trisustituido con F, CO-alquilo (C1-C4), CO-O-alquilen (C0-C4)-arilo (C6-C10), CO-O-alquilen (C0-C4)-cicloalquilo (C3-C13), CO-O-alquilen (C0-C4)-heterocicloalquilo (C3-C15), CO-O-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), CO-O-alquilen (C0-C4)-heteroarilo (C5-C15), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-arilo (C6-C10), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-cicloalquilo (C3-C13), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquilo (C3-C15), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-cicloalquilo (C3-C13), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-cicloalquilo (C3-C13), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heteroarilo (C5-C15), alquilen (C0-C4)-cicloalquilo (C3-C13), alquilen (C0-C4)-heterocicloalquilo (C3-C15), alquilen (C0-C4)-heterocicloalquenilo (C3-C15), alquilen (C0-C4)-heteroarilo (C5-C15), alquilen (C0-C4)-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, alquilen (C0-C4)-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-cicloalquilo (C3-C13), alquilen (C0-C4)-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-arilo (C6-C10), alquilen (C0-C4)-N(alquilen (C0-C4) -H)-alquilen (C0-C4)-heterocicloalquilo (C3-C15), alquilen (C0-C4)-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), alquilen (C0-C4)-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heteroarilo (C5-C15);

Z es un enlace, alquileno (C1-C8), alquenileno (C2-C8), alquilideno (C2-C8), alquilen (C1-C6)-O-alquileno (C1-C6);

R7, R8 se seleccionan independientemente entre el grupo que consiste en H,

halógeno, alquilo (C1-C8), alquilen (C0-C4)-O-alquilen (C0-C4)-H, SCF3, SF5, S(O)2CF3, alquilen (C0-C4)-O-arilo (C6-C12), alquilen (C0-C4)-arilo (C6-C12), NO2, en los que alquilo y alquileno no están sustituidos o están mono, di o trisustituidos con F y arilo no está sustituido o está mono, di o trisustituido con halógeno, alquilo (C1-C4) u O-alquilo (C1-C4);

Otra realización según la invención consiste en compuestos de la fórmula I, en la que

R1 es halógeno, alquilo (C1-C4), alquilen (C0-C4)-O-alquilen (C0-C2)-H, O-alquilen (C0-C2) -cicloalquilo (C3-C6), en el que alquilo y alquileno no están sustituidos o están mono, di o trisustituidos con F.

Otra realización según la invención consiste en compuestos de la fórmula I, en la que

W es alquileno (C1-C3);

Y es N(R6) y

R5 y R6, junto con el átomo de nitrógeno al que están unidos (Y = N(R6)), forman un heterocicloalquilo (C3-C7), un heterocicloalquenilo (C4-C7) o un heteroarilo (C5-C8) que puede contener adicionalmente 1 a 2 heteroátomos N, O, S y que no está sustituido o está mono o disustituido con F, CF3, alquilo (C1-C3), alquilen (C0-C3)-O-alquilen (C0-C3)-H, SO2-alquilo (C1-C3), CO-alquilo (C1-C3), CO-NH2, NH-CO-alquilo (C1-C3), fenilo, heteroarilo (C5-C6), heterocicloalquilo (C3-C7) y heterocicloalquenilo (C4-C7), en los que heterocicloalquilo, heterocicloalquenilo y heteroarilo pueden estar mono o disustituidos con un residuo oxo

Otra realización según la invención consiste en compuestos de la fórmula I, en la que

W es alquileno (C1-C3);

Y es N(R6) y

R5 es H, alquilo (C1-C4), alquilen (C0-C3)-cicloalquilo (C3-C7), alquilen (C0-C3)-fenilo, alquilen (C0-C3)-heterocicloalquilo (C3-C7), alquilen (C0-C4)-heterocicloalquenilo (C4-C7), alquilen (C0-C3)-heteroarilo (C5-C6), CO-alquilo (C0-C3), CO-O-fenilo, en el que alquilo y alquileno pueden estar mono, di o trisustituidos con F, S-alquilo (C1-C3), SO-alquilo (C1-C3), SO2-alquilo (C1-

C3), N(alquilen (C0-C3)-H)-alquilen (C0-C3)-H, CO-O alquilo (C1-C3) y O-alquilen (C0-C3)-H y en los que cicloalquilo, fenilo, heterocicloalquilo, heterocicloalquenilo y heteroarilo están mono, di o trisustituidos con F y alquilen (C0-C4)-O-alquilen (C0-C4)-H;

R6 es H, alquilo (C1-C3) o alquilen (C0-C3)-cicloalquilo (C3-C6), en el que alquilo no está sustituido o está mono, di o trisustituido con O-alquilen (C0-C4)-H; o

Y es S, S(O), S(O)2 y

R5 es alquilo (C1-C3) o alquilen (C0-C3)-cicloalquilo (C3-C6), en el que alquilo no está sustituido o está mono, di o trisustituido con F; o

Y es O y

R5 es alquilo (C1-C4) mono, di o trisustituido con F, CO-alquilo (C1-C3), alquilen (C0-C3)-cicloalquilo (C3-C6), alquilen (C0-C3)-heterocicloalquilo (C3-C7), alquilen (C0-C3)-heteroarilo (C5-C8); o

Z es –CH2-, -CH2-CH2-, -CH2-O-CH2-, -CH=CH-.

Otra realización según la invención consiste en compuestos de la fórmula I, en la que

R1 es F, Cl, alquilo (C1-C4), O-alquilo (C1-C4), en el que alquilo y alquileno no están sustituidos o están mono, bi o trisustituidos con F;

Otra realización según la invención consiste en compuestos de la fórmula I, en la que

R1 es F, Cl, CH3 u OCH3.

Otra realización según la invención consiste en compuestos de la fórmula I, en la que

V es N y U es O; o

V es N y U es S.

Otra realización según la invención consiste en compuestos de la fórmula I, en la que

X es O u O-CH2.

Otra realización según la invención consiste en compuestos de la fórmula I, en la que

X es O.

Otra realización según la invención consiste en compuestos de la fórmula I, en la que

X es OCH2.

Otra realización según la invención consiste en compuestos de la fórmula I, en la que

W es un enlace o –CH2-.

Otra realización según la invención consiste en compuestos de la fórmula I, en la que

R7 está en la posición para.

Otra realización según la invención consiste en compuestos de la fórmula I, en la que

R8 es H.

Otra realización según la invención consiste en compuestos de la fórmula I, en la que

R1 es F u OCH3.

Otra realización según la invención consiste en compuestos de la fórmula I, en la que

R1 es Cl o CH3.

Otra realización según la invención consiste en compuestos de la fórmula I, en la que

R1 es Cl.

Otra realización según la invención consiste en compuestos de la fórmula I, en la que

R1 es halógeno, alquilo (C1-C4), alquilen (C0-C4)-O-alquilen (C0-C2)-H, O-alquilen (C0-C2) -cicloalquilo (C3-C6), en el que alquilo y alquileno no están sustituidos o están mono, di o trisustituidos con F;

W es alquileno (C1-C3);

Y es N(R6) y

R5 y R6, junto con el átomo de nitrógeno al que están unidos (Y = N(R6)), forman un heterocicloalquilo (C3-C7), un heterocicloalquenilo (C4-C7) o un heteroarilo (C5-C8) que puede contener adicionalmente 1 a 2 heteroátomos N, O, S y que no está sustituido o está mono o disustituido con F, CF3, alquilo

(C1-C3), alquilen (C0-C3)-O-alquilen (C0-C3)-H, SO2-alquilo (C1-C3), CO-alquilo (C1-C3), CO-NH2, NH-CO-alquilo (C1-C3), fenilo, heteroarilo (C5-C6), heterocicloalquilo (C3-C7) y heterocicloalquenilo (C4-C7), en los que heterocicloalquilo, heterocicloalquenilo y heteroarilo pueden estar mono o disustituidos con un residuo oxo;

Otra realización según la invención consiste en compuestos de la fórmula I, en la que

R1 es halógeno, alquilo (C1-C4), alquilen (C0-C4)-O-alquilen (C0-C2)-H, O-alquilen (C0-C2) -cicloalquilo (C3-C6), en el que alquilo y alquileno no están sustituidos o están mono, di o trisustituidos con F;

W es alquileno (C1-C3);

Y es N(R6) y

R5 es H, alquilo (C1-C4), alquilen (C0-C3)-cicloalquilo (C3-C7), alquilen (C0-C3)-fenilo, alquilen (C0-C3)-heterocicloalquilo (C3-C7), alquilen (C0-C4)-heterocicloalquenilo (C4-C7), alquilen (C0-C3)-heteroarilo (C5-C6), CO-alquilo (C0-C3), CO-O-fenilo, en el que alquilo y alquileno pueden estar mono, di o trisustituidos con F, S-alquilo (C1-C3), SO-alquilo (C1-C3), SO2-alquilo (C1-C3), N(alquilen (C0-C3)-H)-alquilen (C0-C3)-H, CO-O alquilo (C1-C3) y O-alquilen (C0-C3)-H y en el que cicloalquilo, fenilo, heterocicloalquilo, heterocicloalquenilo y heteroarilo están mono, di o trisustituidos con F y alquilen (C0-C4)-O-alquilen (C0-C4)-H;

R6 es H, alquilo (C1-C3) o alquilen (C0-C3)-cicloalquilo (C3-C6), en el que alquilo no está sustituido o está mono, di o trisustituido con O-alquilen (C0-C4)-H;

Y es S, S(O), S(O)2 y

R5 es alquilo (C1-C3) o alquilen (C0-C3)-cicloalquilo (C3-C6), en el que alquilo no está sustituido o está mono, di o trisustituido con F;

Y es O y

R5 es alquilo (C1-C4) mono, di o trisustituido con F, CO-alquilo (C1-C3), alquilen (C0-C3)-cicloalquilo (C3-C6), alquilen (C0-C3)-heterocicloalquilo (C3-C7), alquilen (C0-C3)-heteroarilo (C5-C8); o

Z es –CH2-, -CH2-CH2-, -CH2-O-CH2-, -CH=CH-.

Otra realización según la invención consiste en compuestos de la fórmula I, en la que

R1 es halógeno, alquilo (C1-C4), alquilen (C0-C4)-O-alquilen (C0-C2)-H, O-alquilen (C0-C2) -cicloalquilo (C3-C6), en el que alquilo y alquileno no están sustituidos o están mono, di o trisustituidos con F;

W es alquileno (C1-C3);

Y es N(R6) y

R5 y R6, junto con el átomo de nitrógeno al que están unidos (Y = N(R6)), forman un heterocicloalquilo (C3-C7), un heterocicloalquenilo (C4-C7) o un heteroarilo (C5-C8) que puede contener adicionalmente 1 a 2 heteroátomos N, O, S y que no está sustituido o está mono o disustituido con F, CF3, alquilo (C1-C3), alquilen (C0-C3)-O-alquilen (C0-C3)-H, SO2-alquilo (C1-C3), CO-alquilo (C1-C3), CO-NH2, NH-CO-alquilo (C1-C3), fenilo, heteroarilo (C5-C6), heterocicloalquilo (C3-C7) y heterocicloalquenilo (C4-C7), en los que heterocicloalquilo, heterocicloalquenilo y heteroarilo pueden estar mono o disustituidos con un residuo oxo;

W es alquileno (C1-C3);

Y es N(R6) y

R5 es H, alquilo (C1-C4), alquilen (C0-C3)-cicloalquilo (C3-C7), alquilen (C0-C3)-fenilo, alquilen (C0-C3)-heterocicloalquilo (C3-C7), alquilen (C0-C4)-heterocicloalquenilo (C4-C7), alquilen (C0-C3)-heteroarilo (C5-C6), CO-alquilo (C0-C3), CO-O-fenilo, en el que alquilo y alquileno pueden estar mono, di o trisustituidos con F, S-alquilo (C1-C3), SO-alquilo (C1-C3), SO2-alquilo (C1-C3), N(alquilen (C0-C3)-H)-alquilen (C0-C3)-H, CO-O alquilo (C1-C3) y O-alquilen (C0-C3)-H y en los que cicloalquilo, fenilo, heterocicloalquilo, heterocicloalquenilo y heteroarilo están mono, di o trisustituidos con F y alquilen (C0-C4)-O-alquilen (C0-C4)-H;

R6 es H, alquilo (C1-C3) o alquilen (C0-C3)-cicloalquilo (C3-C6), en el que alquilo no está sustituido o está mono, di o trisustituido con O-alquilen (C0-C4)-H;

Y es S, S(O), S(O)2 y

R5 es alquilo (C1-C3) o alquilen (C0-C3)-cicloalquilo (C3-C6), en el que alquilo no está sustituido o está mono, di o trisustituido con F;

Y es O y

R5 es alquilo (C1-C4) mono, di o trisustituido con F, CO-alquilo (C1-C3), alquilen (C0-C3)-cicloalquilo (C3-C6), alquilen (C0-C3)-heterocicloalquilo (C3-C7), alquilen (C0-C3)-heteroarilo (C5-C8); o

Z es –CH2-, -CH2-CH2-, -CH2-O-CH2-, -CH=CH-.

Otra realización según la invención consiste en compuestos de la fórmula I en la que uno o más sustituyentes tienen el siguiente significado:

B es C(R4) y

R4 es H.

R1 es halógeno, alquilo (C1-C8), alquilen (C0-C4)-O-alquilen (C1-C4)-H, alquilen (C0-C2)-O-alquilen (C0-C2)-cicloalquilo (C3-C6), en el que alquilo y alquileno no están sustituidos o están mono, bi o trisustituidos con F;

R2 es H;

R3 es H, F, Br;

R4 es H;

X es O, O-CH2;

U es S, O y

V es N

o

U es N y

V es O;

W es un enlace, alquileno (C1-C4);

Y es N(R6) y

R5 se selecciona del grupo que consiste en alquilo (C1-C8), alquilen (C0-C4)-cicloalquilo (C3-C13), alquilen (C0-C4)-arilo (C6-C12), alquilen (C0-C4)-heterocicloalquilo (C3-C15), alquilen (C0-C4)-heterocicloalquenilo (C3-C15), alquilen (C0-C4)-heteroarilo (C5-C15), CO-alquilo (C0-C4), CO-O-arilo (C6-C10), en el que alquilo y alquileno pueden estar mono, di o trisustituidos con F, S-alquilo (C1-C4), SO-alquilo (C1-C4), N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, CO-O alquilo (C1-C4) y O-alquilen (C0-C4)-H y en el que cicloalquilo, arilo,

heterocicloalquilo, heterocicloalquenilo y heteroarilo están mono, di o trisustituidos con F y alquilen (C0-C4)-O-alquilen (C0-C4)-H;

Y es un enlace y

R5 es alquilo (C1-C6) mono, di o trisustituido con F;

Y es O y

R5 es alquilo (C1-C8) mono, di o trisustituido con F, CO-alquilo (C1-C4), alquilen (C0-C4)-cicloalquilo (C3-C6), alquilen (C0-C4)-heterocicloalquilo (C3-C15), alquilen (C0-C4)-heterocicloalquenilo (C3-C15), alquilen (C0-C4)-heteroarilo (C5-C15); o

Z es –CH2-, -CH2-CH2-, -CH2-O-CH2-, -CH=CH-.

R6 es H, alquilo (C1-C8) o alquilen (C0-C4)-cicloalquilo (C3-C6), en el que alquilo no está sustituido o está mono, di o trisustituido con O-alquilen (C0-C4)-H;

R5 y R6, junto con el átomo de nitrógeno al que están unidos (Y = N(R6)), pueden formar un heterocicloalquilo (C3-C8), un heterocicloalquenilo (C3-C10) o un heteroarilo (C5-C8) que puede contener adicionalmente 1 a 3 heteroátomos N, O, S y que no está sustituido o está mono, di o trisustituido con F, CF3, alquilo (C1-C4), alquilen (C0-C4)-O-alquilen (C0-C4)-H, SO2-alquilo (C1-C4), CO-alquilo (C1-C4), CO-NH2, NH-CO-alquilo (C1-C4); fenilo, heteroarilo (C5-C6), heterocicloalquilo (C3-C7) y heterocicloalquenilo (C3-C7), en los que heterocicloalquilo, heterocicloalquenilo y heteroarilo pueden estar mono o disustituidos con un residuo oxo;

Z es un enlace, alquileno (C1-C2), alquenileno (C2), alquilen (C1-C2)-O-alquileno (C1-C2);

R7 es H, O-alquilo (C1-C4), CF3;

R8 es H.,

Otra realización según la invención consiste en compuestos de la fórmula I en la que uno o más sustituyentes tienen el siguiente significado:

B es C(R4) y

R4 es H.

R1 es F, Cl, alquilo (C1-C4), alquilen (C0-C4)-O-alquilen (C1-C4)-H, alquilen (C0-C2)-O-alquilen (C0-C2)-cicloalquilo (C3-C6), en el que alquilo y alquileno no están sustituidos o están mono, bi o trisustituidos con F;

R2 es H;

R3 es H, F, Br;

R4 es H;

X es O, O-CH2;

U es S, O y

V es N

o

U es N y

V es O;

W es un enlace, alquileno (C1-C4);

Y es N(R6) y

R5 se selecciona del grupo que consiste en alquilo (C1-C8), alquilen (C0-C4)-cicloalquilo (C3-C13), alquilen (C0-C4)-arilo (C6-C12), alquilen (C0-C4)-heterocicloalquilo (C3-C15), CO-alquilo (C0-C4), CO-O-arilo (C6-C10), en el que alquilo y alquileno pueden estar mono, di o trisustituidos con S-alquilo (C1-C4), SO-alquilo (C1-C4), N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H y O-alquilen (C0-C4)-H y en el que arilo y heterocicloalquilo están mono, di o trisustituidos con F y alquilen (C0-C4)-O-alquilen (C0-C4)-H;

Y es O y

R5 es alquilo (C1-C8) mono, di o trisustituido con F, CO-alquilo (C1-C4), alquilen (C0-C4)-cicloalquilo (C3-C6); o

Z es –CH2-, -CH2-CH2-, -CH2-O-CH2-, -CH=CH-.

Y es S, S(O), S(O)2 y

R5 es alquilo (C1-C3);

R6 es H, alquilo (C1-C8) o alquilen (C0-C4)-cicloalquilo (C3-C6), en el que alquilo no está sustituido o está mono, di o trisustituido con O-alquilen (C0-C4)-H;

R5 y R6, junto con el átomo de nitrógeno al que están unidos (Y = N(R6)), pueden formar un heterocicloalquilo (C3-C8) o un heterocicloalquenilo (C3-

C10) que puede contener adicionalmente 1 a 3 heteroátomos N, O, S y que puede no estar sustituido o estar mono, di o trisustituido con F, CF3, alquilo (C1-C4), alquilen (C0-C4)-O-alquilen (C0-C4)-H, SO2-alquilo (C1-C4), CO-alquilo (C1-C4), en los que heterocicloalquilo puede estar mono o disustituido con un residuo oxo;

Z es un enlace, alquileno (C1-C2), alquenileno (C2), alquilen (C1-C2)-O-alquileno (C1-C2);

R7 es H, O-alquilo (C1-C4), CF3;

R8 es H.

Otra realización según la invención consiste en compuestos de la fórmula I en la que uno o más sustituyentes tienen el siguiente significado:

R1 es halógeno, alquilo (C1-C4), OH, O-alquilo (C1-C3), en el que alquilo no está sustituido o está mono, di o trisustituido con F;

R2 es H;

R3 es H, F;

B es C(R4) o N, y

R4 es H;

X es O;

uno de U y V es N, el otro es S u O;

W es alquileno (C1-C3);

Y es N(R6) y

R5 y R6, junto con el átomo de nitrógeno al que están unidos (Y = N(R6)), forman un heterocicloalquilo (C3-C7), un heterocicloalquenilo (C4-C7) o un heteroarilo (C5-C8) que puede contener adicionalmente 1 a 2 heteroátomos N, O, S y que no está sustituido o está mono o disustituido con F, CF3, alquilo (C1-C3), alquilen (C0-C3)-O-alquilen (C0-C3)-H, SO2-alquilo (C1-C3), CO-alquilo (C1-C3), CO-NH2, NH-CO-alquilo (C1-C3), fenilo, heteroarilo (C5-C6), heterocicloalquilo (C3-C7) y heterocicloalquenilo (C4-C7), en los que heterocicloalquilo, heterocicloalquenilo y heteroarilo pueden estar mono o disustituidos con un residuo oxo;

Y es N(R6) y

R5 es H, alquilo (C1-C4), alquilen (C0-C3)-cicloalquilo (C3-C7), alquilen (C0-C3)-fenilo, alquilen (C0-C3)-heterocicloalquilo (C3-C7), alquilen (C0-C4)-heterocicloalquenilo (C4-C7), alquilen (C0-C3)-heteroarilo (C5-C6), CO-alquilo (C0-C3), CO-O-fenilo, en el que alquilo y alquileno pueden estar mono, di o trisustituidos con F, S-alquilo (C1-C3), SO-alquilo (C1-C3), SO2-alquilo (C1-C3), N(alquilen (C0-C3)-H)-alquilen (C0-C3)-H, CO-O alquilo (C1-C3) y O-alquilen (C0-C3)-H y en los que cicloalquilo, fenilo, heterocicloalquilo, heterocicloalquenilo y heteroarilo están mono, di o trisustituidos con F y alquilen (C0-C4)-O-alquilen (C0-C4)-H;

R6 es H, alquilo (C1-C3) o alquilen (C0-C3)-cicloalquilo (C3-C6), en el que alquilo no está sustituido o está mono, di o trisustituido con O-alquilen (C0-C4)-H;

Y es S, S(O), S(O)2 y

R5 es alquilo (C1-C3) o alquilen (C0-C3)-cicloalquilo (C3-C6), en el que alquilo no está sustituido o está mono, di o trisustituido con F;

Y es O y

R5 es alquilo (C1-C4) mono, di o trisustituido con F, CO-alquilo (C1-C3), alquilen (C0-C3)-cicloalquilo (C3-C6), alquilen (C0-C3)-heterocicloalquilo (C3-C7), alquilen (C0-C3)-heteroarilo (C5-C8); o

Z es –CH2-, -CH2-CH2-, -CH2-O-CH2-, -CH=CH-.

Z es un enlace, alquileno (C1-C2), alquenileno (C2), alquilen (C1-C2)-O-alquileno (C1-C2);

R7 es H, halógeno, alquilo (C1-C3), O-alquilo (C1-C3), en el que alquilo no está sustituido o está mono, di o trisustituido con F;

R8 es H.

Otra realización según la invención consiste en compuestos de la fórmula I en la que uno o más sustituyentes tienen el siguiente significado:

R1 es F, OH, OCH3, OCHF2, OCH2CF3;

R2 es H;

R3 es H, F;

B es C(R4) o N, y

R4 es H;

X es O;

uno de U y V es N, el otro es S u O;

W es CH2, CH2CH2CH2;

Y es N(R6) y

R5 y R6, junto con el átomo de nitrógeno al que están unidos (Y = N(R6)), forman piperidina, pirrolidina, azetidina, azepina, morfolina, tiomorfolina, tiomorfolina-S-óxido, tiomorfolina-S-dióxido, piperazina, piperazinona, isoindolina, no sustituida o mono o disustituida con F, CF3, alquilo (C1-C3), O-alquilo (C1-C3), OH, CH2OH, SO2CH3, COCH3, fenilo;

Y es S, S(O), S(O)2 y

R5 es CH3;

Z es un enlace;

R7 es CF3;

R8 es H.

Otra realización según la invención consiste en compuestos de la fórmula I en la que uno o más sustituyentes tienen el siguiente significado:

R1 es H, F, Cl;

R2 es H;

R3 es H;

B es C(R4) o N, y

R4 es H;

X es O;

U es S, O y

V es N;

W es CH2;

Y es un enlace u O;

Z es un enlace;

R5 es alquilo (C1-C6) mono, di o trisustituido con F;

R7 está en la posición para y es alquilo (C1-C4), alquilen (C0-C4)-O-alquilen (C0-C4)-H, SF5, alquilen (C0-C4)-O-fenilo, en el que alquilo, alquileno y fenilo están mono, di o trisustituidos con F;

R8 es H.

Los compuestos más preferidos son:

3-{2-Metoxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Cloro-4-[4-morfolin-4-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Metoxi-4-[4-morfolin-4-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{4-[4-(4,4-Difluoro-piperidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Metoxi-4-[4-(4-metil-piperazin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Metoxi-4-[4-pirrolidin-1-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{4-[4-(4-Fluoro-piperidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{4-[4-Dietilaminometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Metoxi-4-[2-(4-trifluorometil-fenil)-4-(3-trifluorometil-pirrolidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{4-[4-{[Etil-(2-metoxi-etil)-amino]-metil}-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{4-[4-[([1,4]Dioxan-2-ilmetil-metil-amino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Metoxi-4-[4-(4-metoxi-piperidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{4-[4-(4-Etil-piperazin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona

Éster metílico del ácido ciclopropil-[5-[3-metoxi-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-ilmetil]-carbámico

3-{4-[4-Ciclopropilaminometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{4-[4-(3-Azetidin-1-il-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Fluoro-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona

3-{4-[4-(4,4-Difluoro-piperidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-fluoro-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Fluoro-4-[4-{[(2-hidroxi-etil)-metil-amino]-metil}-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Fluoro-4-[4-(4-metil-piperazin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Fluoro-4-[4-morfolin-4-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{4-[4-(1,3-Dihidro-isoindol-2-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-fluoro-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Fluoro-4-[4-[(4-fluoro-bencilamino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Fluoro-4-[4-(2-hidroximetil-pirrolidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Fluoro-4-[4-{[(furan-2-ilmetil)-amino]-metil}-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Fluoro-4-[4-[(3-metilsulfanil-propilamino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

4-[5-[3-Fluoro-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-ilmetil]-piperazin-2-ona

3-{2-Fluoro-4-[4-[(4-metoxi-bencilamino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{4-[4-[(1R,4R)-1-(2,5-Diaza-biciclo[2.2.1]hept-2-il)metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-fluoro-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Fluoro-4-[4-(3-hidroximetil-piperidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{5-Bromo-2-metoxi-4-[4-piperidin-1-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{5-Fluoro-2-metoxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

Éster 5-[3-fluoro-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-ilmetílico del ácido acético

Éster 5-[3-metoxi-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-ilmetílico del ácido acético

3-{2-Fluoro-4-[4-pirrolidin-1-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-(2-Metoxi-4-{2-(4-trifluorometil-fenil)-4-[(3,3,3-trifluoro-propilamino)-metil]-tiazol-5-ilmetoxi}-fenil)-4H-[1,2,4]oxadiazol-5-ona

3-{4-[4-((1R,2R,4S)-Biciclo[2.2.1]hept-2-ilaminometil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Metoxi-4-[4-({[(S)-1-(tetrahidro-furan-2-il)metil]-amino}-metil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Metoxi-4-[4-({[(R)-1-(tetrahidro-furan-2-il)metil]-amino}-metil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{4-[4-[(Ciclopropilmetil-amino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{4-[4-Ciclobutilaminometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{4-[4-(4-Metansulfonil-piperazin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{4-[4-{[Bis-(2-hidroxi-etil)-amino]-metil}-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{4-[4-[(2-Metansulfinil-etilamino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Metoxi-4-[4-tiomorfolin-4-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{4-[4-(1,1-Dioxo-1λ^6-tiomorfolin-4-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Metil-4-[4-propilaminometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{4-[4-[(2-Metoxi-etilamino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Metil-4-[4-[[2-(1-metil-pirrolidin-2-il)-etilamino]-metil}-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Metil-4-[4-[(2-pirrolidin-1-il-etilamino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Metil-4-[4-[(2-morfolin-4-il-etilamino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Metil-4-[4-[(2-piperidin-1-il-etilamino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{4-[4-[(2-Dimetilamino-etilamino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-(2-Cloro-4-{4-metil-2-[2-(4-trifluorometil-fenil)-etil]-oxazol-5-ilmetoxi}-fenil)-4H-[1,2,4]oxadiazol-5-ona

3-(2-Cloro-4-{4-metoximetil-2-[2-(4-metoxi-fenil)-vinil]-oxazol-5-ilmetoxi}-fenil)-4H-[1,2,4]oxadiazol-5-ona

3-[4-(2-Benciloximetil-4-metil-oxazol-5-ilmetoxi)-2-cloro-fenil]-4H-[1,2,4]oxadiazol-5-ona

3-{2-Cloro-4-[2-(4-metoxi-bencil)-4-metil-oxazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-(2-Cloro-4-{4-metoximetil-2-[2-(4-trifluorometil-fenil)-vinil]-tiazol-5-ilmetoxi}-fenil)-4H-[1,2,4]oxadiazol-5-ona

3-{2-Cloro-4-[4-(2,2,2-trifluoro-etoximetil)-2-(4-trifluorometil-fenil)-oxazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{4-[4-{[Etil-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{4-[4-Dietilaminometil-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{4-[2-(4-Metoxi-fenil)-4-pirrolidin-1-ilmetil-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{4-[2-(4-Metoxi-fenil)-4-morfolin-4-ilmetil-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{4-[4-{[Bis-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{4-[2-(4-Metoxi-fenil)-4-piperidin-1-ilmetil-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{4-[2-(4-Metoxi-fenil)-5-piperidin-1-ilmetil-oxazol-4-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{4-[2-(4-Metoxi-fenil)-5-pirrolidin-1-ilmetil-oxazol-4-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{4-[2-(4-Metoxi-fenil)-5-morfolin-4-ilmetil-oxazol-4-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{4-[5-{[Bis-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-4-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Cloro-4-[2-(4-metoxi-fenil)-4-morfolin-4-ilmetil-oxazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Cloro-4-[4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{4-[4-{[Bis-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-cloro-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Cloro-4-[4-piperidin-1-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{4-[4-(4-Acetil-piperazin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-cloro-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Cloro-4-[4-(4-metil-piperazin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Cloro-4-[4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{4-[4-{[Bis-(2-metoxi-etil)-amino]-metil}-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-cloro-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Cloro-4-[4-pirrolidin-1-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Cloro-4-[4-dietilaminometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Cloro-4-[4-(4,4-difluoro-piperidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Cloro-4-[4-(4-fenil-piperazin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Cloro-4-[4-(2-morfolin-4-il-etoximetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Cloro-4-[4-(2-ciclohexil-etoximetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Cloro-4-[4-difluorometil-2-(4-metoxi-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-{4-[4-(4-Hidroxi-piperidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-1,2,4-oxadiazol-5-ona

3-{4-[4-(1,4-Dioxa-8-aza-espiro[4.5]dec-8-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-1,2,4-oxadiazol-5-ona

3-{4-[4-(4,4-Dihidroxi-piperidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-1,2,4-oxadiazol-5-ona

3-{2-Metoxi-4-[4-(1-oxo-1λ^4-tiomorfolin-4-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona

3-{2-Metoxi-4-[4-metilsulfanilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona

3-{4-[4-Metansulfinilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-1,2,4-oxadiazol-5-ona

3-{4-[4-Metansulfonilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-1,2,4-oxadiazol-5-ona

3-{4-[4-Aminometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-fluoro-fenil}-4H-1,2,4-oxadiazol-5-ona

N-[5-[3-Fluoro-4-(5-oxo-4,5-dihidro-1,2,4-oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-ilmetil]-acetamida

3-{2-Difluorometoxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona

3-{2-Difluorometoxi-5-fluoro-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona

3-{2-Isopropoxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona

3-{2-Ciclopropilmetoxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona

3-{2-(2,2,2-Trifluoro-etoxi)-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona

3-{5-Fluoro-2-(2,2,2-trifluoro-etoxi)-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona

3-{6-[4-Butil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metil-piridin-3-il}-4H-[1,2,4]oxadiazol-5-ona

3-{2-Metoxi-4-[4-(3-metilsulfanil-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona

3-{4-[4-(3-Metansulfonil-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-1,2,4-oxadiazol-5-ona

3-{2-Metoxi-4-[4-(3-tiomorfolin-4-il-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona

3-{2-Metoxi-4-[4-(3-perhidro-azepin-1-il-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona

3-{2-Metoxi-4-[4-(3-morfolin-4-il-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona

3-{2-Metoxi-4-[4-[3-(4-metil-piperazin-1-il)-propil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona

3-{2-Metoxi-4-[4-(3-piperidin-1-il-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona

3-{2-Metoxi-4-[4-(3-pirrolidin-1-il-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona

3-{2-Fluoro-4-[4-(3-morfolin-4-il-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona

3-{2-Fluoro-4-[4-(3-pirrolidin-1-il-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona

3-{4-[4-[3-(Bencil-metil-amino)-propil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona

3-(2-Metoxi-4-{2-(4-trifluorometil-fenil)-4-[3-(4-trifluorometil-piperidin-1-il)-propil]-tiazol-5-ilmetoxi}-fenil)-4H-[1,2,4]oxadiazol-5-ona.

Esta invención también abarca todas las combinaciones de aspectos preferidos de la invención descritas en esta memoria.

Tal como se usa en la presente memoria, el término alquilo se ha de entender en el sentido más amplio que significa residuos hidrocarbonados saturados que pueden ser lineales, es decir, de cadena recta o ramificada. Si no se define lo contrario, el alquilo tiene 1 a 8 átomos de carbono. Los ejemplos de "alquilo (C1-C8)" son residuos alquilo que contienen 1, 2, 3, 4, 5, 6, 7 u 8 átomos de carbono que son metilo, etilo, propilo, butilo, pentilo, hexilo, heptilo u octilo, los n-isómeros de todos estos residuos, isopropilo, isobutilo, 1-metilbutilo, isopentilo, neopentilo, 2,2-dimetilbutilo, 2-metilpentilo, 3-metilpentilo, isohexilo, sec-butilo, terc-butilo o terc-pentilo. La expresión "alquilo (C0-C8)" es un residuo hidrocarbonado que contiene 1, 2, 3, 4, 5, 6, 7 u 8 átomos de carbono, en los que la expresión „alquilo C0" es un enlace covalente. Todos estos enunciados se aplican también al término alquileno.

Tal como se usa en la presente memoria, el término alquenilo se ha de entender en el sentido más amplio que significa residuos hidrocarbonados, que tiene 1 a 4 dobles enlaces y pueden ser lineales, es decir de cadena recta o ramificada. Si no se define lo contrario, el alquenilo tiene 2 a 8 átomos de carbono. Los ejemplos de „alquenilo (C2-C8)" son residuos alquenilo que contienen 2, 3, 4, 5, 6, 7 u 8 átomos de carbono que son, por ejemplo, vinilo, 1-propenilo, 2-propenilo (= alilo), 2-butenilo, 3-butenilo, 2-metil-2-butenilo, 3-metil-2-butenilo, 5-hexenilo o 1,3-pentadienilo. Todos estos enunciados se aplican también al término alquenileno.

Tal como se usa en la presente memoria, el término alquinilo se ha de entender en el sentido más amplio que significa residuos hidrocarbonados, que tiene 1 a 4 triples enlaces y pueden ser lineales, es decir de cadena recta o ramificada. Si no se define lo contrario, el alquinilo tiene 2 a 8 átomos de carbono. Los ejemplos de „alquinilo (C2-C8)" son residuos alquinilo que contienen 2, 3, 4, 5, 6, 7 u 8 átomos de carbono que son, por ejemplo, etinilo,

1-propinilo, 2-propinilo (= propargilo) o 2-butinilo. Todos estos enunciados se aplican también al término alquilideno.

Todos estos enunciados se aplican también si aparece un grupo alquilo como sustituyente en otro residuo, por ejemplo en un residuo alquiloxi, un residuo alquiloxicarbonilo o un residuo arilalquilo.

Si no se define lo contrario, alquilo, alquileno, alquenilo, alquenileno, alquinilo y alquinileno no están sustituidos o están mono, di o trisustituidos independientemente unos de otros con grupos adecuados tales como, por ejemplo: F, Cl, Br, I, CF3, NO2, CN, COOH, CO-O-alquilen (C0-C4)-arilo (C6-C10), CO-O-alquilo (C1-C4), CO-O-alquilen (C0-C4)-cicloalquilo (C3-C13), CO-O-alquilen (C0-C4)-heterociclo (C3-C15), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-arilo (C6-C10), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)- cicloalquilo (C3-C13), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterociclo (C3-C15), alquilen (C0-C4)-cicloalquilo (C3-C6), alquilen (C0-C4)-arilo (C6-C10), alquilen (C0-C4)-heterociclo (C3-C15), alquenilo (C2-C6), alquinilo (C2-C6), O-alquilo (C0-C6), O-alquilen (C0-C4)-arilo (C6-C10), O-alquilen (C0-C4)-cicloalquilo (C3-C12), O-alquilen (C0-C4)-heterociclo (C3-C15), O-CO-O-alquilen (C0-C4)-arilo (C6-C10), O-CO-O-alquilo (C1-C4), O-CO-O-alquilen (C0-C4)-cicloalquilo (C3-C13), O-CO-O-alquilen (C0-C4)-heterociclo (C3-C15), S-alquilo (C1-C4), S-alquilen (C0-C4)-cicloalquilo (C3-C13), S-alquilen (C0-C4)-arilo (C6-C10), S-alquilen (C0-C4)-heterociclo (C3-C15), SO-alquilo (C1-C4), SO-alquilen (C0-C4)-cicloalquilo (C3-C13), SO-alquilen (C0-C4)-arilo (C6-C10), SO-alquilen (C0-C4)-heterociclo (C3-C15), SO2-alquilo (C1-C4), SO2-alquilen (C0-C4)-cicloalquilo (C3-C13), SO2-alquilen (C0-C4)-arilo (C6-C10), SO2-alquilen (C0-C4)-heterociclo (C3-C15), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-arilo (C6-C10), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-cicloalquilo (C3-C13), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterociclo (C3-C15) en los que el anillo arilo o el anillo heterocíclico no está sustituido o está mono o disustituido con F, Cl, Br, OH, CF3, NO2, CN, OCF3, O-alquilo (C1-C6), alquilo (C1-C6), N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H;

N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H)-cicloalquilo (C1-C6), N(alquien (C0-C4)-H)-alquilen (C0-C4)-arilo (C6-C12), N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterociclo (C3-C15), N(alquilen (C0-C4)-H)-CO-alquilen (C0-C4)-arilo (C6-C12), N(alquilen (C0-C4)-H)-CO-alquilo (C0-C4), N(alquilen (C0-C4)-H)-CO-alquilen (C0-C4)-cicloalquilo (C3-C13), N(alquilen (C0-C4)-H)-CO-alquilen (C0-C4)-heterociclo (C3-C15), N(alquilen (C0-C4)-H)-CO-O-alquilen (C0-C4)-arilo (C6-C12), N(alquilen (C0-C4)-H)-CO-O-alquilo (C0-C4), N(alquilen (C0-C4)-H)-CO-O-alquilen (C0-C4)-cicloalquilo (C3-C13), N(alquilen (C0-C4)-H)-CO-O-alquilen (C0-C4)-heterociclo (C3-C15), N(alquilen (C0-C4)-H)-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-arilo (C6-C12), N(alquilen (C0-C4)-H)-CO-N(alquilen (C0-C4)-H)-alquilo (C0-C4), N(alquilen (C0-C4)-H)-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-cicloalquilo (C3-C13), N(alquilen (C0-C4)-H)-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterociclo (C3-C15), en los que el anillo arilo o el anillo heterocíclico no está sustituido o está mono o disustituido con F, Cl, Br, I, OH, CF3, NO2, CN, OCF3, O-alquilo (C1-C6), alquilo (C1-C6), N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, SO2-CH3, COOH, COO-alquilo (C1-C6), SF5, CONH2.

Por el término cicloalquilo se entenderá un ciclo hidrocarbonado saturado que contiene entre 3 y 13 átomos de carbono en un anillo mono o bicíclico condensado, puente o espirocíclico. Los ejemplos de residuos alquilo cíclicos cicloalquilo (C3-C13) son residuos cicloalquilo que contienen 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 ó 13 átomos de carbono de anillo como ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo, ciclononilo, ciclodecilo, cicloundecilo o ciclododecilo. El término cicloalquilo también incluye grupos biciclicos en los que cualquiera de los anillo cicloalquilo anteriormente mencionados está condensado a un anillo benceno, por ejemplo indano y 1,2,3,4-tetrahidronaftaleno.

Por el término cicloalquenilo se ha de entender un ciclo hidrocarbonado insaturado que contiene entre 3 y 8 átomos de carbono en un anillo mono o biciclico, condensado o en puente, en el que uno, dos o tres dobles enlaces no están ubicados dentro de un grupo alquilo ciclico de modo tal que resulte un

sistema aromático. Los ejemplos de grupos cicloalquenilo son ciclopentenilo o ciclohexenilo, que pueden estar unidos vía cualquier átomo de carbono. El término cicloalquenilo también incluye grupos bicíclicos en los que cualquiera de los anillos cicloalquenilo anteriormente mencionados está condensado a un anillo benceno, por ejemplo 1,2-dihidronaftaleno, 1,4-dihidronaftaleno y 1H-indeno.

Si no se define lo contrario, cicloalquilo o cicloalquenilo no están sustituidos o están mono, di o trisustituidos independientemente unos de otros con grupos adecuados tales como, por ejemplo: F, Cl, Br, I, CF3, NO2, CN, COOH, alquilen CO-O-(C0-C4)-arilo (C6-C10), CO-O-alquilo (C1-C4), CO-O-alquilen (C0-C4)-cicloalquilo (C3-C13), CO-O-alquilen (C0-C4)-heterociclo (C3-C15), CO-N(alquilen (C0-C4)-H)-alquilen (C1-C6)-H, CO-N(alquilen (C0-C4)-H)-cicloalquilo (C1-C6), CON(alquilen (C0-C4)-H)-alquilen (C0-C4)-arilo (C6-C12), alquilen (C0-C4)-cicloalquilo (C3-C6), alquilo (C3-C6), alquenilo (C2-C6), alquinilo (C2-C6), alquilen (C0-C4)-arilo (C6-C10), alquilen (C0-C4)-heterociclo (C3-C15), O-alquilo (C0-C6), alquilen (C0-C4)-O-alquilo (C0-C4), alquilen (C0-C4)-O-alquilen (C0-C4)-cicloalquilo (C3-C13), alquilen (C0-C4)-O-alquilen (C0-C4)-arilo (C6-C10), alquilen (C0-C4)-O-alquilen (C0-C4)-heterociclo (C3-C15), O-CO-O-alquilen (C0-C4)-arilo (C6-C10), O-CO-O-alquilo (C1-C4), O-CO-O-alquilen (C0-C4)-cicloalquilo (C3-C13), O-CO-O-alquilen (C0-C4)-heterociclo (C3-C15), O-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-arilo (C6-C10), O-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, O-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)- cicloalquilo (C3-C13), O-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterociclo (C3-C15), S-alquilo (C1-C4), S-alquilen (C0-C4)-cicloalquilo (C3-C13), S-alquilen (C0-C4)-arilo (C6-C10), S-alquilen (C0-C4)-heterociclo (C3-C15), SO-alquilo (C1-C4), SO-alquilen (C0-C4)-cicloalquilo (C3-C13), SO-alquilen (C0-C4)-arilo (C6-C10), SO-alquilen (C0-C4)-heterociclo (C3-C15), SO2-alquilo (C1-C4), SO2-alquilen (C0-C4)-cicloalquilo (C3-C13), SO2-alquilen (C0-C4)-arilo (C6-C10), SO2-alquilen (C0-C4)-heterociclo (C3-C15), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-arilo (C6-C10), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-cicloalquilo (C3-C13), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterociclo

(C3-C15), en los que el anillo arilo o el anillo heterocíclico no está sustituido o está mono o disustituido con F, Cl, Br, OH, CF3, NO2, CN, OCF3, O-alquilo (C1-C6), alquilo (C1-C6), N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H; N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H)-cicloalquilo (C1-C6), N(alquilen (C0-C4)-H)-alquilen (C0-C4)-arilo (C6-C12), N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterociclo (C3-C15), N(alquilen (C0-C4)-H)-CO-alquilen (C0-C4)-arilo (C6-C12), N(alquilen (C0-C4)-H)-CO-alquilo (C0-C4), N(alquilen (C0-C4)-H)-CO-alquilen (C0-C4)-cicloalquilo (C3-C13), N(alquilen (C0-C4)-H)-CO-alquilen (C0-C4)-heterociclo (C3-C15), N(alquilen (C0-C4)-H)-CO-O-alquilen (C0-C4)-arilo (C6-C12), N(alquilen (C0-C4)-H)-CO-O-alquilo (C0-C4), N(alquilen (C0-C4)-H)-CO-O-alquilen (C0-C4)-cicloalquilo (C3-C13), N(alquilen (C0-C4)-H)-CO-O-alquilen (C0-C4)-heterociclo (C3-C15), N(alquilen (C0-C4)-H)-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-arilo (C6-C12), N(alquilen (C0-C4)-H)-CO-N(alquilen (C0-C4)-H)-alquilo (C0-C4), N(alquilen (C0-C4)-H)-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-cicloalquilo (C3-C13), N(alquilen (C0-C4)-H)-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterociclo (C3-C15), en los que el anillo heterocíclico o arilo no está sustituido o está mono o disustituido con F, Cl, Br, I, OH, CF3, NO2, CN, OCF3, O-alquilo (C1-C6), alquilo (C1-C6), N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, SO2-CH3, COOH, COO-alquilo (C1-C6), SF5, CONH2.

Por el término "arilo" se entiende un anillo hidrocarbonado aromático que contiene entre 6 y 14 átomos de carbono en un anillo mono o bicíclico. Los ejemplos de anillos arilo (C6-C14) son fenilo, naftilo, por ejemplo, 1-naftilo y 2-naftilo, bifenililo, por ejemplo 2-bifenililo, 3-bifenililo y 4-bifenililo, antrilo o fluorenilo. Los anillos bifenililo, anillo naftilo y, en particular, anillo fenilo son otras realizaciones del anillo arilo.

Por el término heterociclo se entiende anillos hidrocarbonados saturados (heterocicloalquilo), parcialmente insaturados (heterocicloalquenilo) o insaturados (heteroarilo) que contienen entre 3 y 15 átomos de carbono en un anillo mono o bicíclico, condensado, en puente o espiro en donde 1 a 5 átomos de carbono de los 3 a 15 átomos de carbono de anillo se reemplazan con

heteroátomos tales como nitrógeno, oxígeno o azufre en los que además los heteroátomos pueden ser oxidados, por ejemplo N=O, S=O, SO2. Los ejemplos de heterociclos son acridinilo, azaindol (1H-pirrolopiridinilo), azabencimidazolilo, azaespirodecanilo, azepinilo, azetidinilo, aziridinilo, bencimidazolilo, benzofuranilo, dihidrobenzofuranilo, benzotiofuranilo, benzotiofenilo, benzoxazolilo, benztiazolilo, benztriazolilo, benztetrazolilo, bencisoxazolilo, benzisotiazolilo, carbazolilo, 4aH-carbazolilo, carbolinilo, cromanilo, cromenilo, cinolinilo, decahidroquinolinilo, 4,5-dihidrooxazolinilo, dioxazolilo, dioxazinilo, 1,3-dioxolanilo, 1,3-dioxolenilo, 3,3-dioxo[1,3,4]oxatiazinilo, 6H-1,5,2-ditiazinilo, dihidrofuro[2,3-b]-tetrahidrofuranilo, furanilo, furazanilo, imidazolidinilo, imidazolinilo, imidazolilo, 1H-indazolilo, indolinilo, indolizinilo, indolilo, 3H-indolilo, isobenzofuranilo, isocromanilo, isoindazolilo, isoindolinilo, isoindolilo, isoquinolinilo (bencimidazolilo), isotiazolilo, isotiazolidinilo, isotiazolinilo, isoxazolilo, isoxazolinilo, isoxazolidinilo, 2-isoxazolinilo, cetopiperazinilo, morfolinilo, naftiridinilo, octahidroisoquinolinilo, oxadiazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,2,5-oxadiazolilo, 1,3,4-oxadiazolilo, 1,2-oxa-tiepanilo, 1,2-oxatiolanilo, 1,4-oxazepanilo, 1,4-oxazepinilo, 1,2-oxazinilo, 1,3-oxazinilo, 1,4-oxazinilo, oxazolidinilo, oxazolinilo, oxazolilo, oxetanilo, oxocanilo, fenantridinilo, fenantrolinilo, fenazinilo, fenotiazinilo, fenoxatiinilo, fenoxazinilo, ftalazinilo, piperazinilo, piperidinilo, pteridinilo, purinilo, piranilo, pirazinilo, pirazolidinilo, pirazolinilo, pirazolilo, piridazinilo, piridooxazolilo, piridoimidazolilo, piridotiazolilo, piridinilo, piridilo, pirimidinilo, pirrolidinilo, pirrolidinonilo, pirrolinilo, 2H-pirrolilo, pirrolilo, quinazolinilo, quinolinilo, 4H-quinolizinilo, quinoxalinilo, quinuclidinilo, tetrahidrofuranilo, tetrahidroisoquinolinilo, tetrahidroquinolinilo, tetrahidrofuranilo, tetrahidropiranilo, tetrahidropiridinilo, tetrahidrotiofenilo, tetrazinilo, tetrazolilo, 6H-1,2,5-tiadiazinilo, 1,2,3-tiadiazolilo, 1,2,4-tiadiazolilo, 1,2,5-tiadiazolilo, 1,3,4-tiadiazolilo, tiantrenilo, 1,2-tiazinilo, 1,3-tiazinilo, 1,4-tiazinilo, 1,3-tiazolilo, tiazolilo, tiazolidinilo, tiazolinilo, tienilo, tietanilo, tienotiazolilo, tienooxazolilo, tienoimidazolilo, tiomorfolinilo, tiofenolilo, tiofenilo, tiopiranilo, 1,2,3-triazinilo, 1,2,4-triazinilo, 1,3,5-triazinilo, 1,2,3-triazolilo, 1,2,3-triazolilo, 1,2,4-triazolilo, 1,2,5-triazolilo, 1,3,4-triazolilo y xantenilo. Los anillos heterocíclicos no están sustituidos o están mono, di o trisustituidos con grupos

adecuados tales como, por ejemplo: F, Cl, Br, I, CF3, NO2, CN, COOH, CO-O-alquilen (C0-C4)-arilo (C6-C10), CO-O-alquilo (C1-C4), CO-O-alquilen (C0-C4)-cicloalquilo (C3-C13), CO-O-alquilen (C0-C4)-heterociclo (C3-C15), CO-N(alquilen (C0-C4)-H)-alquilen (C1-C6)-H, CO-N((alquilen C0-C4)-H)-cicloalquilo (C1-C6), CON(alquilen (C0-C4)-H)-alquilen (C0-C4)-arilo (C6-C12), alquilen (C0-C4)-cicloalquilo (C3-C6), alquilo (C3-C6), alquenilo (C2-C6), alquinilo (C2-C6), alquilen (C0-C4)-arilo (C6-C10), alquilen (C0-C4)-heterociclo (C3-C15), O-alquilo (C0-C6), alquilen (C0-C4)-O-alquilo (C0-C4), alquilen (C0-C4)-O-alquilen (C0-C4)-cicloalquilo (C3-C13), alquilen (C0-C4)-O-alquilen (C0-C4)-arilo (C6-C10), alquilen (C0-C4)-O-alquilen (C0-C4)-heterociclo (C3-C15), O-CO-O-alquilen (C0-C4)-arilo (C6-C10), O-CO-O-alquilo (C1-C4), O-CO-O-alquilen (C0-C4)-cicloalquilo (C3-C13), O-CO-O-alquilen (C0-C4)-heterociclo (C3-C15), O-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-arilo (C6-C10), O-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, O-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-cicloalquilo (C3-C13), O-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterociclo (C3-C15), S-alquilo (C1-C4), S-alquilen (C0-C4)-cicloalquilo (C3-C13), S-alquilen (C0-C4)-arilo (C6-C10), S-alquilen (C0-C4)-heterociclo (C3-C15), SO-alquilo (C1-C4), SO-alquilen (C0-C4)-cicloalquilo (C3-C13), SO-alquilen (C0-C4)-arilo (C6-C10), SO-alquilen (C0-C4)-heterociclo (C3-C15), SO2-alquilo (C1-C4), SO2-alquilen (C0-C4)-cicloalquilo (C3-C13), SO2-alquilen (C0-C4)-arilo (C6-C10), SO2-alquilen (C0-C4)-heterociclo (C3-C15), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-arilo (C6-C10), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-cicloalquilo (C3-C13), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterociclo (C3-C15), en los que el anillo arilo o el anillo heterocíclico no está sustituido o está mono o disustituido con F, Cl, Br, OH, CF3, NO2, CN, OCF3, O-alquilo (C1-C6), alquilo (C1-C6), N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H; N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H)-cicloalquilo (C1-C6), N(alquilen (C0-C4)-H)-alquilen (C0-C4)-arilo (C6-C12), N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterociclo (C3-C15), N(alquilen (C0-C4)-H)-CO-alquilen (C0-C4)-arilo (C6-C12), N(alquilen (C0-C4)-H)-CO-alquilo (C0-C4), N(alquilen (C0-C4)-H)-CO-alquilen (C0-C4)-cicloalquilo (C3-

C13), N(alquilen (C0-C4)-H)-CO-alquilen (C0-C4)-heterociclo (C3-C15), N(alquilen (C0-C4)-H)-CO-O-alquilen (C0-C4)-arilo (C6-C12), N(alquilen (C0-C4)-H)-CO-O-alquilo (C0-C4), N(alquilen (C0-C4)-H)-CO-O-alquilen (C0-C4)-cicloalquilo (C3-C13), N(alquilen (C0-C4)-H)-CO-O-alquilen (C0-C4)-heterociclo (C3-C15), N(alquilen (C0-C4)-H)-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-arilo (C6-C12), N(alquilen (C0-C4)-H)-CO-N(alquilen (C0-C4)-H)-alquilo (C0-C4), N(alquilen (C0-C4)-H)-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-cicloalquilo (C3-C13), N(alquilen (C0-C4)-H)-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterociclo (C3-C15), en los que el anillo heterociclico o arilo no está sustituido o está mono o disustituido con F, Cl, Br, I, OH, CF3, NO2, CN, OCF3, O-alquilo (C1-C6), alquilo (C1-C6), N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H,SO2-CH3, COOH, COO-alquilo (C1-C6), SF5, CONH2.

La expresión "R5 y R6, junto con el átomo de nitrógeno al que están unidos (Y = N(R6)), pueden formar un heterociclo (C3-C9) que por ejemplo puede contener adicionalmente 1 a 3 heteroátomos" se refiere a estructuras de heterociclos que pueden derivar de compuestos tales como por ejemplo pirrolidina, morfolina, tiomorfolina, piperidina, piperazina, azetidina, 2,3-dihidro-1H-isoindol, piperazin-2-ona, azetidina, isoindolina, 2,5-diazabiciclo[2.2.1]heptano, 1-óxido de tiomorfolina, 1,1-dióxido de tiomorfolina, piperidin-4-ona, piperidin-3-ona, homopiperidina, homopiperazina, homomorfolina, 2,3,6,7-tetrahidro-(1H)-1,4-diazepin-5(4H)-ona, 4-oxazolidina, azetidin-3-ona, tiazolidina, 1-óxido de tiazolidina, 1,1-dióxido de tiazolidina, 4-imidazolidinona, 5,6,7,8-tetrahidro-[1,2,4]triazolo[4,3-a]pirazina, 1,4-diazabiciclo[4.3.0]nonano, 2-aza-5-oxabiciclo[2.2.1]heptano, 2-oxa-5-azabiciclo[2.2.1]heptano, diazabiciclo[4.4.0]decano, 4,5,6,7-tetrahidrotieno[3,2-c]piridina, 4,5,6,7-tetrahidro-1H-imidazol[4,5-c]-piridina, 4,5,6,7-tetrahidro-1H-pirazolo[4,3-c]piridina, 3,8-diaza-biciclo[3.2.1]octano, octahidro-pirrolo[3,4-c]pirrol, 2,5-diazabiciclo[2.2.2]octano, 4-espiro-[3-(N-metil-2-pirrolidinona)]-piperidina, 2,8-diaza-espiro[5.5]undecano, 2,7-diaza-espiro[4.4]nonano, 3,9-diaza-espiro[5.5]undecano, 2,8-diaza-espiro[4.5]decano, 2,7-diaza-espiro[3.5]nonano, 2,9-diaza-espiro[5.5]undecano,

2,7-diaza-espiro[4.5]decano, 1-oxa-4,9-diaza-espiro[5.5]undecano, 1-oxa-4,8-diaza-espiro[5.5]undecano.

La expresión "residuo oxo" u "=O" se refiere a residuos tales como carbonilo (-CO-), nitroso (-N=O), sulfinilo (-SO-) o sulfonilo ($-SO_2-$).

Halógeno es flúor, cloro, bromo o yodo.

Los átomos de carbono ópticamente activos presentes en los compuestos de la fórmula I pueden, independientemente unos de otros, tener configuración R o configuración S. Los compuestos de fórmula I pueden estar presentes en forma de enantiómeros puros o diastereoisómeros puros o en forma de mezclas de enantiómeros y/o diastereoisómeros, por ejemplo, en forma de racematos. La presente invención se refiere a enantiómeros puros y a mezclas de enantiómeros, así como a diastereoisómeros puros y a mezclas de diastereoisómeros. La invención comprende mezclas de dos o más de dos estereoisómeros de la fórmula I y comprende todas las relaciones de los estereoisómeros en las mezclas. En el caso en el que los compuestos de fórmula I puedan estar presentes en forma de isómeros E o isómeros Z (o isómeros cis o isómeros trans) la invención se refiere tanto a isómeros E puros como a isómeros Z puros como a mezclas E/Z en todas las proporciones. La invención comprende también todas las formas tautoméricas de los compuestos de la fórmula I.

Los diaestereómeros, que incluyen isómeros E/Z, se pueden separar en isómeros individuales, por ejemplo, por cromatografía. Los racematos pueden separarse en los dos enantiómeros por los métodos habituales, por ejemplo por cromatografía en fases quirales o por resolución, por ejemplo, por cristalización de sales diastereoméricas obtenidas con ácidos o bases ópticamente activos. Los compuestos estereoquímicamente uniformes de la fórmula I también se pueden obtener empleando materiales de partida estereoquímicamente uniformes o usando reacciones estereoselectivas.

Los compuestos de la fórmula I pueden existir en forma de sus racematos, mezclas racémicas, enantiómeros puros, diastereoisómeros y mezclas de diastereoisómeros así como en sus formas tautómeras. La presente invención abarca todas esas formas isómeras y tautómeras de los

compuestos de fórmula I. Esas formas isómeras se pueden obtener por métodos conocidos aunque no se describan especificamente en algunos casos.

Debido a que su solubilidad en agua es mayor que la de los compuestos iniciales o básicos, las sales farmacéuticamente aceptables son particularmente adecuadas para aplicaciones médicas. Estas sales deben tener un anión o catión farmacéuticamente aceptable. Las sales de adición de ácido farmacéuticamente aceptables de los compuestos de la invención adecuadas son sales de ácidos inorgánicos tales como ácido clorhídrico, bromhídrico, fosfórico, metafosfórico, nítrico y ácido sulfúrico, y de ácidos orgánicos tales como, por ejemplo, ácido acético, bencensulfónico, benzoico, cítrico, etanosulfónico, fumárico, glucónico, glicólico, isotiónico, láctico, lactobiónico, maleico, málico, metansulfónico, succínico, p-toluensulfónico y ácido tartárico. Las sales básicas farmacéuticamente aceptables adecuadas son sales de amonio, sales de metales alcalinos (tales como sales de sodio y potasio), sales de metales alcalinotérreos (tales como sales de magnesio y calcio) y sales de trometanol (2-amino-2-hidroximetil-1,3-propanodiol), dietanolamina, lisina o etilendiamina.

Las sales con un anión farmacéuticamente inaceptable, tal como, por ejemplo, el trifluoroacetato, pertenecen igualmente al marco de esta invención como productos intermedios útiles para la preparación o purificación de sales farmacéuticamente aceptables y/o para ser empleadas en aplicaciones no terapéuticas, por ejemplo en aplicaciones *in vitro*.

La expresión "derivado fisiológicamente funcional" utilizada en la presente memoria se refiere a cualquier derivado fisiológicamente tolerado de un compuesto de la fórmula I de la invención, por ejemplo un éster, que tras la administración a un mamífero tal como por ejemplo un ser humano, es capaz de formar (directa o indirectamente) un compuesto de la fórmula I o su metabolito activo.

Los derivados fisiológicamente funcionales también incluyen profármacos de los compuestos de la invención, como lo describen, por ejemplo, H. Okada et al., en Chem. Pharm. Bull.1994, 42, 57-61. Dichos

profármacos se pueden metabolizar *in vivo* a un compuesto de la invención. Estos profármacos pueden ser ellos mismos activos o no serlo.

Los compuestos de la invención también pueden existir en diferentes formas polimórficas, por ejemplo, como formas polimórficas cristalinas y amorfas. Todas las formas polimórficas de los compuestos de la invención pertenecen al marco de la invención y son un aspecto adicional de la invención.

Todas las referencias al "compuesto o compuestos de la fórmula I" en lo sucesivo se refieren al compuesto o a los compuestos de la fórmula I tal como han sido descritos anteriormente, y a sus sales, solvatos y derivados fisiológicamente funcionales tal como se describe en esta memoria.

Uso

Esta invención se refiere además al uso de compuestos de fórmula I y sus composiciones farmacéuticas como ligandos de PPAR. Los ligandos de PPAR de la invención son adecuados como moduladores de la actividad de PPAR.

Los receptores activados por el proliferador de peroxisomas (PPAR) son factores de transcripción que pueden ser activados por ligandos y pertenecen a la clase de receptores de hormonas nucleares. Hay tres isoformas de PPAR, PPAR-alfa, PPAR-gamma y PPAR-delta (idéntica a PPAR-beta), que son codificadas por diferentes genes (Peroxisome proliferator-activated receptor (PPAR): structure, mechanisms of activation and diverse functions: Motojima K., Cell Struct. Funct., 1993, 18(5), 267-77).

En seres humanos, el PPAR-gamma existe en tres variantes, PPAR-gamma1, gamma2 y gamma3, que son el resultado del uso alternativo de promotores y diferente religación de ARNm. Los diferentes PPAR tienen distintas distribuciones tisulares y modulan diferentes funcionas fisiológicas. Los PPAR tienen un papel principal en diferentes aspectos de la regulación de un gran número de genes, y los productos de dichos genes están implicados de forma crucial directa o indirectamente en el metabolismo de lípidos e hidratos de carbono. Así, por ejemplo, el receptor PPAR-alfa tiene un papel importante en la regulación del catabolismo de ácidos grasos o del metabolismo de lipoproteínas en el hígado, mientras que el PPAR-gamma está implicado de

forma crucial, por ejemplo, en la regulación de la diferenciación de células adiposas. Sin embargo, además, los PPAR también están implicados en la regulación de muchos otros procesos fisiológicos, incluyendo los que no están directamente conectados con el metabolismo de hidratos de carbono o lípidos. La actividad de los diferentes PPAR puede ser modulada por diferentes ácidos grasos y derivados de ácidos grasos y compuestos sintéticos en diferentes grados. Para revisiones relevantes sobre las funciones, efectos fisiológicos y fisiopatología, véase: Berger, J. et al., Annu. Rev. Med., 2002, 53, 409-435; Wilson, T. et al., J. Med. Chem., 2000, 43(4), 527-550; Kliewer, S. et al., Recent Prog. Horm. Res., 2001, 56, 239-63; Moller, D.E. and Berger, J.P., Int. J. Obes. Relat. Metab. Disord., 2003, 27 Suppl 3, 17-21; Ram, V.J., Drugs Today, 2003, 39(8),609-32).

De las tres isoformas del PPAR, durante mucho tiempo las funcionas fisiológicas del PPAR-delta han sido un enigma. El primer papel farmacológico propuesto para el PPAR-delta, ha sido la regulación de la homeostasis del colesterol. Se mostró que el ligando de PPAR-delta en cierta medida selectivo L-165041 eleva el colesterol del plasma en un modelo de animal diabético (Berger J. et al., J. Biol. Chem., 1999, 274, 6718-6725; Leibowitz M.D. et al., FEBS Lett., 2000, 473(3), 333-336). En monos rhesus obesos y resistentes a la insulina, el potente y selectivo ligando de PPAR-delta GW501516 aumenta el colesterol HDL y disminuye los niveles de colesterol LDL, triglicéridos e insulina en el plasma (Oliver, W. et al., Proc. Natl. Acad. Sci., 2001, 98, 5306-5361). El agonista doble de PPAR-delta/PPAR-alfa YM-16638 disminuye significativamente los lípidos en el plasma en monos rhesus y cynomologus (Goto, S. et al., Br. J. Pharm., 1996, 118, 174-178) y actúa de forma similar en ensayos clínicos de dos semanas en voluntarios sanos (Shimokawa, T. et al., Drug Dev. Res., 1996, 38, 86-92).

Las publicaciones más recientes subrayan que el PPAR-delta es un objetivo importante para el tratamiento de la dislipidemia, resistencia a la insulina, diabetes de tipo 2, arteriosclerosis y síndrome X (Wang,Y-X. et al., Cell, 2003, 113, 159-170; Luquet, S. et al., FASEB J., 2003, 17, 209-226; Tanaka, T. et al., PNAS, 2003, 100, 15924-15929; Holst, D. et al., BioChem.

Biophys. Acta, 2003, 1633, 43-50; Dressel, U. et al., Mol. Endocrin., 2003, 17, 2477-2493; Lee, C.H. et al., Science, 2003, 302, 453-457).

Además de sus acciones como un regulador del metabolismo de lípidos, glucosa y colesterol, se sabe que el PPAR-delta tiene un papel en el desarrollo, implantación y formación ósea embrionarios (Lim, H. and Dey, S.K., Trends Endocrinol. Metab., 2000, 11(4), 137-42; Ding, N.Z. et al., Mol Reprod Dev., 2003, 66(3), 218-24; Mano, H. et al., J. Biol. Chem., 2000, 275(11), 8126-32).

Numerosas publicaciones demuestran que el PPAR-delta provoca la proliferación y diferenciación de los queratinocitos, lo cual indica su papel en trastornos de la piel y curación de heridas (Di-Poi, N. et al., J. Steroid. Biochem. Mol. Biol., 2003, 85(2-5), 257-65; Tan, N.S. et al., Am. J. Clin. Dermatol., 2003,4(8), 523-30; Wahli, W., Swiss Med Wkly., 2002, 132(7-8), 83-91).

Parece que el PPAR-delta es expresado significativamente en el SNC; sin embargo sigue sin descubrirse la mayor parte de su función en éste. Sin embargo, tiene un interés particular el descubrimiento de que el PPAR-delta era expresado en oligodendrocitos de roedores, las principales células productoras de lípidos del SNC (J. Granneman, et al., J. Neurosci. Res., 1998, 51, 563-573). Además, también se encontró que un agonista selectivo del PPAR-delta aumentaba significativamente la expresión génica de mielina oligodendroglial y el diámetro de la vaina de mielina en cultivos de ratón (I. Saluja et al., Glia, 2001, 33, 194-204). Por lo tanto, los activadores del PPAR-delta se pueden usar para el tratamiento de enfermedades de desmielinización y dismielinización. Se puede demostrar el uso de agonistas delta del receptor activado por el proliferador de peroxisoma para el tratamiento de MS y otras enfermedades de desmielinización tal como se describe en la publicación WO2005/097098.

Los estados de desmielinización se ponen de manifiesto por la pérdida de mielina, las múltiples capas densas de lípidos y proteína que cubren muchas fibras nerviosas. Estas capas son proporcionadas por la oligodendroglia en el sistema nervioso central (SNC), y las células Schwann en el sistema nervioso periférico (SNP). En pacientes con estados de desmielinización, la desmielinización puede ser irreversible; normalmente va acompañada o

seguida de degeneración axonal, y a menudo de degeneración celular. La desmielinización se puede producir como resultado de daño neuronal o daño a la propia mielina, sea debido a respuestas inmunitarias aberrantes, lesión local, isquemia, trastornos metabólicos, agentes tóxicos, o infecciones víricas (Prineas and McDonald, Demyelinating Diseases. In Greenfield's Neuropathology, 6.sup.th ed. (Edward Arnold: New York, 1997) 813-811, Beers and Berkow, eds., The Merck Manual of Diagnosis and Therapy, 17.sup.th ed. (Whitehouse Station, N.J.: Merck Research Laboratories, 1999) 1299, 1437, 1473-76, 1483).

La desmielinización central (desmielinización del SNC) se produce en diferentes estados, a menudo de etiología indeterminada, que se han conocido como las enfermedades de desmielinización primarias. De éstas, la esclerosis múltiple (EM) es la más extendida. Otras enfermedades de desmielinización primarias incluyen adrenoleucodistrofia (ALD), adrenomielonauropatía, mielopatía vacuolar asociada al SIDA, mielopatia asociada a HTLV, atrofia óptica hereditaria de Lebe, leucoencefalopatía multifocal progresiva (LMP), panencefalitis esclerosante subaguda, síndrome de Guillian-Barre y paraparesia espástica tropical. Además, hay estados agudos en los que se puede producir la desmielinización en el SNC, p. ej., en la encefalomielitis diseminada aguda (EMDA) y encefalitis vírica aguda. Además, la mielitis transversa aguda, que es un síndrome en el que una transección aguda de la médula espinal de causa desconocida afecta tanto a la materia gris como a la blanca en uno o más segmentos torácicos adyacentes, puede dar como resultado la desmielinización. También, los trastornos en los que las células gliales formadoras de mielina son dañadas, incluyendo lesiones de la médula espinal, neuropatías y lesión nerviosa.

La presente invención se refiere a compuestos de fórmula I adecuados para modular la actividad de los PPAR, especialmente la actividad de los PPAR-delta y PPAR-alfa. Dependiendo del perfil de modulación, los compuestos de fórmula I son adecuados para el tratamiento, control y profilaxis de las indicaciones descritas en lo sucesivo, y para una serie de aplicaciones farmacéuticas diferentes relacionadas con éstas (véase, por ejemplo, Berger,

J., et al., Annu. Rev. Med., 2002, 53, 409-435; Wilson, T. et al., J. Med. Chem., 2000, 43(4), 527-550; Kliewer, S. et al., Recent Prog. Horm. Res., 2001, 56, 239-63; Fruchart, J.C. et al., 2001, Pharmacological Research, 44(5), 345-52; Kersten, S. et al., Nature, 2000, 405, 421-424; Torra, I.P. et al., Curr Opin Lipidol, 2001,12, 245-254).

Los compuestos de este tipo son particularmente adecuados para el tratamiento y/o prevención de:

1. Trastornos del metabolismo de ácidos grasos y trastornos de uso de la glucosa.

- Trastornos en los que está implicada la resistencia a la insulina

2. Diabetes mellitus, especialmente la diabetes de tipo 2, incluyendo la prevención de las secuelas asociadas con ésta.

Son aspectos particulares relacionados con ésta:

- hiperglucemia,
- mejora de la resistencia a la insulina,
- mejora de la tolerancia a la glucosa
- protección de las células ß pancreáticas
- prevención de trastornos macro y microvasculares

3. Dislipidemias y sus secuelas tales como, por ejemplo, aterosclerosis, enfermedad cardiaca coronaria, trastornos cerebrovasculares etc., especialmente (pero sin limitarse a éstos) aquellos caracterizados por uno o más de los siguientes factores:

- altas concentraciones de triglicéridos en el plasma, altas concentraciones de triglicéridos en el plasma posprandial,
- bajas concentraciones de colesterol HDL
- bajas concentraciones de lipoproteina ApoA
- altas concentraciones de colesterol LDL
- partículas de colesterol LDL de baja densidad
- altas concentraciones de lipoproteina ApoB

4. Diversos trastornos diferentes que se pueden asociar con el sindrome metabólico, tales como:

- obesidad (exceso de peso), incluyendo obesidad central
- trombosis, estados hipercoagulables y protrombóticos (arterial y venoso)
- hipertensión arterial
- insuficiencia cardiaca, tal como por ejemplo (pero no limitada a estos), después de infarto de miocardio, enfermedad cardiaca hipertensiva o cardiomiopatía

5. Trastornos o estados en los que están implicadas reacciones inflamatorias:

- aterosclerosis, tal como, por ejemplo (pero sin limitarse a estas), esclerosis coronaria incluyendo angina de pecho o infarto de miocardio, ictus
- reestenosis o reoclusión vascular
- enfermedades inflamatorias del intestino crónicas, por ejemplo, enfermedad de Crohn y colitis ulcerativa
- asma
- lupus eritematoso (LE) o trastornos reumáticos inflamatorios tales como, por ejemplo, artritis reumatoide
- otros trastornos inflamatorios

6. Trastornos del ciclo celular o de procesos de diferenciación celular

- tumores de células adiposas
- carcinomas lipomatosos tales como, por ejemplo, liposarcomas
- - tumores sólidos y neoplasmas tales como, por ejemplo (pero no limitados a estos), carcinomas del tubo digestivo, del hígado, de las vías biliares y del páncreas, tumores endocrinos, carcinomas de los pulmones, de los riñones y de las vías urinarias, del aparato genital, carcinomas prostáticos, etc.
- trastornos mieloproliferativos agudos y crónicos y linfomas
- angiogénesis

7. Trastornos de desmielinización y otros neurodegenerativos de los sistemas nerviosos central y periférico que incluyen:

- enfermedad de Alzheimer
- esclerosis múltiple
- - enfermedad de Parkinson

- adrenoleucodistrofia (ALD)
- adrenomielonauropatía
- mielopatía vacuolar asociada con el SIDA
- mielopatia asociada con HTLV
- atrofia óptica hereditaria de Leber
- leucoencefalopatía multifocal progresiva (LMP)
- panencefalitis esclerosante subaguda
- síndrome de Guillian-Barre
- paraparesia espástica tropical
- encefalomielitis diseminada aguda(EMDA)
- encefalitis vírica aguda
- mielitis transversa aguda
- trauma de la médula espinal y cerebral
- enfermedad de Charcot-Marie-Tooth

8. Trastornos de la piel y/o trastornos de los procesos de curación de heridas:

- dermatosis eritematoescamosas, tales como, por ejemplo, psoriasis
- acné vulgar
- otros trastornos de la piel y estados dermatológicos que son modulados por el PPAR
- eczemas y neurodermatitis
- dermatitis tales como, por ejemplo, dermatitis seborreica o fotodermatitis
- queratitis y queratosis, tales como por ejemplo, queratosis seborreica, queratosis senil, queratosis actínica, queratosis fotoinducida o queratosis folicular
- queloides y profilaxis queloide
- verrugas, entre ellas condilotoma o condilotoma acuminata
- - infeccionas por el virus del papiloma humano (VPH) tales como, por ejemplo, papilomatosis venéreas, verrugas víricas, tales como, por ejemplo, molusco contagioso, leucoplasia.
- dermatosis papular, por ejemplo, líquen plano
- cáncer de piel tales como, por ejemplo, carcinomas de células basales, melanomas o linfomas cutáneos de células T

- tumores epidérmicos benignos localizados tales como, por ejemplo, queratoderma, nevo epidérmico
- sabañonas
- curación de heridas

9. Otros trastornos

- hipertensión arterial
- pancreatitis
- síndrome X
- síndrome del ovario poliquístico (SOP)
- asma
- artrosis
- lupus eritematoso (LE) o trastornos reumáticos inflamatorios, tales como, por ejemplo, artritis reumatoide
- vasculitis
- síndrome de Wasting (caquexia)
- gota
- síndrome de isquemia/reperfusión
- síndrome de dificultad respiratoria agudo (SDRA)

Formulaciones

La cantidad de un compuesto de fórmula I necesaria para lograr el efecto biológico deseado, depende de una serie de factores, por ejemplo, del compuesto específico elegido, del empleo pretendido, del modo de administración y del estado clínico del paciente. Generalmente la dosis diaria está en el intervalo de 0,001 mg a 100 mg (típicamente de 0,01 mg a 50 mg) por día y por kilogramo de peso corporal, por ejemplo, 0,1-10 mg/kg/día. Una dosis intravenosa puede estar, por ejemplo, en el intervalo de 0,001 mg a 1,0 mg/kg, que se puede administrar adecuadamente en forma de infusión de 10 ng a 100 ng por kilogramo y por minuto. Las disoluciones adecuadas para infusión para estos propósitos, pueden contener, por ejemplo, de 0,1 ng a 10 mg, típicamente de 1 ng a 10 mg, por mililitro. Las dosis solas pueden contener, por ejemplo, de 1 mg a 10 g del ingrediente activo. Por lo tanto, las ampollas para inyectables pueden contener, por ejemplo, de 1 mg a 100 mg, y

las formulaciones de una sola dosis que se pueden administrar por vía oral, tales como, por ejemplo, cápsulas o comprimidos, pueden contener, por ejemplo, de 0,05 a 1000 mg, típicamente de 0,5 a 600 mg. Para la terapia de los estados antes mencionados, los compuestos de fórmula I se pueden usar como el propio compuesto, pero preferiblemente están en forma de una composición farmacéutica con un vehículo aceptable. Por supuesto, el vehículo debe ser aceptable, en el sentido de ser compatible con los otros ingredientes de la composición, y no ser dañino para la salud del paciente. El vehículo puede ser un sólido o un líquido, o ambos, y preferiblemente se formula con el compuesto en forma de una dosis única, por ejemplo, en forma de un comprimido, que puede contener de 0,05% a 95% en peso de ingrediente activo. Del mismo modo, puede haber presentes otras sustancias farmacéuticamente activas, incluyendo otros compuestos de la fórmula I. Las composiciones farmacéuticas de la invención se pueden preparar por uno de los métodos farmacéuticos conocidos, que esencialmente consisten en mezclar los ingredientes con vehículos y/o excipientes farmacológicamente aceptables.

Las composiciones farmacéuticas de la invención son las adecuadas para la administración oral, rectal, tópica, peroral (por ejemplo, sublingual) y parenteral (por ejemplo, subcutánea, intramuscular, intradérmica o intravenosa), aunque la vía de administración más adecuada depende en cada caso individual de la naturaleza y gravedad del trastorno que se va a tratar, y de la naturaleza del compuesto de fórmula I usado en cada caso. Las formulaciones revestidas y formulaciones revestidas de liberación lenta también están dentro del marco de la invención. Se prefieren las formulaciones resistentes a ácidos y a jugo gástrico. Revestimientos adecuados resistentes al jugo gástrico comprenden acetato-ftalato de celulosa, poli(acetato-ftalato de vinilo), ftalato de hidroxipropilmetil-celulosa y polímeros aniónicos de ácido metacrílico y metacrilato de metilo.

Las preparaciones farmacéuticas adecuadas para administración oral pueden estar en forma de unidades separadas tales como, por ejemplo, cápsulas, sellos, comprimidos para chupar o comprimidos, cada uno de los cuales contiene una cantidad definida del compuesto de fórmula I; en forma de

polvos o gránulos, en forma de disolución o suspensión en un líquido acuoso o no acuoso; o en forma de una emulsión de aceite en agua o agua en aceite. Estas composiciones, como ya se ha mencionado, se pueden preparar por cualquier método farmacéutico adecuado que incluya una etapa en la que el principio activo y el vehículo (que puede consistir en uno o más ingredientes adicionales) se ponen en contacto. En general, las composiciones se producen por mezcla uniforme y homogénea del ingrediente activo con un vehículo líquido y/o sólido finamente dividido, después de lo cual el producto se moldea si es necesario. Por lo tanto, se puede preparar un comprimido, por ejemplo, por compresión o moldeo de un polvo o gránulos del compuesto, según sea adecuado con uno o más ingredientes adicionales. Los comprimidos se pueden producir por compresión del compuesto en forma fluida tal como, por ejemplo, un polvo o gránulos, cuando sea adecuado, mezclado con un aglutinante, deslizante, diluyente inerte y/o uno (o más) agente(s) tensioactivo(s)/dispersante(s), en una máquina adecuada. Los comprimidos moldeados se pueden preparar por moldeo del compuesto, que está en forma de polvo y se humedece con un diluyente líquido inerte, en una máquina adecuada.

Las composiciones farmacéuticas que son adecuadas para la administración peroral (sublingual) comprenden comprimidos para chupar que contienen un compuesto de fórmula I con un aroma, normalmente sacarosa y goma arábiga o tragacanto, y pastillas que comprenden el compuesto en una base inerte tal como gelatina y glicerol o sacarosa y goma arábiga.

Las composiciones farmacéuticas adecuadas para administración parenteral comprenden preferiblemente preparaciones acuosas estériles de un compuesto de fórmula I, que preferiblemente son isotónicas con la sangre del receptor al que van dirigidas. Estas preparaciones preferiblemente se administran por vía intravenosa, aunque la administración también puede ser por inyección subcutánea, intramuscular o intradérmica. Estas preparaciones se pueden preparar preferiblemente mezclando el compuesto con agua y haciendo que la disolución resultante sea estéril e isotónica con la sangre. Las

composiciones inyectables de la invención contienen generalmente de 0,1 a 5% en peso del compuesto activo.

Las composiciones farmacéuticas adecuadas para administración rectal, preferiblemente están en forma de supositorios de una sola dosis. Éstas se pueden producir mezclando un compuesto de la fórmula I con uno o más vehículos sólidos convencionales, por ejemplo manteca de cacao, y moldeando la mezcla resultante.

Las composiciones farmacéuticas adecuadas para uso tópico en la piel preferiblemente están en forma de una pomada, crema, loción, pasta, pulverizador, aerosol o aceite. Los vehículos que se pueden usar son vaselina, lanolina, polietilenglicoles, alcoholes y combinaciones de dos o más de estas sustancias. El ingrediente activo está presente, generalmente, en una concentración de 0,1 a 15% en peso de la composición, por ejemplo, de 0,5 a 2%.

También es posible la administración transdérmica. Las composiciones farmacéuticas adecuadas para usos transdérmicos pueden estar en forma de una escayola que es adecuada para un contacto con la epidermis del paciente a largo plazo. Dichas escayolas, contienen adecuadamente el ingrediente activo en una disolución acuosa que está tamponada, cuando es adecuado, disuelta y/o dispersa en un adhesivo o dispersa en un polímero. Una concentración adecuada de ingrediente activo es de aproximadamente 1% a 35 %, preferiblemente de aproximadamente 3% a 15%. Una posibilidad es que el ingrediente activo sea liberado por electrotransporte o iontoforesis, como se describe, por ejemplo, en Pharmaceutical Research, 2(6): 368 (1986).

Los compuestos de la fórmula I se distinguen por los efectos favorables en trastornos metabólicos. Influyen de forma beneficiosa en el metabolismo de lípidos y azúcar, en particular disminuyen el nivel de triglicéridos y son adecuados para la prevención y tratamiento de la diabetes de tipo II y la ateriosclerosis y sus diversas secuelas.

Combinaciones con otros medicamentos

Los compuestos de la invención pueden ser administrados de forma individual o en combinación con una o varias otras sustancias

farmacológicamente activas. En particular, los compuestos de la invención se pueden administrar en combinación con ingredientes activos que tienen una acción farmacológica similar. Por ejemplo, se pueden administrar en combinación con ingredientes activos que tienen efectos favorables en los trastornos metabólicos frecuentemente asociados con ellos. Ejemplos de dichos medicamentos son

1. medicamentos que disminuyen la glucosa en sangre, antidiabéticos,
2. principios activos para el tratamiento de dislipidemias,
3. medicamentos antiateroscleróticos,
4. agentes antiobesidad,
5. ingredientes activos antiinflamatorios
6. principios activos para el tratamiento de tumores malignos
7. ingredientes activos antitrombóticos,
8. ingredientes activos para el tratamiento de la hipertensión arterial,
9. ingredientes activos para el tratamiento de la insuficiencia cardiaca y
10. ingredientes activos para el tratamiento y/o prevención de complicaciones causadas por la diabetes o asociadas con la diabetes.
11. ingredientes activos para el tratamiento de enfermedades neurodegenerativas
12. ingredientes activos para el tratamiento de trastornos del sistema nervioso central
13. ingredientes activos para el tratamiento de adicción a las drogas, nicotina y alcohol
14. analgésicos

Pueden combinarse con los compuestos de la invención de la fórmula I en particular para un aumento sinérgico de actividad. La administración de la combinación del principio activo se puede producir por administración separada de los principios activos al paciente, o en forma de productos de combinación, en los que en una preparación farmacéutica hay una pluralidad de principios activos.

Otros ingredientes activos particularmente adecuados para las preparaciones de combinación son:

Todos los antidiabéticos mencionados en la Rote Liste 2006, Capítulo 12; todos los agentes adelgazantes/supresores del apetito mencionados en Rote Liste 2006, Capítulo 1; todos los agentes reductores de lípidos mencionados en la Rote Liste 2006, Capítulo 58. Pueden combinarse con el compuesto de la fórmula I según la invención, en particular para un aumento sinérgico de actividad. La combinación del compuesto activo puede administrarse bien por administración separada de los compuestos activos al paciente o en la forma de preparaciones de combinación en las que está presente una pluralidad de compuestos activos en una preparación farmacéutica. La mayoría de los compuestos activos mencionados a continuación se describen en el USP Dictionary of USAN and International Drug Names, US Pharmacopeia, Rockville 2001.

Los antidiabéticos incluyen insulina y derivados de insulina, como por ejemplo, Lantus® (véase www.lantus.com) o HMR 1964 o aquellos descritos en la publicación WO2005005477 (Novo Nordisk), insulinas de acción rápida (véase US 6.221.633), insulinas inhalables, como por ejemplo , Exubera® o insulinas orales, como por ejemplo IN-105 (Nobex) u Oral-lyn™ (Generex Biotechnology), derivados de GLP-1, como por ejemplo, Exenatida, Liraglutida o aquellos descritos en la publicación WO 98/08871 o WO2005027978 de Novo Nordisk A/S, en la publicación WO 01/04156 de Zealand o en la publicación WO 00/34331 de Beaufour-Ipsen, acetato de pramlintida (Symlin; Amilin Pharmaceuticals) y también ingredientes activos hipoglucémicos oralmente eficaces.

Los compuestos activos preferiblemente incluyen

sulfonilureas,
biguanidinas,
meglitinidas,
oxadiazolidindionas,
tiazolidindionas,
inhibidores de glucosidasa,
inhibidores de glucógeno fosforilasa,
antagonistas de glucagón,

activadores de glucocinasa,
inhibidores de fructosa-1,6-bisfosfatasa,
moduladores del transportador de glucosa 4 (GLUT4),
inhibidores de glutamina: fructosa-6-fosfato amidotransferasa (GFAT),
agonistas de GLP-1,
abridores del canal de potasio, como por ejemplo aquellos descritos en las publicaciones internacionales WO 97/26265 y WO 99/03861 de Novo Nordisk A/S,
inhibidores de dipeptidilpeptidasa IV (DPP-IV),
sensibilizantes de insulina,
inhibidores de enzimas hepáticas implicadas en la estimulación de gluconeogénesis y/o glucogenólisis,
moduladores de absorción de glucosa, transporte de glucosa y resorción inversa de la glucosa,
inhibidores de 11ß-HSD1,
inhibidores de proteína tirosina fosfatasa 1B (PTP1B),
moduladores del cotransportador de sodio/glucosa 1 ó 2 (SGLT1, SGLT2),
compuestos que alteran el metabolismo de lípidos, como ingredientes activos e ingredientes activos antilipidémicos,
compuestos que reducen la ingesta de alimentos o la absorción de alimentos,
compuestos que aumentan la termogénesis,
moduladores de PPAR y RXR, e
ingredientes activos que actúan sobre el canal de potasio dependiente de ATP de las células beta.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con un inhibidor de HMGCoA reductasa, como simvastatina, fluvastatina, pravastatina, lovastatina, atorvastatina, cerivastatina, rosuvastatina o L-659699.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con un inhibidor de resorción de colesterol, tal como por ejemplo ezetimiba, tiquesida, pamaquesida, FM-VP4 (sitostanol/campesterol ascorbil fosfato; Forbes Medi-Tech, WO2005042692),

MD-0727 (Microbia Inc., WO2005021497) o con compuestos tales como los descritos en la publicación internacional WO2002066464 (Kotobuki Pharmaceutical Co. Ltd.), WO2005062824 (Merck & Co.) o WO2005061451 y WO2005061452 (AstraZeneca AB).

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con un agonista de PPAR gamma, tal como por ejemplo, rosiglitazona, pioglitazona, JTT-501, GI 262570, R-483 o CS-011 (rivoglitazona).

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con un agonista de PPAR alfa, como por ejemplo GW9578, GW-590735, K-111, LY-674, KRP-101 o DRF-10945.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con un agonista mixto de PPAR alfa/gamma, como por ejemplo muraglitazar, tesaglitazar, naveglitazar, LY-510929, ONO-5129, E-3030 o tal como se describe en las publicaciones internacionales WO00/64888, WO00/64876, WO03/020269, WO2004075891, WO2004076402, WO2004075815, WO2004076447, WO2004076428, WO2004076401, WO2004076426, WO2004076427, WO2006018118, WO2006018115 y WO2006018116 o en J.P. Berger et al., TRENDS in Pharmacological Sciences 28(5), 244-251, 2005.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con un agonista de PPAR delta, tal como por ejemplo GW-501516 o como se describe en las publicaciones internacionales WO2005097762, WO2005097786, WO2005097763 y WO2006029699.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con metaglidasen o con MBX-2044 u otros agonistas/antagonistas parciales de PPAR gamma.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con un fibrato, como por ejemplo fenofibrato, clofibrato o bezafibrato.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con un inhibidor de MTP, como por ejemplo

implitapida, BMS-201038, R-103757 o aquellos descritos en la publicación internacional WO2005085226.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con un inhibidor de CETP, como por ejemplo torcetrapib o JTT-705.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con un inhibidor de resorción de ácido biliar (véase, por ejemplo, las publicaciones internacionales US 6.245.744, US 6.221.897 o WO00/61568), como por ejemplo, HMR 1741 o aquellos descritos en las publicaciones internacionales DE 10 2005 033099.1 y DE 10 2005 033100.9.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con un adsorbente de ácido biliar polimérico, como por ejemplo colestiramina o colesevelam.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con un inductor del receptor de LDL (véase la publicación US 6.342.512), tal como por ejemplo HMR1171, HMR1586 o aquellos descritos en la publicación WO2005097738.

En una realización, el compuesto de la fórmula I se administra en combinación con Omacor® (ácidos grasos de omega-3; ésteres etílicos altamente concentrados de ácido eicosapentaenoico y ácido docosahexaenoico).

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con un inhibidor de ACAT, como por ejemplo avasimiba.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con un antioxidante, como por ejemplo OPC-14117, probucol, tocoferol, ácido ascórbico, ß-caroteno o selenio.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con vitamina, como por ejemplo, vitamina B6 o vitamina B12.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con un modulador de lipoproteína lipasa, como por ejemplo ibrolipim (NO-1886).

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con un inhibidor de ATP-citrato liasa, como por ejemplo SB-204990.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con un inhibidor de escualeno sintasa, como por ejemplo BMS-188494 o tal como se describe en la publicación internacional WO2005077907.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con un agonista de lipoproteína (a), como por ejemplo gemcabeno (CI-1027).

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con agonistas del receptor de HM74A, como por ejemplo ácido nicotínico.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con un inhibidor de lipasa, como por ejemplo orlistat o cetilistat (ATL-962).

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con insulina.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con una sulfonilurea, como por ejemplo tolbutamida, glibenclamida, glipizida o glimepirida.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con una biguanida, como por ejemplo metformina.

En otra realización de la invención, el compuesto de la fórmula I se administra en combinación con una meglitinida, como por ejemplo repaglinida o nateglinida.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con una tiazolidindiona, como por ejemplo troglitazona, ciglitazona, pioglitazona, rosiglitazona o los compuestos descritos en la

publicación internacional WO 97/41097 de Dr. Reddy's Research Foundation, en particular 5-[[4-[(3,4-dihidro-3-metil-4-oxo-2-quinazolinil-metoxi]-fenil]metil]-2,4-tiazolidindiona.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con un inhibidor de α-glucosidasa, como por ejemplo miglitol o acarbosa.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con un ingrediente activo que actúa sobre el canal de potasio dependiente de ATP de las células beta, como por ejemplo tolbutamida, glibenclamida, glipizida, glimepirida o repaglinida.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con más de uno de los compuestos anteriormente mencionados, por ejemplo en combinación con una sulfonilurea y metformina, una sulfonilurea y acarbosa, repaglinida y metformina, insulina y una sulfonilurea, insulina y metformina, insulina y troglitazona, insulina y lovastatina, etc.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con un inhibidor de glucógeno fosforilasa, como por ejemplo PSN-357 o FR-258900 o aquellos descritos en las publicaciones internacionales WO2003084922, WO2004007455, WO2005073229-31 o WO2005067932.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con antagonistas del receptor de glucagón, como por ejemplo A-770077, NNC-25-2504 o tales como aquellos descritos en la publicación internacional WO2004100875 o WO2005065680.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con activadores de glucocinasa tales como por ejemplo RO-4389620, LY-2121260 (WO2004063179), PSN-105, PSN-110, GKA-50 o aquellos descritos, por ejemplo, por Prosidion en las publicaciones internacionales WO2004072031, WO2004072066, WO 05103021 o WO 06016178, por Roche en las publicaciones internacionales WO 00058293, WO 00183465, WO 00183478, WO 00185706, WO 00185707, WO 01044216, GB

02385328, WO 02008209, WO 02014312, WO 0246173, WO 0248106, DE 10259786, WO 03095438, US 04067939 o WO 04052869, por Novo Nordisk en las publicaciones internacionales EP 1532980, WO 03055482, WO 04002481, WO 05049019, WO 05066145 o WO 05123132, por Merck/Banyu en las publicaciones internacionales WO 03080585, WO03097824, WO 04081001, WO 05063738 o WO 05090332, por Eli Lilly en las publicaciones internacionales WO 04063194, o por Astra Zeneca en las publicaciones internacionales WO 01020327, WO 03000262, WO 03000267, WO 03015774, WO 04045614, WO 04046139, WO 05044801, WO 05054200, WO 05054233, WO 05056530, WO 05080359, WO 05080360 o WO 05121110.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con un inhibidor de gluconeogénesis, como por ejemplo FR-225654.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con inhibidores de fructosa-1,6-bisfosfatasa (FBPasa), como por ejemplo CS-917.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con moduladores del transportador de glucosa 4 (GLUT4), como por ejemplo, KST-48 (D.-O. Lee et al.: Arzneim.-Forsch. Drug Res. 54 (12), 835 (2004)).

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con inhibidores de glutamina: fructosa-6-fosfato amidotransferasa (GFAT), tal como se describe, por ejemplo, en la publicación internacional WO2004101528.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con inhibidores de dipeptidilpeptidasa IV (DPP-IV), como por ejemplo vildagliptin (LAF-237), sitagliptin (MK-0431), saxagliptin ((BMS-477118), GSK-823093, PSN-9301, SYR-322, SYR-619, TA-6666, TS-021, GRC-8200, GW-825964X o como aquellos descritos en las publicaciones internacionales WO2003074500, WO2003106456, WO200450658, WO2005058901, WO2005012312, WO2005/012308, PCT/EP2005/007821,

PCT/EP2005/008005, PCT/EP2005/008002, PCT/EP2005/008004, PCT/EP2005/008283, DE 10 2005 012874.2 o DE 10 2005 012873.4.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con inhibidores de 11-beta-hidroxisteroide deshidrogenasa-1 (11ß-HSD1), como por ejemplo BVT-2733 o aquellos descritos, por ejemplo, en las publicaciones internacionales WO200190090-94, WO200343999, WO2004112782, WO200344000, WO200344009, WO2004112779, WO2004113310, WO2004103980, WO2004112784, WO2003065983, WO2003104207, WO2003104208, WO2004106294, WO2004011410, WO2004033427, WO2004041264, WO2004037251, WO2004056744, WO2004065351, WO2004089367, WO2004089380, WO2004089470-71, WO2004089896, WO2005016877 o WO2005097759.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con inhibidores de proteína tirosina fosfatasa 1B (PTP1B), tal como se describe, por ejemplo, en las publicaciones internacionales WO200119830-31, WO200117516, WO2004506446, WO2005012295, PCT/EP2005/005311, PCT/EP2005/005321, PCT/EP2005/007151, PCT/EP2005/ o DE 10 2004 060542.4.

En una realización de la invención, el compuesto de la fórmula I se administra con moduladores del cotransportador de sodio/glucosa 1 ó 2 (SGLT1, SGLT2), como por ejemplo KGA-2727, T-1095 y SGL-0010 o tal como se describe, por ejemplo, en las publicaciones internacionales WO2004007517, WO200452903, WO200452902, WO2005121161, WO2005085237, JP2004359630 o como lo describe A. L. Handlon en Expert Opin. Ther. Patents (2005) 15(11), 1531-1540.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con inhibidores de lipasa sensible a hormonas (HSL), tales como aquellos descritos, por ejemplo, en las publicaciones internacionales WO01/17981, WO01/66531, WO2004035550, WO2005073199 o WO03/051842.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con inhibidores de acetil-CoA carboxilasa (ACC),

tales como aquellos descritos, por ejemplo, en las publicaciones internacionales WO199946262, WO200372197, WO2003072197 o WO2005044814.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con un inhibidor de fosfoenolpiruvato carboxicinasa (PEPCK), como aquellos descritos, por ejemplo, en la publicación internacional WO2004074288.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con un inhibidor de glucógeno sintasa cinasa-3 beta (GSK-3 beta), como aquellos descritos, por ejemplo, en las publicaciones internacionales US2005222220, WO2004046117, WO2005085230, WO2005111018, WO2003078403, WO2004022544, WO2003106410, WO2005058908, US2005038023, WO2005009997, US2005026984, WO2005000836, WO2004106343, EP1460075, WO2004014910, WO2003076442, WO2005087727 o WO2004046117.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con un inhibidor de la proteína cinasa C beta (PKC beta), como por ejemplo ruboxistaurina.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con un antagonista del receptor de endotelina-A, como por ejemplo avosentan (SPP-301).

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con inhibidores de "I-kappaB cinasa" (inhibidores IKK), como aquellos descritos, por ejemplo, en las publicaciones internacionales WO2001000610, WO2001030774, WO2004022553 o WO2005097129.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con moduladores del receptor de glucocorticoides, tal como se describe, por ejemplo, en la publicación internacional WO2005090336.

En otra realización de la invención, el compuesto de la fórmula I se administra en combinación con moduladores CART (véase "Cocaine-

amphetamine-regulated transcript influences energy metabolism, anxiety and gastric emptying in mice" Asakawa, A. et al.: Hormona and Metabolic Research (2001), 33(9), 554-558);

Los antagonistas de NPY, tales como por ejemplo hidrocloruro de {4-[(4-aminoquinazolin-2-ilamino)metil]-ciclohexilmetil}naftalen-1-sulfonamida (CGP 71683A);

péptido YY 3-36 (PYY3-36) o compuestos análogos, como por ejemplo CJC-1682 (PYY3-36 conjugados con albúmina de suero humano vía Cys34), CJC-1643 (derivado de PYY3-36 que se conjuga *in vivo* con albúmina de suero) o aquellos descritos en la publicación internacional WO2005080424;

antagonistas del receptor canabinoide 1, tales como por ejemplo rimonabant, SR147778 o aquellos descritos, por ejemplo, en las publicaciones internacionales EP 0656354, WO 00/15609, WO 02/076949, WO2005080345, WO2005080328, WO2005080343, WO2005075450, WO2005080357, WO200170700, WO2003026647-48, WO200302776, WO2003040107, WO2003007887, WO2003027069, US6,509,367, WO200132663, WO2003086288, WO2003087037, WO2004048317, WO2004058145, WO2003084930, WO2003084943, WO2004058744, WO2004013120, WO2004029204, WO2004035566, WO2004058249, WO2004058255, WO2004058727, WO2004069838, US20040214837, US20040214855, US20040214856, WO2004096209, WO2004096763, WO2004096794, WO2005000809, WO2004099157, US20040266845, WO2004110453, WO2004108728, WO2004000817, WO2005000820, US20050009870, WO200500974, WO2004111033-34, WO200411038-39, WO2005016286, WO2005007111, WO2005007628, US20050054679, WO2005027837, WO2005028456, WO2005063761-62, WO2005061509 o WO2005077897;

agonistas de MC4 (por ejemplo [2-(3a-bencil-2-metil-3-oxo-2,3,3a,4,6,7-hexahidro-pirazolo[4,3-c]piridin-5-il)-1-(4-clorofenil)-2-oxoetil]-1-amino-1,2,3,4-tetrahidro-naftaleno-2-carboxamida; (WO 01/91752)) o LB53280, LB53279, LB53278 o THIQ, MB243, RY764, CHIR-785, PT-141 o aquellos descritos en las publicaciones internacionales WO2005060985, WO2005009950, WO2004087159, WO2004078717, WO2004078716, WO2004024720,

US20050124652, WO2005051391, WO2004112793, WOUS20050222014, US20050176728, US20050164914, US20050124636, US20050130988, US20040167201, WO2004005324, WO2004037797, WO2005042516, WO2005040109, WO2005030797, US20040224901, WO200501921, WO200509184, WO2005000339, EP1460069, WO2005047253, WO2005047251, EP1538159, WO2004072076, WO2004072077 o WO2006024390;

antagonistas del receptor de orexina (por ejemplo hidrocloruro de 1-(2-metilbenzoxazol-6-il)-3-[1,5]naftiridin-4-ilurea (SB-334867-A) o aquellos descritos, por ejemplo, en las publicaciones internacionales WO200196302, WO200185693, WO2004085403 o WO2005075458);

agonistas del receptor de histamina H3 (por ejemplo sal de ácido 3-ciclohexil-1-(4,4-dimetil-1,4,6,7-tetrahidroimidazo[4,5-c]piridin-5-il)-propan-1-ona oxálico (WO 00/63208) o aquellos descritos en las publicaciones internacionales WO200064884, WO2005082893);

antagonistas de CRF (por ejemplo [2-metil-9-(2,4,6-trimetilfenil)-9H-1,3,9-triazafluoren-4-il]dipropilamina (WO 00/66585));

antagonistas de CRF BP (por ejemplo urocortina);

agonistas de urocortina;

agonistas de β3 (como por ejemplo hidrocloruro de 1-(4-cloro-3-metansulfonilmetilfenil)-2-[2-(2,3-dimetil-1H-indol-6-iloxi)etilamino]etanol (WO 01/83451));

agonistas de MSH (hormona estimulante de melanocitos);

antagonistas del receptor de MCH (hormona concentradora de melanina) (como por ejemplo, NBI-845, A-761, A-665798, A-798, ATC-0175, T-226296, T-71, GW-803430 o aquellos compuestos descritos en las publicaciones internacionales WO2003/15769, WO2005085200, WO2005019240, WO2004011438, WO2004012648, WO2003015769, WO2004072025, WO2005070898, WO2005070925, WO2006018280, WO2006018279, WO2004039780, WO2003033476, WO2002006245, WO2002002744, WO2003004027 o FR2868780);

agonistas de CCK-A (tales como por ejemplo sal del ácido trifluoroacético del ácido {2-[4-(4-cloro-2,5-dimetoxifenil)-5-(2-ciclohexiletil)-tiazol-2-ilcarbamoil]-5,7-dimetilindol-1-il}acético (WO 99/15525), SR-146131 (WO 0244150) o SSR-125180);

inhibidores de reabsorción de serotonina (por ejemplo dexfenfluramina);

compuestos mixtos de serotonina y noradrenérgicos (por ejemplo WO 00/71549);

agonistas del receptor de 5-HT, por ejemplo sal del ácido 1-(3-etilbenzofuran-7-il)piperazina oxálico (WO 01/09111);

agonistas del receptor de 5-HT2C (como por ejemplo APD-356, BVT-933 o aquellos descritos en las publicaciones internacionales WO200077010, WO20077001-02, WO2005019180, WO2003064423, WO200242304 o WO2005082859);

antagonistas del receptor de 5-HT6, como aquellos descritos, por ejemplo, en la publicación internacional WO2005058858;

agonistas del receptor de bombesina (agonistas de BRS-3);

antagonistas del receptor de galanina;

hormona del crecimiento (por ejemplo hormona humana del crecimiento o AOD-9604);

compuestos que liberan la hormona del crecimiento (terc-butil 6-benciloxi-1-(2-diisopropilamino-etilcarbamoil)-3,4-dihidro-1H-isoquinolina-2-carboxilato (WO 01/85695));

antagonistas del receptor secretagogo de la hormona del crecimiento (antagonistas de ghrelina) como por ejemplo A-778193 o aquellos descritos en la publicación internacional WO2005030734;

agonistas de TRH (véase, por ejemplo EP 0 462 884);

2 ó 3 moduladores de la proteína de desacoplamiento;

agonistas de leptina (véase, por ejemplo Lee, Daniel W.; Leinung, Matthew C.; Rozhavskaya-Arena, Marina; Grasso, Patricia. "Leptin agonists as a potential approach to the treatment of obesity". Drugs of the Future (2001), 26(9), 873-881);

agonistas de DA (bromocriptina o Doprexina);

inhibidores de lipasa/amilasa (tal como se describe, por ejemplo, en la publicación internacional WO 00/40569);

inhibidores de diacilglicerol O-aciltransferasas (DGATs) tal como se describe, por ejemplo, en la publicación internacional US2004/0224997, WO2004094618, WO200058491, WO2005044250, WO2005072740, JP2005206492 o WO2005013907;

inhibidores de sintasa de ácido graso (FAS) tales como, por ejemplo, C75 o aquellos descritos en la publicación internacional WO2004005277;

oxintomodulina;

oleoíl-estrona

o agonistas del receptor de la hormona tiroidea, como por ejemplo KB-2115 o aquellos descritos en las publicaciones internacionales WO20058279, WO200172692, WO200194293, WO2003084915, WO2004018421 o WO2005092316.

En una realización de la invención, el otro ingrediente activo es leptina; véase por ejemplo "Perspectives in the therapeutic use of leptin", Salvador, Javier; Gomez-Ambrosi, Javier; Fruhbeck, Gema, Expert Opinion on Pharmacotherapy (2001), 2 (10), 1615-1622.

En una realización de la invención, el otro ingrediente activo es dexanfetamina o anfetamina.

En una realización de la invención, el otro ingrediente activo es fenfluramina o dexfenfluramina.

En otra realización de la invención, el otro ingrediente activo es sibutramina.

En una realización de la invención, el otro ingrediente activo es mazindol o fentermina.

En una realización de la invención, los compuestos de fórmula I son administrados en combinación con agentes que confieren volumen, preferiblemente agentes que confieren volumen insolubles (véase, por ejemplo, algarroba/Caromax® (Zunft H J; et al., Carob pulp preparation for treatment of hypercholesterolemia, ADVANCES IN THERAPY (2001 Sep-Oct), 18 (5), 230-6). Caromax es un producto que contiene carob de Nutrinova, Nutrition

Specialties & Food Ingredients GmbH, Industriepark Höchst, 65926 Frankfurt/Main). Es posible la combinación con Caromax® dentro de una preparación, o bien se pueden administrar por separado los compuestos de fórmula I y Caromax®. En relación con esto, Caromax® se puede administrar también en forma de productos alimenticios, tales como por ejemplo, en productos de panadería o barras de muesli.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con inhibidores de PDE (fosfodiesterasa), tal como se describe, por ejemplo, en las publicaciones internacionales WO2003/077949 o WO2005012485.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con agonistas del NAR-1 (receptor de ácido nicotínico) tal como se describe, por ejemplo, en la publicación internacional WO2004094429.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con agonistas de CB2 (receptor de canabinoide) tal como se describe, por ejemplo, en la publicación internacional US2005/143448.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con agonistas de histamina 1 tal como se describe, por ejemplo, en la publicación internacional WO2005101979.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con bupropión, tal como se describe en la publicación internacional WO2006017504.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con antagonistas de opioides tal como se describe, por ejemplo, en las publicaciones internacionales WO2005107806 o WO2004094429.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con inhibidores de endopeptidasa neutros, tal como se describe, por ejemplo, en las publicaciones internacionales WO200202513, WO2002/06492, WO 2002040008, WO2002040022 o WO2002047670.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con inhibidores de NPY (neuropéptido Y) tal como se describe, por ejemplo, en la publicación internacional WO2002047670.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con inhibidores de intercambio de sodio/hidrógeno tal como se describe, por ejemplo, en la publicación internacional WO2003092694.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con moduladores del receptor de glucocorticoides, tal como se describe, por ejemplo, en la publicación internacional WO2005090336.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con agonistas del receptor de nicotina, tal como se describe, por ejemplo, en la publicación internacional WO2004094429.

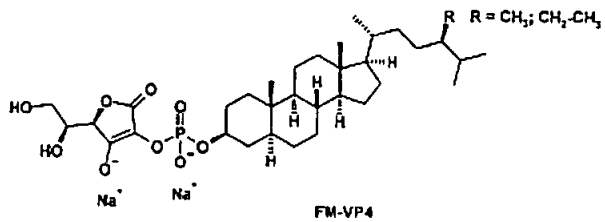
En una realización de la invención, el compuesto de la fórmula I se administra en combinación con NRI (inhibidores de reabsorción de norepinefrina) tal como se describe, por ejemplo, en la publicación internacional WO2002053140.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con MOA (E-beta-metoxiacrilato), tal como por ejemplo segelina, o como se describe, por ejemplo, en la publicación internacional WO2002053140.

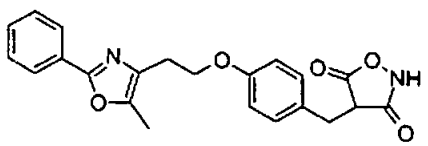
En una realización de la invención, el compuesto de la fórmula I se administra en combinación con ingredientes activos antitrombóticos, tales como por ejemplo clopidrogel.

Se ha de entender que cada combinación adecuada de los compuestos según la invención con uno o más de los compuestos anteriormente mencionados y opcionalmente una o más de otras sustancias farmacológicamente activas tiene como fin incluirse en el alcance de la presente invención.

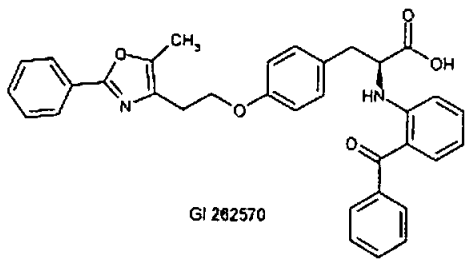
Las fórmulas para algunos de los códigos de desarrollo anteriormente mencionados se exponen a continuación.



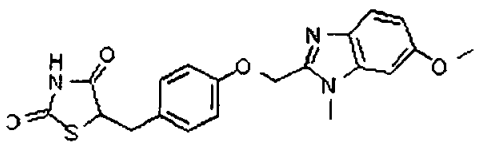
FM-VP4



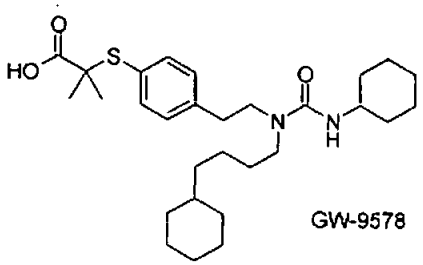
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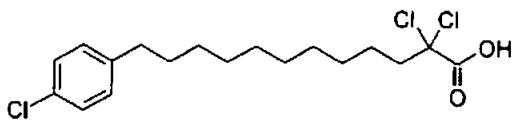


CS-011
Rivoglitazona

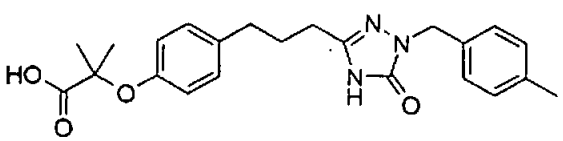


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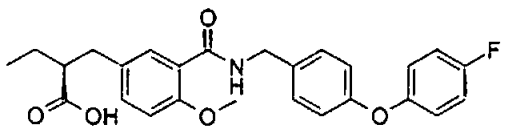
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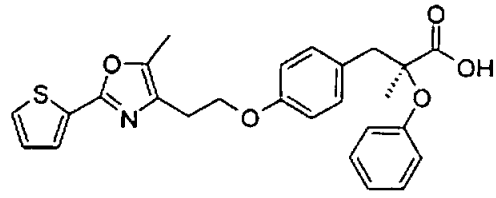
K-111



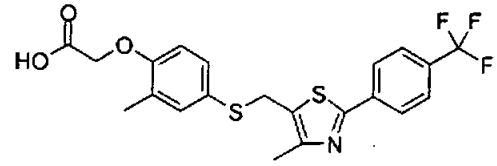
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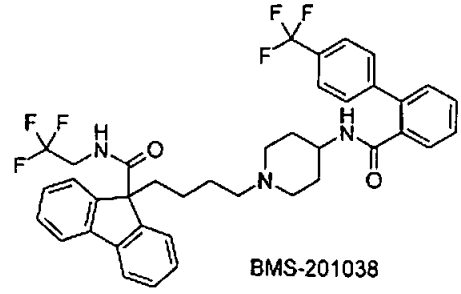
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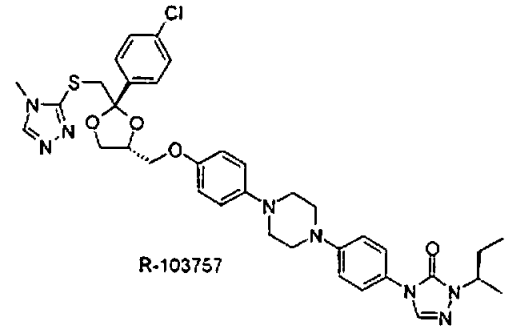
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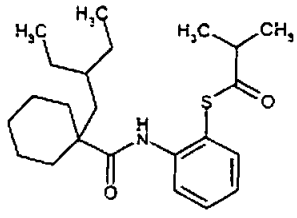
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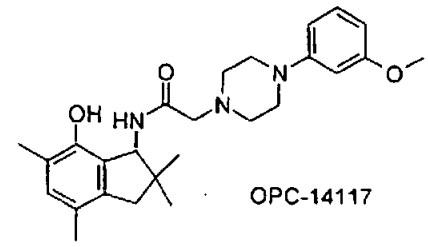
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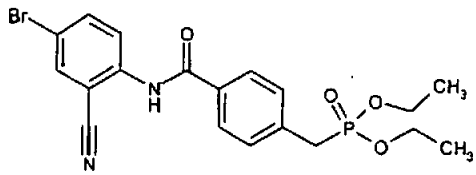
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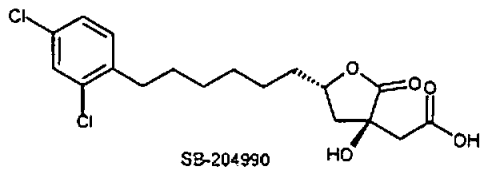
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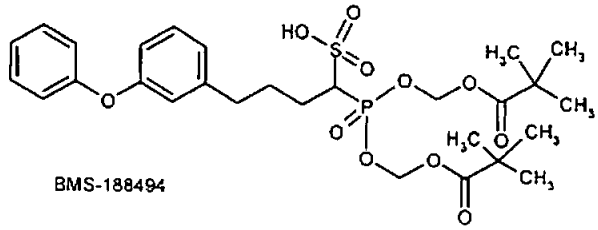
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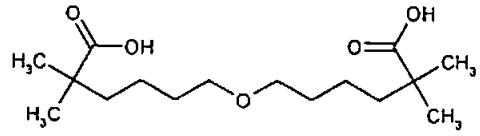
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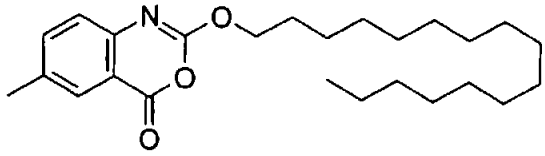
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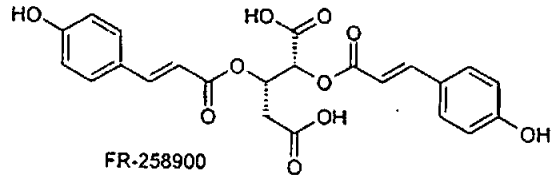
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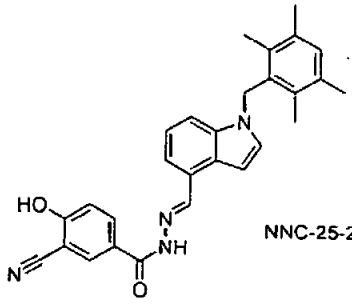
CI-1027



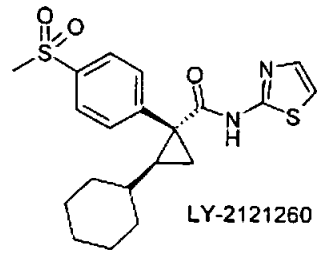
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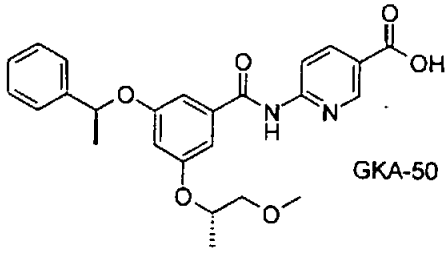
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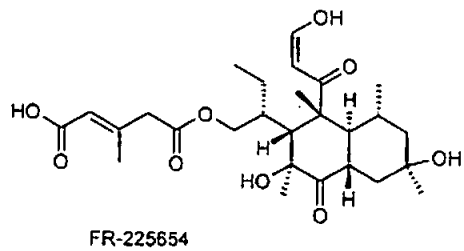
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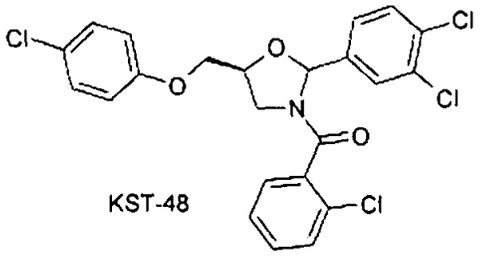
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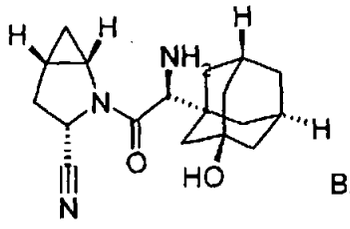
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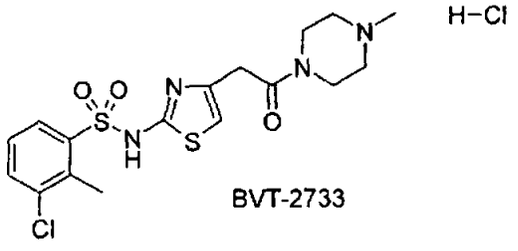
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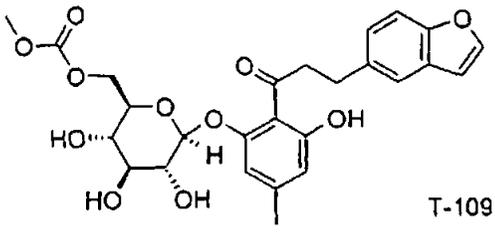


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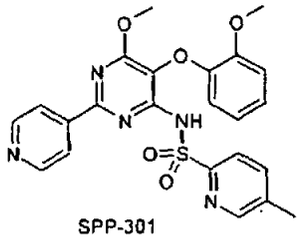


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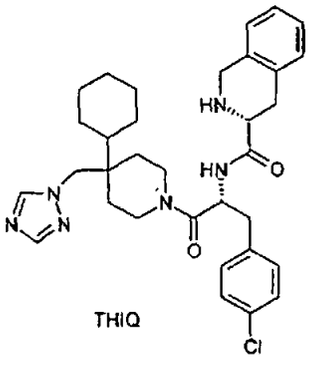
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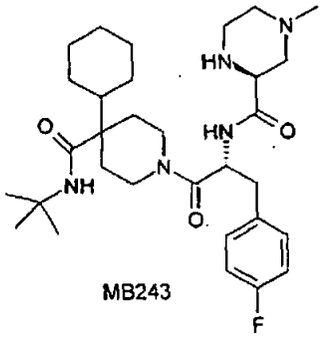
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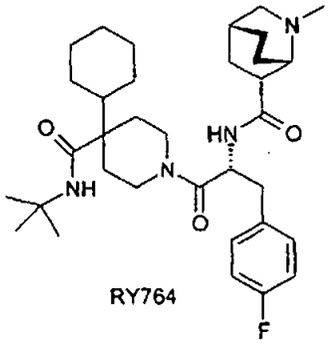
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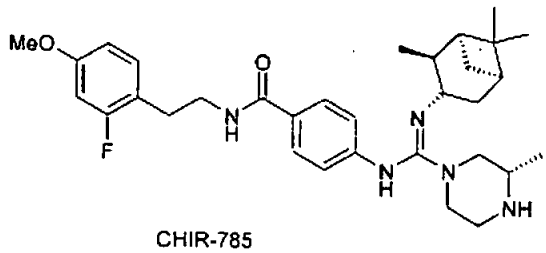


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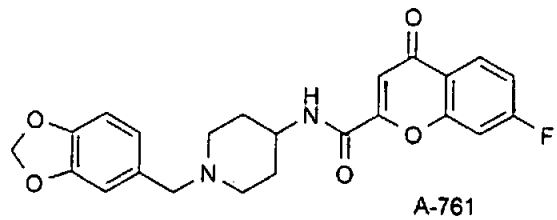


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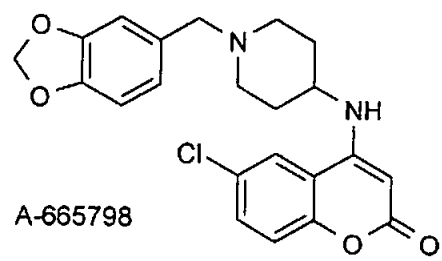
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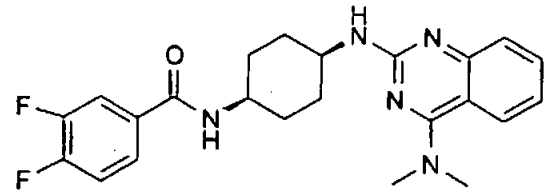
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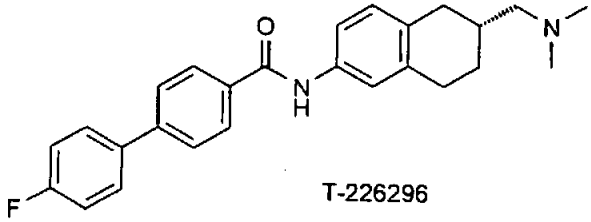
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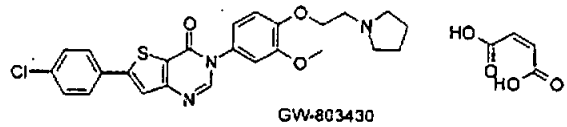
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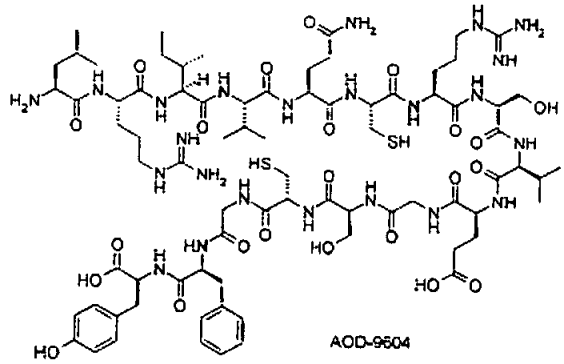


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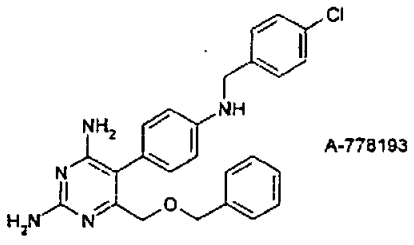


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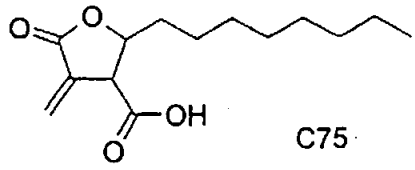
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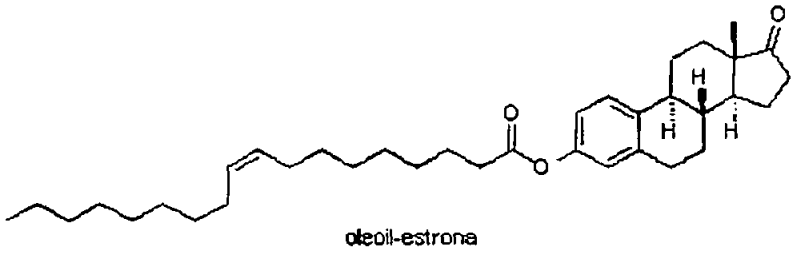
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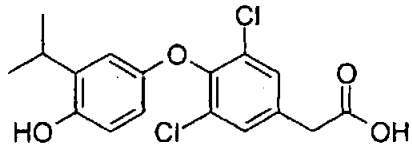
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C75



oleoil-estrona



KB-2115

La actividad de los compuestos se ensayó de la manera siguiente:

Determinación de los valores de CE50 de los agonistas de PPAR en el ensayo de PPAR-alfa celular

Principio

La potencia de las sustancias que se unen al PPAR-alfa humano y lo activan de forma agonista, se analiza usando una línea celular HEK transfectada estable (HEK = riñón embrionario humano), que aquí se denomina línea celular de indicador de PPAR-alfa. Contiene dos elementos genéticos, un elemento indicador de luciferasa (pdeltaM-GAL4-Luc-Zeo) y una proteína de fusión de PPAR-alfa (GR-GAL4-PPAR-alfa-humano-LBD) que media en la expresión del elemento indicador de luciferasa que depende de un ligando del PPAR-alfa. La proteína de fusión GR-GAL4-PPARalfa-humano-LBD expresada constitutiva y establemente, se une en el núcleo celular de la línea celular de indicador de PPAR-alfa por la parte de la proteína GAL4 a los patrones de unión del ADN de GAL4, 5' corriente arriba del elemento indicador de luciferasa que es integrado establemente en el genoma de la línea celular. En ausencia de un ligando de PPAR-alfa sólo hay una expresión débil del gen indicador de

luciferasa, si en el ensayo se usa suero de ternero fetal con reducción de ácidos grasos (cs-FCS). Los ligandos del PPAR-alfa se unen y activan la proteína de fusión de PPAR-alfa, y así estimulan la expresión del gen indicador de luciferasa. La luciferasa que se forma se puede detectar por quimiluminiscencia mediante un sustrato adecuado.

Construcción de la línea celular de indicador de PPAR-alfa

La línea celular de indicador de PPAR-alfa se preparó en dos etapas. Primero, se construyó el elemento indicador de luciferasa y se transfectó establemente en células HEK. Para este propósito, se clonaron cinco sitios de unión del factor de transcripción de levadura GAL4 (nº de acceso # AF264724) 5' corriente arriba de un promotor mínimo de MMTV de 68 pb de longitud (nº de acceso # V01175). La sección promotora mínima de MMTV contiene una caja CCAAT y un elemento TATA con el fin de permitir una transcripción eficaz por la RNA-polimerasa II. La clonación y secuenciación de la construcción de GAL4-MMTV se produce de forma análoga a la descrita por Sambrook J. *et. al.* (Molecular cloning, Cold Spring Harbor Laboratory Press, 1989). Después se clonó el gen de Photinus pyralis (nº de acceso # M15077) 3' corriente abajo del elemento GAL4-MMTV. Después de la secuenciación, el elemento indicador de luciferasa que consistía en cinco sitios de unión de GAL4, promotor de MMTV y gen de luciferasa, se volvió a clonar en un plásmido que confiere resistencia a la zeocina con el fin de obtener el plásmido pdeltaM-GAL4-Luc-Zeo. Este vector se transfectó en células HEK de acuerdo con lo expuesto por Ausubel, F.M. et al. (Current protocols in molecular biology, Vol. 1-3, John Wiley & Sons, Inc., 1995). Después se utilizó medio que contenía zeocina (0,5 mg/ml) para seleccionar un clon de célula estable adecuado que presentó muy poca expresión basal del gen de luciferasa.

En una segunda etapa, la proteína de fusión de PPAR-alfa (GR-GAL4-PPARalfa-humano-LBD) se introdujo en el clon de célula estable descrito. Para este propósito, inicialmente el ADNc que codifica los 76 aminoácidos N-terminales del receptor de glucocorticoides (nº de acceso # P04150) se unió a la sección de ADNc que codifica los aminoácidos 1-147 del factor de transcripción de levadura GAL4 (nº de acceso # P04386). El ADNc del dominio

de unión del ligando del receptor PPAR-alfa humano (aminoácidos S167-Y468; nº de acceso # S74349) se clonó en el extremo 3' de esta construcción GR-GAL4. La construcción de fusión preparada de esta forma (GR-GAL4-PPAR-alfa-humano-LBD) se volvió a clonar en el plásmido pcDNA3 (Invitrogen) con el fin de permitir la expresión constitutiva en él mediante el promotor de citomegalovirus. Este plásmido se linealizó con una endonucleasa de restricción y se transfectó establemente en el clon celular previamente descrito que contenía el elemento indicador de luciferasa. La línea celular del receptor PPAR-alfa acabada que contiene un elemento indicador de luciferasa y expresa constitutivamente la proteína de fusión de PPAR-alfa (GR-GAL4-PPAR-alfa-humano-LBD) se aisló por selección con zeocina (0,5 mg/ml) y G418 (0,5 mg/ml).

Procedimiento de ensayo

La actividad de los agonistas de PPAR-alfa se determina en un ensayo de 3 dias que se describe a continuación:

Día 1

La línea celular de indicador de PPAR-alfa se cultiva hasta 80% de confluencia en DMEM (# 41965-039, Invitrogen) que se mezcla con las siguientes adiciones: cs-FCS al 10% (suero de ternero fetal; #SH-30068.03, Hyclona), 0,5 mg/ml zeocina (#R250-01, Invitrogen), 0,5 mg/ml G418 (#10136-027, Invitrogen), disolución al 1% penicilina-estreptomicina (#15140-122, Invitrogen) y L-glutamina 2 mM (#25030-024, Invitrogen). El cultivo se realiza en frascos de cultivo celular estándar (# 353612, Becton Dickinson) en un incubador de cultivos celulares a 37°C en presencia de 5% CO_2. Las células 80% confluentes se lavan una vez con 15 ml de PBS (#14190-094, Invitrogen), se tratan con 3 ml de disolución de tripsina (#25300-054, Invitrogen) a 37°C durante 2 min, se absorben en 5 ml del DMEM descrito y se cuentan en un contador de células. Después de diluir a 500.000 células/ml, se siembran 35.000 células en cada pocillo de una placa de microvaloración de 96 pocillos con una base de plástico transparente (nº 3610, Corning Costar). Las placas se incuban en el incubador de cultivo celular a 37°C y con CO_2 al 5% durante 24 h.

Día 2

Los agonistas de PPARα que se van a ensayar se disuelven en DMSO con una concentración 10 mM. Esta disolución madre se diluye en DMEM (#41965-039, Invitrogen) que se mezcla con 5% cs-FCS (#SH-30068.03, Hyclona), L-glutamina 2 mM (#25030-024, Invitrogen) y los antibióticos previamente descritos (zeocina, G418, penicilina y estreptomicina).

Las sustancias de ensayo se ensayan con 11 concentraciones diferentes en el intervalo de 10 µM a 100 pM. Los compuestos más potentes se ensayan con concentraciones en el intervalo de 1 µM a 10 pM o entre 100 nM y 1 pM.

El medio de la línea de células con el indicador de PPARα sembrada el día 1 se elimina completamente por aspiración y a las células se les añaden inmediatamente las sustancias de ensayo diluidas en medio. La dilución y adición de las sustancias se lleva a cabo mediante un robot (Beckman FX). El volumen final de las sustancias de ensayo diluidas en medio es 100 µl por pocillo de una placa de microvaloración de 96 pocillos. La concentración de DMSO en el ensayo es menor que 0,1 % en vol/vol con el fin de evitar efectos citotóxicos del disolvente.

Cada placa se cargó con un agonista de PPAR-alfa patrón, que se diluyó igualmente en 11 concentraciones diferentes, con el fin de demostrar el funcionamiento del ensayo en cada placa individual. Las placas de ensayo se incuban en un incubador a 37°C y CO_2 al 5% durante 24 h.

Día 3

Las células con el indicador de PPARα tratadas con las sustancias de ensayo se sacan del incubador y se aspira el medio. Las células se lisan pipeteando 50 µl de reactivo Bright Glo (de Promega) en cada pocillo de una placa de microvaloración de 96 pocillos. Después de incubar a temperatura ambiente en la oscuridad durante 10 minutos, las placas de microvaloración se miden en el luminómetro (Trilux de Wallac). El tiempo de medición para cada pocillo de la placa de microvaloración es 1 segundo.

Evaluación

Los datos sin procesar del luminómetro se transfieren a un fichero de Microsoft Excel. Se calculan las gráficas del efecto de la dosis y los valores

CE50 de los agonistas del PPAR, usando el programa XL.Fit como especifica el fabricante (IDBS).

Los valores de CE50 del PPAR-alfa para los compuestos de los Ejemplos 1 a 112 en este ensayo están en el intervalo de 5 nM a >10 µM. Los compuestos de la invención de fórmula I activan el receptor PPAR-alfa.

Determinación de los valores de CE50 de los agonistas de PPAR en el ensayo de PPAR-delta celular

Principio

La potencia de las sustancias que se unen al PPAR-delta humano y lo activan de forma agonista, se analiza usando una línea celular HEK transfectada estable (HEK = riñón embrionario humano), que aquí se denomina línea celular de indicador de PPAR-delta. Análogamente al ensayo descrito para el PPAR-alfa, la línea celular de indicador de PPAR-alfa también contiene dos elementos genéticos, un elemento indicador de luciferasa (pdeltaM-GAL4-Luc-Zeo) y una proteína de fusión de PPAR-delta (GR-GAL4-PPARdelta-humano-LBD) que media en la expresión del elementos indicador de luciferasa que depende de un ligando de PPAR-delta. La proteína de fusión GR-GAL4-PPARdelta-humano-LBD expresada constitutiva y establemente, se une en el núcleo celular de la línea celular de indicador de PPAR-delta por la parte de la proteína GAL4 a los patrones de unión del ADN de GAL4, 5' corriente arriba del elemento indicador de luciferasa que es integrado establemente en el genoma de la línea celular. En ausencia de un ligando de PPAR-delta sólo hay un poco de expresión del gen indicador de luciferasa, si en este ensayo se usa suero de ternero fetal con reducción de ácidos grasos (cs-FCS). Los ligandos del PPAR-delta se unen y activan la proteína de fusión de PPAR-delta, y así estimulan la expresión del gen indicador de luciferasa. La luciferasa que se forma se puede detectar por quimiluminiscencia mediante un sustrato adecuado.

Construcción de la línea celular de indicador de PPAR-delta

La producción de la línea celular de indicador de PPAR-delta estable se basa en un clon de célula HEK estable que fue establemente transfectado con un elemento indicador de luciferasa. Esta etapa ya se ha descrito antes, en la sección "construcción de la línea celular de indicador de PPAR-delta". En una

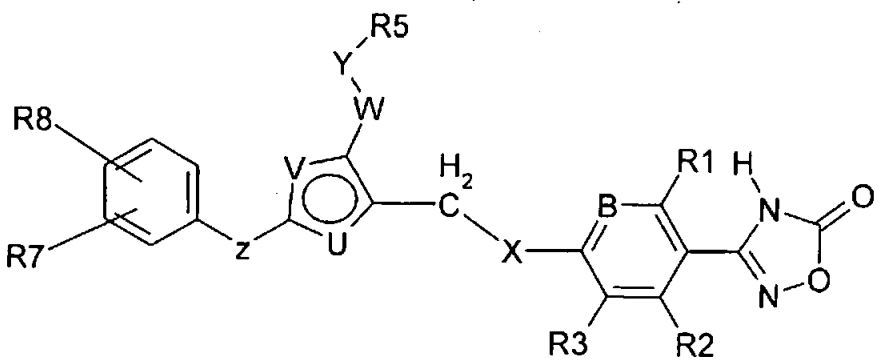
segunda etapa, la proteína de fusión de PPAR-delta (GR-GAL4-PPARdelta-humano-LBD) se introdujo establemente en este clon celular. Para este fin, la codificación de ADNc para los 76 aminoácidos N-terminales del receptor de glucocorticoides (nº de acceso # P04150) se unió a la sección de ADNc que codifica los aminoácidos 1-147 del factor de transcripción de la levadura GAL4 (nº de acceso # P04386). El ADNc del dominio de unión del ligando del receptor PPAR-delta (aminoácidos S139-Y411; nº de acceso # L07592) se clonó en el extremo 3' de esta construcción GR-GAL4. La construcción de fusión preparada de esta forma (GR-GAL4-PPAR-delta-humano-LBD) se volvió a clonar en el plásmido pcDNA3 (Invitrogen) con el fin de permitir la expresión constitutiva mediante el promotor de citomegalovirus. Este plásmido se linealizó con una endonucleasa de restricción y se transfectó establemente en el clon celular previamente descrito que contenía el elemento indicador de luciferasa. La línea celular de indicador de PPAR-delta que contiene un elemento indicador de luciferasa y expresa constitutivamente la proteína de fusión de PPAR-delta (GR-GAL4-PPAR-delta-humano-LBD) se aisló por selección con zeocina (0,5 mg/ml) y G418 (0,5 mg/ml).

Procedimiento de ensayo y evaluación

La actividad de los agonistas de PPAR-delta se determina en un ensayo de 3 días de forma análoga al procedimiento descrito antes para la línea celular de indicador de PPAR-alfa, excepto que se usó la línea celular de indicador de PPAR-delta y un agonista específico para PPAR-delta, como patrón para controlar la eficacia del ensayo.

Se midieron los valores de CE50 para el PPAR-delta en el intervalo de 0,2 nM a >10 µM para los agonistas de PPAR de los Ejemplos 1 a 112 descritos en esta solicitud. Los compuestos de fórmula I de la invención activan al receptor PPAR-delta.

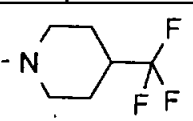
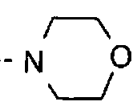
Los ejemplos dados en la Tabla II sirven para ilustrar la invención, pero sin limitarla.

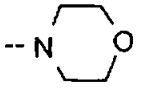
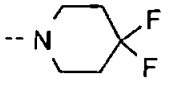
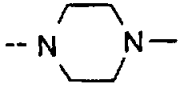
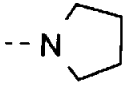
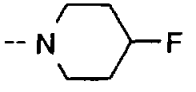
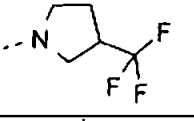
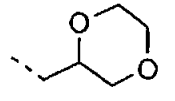


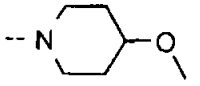
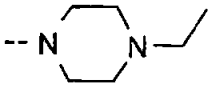
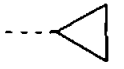
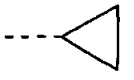
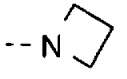
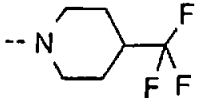
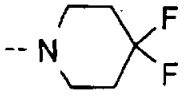
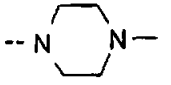
fueron R2 y R8 = H .

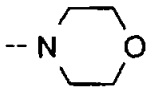
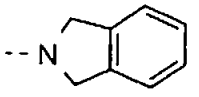
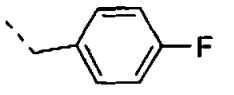
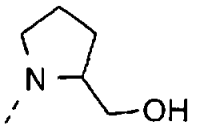
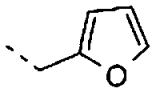
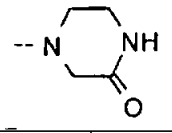
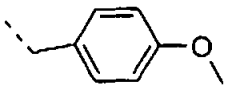
La línea punteada significa el puntó de unión.

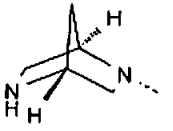
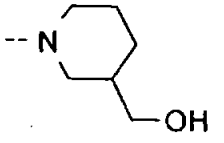
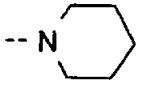
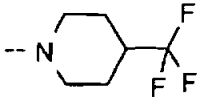
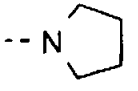
Tabla I

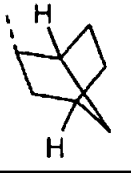
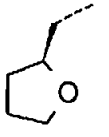
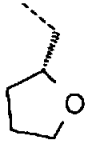
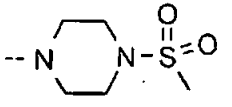
Ejemplo	Z	X	W	Y	R5	R6	U	V	R1	R3	R7	B
1	enlace	O	-CH2-	--			S	N	-OCH3	H	p-CF3	CH
2	enlace	O	-CH2-	--			S	N	Cl	H	p-CF3	CH

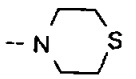
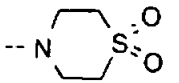
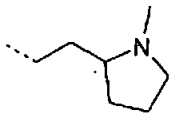
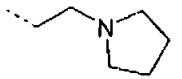
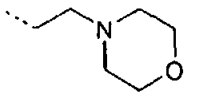
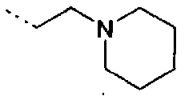
Ejemplo	Z	X	W	Y	R5	R6	U	V	R1	R3	R7	B
3	enlace	O	-CH2-				S	N	-OCH3	H	p-CF3	CH
4	enlace	O	-CH2-				S	N	-OCH3	H	p-CF3	CH
5	enlace	O	-CH2-				S	N	-OCH3	H	p-CF3	CH
6	enlace	O	-CH2-				S	N	-OCH3	H	p-CF3	CH
7	enlace	O	-CH2-				S	N	-OCH3	H	p-CF3	CH
8	enlace	O	-CH2-	N	-CH2CH3	-CH2CH3	S	N	-OCH3	H	p-CF3	CH
9	enlace	O	-CH2CH2-				S	N	-OCH3	H	p-CF3	CH
10	enlace	O	-CH2-	N	-(CH2)2OCH3	-CH2CH3	S	N	-OCH3	H	p-CF3	CH
11	enlace	O	-CH2-	N		-CH3	S	N	-OCH3	H	p-CF3	CH

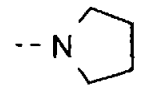
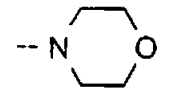
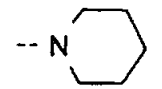
Ejemplo	Z	X	W	Y	R5	R6	U	V	R1	R3	R7	B
12	enlace	O	-CH2-				S	N	-OCH3	H	p-CF3	CH
13	enlace	O	-CH2-				S	N	-OCH3	H	p-CF3	CH
14	enlace	O	-CH2-	N	-(CO)OPh		S	N	-OCH3	H	p-CF3	CH
15	enlace	O	-CH2-	N		H	S	N	-OCH3	H	p-CF3	CH
16	enlace	O	-(CH2)3-				S	N	-OCH3	H	p-CF3	CH
17	enlace	O	-CH2-				S	N	F	H	p-CF3	CH
18	enlace	O	-CH2-				S	N	F	H	p-CF3	CH
19	enlace	O	-CH2-	N	-(CH2)2OH	-CH3	S	N	F	H	p-CF3	CH
20	enlace	O	-CH2-				S	N	F	H	p-CF3	CH

Ejemplo	Z	X	W	Y	R5	R6	U	V	R1	R3	R7	B
21	enlace	O	-CH2-				S	N	F	H	p-CF3	CH
22	enlace	O	-CH2-				S	N	F	H	p-CF3	CH
23	enlace	O	-CH2-	N		H	S	N	F	H	p-CF3	CH
24	enlace	O	-CH2-				S	N	F	H	p-CF3	CH
25	enlace	O	-CH2-	N		H	S	N	F	H	p-CF3	CH
26	enlace	O	-CH2-	N	-CH2CH2CH2SCH3	H	S	N	F	H	p-CF3	CH
27	enlace	O	-CH2-				S	N	F	H	p-CF3	CH
28	enlace	O	-CH2-	N		H	S	N	F	H	p-CF3	CH

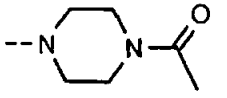
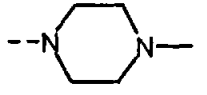
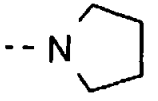
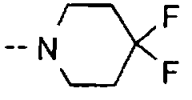
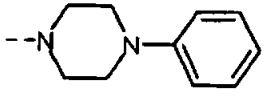
Ejemplo	Z	X	W	Y	R5	R6	U	V	R1	R3	R7	B
29	enlace	O	-CH2-				S	N	F	H	p-CF3	CH
30	enlace	O	-CH2-				S	N	F	H	p-CF3	CH
31	enlace	O	-CH2-				S	N	-OCH3	Br	p-CF3	CH
32	enlace	O	-CH2-				S	N	-OCH3	F	p-CF3	CH
33	enlace	O	-CH2-	O	C(=O)CH3		S	N	F	H	p-CF3	CH
34	enlace	O	-CH2-	O	C(=O)CH3		S	N	-OCH3	H	p-CF3	CH
35	enlace	O	-CH2-				S	N	F	H	p-CF3	CH
36	enlace	O	-CH2-	N	-CH2CH2CF3	H	S	N	-OCH3	H	p-CF3	CH

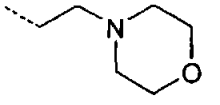
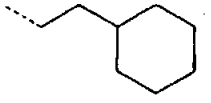
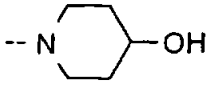
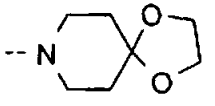
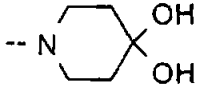
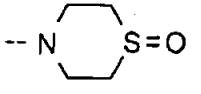
Ejemplo	Z	X	W	Y	R5	R6	U	V	R1	R3	R7	B
37	enlace	O	-CH2-	N		H	S	N	-OCH3	H	p-CF3	CH
38	enlace	O	-CH2-	N		H	S	N	-OCH3	H	p-CF3	CH
39	enlace	O	-CH2-	N		H	S	N	-OCH3	H	p-CF3	CH
40	enlace	O	-CH2-	N		H	S	N	-OCH3	H	p-CF3	CH
41	enlace	O	-CH2-	N		H	S	N	-OCH3	H	p-CF3	CH
42	enlace	O	-CH2-				S	N	-OCH3	H	p-CF3	CH
43	enlace	O	-CH2-	N	-(CH2)2-OH	-(CH2)2-OH	S	N	-OCH3	H	p-CF3	CH
44	enlace	O	-CH2-	N	-CH2CH2S(=O)CH3	H	S	N	-OCH3	H	p-CF3	CH

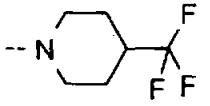
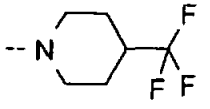
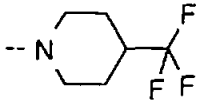
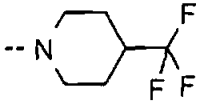
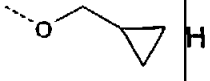
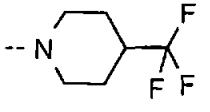
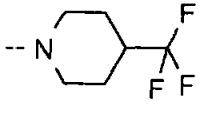
Ejemplo	Z	X	W	Y	R5	R6	U	V	R1	R3	R7	B
45	enlace	O	-CH2-				S	N	-OCH3	H	p-CF3	CH
46	enlace	O	-CH2-				S	N	-OCH3	H	p-CF3	CH
47	enlace	O	-CH2-	N	-(CH2)2CH3	H	S	N	-CH3	H	p-CF3	CH
48	enlace	O	-CH2-	N	-(CH2)2OCH3	H	S	N	-CH3	H	p-CF3	CH
49	enlace	O	-CH2-	N		H	S	N	-CH3	H	p-CF3	CH
50	enlace	O	-CH2-	N		H	S	N	-CH3	H	p-CF3	CH
51	enlace	O	-CH2-	N		H	S	N	-CH3	H	p-CF3	CH
52	enlace	O	-CH2-	N		H	S	N	-CH3	H	p-CF3	CH
53	enlace	O	-CH2-	N	-(CH2)2N(CH3)2	H	S	N	-CH3	H	p-CF3	CH
54	-(CH2)2-	O	-CH2-	enlace	H	-	O	N	-Cl	H	p-CF3	CH

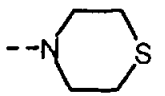
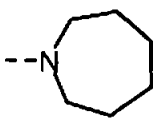
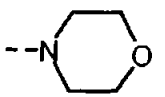
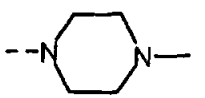
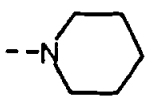
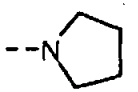
Ejemplo	Z	X	W	Y	R5	R6	U	V	R1	R3	R7	B
55	-CH=CH-	O	-CH2-	O	-CH3	-	O	N	-Cl	H	p-OCH3	CH
56	-CH2OCH2-	O	-CH2-	enlace	H	-	O	N	-Cl	H	H	CH
57	-CH2-	O	-CH2-	enlace	H	-	O	N	-Cl	H	p-OCH3	CH
58	-CH=CH-	O	-CH2-	O	-CH3	-	S	N	-Cl	H	p-CF3	CH
59	enlace	O	-CH2-	O	-CH2CF3	-	O	N	-Cl	H	p-CF3	CH
60	enlace	O	-CH2-	N	-(CH2)2OCH3	-CH2CH3	O	N	-CH3	H	p-OCH3	CH
61	enlace	O	-CH2-	N	-CH2CH3	-CH2CH3	O	N	-CH3	H	p-OCH3	CH
62	enlace	O	-CH2-				O	N	-CH3	H	p-OCH3	CH
63	enlace	O	-CH2-				O	N	-CH3	H	p-OCH3	CH
64	enlace	O	-CH2-	N	-(CH2)2OCH3	-(CH2)2OCH3	O	N	-CH3	H	p-OCH3	CH
65	enlace	O	-CH2-				O	N	-CH3	H	p-OCH3	CH

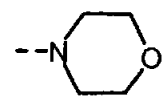
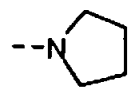
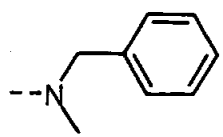
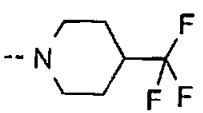
Ejemplo	Z	X	W	Y	R5	R6	U	V	R1	R3	R7	B
66	enlace	O	-CH2-	-- N			N	O	-CH3	H	p-OCH3	CH
67	enlace	O	-CH2-	-- N			N	O	-CH3	H	p-OCH3	CH
68	enlace	O	-CH2-	-- N O			N	O	-CH3	H	p-OCH3	CH
69	enlace	O	-CH2-	N	-(CH2)2OCH3	-(CH2)2OCH3	N	O	-CH3	H	p-OCH3	CH
70	enlace	O	-CH2-	-- N O			O	N	Cl	H	p-OCH3	CH
71	enlace	O	-CH2-	N	-(CH2)2OCH3	-CH2CH3	O	N	Cl	H	p-OCH3	CH
72	enlace	O	-CH2-	N	-(CH2)2OCH3	-(CH2)2OCH3	O	N	Cl	H	p-OCH3	CH
73	enlace	O	-CH2-	-- N			S	N	Cl	H	p-CF3	CH

Ejemplo	Z	X	W	Y	R5	R6	U	V	R1	R3	R7	B
74	enlace	O	-CH2-				S	N	Cl	H	p-CF3	CH
75	enlace	O	-CH2-				S	N	Cl	H	p-CF3	CH
76	enlace	O	-CH2-	N	-(CH2)2OCH3	-CH2CH3	S	N	Cl	H	p-CF3	CH
77	enlace	O	-CH2-	N	-(CH2)2OCH3	-(CH2)2OCH3	S	N	Cl	H	p-CF3	CH
78	enlace	O	-CH2-				S	N	Cl	H	p-CF3	CH
79	enlace	O	-CH2-	N	-CH2CH3	-CH2CH3	S	N	Cl	H	p-CF3	CH
80	enlace	O	-CH2-				S	N	Cl	H	p-CF3	CH
81	enlace	O	-CH2-				S	N	Cl	H	p-CF3	CH

Ejemplo	Z	X	W	Y	R5	R6	U	V	R1	R3	R7	B
82	enlace	O	-CH2-	O		-	S	N	Cl	H	p-CF3	CH
83	enlace	O	-CH2-	O		-	S	N	Cl	H	p-CF3	CH
84	enlace	O	enlace	enlace	CHF2	-	S	N	Cl	H	p-OCH3	CH
85	enlace	O	-CH2-				S	N	-OCH3	H	p-CF3	CH
86	enlace	O	-CH2-				S	N	-OCH3	H	p-CF3	CH
87	enlace	O	-CH2-				S	N	-OCH3	H	p-CF3	CH
88	enlace	O	-CH2-				S	N	-OCH3	H	p-CF3	CH
89	enlace	O	-CH2-	S	CH3	-	S	N	-OCH3	H	p-CF3	CH
90	enlace	O	-CH2-	S(O)	CH3	-	S	N	-OCH3	H	p-CF3	CH
91	enlace	O	-CH2-	S(O)2	CH3	-	S	N	-OCH3	H	p-CF3	CH

Ejemplo	Z	X	W	Y	R5	R6	U	V	R1	R3	R7	B
92	enlace	O	-CH2-	N	H	H	S	N	F	H	p-CF3	CH
93	enlace	O	-CH2-	N	-C(O)CH3	H	S	N	F	H	p-CF3	CH
94	enlace	O	-CH2-				S	N	-OCHF2	H	p-CF3	CH
95	enlace	O	-CH2-				S	N	-OCHF2	F	p-CF3	CH
96	enlace	O	-CH2-				S	N	-OiPr	H	p-CF3	CH
97	enlace	O	-CH2-				S	N		H	p-CF3	CH
98	enlace	O	-CH2-				S	N	-OCH2CF3	H	p-CF3	CH
99	enlace	O	-CH2-				S	N	-OCH2CF3	F	p-CF3	CH
100	enlace	O	-(CH2)3-	enlace	-CH3	-	S	N	-CH3	H	p-CF3	N

Ejemplo	Z	X	W	Y	R5	R6	U	V	R1	R3	R7	B
101	enlace	O	-(CH2)3-	S	CH3	-	S	N	-OCH3	H	p-CF3	CH
102	enlace	O	-(CH2)3-	S(O)2	CH3	-	S	N	-OCH3	H	p-CF3	CH
103	enlace	O	-(CH2)3-				S	N	-OCH3	H	p-CF3	CH
104	enlace	O	-(CH2)3-				S	N	-OCH3	H	p-CF3	CH
105	enlace	O	-(CH2)3-				S	N	-OCH3	H	p-CF3	CH
106	enlace	O	-(CH2)3-				S	N	-OCH3	H	p-CF3	CH
107	enlace	O	-(CH2)3-				S	N	-OCH3	H	p-CF3	CH
108	enlace	O	-(CH2)3-				S	N	-OCH3	H	p-CF3	CH

Ejemplo	Z	X	W	Y R5	R6	U	V	R1	R3	R7	B
109	enlace	O	-(CH2)3-			S	N	-F	H	p-CF3	CH
110	enlace	O	-(CH2)3-			S	N	-F	H	p-CF3	CH
111	enlace	O	-(CH2)3-			S	N	-OCH3	H	p-CF3	CH
112	enlace	O	-(CH2)3-			S	N	-OCH3	H	p-CF3	CH

La potencia de algunos de los ejemplos descritos en los ensayos de GAL4 humano se indica en la siguiente tabla:

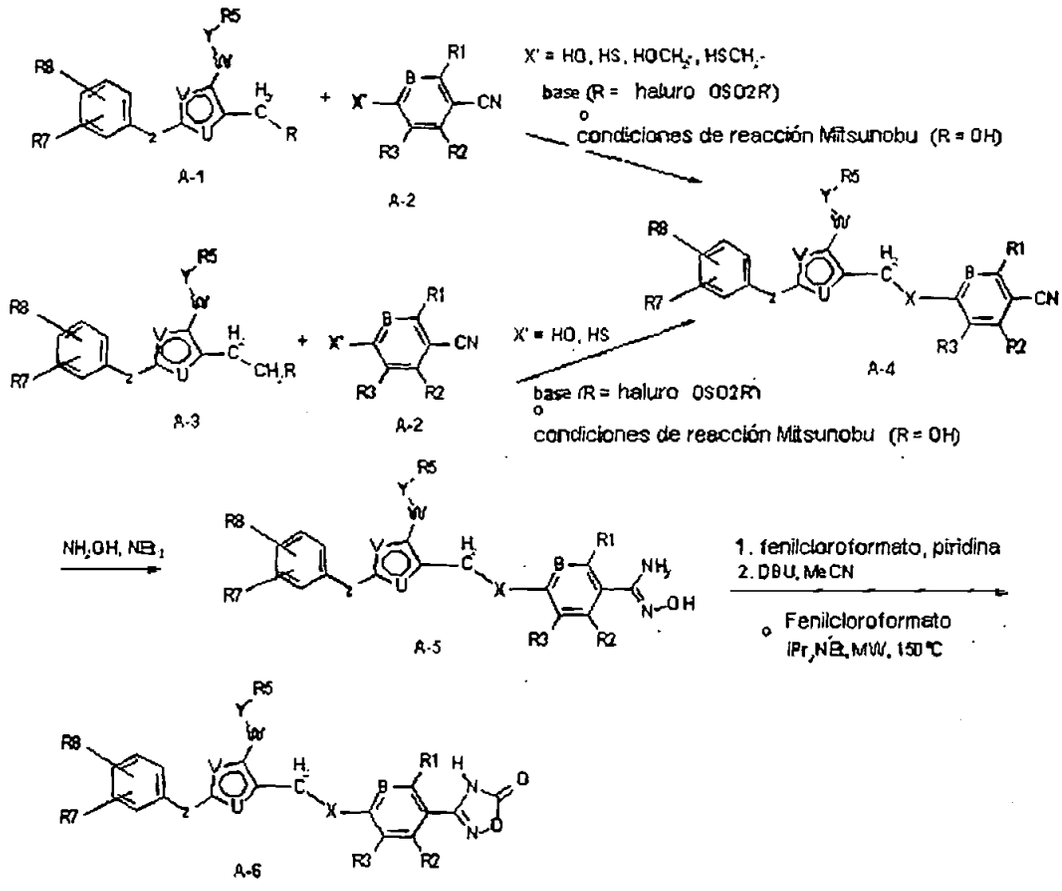
Ejemplo	PPAR-delta CE50 (μM)	PPAR-alfa CE50 (μM)
1	0,056	0,830
9	0,056	0,729
15	0,153	> 10
19	0,171	1,19
33	0,299	1,41
51	0,228	1,21
55	0,003	0,319
56	0,358	2,19
68	0,661	1,20
77	0,003	0,530
83	0,012	0,398
89	0,153	2,62
94	0,018	0,664
100	0,008	0,315
102	0,022	1,780
103	0,008	0,483

5

Procedimientos

Los compuestos de la fórmula general I de acuerdo con la invención se pueden obtener como se indica en los siguientes esquemas de reacción.

Procedimiento A



Un compuesto de fórmula general A-2 en el que X' es -OH, -SH, -CH2OH o -CH2SH y R1, R2, R3, B tal como se definió anteriormente, bien se hace reaccionar con un compuesto de fórmula general A-1 en la que R es haluro (I, Br, Cl) o un sulfonato (OSO_2CH_3, $OSO_2C_6H_4CH_3$) y R5, R7, R8, U, V, W, Y y Z son tal como se definió anteriormente en presencia de una base o carbonato de cesio o hidruro de sodio en un disolvente como dimetilformamida o con un alcohol de fórmula general A-1, en la que R = OH, y R5, R7, R8, U, V, W, Y y Z son tal como se definió anteriormente bajo condiciones de reacción Mitsunobu (trifenilfosfina, dietilazodicarboxilato, por ejemplo) en un disolvente apolar como diclorometano para producir un compuesto de fórmula general A-4

en la que X= O, S, -OCH_2- o -SCH_2-. Este procedimiento se puede aplicar a un compuesto de fórmula general A-3, en la que R es haluro (I, Br, Cl) o un sulfonato (OSO_2CH_3, OSO_2PhCH_3) y R5, R7, R8, U, V, W, Y y Z son tal como se definió anteriormente o con un alcohol de fórmula general A-3 en la que R = OH, y R5, R7, R8, U, V, W, Y y Z son tal como se definió anteriormente bajo condiciones de reacción tales como las previamente descritas para conducir un compuesto de fórmula general A-4 en la que X= -CH_2O- o -CH_2O-.

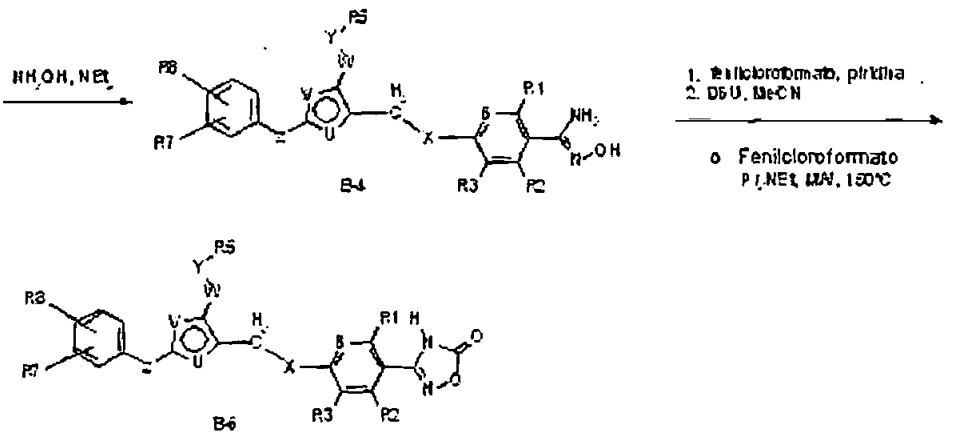
El compuesto de fórmula general A-4 se hace reaccionar con hidrocloruro de hidroxilamina en presencia de una base como trietilamina en un disolvente como tetrahidrofurano y metanol para obtener un compuesto de fórmula general A-5. Esta reacción se puede facilitar calentando la mezcla de reacción bajo irradiación de microondas. Este compuesto de fórmula general A-5 se convierte al producto de fórmula general A-6 por reacción con fenilcloroformato en presencia de una base como piridina o diisopropiletilamina seguido de calentamiento de la mezcla de reacción con irradiación de microondas para permitir la ciclización, o alternativamente aislando el intermedio resultante y tratando con una base como 1,8-diazabiciclo[5.4.0]undec-7-eno en un disolvente como acetonitrilo.

Cuando R5 es H en el sustrato A-5, se forma el compuesto de fórmula general A-6 con R5= $C(=O)C_6H_5$ que se puede hidrolizar con una sal de hidróxido tal como hidróxido de potasio en un producto de fórmula general A-6 en la que R5 es H.

Los ejemplos 54 – 59 se obtuvieron de acuerdo con el procedimiento A.

Se pueden obtener otros compuestos de acuerdo con, o por procedimientos conocidos.

Procedimiento B

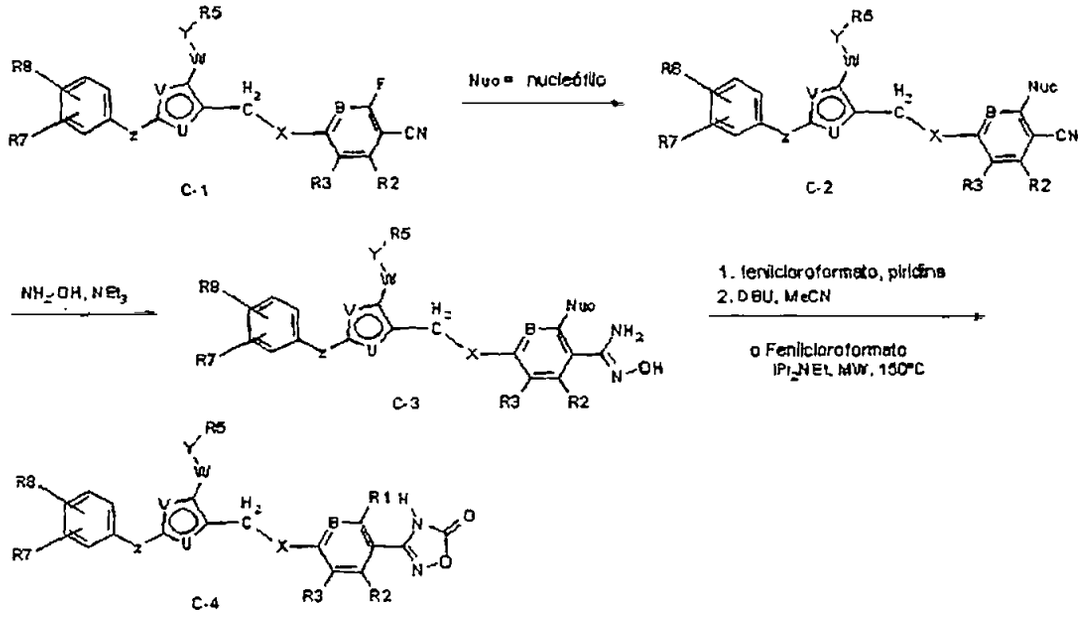


Un compuesto de fórmula general B-1 en la que X es O, S, CH_2O o CH_2S y R5, R7, R8, U, V, W, Y y Z son tal como se definió anteriormente se hace reaccionar con un fluoro-nitrilo de fórmula general B-2, en la que B, R1, R2 y R3 son tal como se definió anteriormente en presencia de una base tal como carbonato de cesio, hidruro de sodio o terc-butóxido de potasio en un disolvente tal como dimetilformamida para producir un compuesto de fórmula general B-3. Esta reacción se puede llevar a cabo calentando la mezcla de reacción a 60ºC bajo irradiación de microondas. Tal como se describe en el procedimiento A, el compuesto B-3 se trata con hidrocloruro de hidroxilamina en presencia de una base tal como trietilamina en un disolvente como tetrahidrofurano y metanol para obtener un compuesto de fórmula general B-4. Esta reacción se puede facilitar calentando la mezcla de reacción bajo irradiación de microondas. El compuesto B-4 se convierte al producto de fórmula general B-5 por reacción con fenilcloroformato en presencia de una base como piridina o diisopropiletilamina seguida de calentamiento de la mezcla de reacción bajo irradiación de microondas para permitir la ciclización, o alternativamente por aislamiento del intermedio resultante y tratamiento con una base como 1,8-diazabiciclo[5.4.0]undec-7-eno en un disolvente como acetonitrilo.

Los ejemplos 1 – 15, 94-98 y el ejemplo 100 se obtuvieron de acuerdo con el procedimiento B.

Se pueden obtener otros compuestos de acuerdo con, o por procedimientos conocidos.

Procedimiento C

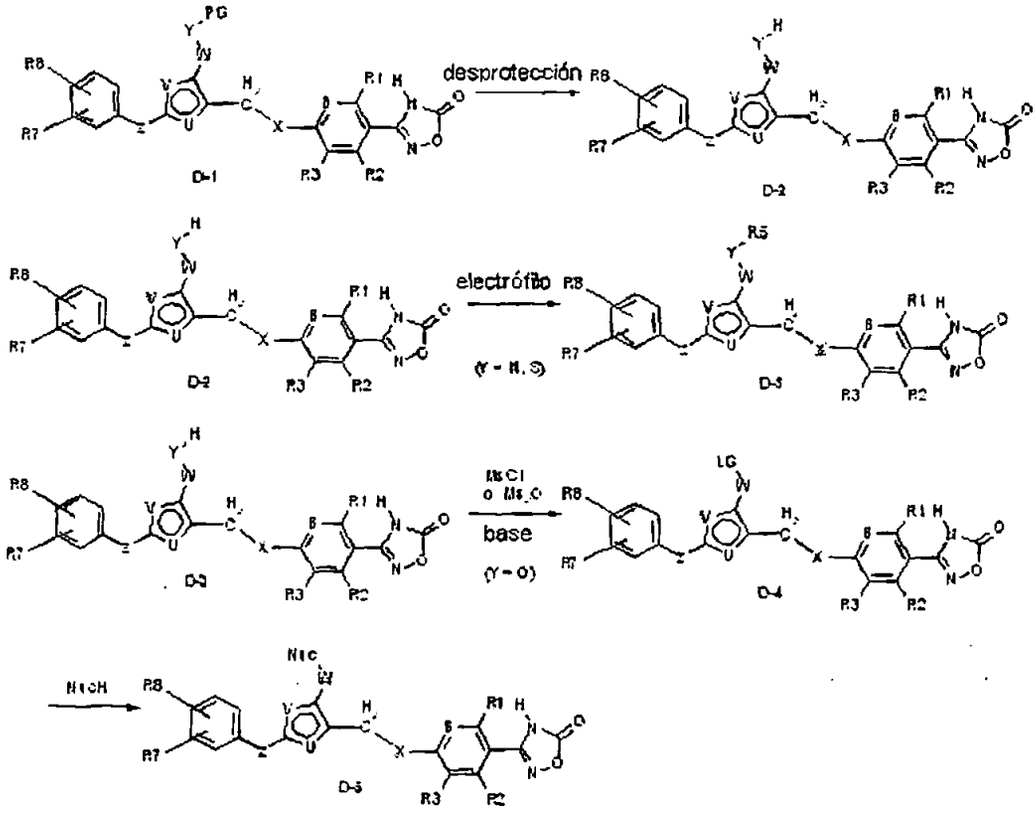


Se hace reaccionar un compuesto de fórmula general C-1, en la que R1 = F y B, R2, R3, R5, R7, R8, U, V, W, Y y Z son tal como se definió anteriormente, con un nucleófilo, p. ej., metilato de sodio, para obtener un compuesto de fórmula general C-2. Un compuesto de fórmula general C-2 se hace reaccionar con hidrocloruro de hidroxilamina en presencia de una base como trietilamina en un disolvente como tetrahidrofurano y metanol para obtener un compuesto de fórmula general C-3. Esta reacción se puede facilitar calentando la mezcla de reacción bajo irradiación de microondas. Un compuesto de fórmula general C-3 se convierte al producto de fórmula general C-4 por reacción con fenilcloroformato en presencia de una base como piridina o diisopropiletilamina seguida de calentamiento de la mezcla de reacción con irradiación de microondas para permitir la ciclización, o alternativamente aislando el intermedio resultante y tratándolo con una base como 1,8-diazabiciclo[5.4.0]undec-7-eno en un disolvente tal como acetonitrilo.

El ejemplo 99 se obtuvo de acuerdo con el procedimiento C.

Se pueden obtener otros compuestos de acuerdo con, o por procedimientos conocidos.

Procedimiento D:



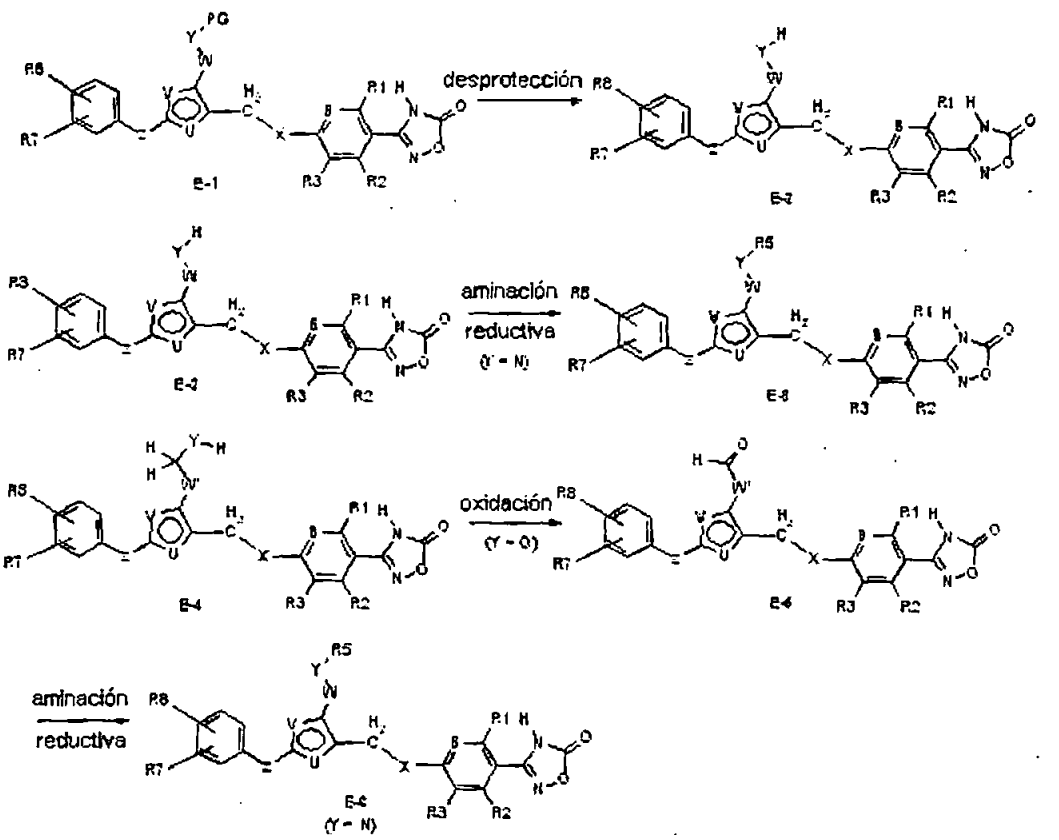
Un compuesto de fórmula general D-1, en la que PG es un grupo protector y R1, R2, R3, R7, R8, B, U, V, W, Y y X son tal como se definió anteriormente, se desprotege bajo condiciones de reacción apropiadas dependiendo de Y y su grupo protector según métodos conocidos por la persona con experiencia en la técnica para producir el compuesto de fórmula general D-2. Si Y = N, el compuesto de fórmula D-2 se puede hacer reaccionar con un electrófilo tal como un haluro de alquilo o un haluro de acilo en presencia de una base tal como diisopropil etil amina en un disolvente polar tal como dimetilformamida para obtener el compuesto de fórmula general D-3 en la que Y = N. Si Y = S, el compuesto de fórmula D-2 se puede hacer reaccionar con un electrófilo tal como un haluro de alquilo o un haluro de acilo en presencia de una base más fuerte tal como metóxido de sodio en un disolvente polar tal como dimetilformamida para obtener el compuesto de fórmula general D-3 en la que Y = S.

Si Y = O, el alcohol de fórmula D-2 se puede convertir a un electrófilo de fórmula general D-4 tal como un haluro (LG = Br, I, Cl) o como un sulfonato, por ejemplo mesilato (LG = OSO_2CH_3) por tratamiento con cloruro de mesilo o anhídrido de mesilo en presencia de una base tal como trietilamina en un disolvente polar como dimetilformamida. El compuesto de fórmula general D-4 se hace reaccionar con un nucleófilo, por ejemplo una amina primaria o secundaria o una sal de sodio de un tiol o un alcohol, en un disolvente polar tal como dimetilformamida para obtener el compuesto de fórmula general D-5. Esta reacción se puede facilitar calentando la mezcla de reacción bajo irradiación de microondas.

Los ejemplos 16, 42-46, 85-91, 101-112 se obtuvieron de acuerdo con el procedimiento D.

Se pueden obtener otros compuestos de acuerdo con, o por procedimientos conocidos.

Procedimiento E:



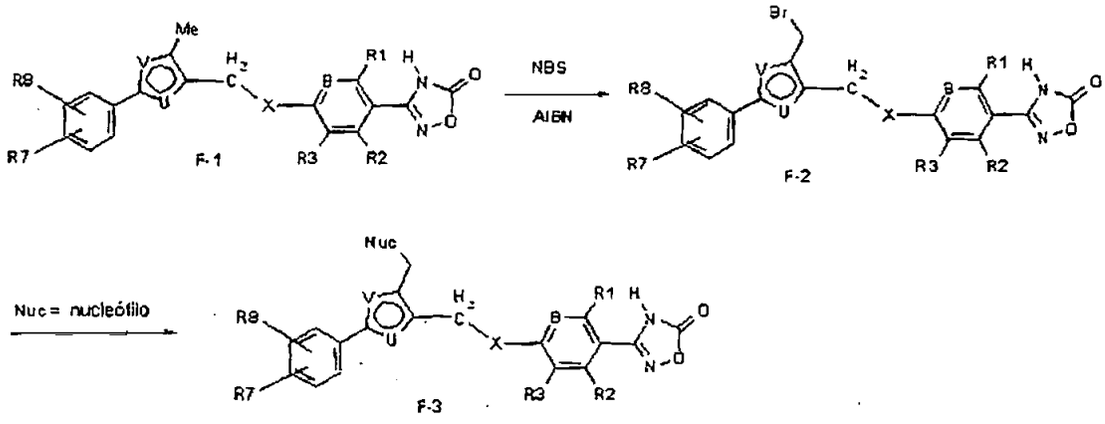
Un compuesto de fórmula general E-1, en la que PG es un grupo protector y R1, R2, R3, R7, R8, B, U, V, W, Y y X son tal como se definió anteriormente, se desprotege bajo condiciones de reacción apropiadas dependiendo de Y y su grupo protector según métodos conocidos por la persona con experiencia en la técnica para producir el compuesto de fórmula general E-2. Si Y = N, la amina de fórmula E-2 se puede transformar en una amina de fórmula general E-3 por aminación reductiva después de un procedimiento en dos etapas que implique formación de imina con un aldehído y trietilamina en un disolvente tal como metanol, luego reducción por adición de un agente reductor tal como borohidruro de sodio, o un procedimiento en una sola etapa que usa aldehído y un agente reductor tal como triacetoxiborohidruro de sodio en un disolvente tal como diclorometano.

Si Y = O y W = W'CH2 en E-2, en la que W' sigue la definición de W previamente citada, el alcohol primario correspondiente de fórmula E-4 se puede oxidar hasta un aldehído de fórmula general E-5 con uno de los métodos conocidos por la persona con experiencia en la técnica, como tratamiento con peryodinano Dess-Martin en un disolvente como diclorometano o dimetilformamida. El compuesto de fórmula general E-5 se convierte en una amina de fórmula general E-6 por aminación reductiva siguiendo bien un procedimiento en dos etapas que implica formación de imina con una amina primaria o secundaria y trietilamina en un disolvente tal como metanol, luego reducción añadiendo un agente reductor tal como borohidruro de sodio, o un procedimiento en una sola etapa que usa una amina primaria o secundaria y un agente reductor tal como triacetoxiborohidruro de sodio en un disolvente tal como diclorometano.

Los ejemplos 35 – 41 y 47 - 53 se obtuvieron de acuerdo con el procedimiento E.

Se pueden obtener otros compuestos de acuerdo con, o por procedimientos conocidos.

Procedimiento F:

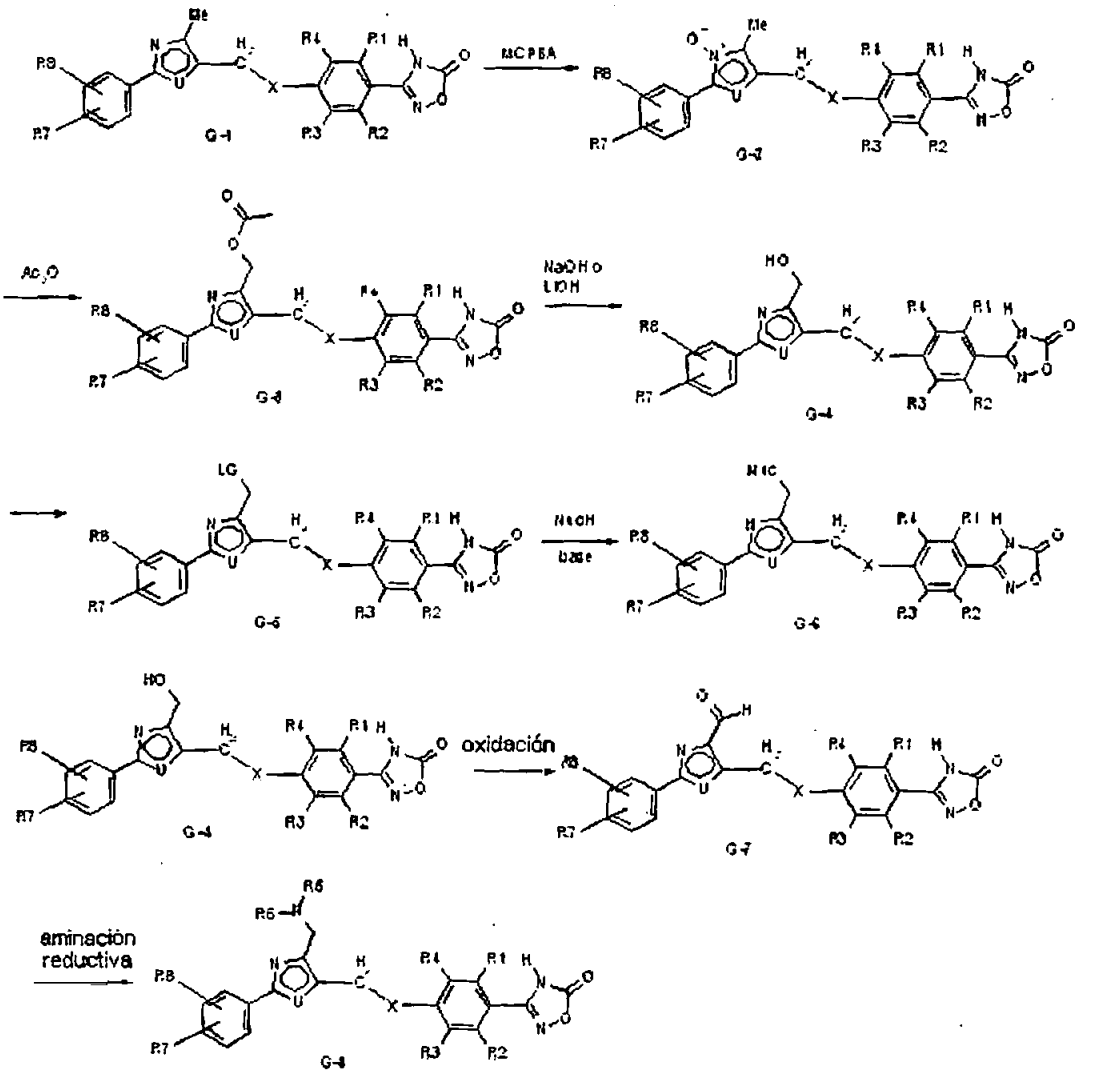


Un compuesto de fórmula general F-1, en la que WYR5 = CH3 y R1, R2, R3, R7, R8, B, U, V y X son tal como se definió anteriormente, se hace reaccionar con N-bromosuccinimida o bromo en un disolvente inerte tal como tetracloruro de carbono (se puede añadir un co-disolvente polar inerte tal como hexafluoroisopropanol para ayudar a solubilizar el material de partida) en presencia de un iniciador radical tal como AIBN o un peróxido para obtener el compuesto de fórmula general F-2. El bromuro resultante de fórmula general F-2 se desplaza con un nucleófilo, por ejemplo una amina primaria o secundaria, en un disolvente polar tal como dimetilformamida para producir un compuesto de fórmula general F-3.

Los ejemplos 17 – 32 y 92 -93 se obtuvieron de acuerdo con el procedimiento F.

Se pueden obtener otros compuestos de acuerdo con, o por procedimientos conocidos.

Procedimiento G:



Un compuesto de fórmula general G-1, en la que B=C(R4), WYR5 = CH3, V = N, X = O u OCH_2 y R1, R2, R3, R4, R7, R8 y U son tal como se definió anteriormente, se hace reaccionar con un oxidante tal como ácido meta-cloroperbenzoico MCPBA en un disolvente tal como diclorometano (se puede añadir un co-disolvente polar tal como hexafluoroisopropanol para ayudar a solubilizar el material de partida) para producir el N-óxido de fórmula general G-2. El compuesto de fórmula general G-2 se somete a una redisposición de tipo Polonovsky calentándose con anhidrido acético para conducir a un acetato de fórmula general G-3. Este acetato se puede hidrolizar al alcohol correspondiente de fórmula general G-4, por ejemplo con hidróxido de litio en agua y un disolvente orgánico tal como metanol o tetrahidrofurano. El alcohol

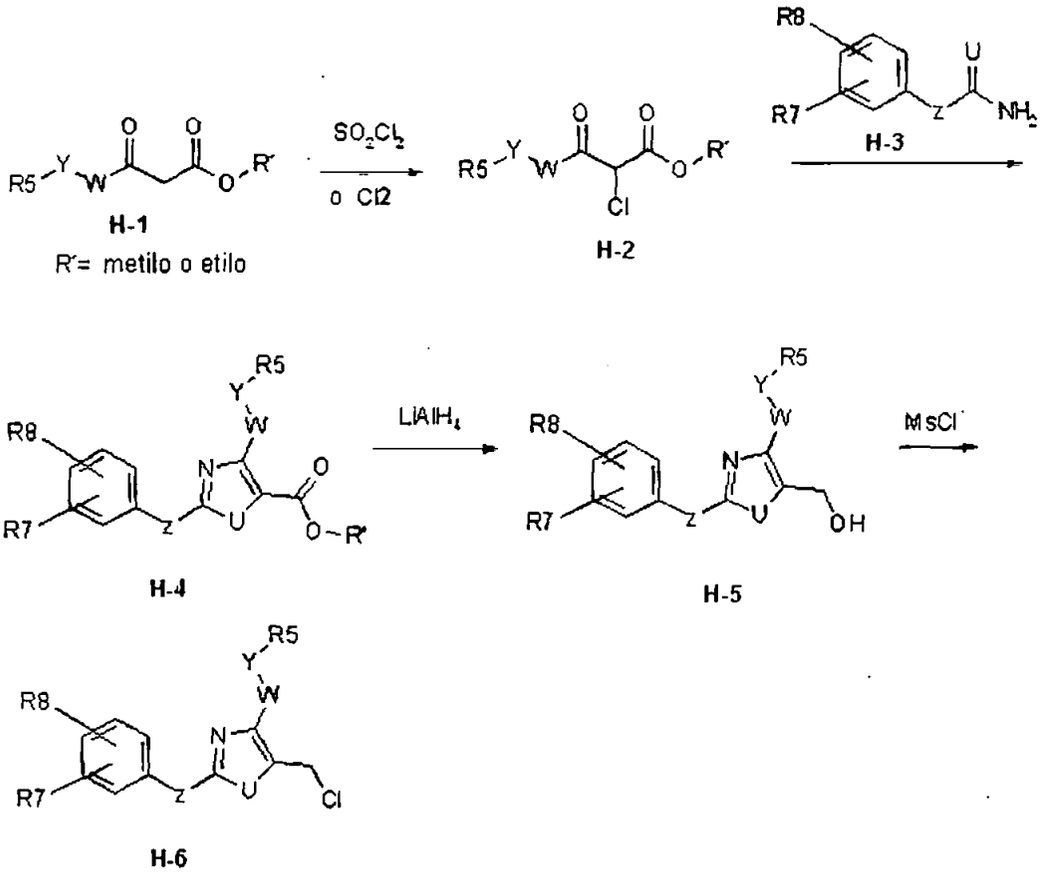
de fórmula general G-4 se puede convertir a un electrófilo de fórmula general G-5 tal como un haluro (LG = Br, I, Cl) o como un sulfonato, por ejemplo mesilato (LG = OSO_2CH_3) por tratamiento con cloruro de mesilo o anhidrido de mesilo en presencia de una base como trietilamina en un disolvente polar como dimetilformamida. El compuesto de fórmula general G-5 se hace reaccionar con un nucleófilo, por ejemplo una amina primaria o secundaria, para obtener el compuesto de fórmula general G-6.

Alternativamente, el alcohol de fórmula general G-4 se puede oxidar hasta un aldehído de fórmula general G-7 con uno de los métodos conocidos por la persona experimentada en la técnica, como tratamiento con dióxido de manganeso en un disolvente tal como diclorometano o dimetilformamida o con peryodinano Dess-Martin. El compuesto de fórmula general G-7 se convierte a una amina de fórmula general G-8 por aminación reductiva siguiendo bien un procedimiento en dos etapas que implica formación de imina con una amina primaria o secundaria y trietilamina en un disolvente tal como metanol, luego reducción añadiendo un agente reductor tal como borohidruro de sodio, o un procedimiento en una sola etapa usando una amina primaria o secundaria y un agente reductor tal como triacetoxiborohidruro de sodio en un disolvente como diclorometano.

Los ejemplos 33 – 34 se obtuvieron de acuerdo con el procedimiento G.

Se pueden obtener otros compuestos de acuerdo con, o por procedimientos conocidos.

Procedimiento H:



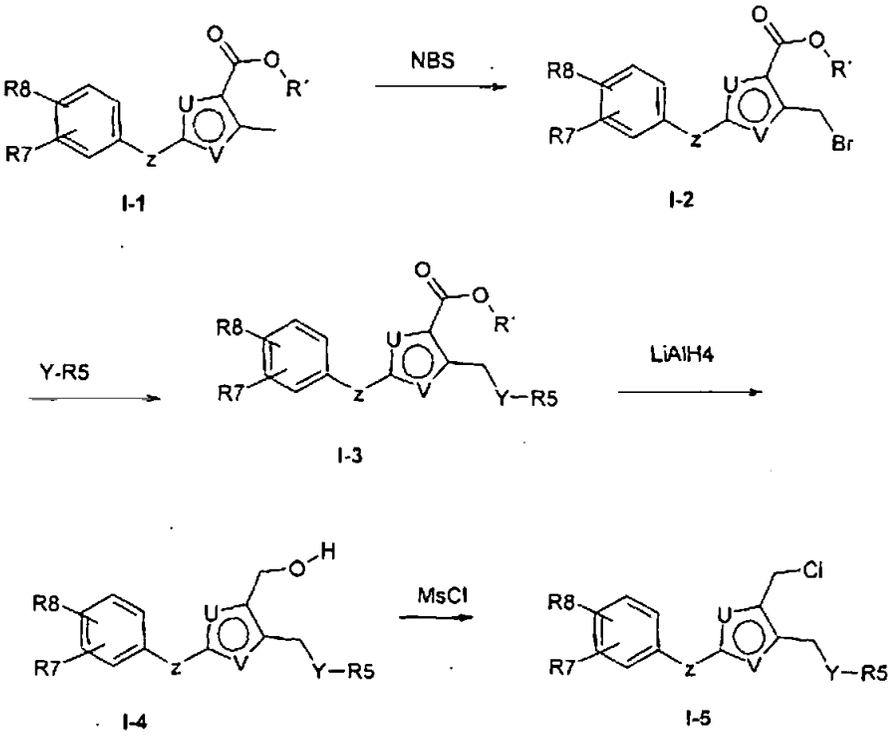
Se hace reaccionar éster metílico o etílico del ácido 3-oxo-carboxílico de fórmula general H-1, en la que R5, Y y W son tal como se definió anteriormente, con cloro o cloruro de sulfurilo para producir el cloruro correspondiente de fórmula general H-2. Este compuesto de fórmula general H-2 se hace reaccionar con una benzamida o tiobenzamida de fórmula general H-3, en la que U es S u O y R7, R8 y Z son tal como se definió anteriormente para obtener un feniltiazol o feniloxazol éster de fórmula general H-4. El éster de fórmula general H-4 se reduce con un agente reductor, por ejemplo hidruro de aluminio y litio, al alcohol de fórmula general H-5. El alcohol de fórmula general H-5 se hace reaccionar con cloruro de metansulfonilo en presencia de una base como trietilamina en un disolvente como diclorometano para obtener la unidad estructural de fórmula general H-6, en la que R5, R7, R8, U, W, Y y Z son tal como se definió anteriormente.

Se pueden obtener otros compuestos de acuerdo con, o por

procedimientos conocidos.

Procedimiento I:

Este procedimiento se utiliza para sintetizar las unidades estructurales I-4, que corresponde a la fórmula general A-1 del procedimiento A, en la que R = OH , W es CH2, R9 y R10 son H, Z es un enlace, alquilo (C2-C6), -CH=CH-, -C□C- y U, V, Y, R5, R7 y R8 son tal como se define y I-5, que corresponde a la fórmula general A-3 del procedimiento A, en la que R = Cl, W es CH2 , R9 y R10 son H, Z es un enlace, alquilo (C2-C6), -CH=CH-, -C□C- y U, V, Y, R5, R7 y R8 son tal como se define.



El oxazol o tiazol éster de fórmula general I-1, en la que Z es un enlace, alquilo (C2-C6), -CH=CH- o -C□C-, W es CH2, Y es un enlace, R5 es H y U, V, R7 y R8 son tal como se define, se broma por el tratamiento con N-bromosuccinimida en tetraclorometano a reflujo en presencia de un iniciador radical como AIBN para producir el producto bromado de fórmula general I-2. En el caso de que Z sea alquilo (C2-C6), el átomo de carbono directamente unido al anillo oxazol o tiazol también se broma. El producto bromado de fórmula general I-2 se hace reaccionar con un nucleófilo Y-R5, en el que Y es

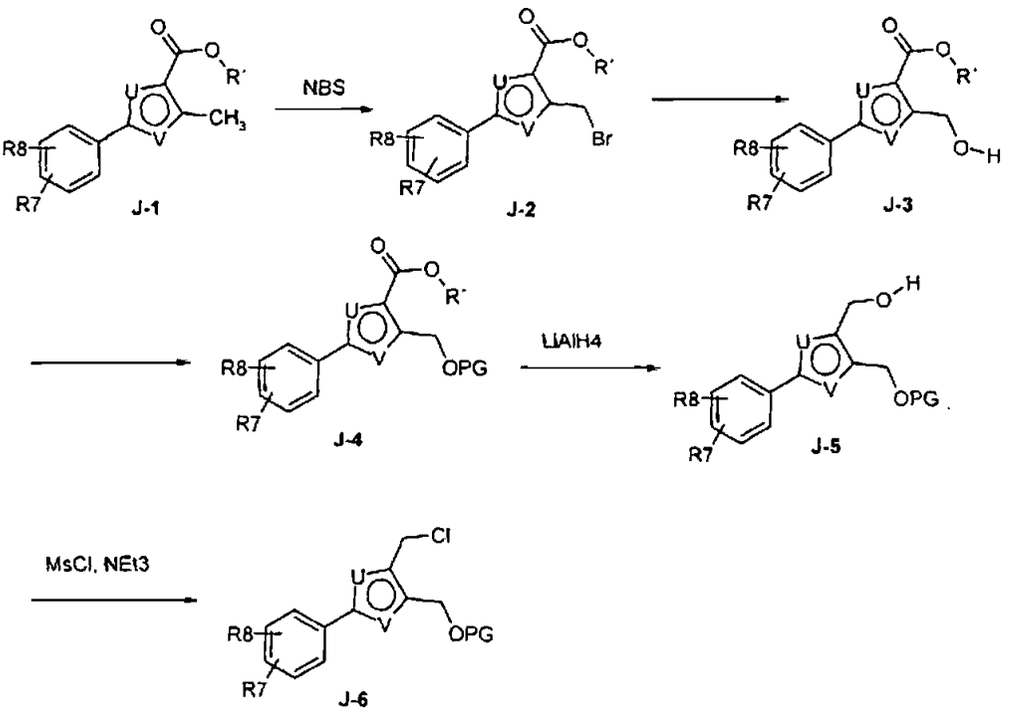
OH o Y es NH(R6) y R5 es tal como se define en un disolvente polar como tetrahidrofurano en presencia de una base como DBU para obtener un compuesto de fórmula general I-3. En caso de que el átomo de carbono directamente unido al anillo oxazol o tiazol del compuesto de fórmula general I-2 también esté bromado, este se eliminará bajo condiciones de reacción para producir el doble enlace. En caso de que Z sea –CH2-CH2-, la eliminación tendrá lugar bajo condiciones de bromación. El doble enlace se puede hidrogenar con hidrógeno en presencia de un catalizador de paladio en un disolvente polar como etanol o metanol.

El éster de fórmula general I-3 se reduce con un agente reductor, p. ej., hidruro de aluminio y litio, al alcohol de fórmula general I-4. El alcohol de fórmula general I-4 se hace reaccionar con cloruro de metansulfonilo en presencia de una base como trietilamina en un disolvente como diclorometano para obtener la unidad estructural de fórmula general I-5.

Se pueden obtener otros compuestos de acuerdo con, o por procedimientos conocidos.

Procedimiento J:

Este procedimiento se usa para sintetizar las unidades estructurales J-5 y J-6, que corresponde a la fórmula general A-1 del procedimiento A, en la que R5 = PG (PG = grupo protector), Y = O, Z es un enlace, W = -CH2, R9 y R10 son H, R = -OH o –Cl y U, V, R7 y R8 son tal como se definió anteriormente.



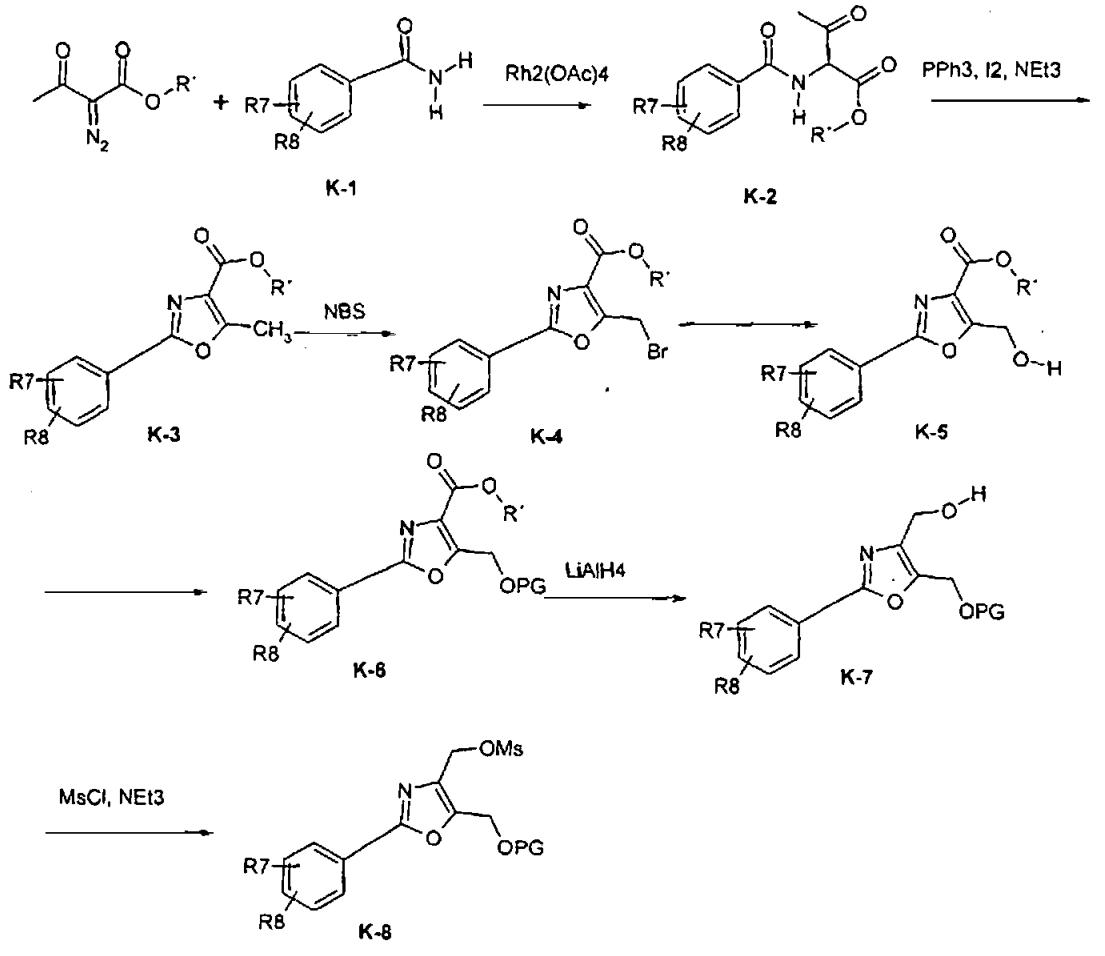
Un compuesto de la fórmula general J-1 en la que R' es alquilo como metilo o etilo, y U, V, R8 y R7 son tal como se definió anteriormente, se broma tras el tratamiento con N-bromosuccinimida en un disolvente apolar como tetraclorometano para obtener un compuesto de fórmula general J-2. El bromuro de fórmula general J-2 se convierte en el alcohol de fórmula general J-3 por tratamiento con trifluoroacetato de plata en un disolvente como dimetilformamida y posterior calentamiento del trifluoroacetato resultante en un disolvente como etanol. El grupo hidroxilo del compuesto de fórmula general J-2 se protege por ejemplo como éter tetrahidropiranílico por tratamiento con 3,4-dihidro-2H-pirano en un disolvente como diclorometano en presencia de ácido como para-toluensulfonato de piridinilo para obtener un compuesto de fórmula general J-4. El éster del compuesto de fórmula general J-4 se reduce con un agente como hidruro de aluminio y litio en un disolvente como tetrahidrofurano para obtener el compuesto de fórmula general J-5, en el que R es OH. El grupo hidroxilo se puede convertir a un cloro por tratamiento con cloruro de metansulfonilo en presencia de una base como trietilamina en un disolvente como diclorometano para obtener un compuesto de fórmula general J-6, en la que R es Cl.

Se pueden obtener otros compuestos de acuerdo con, o por

procedimientos conocidos.

Procedimiento K:

Este procedimiento se utiliza para sintetizar las unidades estructurales K7 y K-8, que corresponde a la fórmula general A-1 del procedimiento A, en la que R5 = PG (PG = grupo protector), Y = O, W = -CH2-, V es O y U es N, R = -OH o –OMs, R9 = H, R10 = H, Z es un enlace, R8 y R7 son tal como se definió anteriormente.

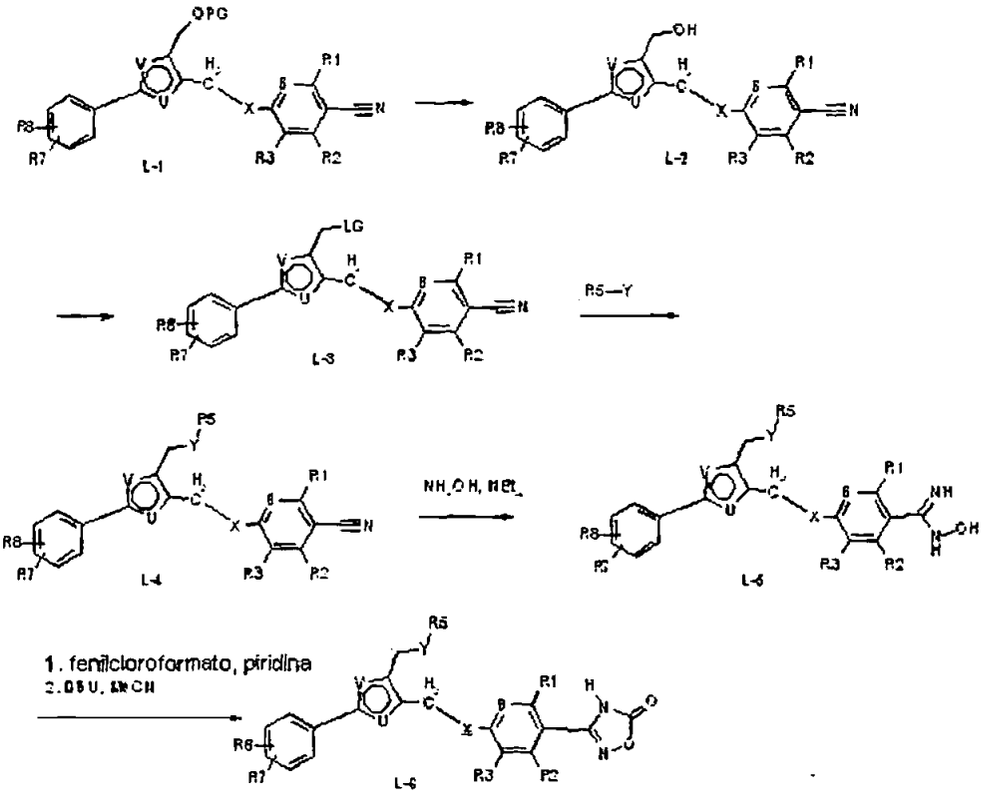


Se hace reaccionar Metil 2-diazo-3-oxobutanoato (R´= Me) o Etil-2-diazo-3-oxobutanoato (R´= Et) con una benzamida de fórmula general K-1, en la que R8 y R7 son tal como se definió anteriormente en presencia de tetraacetato de di-rodio en un disolvente apolar como 1,2-dicloroetano para obtener un compuesto de fórmula general K-2. El compuesto de fórmula general K-2 se cicla para obtener un compuesto de fórmula general K-3 por

tratamiento con trifenilfosfina y yodo en un disolvente apolar como diclorometano.

El compuesto de fórmula general K-3 se broma por tratamiento con N-bromosuccinimida en un disolvente apolar como tetraclorometano para obtener un compuesto de fórmula general K-4. El bromuro de fórmula general K-4 se convierte en el alcohol de fórmula general K-5 por tratamiento con trifluoroacetato de plata en un disolvente como dimetilformamida y posterior calentamiento del trifluoroacetato resultante en un disolvente como etanol. El grupo hidroxilo del compuesto de fórmula general K-5 se protege por ejemplo como éter tetrahidropiranílico por tratamiento con 3,4-dihidro-2H-pirano en un disolvente como diclorometano en presencia de ácido como para-toluensulfonato de piridinio para obtener un compuesto de fórmula general K-6. El éster del compuesto de fórmula general K-6 se reduce con un agente reductor como hidruro de aluminio y litio en un disolvente como tetrahidrofurano para obtener el compuesto de fórmula general K-7. El grupo hidroxilo se puede convertir en un mesilato por tratamiento con cloruro de metansulfonilo en presencia de una base como trietilamina en un disolvente como diclorometano para obtener un compuesto de fórmula general K-8.

Procedimiento L



Un compuesto de fórmula general L-1 (que se puede sintetizar de acuerdo con el procedimiento A, en el que el sustituyente W-Y-R5 de las unidades estructurales A-1 es -CH2-OPG; la síntesis de esta unidad estructural se describe en los procedimientos J y K) en la que B, U, V, X, R1, R2, R3 , R4 , R7 y R8 son tal como se define y PG significa un grupo protector como por ejemplo un tetrahidropiraniléter. El grupo protector del compuesto de fórmula general L-1 se elimina, en el caso de que PG se un tetrahidropiraniléter, por ejemplo, por tratamiento con un ácido en un disolvente polar como metanol para obtener un compuesto de fórmula general I-2. El grupo hidroxilo del compuesto de fórmula general L-2 se convierte a un grupo saliente (LG), por ejemplo un mesilato o cloruro por tratamiento con cloruro de metansulfonilo en presencia de una base como diclorometano para obtener un compuesto de fórmula general L-3. El compuesto de fórmula general L-3 se hace reaccionar con un nucleófilo Y-R5, en el que Y es OH o Y es NH(R6) y R5 es tal como se define en un disolvente polar como tetrahidrofurano en presencia de una base como DBU para obtener un compuesto de fórmula general L-4. El compuesto de fórmula general L-4 se hace reaccionar con hidrocloruro de hidroxilamina en

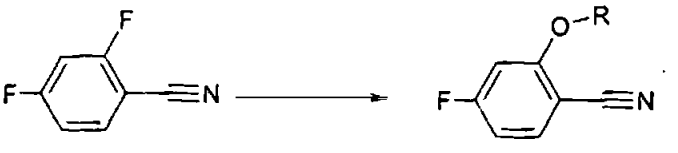
presencia de una base como trietilamina en un disolvente como tetrahidrofurano y metanol para obtener un compuesto de la fórmula general L-5. Un compuesto de la fórmula general L-5 se convierte al producto de fórmula general L-6 por reacción con fenilcloroformato en presencia de una base como piridina y tratando este intermedio con una base como 1,8-diazabiciclo[5.4.0]undec-7-eno en un disolvente como acetonitrilo.

Los ejemplos 60 – 83 se obtuvieron de acuerdo con el procedimiento L.

Se pueden obtener otros compuestos de acuerdo con, o por procedimientos conocidos.

Procedimiento M:

Este procedimiento se utiliza para sintetizar las unidades estructurales M-2, que corresponde a la fórmula general B-2 del procedimiento B, en la que B = C(R4), R1 = OR, R es alquilo (C1-C4) o alquilen (C0-C2)-cicloalquilo (C3-C6) donde alquilo y alquileno no están sustituidos o están mono, di o trisustituidos con F, y donde R2, R3 y R4 son H.



M-1 M-2

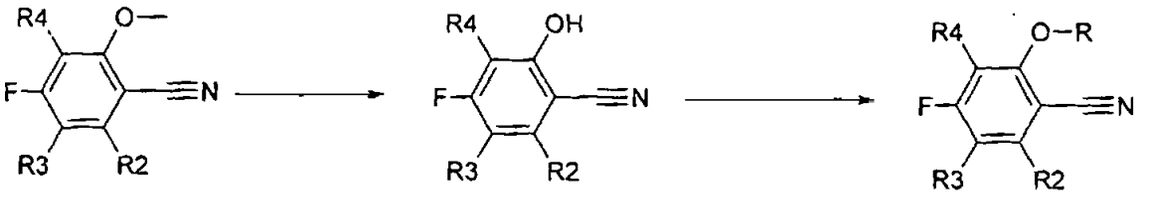
Se trata 2,4-difluoro-benzonitrilo de fórmula M-1 con un alcohol ROH en un disolvente tal como tetrahidrofurano en presencia de una base tal como terc-butóxido de potasio a 0-5°C para producir el éter de fórmula general M-2 en la que R es alquilo (C1-C4) o alquilen (C0-C2)-cicloalquilo (C3-C6) en la que alquilo y alquileno no están sustituidos o están mono, di o trisustituidos con F.

Se pueden obtener otros compuestos de acuerdo con, o por procedimientos conocidos.

Procedimiento N:

Este procedimiento se utiliza para sintetizar las unidades estructurales N-3, que corresponde a la fórmula general B-2 del procedimiento B, en la que B

= C(R4), R1 = OR, R es alquilo (C1-C4) o alquilen (C0-C2)-cicloalquilo (C3-C6) en la que alquilo y alquileno no están sustituidos o están mono, di o trisustituidos con F, y en la que R2, R3 y R4 son tal como se definió anteriormente.



N-1 N-2 N-3

El éter aril metílico de fórmula general N-1, en la que R2, R3 y R4 son tal como se definió anteriormente, se desmetila por tratamiento con tricloruro de aluminio en dicloroetano a reflujo para producir el fenol de fórmula general N-2. El fenol de fórmula general N-2 se hace reaccionar con un electrófilo RX en el que X es un grupo saliente tal como haluro o un sulfonato en un disolvente polar como dimetilformamida en presencia de una base como carbonato de potasio para obtener un compuesto de fórmula general N-3. Cuando se usa clorodifluororacetato de metilo como electrófilo y se calienta la mezcla de reacción hasta 60-120°C en un disolvente tal como dimetilformamida o dimetilacetamida, se obtiene el compuesto de fórmula general N-3, en la que R es CHF2.

Se pueden obtener otros compuestos de acuerdo con, o por procedimientos conocidos.

Lista de abreviaturas:

Ac	Acetilo
AIBN	2,2´-azobis(2-metilpropionitrilo)
Bn	bencilo
iBu	isobutilo
tBu	terc-Butilo
BuLi	n-butil-litio
Bz	benzoilo

CI	Ionización química (MS)
Cy	ciclohexilo
DBU	1,8-diazabiciclo[5.4.0]undec-7-eno
DEAD	dietilazodicarboxilato
DCI	Ionización química directa (EM)
DCM	diclorometano
DMAP	N,N-dimetilaminopiridina
DMF	N,N-dimetilformamida
DMSO	dimetilsulfóxido
EE	acetato de etilo
eq	equivalentes
EI	Ionización por impacto de electrones (MS)
ESI	Ionización por electropulverización (MS)
FG	Grupo funcional
F-TEDA	1-clorometil-4-fluoro-1,4-diazoniabiciclo[2.2.2]octano bis(tetrafluoroborato)
Hal	halógeno
HPLC	Cromatografía líquida de alta eficacia
LC-MS	cromatografía de líquidos acoplada con espectrometría de masas
GS	Grupo lábil
Me	Metilo
MCPBA	Ácido meta-cloroperbenzoico
MS	espectrometría de masas
MsCl	Cloruro de metansulfonilo
MW	microondas
NBS	N-bromosuccinimida
RMN	Resonancia magnética nuclear
p	Para
Pd/C	paladio sobre carbono
PG	Grupo Protector

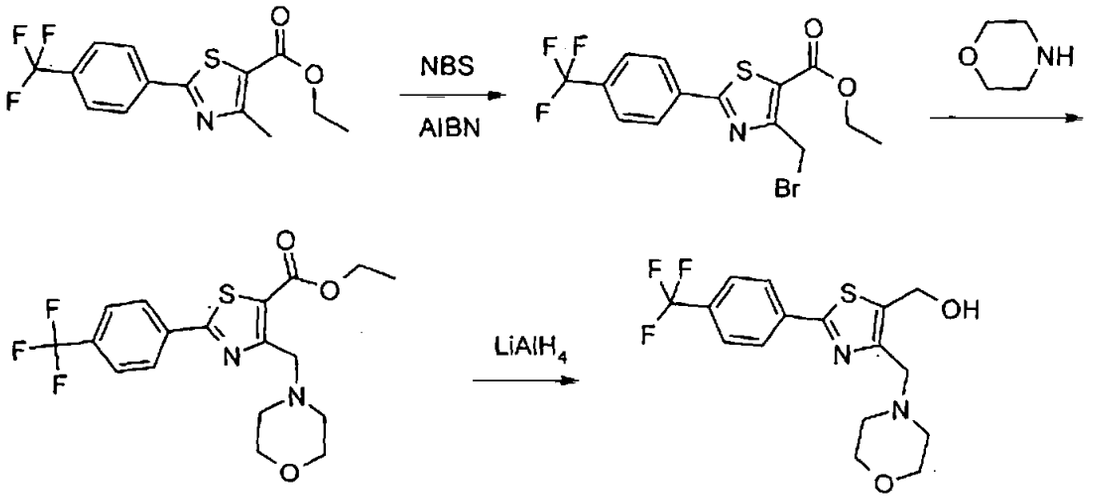
iPr	isopropilo
nPr	n-propilo
pTsOH	Ácido p-toluensulfónico
Rf	factor de retención (TLC)
terc	terciario
TLC	Cromatografía en capa fina
TMS	trimetilsililo

Los compuestos adicionales de la fórmula I se pueden preparar de forma correspondiente o por procedimientos conocidos.

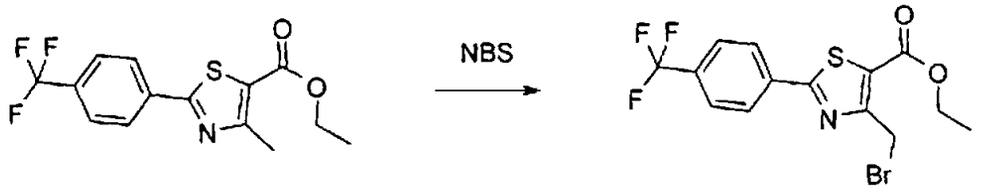
A continuación se describen los procedimientos experimentales para preparar los ejemplos antes mencionados.

Síntesis de las unidades estructurales según el procedimiento K:

2-(4-Trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-il]-metanol



Éster etílico del ácido 4-bromometil-2-(4-trifluorometil-fenil)-tiazol-5-carboxílico[1]

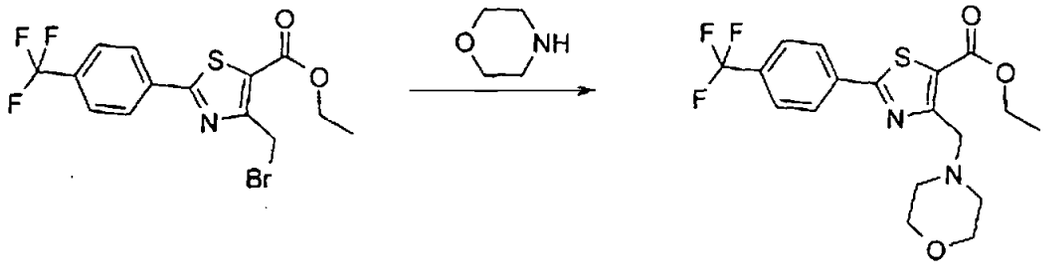


[1]WO02067912

A una disolución de 1 g de éster etílico del ácido 4-metil-2-(4-trifluorometil-fenil)-tiazol-5-carboxílico en 8 mL de tetracloruro de carbono se le añadió en porciones 0,1 g de peróxido de benzoílo y 0,56 g de NBS. La mezcla resultante se calentó hasta 80°C durante 1,5 h. Se añadió 0,1 g de NBS y la mezcla de reacción se calentó hasta 80°C durante toda la noche. Se añadió 0,1 g de NBS adicional y la mezcla de reacción se calentó hasta 80°C durante 2 h. Luego se vertió en agua y se extrajo con diclorometano. Los extractos orgánicos se secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida. El producto bruto se purificó por cromatografía en columna sobre gel de sílice (heptano 1/ tolueno 1 seguido de tolueno puro) para producir 1,02 g de éster etílico del ácido 4-bromometil-2-(4-trifluorometil-fenil)-tiazol-5-carboxílico.

C14H11BrF3NO2S (394,21), MS(EI): 394 ($M+H^+$).

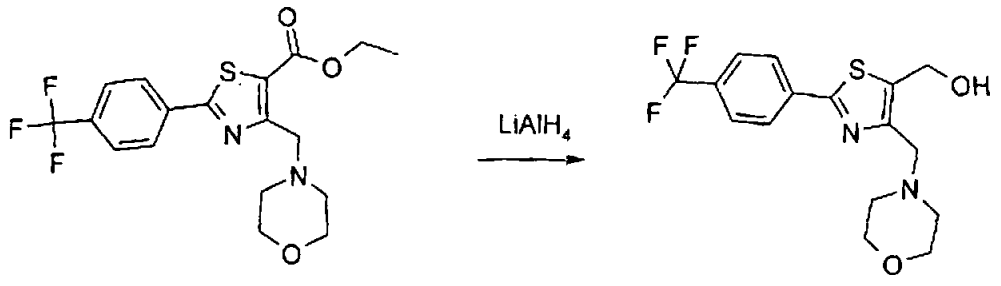
Éster etílico del ácido 4-morfolin-4-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-carboxílico



A una disolución de 500 mg de éster etílico del ácido 4-bromometil-2-(4-trifluorometil-fenil)-tiazol-5-carboxílico en 5 mL de acetonitrilo se le añadieron 190 mg de carbonato de potasio y 110,5 mg de morfolina. La mezcla resultante se agitó a temperatura ambiente durante la noche. Se añadió agua y la mezcla se extrajo con diclorometano. Los extractos orgánicos se secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida. El producto bruto se purificó por cromatografía en columna sobre gel de sílice (gradiente de diclorometano/metanol de 100/0 a 50/50) seguido de lavado del sólido recogido con éter diisopropílico para producir 355 mg de éster etílico del ácido 4-morfolin-4-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-carboxílico.

C18H19F3N2O3S (400,42), MS(EI): 400 (M^+).

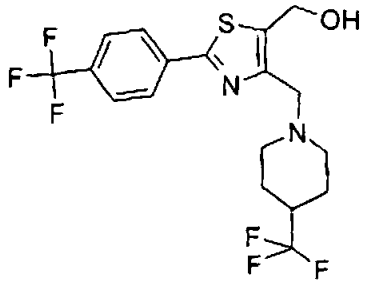
[4-Morfolin-4-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol



A una disolución de 355 mg de éster etílico del ácido 4-morfolin-4-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-carboxílico en 1 mL de tetrahidrofurano se le añadió 0,88 mL de una disolución 1M de hidruro de aluminio y litio en tetrahidrofurano. La mezcla resultante se agitó a temperatura ambiente durante 1 h. Se añadió agua lentamente y la mezcla se extrajo con diclorometano. Los extractos orgánicos se secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida. El producto bruto se purificó por cromatografía en columna sobre gel de sílice (gradiente de diclorometano/metanol de 100/0 a 90/10) para producir 276 mg de [4-morfolin-4-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol.

C16H17F3N2O2S (358,39), MS(EI): 358 (M^+).

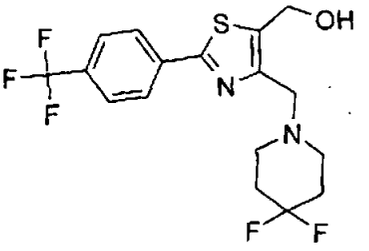
[2-(4-Trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-il]-metanol



De acuerdo con el método descrito para [4-morfolin-4-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol, se obtuvo [2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-il]-metanol a partir de éster etilico del ácido 4-bromometil-2-(4-trifluorometil-fenil)-tiazol-5-carboxílico y 4-trifluorometil-piperidina.

C18H18F6N2OS (424,41), MS(ESI): 425 ($M+H^+$).

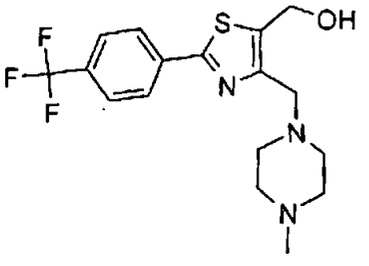
[4-(4,4-Difluoro-piperidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol



De acuerdo con el método descrito para [4-morfolin-4-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol, se obtuvo 4-(4,4-difluoro-piperidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol a partir de éster etílico del ácido 4-bromometil-2-(4-trifluorometil-fenil)-tiazol-5-carboxílico y 4,4-difluoro-piperidina.

C17H17F5N2OS (392,39), MS(EI): 392 (M^+).

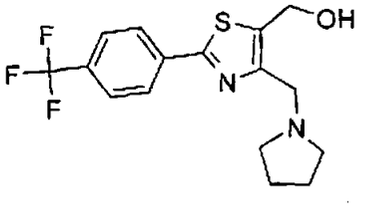
[4-(4-Metil-piperazin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol



De acuerdo con el método descrito para [4-morfolin-4-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol, se obtuvo [4-(4-metil-piperazin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol a partir de éster etílico del ácido 4-bromometil-2-(4-trifluorometil-fenil)-tiazol-5-carboxilico y 1-metil-piperazina.

C17H20F3N3OS (371,43), MS(EI): 371 (M^+).

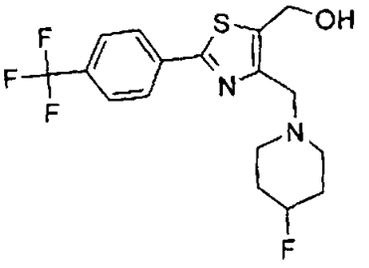
[4-Pirrolidin-1-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol



De acuerdo con el método descrito para [4-morfolin-4-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol, se obtuvo [4-pirrolidin-1-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol a partir de éster etílico del ácido 4-bromometil-2-(4-trifluorometil-fenil)-tiazol-5-carboxílico y pirrolidina.

C16H17F3N2OS (342,38), MS(ESI): 343 ($M+H^+$).

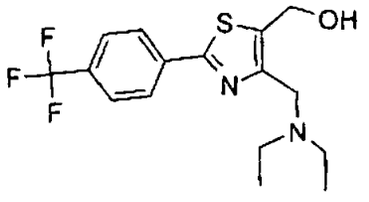
[4-(4-Fluoro-piperidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol



De acuerdo con el método descrito para [4-morfolin-4-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol, se obtuvo [4-(4-fluoro-piperidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol a partir de éster etílico del ácido 4-bromometil-2-(4-trifluorometil-fenil)-tiazol-5-carboxílico y 4-fluoro-piperidina.

$C_{17}H_{18}F_4N_2OS$ (374,40), MS(ESI): 375 ($M+H^+$).

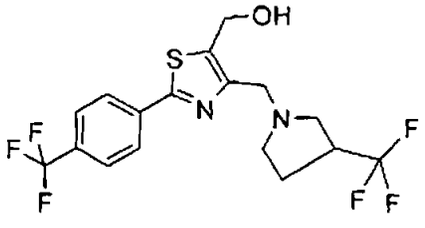
[4-Dietilaminometil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol



De acuerdo con el método descrito para [4-morfolin-4-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol, se obtuvo [4-dietilaminometil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol a partir de éster etílico del ácido 4-bromometil-2-(4-trifluorometil-fenil)-tiazol-5-carboxílico y dietilamina.

$C_{16}H_{19}F_3N_2OS$ (344,40), MS(ESI): 345 ($M+H^+$).

[2-(4-Trifluorometil-fenil)-4-(3-trifluorometil-pirrolidin-1-ilmetil)-tiazol-5-il]-metanol

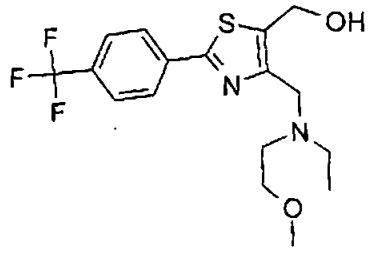


De acuerdo con el método descrito para [4-morfolin-4-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol, se obtuvo [2-(4-trifluorometil-fenil)-4-(3-trifluorometil-pirrolidin-1-ilmetil)-tiazol-5-il]-metanol racémico a partir de éster

etílico del ácido 4-bromometil-2-(4-trifluorometil-fenil)-tiazol-5-carboxílico y 4-trifluorometil-pirrolidina racémica.

C17H16F6N2OS (410,38), MS(ESI): 411 ($M+H^+$).

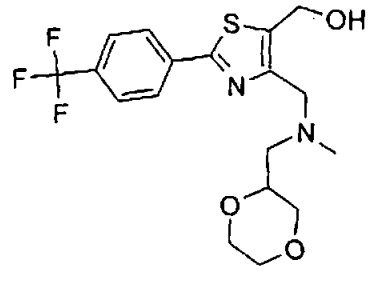
[4-{[Etil-(2-metoxi-etil)-amino]-metil}-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol



De acuerdo con el método descrito para [4-morfolin-4-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol, se obtuvo [4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol a partir de éster etílico del ácido 4-bromometil-2-(4-trifluorometil-fenil)-tiazol-5-carboxílico y etil-(2-metoxi-etil)-amina.

C17H21F3N2O2S (374,42), MS(ESI): 375 ($M+H^+$).

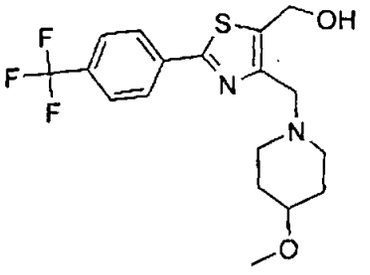
[4-[([1,4]Dioxan-2-ilmetil-metil-amino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol



De acuerdo con el método descrito para [4-morfolin-4-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol, se obtuvo [4-[([1,4]dioxan-2-ilmetil-metil-amino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol racémico a partir de éster etílico del ácido 4-bromometil-2-(4-trifluorometil-fenil)-tiazol-5-carboxílico y [1,4]dioxan-2-ilmetil-metil-amina racémica.

C18H21F3N2O3S (402,43), MS(ESI): 403 ($M+H^+$).

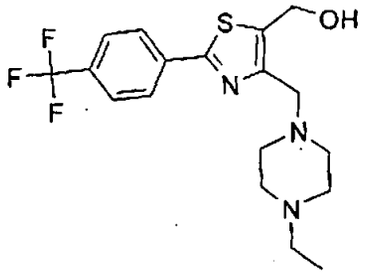
[4-(4-Metoxi-piperidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol



De acuerdo con el método descrito para [4-Morfolin-4-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol, se obtuvo [4-(4-metoxi-piperidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol a partir de éster etílico del ácido 4-bromometil-2-(4-trifluorometil-fenil)-tiazol-5-carboxílico y 4-metoxi-piperidina.

$C_{18}H_{21}F_3N_2O_2S$ (386,44), MS(ESI): 387 ($M+H^+$).

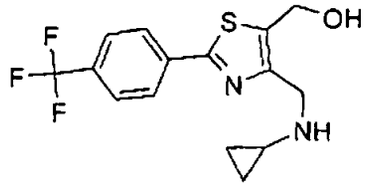
[4-(4-Etil-piperazin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol



De acuerdo con el método descrito para [4-morfolin-4-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol, se obtuvo [4-(4-etil-piperazin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol a partir de éster etílico del ácido 4-bromometil-2-(4-trifluorometil-fenil)-tiazol-5-carboxílico y 1-piperazin-1-il-etanona. La función amida en el grupo piperazina se reduce a la amina correspondiente en la etapa de reducción. Esta unidad estructural podría también prepararse comenzando por 4-etil-piperazina.

$C_{18}H_{22}F_3N_3OS$ (385,45), MS(ESI): 386 ($M+H^+$).

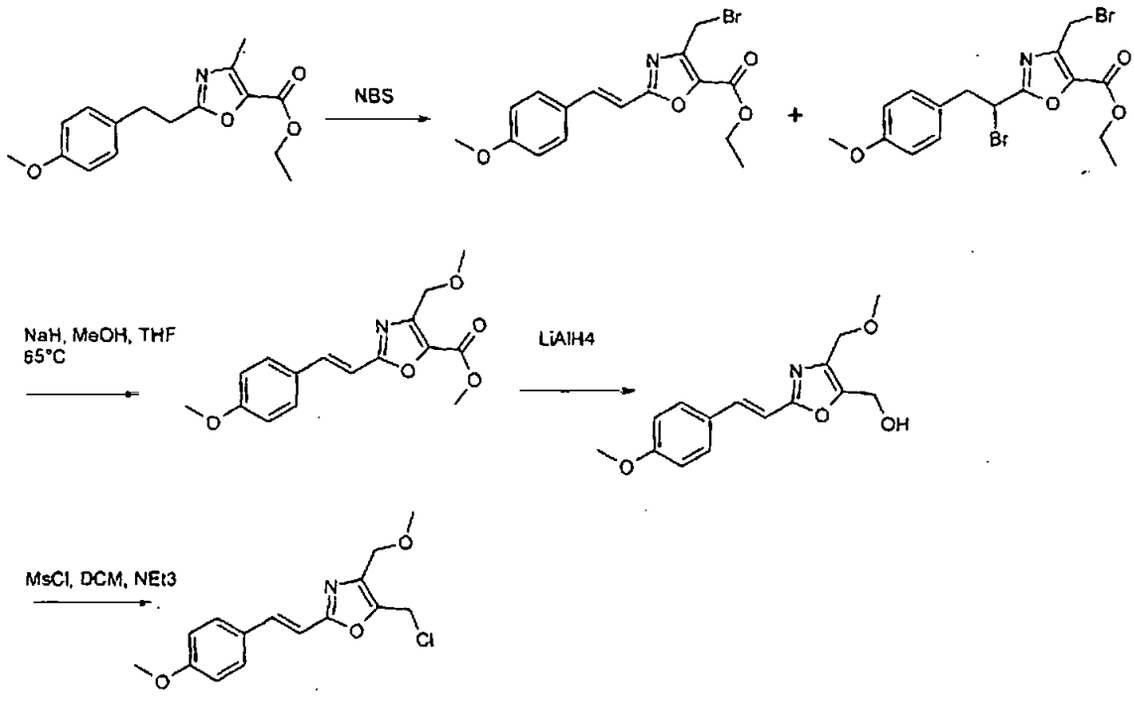
[4-Ciclopropilaminometil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol



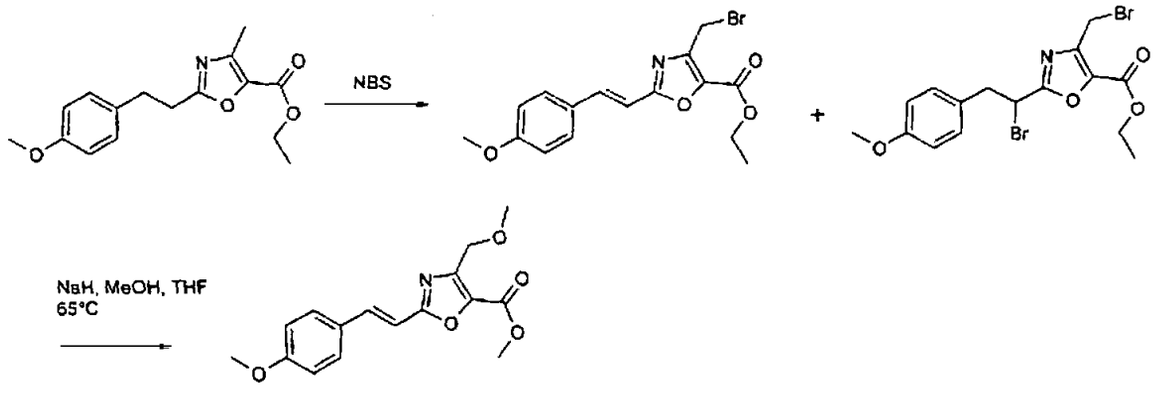
De acuerdo con el método descrito para [4-morfolin-4-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol, se obtuvo [4-ciclopropilaminometil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol a partir de éster etílico del ácido 4-bromometil-2-(4-trifluorometil-fenil)-tiazol-5-carboxílico y ciclopropilamina.

C15H15F3N2OS (328,36), MS(ESI): 329 ($M+H^+$).

5-Clorometil-4-metoximetil-2-[2-(4-metoxi-fenil)-vinil]-oxazol



Éster metílico del ácido 4-metoximetil-2-[2-(4-metoxi-fenil)-vinil]-oxazol-5-carboxílico



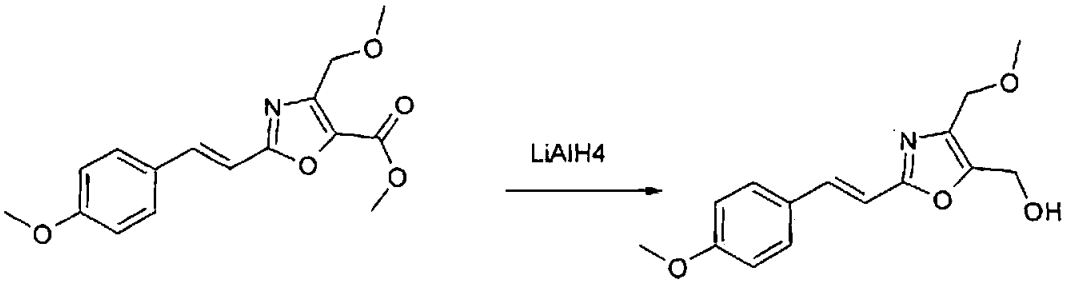
A una mezcla en reflujo de 6,40 g de éster etílico del ácido 2-[2-(4-metoxi-fenil)-etil]-4-metil-oxazol-5-carboxílico (sintetizada de acuerdo con el método descrito para 5-clorometil-4-metil-2-[2-(4-trifluorometil-fenil)-etil]-oxazol

a partir de 3-(4-metoxifenil)propionamida y 2-cloroacetoacetato), en 90 ml de tetraclorometano, se le añadió en porciones una mezcla de 9,82 g de N-bromosuccinimida y 3,63 g de 2,2'-azobis(2-metilpropionitrilo). La mezcla de reacción se calentó a reflujo durante tres horas.. La mezcla de reacción enfriada se filtró sobre un lecho de celita, el filtrado se evaporó *in vacuo* y el residuo resultante se purificó por cromatografía sobre gel de sílice con el eluyente n-heptano: acetato de etilo = 15:1 => 5:1 para proveer 11,0 g de una mezcla de éster etílico del ácido 4-bromometil-2-[2-(4-metoxi-fenil)-vinil]-oxazol-5-carboxílico y éster etílico del ácido 2-[1-bromo-2-(4-metoxi-fenil)-etil]-4-bromometil-oxazol-5-carboxílico.

Esta mezcla se disolvió en una mezcla de 50 ml de metanol y 10 ml de tetrahidrofurano. Se añadió 1,87 g de hidruro de sodio y la mezcla de reacción se agitó a 65°C durante una hora. La mezcla de reacción enfriada se neutralizó por adición de ácido acético (pH ~ 6). Los disolventes se eliminaron *in vacuo*, el residuo se disolvió en 100 ml de acetato de etilo y se lavó con 50 ml de salmuera. La fase orgánica se secó sobre MgSO4. El disolvente se separó a vacío. El residuo se purificó por RP-HPLC para obtener 1,1 g de éster metílico del ácido 4-metoximetil-2-[2-(4-metoxi-fenil)-vinil]-oxazol-5-carboxílico como un aceite.

C16H17NO5 (303,32), MS(ESI): 304,2 ($M+H^+$).

{4-Metoximetil-2-[2-(4-metoxi-fenil)-vinil]-oxazol-5-il}-metanol



Se disolvió 1,10 g de éster metílico del ácido 4-metoximetil-2-[2-(4-metoxi-fenil)-vinil]-oxazol-5-carboxílico en 15 ml de tetrahidrofurano y se añadió a una disolución enfriada con hielo de 137 mg de hidruro de aluminio y litio en 7 ml de tetrahidrofurano. La mezcla de reacción se agitó a 0°C durante una hora. Luego se añadieron 50 ml de acetato de etilo y 20 ml de disolución de NH4Cl. El precipitado se filtró a través de un lecho de celita y se lavó con acetato de

etilo. Se separó la capa orgánica del filtrado. La capa acuosa del filtrado se extrajo dos veces con porciones de 100 ml de acetato de etilo. Las capas orgánicas combinadas se secaron sobre MgSO4. El disolvente se eliminó *in vacuo* y el residuo se purificó por RP-HPLC para obtener hasta 420 mg de {4-metoximetil-2-[2-(4-metoxi-fenil)-vinil]-oxazol-5-il}-metanol como un aceite.

C15H17NO4 (275,31), MS(ESI): 276,2.

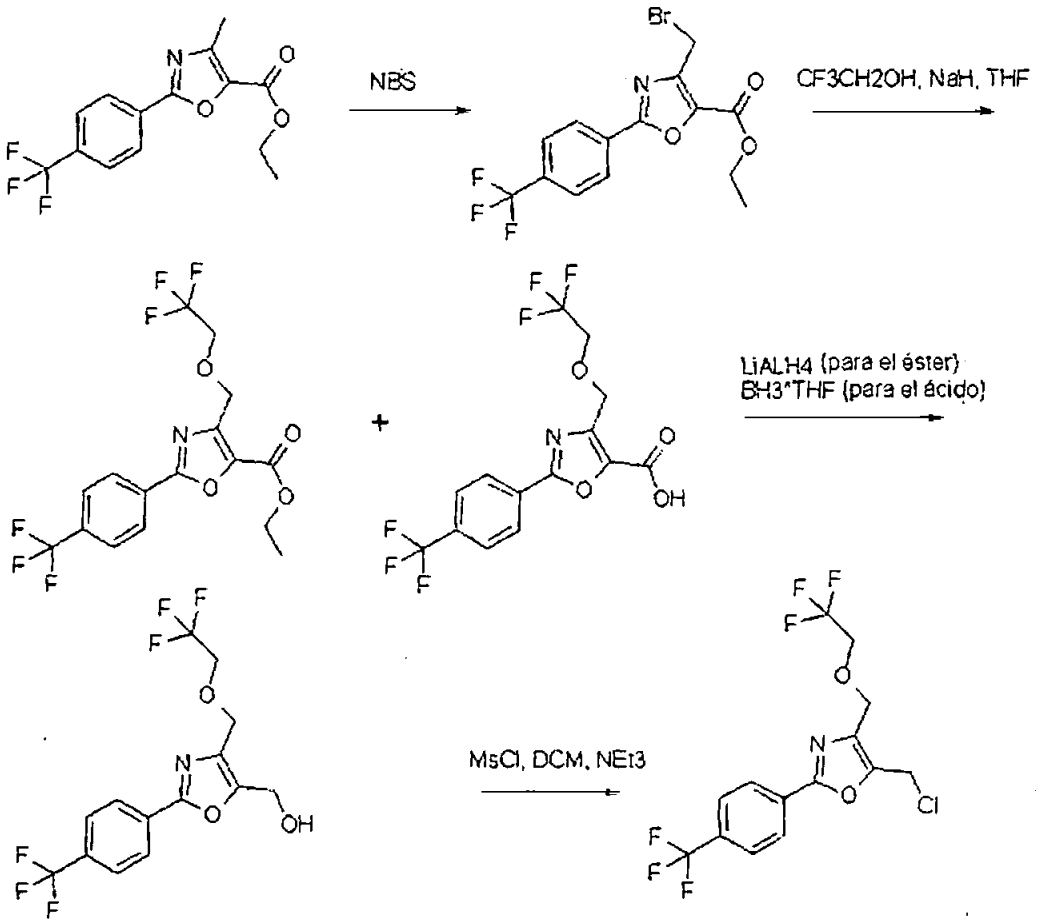
5-Clorometil-4-metoximetil-2-[2-(4-metoxi-fenil)-vinil]-oxazol



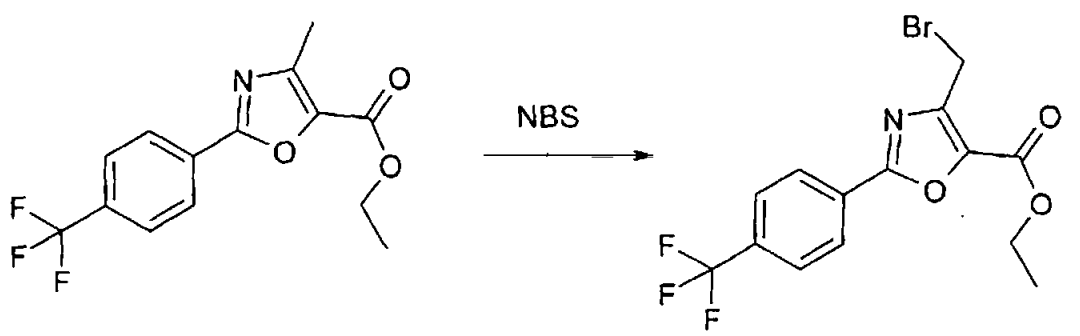
Se disolvieron 420 mg de {4-metoximetil-2-[2-(4-metoxi-fenil)-vinil]-oxazol-5-il}-metanol en 5 ml de diclorometano y se enfriaron en un baño de hielo. Se añadió 0,32 ml de trietilamina, seguidos de la adición de 141 µl de cloruro de metansulfonilo. Se quitó el baño de hielo, y la mezcla resultante se agitó a temperatura ambiente durante la noche. Se añadieron 50 ml de diclorometano y la mezcla de reacción se lavó luego con agua y salmuera, se secó sobre MgSO4 y el disolvente se eliminó *in vacuo* para obtener 491 mg de 5-clorometil-4-metoximetil-2-[2-(4-metoxi-fenil)-vinil]-oxazol como un aceite que se utilizó sin purificación adicional.

C15H16ClNO3 (293,75), Rf(acetato de etilo: n-heptano = 1:1) = 0,44.

5-Clorometil-4-(2,2,2-trifluoro-etoximetil)-2-(4-trifluorometil-fenil)-oxazol



Éster etílico del ácido 4-bromometil-2-(4-trifluorometil-fenil)-oxazol-5-carboxílico

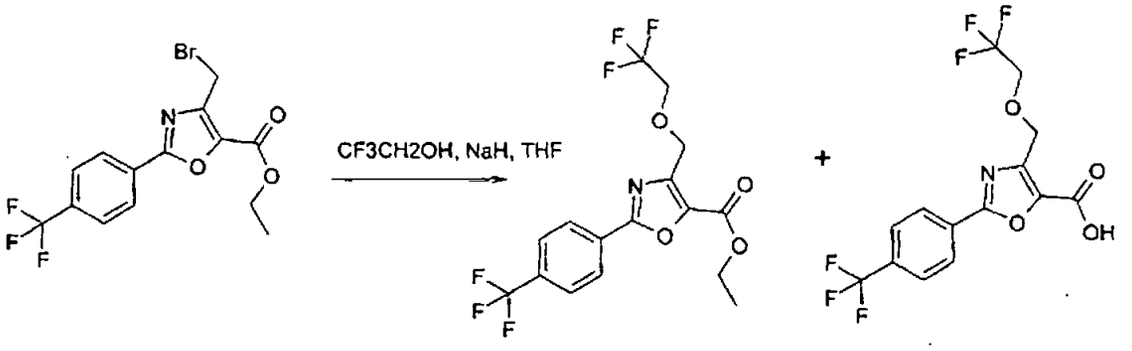


A una mezcla en reflujo de 21,5 g de éster etílico del ácido 4-metil-2-(4-trifluorometil-fenil)-oxazol-5-carboxílico (sintetizada de acuerdo con el método descrito para 5-clorometil-4-metil-2-[2-(4-trifluorometil-fenil)-etil]-oxazol a partir de 4-trifluorometil-benzamida y 2-cloroacetoacetato) en 180 ml de tetracloro-metano se le añadió en porciones una mezcla de 15,4 g de N-bromosuccinimida y 4,73 g de 2,2´-azobis(2-metilpropionitrilo). La mezcla de

reacción se calentó a reflujo durante cinco horas. La mezcla de reacción enfriada se filtró sobre un lecho de celita, el filtrado se evaporó *in vacuo* y el residuo resultante se purificó por cromatografía sobre gel de sílice con el eluyente petróleo benceno: diclorometano = 7: 3 para proveer 18,5 g de éster etílico del ácido 4-bromometil-2-(4-trifluorometil-fenil)-oxazol-5-carboxílico.

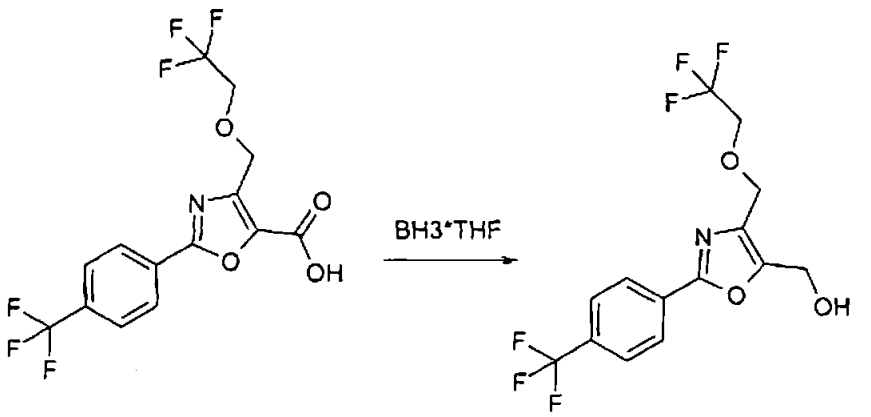
C14H11BrF3NO3 (378,15), MS(ESI): 378,3, 380,3 ($M+H^+$).

Éster etílico del ácido 4-(2,2,2-trifluoro-etoximetil)-2-(4-trifluorometil-fenil)-oxazol-5-carboxílico y ácido 4-(2,2,2-Trifluoro-etoximetil)-2-(4-trifluorometil-fenil)-oxazol-5-carboxílico



Se disuelven 4,0 g de éster etílico del ácido 4-bromometil-2-(4-trifluorometil-fenil)-oxazol-5-carboxílico en una mezcla de 20 ml de tetrahidrofurano y 50 ml de 2,2,2-trifluoroetanol. Se añadieron 635 mg de hidruro de sodio y la mezcla de reacción se agitó a 60°C durante tres horas. La mezcla de reacción enfriada se neutralizó por adición de ácido acético (pH ~ 6). Los disolventes se eliminaron *in vacuo*, el residuo se disolvió en 250 ml de acetato de etilo y se lavó con 100 ml de salmuera. La fase orgánica se secó sobre MgSO4. El disolvente se separó a vacío. El residuo se purificó por RP-HPLC para obtener 1,0 g de ácido 4-(2,2,2-trifluoro-etoximetil)-2-(4-trifluorometil-fenil)-oxazol-5-carboxílico C14H9F6NO4 (369,22), MS(ESI): 369,9 (M+H+). y 830 mg de éster etílico del ácido 4-(2,2,2-trifluoro-etoximetil)-2-(4-trifluorometil-fenil)-oxazol-5-carboxílico. C16H13F6NO4 (397,28), MS(ESI): 398,0 (M+H+).

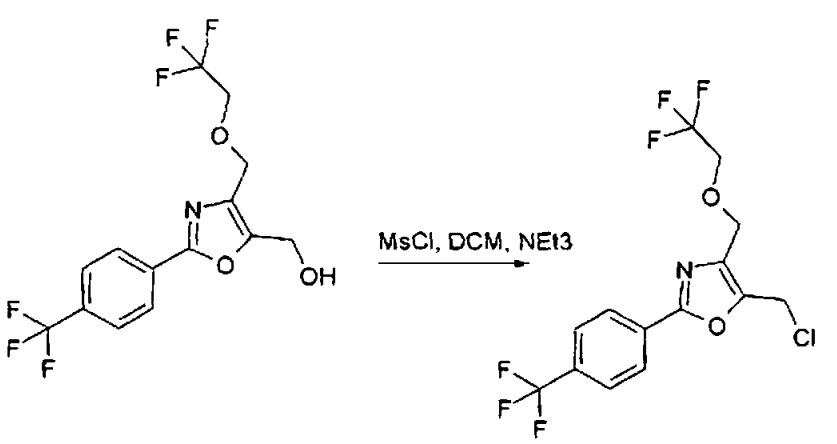
[4-(2,2,2-Trifluoro-etoximetil)-2-(4-trifluorometil-fenil)-oxazol-5-il]-metanol



Se disolvió 1,0 g de ácido 4-(2,2,2-trifluoro-etoximetil)-2-(4-trifluorometil-fenil)-oxazol-5-carboxílico en 30 ml de tetrahidrofurano. A 0-5°C, se le añadieron 6,6 ml de una disolución 1 molar de complejo de borano y tetrahidrofurano. La mezcla de reacción se agitó a temperatura ambiente durante tres horas y a 60°C durante una hora. La mezcla de reacción enfriada se diluyó por adición de 100 ml de acetato de etilo y se lavó con 50 ml de agua. La fase orgánica se secó sobre MgSO4, luego se eliminó el disolvente *in vacuo*. El residuo se purificó por RP-HPLC para obtener 422 mg de [4-(2,2,2-trifluoro-etoximetil)-2-(4-trifluorometil-fenil)-oxazol-5-il]-metanol.

C14H11F6NO3 (355,24), MS(ESI): 356,0 (M+H+).

5-Clorometil-4-(2,2,2-trifluoro-etoximetil)-2-(4-trifluorometil-fenil)-oxazol



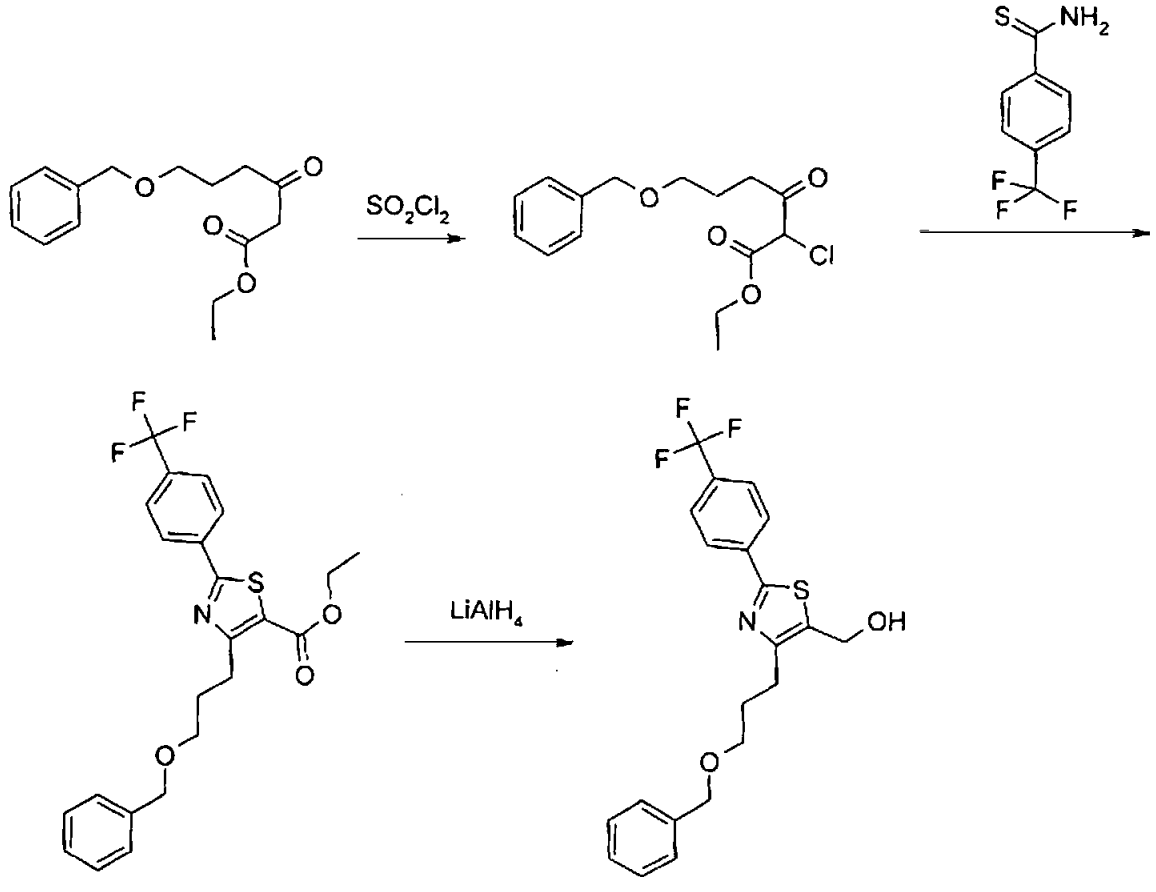
Se disolvieron 422 mg de [4-(2,2,2-trifluoro-etoximetil)-2-(4-trifluorometil-fenil)-oxazol-5-il]-metanol en 5 ml de diclorometano y se enfrió en un baño de hielo. Se añadieron 247 µl de trietilamina, seguida de adición de 110 µl de cloruro de metansulfonilo. Se quitó el baño de hielo, y la mezcla resultante se agitó a temperatura ambiente durante la noche. Se añadieron 50 ml de

diclorometano y la mezcla de reacción se lavó luego con agua y salmuera sobre MgSO4 y el disolvente se eliminó *in vacuo* para obtener 509 mg de 5-clorometil-4-(2,2,2-trifluoro-etoximetil)-2-(4-trifluorometil-fenil)-oxazol como un aceite que se utilizó sin purificación adicional.

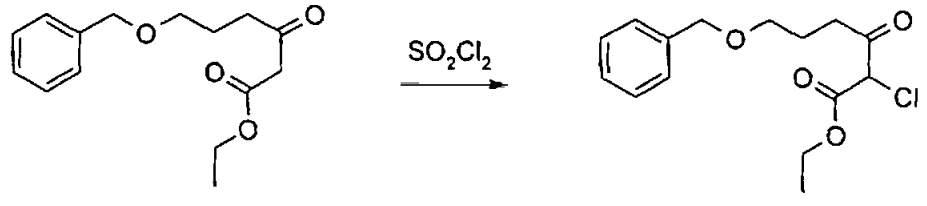
C14H10ClF6NO2 (373,68), MS(ESI): 373,9 (M+H+).

Síntesis de las unidades estructurales de acuerdo con el procedimiento H:

[4-(3-Benciloxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol

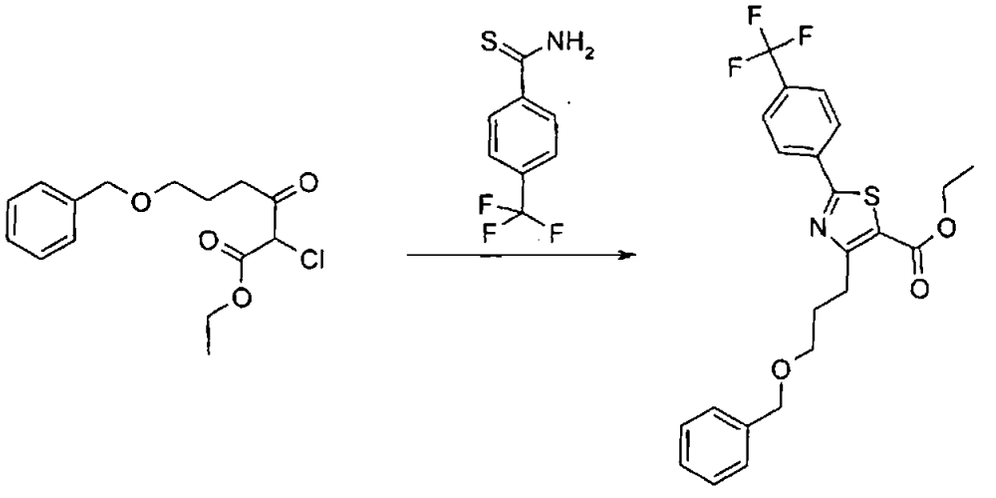


Éster etílico del ácido 6-benciloxi-2-cloro-3-oxo-hexanoico



A una disolución de 1 g de éster etílico del ácido 6-benciloxi-3-oxo-hexanoico en [2]10 ml de diclorometano anhidro a 0°C se le añadió gota a gota 0,307 ml de cloruro de sulfurilo. La mezcla de reacción se agitó a temperatura ambiente durante 30 minutos a 0°C y 1h a temperatura ambiente. La mezcla de reacción se vertió en 20 ml de agua y se extrajo dos veces con porciones de 100 ml de diclorometano. Los extractos orgánicos combinados se lavaron con agua, se secaron sobre sulfato de magnesio, se filtraron y concentraron a presión reducida para proveer 1,15 g de éster etílico del ácido 6-benciloxi-2-cloro-3-oxo-hexanoico que se utilizó en la etapa siguiente sin purificación adicional.

Éster etílico del ácido 4-(3-benciloxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-carboxílico



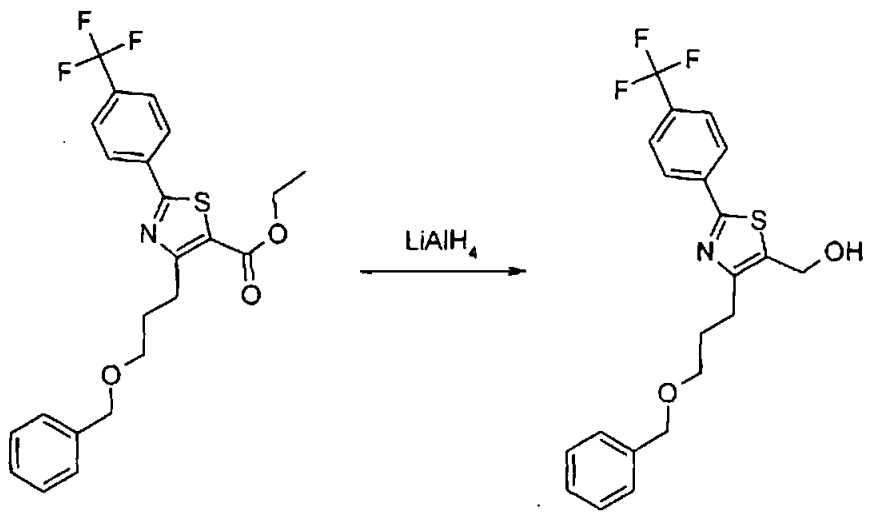
A una disolución de 1,15 g de éster etílico del ácido 6-benciloxi-2-cloro-3-oxo-hexanoico en 10 ml de etanol se le añadió 0,932 g de 4-(trifluorometil)tiobenzamida. La mezcla de reacción se sometió a reflujo durante toda la noche. El disolvente se eliminó a presión reducida. El residuo resultante se absorbió en acetato de etilo y se lavó con agua. La capa acuosa se separó y se extrajo con acetato de etilo. Los extractos orgánicos combinados se lavaron con agua, se secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida. El producto bruto se purificó por cromatografía en columna sobre gel de sílice (heptano 90/acetato de etilo 10) para producir 1,15 g de

[2] Paulvannan, K.; Stille, J.R. *J. Org. Chem.*, 1994, *59*, 1613-1620.

éster etílico del ácido 4-(3-benciloxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-carboxílico como un líquido incoloro.

C23H22F3NO3S (449,49), MS(ESI): 450 ($M+H^+$).

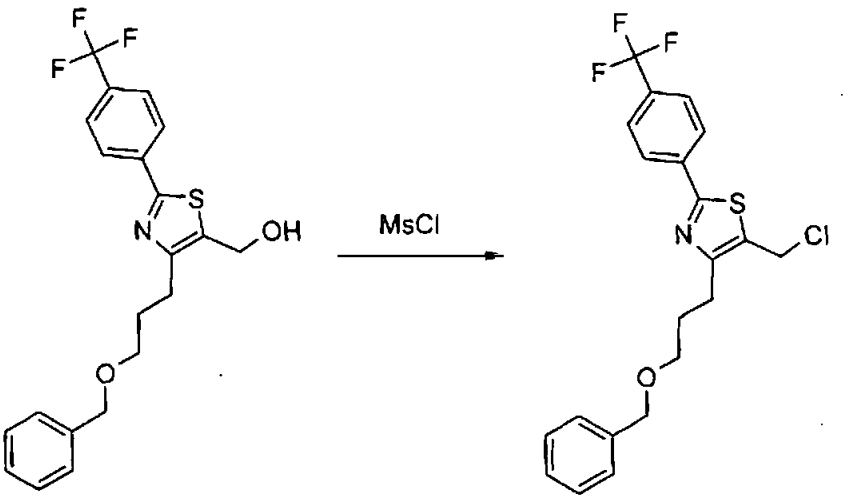
[4-(3-Benciloxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol



A una disolución de 2,76 g de éster etílico del ácido 4-(3-benciloxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-carboxílico en 50 mL de tetrahidrofurano se le añadieron 6,14 mL de una disolución 1M de hidruro de aluminio y litio en tetrahidrofurano. La mezcla resultante se agitó a temperatura ambiente durante 1 h. Se añadió acetato de etilo seguido de una disolución saturada acuosa de cloruro de amonio. La capa acuosa se separó y se extrajo tres veces con acetato de etilo. Los extractos orgánicos combinados se lavaron con agua, se secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida. El producto bruto se purificó por cromatografía en columna sobre gel de sílice (heptano 70/ acetato de etilo 30) para producir 1,69 g de [4-(3-benciloxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol como un sólido blanco.

C21H20F3NO2S (407,45), MS(ESI): 408 ($M+H^+$).

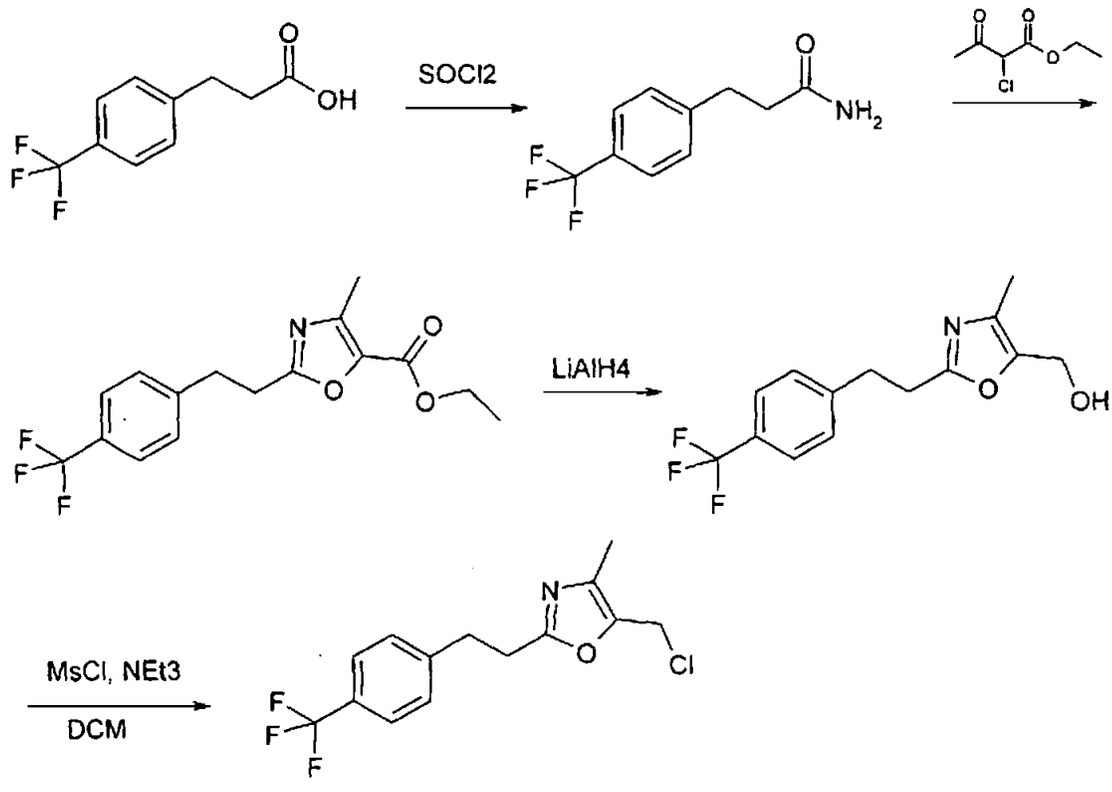
4-(3-Benciloxi-propil)-5-clorometil-2-(4-trifluorometil-fenil)-tiazol



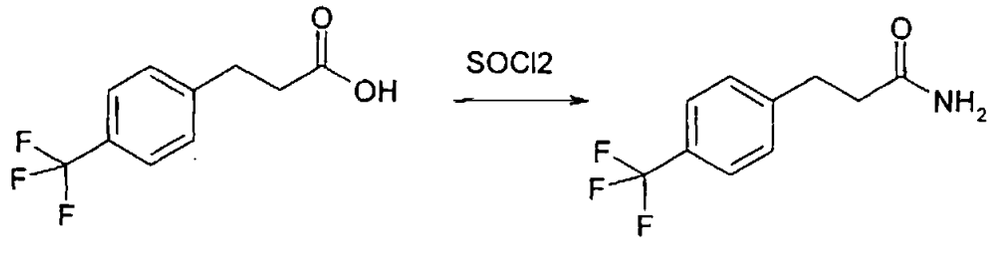
A una disolución de 1,5 g de [4-(3-benciloxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol en 15 mL de diclorometano, se le añadieron 1,026 mL de trietilamina y 0,484 mL de cloruro de metansulfonilo. La mezcla resultante se agitó a temperatura ambiente durante 2 h. La mezcla se diluyó luego con diclorometano y se añadió agua. La capa acuosa se separó y se extrajo tres veces con diclorometano. Los extractos orgánicos combinados se lavaron con agua, se secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida. El producto bruto se purificó por cromatografía en columna sobre gel de sílice (heptano 90/ acetato de etilo 10) para producir 0,84 g de 4-(3-benciloxi-propil)-5-clorometil-2-(4-trifluorometil-fenil)-tiazol como un aceite amarillo.

C21H19ClF3NOS (425,90), MS(EI): 425 (M^+).

5-Clorometil-4-metil-2-[2-(4-trifluorometil-fenil)-etil]-oxazol



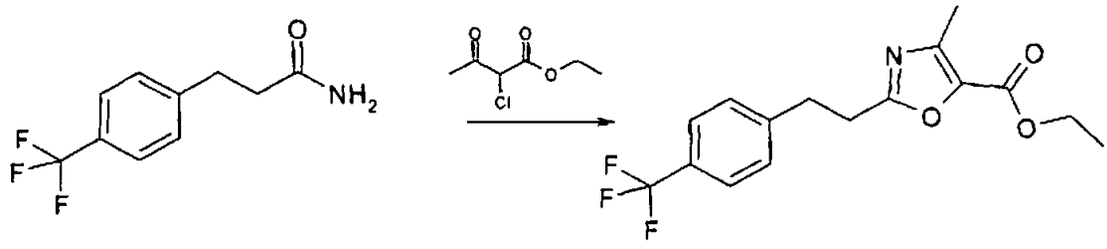
3-(4-Trifluorometil-fenil)-propionamida



Se calentaron 20,0 g de ácido 4-(trifluorometil)hidrocinámico a reflujo en 150 ml de cloruro de tionilo durante tres horas. El cloruro de tionilo se eliminó *in vacuo* y el residuo se disolvió en 150 ml de tetrahidrofurano y se añadió gota a gota a una disolución agitada de amoníaco concentrado en agua. La mezcla de reacción se agitó a temperatura ambiente. Después de 15 minutos la capa orgánica se separó y la capa acuosa se extrajo dos veces con porciones de 100 ml de acetato de etilo. Las capas orgánicas combinadas se secaron sobre MgSO4. El disolvente se eliminó *in vacuo* para obtener 18,6 g de 3-(4-trifluorometil-fenil)-propionamida como un sólido blanco.

C10H10F3NO (217,19), MS(ESI): 218,1.

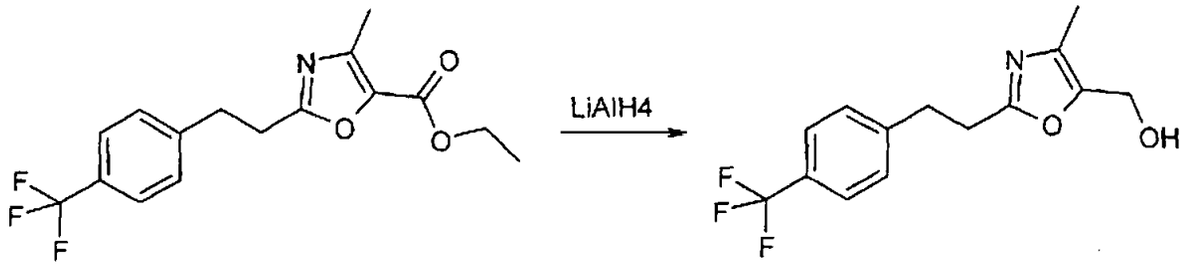
Éster etílico del ácido 4-metil-2-[2-(4-trifluorometil-fenil)-etil]-oxazol-5-carboxílico



Se mezclaron 18,6 g de 3-(4-trifluorometil-fenil)-propionamida y 42,8 ml de 2-cloroacetoacetato de etilo y se agitaron a 150 °C durante ocho horas. Se eliminó el exceso de 2-cloroacetoacetato de etilo *in vacuo* (bomba de aceite) y el residuo se purificó por cromatografía sobre gel de sílice con el eluyente de petróleo benceno: acetato de etilo = 3: 1 para obtener 13,75 g de éster etílico del ácido 4-metil-2-[2-(4-trifluorometil-fenil)-etil]-oxazol-5-carboxílico como un aceite.

C16H16F3NO3 (327,31), MS(ESI): 328,2.

{4-Metil-2-[2-(4-trifluorometil-fenil)-etil]-oxazol-5-il}-metanol

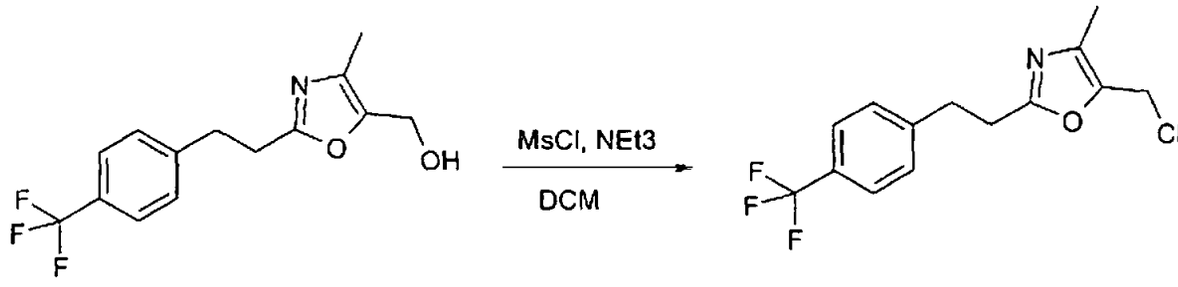


Se disolvieron 9,70 g de éster etílico del ácido 4-metil-2-[2-(4-trifluorometil-fenil)-etil]-oxazol-5-carboxílico en 20 ml de tetrahidrofurano y se añadieron a una disolución enfriada de 1,13 g de hidróxido de aluminio y litio en 10 ml de tetrahidrofurano. La mezcla de reacción se agitó a 0°C durante una hora. Luego se añadieron 100 ml de acetato de etilo y 50 ml de disolución saturada de NH4Cl. El precipitado se filtró a través de un lecho de celita y se lavó con acetato de etilo. Se separó la capa orgánica del filtrado. La capa acuosa del filtrado se extrajo dos veces con porciones de 100 ml de acetato de etilo. Las capas orgánicas combinadas se secaron sobre MgSO4. El disolvente

se eliminó *in vacuo* y el residuo se purificó por cromatografía sobre gel de sílice con el eluyente petróleo benceno: acetato de etilo = 1: 1 para obtener 4,20 g de {4-metil-2-[2-(4-trifluorometil-fenil)-etil]-oxazol-5-il}-metanol como un sólido amarillo.

C14H14F3NO2 (285,27), MS(ESI): 286,2.

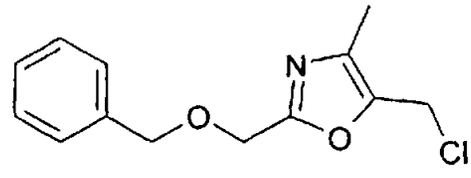
5-Clorometil-4-metil-2-[2-(4-trifluorometil-fenil)-etil]-oxazol



Se disolvieron 4,20 g de {4-Metil-2-[2-(4-trifluorometil-fenil)-etil]-oxazol-5-il}-metanol en 20 ml de diclorometano y se enfrió en un baño de hielo. Se añadieron 3,10 ml de trietilamina, seguido por la adición de 1,37 ml de cloruro de metansulfonilo. Se quitó el baño de hielo, y la mezcla resultante se agitó a temperatura ambiente durante la noche. La mezcla de reacción se lavó luego con agua y salmuera, se secó sobre MgSO4 y el disolvente se eliminó *in vacuo* para obtener 4,0 g de 5-clorometil-4-metil-2-[2-(4-trifluorometil-fenil)-etil]-oxazol como un aceite que se utilizó sin purificación adicional.

C14H13ClF3NO (303,71), MS(ESI): 304,1 ($M+H^+$), Rf(acetato de etilo: n-heptano = 1:1) = 0,52.

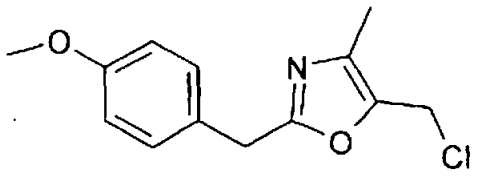
2-Benciloximetil-5-clorometil-4-metil-oxazol



De acuerdo con el método descrito para 5-clorometil-4-metil-2-[2-(4-trifluorometil-fenil)-etil]-oxazol, se obtuvo 2-benciloximetil-5-clorometil-4-metil-oxazol a partir de ácido benciloxaacético y 2-cloroacetoacetato de etilo.

C13H14ClNO2 (251.72), Rf (n-heptano: acetato de etilo = 1:1) = 0,51.

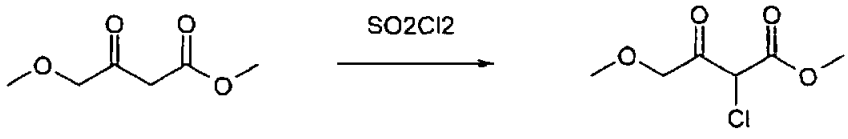
5-Clorometil-2-(4-metoxi-bencil)-4-metil-oxazol



De acuerdo con el método descrito para 5-clorometil-4-metil-2-[2-(4-trifluorometil-fenil)-etil]-oxazol, se obtuvo 5-clorometil-2-(4-metoxi-bencil)-4-metil-oxazol a partir de 4-metoxifenilacetamida y 2-cloroacetoacetato de etilo.

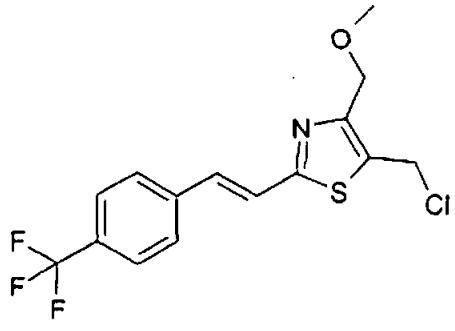
C13H14ClNO2 (251,72), MS(ESI): 252,1 ($M+H^+$), Rf(n-heptano: acetato de etilo = 1:1) = 0,49.

Éster metílico del ácido 2-cloro-4-metoxi-3-oxo-butírico



Se disolvieron 46,0 g de metil 4-metoxiacetoacetato en 500 ml de diclorometano. Se añadieron 28,1 ml de cloruro de sulfurilo en una porción. La mezcla de reacción se agitó toda la noche a temperatura ambiente. El disolvente se eliminó a presión reducida, el residuo resultante se disolvió en 300 ml de acetato de etilo y se lavó con 100 ml de agua y 100 ml de salmuera. La capa orgánica se secó sobre MgSO4 y el disolvente se separó a presión reducida. El residuo resultante se purificó por cromatografía sobre gel de sílice con el eluyente n-heptano: acetato de etilo = 5:1 => 2:1 para obtener 45,0 g de éster metílico del ácido 2-cloro-4-metoxi-3-oxo-butírico como un aceite amarillo. C6H9ClO4 (180,59), MS(ESI): 181,2 ($M+H^+$), Rf (n-heptano: acetato de etilo = 2:1) = 0,31.

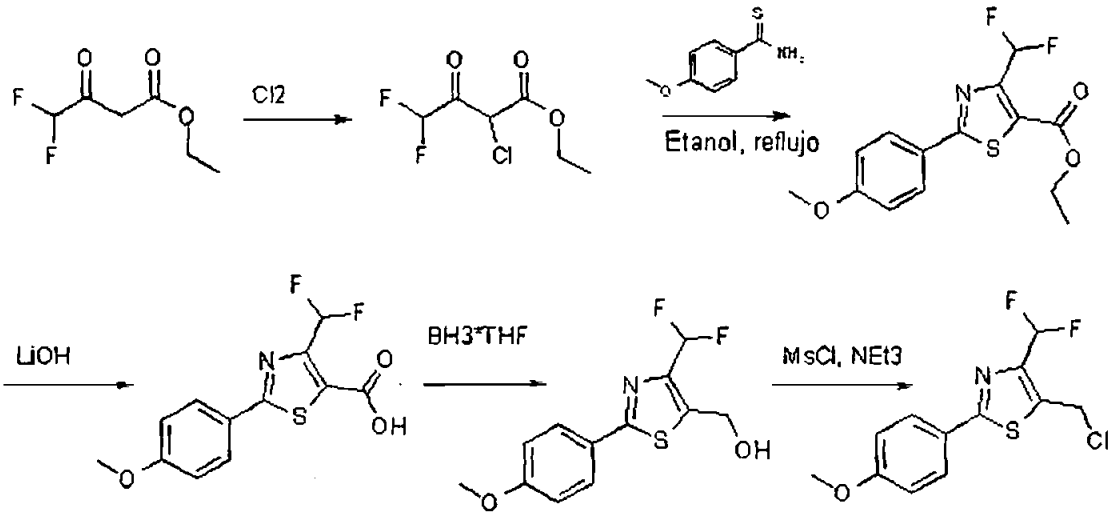
5-Clorometil-4-metoximetil-2-[2-(4-trifluorometil-fenil)-vinil]-tiazol



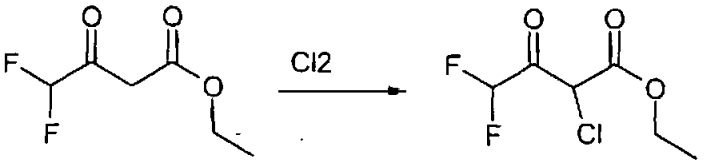
De acuerdo con el método descrito para 5-clorometil-4-metil-2-[2-(4-trifluorometil-fenil)-etil]-oxazol, se obtuvo 5-clorometil-4-metoximetil-2-[2-(4-trifluorometil-fenil)-vinil]-tiazol a partir de 4-(trifluorometil)cinamida y éster metílico del ácido 2-cloro-4-metoxi-3-oxo-butírico.

C15H13ClF3NOS (347,79), MS(ESI): 348,0 ($M+H^+$).

5-Clorometil-4-difluorometil-2-(4-metoxi-fenil)-tiazol



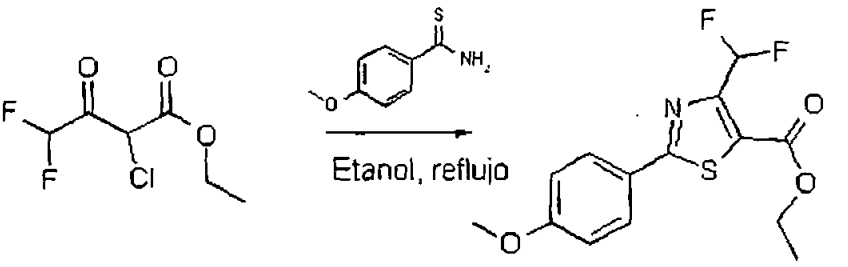
Éster etílico del ácido 2-cloro-4,4-difluoro-3-oxo-butírico



Se burbujeó cloro a través de 10,0 g de 4,4-difluoroacetoacetato de etilo durante quince minutos a temperatura ambiente. Luego se burbujeó argón. Se obtuvieron 11,67 g de éster etílico del ácido 2-cloro-4,4-difluoro-3-oxo-butírico como material bruto que se utilizó sin purificación adicional.

C6H7ClF2O3 (200,57), MS(ESI): 200,95 ($M+H^+$), Rf (n-heptano: acetato de etilo = 1:1) = 0,10.

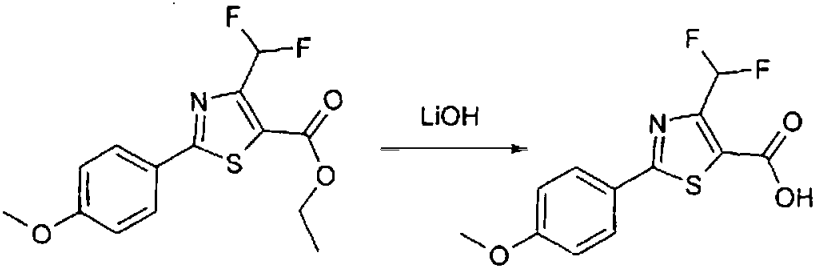
Éster etílico del ácido 4-difluorometil-2-(4-metoxi-fenil)-tiazol-5-carboxílico



Se disolvieron 8,84 g de 4-metoxitiobenzamida en 100 ml de etanol y se calentó hasta 50°C. Luego se añadieron 10,59 g de éster etílico del ácido 2-cloro-4,4-difluoro-3-oxo-butírico y la mezcla de reacción se agitó a reflujo durante tres horas. La mezcla de reacción enfriada se evaporó *in vacuo* y el residuo se purificó por cromatografía sobre gel de sílice con el eluyente acetato de etilo / petróleo benceno = 1: 4 para obtener 7,04 g de éster etílico del ácido 4-difluorometil-2-(4-metoxi-fenil)-tiazol-5-carboxílico como un sólido amarillo pálido.

C14H13F2NO3S (313,33), MS(ESI): 313,95 ($M+H^+$).

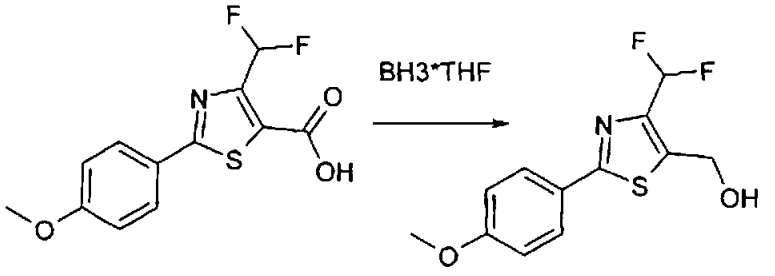
Ácido 4-difluorometil-2-(4-metoxi-fenil)-tiazol-5-carboxílico



Se disolvieron 3,0 g de éster etílico del ácido 4-difluorometil-2-(4-metoxi-fenil)-tiazol-5-carboxílico en 90 ml de tetrahidrofurano. Se añadió una disolución de 2,29 g de hidróxido de litio disueltos en 30 ml de agua y la mezcla de reacción se agitó a temperatura ambiente durante toda la noche. Se añadió ácido acético concentrado hasta que se logró un pH de ~ 6, luego se eliminó el tetrahidrofurano *in vacuo*. La fase acuosa residual se extrajo tres veces con porciones de 100 ml de acetato de etilo. Las capas orgánicas combinadas se secaron sobre MgSO4. Luego el disolvente se eliminó *in vacuo* para obtener 2,73 g de ácido 4-difluorometil-2-(4-metoxi-fenil)-tiazol-5-carboxílico como un sólido amarillo pálido.

C12H9F2NO3S (285,27), MS(ESI): 285,90 ($M+H^+$).

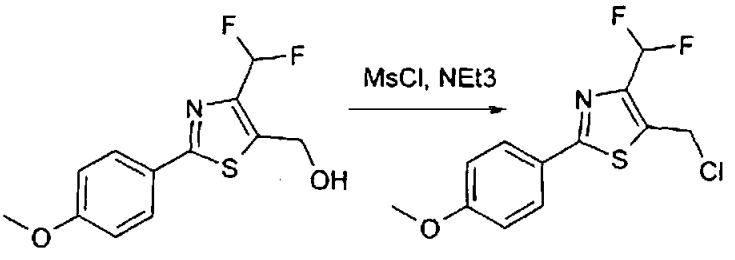
[4-Difluorometil-2-(4-metoxi-fenil)-tiazol-5-il]-metanol



Se disolvieron 2,73 g de ácido 4-difluorometil-2-(4-metoxi-fenil)-tiazol-5-carboxílico en 30 ml de tetrahidrofurano. Se añadieron 23 ml de una disolución 1 molar de complejo de borano y tetrahidrofurano y la mezcla de reacción se agitó a 40°C durante tres horas. La mezcla de reacción enfriada se vertió en agua con hielo y se extrajo tres veces con porciones de 100 ml de acetato de etilo. Las capas orgánicas combinadas se secaron sobre MgSO4. Luego el disolvente se eliminó *in vacuo* para obtener 2,70 g de [4-difluorometil-2-(4-metoxi-fenil)-tiazol-5-il]-metanol.

C12H11F2NO2S (271,29), MS(ESI): 272,0 ($M+H^+$).

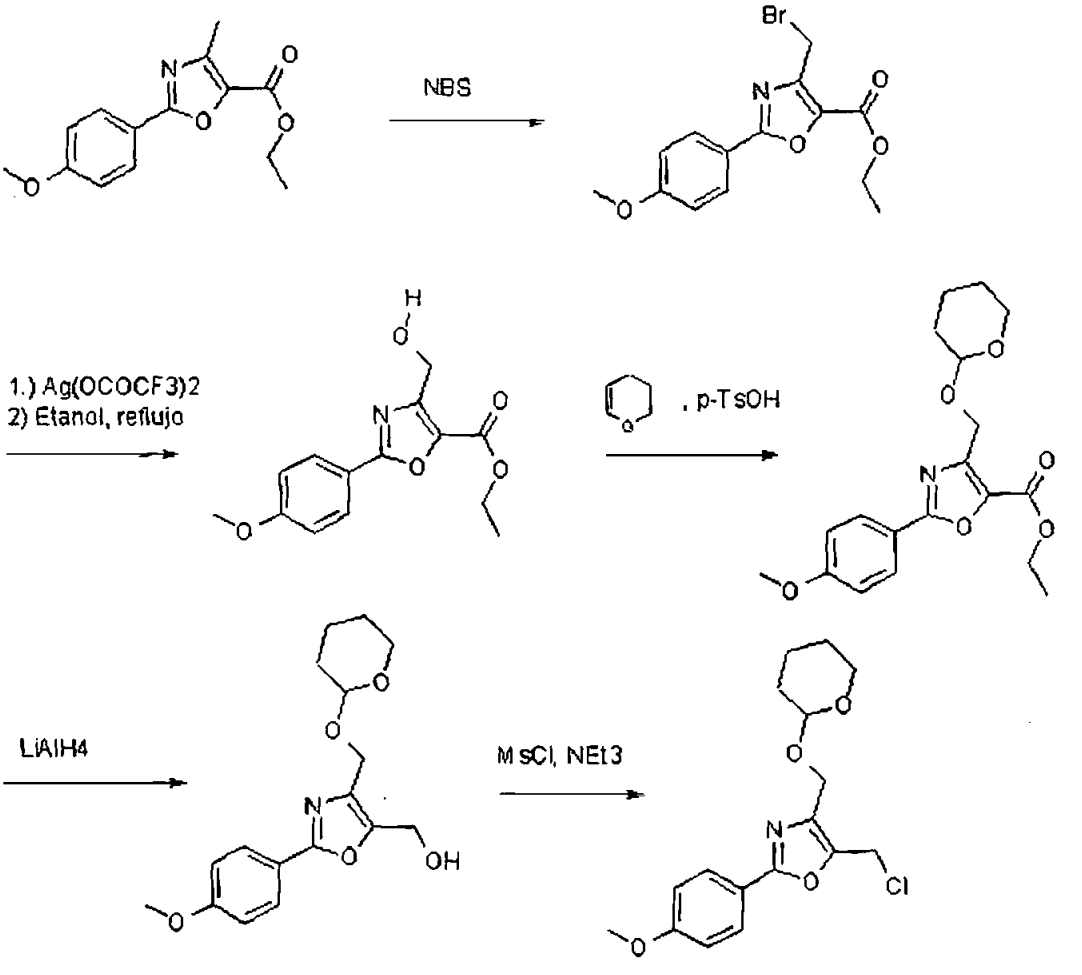
5-Clorometil-4-difluorometil-2-(4-metoxi-fenil)-tiazol



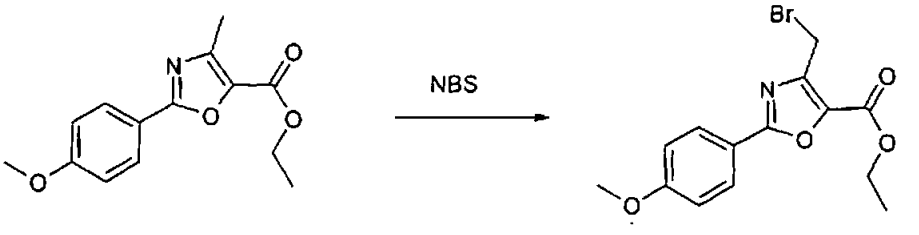
Se disolvieron 2,70 g de [4-difluorometil-2-(4-metoxi-fenil)-tiazol-5-il]-metanol en 15 ml de diclorometano y se enfrió en un baño de hielo. Se añadieron 2,07 ml de trietilamina, seguidos de adición de 0,92 ml de cloruro de metansulfonilo. Se quitó el baño de hielo, y la mezcla resultante se agitó a temperatura ambiente durante la noche. Luego se añadieron 2,07 ml de trietilamina y 0,92 ml de cloruro de metansulfonilo nuevamente y la mezcla de reacción se agitó a temperatura ambiente durante cuatro horas adicionales. La mezcla de reacción se lavó luego con agua y salmuera, se secó sobre MgSO4 y el disolvente se eliminó *in vacuo* para obtener 3,0 g de 5-clorometil-4-difluorometil-2-(4-metoxi-fenil)-tiazol bruto como un aceite que se utilizó sin purificación adicional.

C12H10ClF2NOS (289,73), MS(ESI): 289,9 ($M+H^+$), Rf(acetato de etilo: n-heptano = 1:1) = 0,76.

Síntesis de las unidades estructurales según el procedimiento J: [2-(4-metoxi-fenil)-4-(tetrahidro-piran-2-iloximetil)-oxazol-5-il]-metanol y 5-clorometil-2-(4-metoxi-fenil)-4-(tetrahidro-piran-2-iloximetil)-oxazol



Éster etílico del ácido 4-bromometil-2-(4-metoxi-fenil)-oxazol-5-carboxílico

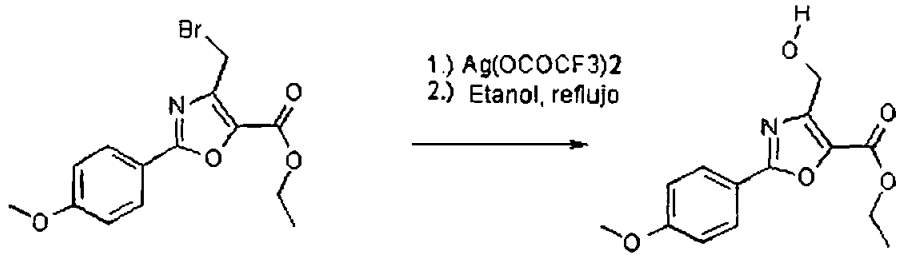


A una disolución en ebullición de 23,5 g de éster etílico del ácido 2-(4-metoxi-fenil)-4-metil-oxazol-5-carboxílico en 250 ml de tetracloro-metano se añadió poco a poco una mezcla de 5,92 g de 2,2´-azobis(2-metilpropionitrilo) y

19,3 g de N-bromosuccinimida. La mezcla de reacción se puso a reflujo durante siete horas. La mezcla de reacción enfriada se filtró sobre un lecho de celita y el disolvente se eliminó a vacío para obtener 30,7 g del éster etílico del ácido 4-bromometil-2-(4-metoxi-fenil)-oxazol-5-carboxílico bruto. El material se usó en la siguiente etapa sin purificación adicional.

C14H14BrNO4 (340,18), MS(ESI): 340,0 y 342,0 ($M+H^+$), Rf(acetato de etilo: n-heptano = 7:3) = 0,43).

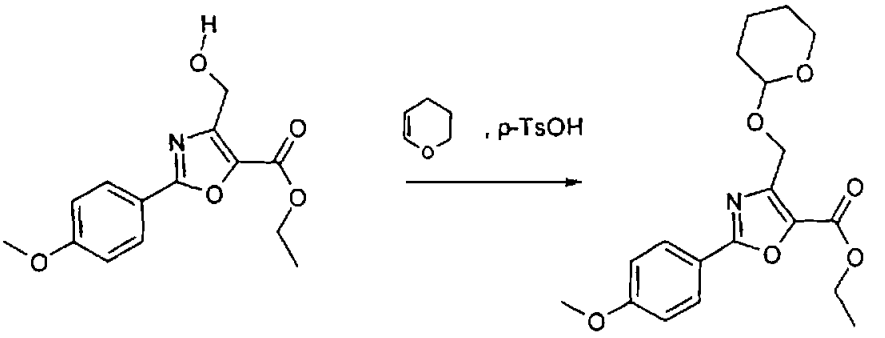
Éster etílico del ácido 4-hidroximetil-2-(4-metoxi-fenil)-oxazol-5-carboxílico



Se disolvieron 30,7 g de éster etílico del ácido 4-bromometil-2-(4-metoxi-fenil)-oxazol-5-carboxílico bruto en 170 ml de dimetilformamida seca. Se añadieron 29,95 g de trifluoroacetato de plata y la mezcla se agitó a temperatura ambiente durante la noche. Se añadieron 100 ml de salmuera y la mezcla se agitó durante una hora. La mezcla de reacción se filtró con un lecho de celita, el disolvente se eliminó a vacío y el residuo resultante se disolvió en 200 ml de etanol. La mezcla se calentó a reflujo durante tres horas. Después el disolvente se eliminó a vacío y el residuo se disolvió en agua y se extrajo cinco veces con acetato de etilo. Las capas orgánicas combinadas se secaron sobre $MgSO_4$, el disolvente se eliminó a vacío y el residuo se purificó mediante cromatografía de desarrollo rápido sobre gel de sílice (eluyendo con n-heptano: acetato de etilo = 5:1 => acetato de etilo) para obtener 17,8 g del éster etílico del ácido 4-hidroximetil-2-(4-metoxi-fenil)-oxazol-5-carboxílico como un sólido.

C14H15NO5 (277,28), MS(ESI): 278,1 ($M+H^+$), Rf(acetato de etilo: n-heptano = 1:2) = 0,11.

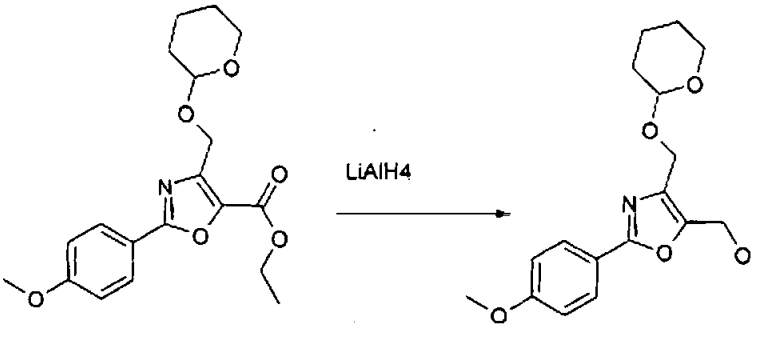
Éster etílico del ácido 2-(4-metoxi-fenil)-4-(tetrahidro-piran-2-iloximetil)-oxazol-5-carboxílico



Se disolvieron 10,0 g del éster etílico del ácido 4-hidroximetil-2-(4-metoxi-fenil)-oxazol-5-carboxílico en 85 ml de diclorometano. Se añadieron 4,0 ml de 3,4-dihidro-2H-pirano y 1,85 mg de p-toluensulfonato de piridinio y la mezcla de reacción se agitó a temperatura ambiente durante la noche. Se eliminó el disolvente *in vacuo* y el residuo se purificó por cromatografía de desarrollo rápido sobre gel de sílice (eluyendo con n-heptano: acetato de etilo = 4:1 => 1:1) hasta obtener 12,3 g de éster etílico del ácido 2-(4-metoxi-fenil)-4-(tetrahidro-piran-2-iloximetil)-oxazol-5-carboxílico como un aceite.

$C_{19}H_{23}NO_6$ (361,40), MS(ESI): 362,2 ($M+H^+$), 278,2 ($M-THP+H^+$), Rf(acetato de etilo: n-heptano = 1:1) = 0,56.

[2-(4-Metoxi-fenil)-4-(tetrahidro-piran-2-iloximetil)-oxazol-5-il]-metanol

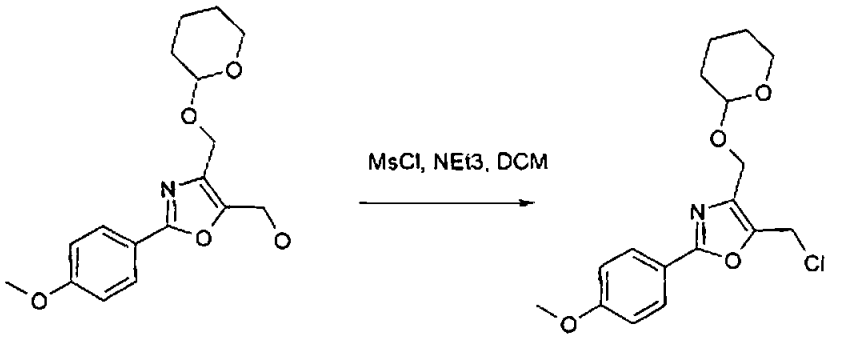


A una suspensión enfriada de 2,73 g de hidruro de litio y aluminio en 180 ml de tetrahidrofurano se añadió una disolución de 12,3 g del éster etílico del ácido 2-(4-metoxi-fenil)-4-(tetrahidro-piran-2-iloximetil)-oxazol-5-carboxílico en 120 ml de tetrahidrofurano a 0°C. Se quitó el baño de hielo, y la mezcla de reacción se agitó a temperatura ambiente durante una hora. La mezcla de reacción se enfrió en un baño de hielo nuevamente y se añadieron 100 ml de acetato de etilo seguidos de la adición de 300 ml de éter metil-terc-butílico. Después se añadió una disolución de 10,92 g de hidróxido sódico en 12,3 ml de agua. El precipitado sólido se filtró a través de un tapón de celita. El filtrado

se secó sobre MgSO4 y después se eliminó el disolvente a vacío para obtener 11,8 g de [2-(4-metoxi-fenil)-4-(tetrahidro-piran-2-iloximetil)-oxazol-5-il]-metanol como un sólido.

C17H21NO5 (319,36), MS(ESI): 320,2 ($M+H^+$), Rf(acetato de etilo: n-heptano = 1:1) = 0,18.

5-Clorometil-2-(4-metoxi-fenil)-4-(tetrahidro-piran-2-iloximetil)-oxazol

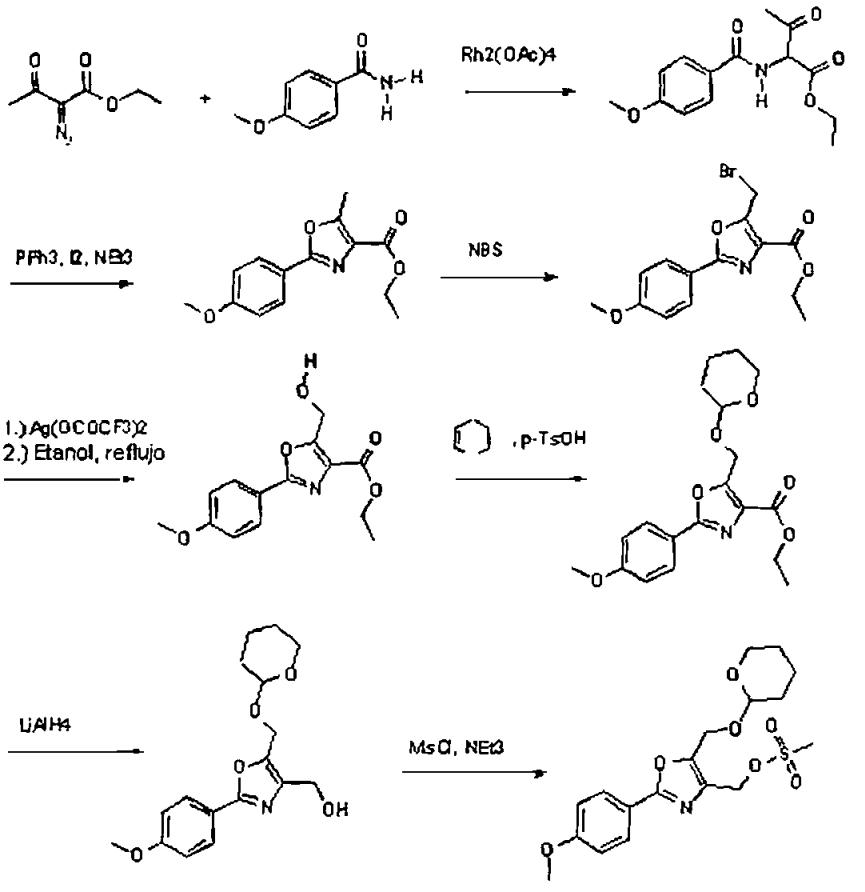


Se disolvieron 2,0 g de [2-(4-metoxi-fenil)-4-(tetrahidro-piran-2-iloximetil)-oxazol-5-il]-metanol en 30 ml de diclorometano y se enfriaron en un baño de hielo. Se añadió 0,88 ml de trietilamina, seguida de adición de 0,49 ml de cloruro de metansulfonilo. Se quitó el baño de hielo, y la mezcla resultante se agitó a temperatura ambiente durante la noche. Después la mezcla de reacción se lavó con agua y salmuera, se secó sobre MgSO4 y se eliminó el disolvente a vacío para obtener 2,5 g de 5-clorometil-2-(4-metoxi-fenil)-4-(tetrahidro-piran-2-iloximetil)-oxazol como un aceite que se utilizó sin purificación adicional.

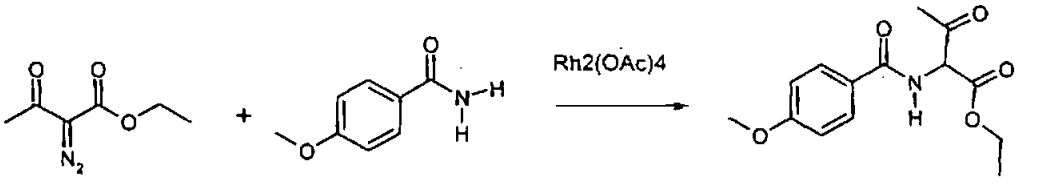
C17H20ClNO4 (337,81), MS(ESI): 338,2 ($M+H^+$), Rf(acetato de etilo: n-heptano = 1:1) = 0,42.

Síntesis de las unidades estructurales según el procedimiento K:

[2-(4-Metoxi-fenil)-5-(tetrahidro-piran-2-iloximetil)-oxazol-4-il]-metanol y éster 2-(4-metoxi-fenil)-5-(tetrahidro-piran-2-iloximetil)-oxazol-4-ilmetílico del ácido metansulfónico



Éster etílico del ácido 2-(4-metoxi-benzoilamino)-3-oxo-butírico

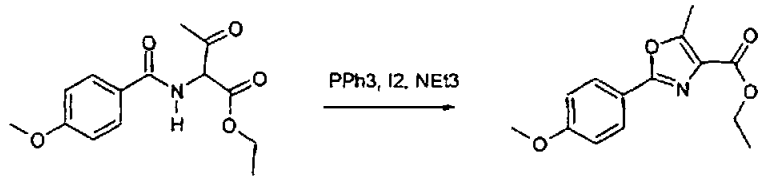


Durante 5 horas se añadió gota a gota una disolución de 12,1 g de 2-diazo-3-oxobutanoato de etilo[3] en 100 ml de 1,2-dicloroetano a una disolución en ebullición de 9,0 g de 4-metoxibenzamida y 1,05 g de dímero de acetato de rodio(II) en 200 ml de 1,2-dicloroetano seco. La mezcla se sometió a reflujo durante treinta minutos, se dejó enfriar *in vacuo* y se purificó por cromatografía de desarrollo rápido sobre gel de sílice para obtener 11,3 g de éster etílico del ácido 2-(4-metoxi-benzoilamino)-3-oxo-butírico.

C14H17NO5 (279,30), MS(ESI): 280,2 ($M+H^+$), Rf(acetato de etilo: n-heptano = 1:1) = 0,32.

[3] J.Chem.Soc., Perkin Trans. 1, 1998, 591-600.

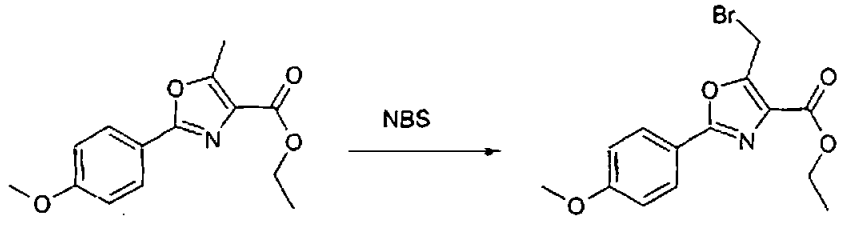
Éster etílico del ácido 2-(4-Metoxi-fenil)-5-metil-oxazol-4-carboxílico



Se añadieron en secuencias 23,2 ml de trietilamina y una disolución de 11,3 g de éster etílico del ácido 2-(4-metoxi-benzoilamino)-3-oxo-butírico en 200 ml de diclorometano a una disolución agitada de 20,5 g de yodo y 21,2 g de trifenilfosfina en 500 ml de diclorometano seco. La mezcla de reacción se agitó a temperatura ambiente durante la noche. El disolvente se evaporó a vacío y el residuo resultante se purificó mediante cromatografía de desarrollo rápido sobre gel de sílice para obtener 6,0 g del éster etílico del ácido 2-(4-metoxi-fenil)-5-metil-oxazol-4-carboxílico como un sólido amarillo claro.

$C_{14}H_{15}NO_4$ (261,28), MS(ESI): 262,2 ($M+H^+$), Rf(acetato de etilo: n-heptano = 2:1) = 0,31.

Éster etílico del ácido 5-bromometil-2-(4-metoxi-fenil)-oxazol-4-carboxílico

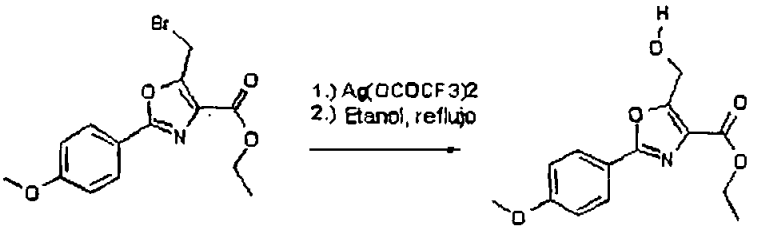


A una disolución en ebullición de 6,0 g del éster etílico del ácido 2-(4-metoxi-fenil)-5-metil-oxazol-4-carboxílico en 100 ml de tetracloro-metano se añadió poco a poco una mezcla de 1,51 g de 2,2´-azobis(2-metilpropionitrilo) y 4,9 g de N-bromosuccinimida. La mezcla de reacción se puso a reflujo durante tres horas. La mezcla de reacción enfriada se filtró sobre un lecho de celita y el disolvente se eliminó a vacío para obtener 10,6 g del éster etílico del ácido 5-bromometil-2-(4-metoxi-fenil)-oxazol-4-carboxílico bruto, que contenía algo del subproducto dibromado. El material se usó en la siguiente etapa sin purificación adicional.

$C_{14}H_{14}BrNO_4$ (340,18), MS(ESI): 340,0 y 342,0 ($M+H^+$), Rf(acetato de etilo:n-heptano = 2:1) = 0,27).

302

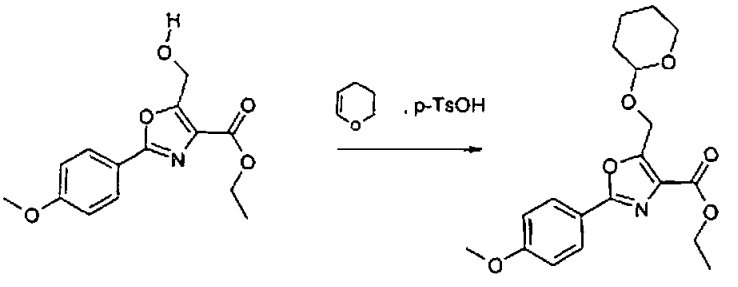
Éster etílico del ácido 5-hidroximetil-2-(4-metoxi-fenil)-oxazol-4-carboxílico



Se disolvieron 8,0 g del éster etílico del ácido 5-bromometil-2-(4-metoxi-fenil)-oxazol-4-carboxílico en 50 ml de dimetilformamida seca. Se añadieron 7,8 g de trifluoroacetato de plata y la mezcla se agitó a temperatura ambiente durante dos horas. Se añadieron 30 ml de salmuera y la mezcla se agitó durante dos horas. La mezcla de reacción se filtró con un lecho de celita, el disolvente se eliminó a vacío y el residuo resultante se disolvió en 200 ml de etanol. La mezcla se calentó a reflujo durante tres horas. Después el disolvente se eliminó a vacío y el residuo se disolvió en agua y se extrajo cinco veces con acetato de etilo. Las capas orgánicas combinadas se secaron sobre MgSO4, el disolvente se eliminó a vacio y el residuo se purificó mediante cromatografía de desarrollo rápido sobre gel de sílice (eluyendo con n-heptano: acetato de etilo = 2:3 => acetato de etilo) para obtener 4,8 g del éster etílico del ácido 5-hidroximetil-2-(4-metoxi-fenil)-oxazol-4-carboxílico como un sólido.

C14H15NO5 (277,28), MS(ESI): 278,1 ($M+H^+$), Rf(acetato de etilo: n-heptano = 1:2) = 0,09.

Éster etílico del ácido 2-(4-metoxi-fenil)-5-(tetrahidro-piran-2-iloximetil)-oxazol-4-carboxílico

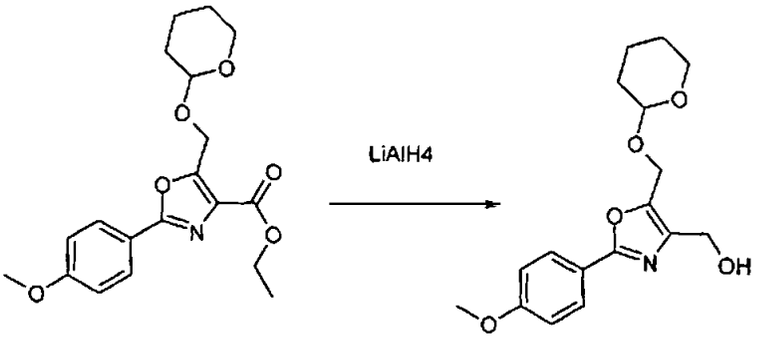


Se disolvieron 4,8 g del éster etílico del ácido 5-hidroximetil-2-(4-metoxi-fenil)-oxazol-4-carboxílico en 75 ml de diclorometano. Se añadieron 1,9 ml de 3,4-dihidro-2H-pirano y 870 mg de p-toluensulfonato de piridinio y la mezcla de

reacción se agitó a temperatura ambiente durante la noche. Se eliminó el disolvente a vacío y el residuo se purificó mediante cromatografía de desarrollo rápido sobre gel de sílice (eluyendo con n-heptano: acetato de etilo = 3:1 => 1:1) para obtener 5,3 g del éster etílico del ácido 2-(4-metoxi-fenil)-5-(tetrahidro-piran-2-iloximetil)-oxazol-4-carboxílico.

C19H23NO6 (361,40), MS(ESI): 362,2 ($M+H^+$), 278,1 ($M-THP+H^+$).

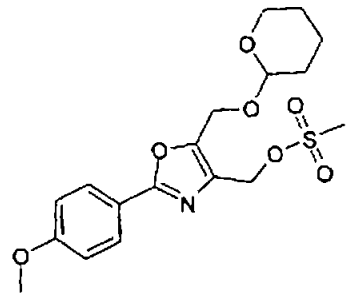
[2-(4-Metoxi-fenil)-5-(tetrahidro-piran-2-iloximetil)-oxazol-4-il]-metanol



Se disolvieron 5,3 g del éster etílico del ácido 2-(4-metoxi-fenil)-5-(tetrahidro-piran-2-iloximetil)-oxazol-4-carboxílico en 100 ml de tetrahidrofurano y se enfriaron en un baño de hielo. Se añadieron 21,8 ml de una disolución 1 molar de hidruro de litio y aluminio en tetrahidrofurano. Se quitó el baño de hielo, y la mezcla de reacción se agitó a temperatura ambiente durante treinta minutos. De nuevo se enfrió la mezcla de reacción en un baño de hielo y se añadieron secuencialmente 6 ml de agua, 12 ml de NaOH al 15% y 18 ml de agua. Después de agitar durante una hora a temperatura ambiente, la mezcla de reacción se filtró sobre un lecho de celita y se lavó con acetato de etilo. El filtrado se secó sobre MgSO4 y el disolvente se eliminó *in vacuo* y el residuo se purificó por cromatografía de desarrollo rápido sobre gel de sílice (eluyendo con n-heptano: acetato de etilo = 6:4 => 9:1 => acetato de etilo) para obtener 3,0 g de [2-(4-metoxi-fenil)-5-(tetrahidro-piran-2-iloximetil)-oxazol-4-il]-metanol.

C17H21NO5 (319,36), MS(ESI): 320,2 ($M+H^+$).

Éster 2-(4-metoxi-fenil)-5-(tetrahidro-piran-2-iloximetil)-oxazol-4-ilmetílico del ácido metansulfónico

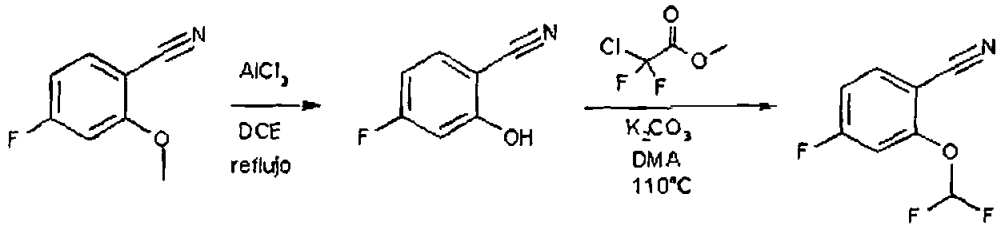


Se disolvieron 0,44 g de [2-(4-metoxi-fenil)-5-(tetrahidro-piran-2-iloximetil)-oxazol-4-il]-metanol en 30 ml de diclorometano y se enfriaron en un baño de hielo. Se añadió 0,29 ml de trietilamina, seguido de adición de 0,13 ml de cloruro de metansulfonilo. La mezcla de reacción se agitó a 0°C durante una hora, después se quitó el baño de hielo y la mezcla resultante se agitó a temperatura ambiente durante una hora más. Después la mezcla de reacción se lavó con agua y salmuera, se secó sobre MgSO4 y se eliminó el disolvente a vacío para obtener 0,55 mg del éster 2-(4-metoxi-fenil)-5-(tetrahidro-piran-2-iloximetil)-oxazol-4-ilmetílico del ácido metansulfónico como un aceite que se utilizó sin purificación adicional.

C18H23NO7S (397,45), MS(ESI): 398,2 ($M+H^+$).

Síntesis de las unidades estructurales según el procedimiento N:

2-Difluorometoxi-4-fluoro-benzonitrilo



Se preparó 4-fluoro-2-metoxi-benzonitrilo de acuerdo con una publicación previa:[4]

A una disolución de 1 g de 4-fluoro-2-metoxi-benzonitrilo en 15 mL de dicloroetano se le añadió 1,1 g de tricloruro de aluminio. La mezcla resultante se sometió a reflujo durante 1 día, luego se vertió lentamente en agua y se extrajo con acetato de etilo. Los extractos orgánicos se lavaron dos veces con disolución acuosa al 10% de hidróxido de sodio. Las capas básicas

[4] JP9143139

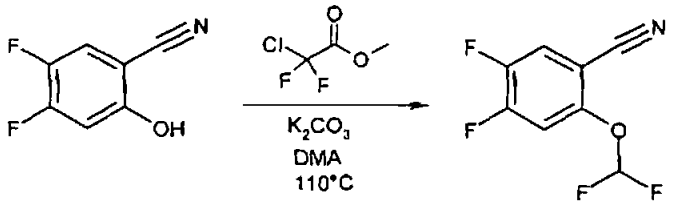
combinadas se lavaron dos veces con acetato de etilo, se acidificaron con disolución acuosa de ácido clorhídrico y se extrajeron tres veces con acetato de etilo. Los extractos orgánicos combinados se lavaron con agua, con salmuera, se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida para producir 0,78 g de 4-fluoro-2-hidroxi-benzonitrilo como un sólido blanco.

C7H4FNO (137,11), MS(ESI): 138,17 ($M+H^+$).

A una disolución de 4,6 g de 4-fluoro-2-hidroxi-benzonitrilo en 15 mL de dimetilacetamida anhidra se le añadieron 6,8 g de clorodifluororacetato de metilo y 6,5 g de carbonato de potasio. La mezcla resultante se desgaseó burbujeando argón a través de ella y se calentó hasta 110°C durante 2h, luego se añadieron 6,5 g adicionales de clorodifluororacetato de metilo y 6,5 g de carbonato de potasio. La mezcla resultante se calentó hasta 110°C durante otra hora, luego se concentró a presión reducida. El residuo se absorbió en acetato de etilo, se lavó dos veces con una disolución acuosa molar de hidróxido de sodio, con agua y salmuera, se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía en columna sobre gel de sílice (gradiente de heptano 100 a heptano 80/ acetato de etilo 20) para proveer 4,78 g de 2-difluorometoxi-4-fluoro-benzonitrilo como un líquido amarillento.

C8H4F3NO (187,12), MS(ESI): 188,0 ($M+H^+$).

2-Difluorometoxi-4,5-difluoro-benzonitrilo



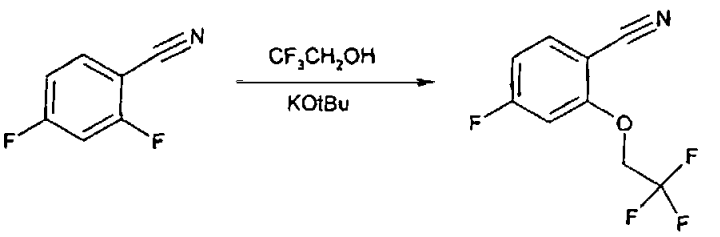
A una disolución de 1 g de 4,5-difluoro-2-hidroxi-benzonitrilo existente en el mercado, en 5 mL de dimetilacetamida anhidra, se le añadieron 1,3 g de clorodifluororacetato de metilo y 1,28 g de carbonato de potasio. La mezcla resultante se desgaseó burbujeando argón a través de ella y se calentó hasta 110°C durante 1,5h, luego se concentró a presión reducida. El residuo se absorbió en acetato de etilo, se lavó dos veces con una disolución acuosa

molar de hidróxido de sodio, con agua y salmuera, se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía en columna sobre gel de sílice (gradiente de heptano 100 a heptano 80/ acetato de etilo 20) para producir 0,42 g de 2-difluorometoxi-4,5-difluoro-benzonitrilo como un líquido amarillento.

C8H3F4NO (205,11), MS(EI): 205 (M^+).

Síntesis de las unidades estructurales según el procedimiento M:

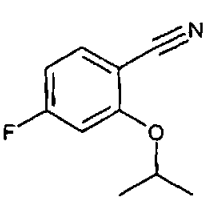
4-Fluoro-2-(2,2,2-trifluoro-etoxi)-benzonitrilo



A una disolución de 359 mg de trifluoroetanol en 3 mL de tetrahidrofurano anhidro a 5°C se le añadieron lentamente 3,6 mL de una disolución molar de terc-butóxido de potasio en terc-butanol. La disolución resultante se agitó durante 30 minutos a 5°C y se añadió lentamente a una disolución de 500 mg de 2,4-difluoro-benzonitrilo en 3 mL de tetrahidrofurano anhidro a 5°C. La mezcla resultante se agitó durante 1h a 5°C, luego se vertió en agua y se extrajo con acetato de etilo. Los extractos orgánicos se secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida. El producto bruto se purificó por cromatografía en columna sobre gel de sílice (gradiente de heptano 100 a heptano 90/ acetato de etilo 10) para producir 640 mg de 4-fluoro-2-(2,2,2-trifluoro-etoxi)-benzonitrilo como un sólido blanco.

C9H5F4NO (219,14), MS(ESI): 220 ($M+H^+$).

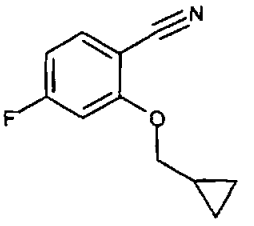
4-Fluoro-2-isopropoxi-benzonitrilo



De acuerdo con el método descrito para 4-fluoro-2-(2,2,2-trifluoro-etoxi)-benzonitrilo, se obtuvo 4-fluoro-2-isopropoxi-benzonitrilo a partir de 2,4-difluoro-benzonitrilo e isopropanol.

C10H10FNO (179,20), MS(ESI): 180 ($M+H^+$).

2-Ciclopropilmetoxi-4-fluoro-benzonitrilo



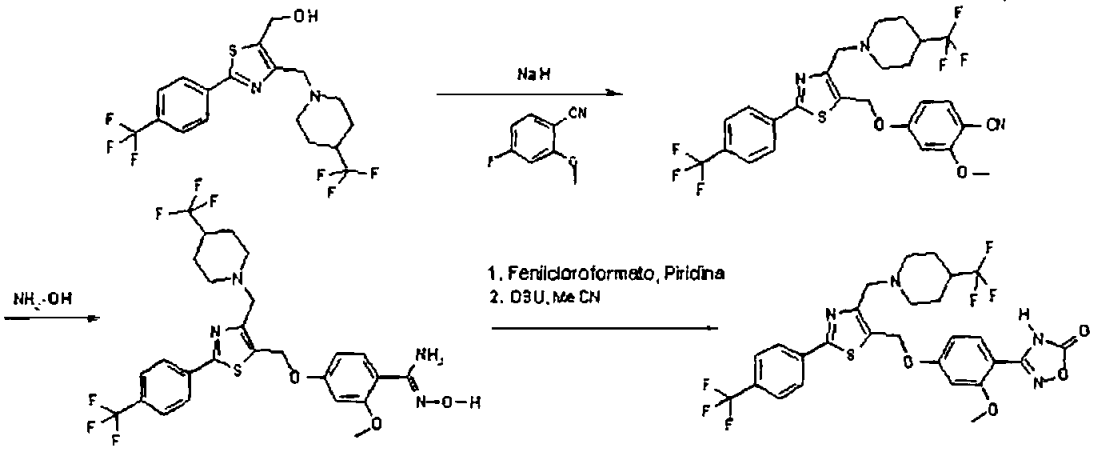
De acuerdo con el método descrito para 4-fluoro-2-(2,2,2-trifluoro-etoxi)-benzonitrilo, se obtuvo 2-ciclopropilmetoxi-4-fluoro-benzonitrilo a partir de 2,4-difluoro-benzonitrilo y ciclopropilmetanol.

C11H10FNO (191,21), MS(EI): 205 (M^+).

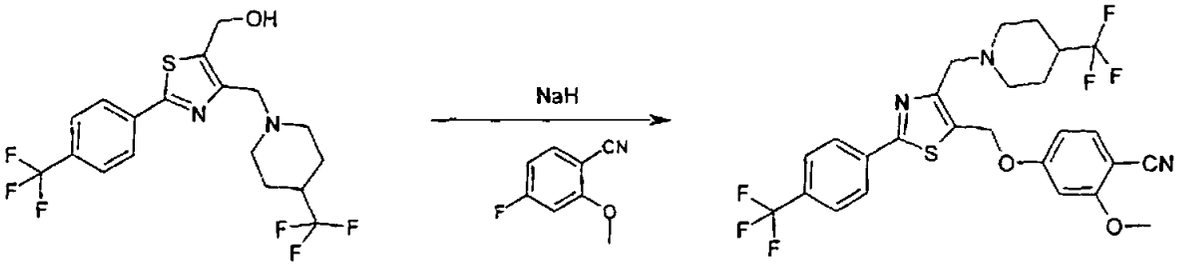
Los siguientes ejemplos se prepararon de acuerdo con el procedimiento B:

Ejemplo 1

3-{2-Metoxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona



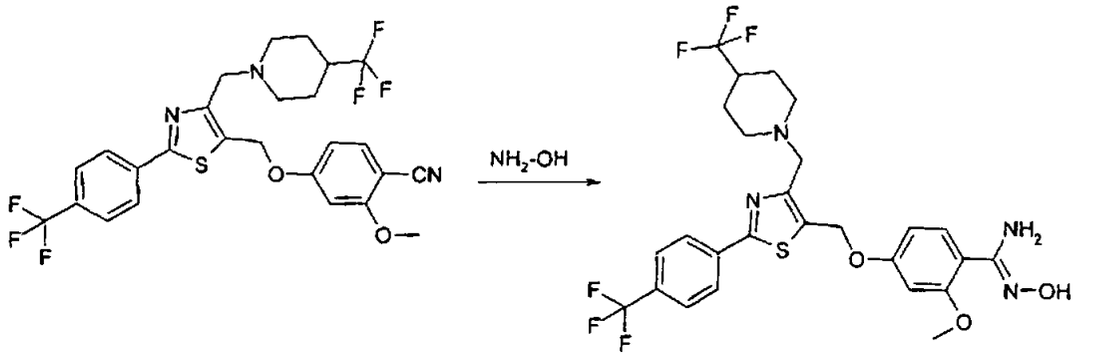
2-Metoxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-benzonitrilo



A una disolución de 474 mg de [2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-il]-metanol en 2,9 mL de dimetilformamida se le añadieron de 60 mg de hidruro de sodio. La mezcla resultante se agitó durante 30 minutos a 0°C, luego se añadieron 208 mg de 4-fluoro-2-metoxibenzonitrilo. Después de agitar durante 30 minutos a 0°C, la temperatura se dejó calentar hasta temperatura ambiente y la mezcla de reacción se agitó durante 30 minutos. El disolvente se eliminó a presión reducida y se añadió diclorometano/agua al residuo. La capa orgánica se separó y la capa acuosa se extrajo tres veces con diclorometano. Los extractos orgánicos se secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida. El producto bruto se purificó por cromatografía en columna sobre gel de sílice (diclorometano 95/ metanol 5) para producir 279 mg de 2-metoxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-benzonitrilo.

C26H23F6N3O2S (555,55), MS(ESI): 556 ($M+H^+$).

<u>*N*-hidroxi-2-metoxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-benzamidina</u>

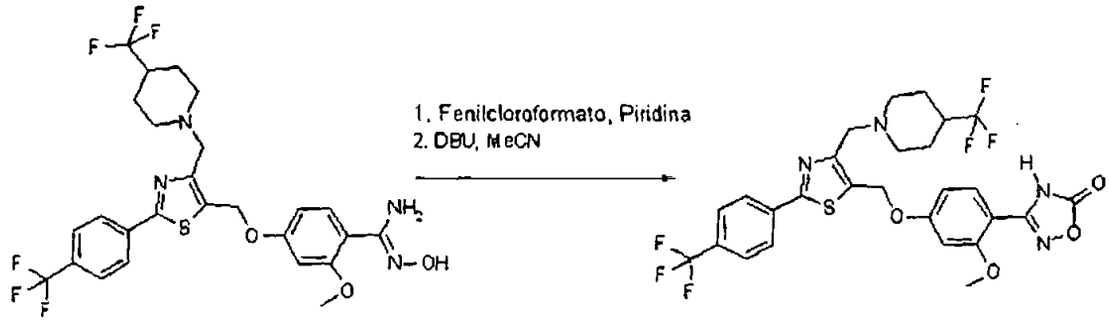


A una disolución de 279 mg de 2-metoxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-benzonitrilo en 3 mL de

tetrahidrofurano y 1,5 mL de metanol se le añadieron 333 mg de hidrocloruro de hidroxilamina seguidos de 0,69 mL de trietilamina. La mezcla resultante se calentó a 60°C toda la noche. Después de dejar enfriar hasta temperatura ambiente, la mezcla se vertió en agua y se extrajo con diclorometano. Los extractos orgánicos se secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida. El producto bruto se purificó por cromatografía en columna sobre gel de sílice (gradiente de diclorometano 100 a diclorometano 95/ metanol 5) para producir 154 mg de *N*-hidroxi-2-metoxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-benzamidina.

C26H26F6N4O3S (588,58), MS(ESI): 589 (M^++H).

3-{2-Metoxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona



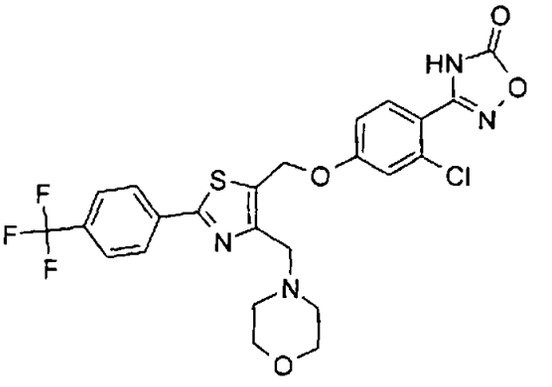
A una disolución de 150 mg de *N*-hidroxi-2-metoxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-benzamidina en 5 mL de diclorometano anhidro a 0°C se le añadieron gota a gota 50 µL de piridina seguidos de 40 µL de fenilcloroformato. La mezcla resultante se agitó a temperatura ambiente durante 1 h, luego se añadieron agua y diclorometano. La capa acuosa se separó y se extrajo con diclorometano. Los extractos orgánicos se secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida. A una disolución del residuo resultante en 2,7 ml de acetonitrilo, se añadieron 60 µl de 1,8-diazabiciclo[5.4.0]undec-7-eno. La mezcla se agitó a temperatura ambiente toda la noche. El disolvente se separó al vacío. El residuo resultante se absorbió en tetrahidrofurano/acetato de etilo 50/50, se lavó con agua, se secó sobre sulfato de magnesio, se filtró y se

concentró a presión reducida. El producto bruto se purificó por cromatografía en columna sobre gel de sílice (gradiente de diclorometano 100 a diclorometano 90/ metanol 10) para producir 105 mg de 3-{2-metoxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona.

C27H24F6N4O4S (614,57), MS (EI): 614 (M^+).

Ejemplo 2

3-{2-Cloro-4-[4-morfolin-4-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

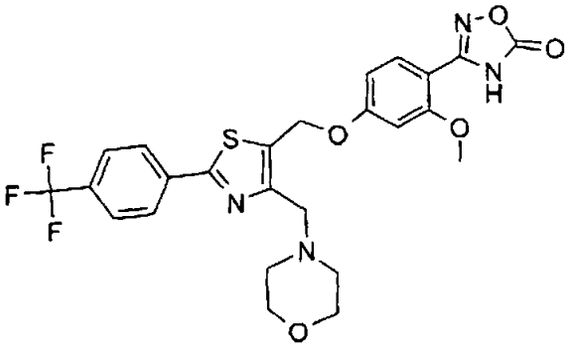


De acuerdo con el método descrito en el Ejemplo 1, se obtuvo 3-{2-cloro-4-[4-morfolin-4-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de [4-morfolin-4-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol y 2-cloro-4-fluoro-benzonitrilo existente en el mercado.

C24H20ClF3N4O4S (552,96), MS(EI): 552 (M^+).

Ejemplo 3

3-{2-Metoxi-4-[4-morfolin-4-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

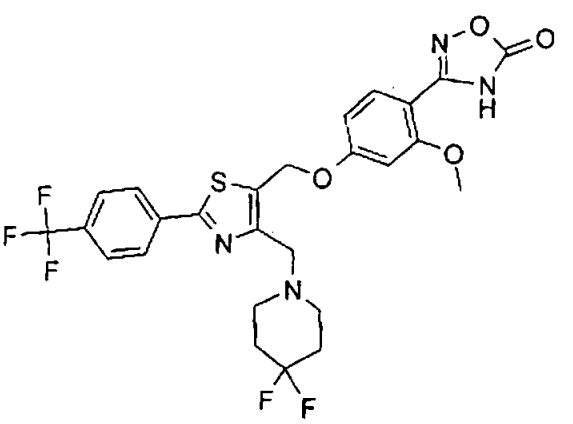


De acuerdo con el método descrito en el Ejemplo 1, se obtuvo 3-{2-metoxi-4-[4-morfolin-4-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de [4-morfolin-4-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol y 4-fluoro-2-metoxibenzonitrilo existente en el mercado.

C25H23F3N4O5S (548,54), MS(ESI): 549 ($M+H^+$).

Ejemplo 4

3-{4-[4-(4,4-Difluoro-piperidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona

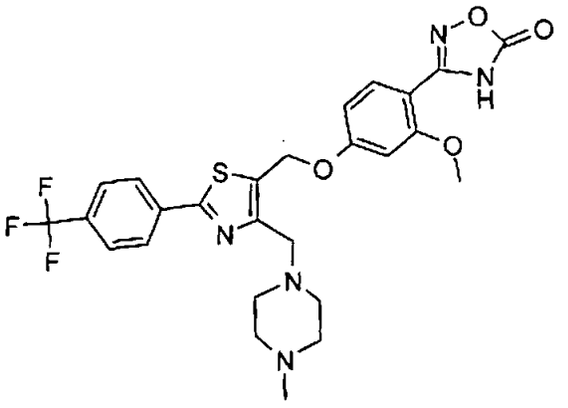


De acuerdo con el método descrito en el Ejemplo 1, se obtuvo 3-{4-[4-(4,4-difluoro-piperidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 4-(4,4-difluoro-piperidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol y 4-fluoro-2-metoxibenzonitrilo existente en el mercado.

C26H23F5N4O4S (582,55), MS(ESI): 583 ($M+H^+$).

Ejemplo 5

3-{2-Metoxi-4-[4-(4-metil-piperazin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

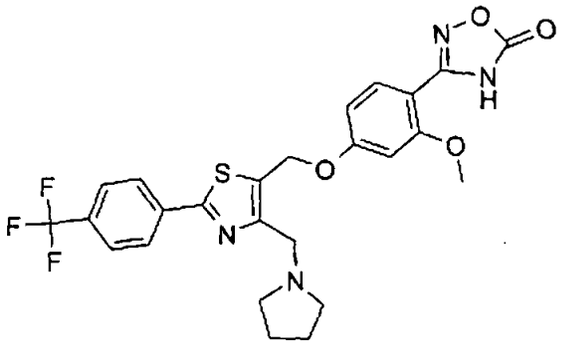


De acuerdo con el método descrito en el Ejemplo 1, se obtuvo 3-{2-metoxi-4-[4-(4-metil-piperazin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de [4-(4-metil-piperazin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol y 4-fluoro-2-metoxibenzonitrilo existente en el mercado.

C26H26F3N5O4S (561,59), MS(ESI): 562 ($M+H^+$).

Ejemplo 6

3-{2-Metoxi-4-[4-pirrolidin-1-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

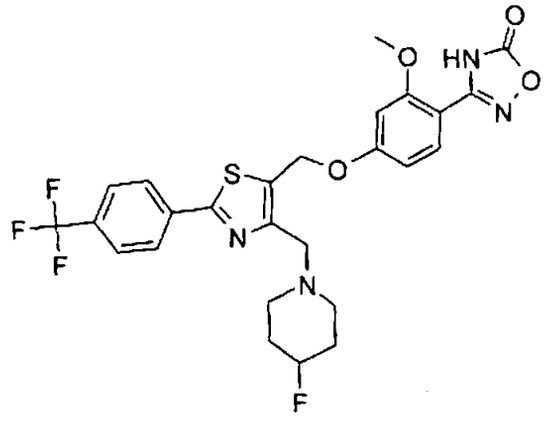


De acuerdo con el método descrito en el Ejemplo 1, se obtuvo 3-{2-metoxi-4-[4-pirrolidin-1-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de [4-pirrolidin-1-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol y 4-fluoro-2-metoxibenzonitrilo existente en el mercado.

C25H23F3N4O4S (532,54), MS(ESI): 533 ($M+H^+$).

Ejemplo 7.

3-{4-[4-(4-Fluoro-piperidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona

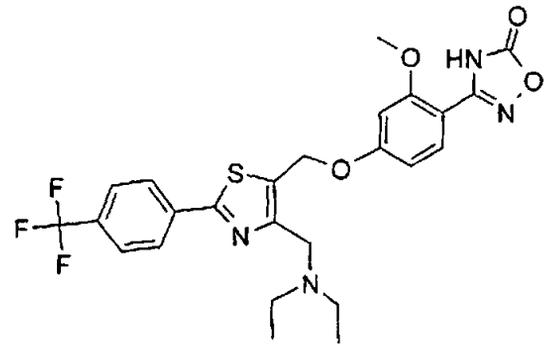


De acuerdo con el método descrito en el Ejemplo 1, se obtuvo 3-{4-[4-(4-fluoro-piperidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de [4-(4-fluoro-piperidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol y 4-fluoro-2-metoxibenzonitrilo existente en el mercado.

C26H24F4N4O4S (564,56), MS(ESI): 565 ($M+H^+$).

Ejemplo 8

3-{4-[4-Dietilaminometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona

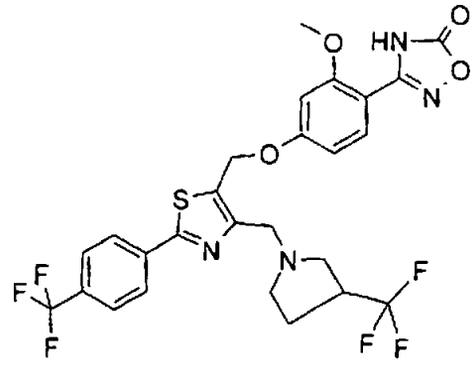


De acuerdo con el método descrito en el Ejemplo 1, se obtuvo 3-{4-[4-dietilaminometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de [4-dietilaminometil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol y 4-fluoro-2-metoxibenzonitrilo existente en el mercado.

C25H25F3N4O4S (534,56), MS(ESI): 535 ($M+H^+$).

Ejemplo 9

3-{2-Metoxi-4-[2-(4-trifluorometil-fenil)-4-(3-trifluorometil-pirrolidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

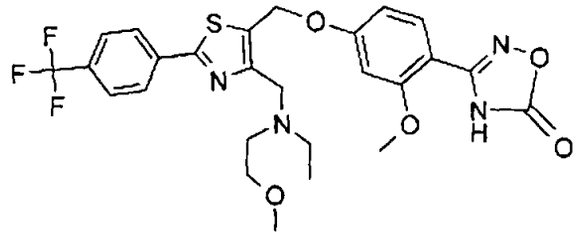


De acuerdo con el método descrito en el Ejemplo 1, se obtuvo 3-{2-metoxi-4-[2-(4-trifluorometil-fenil)-4-(3-trifluorometil-pirrolidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona racémica a partir de [2-(4-trifluorometil-fenil)-4-(3-trifluorometil-pirrolidin-1-ilmetil)-tiazol-5-il]-metanol racémico y 4-fluoro-2-metoxibenzonitrilo existente en el mercado.

C26H22F6N4O4S (600,54), MS(ESI): 601 ($M+H^+$).

Ejemplo 10

3-{4-[4-{[Etil-(2-metoxi-etil)-amino]-metil}-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona

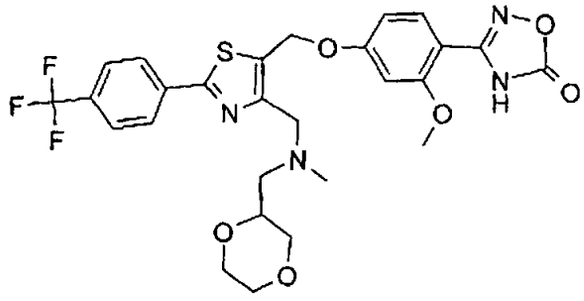


De acuerdo con el método descrito en el Ejemplo 1, se obtuvo 3-{4-[4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de [4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol y 4-fluoro-2-metoxibenzonitrilo existente en el mercado.

C26H27F3N4O5S (564,59), MS(CI): 565 ($M+H^+$).

Ejemplo 11

3-{4-[4-[([1,4]Dioxan-2-ilmetil-metil-amino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona

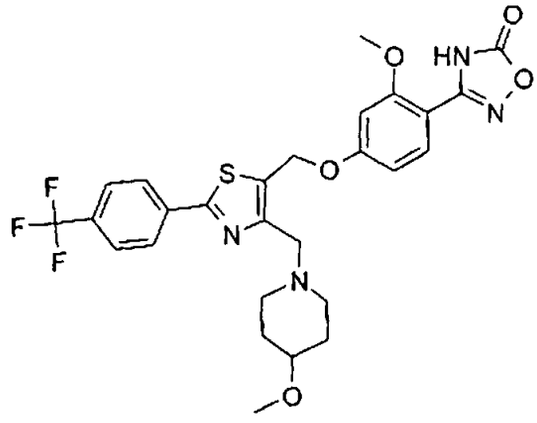


De acuerdo con el método descrito en el Ejemplo 1, se obtuvo 3-{4-[4-[([1,4]dioxan-2-ilmetil-metil-amino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona racémica a partir de [4-[([1,4]dioxan-2-ilmetil-metil-amino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol racémico y 4-fluoro-2-metoxibenzonitrilo existente en el mercado.

C27H27F3N4O6S (592,60), MS(ESI): 593 ($M+H^+$).

Ejemplo 12

3-{2-Metoxi-4-[4-(4-metoxi-piperidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

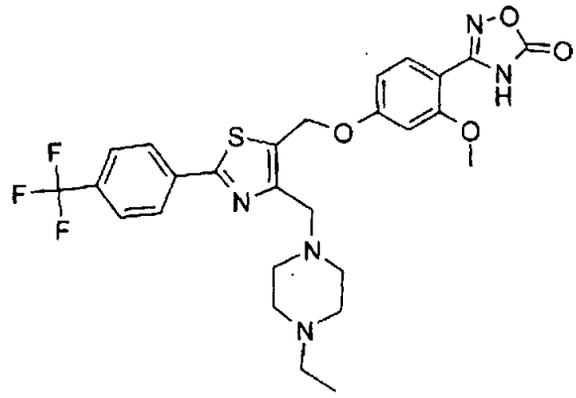


De acuerdo con el método descrito en el Ejemplo 1, se obtuvo 3-{2-metoxi-4-[4-(4-metoxi-piperidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de [4-(4-metoxi-piperidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol y 4-fluoro-2-metoxibenzonitrilo existente en el mercado.

C27H27F3N4O5S (576,60), MS(ESI): 577 ($M+H^+$).

Ejemplo 13

3-{4-[4-(4-Etil-piperazin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona

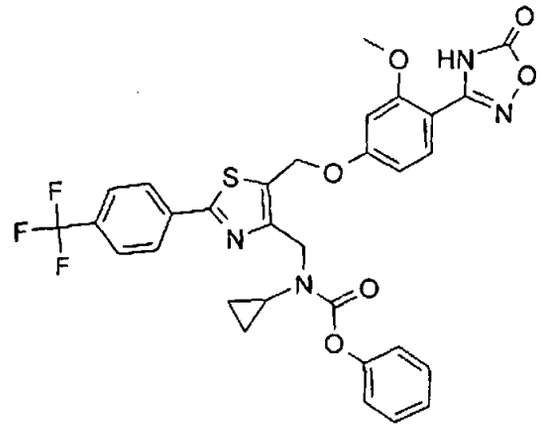


De acuerdo con el método descrito en el Ejemplo 1, se obtuvo 3-{4-[4-(4-etil-piperazin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de [4-(4-etil-piperazin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol y 4-fluoro-2-metoxibenzonitrilo existente en el mercado.

C27H28F3N5O4S (575,61), MS(ESI): 576 ($M+H^+$).

Ejemplo 14

Éster fenílico del ácido ciclopropil-[5-[3-metoxi-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-ilmetil]-carbámico



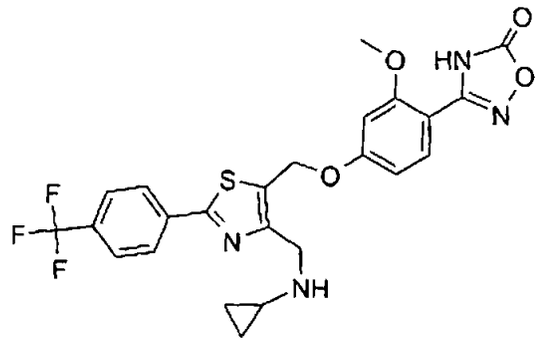
De acuerdo con el método descrito en el Ejemplo 1, se obtuvo éster fenílico del ácido ciclopropil-[5-[3-metoxi-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-ilmetil]-carbámico a partir de [4-ciclopropilaminometil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol y 4-fluoro-2-metoxibenzonitrilo existente en el mercado. Durante la formación del anillo de

oxadiazolona, la ciclopropilamina secundaria reaccionó con cloroformato de fenilo para producir el carbamato de fenilo mencionado.

C31H25F3N4O6S (638.63), MS(CI): 639 ($M+H^+$).

Ejemplo 15

3-{4-[4-Ciclopropilaminometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona



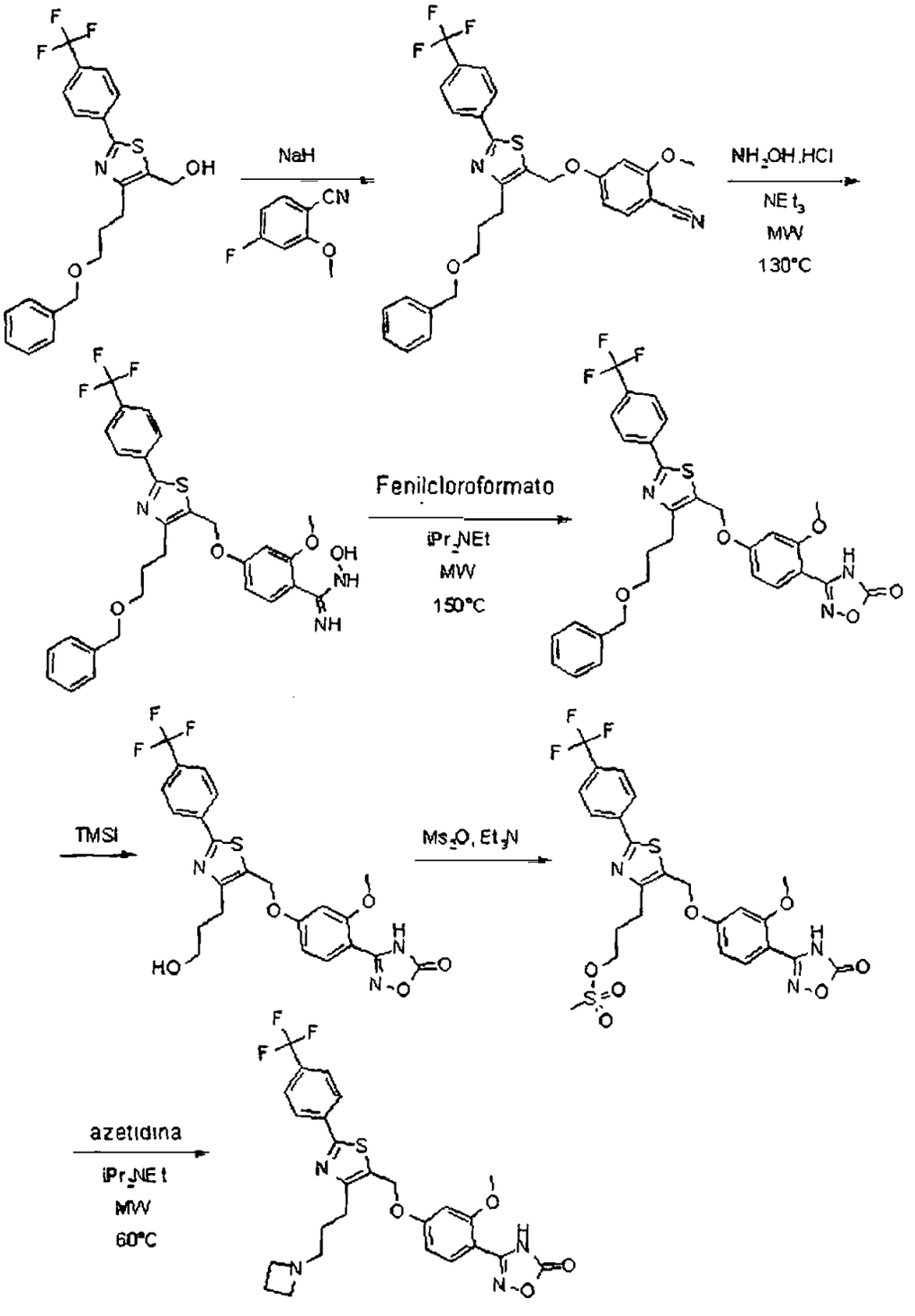
A una disolución de 32,6 mg de éster fenílico del ácido ciclopropil-[5-[3-metoxi-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-ilmetil]-carbámico en 2 mL de etilenglicol se le añadieron 2 mL de una disolución saturada de hidróxido de potasio en agua. La mezcla resultante se agitó en un tubo sellado bajo irradiación de microondas durante 25 minutos hasta 100°C, luego 10 minutos adicionales hasta 120°C y finalmente 15 minutos más hasta 140°C. Se extrajo luego con diclorometano. Los extractos orgánicos se lavaron con agua, secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida. El producto bruto se purificó por cromatografía en columna sobre gel de sílice (gradiente de diclorometano 100 a diclorometano 90/ metanol 10) para producir 9,5 mg de 3-{4-[4-ciclopropilaminometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona.

C24H21F3N4O4S (518,52), MS(ESI): 519 ($M+H^+$).

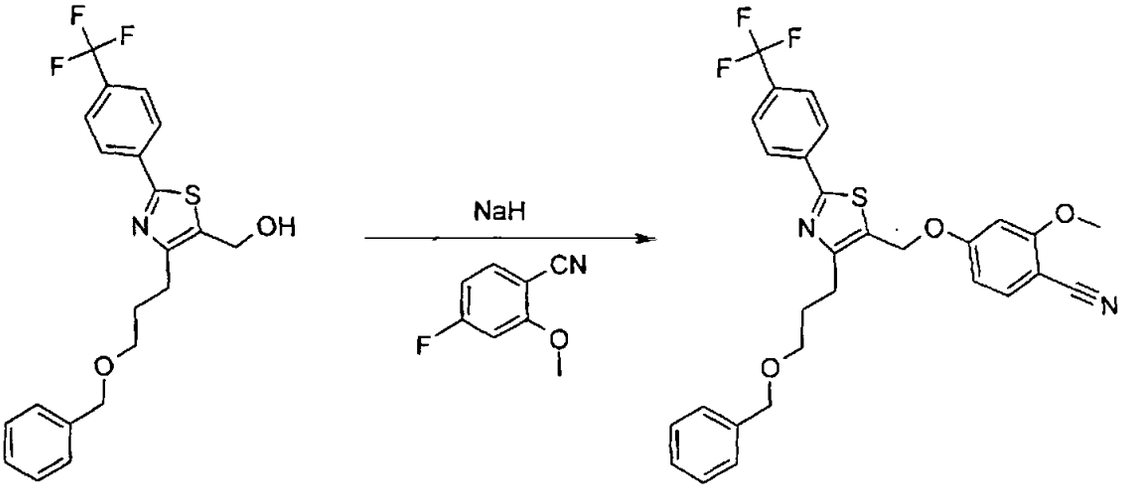
Los siguientes ejemplos se prepararon de acuerdo con el procedimiento D, en el que las dos primeras etapas de reacción se realizaron de acuerdo con el procedimiento B:

Ejemplo 16

3-{4-[4-(3-Azetidin-1-il-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona



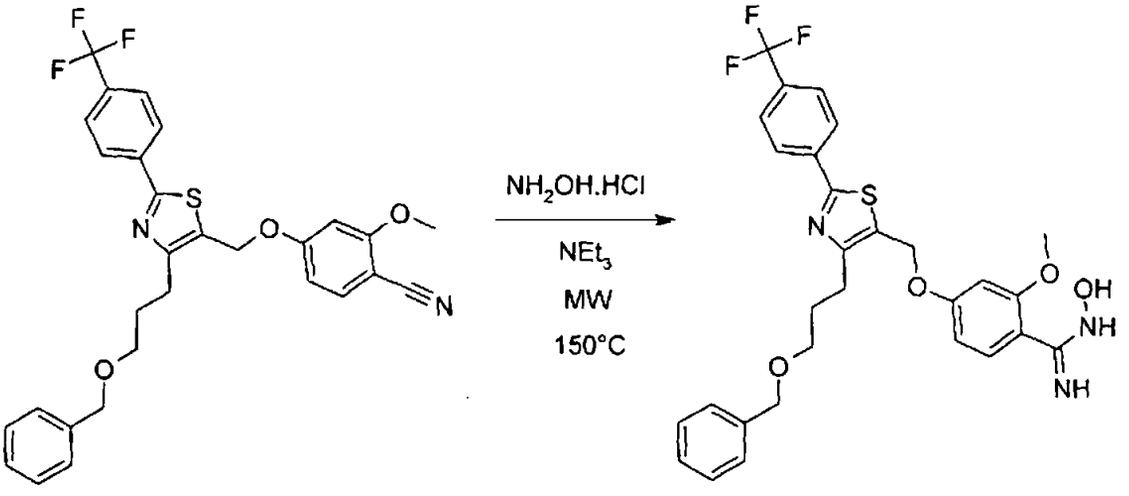
4-[4-(3-Benciloxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-benzonitrilo



A una disolución de 1,34 g de [4-(3-benciloxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol en 20 mL de dimetilformamida a 0°C se le añadieron 158 mg de una suspensión al 60% de hidruro de sodio en aceite mineral. La mezcla resultante se agitó durante 10 minutos a 0°C, luego se añadieron 497 mg de 4-fluoro-2-metoxibenzonitrilo. Después de agitar durante 30 minutos a 0°C, se dejó calentar la temperatura hasta temperatura ambiente y la mezcla de reacción se agitó hasta completarse. El disolvente se eliminó a presión reducida y se añadió diclorometano/agua al residuo. La capa orgánica se separó y la capa acuosa se extrajo tres veces con diclorometano. Los extractos orgánicos combinados se lavaron con salmuera, se secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida para producir 1,82 g de producto bruto como un aceite amarillo. Se añadió una disolución 1/1 de heptano/éter diisopropílico al residuo y el producto solidificado se filtró para proveer un primer cultivo de 1,26 g del producto deseado. El licor madre se concentró y purificó por cromatografía en columna sobre gel de sílice (heptano 60/ acetato de etilo 40) para proveer 110 mg adicionales. Las dos fracciones se combinaron para obtener 1,37 g de 4-[4-(3-benciloxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-benzonitrilo.

$C_{29}H_{25}F_3N_2O_3S$ (538,59), MS(ESI): 539 ($M+H^+$).

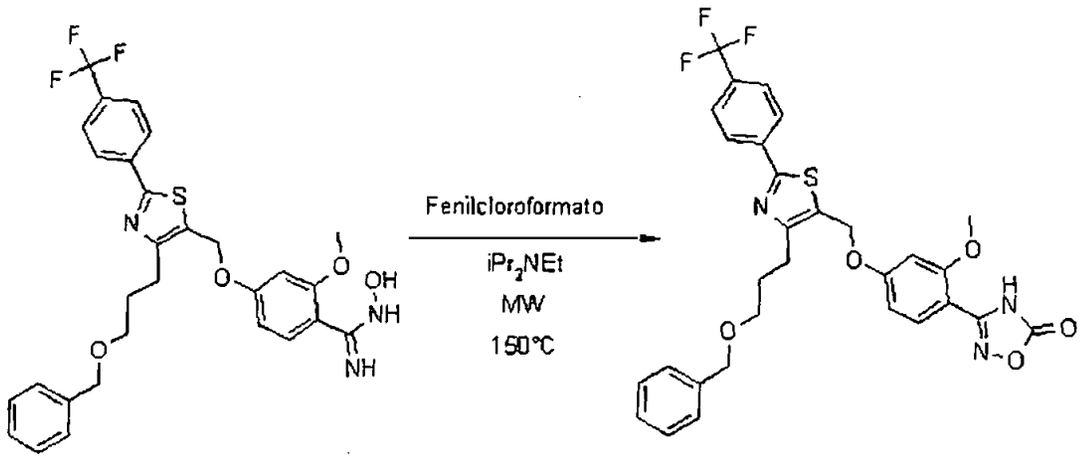
4-[4-(3-Benciloxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-*N*-hidroxi-2-metoxi-benzamidina



A una disolución de 300 mg de 4-[4-(3-benciloxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-benzonitrilo en 1,8 mL de tetrahidrofurano y 2 mL de metanol se le añadieron 387 mg de hidrocloruro de hidroxilamina seguidos de 0,62 mL de trietilamina. La mezcla resultante se calentó hasta 150°C bajo irradiación de microondas durante 10 minutos. Después de dejar enfriar hasta temperatura ambiente, la mezcla se concentró a presión reducida y se añadió diclorometano/agua al residuo. La capa orgánica se separó y la capa acuosa se extrajo tres veces con diclorometano. Los extractos orgánicos se secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida. El producto bruto se purificó por cromatografía en columna sobre gel de sílice (heptano 50/ acetato de etilo 50) para producir 162 mg de 4-[4-(3-benciloxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-*N*-hidroxi-2-metoxi-benzamidina.

C29H28F3N3O4S (571,62), MS(ESI): 572 ($M+H^+$).

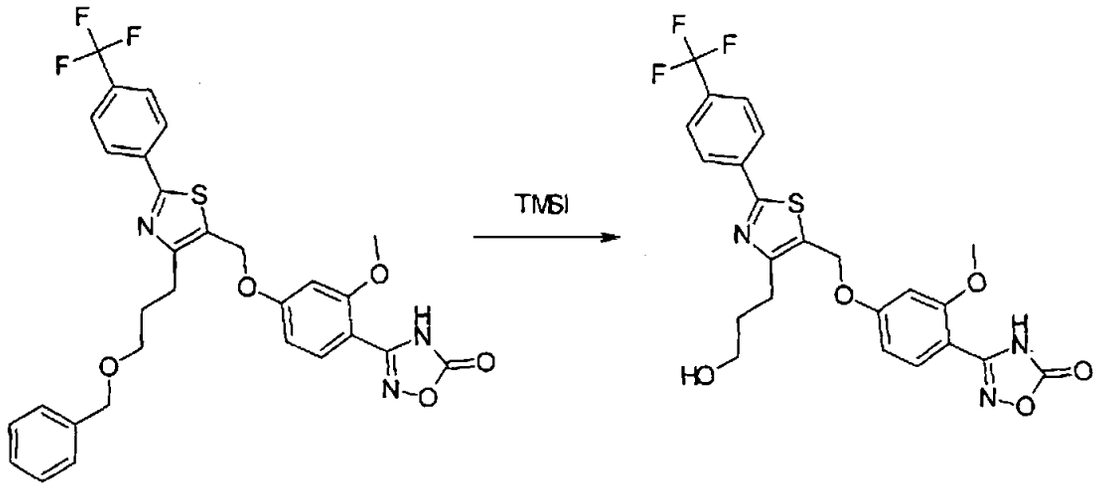
3-{4-[4-(3-Benciloxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona



A una disolución de 1,05 g de 4-[4-(3-benciloxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-*N*-hidroxi-2-metoxi-benzamidina en 5 mL de tetrahidrofurano se le añadieron 254 µL de cloroformato de fenilo y 607 µL de diisopropiletilamina. La mezcla resultante se calentó hasta 150°C bajo irradiación de microondas durante 20 minutos. Después de dejar enfriar hasta temperatura ambiente, la mezcla se concentró a presión reducida y se añadió diclorometano/agua al residuo. La capa orgánica se separó y la capa acuosa se extrajo tres veces con diclorometano. Los extractos orgánicos se secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida. Se añadió éter diisopropílico al residuo y el sólido se recogió por filtración y se lavó con éter diisopropílico para producir 558 mg de 3-{4-[4-(3-benciloxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona.

C30H26F3N3O5S (597,62), MS(ESI): 598 ($M+H^+$).

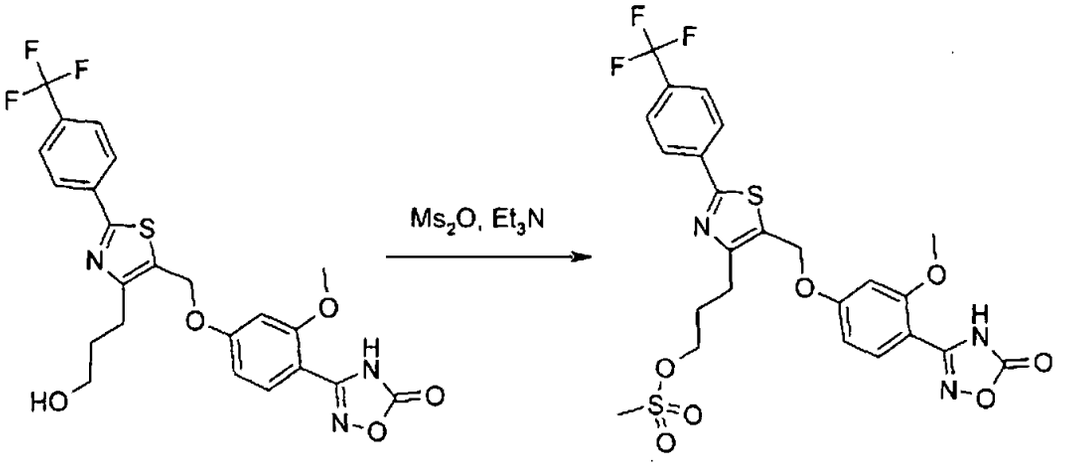
3-{4-[4-(3-Hidroxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona



Se disolvieron 118 mg de 3-{4-[4-(3-benciloxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona en 14 mL de diclorometano calentando y dejando enfriar hasta temperatura ambiente. A la disolución resultante se le añadieron 144 µL de yodotrimetilsilano. La mezcla resultante se agitó a temperatura ambiente durante 6,5 h y se añadieron 6 mL de metanol seguidos de una disolución saturada acuosa de bicarbonato de sodio. La mezcla se agitó durante 1 h, se filtró y se concentró a presión reducida. Se añadieron diclorometano/agua al residuo. La capa orgánica se separó y la capa acuosa se extrajo tres veces con diclorometano. Los extractos orgánicos se secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida. El producto bruto se purificó por cromatografía en columna sobre gel de sílice (diclorometano 90/ metanol 10) para producir 40 mg de 3-{4-[4-(3-hidroxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona.

C23H20F3N3O5S (507,49), MS(ESI): 508 ($M+H^+$).

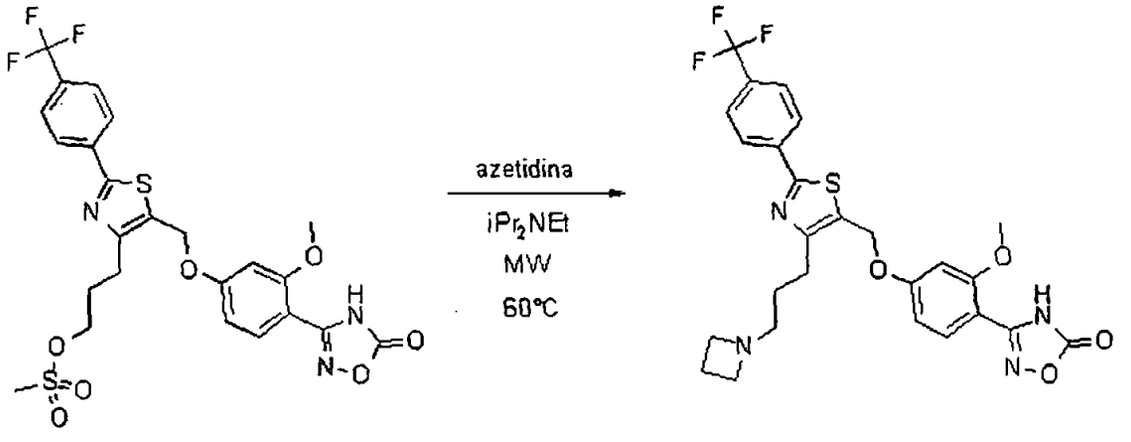
<u>Éster 3-[5-[3-metoxi-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-il]-propílico del ácido metansulfónico</u>



A una disolución de 300 mg de 3-{4-[4-(3-hidroxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona en 15 mL de diclorometano se le añadieron 1,2 mL de trietilamina y 217 mg de anhídrido metansulfónico. La mezcla resultante se agitó a temperatura ambiente durante 1 hora. Se añadió una disolución saturada acuosa de cloruro de amonio. La capa orgánica se separó y la capa acuosa se extrajo tres veces con diclorometano. Los extractos orgánicos combinados se secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida para producir 228 mg de éster 3-[5-[3-metoxi-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-il]-propílico de ácido metansulfónico que se utilizó en la etapa siguiente sin purificación adicional.

C24H22F3N3O7S2 (585,58), MS(ESI): 586 ($M+H^+$).

3-{4-[4-(3-Azetidin-1-il-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona



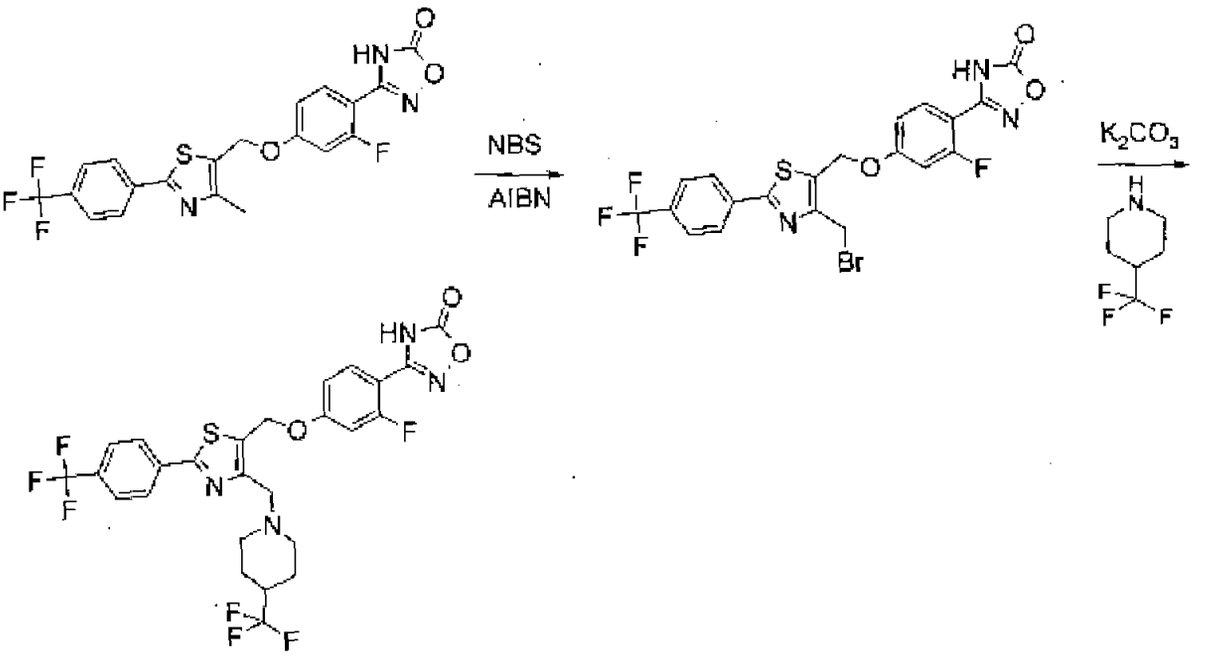
A una suspensión de 130 mg de éster 3-[5-[3-metoxi-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-il]-propílico del ácido metansulfónico en 7 mL de acetonitrilo se le añadieron 25 µL de azetidina y 57 mg de diisopropiletil amina. La mezcla resultante se calentó en un tubo sellado hasta 60°C bajo irradiación de microondas durante 30 minutos y luego se concentró a presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (gradiente de diclorometano 100 a diclorometano 90/ metanol 10/agua 1/ácido acético 1) seguida de una columna de 2g SCX Waters con gradiente CH2Cl2/MeOH 30/70 a 7N NH3 en MeOH y otro cromatografía en columna sobre gel de sílice (eluyendo con diclorometano 90/ metanol 10) para producir 3,5 mg de 3-{4-[4-(3-azetidin-1-il-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona.

C26H25F3N4O4S (546,57), MS(ESI): 547 ($M+H^+$).

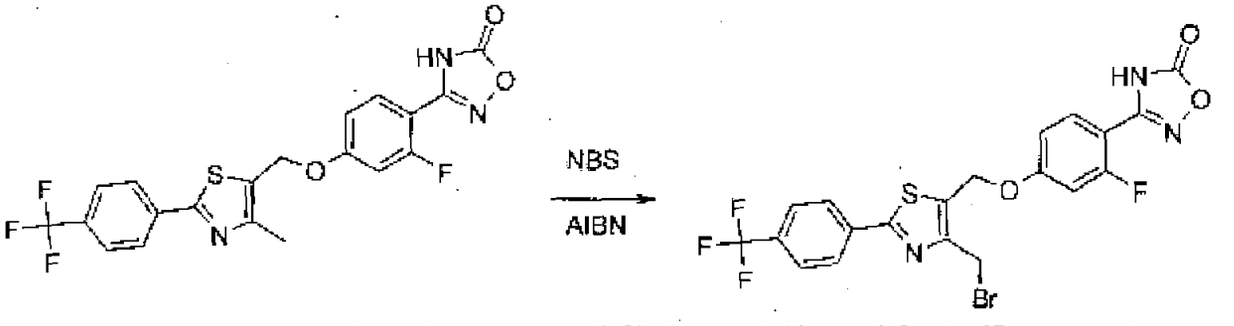
Los siguientes ejemplos se prepararon de acuerdo con el procedimiento F:

Ejemplo 17

3-{2-Fluoro-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona



3-{4-[4-Bromometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-fluoro-fenil}-4H-[1,2,4]oxadiazol-5-ona



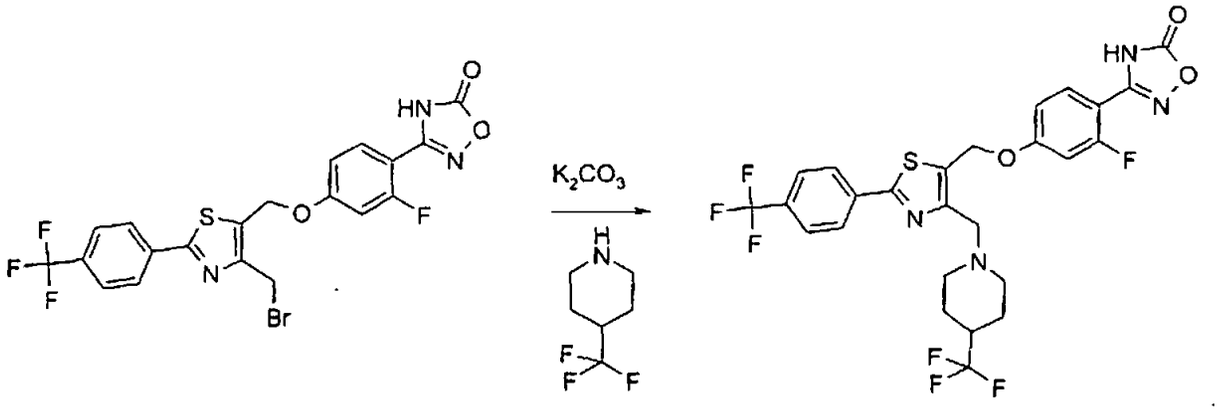
A una mezcla de 100 mg de 3-{2-fluoro-4-[4-metil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona[5] en 3 mL de tetracloruro de carbono y 2 mL de hexafluoroisopropanol a reflujo se le añadieron 100 mg de N-bromosuccinimida y 10 mg de AIBN. La mezcla resultante se sometió a reflujo durante 1 h. Luego se vertió en agua y se extrajo con diclorometano. Los extractos orgánicos se secaron sobre sulfato magnésico, se filtraron y se

[5] Ejemplo 1 de la solicitud WO2006/097786

concentraron a presión reducida. El sólido se absorbió en diclorometano, precipitó añadiendo éter diisopropílico, se filtró y se lavó con éter diisopropílico. El sólido blanco se purificó por cromatografía en columna sobre gel de sílice (gradiente de diclorometano/metanol a partir de 100/0 a 80/20) para producir 59 mg de 3-{4-[4-bromometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-fluoro-fenil}-4H-[1,2,4]oxadiazol-5-ona como un sólido blanco.

C20H12BrF4N3O3S (530,29), MS(CI): 530 ($M+H^+$).

3-{2-Fluoro-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

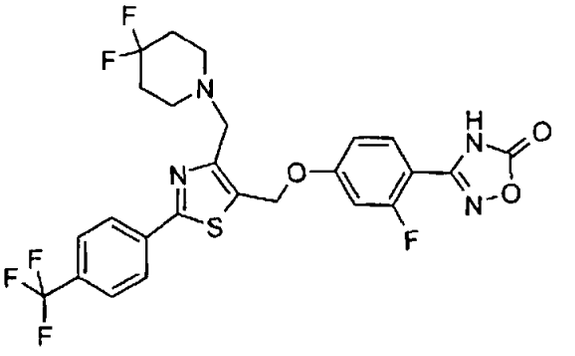


A una mezcla de 136 mg de 3-{4-[4-bromometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-fluoro-fenil}-4H-[1,2,4]oxadiazol-5-ona en 17 mL de acetonitrilo se le añadieron 48,6 mg de hidrocloruro de 4-trifluoropiperidina y 70 mg de carbonato de potasio. La mezcla resultante se agitó durante toda la noche y luego se concentró a presión reducida. Se absorbió luego en diclorometano y se lavó con agua. La capa acuosa se extrajo con diclorometano. Los extractos orgánicos se secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida. El producto bruto se purificó por cromatografía en columna sobre gel de sílice (diclorometano 98/metanol 2) para producir 51,6 mg de 3-{2-fluoro-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona como un sólido blanco.

C26H21F7N4O3S (602,53), MS(ESI): 603 ($M+H^+$).

Ejemplo 18

3-{4-[4-(4,4-Difluoro-piperidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-fluoro-fenil}-4H-[1,2,4]oxadiazol-5-ona

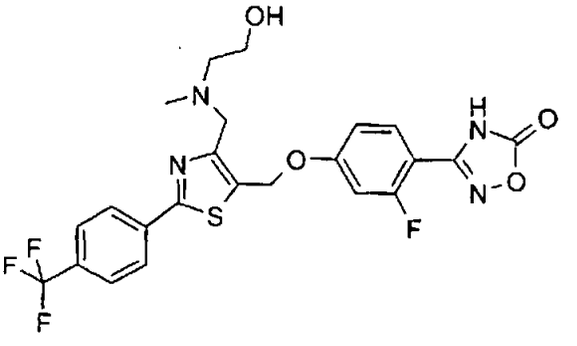


De acuerdo con el método descrito para 3-{2-fluoro-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona, se obtuvo 3-{4-[4-butil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2,6-difluoro-fenil}-4*H*-[1,2,4]oxadiazol-5-ona a partir de 3-{2-fluoro-4-[4-metil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona e hidrocloruro de 4,4-difluoro-piperidina.

C25H20F6N4O3S (570,51), MS(ESI): 571 ($M+H^+$).

Ejemplo 19

3-{2-Fluoro-4-[4-{[(2-hidroxi-etil)-metil-amino]-metil}-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

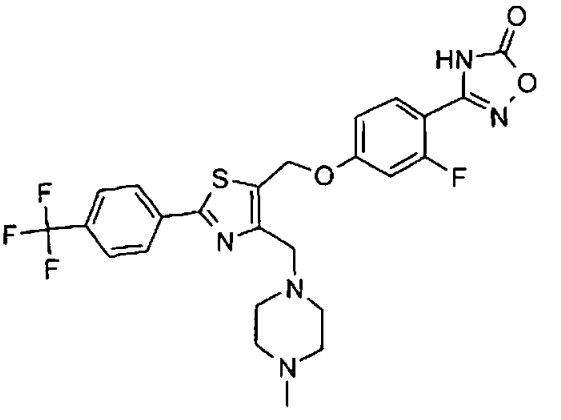


De acuerdo con el método descrito para 3-{2-fluoro-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona, se obtuvo 3-{2-fluoro-4-[4-{[(2-hidroxi-etil)-metil-amino]-metil}-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 3-{2-fluoro-4-[4-metil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona y 2-metilaminoetanol.

C23H20F4N4O4S (524,49), MS(ESI): 525 ($M+H^+$).

Ejemplo 20

3-{2-Fluoro-4-[4-(4-metil-piperazin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

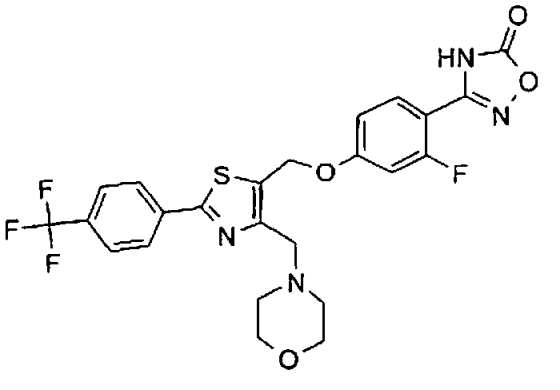


De acuerdo con el método descrito para 3-{2-fluoro-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona, se obtuvo 3-{2-fluoro-4-[4-(4-metil-piperazin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 3-{2-fluoro-4-[4-metil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona y 4-metil-piperazina.

C25H23F4N5O3S (549,55), MS(ESI): 550 ($M+H^+$).

Ejemplo 21

3-{2-Fluoro-4-[4-morfolin-4-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona



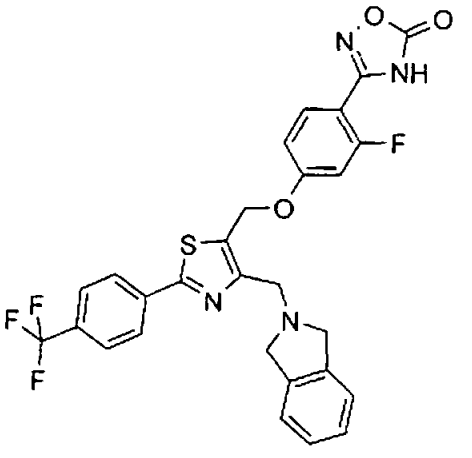
De acuerdo con el método descrito para 3-{2-fluoro-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona, se obtuvo 3-{2-fluoro-4-[4-morfolin-4-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de

3-{2-fluoro-4-[4-metil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona y morfolina.

C24H20F4N4O4S (536,50), MS(ESI): 537 ($M+H^+$).

Ejemplo 22

3-{4-[4-(1,3-Dihidro-isoindol-2-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-fluoro-fenil}-4H-[1,2,4]oxadiazol-5-ona

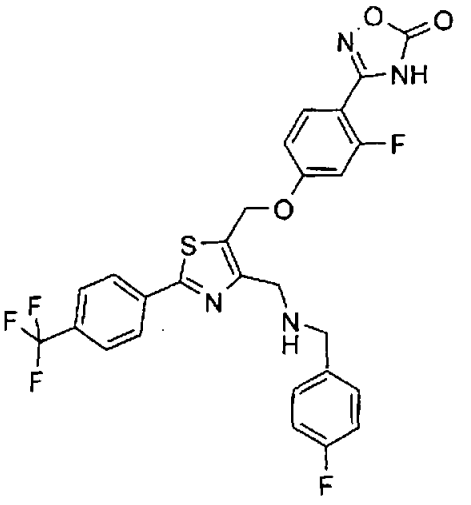


De acuerdo con el método descrito para 3-{2-fluoro-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona, se obtuvo 3-{4-[4-(1,3-dihidro-isoindol-2-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-fluoro-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 3-{2-fluoro-4-[4-metil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona y 2,3-dihidro-1H-isoindol.

C28H20F4N4O3S (568,55), MS(ESI): 569 ($M+H^+$).

Ejemplo 23

3-{2-Fluoro-4-[4-[(4-fluoro-bencilamino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

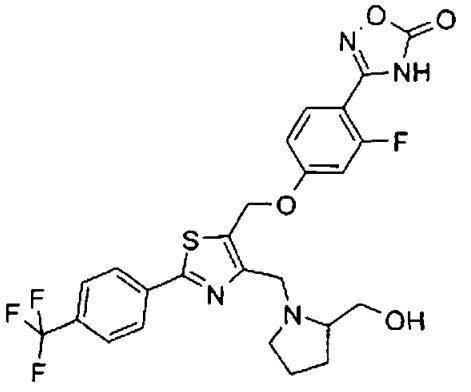


De acuerdo con el método descrito para 3-{2-fluoro-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona, se obtuvo 3-{2-fluoro-4-[4-[(4-fluoro-bencilamino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 3-{2-fluoro-4-[4-metil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona y 4-fluoro-bencilamina.

C27H19F5N4O3S (574,53), MS(ESI): 575 ($M+H^+$).

Ejemplo 24

3-{2-Fluoro-4-[4-(2-hidroximetil-pirrolidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona



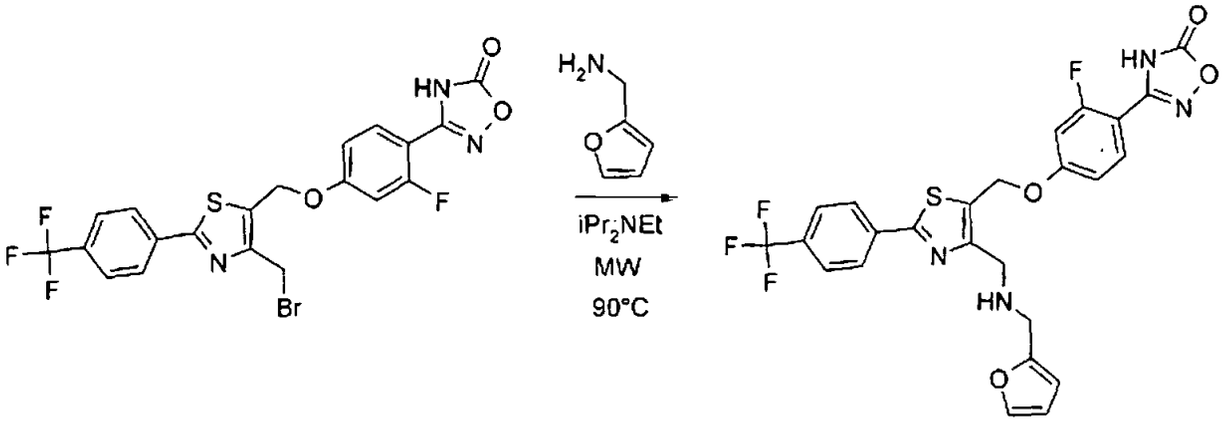
De acuerdo con el método descrito para 3-{2-fluoro-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona, se obtuvo 3-{2-fluoro-4-[4-(2-hidroximetil-pirrolidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

racémica a partir de 3-{2-fluoro-4-[4-metil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona y 2-hidroximetil-pirrolidina racémica.

C25H22F4N4O4S (550,53), MS(ESI): 551 ($M+H^+$).

Ejemplo 25

3-{2-Fluoro-4-[4-{[(furan-2-ilmetil)-amino]-metil}-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

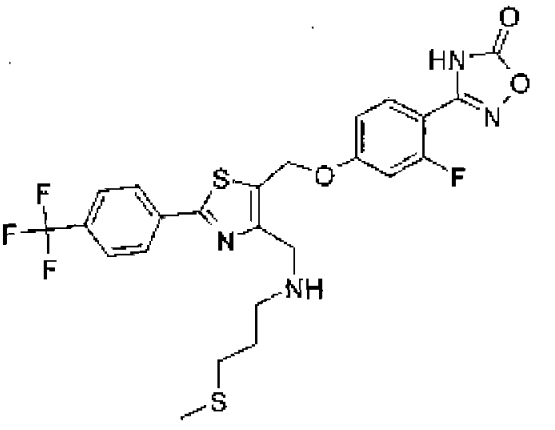


A una disolución de 50 mg de 3-{4-[4-bromometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-fluoro-fenil}-4H-[1,2,4]oxadiazol-5-ona en 2,5 mL de acetonitrilo se le añadieron 12 mg de furfurilamina y 25 mg de diisopropiletil amina. La mezcla resultante se calentó en un tubo sellado hasta 90°C bajo irradiación de microondas durante 5 minutos y luego se concentró a presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (gradiente de diclorometano 100 a diclorometano 90/ metanol 10/agua 1/ácido acético 1) seguida de lavados con éter diisopropílico para producir 18 mg de 3-{2-fluoro-4-[4-{[(furan-2-ilmetil)-amino]-metil}-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona.

C25H18F4N4O4S (546,50), MS(ESI): 547 ($M+H^+$).

Ejemplo 26

3-{2-Fluoro-4-[4-[(3-metilsulfanil-propilamino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

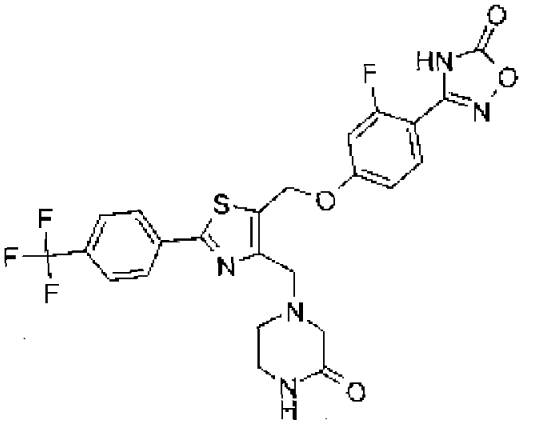


De acuerdo con el método descrito para 3-{2-fluoro-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona, se obtuvo 3-{2-fluoro-4-[4-[(3-metilsulfanil-propilamino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 3-{2-fluoro-4-[4-metil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona y 3-metilsulfanil-propilamina.

C24H22F4N4O3S2 (554,59),MS(ESI): 555 ($M+H^+$).

Ejemplo 27

4-[5-[3-Fluoro-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-ilmetil]-piperazin-2-ona

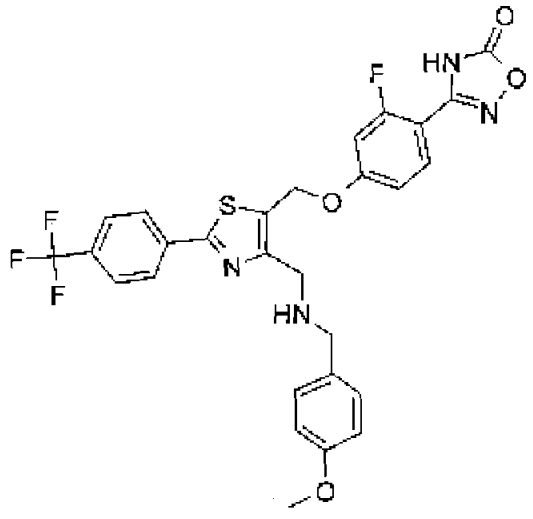


De acuerdo con el método descrito para 3-{2-fluoro-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona, se obtuvo 4-[5-[3-fluoro-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-ilmetil]-piperazin-2-ona a partir de 3-{2-fluoro-4-[4-metil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona y piperazin-2-ona.

C24H19F4N5O4S (549,50), MS(ESI): 550 ($M+H^+$).

Ejemplo 28

3-{2-Fluoro-4-[4-[(4-metoxi-bencilamino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

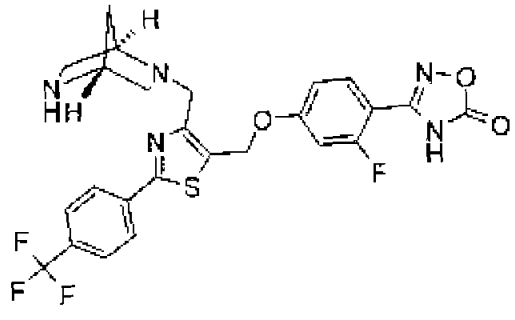


De acuerdo con el método descrito para 3-{2-fluoro-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona, se obtuvo 3-{2-fluoro-4-[4-[(4-metoxi-bencilamino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 3-{2-fluoro-4-[4-metil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona y 4-metoxi-bencilamina.

C28H22F4N4O4S (586,56), MS(ESI): 587 ($M+H^+$).

Ejemplo 29

3-{4-[4-[(1R,4R)-1-(2,5-Diaza-biciclo[2.2.1]hept-2-il)metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-fluoro-fenil}-4H-[1,2,4]oxadiazol-5-ona

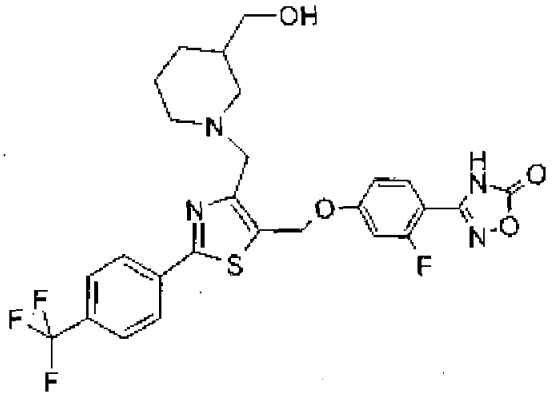


De acuerdo con el método descrito para 3-{2-fluoro-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona, se obtuvo 3-{4-[4-[(1R,4R)-1-(2,5-diaza-biciclo[2.2.1]hept-2-il)metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-fluoro-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 3-{2-fluoro-4-[4-metil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona y (1R,4R)-2,5-diaza-biciclo[2.2.1]heptano.

$C_{25}H_{21}F_4N_5O_3S$ (547,53), MS(ESI): 548 ($M+H^+$).

Ejemplo 30

3-{2-Fluoro-4-[4-(3-hidroximetil-piperidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

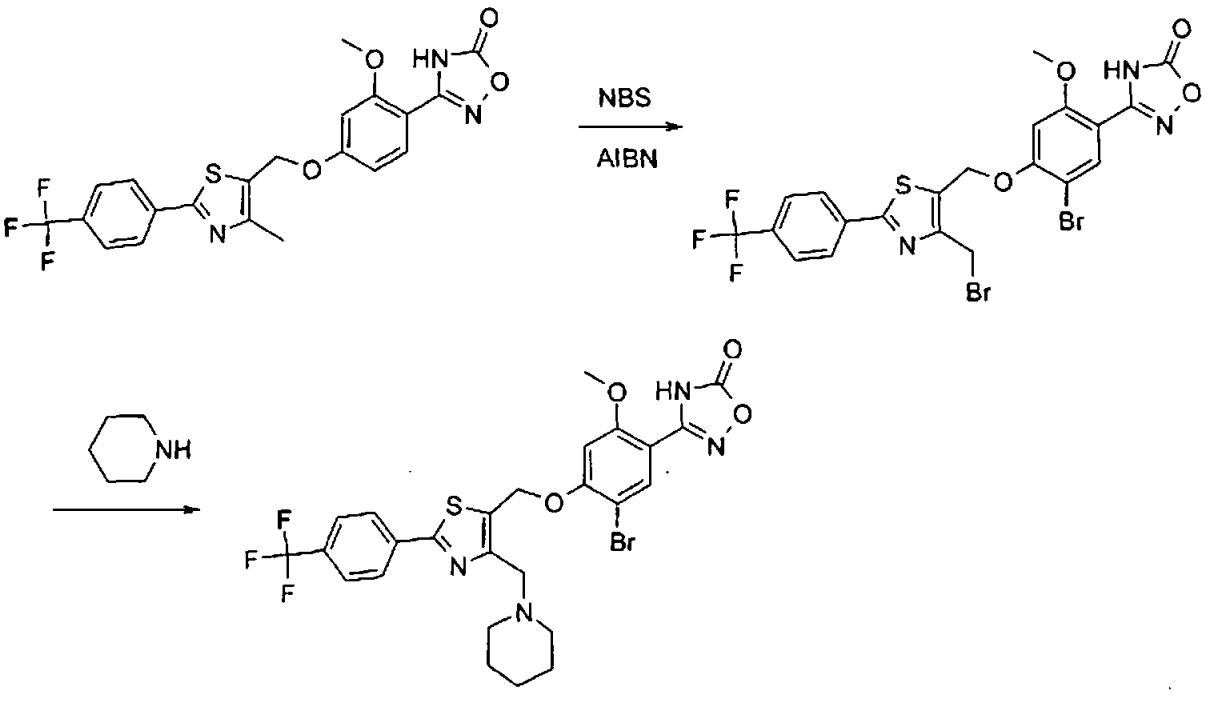


De acuerdo con el método descrito para 3-{2-fluoro-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona, se obtuvo 3-{2-fluoro-4-[4-(3-hidroximetil-piperidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona racémica a partir de 3-{2-fluoro-4-[4-metil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona y 3-hidroximetil-piperidina racémica.

$C_{26}H_{24}F_4N_4O_4S$ (564,56), MS(ESI): 565 ($M+H^+$).

Ejemplo 31

3-{5-Bromo-2-metoxi-4-[4-piperidin-1-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona



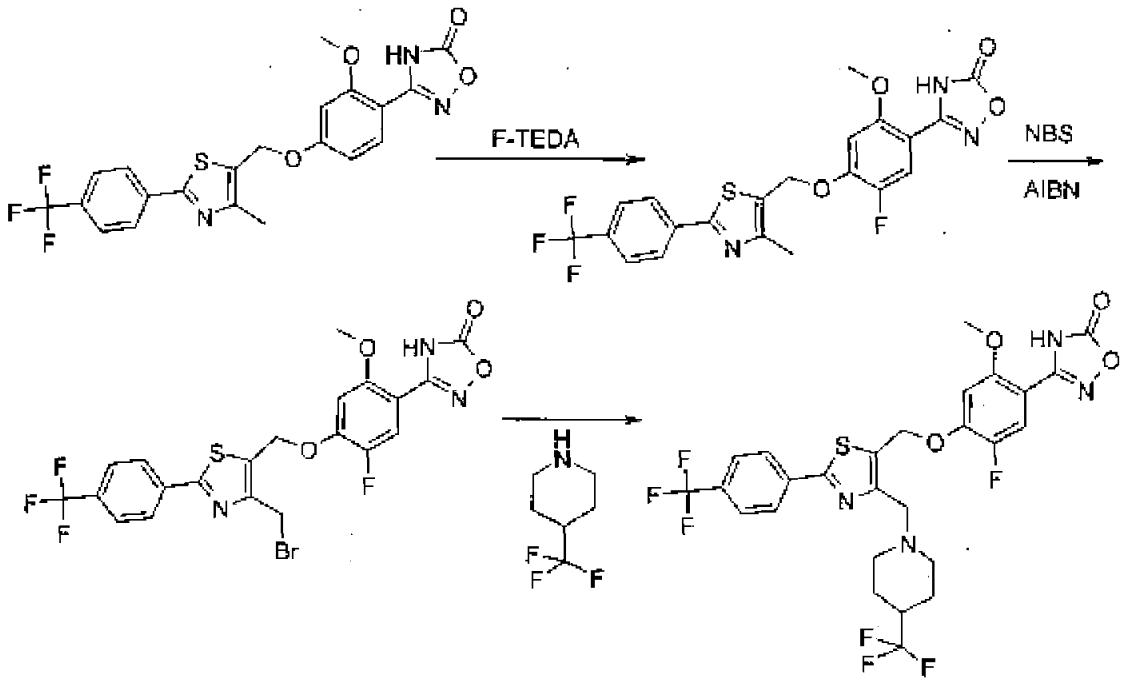
De acuerdo con el método descrito para 3-{2-fluoro-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona, se obtuvo 3-{5-bromo-2-metoxi-4-[4-piperidin-1-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 3-{2-metoxi-4-[4-metil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona y[6]piperidina. Durante la etapa de bromación en 3-{2-metoxi-4-[4-metil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona, se obtuvo 3-{5-bromo-4-[4-bromometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona. Se convirtió luego al producto mencionado tras la reacción con piperidina.

C26H24BrF3N4O4S (625,46), MS(ESI): 625 ($M+H^+$).

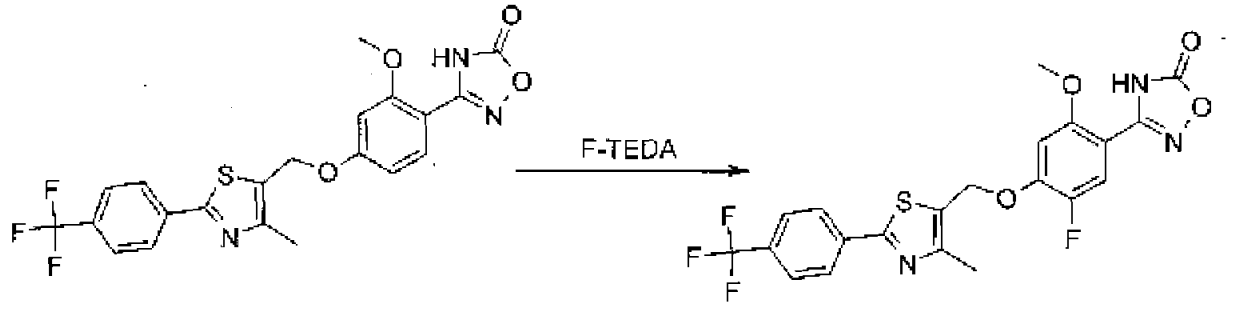
Ejemplo 32

3-{5-Fluoro-2-metoxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

[6] Ejemplo 11 de la solicitud WO2005/097786



3-{5-Fluoro-2-metoxi-4-[4-metil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

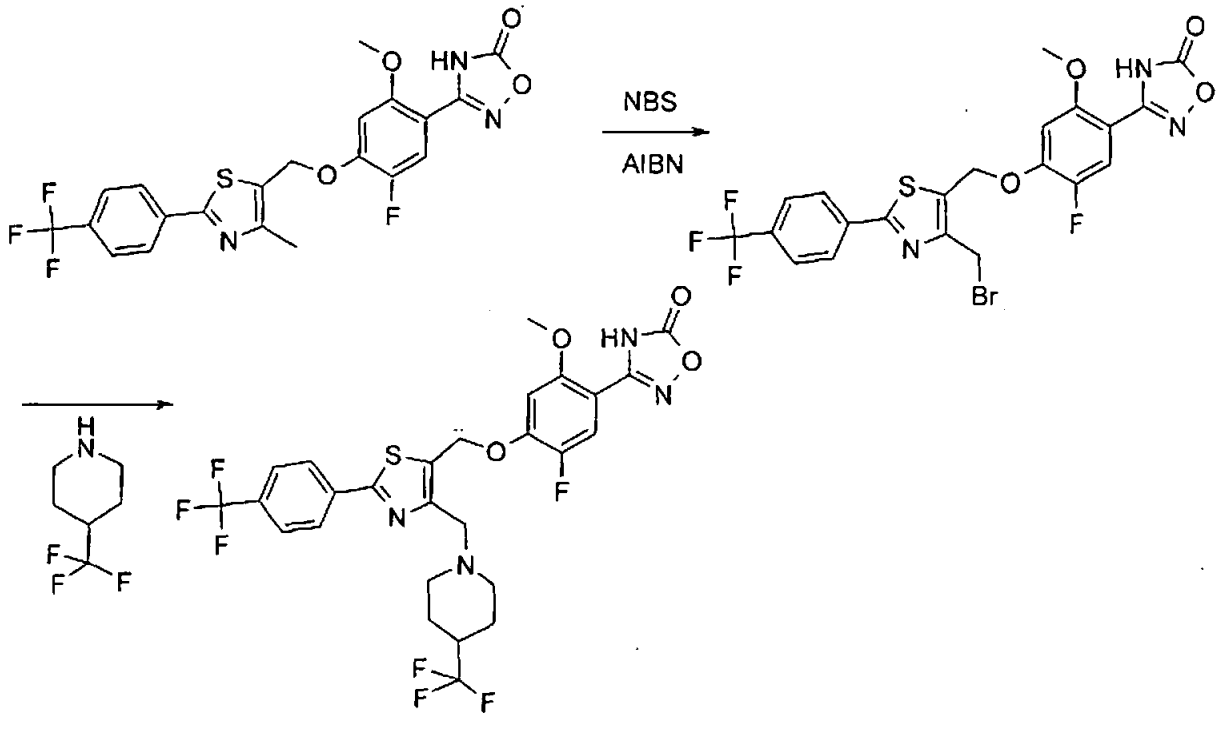


A una disolución de 1,13 g de 3-{2-metoxi-4-[4-metil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona en 40 mL de ácido trifluoroacético se le añadieron 738 mg de 1-clorometil-4-fluoro-1,4-diazoniabiciclo[2.2.2]octano bis(tetrafluoroborato) (F-TEDA). La mezcla resultante se calentó hasta 70°C durante 6 h, luego se vertió en agua y se extrajo con diclorometano. Los extractos orgánicos se secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida. El producto bruto se purificó por cromatografía en columna sobre gel de sílice (gradiente de diclorometano 100 a diclorometano 80/ metanol 20) para producir 164 mg de

una mezcla 1/1 de 3-{5-fluoro-2-metoxi-4-[4-metil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona y material de partida que se utilizó en la etapa siguiente sin purificación adicional.

C21H15F4N3O4S (481,42), MS(ESI): 482 ($M+H^+$).

3-{5-Fluoro-2-metoxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona



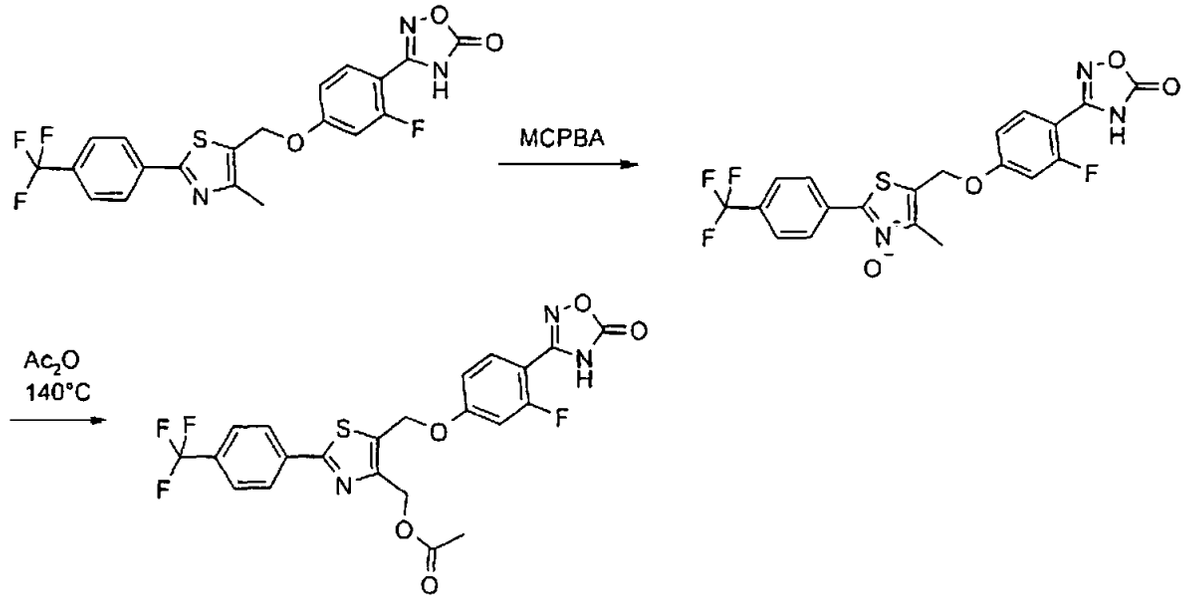
De acuerdo con el método descrito para 3-{2-fluoro-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona, se obtuvo 3-{5-fluoro-2-metoxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 3-{5-fluoro-2-metoxi-4-[4-metil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona y 4-trifluorometil-piperidina.

C27H23F7N4O4S (632,55), MS(ESI): 633 ($M+H^+$).

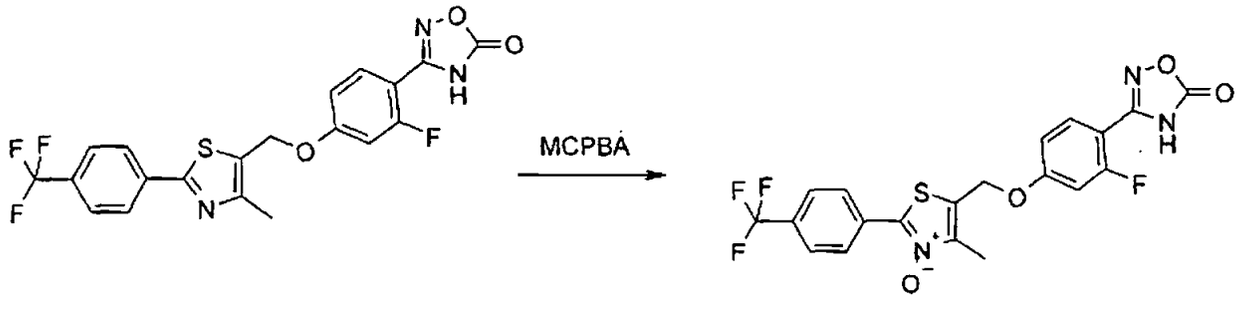
Los siguientes ejemplos se prepararon de acuerdo con el procedimiento G:

Ejemplo 33

Éster 5-[3-fluoro-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-ilmetílico del ácido acético



3-{2-Fluoro-4-[4-metil-3-oxi-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

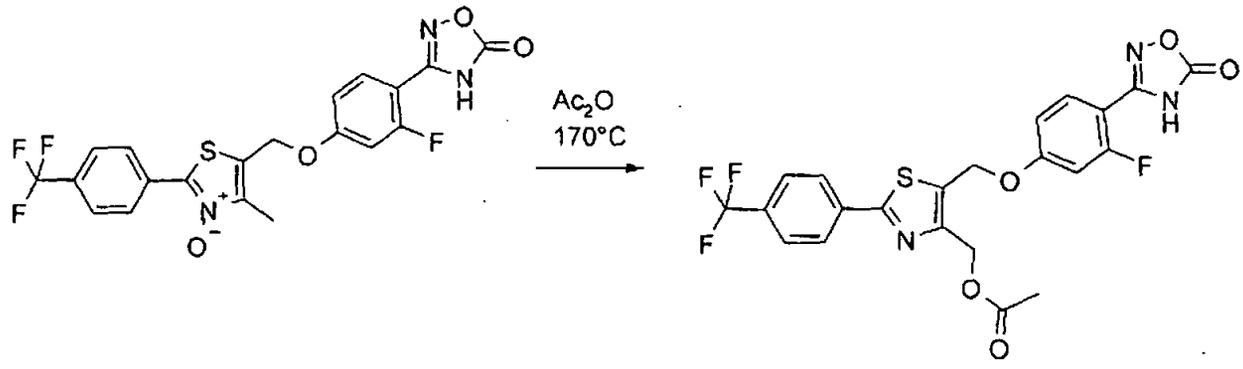


Se disolvió 1 g de 3-{2-fluoro-4-[4-metil-3-oxi-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona en 23 mL de hexafluoroisopropanol. A la disolución resultante se le añadieron 2,1 g de MCPBA (70% puro). La mezcla resultante se calentó hasta 50°C durante 6 h y se agitó a temperatura ambiente durante toda la noche. Se filtró el precipitado. El filtrado se concentró a presión reducida y se añadieron 8 mL de acetato de etilo al residuo. El sólido se filtró y se lavó con acetato de etilo para producir

0,48 g de un primer cultivo del producto deseado como un sólido blanco. El filtrado se concentró y recristalizó en metanol para proveer 0,19 g adicional de producto deseado como un sólido blanco. El licor madre se concentró y purificó por cromatografía en columna sobre gel de sílice (heptano 1/ acetato de etilo 3, luego diclorometano 95/ metanol 5). Los cultivos se combinaron para producir 0,67 g de 3-{2-fluoro-4-[4-metil-3-oxi-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona como un sólido blanco.

C20H13F4N3O4S (467,40), MS(ESI): 468 ($M+H^+$).

Éster 5-[3-fluoro-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-ilmetílico del ácido acético

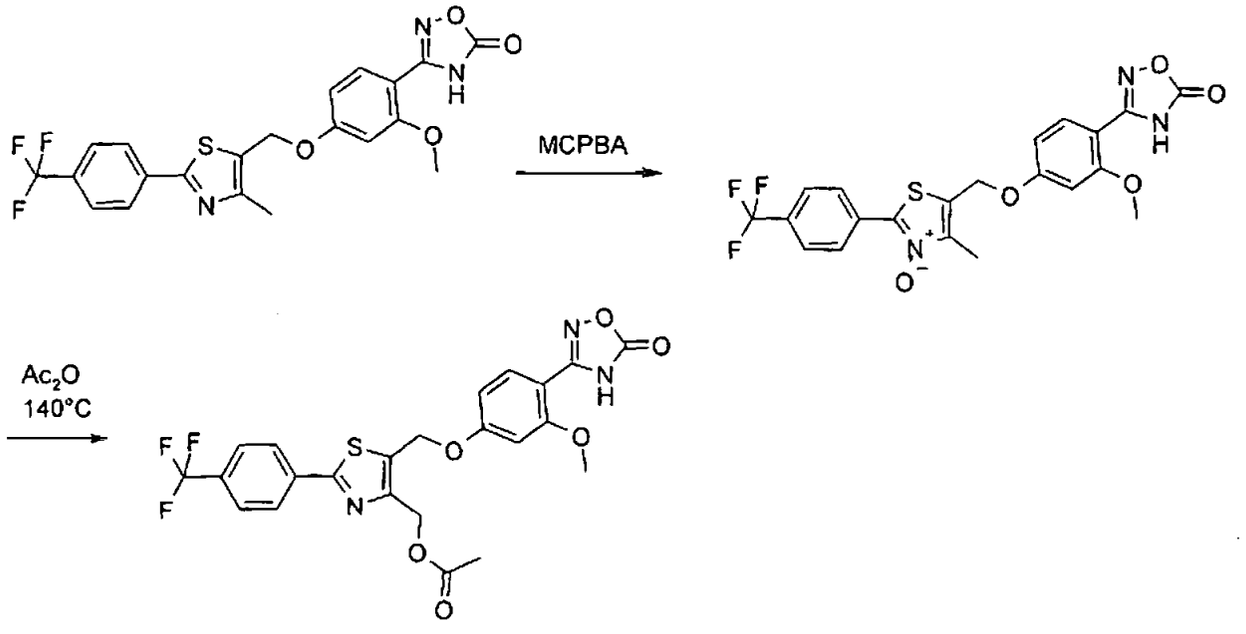


Se calentó una mezcla de 470 mg de 3-{2-fluoro-4-[4-metil-3-oxi-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona en 5 mL de anhídrido acético hasta 170°C durante 18 minutos. La mezcla se vertió en agua/acetato de etilo. La capa orgánica se separó y la capa acuosa se extrajo tres veces con acetato de etilo. Los extractos orgánicos se secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida. El producto bruto se purificó por cromatografía en columna sobre gel de sílice (gradiente de heptano 4/ acetato de etilo 1 a heptano 1/ acetato de etilo 1) para producir 180 mg de éster 5-[3-fluoro-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-ilmetílico del ácido acético como un sólido beis.

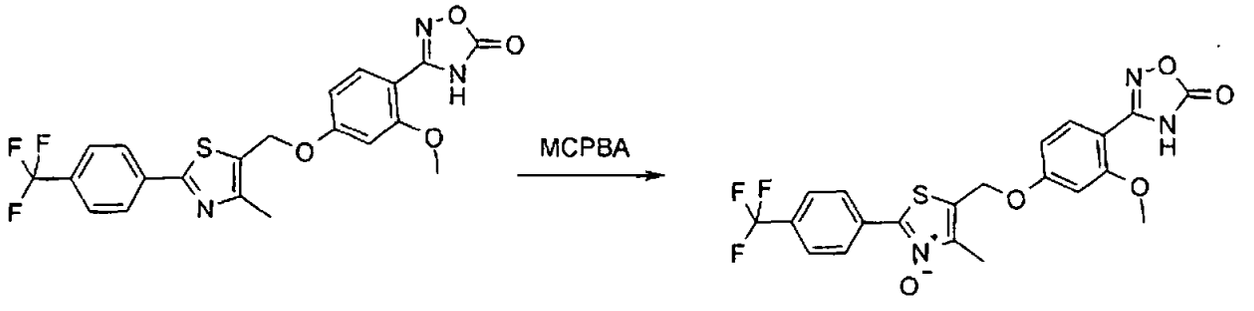
C22H15F4N3O5S (509,43), MS(ESI): 510 ($M+H^+$).

Ejemplo 34

Éster 5-[3-metoxi-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-ilmetílico del ácido acético



3-{2-Metoxi-4-[4-metil-3-oxi-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

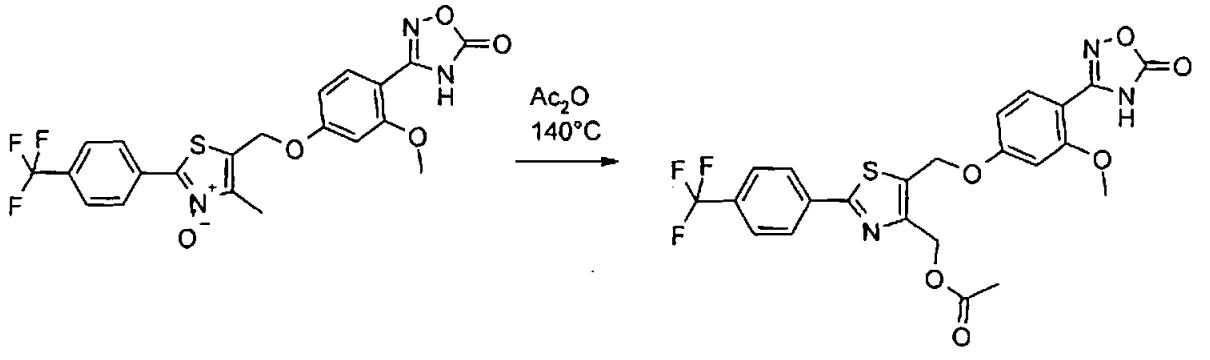


Se disolvieron 7,55 g de 3-{2-metoxi-4-[4-metil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona añadiendo 210 mL de hexafluoroisopropanol seguidos de 2,5 mL de diclorometano. A la disolución resultante se le añadieron 16,3 g de MCPBA (70% puro). La mezcla resultante se calentó hasta 50°C durante 5 h y se agitó a temperatura ambiente durante el fin de semana. El precipitado se filtró y se lavó con 3 mL de hexafluoroisopropanol. El filtrado se concentró a presión reducida y se añadieron 250 mL de acetato de etilo al residuo. La suspensión resultante se agitó a temperatura ambiente durante 3 h, luego se filtró y se lavó con una

mezcla de hexano y éter diisopropílico para producir 4,77 g de 3-{2-metoxi-4-[4-metil-3-oxi-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona como un sólido blanco que se utilizó en la etapa siguiente sin purificación adicional.

C21H16F3N3O5S (479,43), MS(ESI): 480 ($M+H^+$).

Éster 5-[3-metoxi-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-ilmetílico del ácido acético

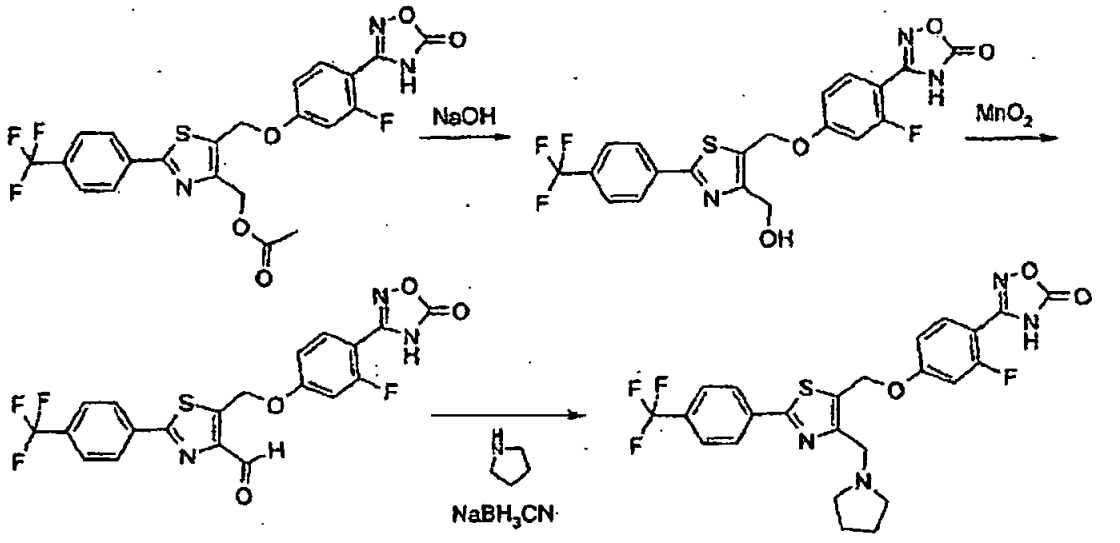


Se calentó una suspensión de 0,4 g de 3-{2-metoxi-4-[4-metil-3-oxi-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona en 15 mL de anhídrido acético hasta 140°C durante 1,5 h. La mezcla se dejó enfriar hasta temperatura ambiente. Se añadieron 20 mL de tolueno y la mezcla se concentró a presión reducida para producir 0,5 g de éster 5-[3-metoxi-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-ilmetílico del ácido acético que se utilizó sin purificación adicional en la etapa siguiente.

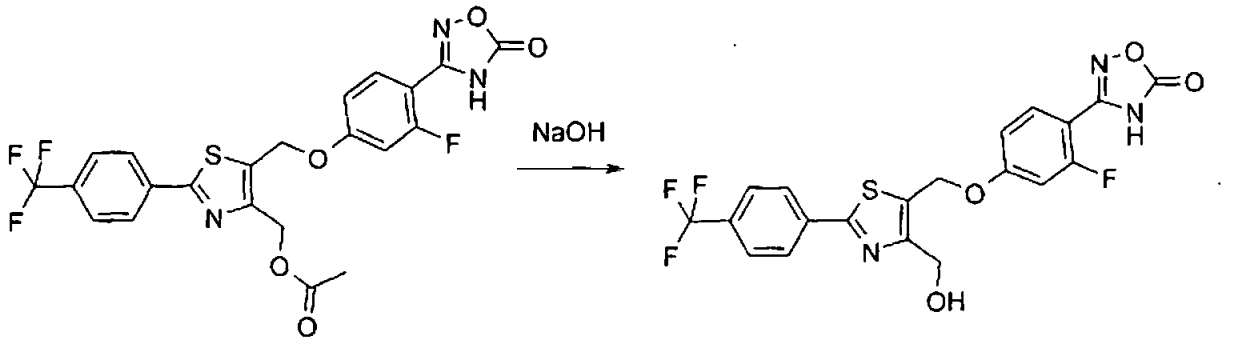
C21H16F3N3O5S (479,43), MS(ESI): 478 ($M-H^+$).

Los siguientes ejemplos se prepararon de acuerdo con el procedimiento E:

3-{2-Fluoro-4-[4-pirrolidin-1-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona



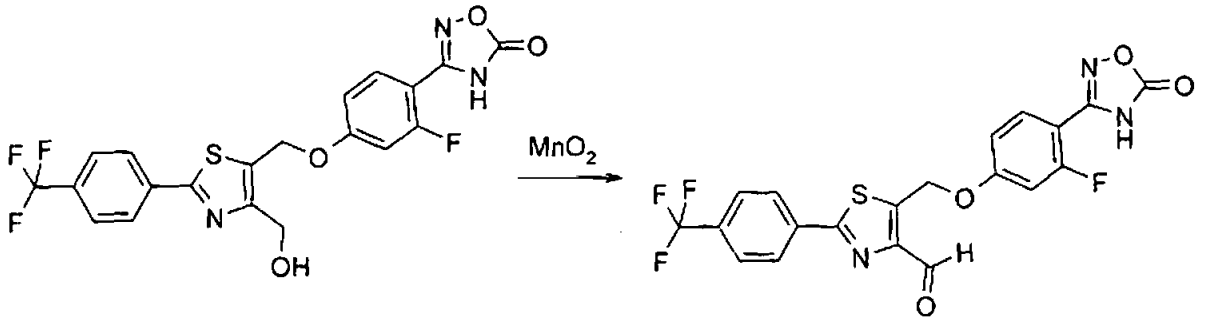
3-{2-Fluoro-4-[4-hidroximetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona



A una suspensión de 150 mg de éster 5-[3-fluoro-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-ilmetílico del ácido acético en 5 mL de metanol a 0°C se le añadió gota a gota 0,29 mL de una disolución 1 molar de hidróxido de sodio. Después de agitar durante 15 minutos a 10°C, la mezcla de reacción se concentró a presión reducida. Se añadió acetato de etilo/ disolución acuosa 1 molar de hidrógeno fosfato sódico. La capa orgánica se separó y la capa acuosa se extrajo tres veces con acetato de etilo. Los extractos orgánicos combinados se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida para producir 110 mg de 3-{2-fluoro-4-[4-hidroximetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona como un sólido amarillento.

C20H13F4N3O4S (467,40), MS(ESI): 468 ($M+H^+$).

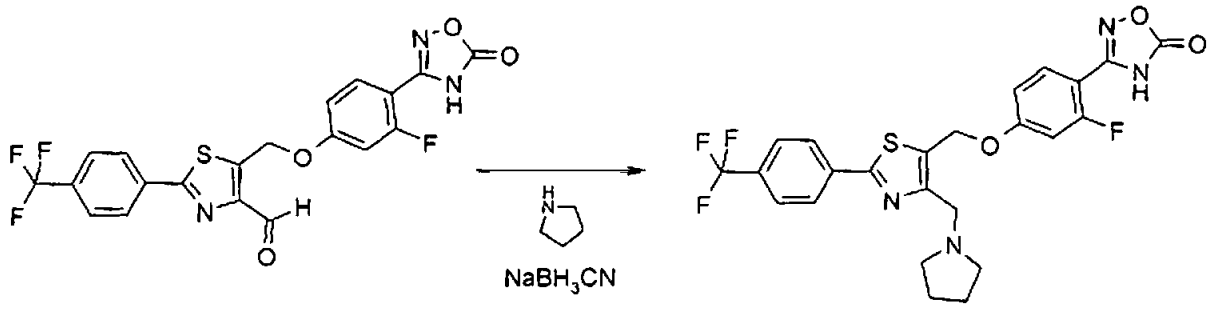
5-[3-Fluoro-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-carbaldehído



A una mezcla de 20 mg de 3-{2-fluoro-4-[4-hidroximetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona en 10 mL de cloroformo se le añadieron 23 mg de dióxido de manganeso. Después de agitar a temperatura ambiente durante toda la noche, la mezcla de reacción se filtró a través de celita y se lavó con diclorometano/metanol. El filtrado se concentró a presión reducida para producir 200 mg de 5-[3-fluoro-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-carbaldehído como un sólido beis.

C20H11F4N3O4S (465,39), MS(CI): 483 ($M+NH4^+$).

3-{2-Fluoro-4-[4-pirrolidin-1-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona



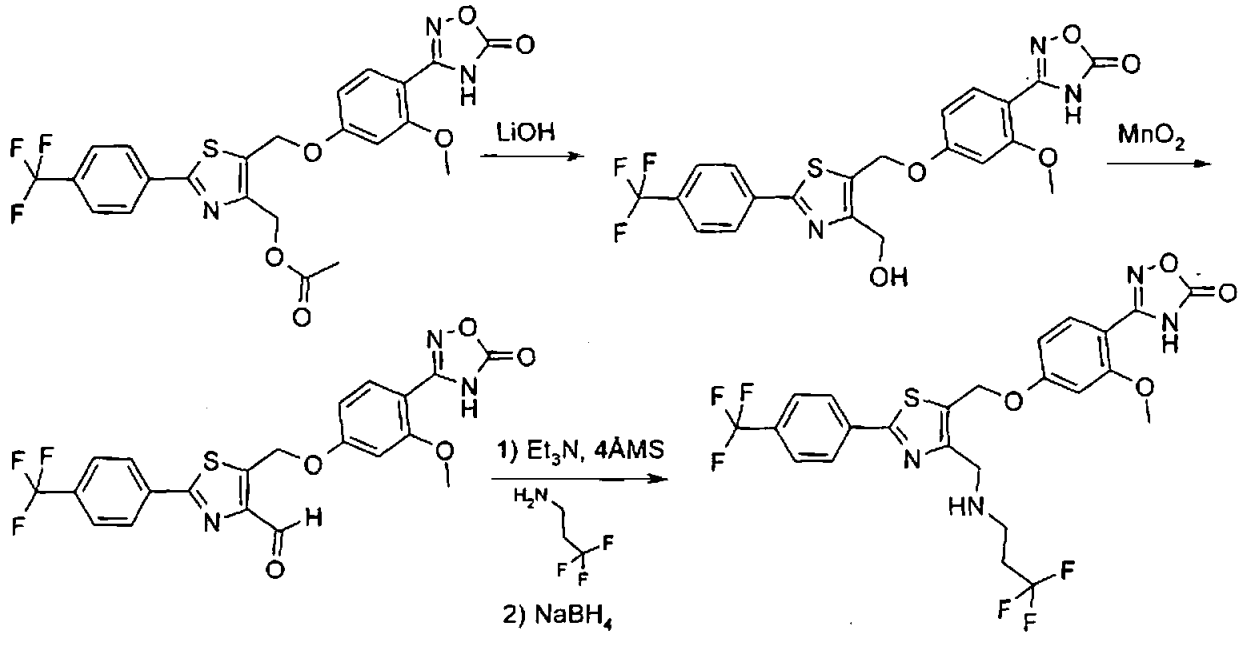
A una suspensión de 50 mg de 5-[3-fluoro-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-carbaldehído en 2 mL de metanol se le añadió 0,03 mL de pirrolidina. La disolución resultante se agitó a temperatura ambiente durante 1,5 h, luego se añadieron 13,5 mg de cianoborohidruro de sodio. Después de agitar a temperatura

ambiente durante 4 h, la mezcla de reacción se concentró a presión reducida. Se añadió acetato de etilo/agua al residuo. La capa orgánica se separó y la capa acuosa se extrajo tres veces con acetato de etilo. Los extractos orgánicos se secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida. El producto bruto se purificó por cromatografía en columna sobre gel de sílice (diclorometano 80/ metanol 20) para producir 9 mg de 3-{2-fluoro-4-[4-pirrolidin-1-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona como un sólido beis.

$C_{24}H_{20}F_4N_4O_3S$ (520,51), MS(ESI): 521 ($M+H^+$).

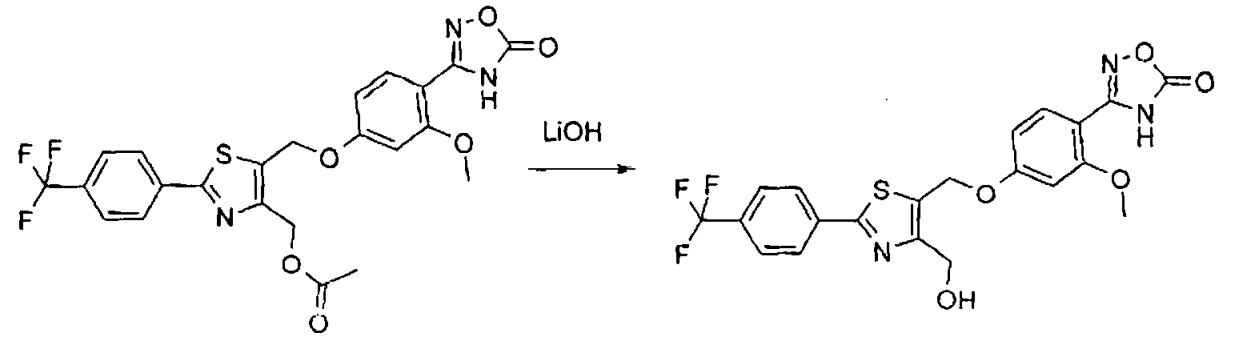
Ejemplo 36

3-(2-Metoxi-4-{2-(4-trifluorometil-fenil)-4-[(3,3,3-trifluoro-propilamino)-metil]-tiazol-5-ilmetoxi}-fenil)-4H-[1,2,4]oxadiazol-5-ona



3-{4-[4-Hidroximetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona

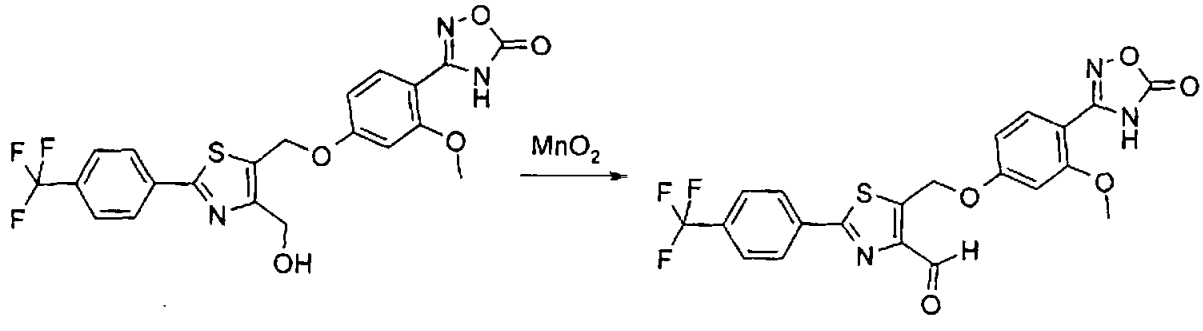
A una suspensión de 0,5 g de éster 5-[3-metoxi-4-(5-oxo-4,5-dihidro-



[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-ilmetílico del ácido acético en 5 mL de metanol a 0°C se le añadió 0,22 g de hidróxido de litio. La disolución resultante se agitó durante 45 minutos a 0°C, luego se dejó calentar hasta temperatura ambiente. El disolvente se eliminó parcialmente a presión reducida y se añadió acetato de etilo/ disolución acuosa 1 molar de KH2PO4. La capa orgánica se separó y la capa acuosa se extrajo tres veces con acetato de etilo. Los extractos orgánicos se secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida. Se añadieron 40 mL de acetato de etilo al residuo y, después de agitar durante 30 minutos, el sólido resultante se recogió por filtración para producir 225 mg de 3-{4-[4-hidroximetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona como un sólido beis.

C21H16F3N3O5S (479,44), MS(ESI): 480 ($M+H^+$).

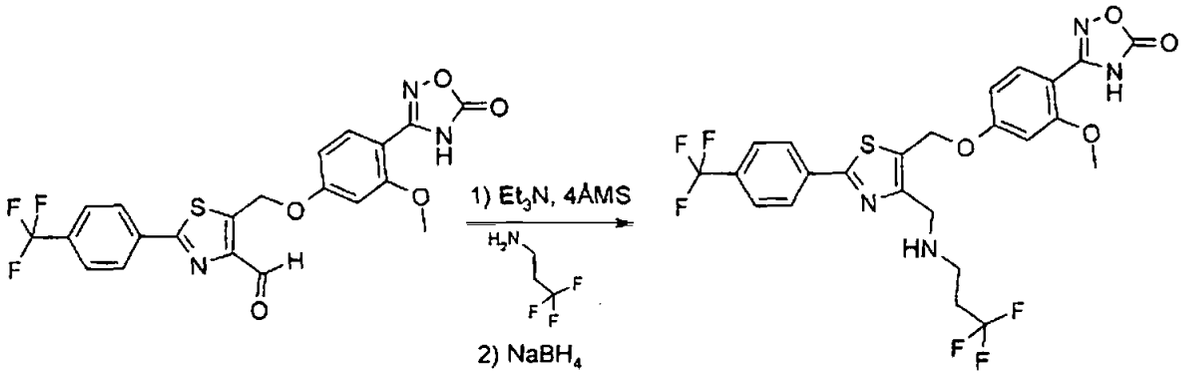
5-[3-Metoxi-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-carbaldehído



Se disolvieron 50 mg de 3-{4-[4-hidroximetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona en 2 mL de dimetilformamida calentando hasta 60°C y se añadieron 2 mL de diclorometano. A la disolución resultante se le añadieron 90 mg de dióxido de manganeso. La mezcla de reacción se calentó a 60°C toda la noche. Se añadieron 5 mL de dimetilformamida. La mezcla caliente se filtró a través de celita y se lavó con diclorometano/metanol. El filtrado se concentró a presión reducida para producir 30 mg de 5-[3-metoxi-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-carbaldehído que se utilizó en la etapa siguiente sin purificación adicional.

C21H14F3N3O5S (477,42), MS(ESI): 478 ($M+H^+$).

3-(2-Metoxi-4-{2-(4-trifluorometil-fenil)-4-[(3,3,3-trifluoro-propilamino)-metil]-tiazol-5-ilmetoxi}-fenil)-4H-[1,2,4]oxadiazol-5-ona

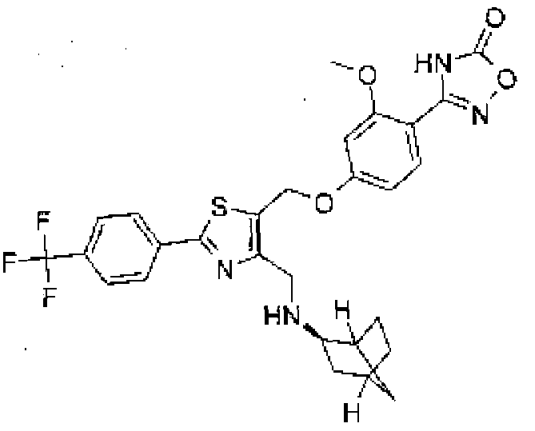


A una suspensión de 30 mg de 5-[3-metoxi-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-carbaldehído en 1,5 mL de metanol se le añadieron 0,018 mL de trietilamina, 10 mg de hidrocloruro de 3,3,3-trifluoro-propilamina y 0,5 g de tamices moleculares en polvo 4Å. La mezcla resultante se agitó a temperatura ambiente durante 1 h, luego se añadieron 2,4 mg de borohidruro de sodio. Después de agitar a temperatura ambiente durante 45 h, la mezcla de reacción se concentró a presión reducida. El producto bruto se purificó por cromatografía en capa fin preparativa sobre gel de sílice (diclorometano 90/ metanol 10/ agua 1/ ácido acético 1) seguida de eliminación de azeotropos de rastros de ácido acético con ciclohexano para producir 6,5 mg de 3-(2-metoxi-4-{2-(4-trifluorometil-fenil)-4-[(3,3,3-trifluoro-propilamino)-metil]-tiazol-5-ilmetoxi}-fenil)-4H-[1,2,4]oxadiazol-5-ona como un sólido blanco.

C24H20F6N4O4S (574,50), MS(ESI): 575 ($M+H^+$).

Ejemplo 37

3-{4-[4-((1R,2R,4S)-Biciclo[2.2.1]hept-2-ilaminometil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona

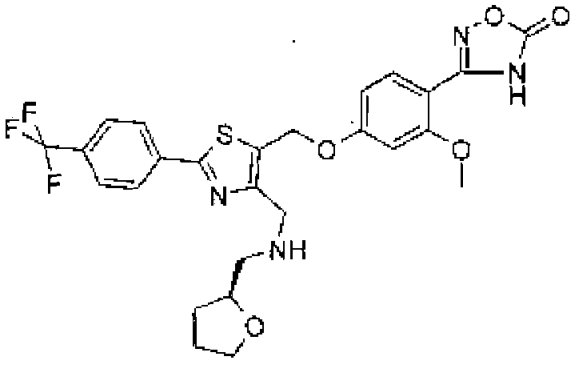


De acuerdo con el método descrito para 3-(2-metoxi-4-[2-(4-trifluorometil-fenil)-4-[(3,3,3-trifluoro-propilamino)-metil]-tiazol-5-ilmetoxi}-fenil)-4H-[1,2,4]oxadiazol-5-ona, se obtuvo 3-{4-[4-((1R,2R,4S)-biciclo[2.2.1]hept-2-ilaminometil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 5-[3-metoxi-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-carbaldehído y exo-2-aminonorbornano.

C28H27F3N4O4S (572,61), MS(ESI): 573 ($M+H^+$).

Ejemplo 38

3-{2-Metoxi-4-[4-({[(S)-1-(tetrahidro-furan-2-il)metil]-amino}-metil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona



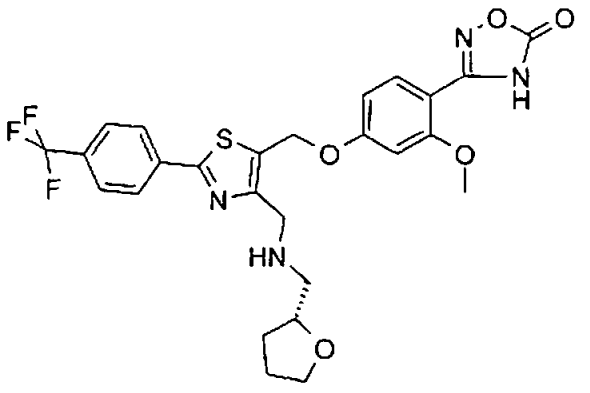
De acuerdo con el método descrito para 3-(2-metoxi-4-[2-(4-trifluorometil-fenil)-4-[(3,3,3-trifluoro-propilamino)-metil]-tiazol-5-ilmetoxi}-fenil)-4H-[1,2,4]oxadiazol-5-ona, se obtuvo 3-{2-metoxi-4-[4-({[(S)-1-(tetrahidro-furan-2-il)metil]-amino}-metil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 5-[3-metoxi-4-(5-oxo-4,5-dihidro-

[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-carbaldehído y (S)-(+)-tetrahidrofurfurilamina.

C26H25F3N4O5S (562,57), MS(ESI): 563 ($M+H^+$).

Ejemplo 39

3-{2-Metoxi-4-[4-({[(R)-1-(tetrahidro-furan-2-il)metil]-amino}-metil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

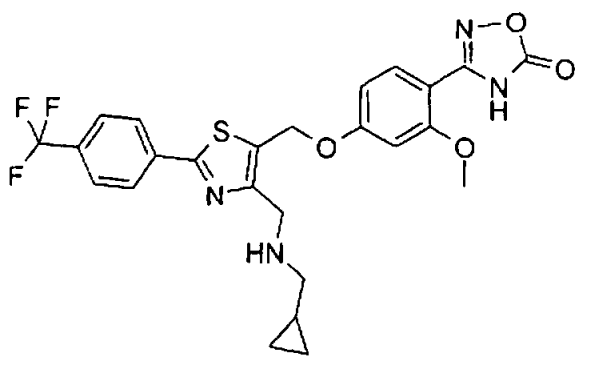


De acuerdo con el método descrito para 3-(2-metoxi-4-{2-(4-trifluorometil-fenil)-4-[(3,3,3-trifluoro-propilamino)-metil]-tiazol-5-ilmetoxi}-fenil)-4H-[1,2,4]oxadiazol-5-ona, se obtuvo 3-{2-metoxi-4-[4-({[(R)-1-(tetrahidro-furan-2-il)metil]-amino}-metil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 5-[3-metoxi-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-carbaldehído y (R)-(-)-tetrahidrofurfuril amina.

C26H25F3N4O5S (562,57), MS(ESI): 563 ($M+H^+$).

Ejemplo 40

3-{4-[4-[(Ciclopropilmetil-amino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona

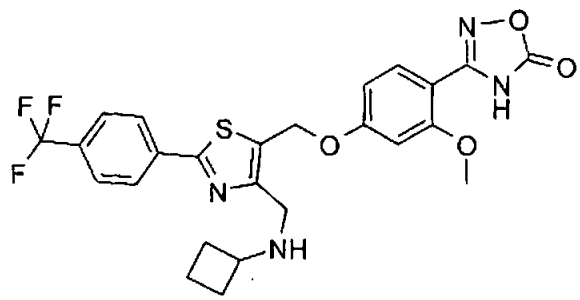


De acuerdo con el método descrito para 3-(2-metoxi-4-{2-(4-trifluorometil-fenil)-4-[(3,3,3-trifluoro-propilamino)-metil]-tiazol-5-ilmetoxi}-fenil)-4H-[1,2,4]oxadiazol-5-ona, se obtuvo 3-{4-[4-[(ciclopropilmetil-amino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 5-[3-metoxi-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-carbaldehído y ciclopropilmetil amina.

C25H23F3N4O4S (532,54), MS(ESI): 533 ($M+H^+$).

Ejemplo 41

3-{4-[4-Ciclobutilaminometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona



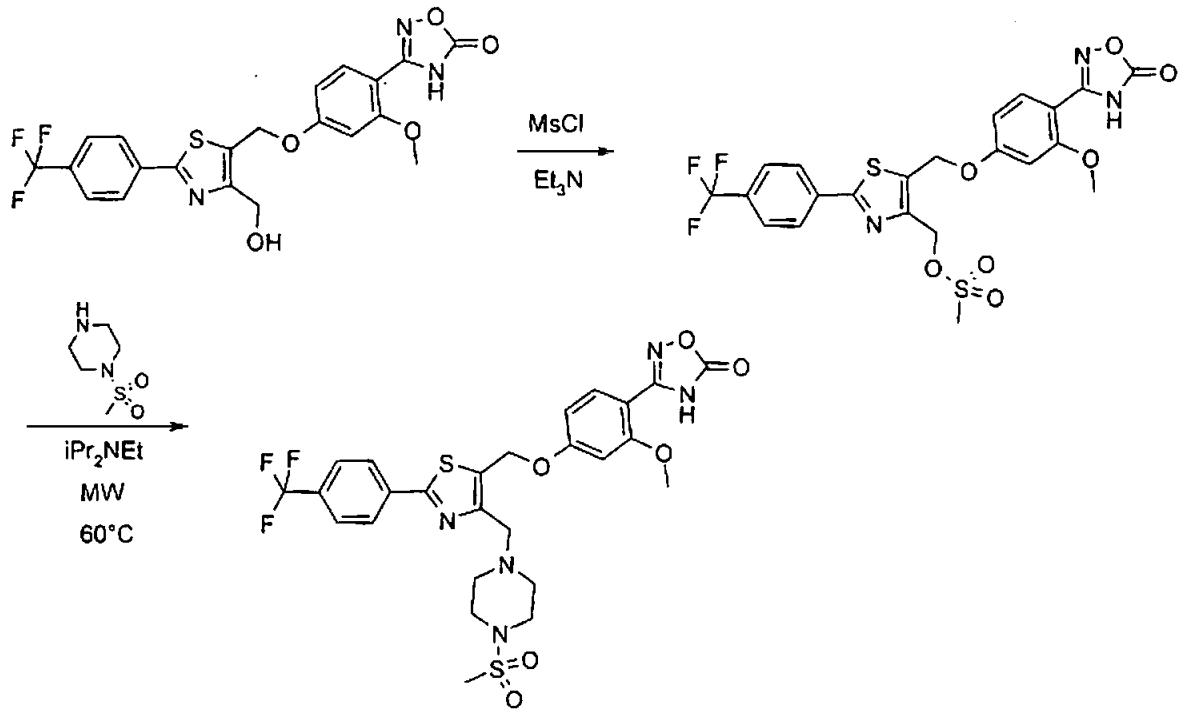
De acuerdo con el método descrito para 3-(2-metoxi-4-{2-(4-trifluorometil-fenil)-4-[(3,3,3-trifluoro-propilamino)-metil]-tiazol-5-ilmetoxi}-fenil)-4H-[1;2,4]oxadiazol-5-ona, se obtuvo 3-{4-[4-ciclobutilaminometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 5-[3-metoxi-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-carbaldehído y ciclobutilamina.

C25H23F3N4O4S (532,54), MS(ESI): 533 ($M+H^+$).

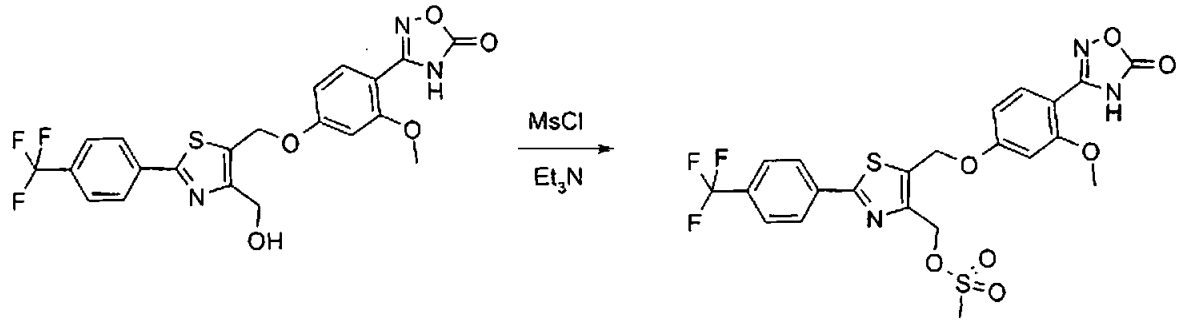
Los siguientes ejemplos se prepararon de acuerdo con el procedimiento D:

Ejemplo 42

3-{4-[4-(4-Metansulfonil-piperazin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona



Éster 5-[3-metoxi-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-ilmetílico del ácido metansulfónico

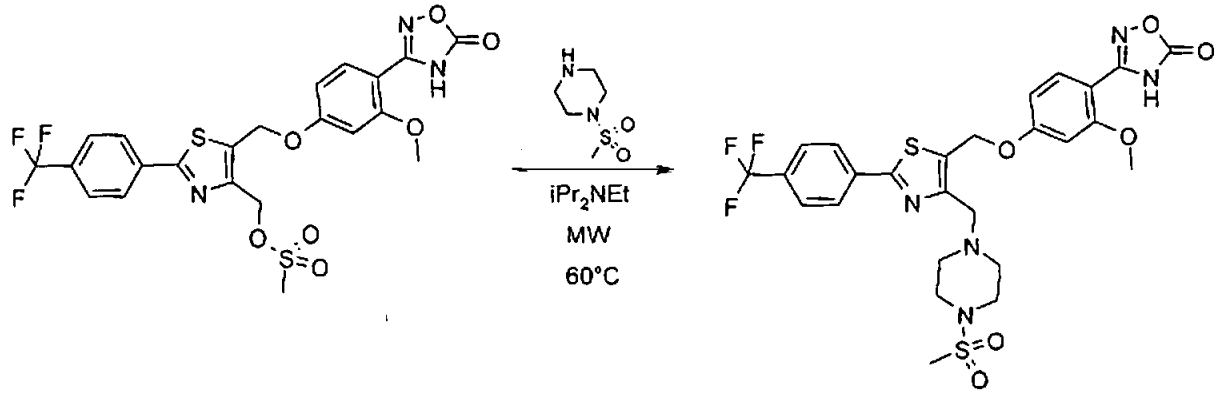


A una disolución de 400 mg de 3-{4-[4-hidroximetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona en 8 mL de dimetilformamida se le añadió 0,42 mL de trietilamina seguida de la adición gota a gota de 0,1 mL de cloruro de metansulfonilo. La mezcla resultante se agitó a temperatura ambiente durante 45 minutos, luego se concentró a presión reducida para producir 830 mg de éster 5-[3-metoxi-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-ilmetílico del ácido metansulfónico bruto que se utilizó sin purificación adicional en la etapa siguiente.

C22H18F3N3O7S2 (557,52), MS(ESI): 558 ($M+H^+$).

3-{4-[4-(4-Metansulfonil-piperazin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona

A una disolución de 50 mg de éster 5-[3-metoxi-4-(5-oxo-4,5-dihidro-

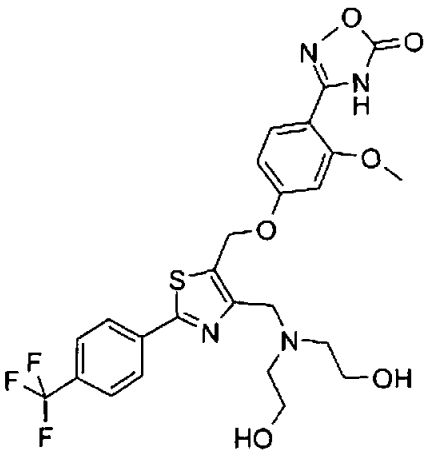


[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-ilmetílico del ácido metansulfónico en 2 mL de dimetilformamida se le añadieron 80 µL de diisopropiletil amina y 19,2 mg de 1-metilsulfonilpiperazina. La mezcla resultante se calentó en un tubo sellado hasta 90°C bajo irradiación de microondas durante 5 minutos y luego se concentró a presión reducida. El residuo se purificó por cromatografía en una columna SCX Waters con gradiente CH2Cl2/MeOH 30/70 a 7N NH3 en MeOH con posterior cristalización en diclorometano 9/ metanol 1 para producir 6,7 mg de 3-{4-[4-(4-metansulfonil-piperazin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona.

C26H26F3N5O6S2 (625,65), MS(ESI): 626.

Ejemplo 43

3-{4-[4-{[Bis-(2-hidroxi-etil)-amino]-metil}-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona

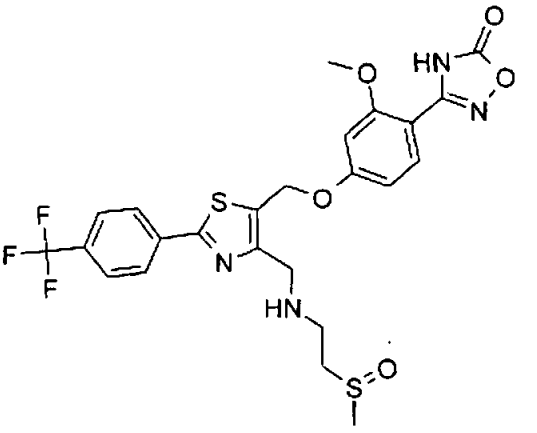


De acuerdo con el método descrito para 3-{4-[4-(4-metansulfonil-piperazin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona, se obtuvo 3-{4-[4-{[bis-(2-hidroxi-etil)-amino]-metil}-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de éster 5-[3-metoxi-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-ilmetilico del ácido metansulfónico y dietanolamina.

C25H25F3N4O6S (566,55), MS(ESI): 567.

Ejemplo 44

3-{4-[4-[(2-Metansulfinil-etilamino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona



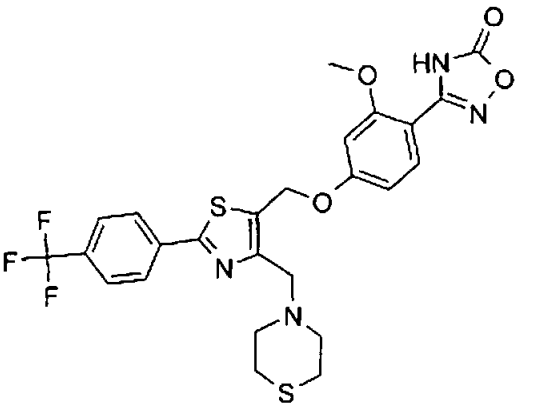
De acuerdo con el método descrito para 3-{4-[4-(4-metansulfonil-piperazin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona, se obtuvo 3-{4-[4-[(2-metansulfinil-etilamino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona a

partir del éster 5-[3-metoxi-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-ilmetílico del ácido metansulfónico y 2-metansulfinil-etilamina.

C24H23F3N4O5S2 (568,59), MS(ESI): 569.

Ejemplo 45

3-{2-Metoxi-4-[4-tiomorfolin-4-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

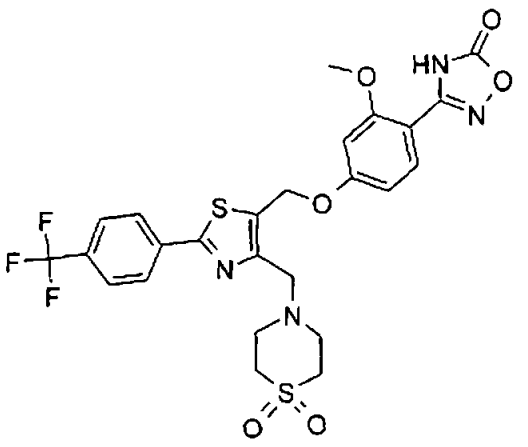


De acuerdo con el método descrito para 3-{4-[4-(4-metansulfonil-piperazin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona, se obtuvo 3-{2-metoxi-4-[4-tiomorfolin-4-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de éster 5-[3-metoxi-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-ilmetílico del ácido metansulfónico y tiomorfolina.

C25H23F3N4O4S2 (564,61), MS(ESI): 565.

Ejemplo 46

3-{4-[4-(1,1-Dioxo-1□^{6}-tiomorfolin-4-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona



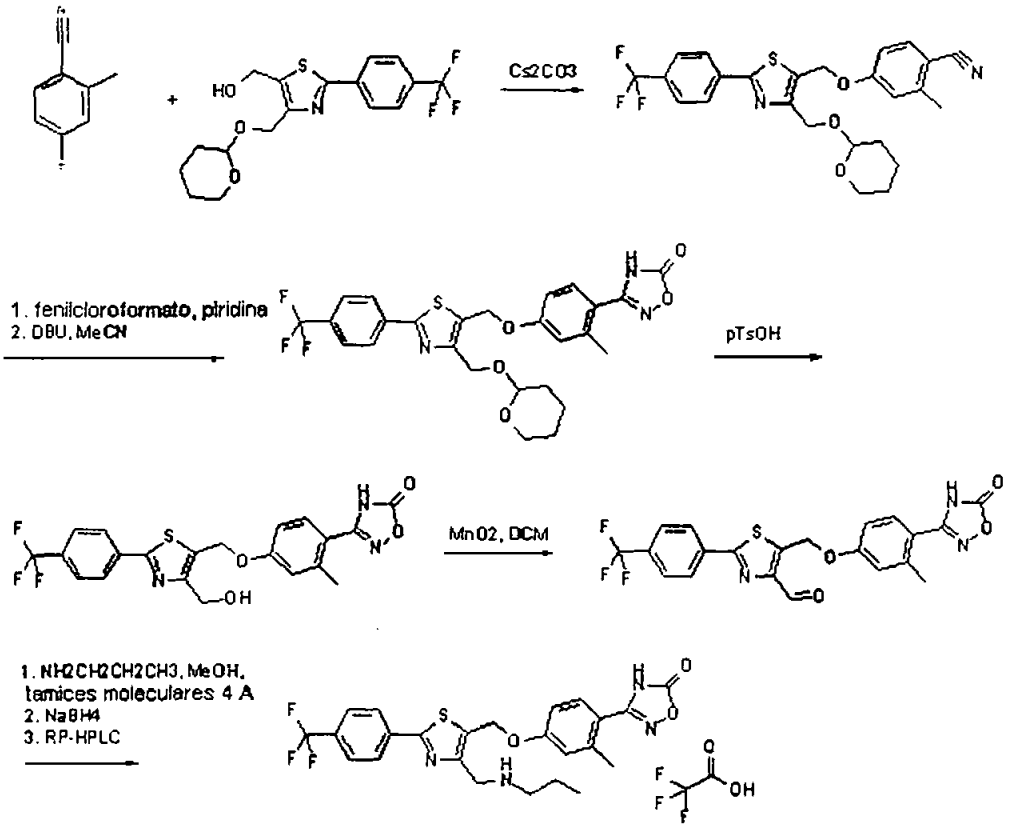
Se suspendieron 50 mg de 3-{2-Metoxi-4-[4-tiomorfolin-4-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona en 3 mL de una disolución 2N de ácido clorhídrico en éter y se añadieron 3 mL de metanol. La disolución resultante se concentró a presión reducida. A una suspensión del hidrocloruro resultante en 1,5 mL de acetonitrilo y 0,5 mL de agua se le añadieron 108 mg de Oxone® (peroximonosulfato de potasio). La mezcla resultante se agitó a temperatura ambiente durante 1 h, luego se vertió en diclorometano/agua. La capa orgánica se separó, se lavó con disolución saturada acuosa de Na2S2O3, se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía en capa fina preparativa sobre gel de sílice (diclorometano 95/ acetona 5) para producir 4,5 mg de 3-{4-[4-(1,1-dioxo-1λ^6-tiomorfolin-4-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona.

C25H23F3N4O6S2 (596,60), MS(ESI): 597.

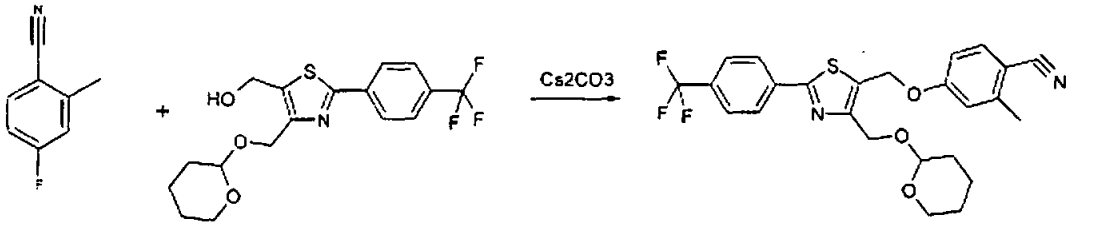
Los siguientes ejemplos se prepararon de acuerdo con el procedimiento E, en el que las dos primeras etapas de reacción se realizaron de acuerdo con el procedimiento B:

Ejemplo 47

3-{2-Metil-4-[4-propilaminometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona



2-Metil-4-[4-(tetrahidro-piran-2-iloximetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-benzonitrilo



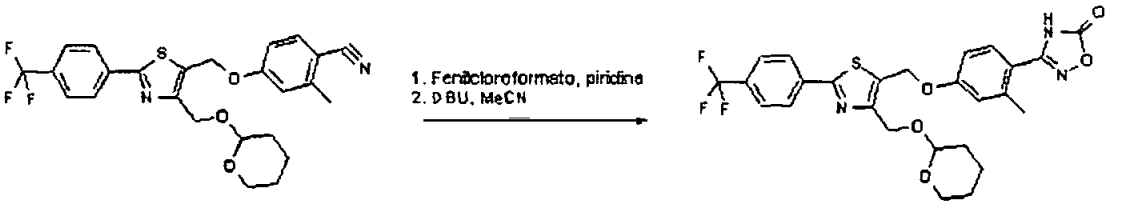
A una disolución agitada de 1,09 g de 4-fluoro-2-metilbenzonitrilo en 50 ml de dimetilformamida se le añadieron 3,0 g de [4-(tetrahidro-piran-2-iloximetil)-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol[7] y 2,62 g de carbonato de cesio. La mezcla de reacción se agitó a temperatura ambiente durante la noche. Se añadieron 250 ml de acetato de etilo y la mezcla se lavó cinco veces con porciones de 50 ml de agua y salmuera. La capa orgánica se secó sobre MgSO4, luego se eliminó el disolvente *in vacuo*. El residuo se purificó por cromatografía sobre gel de sílice con el eluyente n-heptano: acetato de etilo =

7WO 2002067912, WO 2002059098

15: 1 => 2: 1 para obtener 1,5 g de 2-metil-4-[4-(tetrahidro-piran-2-iloximetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-benzonitrilo como un sólido amarillo pálido.

C25H23F3N2O3S (488,53), MS(ESI): 489,2, 405,2 , Rf(n-heptano: acetato de etilo = 2: 1) = 0,36.

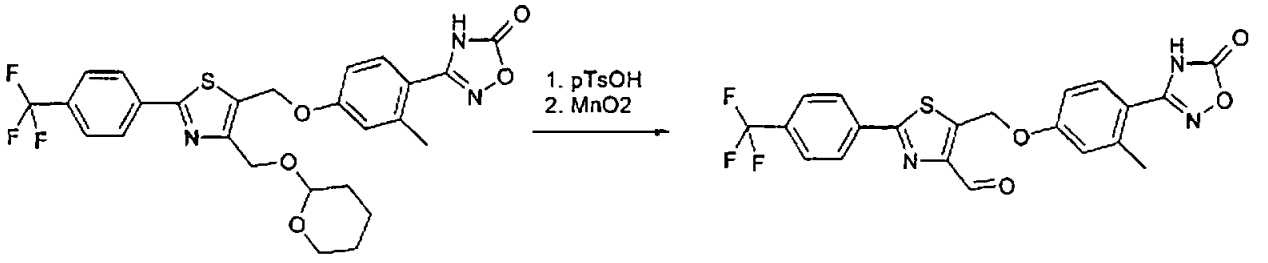
3-{2-Metil-4-[4-(tetrahidro-piran-2-iloximetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona



Se disolvió 1,5 g de 2-metil-4-[4-(tetrahidro-piran-2-iloximetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-benzonitrilo en una mezcla de 10 ml de tetrahidrofurano y 10 ml de metanol. Se añadieron 2,12 g de hidrocloruro de hidroxilamina seguidos de la adición de 5,08 ml de trietilamina. La mezcla de reacción se agitó a 65°C toda la noche. Los disolventes se separaron a vacío y el residuo resultante se vertió en agua y se extrajo cinco veces con acetato de etilo. Los extractos orgánicos combinados se lavaron con salmuera, se secaron sobre MgSO4 y el disolvente se evaporó *in vacuo*. El residuo se disolvió en 10 ml de diclorometano. Se añadieron 0,32 ml de piridina y 0,49 ml de fenilcloroformato y la mezcla se agitó a temperatura ambiente durante quince minutos. La mezcla se diluyó por adición de 50 ml de acetonitrilo y se añadieron 2,28 ml de 1,8-diazabiciclo[5.4.0]undec-7-eno. La mezcla de reacción se agitó a temperatura ambiente durante treinta minutos. La mezcla se evaporó *in vacuo* y el material bruto resultante se purificó por cromatografía sobre gel de sílice con el eluyente n-heptano: acetato de etilo = 4: 1 => acetato de etilo => acetato de etilo: metanol = 4:1 para obtener 1,05 g de 3-{2-metil-4-[4-(tetrahidro-piran-2-iloximetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona como un sólido amarillo.

C26H24F3N3O5S (547,56), MS(ESI): 464,2.

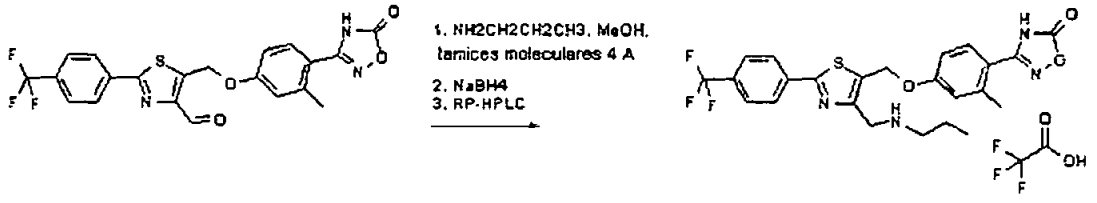
5-[3-Metil-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-carbaldehído



Se suspendió 1,05 g de 3-{2-metil-4-[4-(tetrahidro-piran-2-iloximetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona en 80 ml de metanol. Se añadieron 66,0 mg de ácido p-toluensulfónico y la mezcla de reacción se calentó hasta 60°C hasta que la mezcla de reacción se convirtió en una disolución clara. La mezcla de reacción enfriada se evaporó *in vacuo*. El residuo se disolvió en una mezcla de 10 ml de dimetilformamida y 40 ml de diclorometano. Se añadieron 3,76 g de óxido de manganeso (IV) sobre carbón activado y la mezcla de reacción se calentó hasta reflujo durante dos horas. La mezcla de reacción enfriada se filtró a través de un lecho de celita. El filtrado se evaporó *in vacuo* para obtener 670 mg de 5-[3-metil-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-carbaldehído bruto que se utilizó sin purificación adicional.

C21H14F3N3O4S (461,42), MS(ESI):462,0, Rf(acetato de etilo: metanol = 19: 1) = 0,52.

3-{2-Metil-4-[4-propilaminometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona



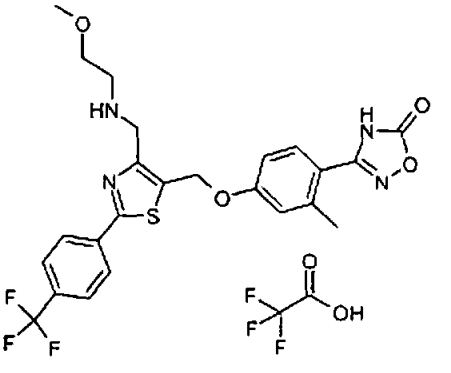
Se suspendieron 100 mg de 5-[3-metil-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-carbaldehído y

12,8 mg de propilamina en 3 ml de metanol. Se añadieron 30,0 µl de trietilamina cuando la mezcla de reacción se convirtió en una disolución clara. Se añadieron 400 mg de tamices moleculares cuatro angstrom y la mezcla de reacción se agitó a temperatura ambiente durante dos horas. Luego se añadieron 8,2 mg de borohidruro de sodio y la mezcla de reacción se agitó a temperatura ambiente durante treinta minutos. La mezcla de reacción se filtró a través de un lecho de celita. El filtrado se evaporó *in vacuo* y luego se evaporó *in vacuo*. El residuo se purificó por RP-HPLC para obtener 45,7 mg de 3-{2-metil-4-[4-propilaminometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona como su sal de trifluoroacetato.

C24H23F3N4O3S.C2HF3O2(618,56), MS(ESI): 505,1.

Ejemplo 48

3-{4-[4-[(2-Metoxi-etilamino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona

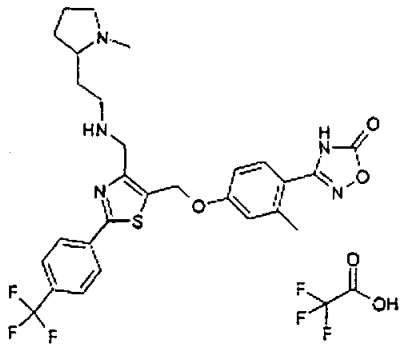


De acuerdo con el método descrito para 3-{2-metil-4-[4-propilaminometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 47, se obtuvo 3-{4-[4-[(2-metoxi-etilamino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 5-[3-Metil-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-carbaldehído y 2-metoxietilamina. El compuesto se obtuvo como su sal de trifluoroacetato.

C24H23F3N4O4S.C2HF3O2 (634,56), MS(ESI): 521,1.

Ejemplo 49

3-{2-Metil-4-[4-[[2-(1-metil-pirrolidin-2-il)-etilamino]-metil}-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

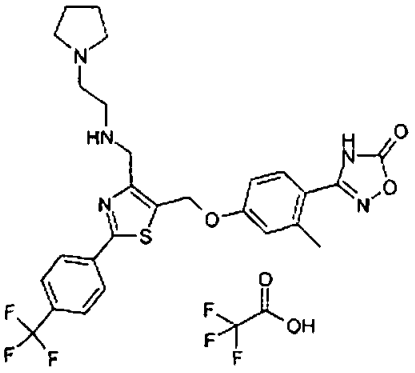


De acuerdo con el método descrito para 3-{2-metil-4-[4-propilaminometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 47, se obtuvo 3-{2-metil-4-[4-{[2-(1-metil-pirrolidin-2-il)-etilamino]-metil}-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 5-[3-metil-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-carbaldehído y 2-(2-aminoetil)-1-metilpirrolidina. El compuesto se obtuvo como su sal de trifluoroacetato.

C24H23F3N4O3S.C2HF3O2 (618,56), MS(ESI):574,2.

Ejemplo 50

<u>3-{2-Metil-4-[4-[(2-pirrolidin-1-il-etilamino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona</u>

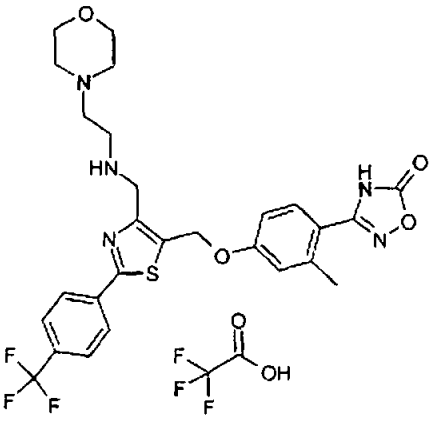


De acuerdo con el método descrito para 3-{2-metil-4-[4-propilaminometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 47, se obtuvo 3-{2-metil-4-[4-[(2-pirrolidin-1-il-etilamino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 5-[3-metil-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-carbaldehído y N-(2-aminoetil)pirrolidina. El compuesto se obtuvo como su sal de trifluoroacetato.

C27H28F3N5O3S.2C2HF3O2 (787,66), MS(ESI): 560,2.

Ejemplo 51

3-{2-Metil-4-[4-[(2-morfolin-4-il-etilamino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

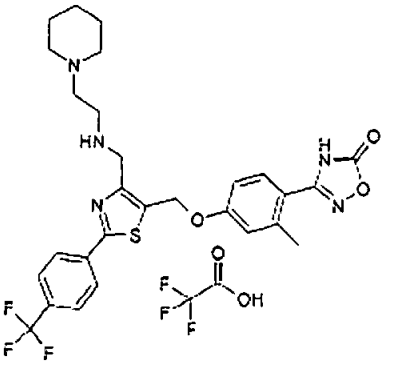


De acuerdo con el método descrito para 3-{2-metil-4-[4-propilaminometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 47, se obtuvo 3-{2-metil-4-[4-[(2-morfolin-4-il-etilamino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 5-[3-metil-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-carbaldehído y N-(2-aminoetil)-morfolina. El compuesto se obtuvo como su sal de trifluoroacetato.

C27H28F3N5O4S.C2HF3O2 (803,66), MS(ESI): 576,2.

Ejemplo 52

3-{2-Metil-4-[4-[(2-piperidin-1-il-etilamino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

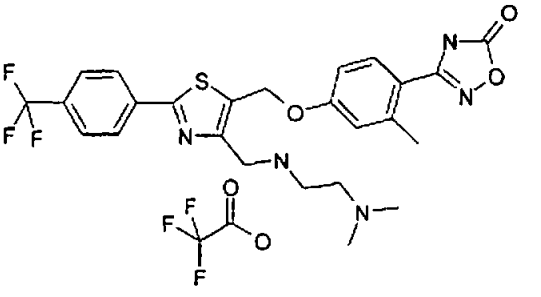


De acuerdo con el método descrito para 3-{2-metil-4-[4-propilaminometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 47, se obtuvo 3-{2-metil-4-[4-[(2-piperidin-1-il-etilamino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 5-[3-metil-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-carbaldehído y 1-(2-aminoetil)piperidina. El compuesto se obtuvo como su sal de trifluoroacetato.

C28H30F3N5O3S.C2HF3O2 (801,69), MS(ESI): 574,2.

Ejemplo 53

3-{4-[4-[(2-Dimetilamino-etilamino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona



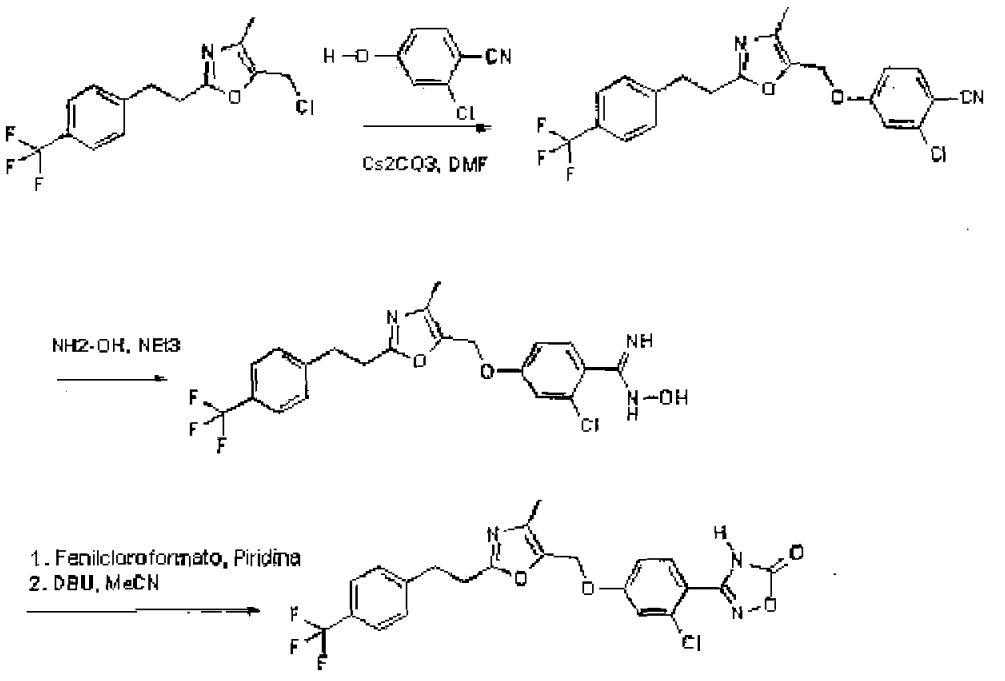
De acuerdo con el método descrito para 3-{2-metil-4-[4-propilaminometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 47, se obtuvo 3-{4-[4-[(2-dimetilamino-etilamino)-metil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 5-[3-metil-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-carbaldehído y N,N-dimetiletilendiamina. El compuesto se obtuvo como su sal de trifluoroacetato.

C25H26F3N5O3S.C2HF3O2 (761,63), MS(ESI): 534,2.

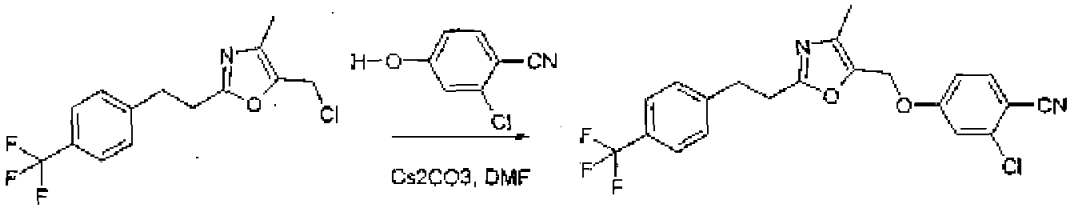
Los siguientes ejemplos se prepararon de acuerdo con el procedimiento A:

Ejemplo 54

3-(2-Cloro-4-{4-metil-2-[2-(4-trifluorometil-fenil)-etil]-oxazol-5-ilmetoxi}-fenil)-4H-[1,2,4]oxadiazol-5-ona



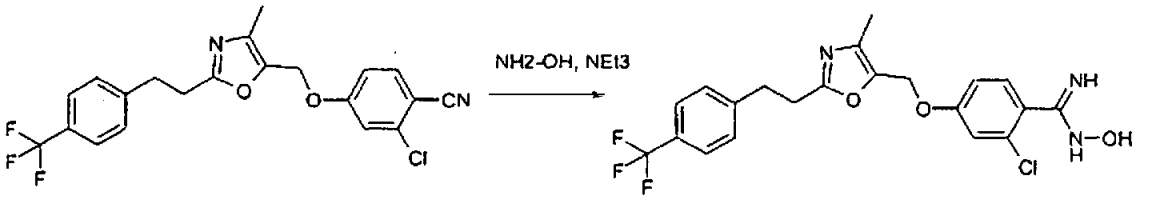
2-Cloro-4-{4-metil-2-[2-(4-trifluorometil-fenil)-etil]-oxazol-5-ilmetoxi}-benzonitrilo



A una disolución de 2,63 g de 2-cloro-4-hidroxi-benzonitrilo en 25 ml de dimetilformamida se le añadieron 4,0 g de 5-clorometil-4-metil-2-[2-(4-trifluorometil-fenil)-etil]-oxazol y 8,58 g de carbonato de cesio. La mezcla se agitó a temperatura ambiente toda la noche. Luego se añadieron 150 ml de acetato de etilo, la mezcla se lavó con 40 ml de agua y salmuera y luego se secó sobre MgSO4. El disolvente se separó a vacio. El material bruto resultante se purificó por RP-HPLC para obtener 3,0 g de 2-cloro-4-{4-metil-2-[2-(4-trifluorometil-fenil)-etil]-oxazol-5-ilmetoxi}-benzonitrilo.

C21H16ClF3N2O2 (420,82), MS(ESI): 421,1 ($M+H^+$).

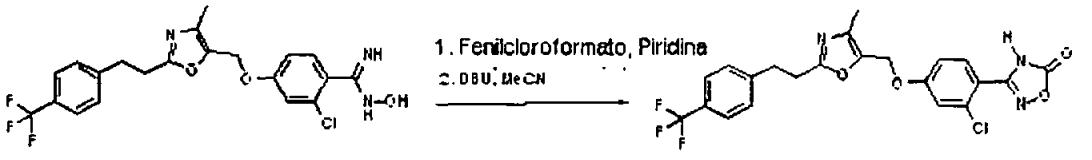
2-Cloro-N-hidroxi-4-{4-metil-2-[2-(4-trifluorometil-fenil)-etil]-oxazol-5-ilmetoxi}-benzamidina



Se disolvieron 3,0 g de 2-cloro-4-{4-metil-2-[2-(4-trifluorometil-fenil)-etil]-oxazol-5-ilmetoxi}- benzonitrilo en una mezcla de 20 ml de tetrahidrofurano y 20 ml de metanol. Se añadieron 9,91 g de hidrocloruro de hidroxilamina seguidos de la adición de 19,9 ml de trietilamina. La mezcla de reacción se agitó a 65ºC toda la noche. Los disolventes se separaron a vacío y el residuo resultante se vertió en agua y se extrajo cinco veces con acetato de etilo. Los extractos orgánicos combinados se lavaron con salmuera, se secaron sobre MgSO4 y el disolvente se evaporó *in vacuo* para obtener 4,4 g de 2-cloro-N-hidroxi-4-{4-metil-2-[2-(4-trifluorometil-fenil)-etil]-oxazol-5-ilmetoxi}-benzamidina bruto que se utilizó sin purificación adicional.

C21H19ClF3N3O3 (453,85), MS(ESI): 454,2 ($M+H^+$).

<u>3-(2-Cloro-4-{4-metil-2-[2-(4-trifluorometil-fenil)-etil]-oxazol-5-ilmetoxi}-fenil)-4H-[1,2,4]oxadiazol-5-ona</u>

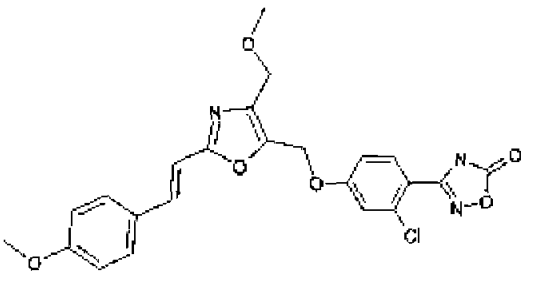


Se disolvieron 4,4 g de 2-cloro-N-hidroxi-4-{4-metil-2-[2-(4-trifluorometil-fenil)-etil]-oxazol-5-ilmetoxi}-benzamidina bruta en 20 ml de diclorometano. Se añadieron 0,94 ml de piridina y 1,46 ml de cloroformiato de fenilo, y la mezcla se agitó a temperatura ambiente durante diez minutos. La mezcla se diluyó por adición de 40 ml de acetonitrilo y se añadieron 7,25 ml de 1,8-diazabiciclo[5.4.0]undec-7-eno. La mezcla de reacción se agitó a temperatura ambiente durante 10 minutos. La mezcla se evaporó *in vacuo* y el material bruto resultante se purificó por HPLC de fase inversa para obtener 460 mg de 3-(2-cloro-4-{4-metil-2-[2-(4-trifluorometil-fenil)-etil]-oxazol-5-ilmetoxi}- fenil)-4H-[1,2,4]oxadiazol-5-ona.

C22H17ClF3N3O4 (479,85), MS(ESI): 479,98 ($M+H^+$).

Ejemplo 55

3-(2-Cloro-4-{4-metoximetil-2-[2-(4-metoxi-fenil)-vinil]-oxazol-5-ilmetoxi}-fenil)-4H-[1,2,4]oxadiazol-5-ona

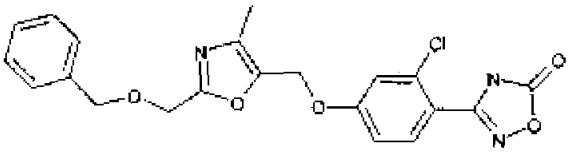


De acuerdo con el método descrito para 3-(2-cloro-4-{4-metil-2-[2-(4-trifluorometil-fenil)-etil]-oxazol-5-ilmetoxi}-fenil)-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 54, se obtuvo 3-(2-cloro-4-{4-metoximetil-2-[2-(4-metoxi-fenil)-vinil]-oxazol-5-ilmetoxi}-fenil)-4H-[1,2,4]oxadiazol-5-ona a partir de 5-clorometil-4-metoximetil-2-[2-(4-metoxi-fenil)-vinil]-oxazol y 2-cloro-4-hidroxi-benzonitrilo.

C23H20ClN3O6 (469,88), MS(ESI): 470,0 ($M+H^+$).

Ejemplo 56

3-[4-(2-Benciloximetil-4-metil-oxazol-5-ilmetoxi)-2-cloro-fenil]-4H-[1,2,4]oxadiazol-5-ona

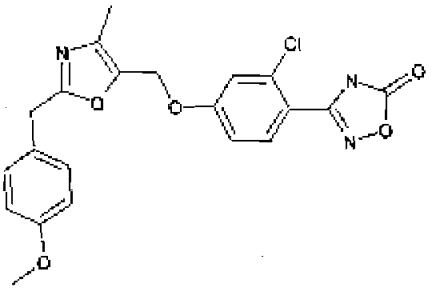


De acuerdo con el método descrito para 3-(2-cloro-4-{4-metil-2-[2-(4-trifluorometil-fenil)-etil]-oxazol-5-ilmetoxi}-fenil)-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 54, se obtuvo 3-[4-(2-benciloximetil-4-metil-oxazol-5-ilmetoxi)-2-cloro-fenil]-4H-[1,2,4]oxadiazol-5-ona a partir de 2-benciloximetil-5-clorometil-4-metil-oxazol y 2-cloro-4-hidroxi-benzonitrilo.

C21H18ClN3O5 (427,85), MS(ESI): 428,4 ($M+H^+$).

Ejemplo 57

3-{2-Cloro-4-[2-(4-metoxi-bencil)-4-metil-oxazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

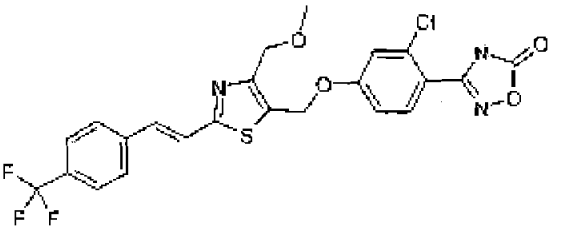


De acuerdo con el método descrito para 3-(2-cloro-4-{4-metil-2-[2-(4-trifluorometil-fenil)-etil]-oxazol-5-ilmetoxi}-fenil)-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 54, se obtuvo 3-{2-cloro-4-[2-(4-metoxi-bencil)-4-metil-oxazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 5-clorometil-2-(4-metoxi-bencil)-4-metil-oxazol y 2-cloro-4-hidroxi-benzonitrilo.

C21H18ClN3O5 (427,85), MS(ESI): 428,2 ($M+H^+$).

Ejemplo 58

3-(2-Cloro-4-{4-metoximetil-2-[2-(4-trifluorometil-fenil)-vinil]-tiazol-5-ilmetoxi}-fenil)-4H-[1,2,4]oxadiazol-5-ona

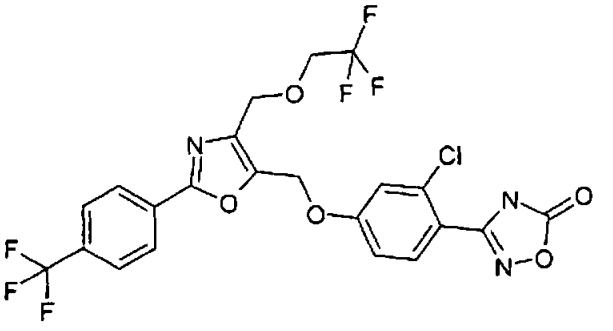


De acuerdo con el método descrito para 3-(2-cloro-4-{4-metil-2-[2-(4-trifluorometil-fenil)-etil]-oxazol-5-ilmetoxi}-fenil)-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 54, se obtuvo 3-(2-cloro-4-{4-metoximetil-2-[2-(4-trifluorometil-fenil)-vinil]-tiazol-5-ilmetoxi}-fenil)-4H-[1,2,4]oxadiazol-5-ona a partir de 5-clorometil-4-metoximetil-2-[2-(4-trifluorometil-fenil)-vinil]-tiazol y 2-cloro-4-hidroxi-benzonitrilo.

C23H17ClF3N3O4S (523,92), MS(ESI): 524,0 ($M+H^+$).

Ejemplo 59

3-{2-Cloro-4-[4-(2,2,2-trifluoro-etoximetil)-2-(4-trifluorometil-fenil)-oxazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona



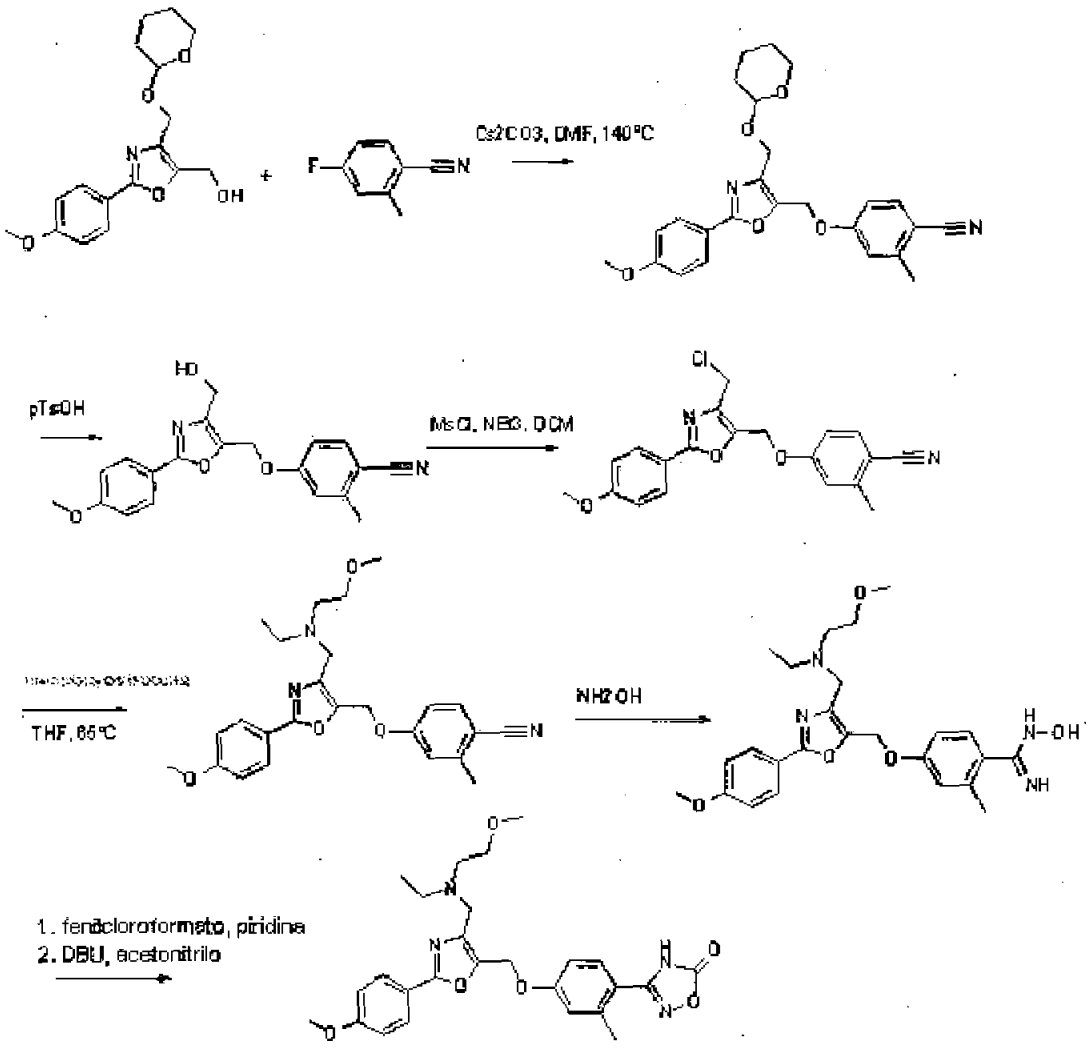
De acuerdo con el método descrito para 3-(2-cloro-4-{4-metil-2-[2-(4-trifluorometil-fenil)-etil]-oxazol-5-ilmetoxi}-fenil)-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 54, se obtuvo 3-{2-cloro-4-[4-(2,2,2-trifluoro-etoximetil)-2-(4-trifluorometil-fenil)-oxazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 5-clorometil-4-(2,2,2-trifluoro-etoximetil)-2-(4-trifluorometil-fenil)-oxazol y 2-cloro-4-hidroxi-benzonitrilo.

$C_{22}H_{14}ClF_6N_3O_5$ (549,82), MS(ESI): 550,2 ($M+H^+$).

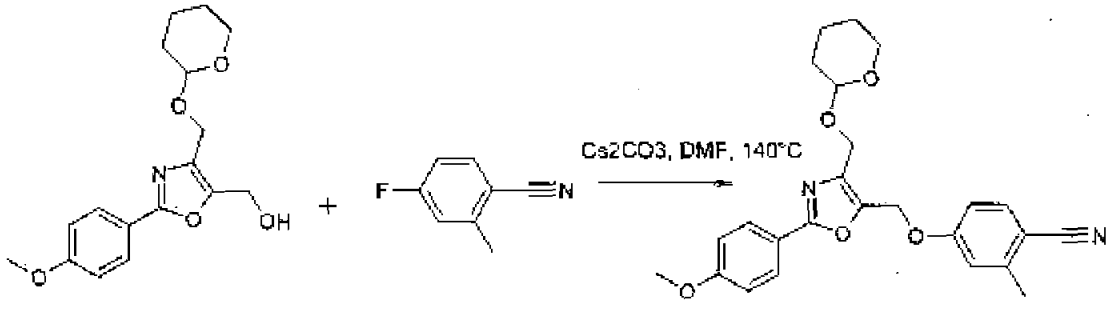
Los siguientes ejemplos se prepararon de acuerdo con el procedimiento L, en el que la primera etapa de reacción se llevó a cabo de acuerdo con el procedimiento general B [B1 + B2 => B3]:

Ejemplo 60

3-{4-[4-{[Etil-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona



4-[2-(4-Metoxi-fenil)-4-(tetrahidro-piran-2-iloximetil)-oxazol-5-ilmetoxil-2-metil-benzonitrilo

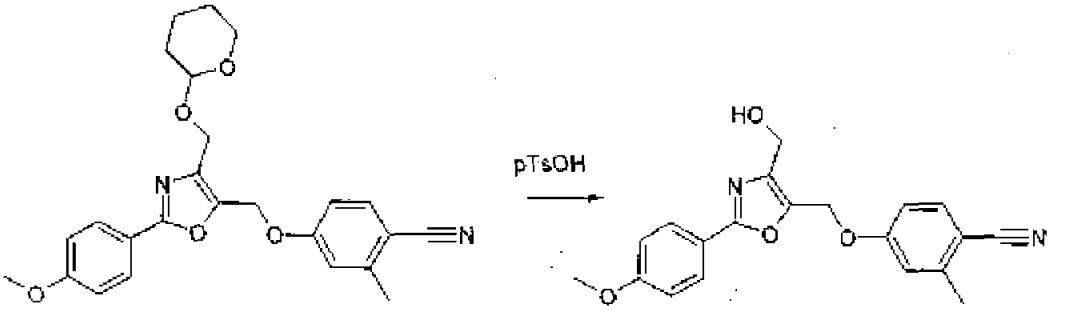


A una disolución de 3,2 g de 4-fluoro-2-metilbenzonitrilo en 50 ml de dimetilformamida se le añadieron 5,0 g de [2-(4-metoxi-fenil)-4-(tetrahidro-piran-2-iloximetil)-oxazol-5-il]-metanol seguidos de la adición de 10,2 g de carbonato de cesio. La mezcla de reacción se agitó a 140°C toda la noche. La mezcla de reacción enfriada se diluyó con 200 ml de acetato de etilo y se lavó cinco veces

con porciones de 50 ml de agua y salmuera. La fase orgánica se secó sobre MgSO4 y el disolvente se evaporó *in vacuo*. El residuo se purificó por cromatografía sobre gel de sílice con el eluyente n-heptano: acetato de etilo = 5:1 => 2:1 para obtener 5,96 g de 4-[2-(4-Metoxi-fenil)-4-(tetrahidro-piran-2-iloximetil)-oxazol-5-ilmetoxi]-2-metil- benzonitrilo como un aceite.

C25H26N2O5 (434,50), MS(ESI): 435,2 ($M+H^+$), Rf(n-heptano: acetato de etilo = 1:1) = 0,42.

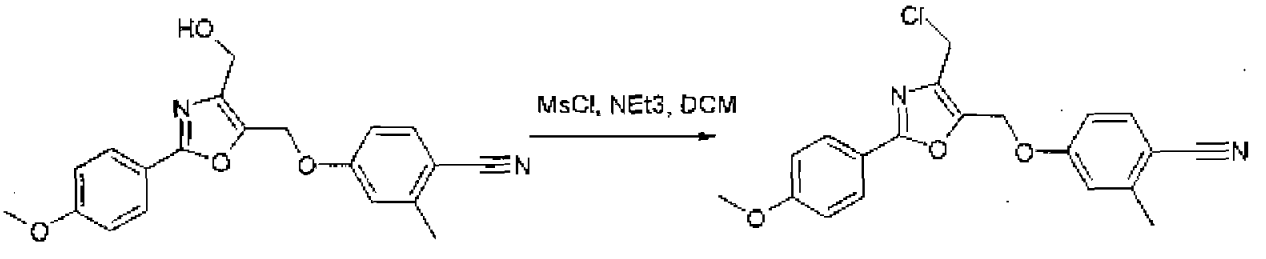
4-[4-Hidroximetil-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-benzonitrilo



Se disolvieron 5,96 g de 4-[2-(4-metoxi-fenil)-4-(tetrahidro-piran-2-iloximetil)-oxazol-5-ilmetoxi]-2-metil-benzonitrilo en 100 ml de metanol. Se añadieron 522 mg de ácido p-toluensulfónico monohidratado y la mezcla de reacción se agitó a temperatura ambiente durante una hora. El disolvente se separó al vacío. El residuo se disolvió en 150 ml de acetato de etilo y se lavó con 80 ml de disolución saturada de NaHCO3 y salmuera. La fase orgánica se secó sobre MgSO4 y el disolvente se evaporó *in vacuo* para obtener 4,1 g de 4-[4-hidroximetil-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-benzonitrilo como un sólido amarillo pálido.

C20H18N2O4 (350,38), MS(ESI): 351,2 ($M+H^+$).

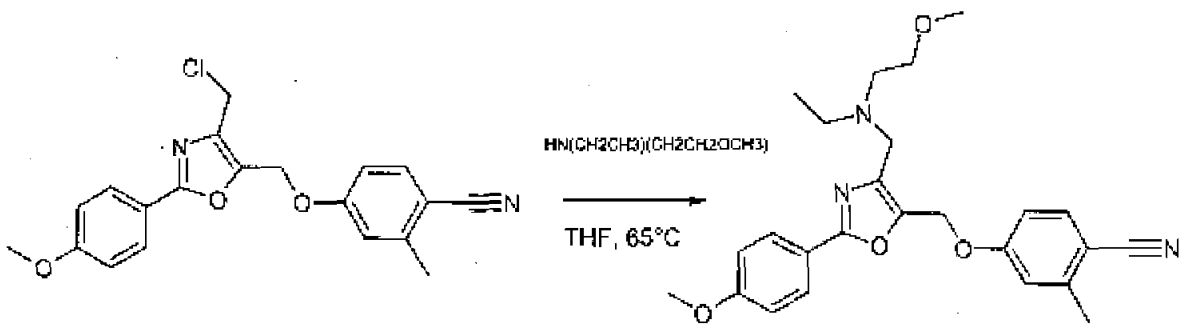
4-[4-Clorometil-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-benzonitrilo



Se disolvieron 4,1 g de 4-[4-hidroximetil-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-benzonitrilo en 90 ml de diclorometano y se enfrió en un baño de hielo. Se añadieron 2,44 ml de trietilamina, seguidos de adición de 1,08 ml de cloruro de metansulfonilo. Se quitó el baño de hielo, y la mezcla resultante se agitó a temperatura ambiente durante la noche. Después la mezcla de reacción se lavó con agua y salmuera, se secó sobre MgSO4 y se eliminó el disolvente a vacío para obtener 2,5 g de 5-clorometil-2-(4-metoxi-fenil)-4-(tetrahidro-piran-2-iloximetil)-oxazol como un aceite que se utilizó sin purificación adicional.

C20H17ClN2O3 (368,82), MS(ESI): 369,1 ($M+H^+$), Rf(acetato de etilo: *n*-heptano = 1:1) = 0,59.

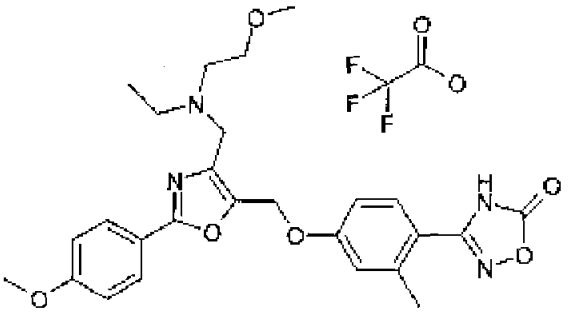
4-[4-{[Etil-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-benzonitrilo



Se disolvieron 200 mg de 5-clorometil-2-(4-metoxi-fenil)-4-(tetrahidro-piran-2-iloximetil)-oxazol y 224 mg de N-(2-metoxietil)etilamina en 5 ml de tetrahidrofurano y se agitó a 60°C durante seis horas. La mezcla de reacción enfriada se diluyó con 50 ml de acetato de etilo y se lavó con porciones de 20 ml de agua y salmuera, luego se secó sobre MgSO4. El disolvente se eliminó *in vacuo* para obtener 158 mg de 4-[4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2- metil-benzonitrilo como un aceite.

C25H29N3O4 (435,53), MS(ESI): 436,3 (M+H+).

3-{4-[4-{[Etil-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona

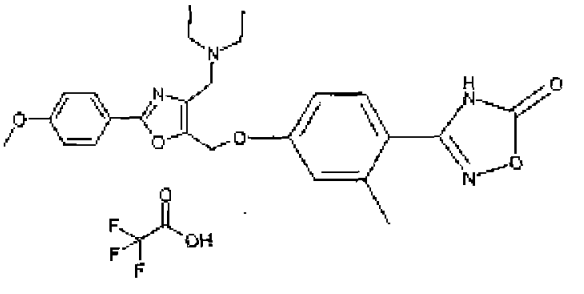


De acuerdo con el método descrito para 3-(2-cloro-4-{4-metil-2-[2-(4-trifluorometil-fenil)-etil]-oxazol-5-ilmetoxi}- fenil)-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 54, se obtuvo 3-{4-[4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 4-[4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-benzonitrilo. El compuesto se obtuvo como su sal de trifluoroacetato.

C26H30N4O6.C2HF3O2 (608,57), MS(ESI): 495,1 ($M+H^+$).

Ejemplo 61

3-{4-[4-Dietilaminometil-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona

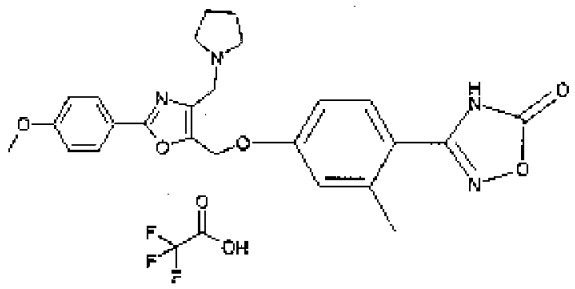


De acuerdo con el método descrito para 3-{4-[4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 60, se obtuvo 3-{4-[4-dietilaminometil-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 5-clorometil-2-(4-metoxi-fenil)-4-(tetrahidro-piran-2-iloximetil)-oxazol y dietilamina. El compuesto se obtuvo como su sal de trifluoroacetato.

C25H28N4O5.C2HF3O2 (578,55), MS(ESI): 465,1 ($M+H^+$).

Ejemplo 62

3-{4-[2-(4-Metoxi-fenil)-4-pirrolidin-1-ilmetil-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona

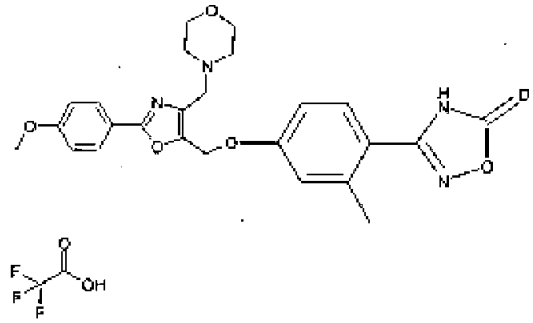


De acuerdo con el método descrito para 3-{4-[4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 60, se obtuvo 3-{4-[2-(4-metoxi-fenil)-4-pirrolidin-1-ilmetil-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 5-clorometil-2-(4-metoxi-fenil)-4-(tetrahidro-piran-2-iloximetil)-oxazol y pirrolidina. El compuesto se obtuvo como su sal de trifluoroacetato.

$C_{25}H_{26}N_4O_5.C_2HF_3O_2$ (576,53), MS(ESI): 463,2 ($M+H^+$).

Ejemplo 63

<u>3-{4-[2-(4-Metoxi-fenil)-4-morfolin-4-ilmetil-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona</u>

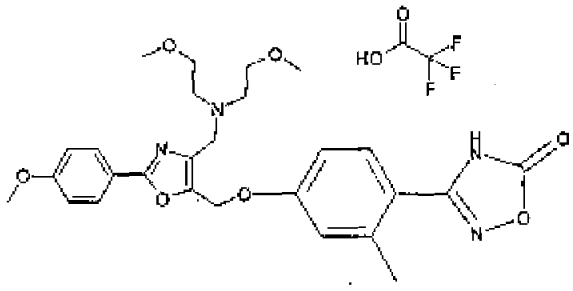


De acuerdo con el método descrito para 3-{4-[4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 60, se obtuvo 3-{4-[2-(4-metoxi-fenil)-4-morfolin-4-ilmetil-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 5-clorometil-2-(4-metoxi-fenil)-4-(tetrahidro-piran-2-iloximetil)-oxazol y morfolina. El compuesto se obtuvo como su sal de trifluoroacetato.

$C_{25}H_{26}N_4O_6.C_2HF_3O_2$ (592,53), MS(ESI): 479,3 ($M+H^+$).

Ejemplo 64

<u>3-{4-[4-{[Bis-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona</u>

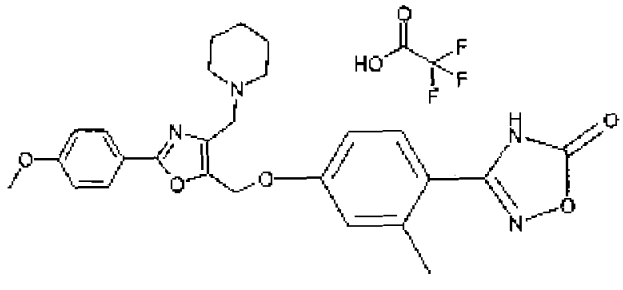


De acuerdo con el método descrito para 3-{4-[4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 60, se obtuvo 3-{4-[4-{[bis-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 5-clorometil-2-(4-metoxi-fenil)-4-(tetrahidro-piran-2-iloximetil)-oxazol y bis-(2-metoxi-etil)-amina. El compuesto se obtuvo como su sal de trifluoroacetato.

C27H32N4O7.C2HF3O2 (638,60), MS(ESI): 525,1 ($M+H^+$).

Ejemplo 65

<u>3-{4-[2-(4-Metoxi-fenil)-4-piperidin-1-ilmetil-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona</u>

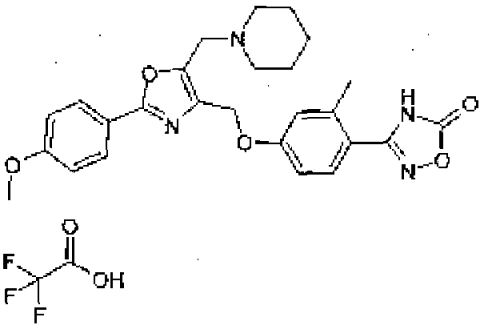


De acuerdo con el método descrito para 3-{4-[4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 60, se obtuvo 3-{4-[2-(4-metoxi-fenil)-4-piperidin-1-ilmetil-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 5-clorometil-2-(4-metoxi-fenil)-4-(tetrahidro-piran-2-iloximetil)-oxazol y piperidina. El compuesto se obtuvo como su sal de trifluoroacetato.

C26H28N4O5.C2HF3O2 (590,56), MS(ESI): 477,2 ($M+H^+$).

Ejemplo 66

<u>3-{4-[2-(4-Metoxi-fenil)-5-piperidin-1-ilmetil-oxazol-4-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona</u>

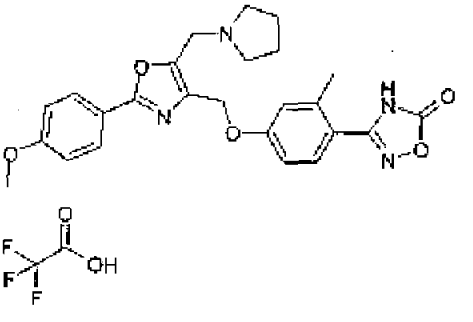


De acuerdo con el método descrito para 3-{4-[4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 60, se obtuvo 3-{4-[2-(4-metoxi-fenil)-5-piperidin-1-ilmetil-oxazol-4-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de éster 2-(4-metoxi-fenil)-5-(tetrahidro-piran-2-iloximetil)-oxazol-4-ilmetílico del ácido metansulfónico, 4-fluoro-2-metilbenzonitrilo y piperidina. El compuesto se obtuvo como su sal de trifluoroacetato.

C26H28N4O5.C2HF3O2 (590,56), MS(ESI): 477,3 ($M+H^+$).

Ejemplo 67

3-{4-[2-(4-Metoxi-fenil)-5-pirrolidin-1-ilmetil-oxazol-4-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona

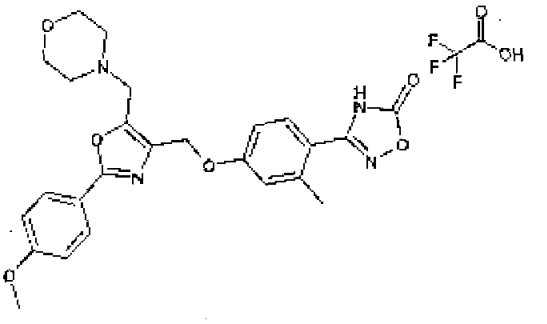


De acuerdo con el método descrito para 3-{4-[4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 60, se obtuvo 3-{4-[2-(4-metoxi-fenil)-5-pirrolidin-1-ilmetil-oxazol-4-ilmetoxi]-2-metil-fenil}- 4H-[1,2,4]oxadiazol-5-ona a partir de éster 2-(4-metoxi-fenil)-5-(tetrahidro-piran-2-iloximetil)-oxazol-4-ilmetílico del ácido metansulfónico, 4-fluoro-2-metilbenzonitrilo y pirrolidina. El compuesto se obtuvo como su sal de trifluoroacetato.

C25H26N4O5.C2HF3O2 (576,53), MS(ESI): 463,3 ($M+H^+$).

Ejemplo 68

3-{4-[2-(4-Metoxi-fenil)-5-morfolin-4-ilmetil-oxazol-4-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona

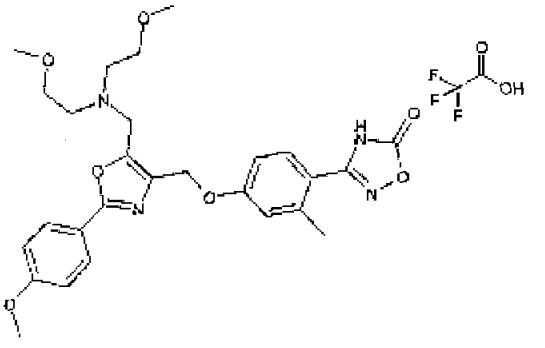


De acuerdo con el método descrito para 3-{4-[4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 60, se obtuvo 3-{4-[2-(4-metoxi-fenil)-5-morfolin-4-ilmetil-oxazol-4-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de éster 2-(4-metoxi-fenil)-5-(tetrahidro-piran-2-iloximetil)-oxazol-4-ilmetílico del ácido metansulfónico, 4-fluoro-2-metilbenzonitrilo y morfolina. El compuesto se obtuvo como su sal de trifluoroacetato.

C25H26N4O6.C2HF3O2 (592,53), MS(ESI): 479,2 ($M+H^+$).

Ejemplo 69

3-{4-[5-{[Bis-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-4-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona



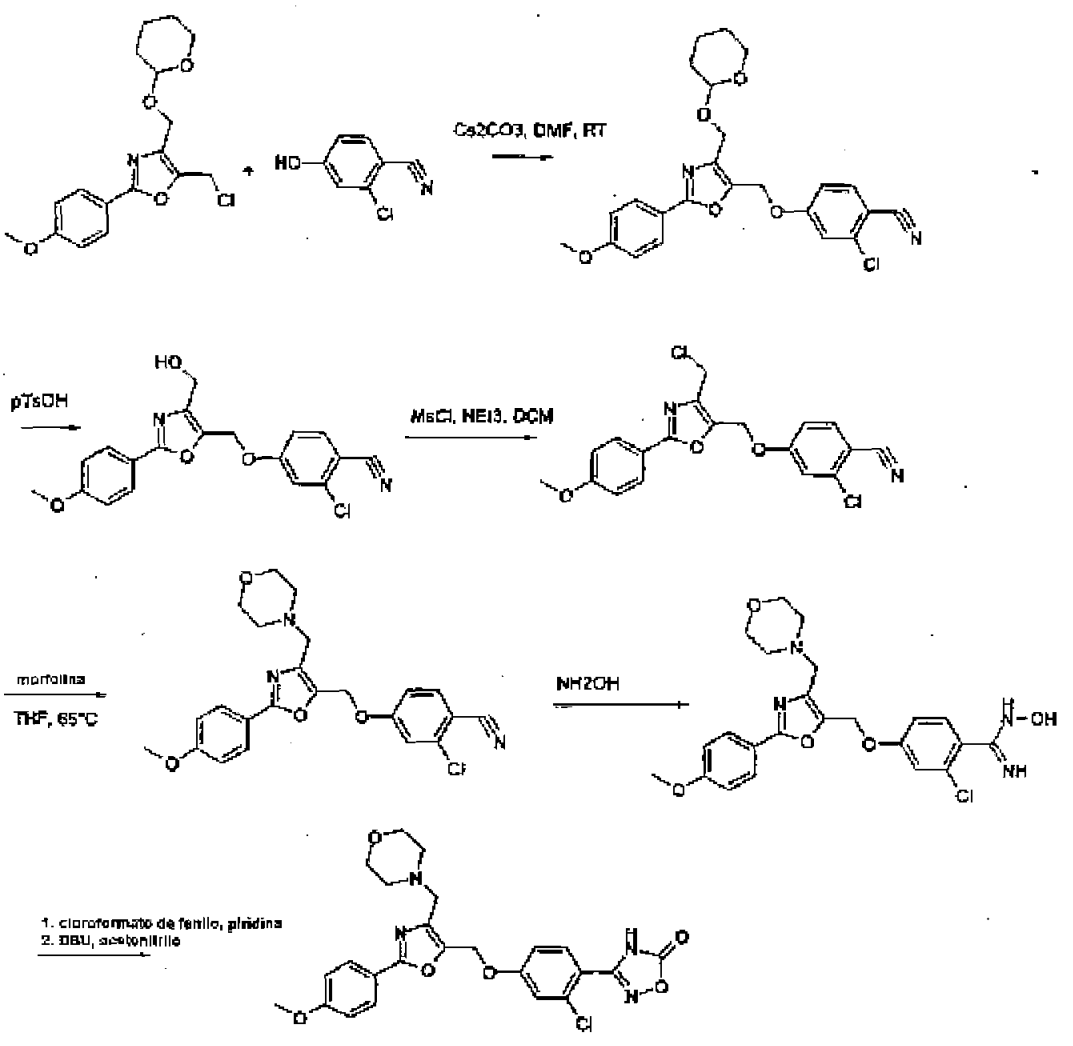
De acuerdo con el método descrito para 3-{4-[4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 60, se obtuvo 3-{4-[5-{[bis-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-4-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de éster 2-(4-metoxi-fenil)-5-(tetrahidro-piran-2-iloximetil)-oxazol-4-ilmetílico del ácido metansulfónico, 4-fluoro-2-metilbenzonitrilo y bis-(2-metoxi-etil)-amina.

$C_{27}H_{32}N_4O_7$ (524,57), MS(ESI): 525,2 ($M+H^+$).

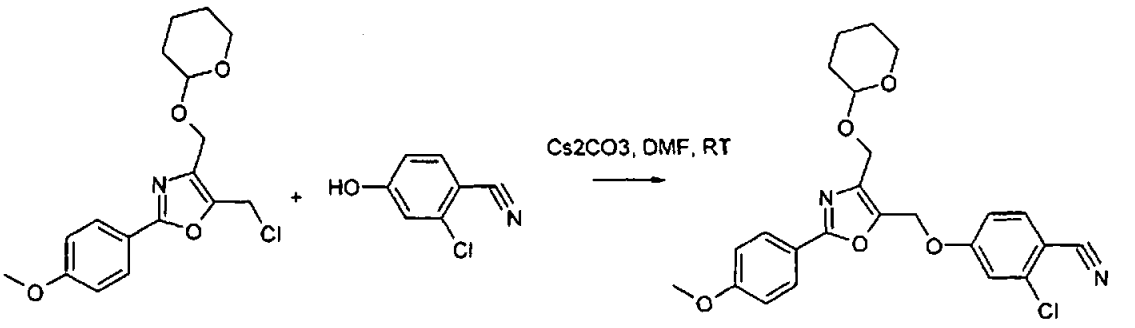
Los siguientes ejemplos se prepararon de acuerdo con el procedimiento L, en el que la primera etapa de reacción se llevó a cabo de acuerdo con el procedimiento general A [A1 + A2 => A3]:

Ejemplo 70

3-{2-Cloro-4-[2-(4-metoxi-fenil)-4-morfolin-4-ilmetil-oxazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona



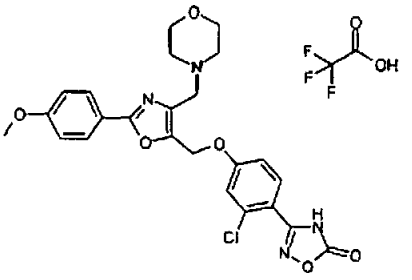
2-Cloro-4-[2-(4-metoxi-fenil)-4-(tetrahidro-piran-2-iloximetil)-oxazol-5-ilmetoxi]- benzonitrilo



Se disolvieron 2,5 g de 5-clorometil-2-(4-metoxi-fenil)-4-(tetrahidro-piran-2-iloximetil)-oxazol y 1,48 g de 2-cloro-4-hidroxibenzonitrilo en 20 ml de dimetilformamida. Se añadieron 4,82 g de carbonato de cesio y la mezcla de reacción se agitó a temperatura ambiente durante toda la noche. La mezcla de reacción se diluyó con 200 ml de acetato de etilo y se lavó cinco veces con porciones de 50 ml de agua y salmuera. La fase orgánica se secó sobre MgSO4 y el disolvente se evaporó in vacuo para obtener 4,0 g de 2-cloro-4-[2-(4-metoxi-fenil)-4-(tetrahidro-piran-2-iloximetil)-oxazol-5-ilmetoxi]-benzonitrilo bruto. Este material se usó sin purificación adicional.

C24H23ClN2O5 (454,91), MS(ESI): 455,2 ($M+H^+$).

<u>3-{2-Cloro-4-[2-(4-metoxi-fenil)-4-morfolin-4-ilmetil-oxazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona</u>

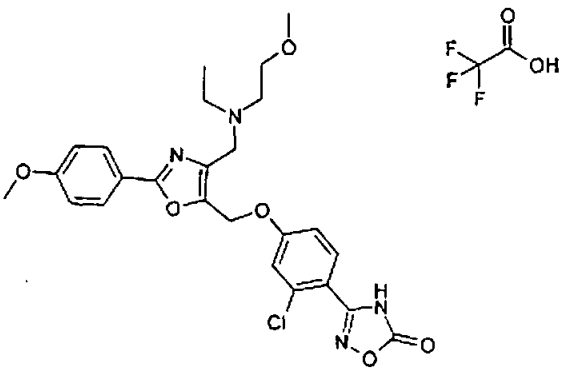


De acuerdo con el método descrito para 3-{4-[4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 60, se obtuvo 3-{2-cloro-4-[2-(4-metoxi-fenil)-4-morfolin-4-ilmetil-oxazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 2-cloro-4-[2-(4-metoxi-fenil)-4-(tetrahidro-piran-2-iloximetil)-oxazol-5-ilmetoxi]-benzonitrilo y morfolina. El compuesto se obtuvo como su sal de trifluoroacetato.

C24H23ClN4O6.C2HF3O2 (612,95), MS(ESI): 499,2 ($M+H^+$).

Ejemplo 71

3-{2-Cloro-4-[4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

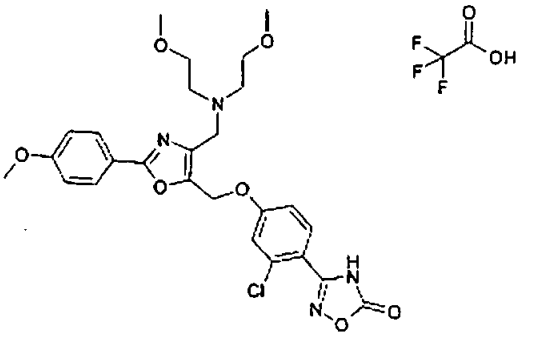


De acuerdo con el método descrito para 3-{4-[4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 60, se obtuvo 3-{2-cloro-4-[4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 2-cloro-4-[2-(4-metoxi-fenil)-4-(tetrahidro-piran-2-iloximetil)-oxazol-5-ilmetoxi]-benzonitrilo y etil-(2-metoxi-etil)-amina. El compuesto se obtuvo como su sal de trifluoroacetato.

C25H27ClN4O6.C2HF3O2 (628,99), MS(ESI): 515,2 ($M+H^+$).

Ejemplo 72

3-{4-[4-{[Bis-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-cloro-fenil}-4H-[1,2,4]oxadiazol-5-ona



De acuerdo con el método descrito para 3-{4-[4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 60, se obtuvo 3-{4-[4-{[bis-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-cloro-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 2-cloro-4-[2-(4-metoxi-fenil)-4-(tetrahidro-

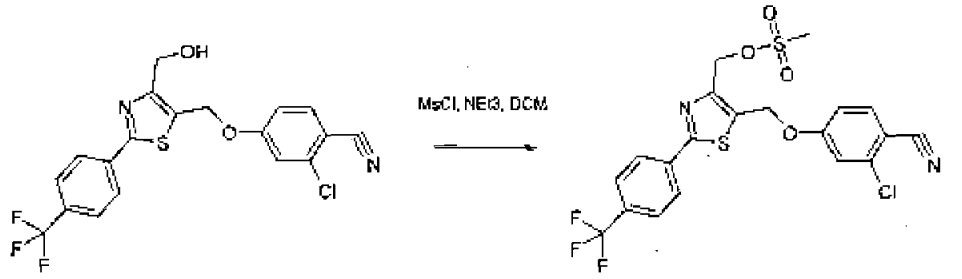
piran-2-iloximetil)-oxazol-5-ilmetoxi]-benzonitrilo y bis-(2-metoxi-etil)-amina. El compuesto se obtuvo como su sal de trifluoroacetato.

C26H29ClN4O7.C2HF3O2 (659,02), MS(ESI): 545,3 ($M+H^+$).

Ejemplo 73

3-[2-Cloro-4-[4-piperidin-1-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil]-4H-[1,2,4]oxadiazol-5-ona

Éster 5-(3-cloro-4-ciano-fenoximetil)-2-(4-trifluorometil-fenil)-tiazol-4-ilmetílico del ácido metansulfónico

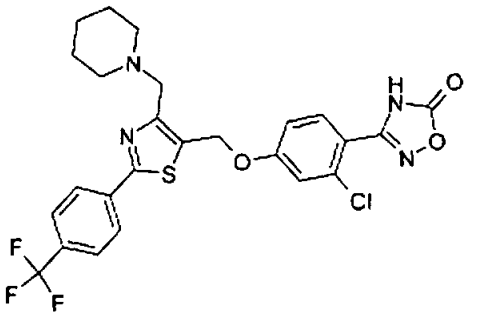


Se suspendieron 2,0 g de 2-cloro-4-[4-hidroximetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-benzonitrilo [obtenido a partir de 5-clorometil-4-(tetrahidro-piran-2-iloximetil)-2-(4-trifluorometil-fenil)-tiazol[8] y 2-cloro-4-hidroxibenzonitrilo de acuerdo con el método descrito en el ejemplo 70] en 50 ml de diclorometano. A 0°C, se le añadieron 0,44 ml de cloruro de metansulfonilo y 0,98 ml de trietilamina y la mezcla de reacción se agitó a 0°C durante una hora. La mezcla de reacción se diluyó con 150 ml de acetato de etilo y se lavó con 50 ml de agua y salmuera. La fase orgánica se secó sobre MgSO4, luego el disolvente se evaporó *in vacuo* para obtener 2,5 g de éster 5-(3-cloro-4-ciano-fenoximetil)-2-(4-trifluorometil-fenil)-tiazol-4-ilmetílico del ácido metansulfónico como un sólido amarillo pálido.

C20H14ClF3N2O4S2 (502,92), MS(ESI): 503,1 ($M+H^+$).

3-[2-Cloro-4-[4-piperidin-1-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil]-4H-[1,2,4]oxadiazol-5-ona

8WO 2002067912, WO 2002059098

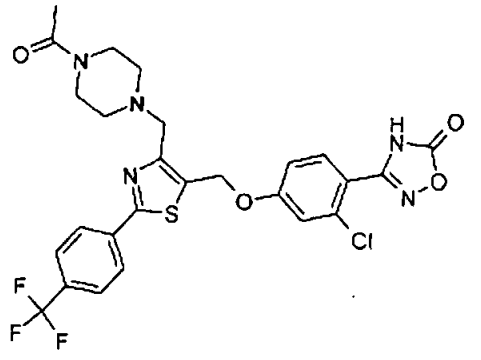


De acuerdo con el método descrito para 3-{4-[4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 60, se obtuvo 3-{2-cloro-4-[4-piperidin-1-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de éster 5-(3-cloro-4-ciano-fenoximetil)-2-(4-trifluorometil-fenil)-tiazol-4-ilmetílico del ácido metansulfónico y piperidina.

C25H22ClF3N4O3S (550,99), MS(ESI): 551,1 ($M+H^+$).

Ejemplo 74

3-{4-[4-(4-Acetil-piperazin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-cloro-fenil}-4H-[1,2,4]oxadiazol-5-ona

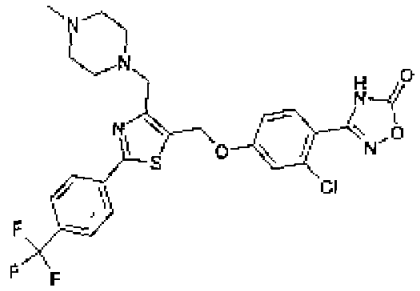


De acuerdo con el método descrito para 3-{4-[4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 60, se obtuvo 3-{4-[4-(4-acetil-piperazin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-cloro-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de éster 5-(3-cloro-4-ciano-fenoximetil)-2-(4-trifluorometil-fenil)-tiazol-4-ilmetílico del ácido metansulfónico y 4-acetilpiperazina.

C26H23ClF3N5O4S (594,02), MS(ESI): 594,2 ($M+H^+$).

Ejemplo 75

3-{2-Cloro-4-[4-(4-metil-piperazin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

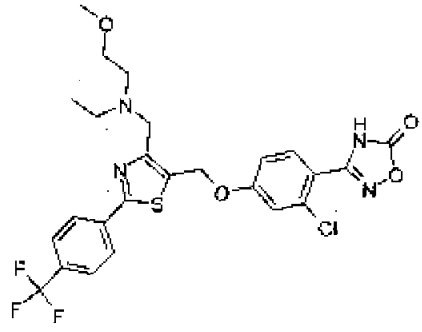


De acuerdo con el método descrito para 3-{4-[4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 60, se obtuvo 3-{2-cloro-4-[4-(4-metil-piperazin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de éster 5-(3-cloro-4-ciano-fenoximetil)-2-(4-trifluorometil-fenil)- tiazol-4-ilmetílico del ácido metansulfónico y 4-metil-piperazina.

C25H23ClF3N5O3S (566,01), MS(ESI): 566,2 (M+H+).

Ejemplo 76

3-{2-Cloro-4-[4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

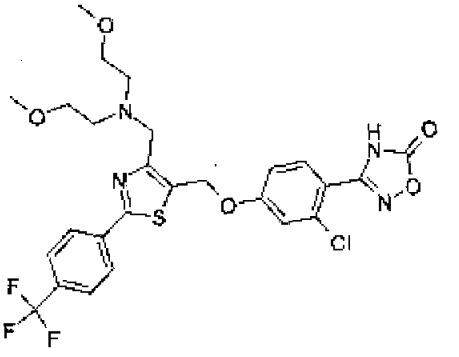


De acuerdo con el método descrito para 3-{4-[4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 60, se obtuvo 3-{2-cloro-4-[4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de éster 5-(3-cloro-4-ciano-fenoximetil)-2-(4-trifluorometil-fenil)-tiazol-4-ilmetílico del ácido metansulfónico y N-(2-metoxietil)etilamina.

C25H24ClF3N4O4S (569,01), MS(ESI): 569,1 ($M+H^+$).

Ejemplo 77

3-{4-[4-{[Bis-(2-metoxi-etil)-amino]-metil}-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-cloro-fenil}-4H-[1,2,4]oxadiazol-5-ona

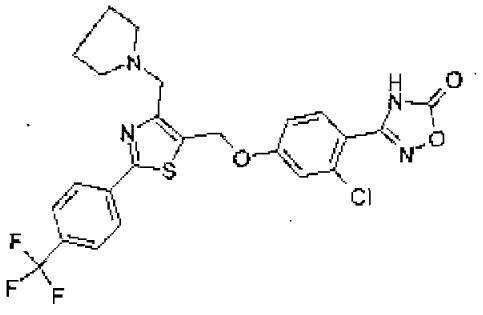


De acuerdo con el método descrito para 3-{4-[4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 60, se obtuvo 3-{4-[4-{[bis-(2-metoxi-etil)-amino]-metil}-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-cloro-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de éster 5-(3-cloro-4-ciano-fenoximetil)-2-(4-trifluorometil-fenil)-tiazol-4-ilmetílico del ácido metansulfónico y bis-(2-metoxi-etil)-amina.

C26H26ClF3N4O5S (599,03), MS(ESI): 599,2 ($M+H^+$).

Ejemplo 78

3-{2-Cloro-4-[4-pirrolidin-1-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona



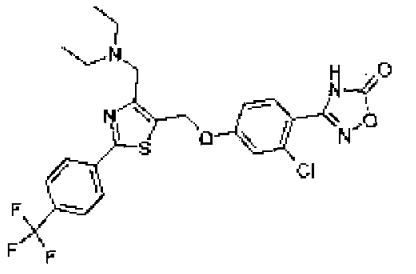
De acuerdo con el método descrito para 3-{4-[4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 60, se obtuvo 3-{2-cloro-4-[4-pirrolidin-1-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

a partir de éster 5-(3-cloro-4-ciano-fenoximetil)-2-(4-trifluorometil-fenil)- tiazol-4-ilmetílico del ácido metansulfónico y pirrolidina.

C24H20ClF3N4O3S (536,96), MS(ESI): 537,2 ($M+H^+$).

Ejemplo 79

3-{2-Cloro-4-[4-dietilaminometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

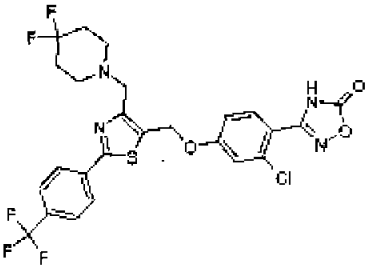


De acuerdo con el método descrito para 3-{4-[4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 60, se obtuvo 3-{2-cloro-4-[4-dietilaminometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de éster 5-(3-cloro-4-ciano-fenoximetil)-2-(4-trifluorometil-fenil)-tiazol-4-ilmetílico del ácido metansulfónico y dietilamina.

C24H22ClF3N4O3S (538,98), MS(ESI): 539,1 ($M+H^+$).

Ejemplo 80

3-{2-Cloro-4-[4-(4,4-difluoro-piperidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona



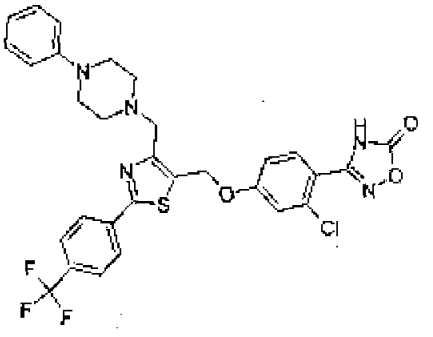
De acuerdo con el método descrito para 3-{4-[4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 60, se obtuvo 3-{2-cloro-4-[4-(4,4-difluoro-piperidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de éster 5-(3-cloro-4-ciano-fenoximetil)-2-(4-

trifluorometil-fenil)-tiazol-4-ilmetílico del ácido metansulfónico y 4,4-difluoro-piperidina.

C25H20ClF5N4O3S (586,97), MS(ESI): 587,1 ($M+H^+$).

Ejemplo 81

3-{2-Cloro-4-[4-(4-fenil-piperazin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona



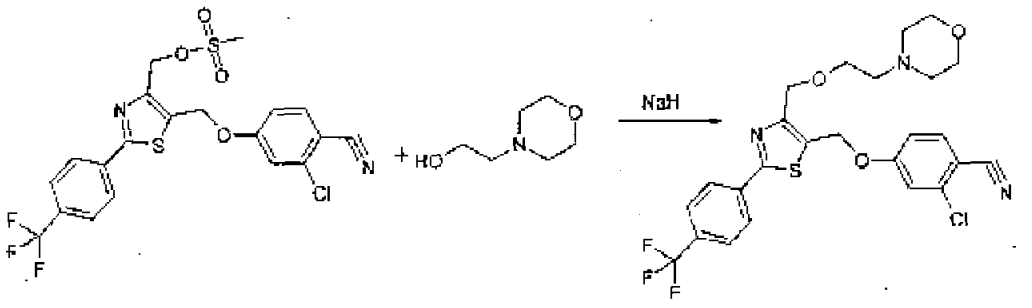
De acuerdo con el método descrito para 3-{4-[4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 60, se obtuvo 3-{2-cloro-4-[4-(4-fenil-piperazin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir del éster 5-(3-cloro-4-ciano-fenoximetil)-2-(4-trifluorometil-fenil)-tiazol-4-ilmetílico del ácido metansulfónico y 4-fenil-piperidina.

C30H25ClF3N5O3S (628,08), MS(ESI): 628,1 ($M+H^+$).

Ejemplo 82

3-{2-Cloro-4-[4-(2-morfolin-4-il-etoximetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

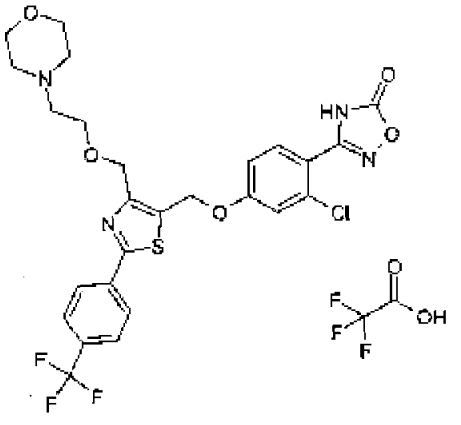
2-Cloro-4-[4-(2-morfolin-4-il-etoximetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-benzonitrilo



Se disolvieron 120 mg de éster 5-(3-cloro-4-ciano-fenoximetil)-2-(4-trifluorometil-fenil)-tiazol-4-ilmetílico del ácido metansulfónico en 5 ml de N-(2-hidroxietil)morfolina. Se añadieron 10 mg de hidruro de sodio y la mezcla de reacción se agitó a 50°C durante una hora. Se añadieron 10 ml de agua y la mezcla de reacción se extrajo con 50 ml de acetato de etilo. La capa orgánica se separó y se lavó dos veces con 20 ml de salmuera. La capa orgánica se secó sobre MgSO4 y se eliminó el disolvente *in vacuo*. El residuo se purificó por RP-HPLC para obtener 40 mg de 2-cloro-4-[4-(2-morfolin-4-il-etoximetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-benzonitrilo como su sal de trifluoro-acetato.

C25H23ClF3N3O3S.C2HF3O2 (652,02), MS(ESI): 538,2 ($M+H^+$).

3-{2-Cloro-4-[4-(2-morfolin-4-il-etoximetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

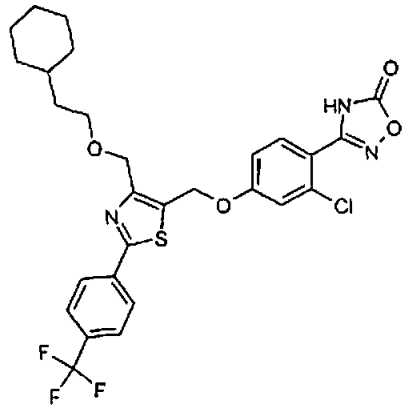


De acuerdo con el método descrito para 3-{4-[4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 60, se obtuvo 3-{2-cloro-4-[4-(2-morfolin-4-il-etoximetil)-2-(4-trifluorometil-fenil)-tiazol-5- ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 2-cloro-4-[4-(2-morfolin-4-il-etoximetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-benzonitrilo. El compuesto se obtuvo como su sal de trifluoroacetato.

C26H24ClF3N4O5S.C2HF3O2 (711,04), MS(ESI): 597,3 ($M+H^+$).

Ejemplo 83

3-{2-Cloro-4-[4-(2-ciclohexil-etoximetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona



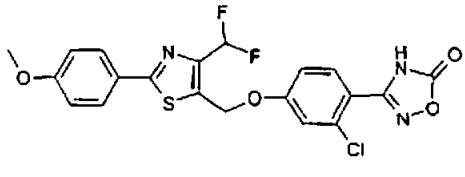
De acuerdo con el método descrito para 3-{2-cloro-4-[4-(2-morfolin-4-il-etoximetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 82 y 3-{4-[4-{[etil-(2-metoxi-etil)-amino]-metil}-2-(4-metoxi-fenil)-oxazol-5-ilmetoxi]-2-metil-fenil}-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 60, se obtuvo 3-{2-cloro-4-[4-(2-ciclohexil-etoximetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de éster 5-(3-cloro-4-ciano-fenoximetil)-2-(4-trifluorometil-fenil)- tiazol-4-ilmetílico del ácido metansulfónico y 2-ciclohexiletanol.

C28H27ClF3N3O4S (594,06), MS(ESI): 594,3 ($M+H^+$).

El siguiente ejemplo se obtuvo de acuerdo con el procedimiento A:

Ejemplo 84

3-{2-Cloro-4-[4-difluorometil-2-(4-metoxi-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona



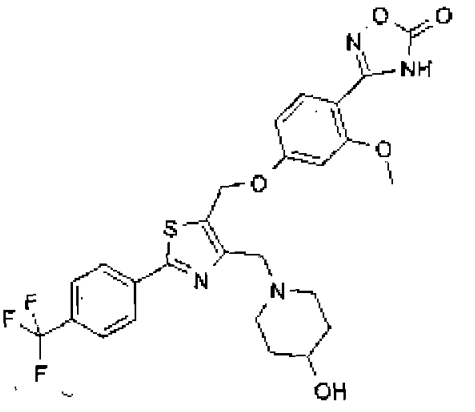
De acuerdo con el método descrito para 3-(2-cloro-4-{4-metil-2-[2-(4-trifluorometil-fenil)-etil]-oxazol-5-ilmetoxi}-fenil)-4H-[1,2,4]oxadiazol-5-ona en el ejemplo 54, se obtuvo 3-{2-cloro-4-[4-difluorometil-2-(4-metoxi-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 5-clorometil-4-difluorometil-2-(4-metoxi-fenil)-tiazol y 2-cloro-4-hidroxi-benzonitrilo.

C20H14ClF2N3O4S (465,87), MS(ESI): 466,0 ($M+H^+$).

Los siguientes ejemplos se prepararon de acuerdo con el procedimiento D:

Ejemplo 85

3-{4-[4-(4-Hidroxi-piperidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-1,2,4-oxadiazol-5-ona

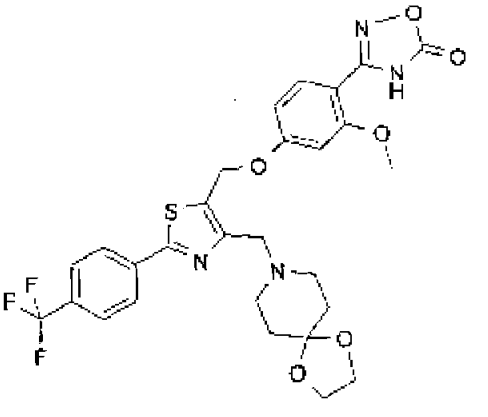


De acuerdo con el método descrito para 3-{4-[4-(4-metansulfonil-piperazin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona, se obtuvo 3-{4-[4-(4-hidroxi-piperidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-1,2,4-oxadiazol-5-ona a partir de éster 5-[3-metoxi-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-ilmetílico del ácido metansulfónico y 4-hidroxi-piperidina.

C26H25F3N4O5S (562,57), MS(ESI): 563 ($M+H^+$).

Ejemplo 86

3-{4-[4-(1,4-Dioxa-8-aza-espiro[4.5]dec-8-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-1,2,4-oxadiazol-5-ona



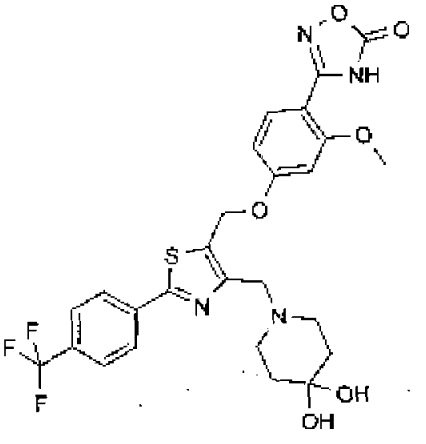
De acuerdo con el método descrito para 3-{4-[4-(4-metansulfonil-piperazin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona, se obtuvo 3-{4-[4-(1,4-dioxa-8-aza-espiro[4.5]dec-8-

ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-1,2,4-oxadiazol-5-ona a partir de éster 5-[3-metoxi-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-ilmetílico del ácido metansulfónico y 1,4-dioxa-8-aza-espiro[4.5]decano.

C28H27F3N4O6S (604,61), MS(ESI): 605 ($M+H^+$).

Ejemplo 87

3-{4-[4-(4,4-Dihidroxi-piperidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-1,2,4-oxadiazol-5-ona

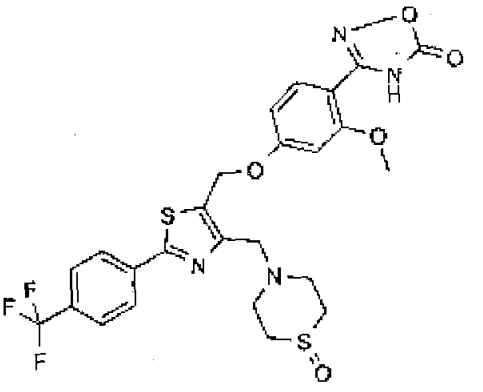


A una suspensión de 10 mg de 3-{4-[4-(1,4-dioxa-8-aza-espiro[4.5]dec-8-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-1,2,4-oxadiazol-5-ona en 2 mL de dioxano se le añadió 0,5 mL de una disolución acuosa 6N de ácido clorhídrico. La mezcla resultante se calentó hasta 50°C durante 2h y se vertió en una disolución saturada acuosa de hidrógeno carbonato sódico y se extrajo con acetato de etilo. Los extractos orgánicos se lavaron con agua, se secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida. El producto bruto se recristalizó en acetonitrilo para producir 6 mg de 3-{4-[4-(4,4-dihidroxi-piperidin-1-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-1,2,4-oxadiazol-5-ona como un sólido amarillento.

C26H25F3N4O6S (578,57), MS(ESI): 579 ($M+H^+$).

Ejemplo 88

3-{2-Metoxi-4-[4-(1-oxo-1λ^4-tiomorfolin-4-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona

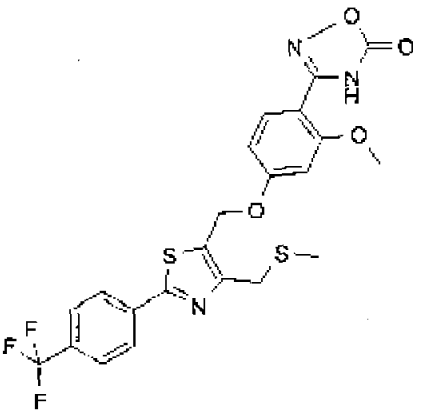


A una disolución de 80 mg de 3-{2-metoxi-4-[4-tiomorfolin-4-ilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona en 1 mL de metanol se le añadieron 2 mL de una disolución 2N de ácido clorhídrico en éter dietílico. La mezcla resultante se concentró a presión reducida. A una disolución del residuo en 1 mL de acetonitrilo se le añadió 1 mL de agua y 88 mg de Oxone®. La mezcla resultante se agitó a temperatura ambiente durante 1 h, luego se vertió en agua y se extrajo con diclorometano. Los extractos orgánicos se lavaron con agua, se secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida. El producto bruto se purificó por cromatografía en columna sobre gel de sílice (gradiente de metanol en diclorometano) para producir 10,5 mg de 3-{2-metoxi-4-[4-(1-oxo-1λ^4-tiomorfolin-4-ilmetil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona como un sólido blanco.

C25H23F3N4O5S2 (580,61), MS(ESI): 581 ($M+H^+$).

Ejemplo 89

3-{2-Metoxi-4-[4-metilsulfanilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona

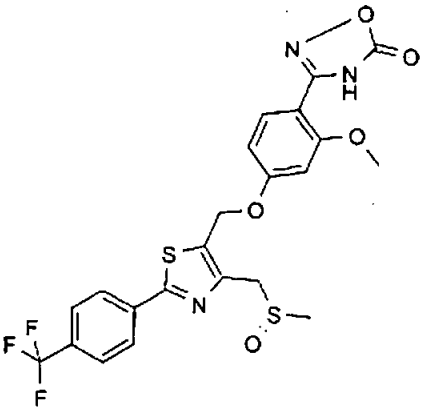


A una disolución de 200 mg de éster 5-[3-metoxi-4-(5-oxo-4,5-dihidro-[1,2,4]oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-ilmetilico del ácido metansulfónico en 5 mL de dimetilformamida se le añadieron 50,3 mg de metóxido de sodio. La mezcla resultante se calentó en un tubo sellado hasta 90°C bajo irradiación de microondas durante 5 minutos y se concentró a presión reducida. El residuo se absorbió en acetato de etilo, se lavó con agua y se concentró a presión reducida. El producto bruto se purificó por cromatografía en columna sobre gel de sílice (gradiente de acetona en diclorometano) para producir 55 mg de 3-{2-metoxi-4-[4-metilsulfanilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona.

C22H18F3N3O4S2 (509,53), MS(ESI): 510 ($M+H^+$).

Ejemplo 90

3-{4-[4-Metansulfinilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-1,2,4-oxadiazol-5-ona



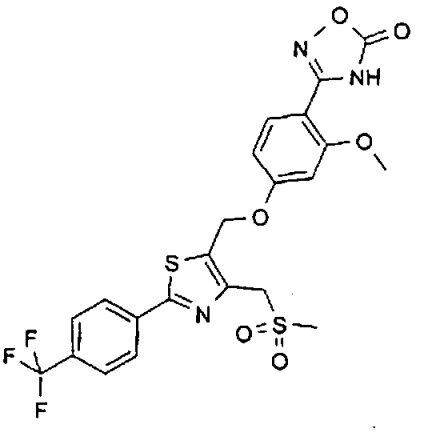
A una disolución de 32 mg de 3-{2-metoxi-4-[4-metilsulfanilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona en 4 mL de dimetilformamida se le añadieron 15 mg de ácido metacloroperbenzoico. La mezcla resultante se agitó durante 45 min a temperatura ambiente, luego se vertió en agua y se extrajo con diclorometano. Los extractos orgánicos se lavaron con una disolución saturada acuosa de bicarbonato sódico y se concentraron a presión reducida. El producto bruto se purificó por cromatografía en columna sobre gel de sílice (gradiente de metanol en diclorometano) para producir 25 mg de 3-{4-[4-metansulfinilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-1,2,4-oxadiazol-5-ona

como un sólido blanco que se purificó adicionalmente por trituración con éter diisopropílico.

C22H18F3N3O5S2 (525,53), MS(ESI): 526 ($M+H^+$).

Ejemplo 91

3-{4-[4-Metansulfonilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-1,2,4-oxadiazol-5-ona



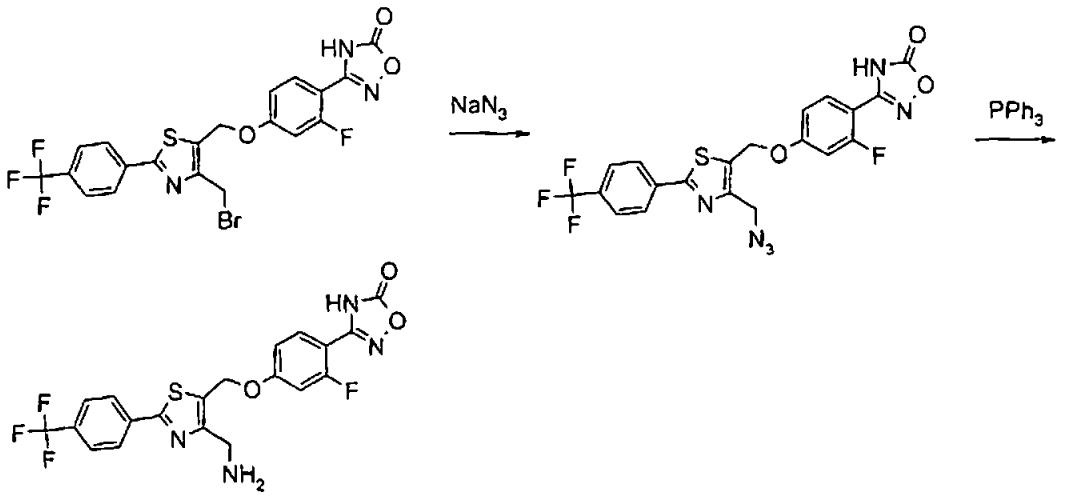
A una suspensión de 35 mg de 3-{2-metoxi-4-[4-metilsulfanilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona en 4 mL de acetonitrilo se le añadieron 1 mL de agua y 84 mg de Oxone®. La mezcla resultante se agitó durante toda la noche a temperatura ambiente, luego se vertió en agua y se extrajo con diclorometano. Los extractos orgánicos se lavaron con una disolución saturada acuosa de bicarbonato sódico y se concentraron a presión reducida. El producto bruto se trituró con diclorometano/metanol/tetrahidrofurano/acetona para proveer 26 mg de 3-{4-[4-metansulfonilmetil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-1,2,4-oxadiazol-5-ona como un sólido blanco.

C22H18F3N3O6S2 (541,53), MS(ESI): 542 ($M+H^+$).

Los siguientes ejemplos se prepararon de acuerdo con el procedimiento F:

Ejemplo 92

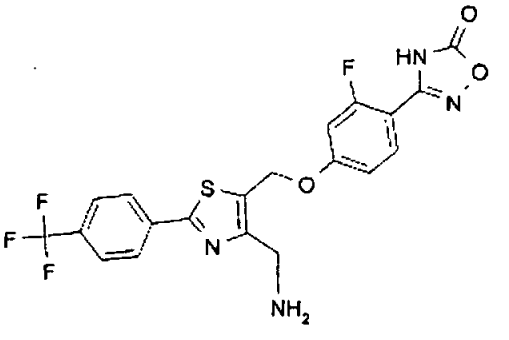
3-{4-[4-Aminometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-fluoro-fenil}-4H-1,2,4-oxadiazol-5-ona



3-{4-[4-Azidometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-fluoro-fenil}-4H-1,2,4-oxadiazol-5-ona

A una disolución de 126 mg de 3-{4-[4-bromometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-fluoro-fenil}-4H-[1,2,4]oxadiazol-5-ona en 1,3 mL de dimetilformamida se le añadieron 43,5 mg de azida de sodio. La disolución resultante se agitó durante 5h y luego se concentró a presión reducida para producir 118 mg de 3-{4-[4-azidometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-fluoro-fenil}-4H-1,2,4-oxadiazol-5-ona que se utilizó en la etapa siguiente sin purificación adicional.

3-{4-[4-Aminometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-fluoro-fenil}-4H-1,2,4-oxadiazol-5-ona



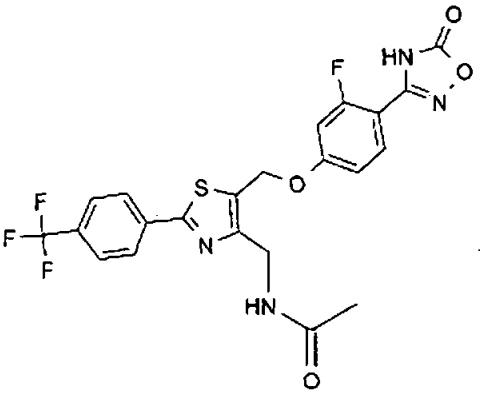
A una mezcla de 118 mg de 3-{4-[4-azidometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-fluoro-fenil}-4H-1,2,4-oxadiazol-5-ona en 0,25 mL de dimetilformamida y 0,022 mL de agua se le añadieron 31 mg de trifenilfosfina. La mezcla resultante se agitó a temperatura ambiente durante 20 h y luego se concentró a presión reducida. El producto bruto se purificó por cromatografía

en columna sobre gel de sílice (gradiente de diclorometano 100 a diclorometano 90/ metanol 10/agua 1/ácido acético 1) seguida de cromatografía en una columna SCX Waters con gradiente CH2Cl2/MeOH 30/70 a 7N NH3 en MeOH para producir 5,5 mg de 3-{4-[4-aminometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-fluoro-fenil}-4H-1,2,4-oxadiazol-5-ona.

C20H14F4N4O3S (466,42), MS(ESI): 467 ($M+H^+$).

Ejemplo 93

N-[5-[3-Fluoro-4-(5-oxo-4,5-dihidro-1,2,4-oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-ilmetil]-acetamida



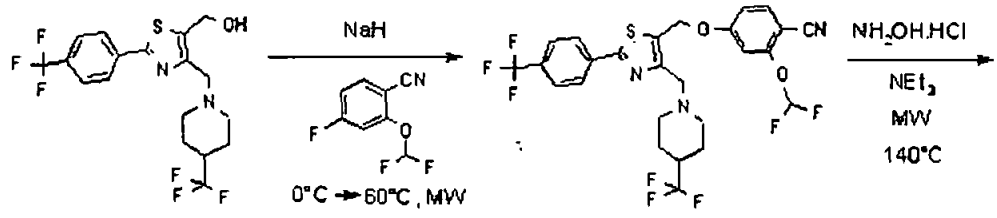
A una suspensión de 53,3 mg de 3-{4-[4-aminometil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-fluoro-fenil}-4H-1,2,4-oxadiazol-5-ona en 1 mL de diclorometano se le añadieron 27 mg de piridina y 19 mg de anhídrido acético. La mezcla resultante se agitó durante 1,5h a temperatura ambiente y luego se añadió una gota de piridina y anhídrido acético. Después de agitar durante 25 minutos a temperatura ambiente, se vertió en agua y se extrajo con diclorometano. Los extractos orgánicos se secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida. El producto bruto se purificó por cromatografía en columna sobre gel de sílice (gradiente de diclorometano 100 a diclorometano 90/ metanol 10/agua 1/ácido acético 1) para producir 6,2 mg de N-[5-[3-fluoro-4-(5-oxo-4,5-dihidro-1,2,4-oxadiazol-3-il)-fenoximetil]-2-(4-trifluorometil-fenil)-tiazol-4-ilmetil]-acetamida.

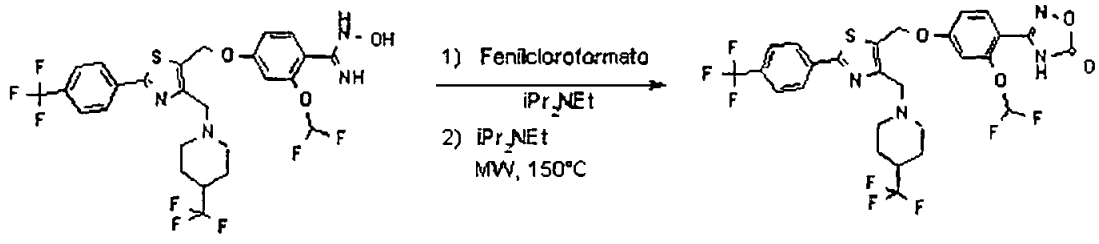
C22H16F4N4O4S (508,45), MS(ESI): 509 ($M+H^+$).

Los siguientes ejemplos se prepararon de acuerdo con B:

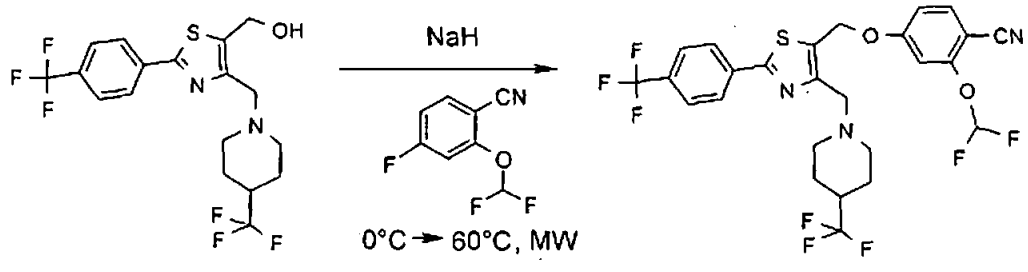
Ejemplo 94

3-{2-Difluorometoxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona





2-Difluorometoxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-benzonitrilo

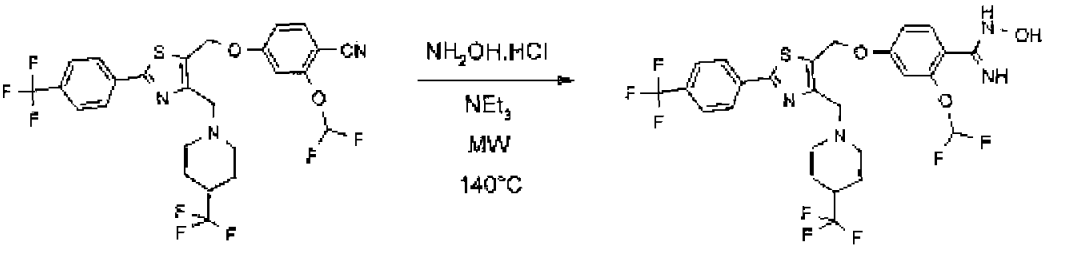


A una disolución de 3 g de [2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-il]-metanol en 12 mL de dimetilformamida a 5°C se le añadieron 319 mg de una suspensión al 55% de hidruro de sodio en aceite mineral. La mezcla resultante se agitó durante 30 minutos a 5°C. Se añadieron lentamente 4,7 mL de la disolución resultante a una disolución de 319 mg de 2-difluorometoxi-4-fluoro-benzonitrilo en 1,2 mL de dimetilformamida a 5°C. La mezcla resultante se agitó a 5°C dejando que la temperatura se calentara hasta temperatura ambiente. Luego se calentó en un tubo sellado hasta 60°C bajo irradiación de microondas durante 15 minutos. Después de dejar enfriar hasta temperatura ambiente, la mezcla se vertió en agua y se extrajo con diclorometano. Los extractos orgánicos se secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida. El producto bruto se purificó por cromatografía en columna sobre gel de sílice (gradiente de heptano 100 a heptano 50/ acetato de etilo 50) para producir 0,83 g de 2-difluorometoxi-4-[2-

(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-benzonitrilo.

C26H22F8N3O2S (592,54), MS(ESI): ($M+H^+$) 593,1 ($M+H^+$).

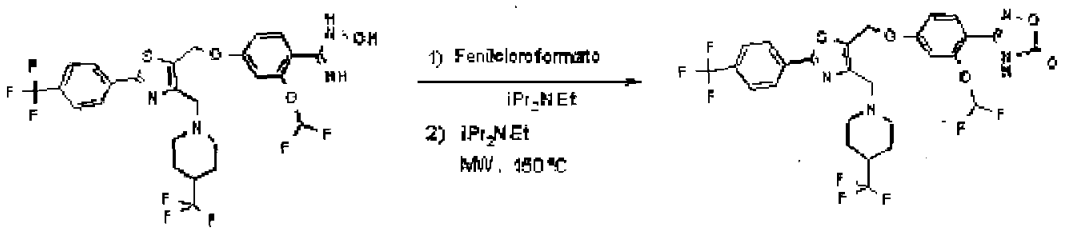
2-Difluorometoxi-N-hidroxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-benzamidina



A una disolución de 830 mg de 2-difluorometoxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-benzonitrilo en 13 mL de metanol se le añadieron 5,7 mL de trietilamina seguidos de 430 mg de hidrocloruro de hidroxilamina. La mezcla resultante se calentó en un tubo sellado hasta 140°C bajo irradiación de microondas durante 30 minutos. Después de dejar enfriar hasta temperatura ambiente, la mezcla se vertió en agua y se extrajo con diclorometano. Los extractos orgánicos se secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida. El producto bruto se purificó por cromatografía en columna sobre gel de sílice (gradiente de heptano 100 a heptano 60/ acetato de etilo 40) para producir 480 mg de 2-difluorometoxi-N-hidroxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-benzamidina.

C26H24F8N4O3S (624,56), MS(ESI): 625,0 ($M+H^+$).

3-{2-Difluorometoxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona



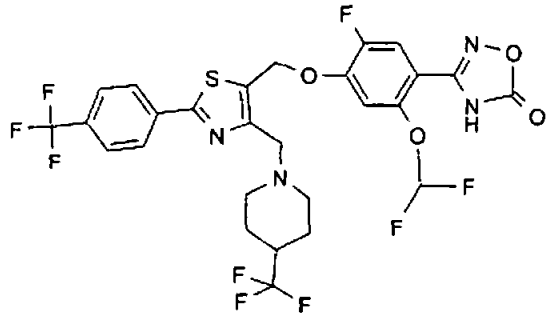
A una disolución de 475 mg de 2-difluorometoxi-N-hidroxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-benzamidina en 7,8 mL de tetrahidrofurano a 0°C se le añadió 1,8 mL de

diisopropiletilamina seguida de 0,1 mL de cloroformato de fenilo. La mezcla resultante se agitó durante 5 minutos a 0°C, luego se vertió en agua y se extrajo con diclorometano. Los extractos orgánicos se secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida. El residuo se disolvió en 7,8 mL de tetrahidrofurano y 0,33 mL de diisopropiletilamina. La disolución resultante se calentó en un tubo sellado hasta 150°C bajo irradiación de microondas durante 15 minutos. Después de dejar enfriar hasta temperatura ambiente, la mezcla se vertió en agua y se extrajo con diclorometano. Los extractos orgánicos se secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida. El producto bruto se purificó por cromatografía en columna sobre gel de sílice (éter diisoproprílico 100 seguido de un gradiente de diclorometano 100 a diclorometano 90/ metanol 10) seguida de otra cromatografía en columna sobre gel de sílice (gradiente de diclorometano 100 a diclorometano 90/ tetrahidrofurano 10) para producir 70 mg de 3-{2-difluorometoxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona.

C27H22F8N4O4S (650,55), MS(ESI): 651,2 ($M+H^+$).

Ejemplo 95

3-{2-Difluorometoxi-5-fluoro-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona



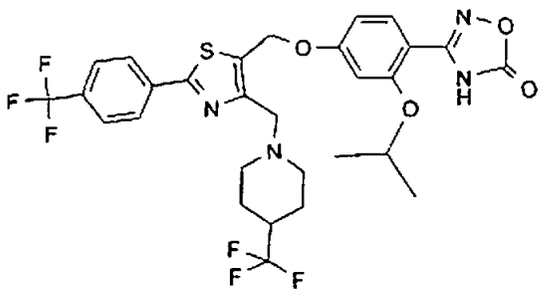
De acuerdo con el método descrito para 3-{2-difluorometoxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona, se obtuvo 3-{2-difluorometoxi-5-fluoro-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona a partir de [2-(4-trifluorometil-fenil)-4-(4-trifluorometil-

piperidin-1-ilmetil)-tiazol-5-il]-metanol y 2-difluorometoxi-4,5-difluoro-benzonitrilo.

C27H21F9N4O4S (668,54), MS(ESI): 669,9 ($M+H^+$).

Ejemplo 96

3-{2-Isopropoxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona

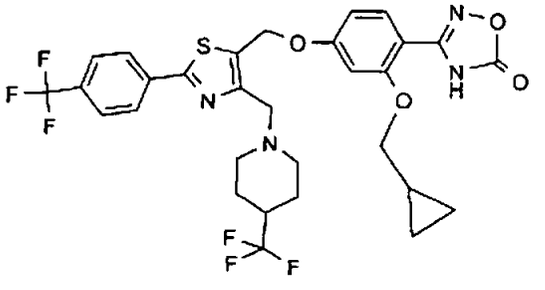


De acuerdo con el método descrito para 3-{2-difluorometoxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona, se obtuvo 3-{2-isopropoxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona a partir de [2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-il]-metanol y 4-fluoro-2-isopropoxi-benzonitrilo.

C29H28F6N4O4S (642,63), MS(ESI): 643,0 ($M+H^+$).

Ejemplo 97

3-{2-Ciclopropilmetoxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona



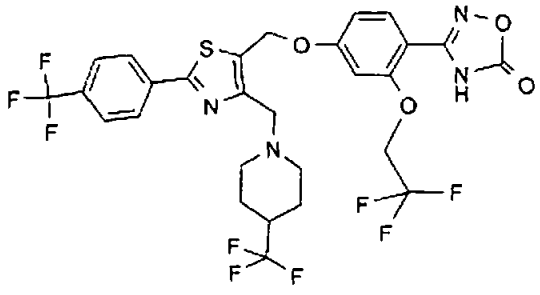
De acuerdo con el método descrito para 3-{2-difluorometoxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona, se obtuvo 3-{2-ciclopropilmetoxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-

oxadiazol-5-ona a partir de [2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-il]-metanol y 2-ciclopropilmetoxi-4-fluoro-benzonitrilo.

C30H28F6N4O4S (654,64), MS(ESI): 656,1 ($M+H^+$).

Ejemplo 98

3-{2-(2,2,2-Trifluoro-etoxi)-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona



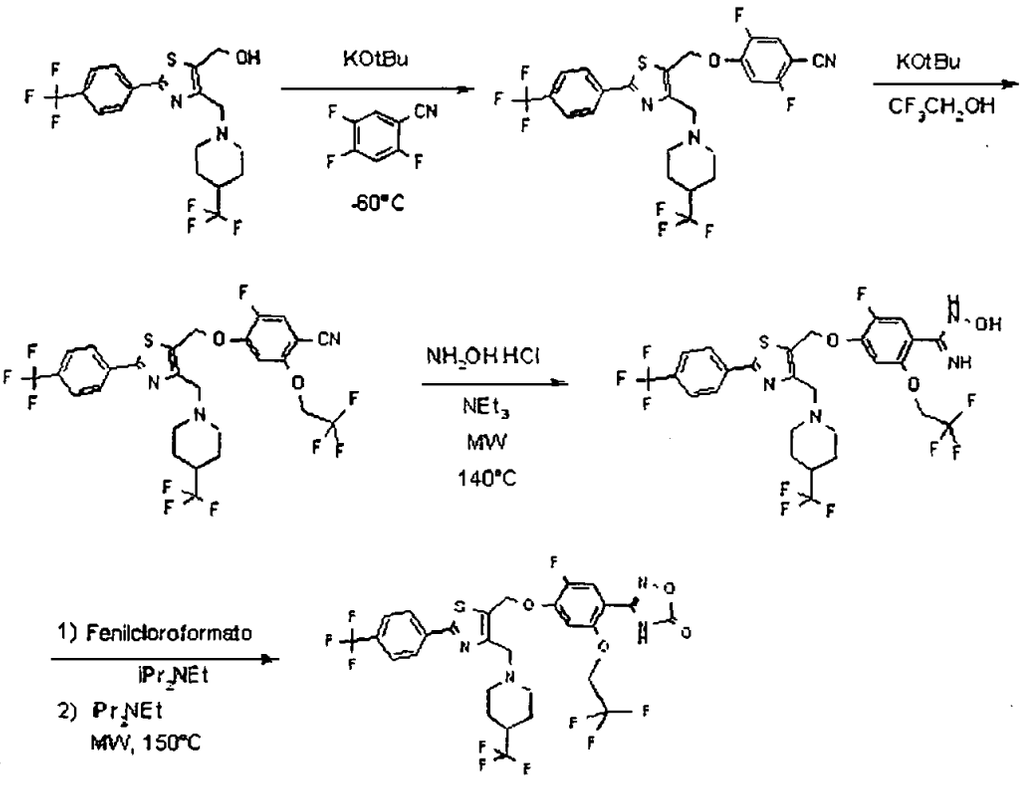
De acuerdo con el método descrito para 3-{2-difluorometoxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona, se obtuvo 3-{2-(2,2,2-trifluoro-etoxi)-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona a partir de [2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-il]-metanol y 4-fluoro-2-(2,2,2-trifluoro-etoxi)-benzonitrilo.

C28H23F9N4O4S (682,57), MS(ESI): 683,1 ($M+H^+$).

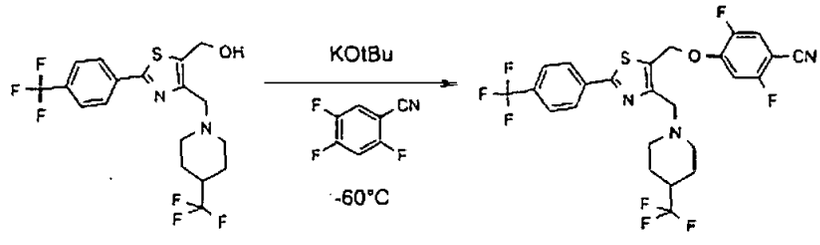
El siguiente ejemplo se obtuvo de acuerdo con el procedimiento C:

Ejemplo 99

3-{5-Fluoro-2-(2,2,2-trifluoro-etoxi)-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona



2,5-Difluoro-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-benzonitrilo

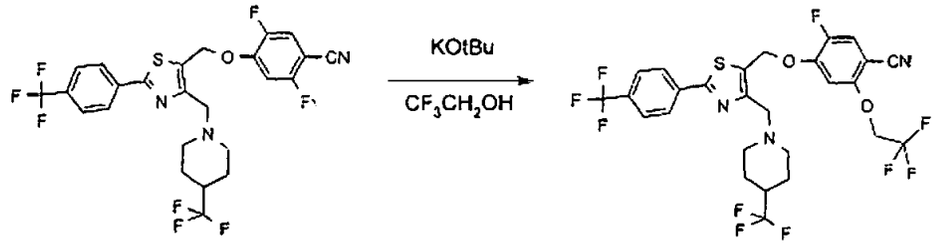


A una disolución de 800 mg de [2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-il]-metanol en 4 mL de tetrahidrofurano a 5°C se le añadieron lentamente 2,13 mL de una disolución molar de terc-butóxido de potasio en terc-butanol. Después de agitar a 5°C durante 30 minutos, la disolución resultante se añadió lentamente a una disolución de 296 mg de 2,4,5-trifluoro-benzonitrilo en 1 mL de tetrahidrofurano a -60°C. La mezcla resultante se agitó durante 1h a -60°C, luego se agitó durante la noche, dejando calentar hasta temperatura ambiente. Se vertió luego en agua y se extrajo con diclorometano. Los extractos orgánicos se secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida. El producto bruto se recristalizó a partir de metanol y se lavó con éter diisopropílico para producir

890 mg de 2,5-difluoro-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-benzonitrilo.

C25H19F8N3OS (561,50), MS(ESI): 563,1 ($M+H^+$).

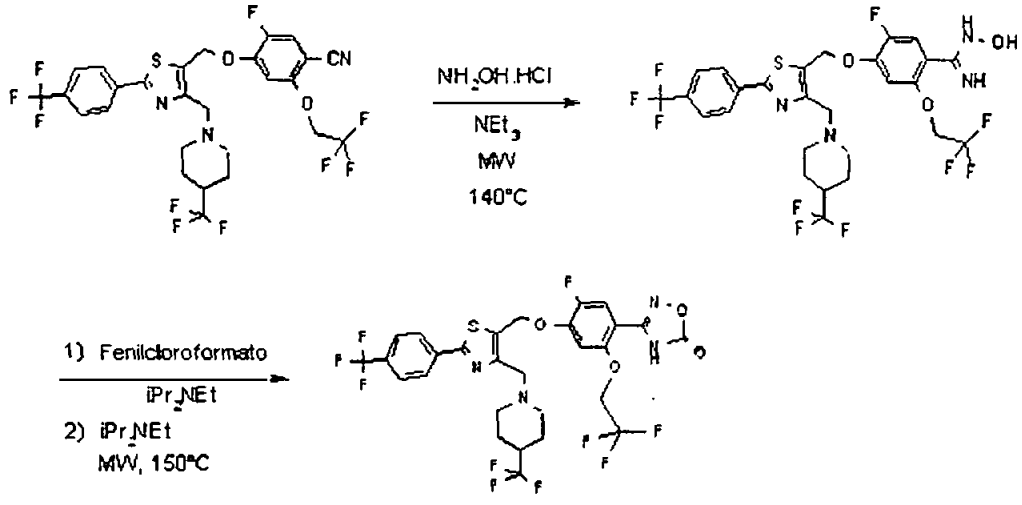
5-Fluoro-2-(2,2,2-trifluoro-etoxi)-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-benzonitrilo



A una disolución de 190 mg de trifluoroetanol en 1,16 mL de tetrahidrofurano a 5°C se le añadieron lentamente 2,2 mL de una disolución molar de terc-butóxido de potasio en terc-butanol. Después de agitar a 5°C durante 30 minutos, la disolución resultante se añadió lentamente a una disolución de 890 mg de 2,5-difluoro-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-benzonitrilo en 3,1 mL de tetrahidrofurano a -60°C. La mezcla resultante se agitó durante toda la noche dejando que la temperatura subiera hasta temperatura ambiente. Se vertió luego en agua y se extrajo con diclorometano. Los extractos orgánicos se secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida. El producto bruto se trituró con éter diisopropílico y se filtró para producir 410 mg de 5-fluoro-2-(2,2,2-trifluoro-etoxi)-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-benzonitrilo como un sólido blanco.

C27H21F10N3O2S (641,54), MS(ESI): 642,1 ($M+H^+$).

3-{5-Fluoro-2-(2,2,2-trifluoro-etoxi)-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona



De acuerdo con el método descrito para 3-{2-difluorometoxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona, se obtuvo 3-{5-fluoro-2-(2,2,2-trifluoro-etoxi)-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona a partir de 5-fluoro-2-(2,2,2-trifluoro-etoxi)-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-benzonitrilo.

C28H22F10N4O4S (700,56), MS(ESI): 701,9 ($M+H^+$).

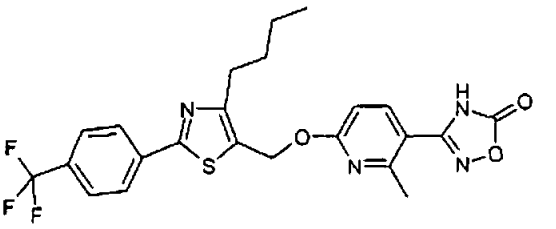
3-{5-fluoro-2-(2,2,2-trifluoro-etoxi)-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona también puede prepararse de acuerdo con el método descrito para 3-{2-difluorometoxi-4-[2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona, comenzando por [2-(4-trifluorometil-fenil)-4-(4-trifluorometil-piperidin-1-ilmetil)-tiazol-5-il]-metanol y 4,5-difluoro-2-(2,2,2-trifluoro-etoxi)-benzonitrilo.[9]

El siguiente ejemplo se preparó de acuerdo con el procedimiento B:

Ejemplo 100

3-{6-[4-Butil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metil-piridin-3-il}-4H-[1,2,4]oxadiazol-5-ona

[9] WO2005/111003



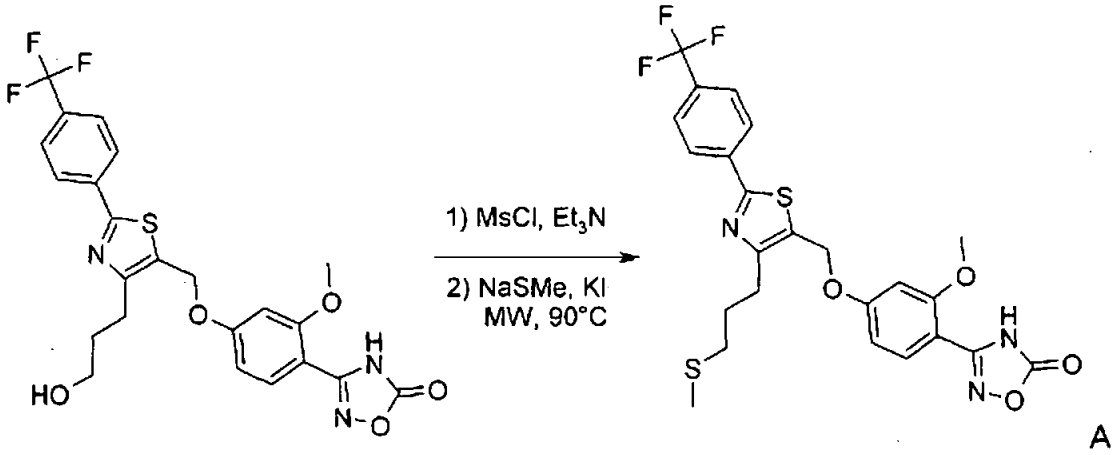
De acuerdo con el método descrito en el Ejemplo 1, se obtuvo 3-{6-[4-butil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metil-piridin-3-il}-4H-[1,2,4]oxadiazol-5-ona a partir de [4-butil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol[10] y 6-Fluoro-2-metil-nicotinonitrilo existente en el mercado.

C23H21F3N4O3S (490,51), MS(ESI): 491 ($M+H^+$).

Los siguientes ejemplos se prepararon de acuerdo con el procedimiento D:

Ejemplo 101

3-{2-Metoxi-4-[4-(3-metilsulfanil-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona



A

A una disolución de 100 mg de 3-{4-[4-(3-hidroxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona en 1 mL de dimetilformamida a 0°C se le añadieron 0,077 mL de trietilamina y 0,015 mL de cloruro de metansulfonilo. La mezcla resultante se agitó a 0°C durante 30 minutos y luego se concentró a presión reducida. El producto se disolvió en 3 mL de dimetilformamida. A la disolución resultante se le añadieron 5,5 mg de metantiolato de sodio y 13 mg de yoduro de potasio. La mezcla de reacción se calentó durante 10 minutos hasta 90°C bajo irradiación de

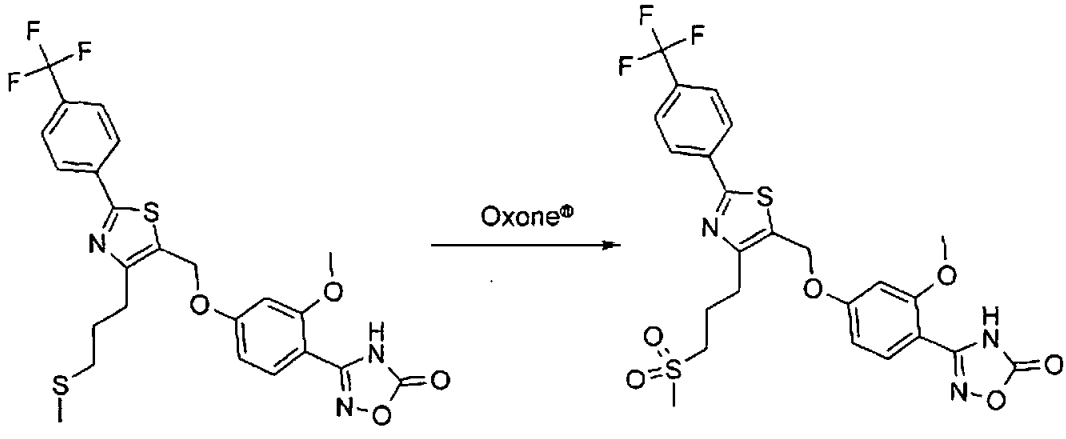
[10] EP1586573

microondas en un tubo sellado. Luego se concentró a presión reducida, se absorbió en diclorometano, se lavó con agua, se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida para producir 20 mg de 3-{2-metoxi-4-[4-(3-metilsulfanil-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona.

C24H22F3N3O4S2 (537,58), EM (ESI): 538 ($M+H^+$).

Ejemplo 102

3-{4-[4-(3-Metansulfonil-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-1,2,4-oxadiazol-5-ona

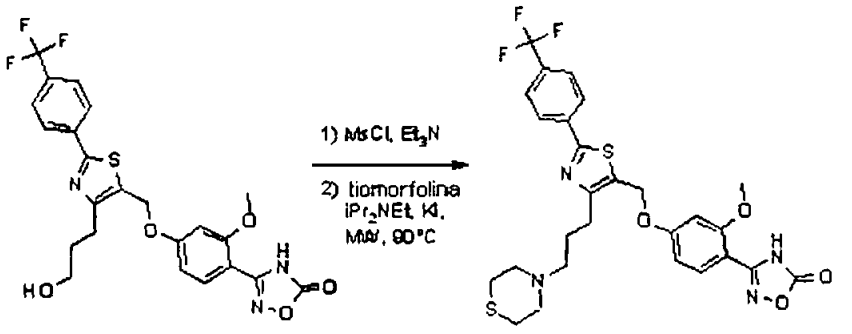


A una suspensión de 60 mg de metoxi-4-[4-(3-metilsulfanil-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona en 2 mL de acetonitrilo y 0,5 mL de agua se le añadieron 230 mg de Oxone® (peroximonosulfato de potasio). La mezcla resultante se agitó a temperatura ambiente durante 3 h, luego se vertió en acetato de etilo/agua. La capa orgánica se separó, se lavó con disolución saturada acuosa de Na2S2O3, se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se trituró con 1 mL de acetonitrilo y se filtró para producir 16 mg de 3-{4-[4-(3-metansulfonil-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-1,2,4-oxadiazol-5-ona como un sólido beis.

C24H22F3N3O6S2 (569,58), MS(ESI): 570 ($M+H^+$).

Ejemplo 103

3-{2-Metoxi-4-[4-(3-tiomorfolin-4-il-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona

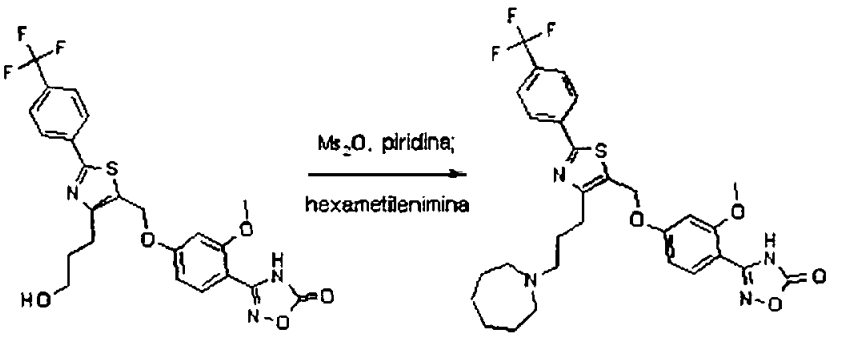


A una disolución de 50 mg de 3-{4-[4-(3-hidroxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona en 1,5 mL de dimetilformamida a 0°C se le añadieron 0,015 mL de trietilamina y 0,008 mL de cloruro de metansulfonilo. La mezcla resultante se agitó a 0°C durante 30 minutos y luego se concentró a presión reducida, se absorbió en diclorometano, se lavó con agua, se secó sobre sulfato magnésico, se filtró y se concentró a presión reducida. El producto bruto se disolvió en 4 mL de dimetilformamida. A la disolución resultante se le añadieron 0,012 mL de tiomorfolina, 0,017 mL de diisopropiletil amina y 29 mg de yoduro de potasio. La mezcla de reacción se calentó durante 10 minutos hasta 90°C bajo irradiación de microondas en un tubo sellado. Luego se concentró a presión reducida, se absorbió en diclorometano, se lavó con agua, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (gradiente de metanol en diclorometano), se trituró en acetonitrilo y se filtró para producir 5,3 mg de 3-{2-metoxi-4-[4-(3-tiomorfolin-4-il-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona.

C27H27F3N4O4S2 (592,66), MS(ESI): 593 ($M+H^+$).

Ejemplo 104

3-{2-Metoxi-4-[4-(3-perhidro-azepin-1-il-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona

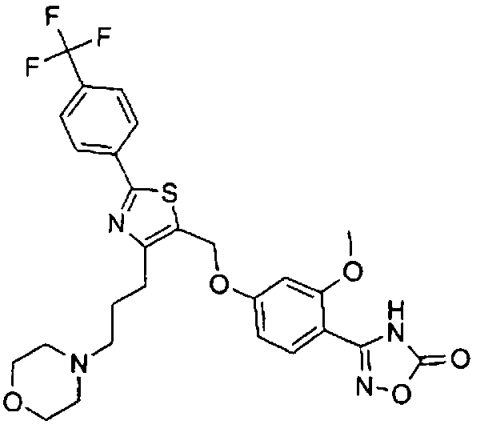


A una mezcla de 150 mg de 3-{4-[4-(3-hidroxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona en 6 mL de acetonitrilo se le añadieron 0,100 mL de piridina y 0,200 mL de anhídrido metansulfónico. La mezcla resultante se agitó a temperatura ambiente durante 5 h, luego se añadieron 0,250 ml de hexametilenimina. La mezcla resultante se agitó a temperatura ambiente durante toda la noche y luego se concentró a presión reducida. El residuo se purificó por HPLC preparativa en fase normal acoplada a MS (gradiente de metanol 5 en diclorometano que contenía NH4OH), luego se precipitó a partir de diclorometano/pentano para producir 26 mg de 3-{2-metoxi-4-[4-(3-perhidro-azepin-1-il-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona como un sólido blanco.

C29H31F3N4O4S (588,65), MS(ESI): 589 ($M+H^+$).

Ejemplo 105

<u>3-{2-Metoxi-4-[4-(3-morfolin-4-il-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona</u>



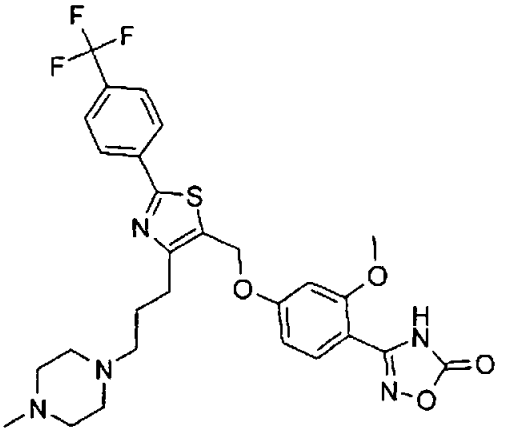
De acuerdo con el método descrito para 3-{2-metoxi-4-[4-(3-perhidro-azepin-1-il-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona, se obtuvo 3-{2-metoxi-4-[4-(3-morfolin-4-il-propil)-2-(4-

trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona a partir de 3-{4-[4-(3-hidroxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona y morfolina.

C27H27F3N4O5S (576,60), MS(ESI): 577 ($M+H^+$).

Ejemplo 106

3-{2-Metoxi-4-[4-[3-(4-metil-piperazin-1-il)-propil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona

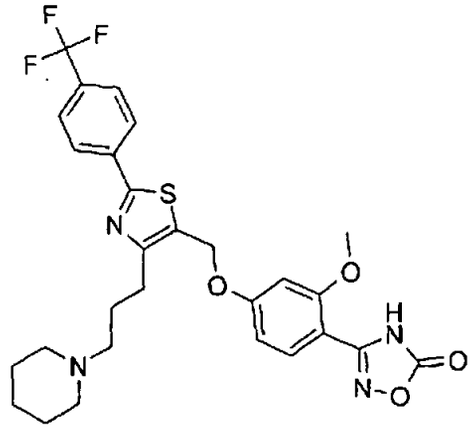


De acuerdo con el método descrito 3-{2-metoxi-4-[4-(3-perhidro-azepin-1-il-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona, se obtuvo 3-{2-metoxi-4-[4-[3-(4-metil-piperazin-1-il)-propil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona a partir de 3-{4-[4-(3-hidroxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona y 1-metilpiperazina.

C28H30F3N5O4S (589,64), MS(ESI): 590 ($M+H^+$).

Ejemplo 107

3-{2-Metoxi-4-[4-(3-piperidin-1-il-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona

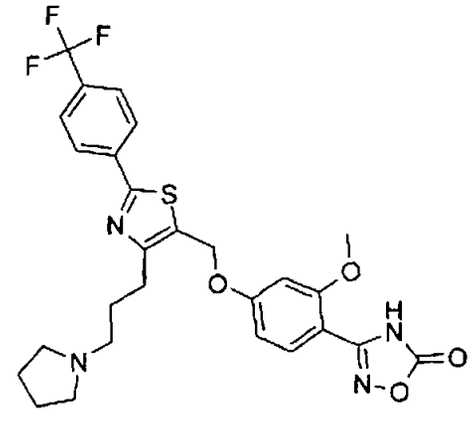


De acuerdo con el método descrito 3-{2-metoxi-4-[4-(3-perhidro-azepin-1-il-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona, se obtuvo 3-{2-metoxi-4-[4-(3-piperidin-1-il-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona a partir de 3-{4-[4-(3-hidroxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona y piperidina.

$C_{28}H_{29}F_3N_4O_4S$ (574,63), MS(ESI): 575 ($M+H^+$).

Ejemplo 108

3-{2-Metoxi-4-[4-(3-pirrolidin-1-il-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona



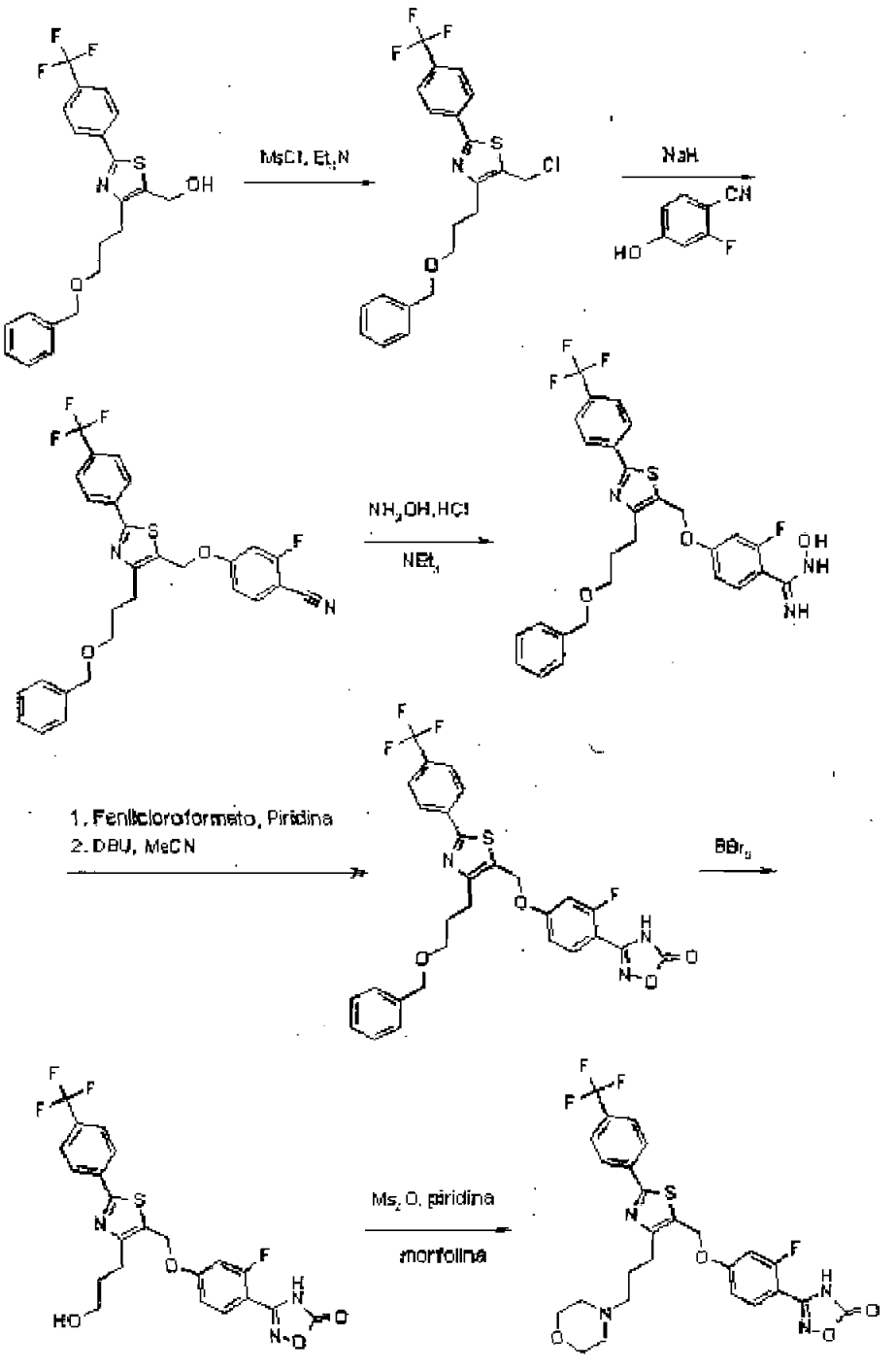
De acuerdo con el método descrito 3-{2-metoxi-4-[4-(3-perhidro-azepin-1-il-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona, se obtuvo 3-{2-metoxi-4-[4-(3-pirrolidin-1-il-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona a partir de 3-{4-[4-(3-hidroxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona y pirrolidina.

$C_{27}H_{27}F_3N_4O_4S$ (560,60), MS(ESI): 561 ($M+H^+$).

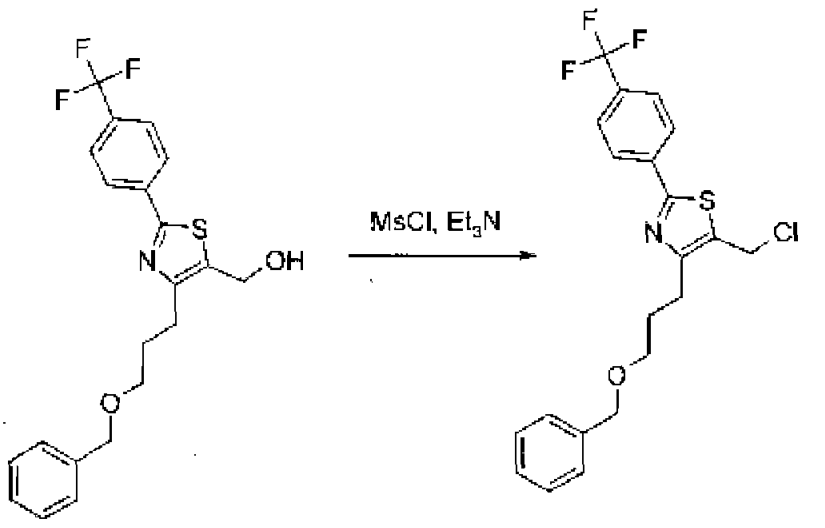
Los siguientes ejemplos se prepararon de acuerdo con el procedimiento D, en el que las dos primeras etapas de reacción se realizaron de acuerdo con el procedimiento B:

Ejemplo 109

3-{2-Fluoro-4-[4-(3-morfolin-4-il-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona



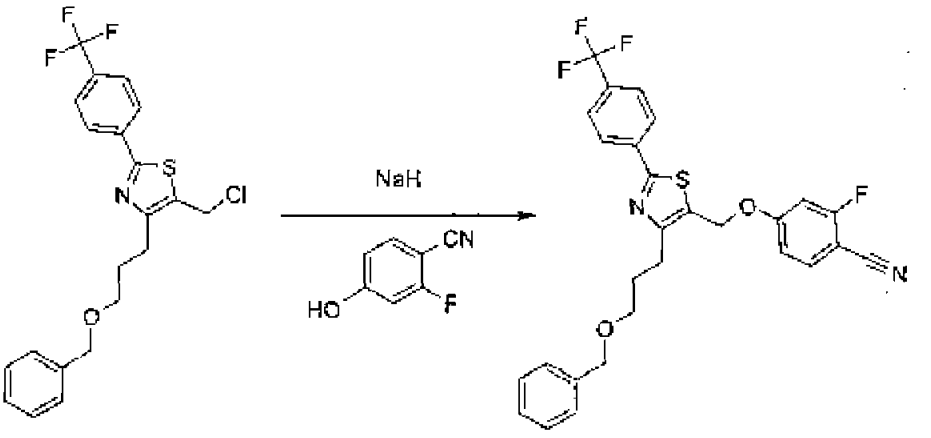
4-(3-Benciloxi-propil)-5-clorometil-2-(4-trifluorometil-fenil)-tiazol



A una disolución agitada de 1,5 g de {4-[3-(benciloxi)propil]-2-[4-(trifluorometil)fenil]-1,3-tiazol-5-il}-metanol en 15 mL de diclorometano se le añadieron 0,484g de cloruro de metansulfonilo y 1,03 mL de trietilamina. La disolución se agitó durante 2 h a temperatura ambiente. La mezcla se diluyó con diclorometano y se vertió en agua. La capa acuosa se separó y se extrajo tres veces con diclorometano. Los orgánicos combinados se secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida para producir 1,65 g de producto bruto como un aceite amarillo. La purificación por cromatografía en columna sobre gel de sílice (heptano 90/ acetato de etilo 10) produjo 0,840 g de 4-(3-benciloxi-propil)-5-clorometil-2-(4-trifluorometil-fenil)-tiazol.

C21H19ClF3NOS (425,90), MS(ESI): 426 ($M+H^+$).

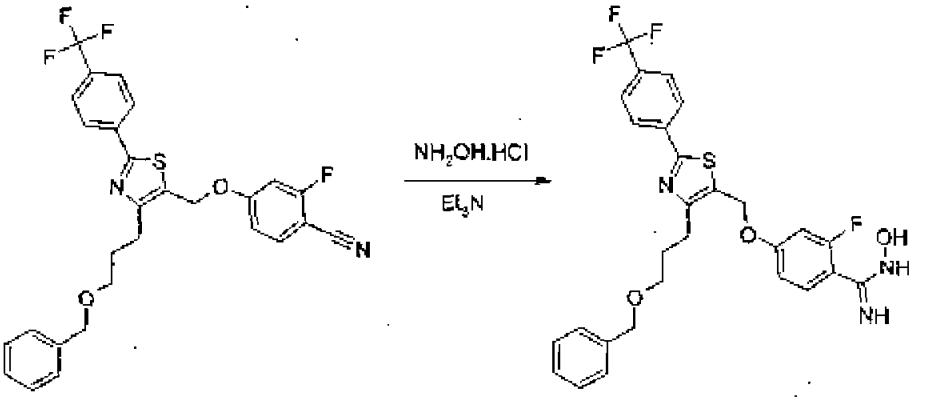
4-[4-(3-Benciloxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-fluoro-benzonitrilo



A una disolución agitada de 0,82 g de 4-(3-benciloxi-propil)-5-clorometil-2-(4-trifluorometil-fenil)-tiazol en 12 mL de DMF a 0°C se le añadió 0,1 g de NaH 55%. La mezcla de reacción se agitó a 0°C durante 10 min, luego se añadieron 2-0,264 g de fluoro-4-hidroxibenzonitrilo a esta temperatura. La mezcla de reacción se agitó a 0°C durante 1h30, se dejó calentar hasta temperatura ambiente y luego se agitó durante 4h a temperatura ambiente. El disolvente se eliminó y el residuo resultante se absorbió en diclorometano, luego se añadió agua. Después de la decantación y separación, la capa acuosa se extrajo tres veces con diclorometano. Las capas orgánicas combinadas se lavaron con agua, se secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida para producir 0,91 g de producto bruto como un aceite amarillo. La purificación por cromatografía en columna sobre gel de sílice (heptano 1/ éter 1) produjo 840 mg de 4-[4-(3-benciloxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-fluoro-benzonitrilo como una espuma blanca.

C28H22F4N2O2S (526,56), MS(ESI): 527 ($M+H^+$).

<u>4-[4-(3-Benciloxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-fluoro-N-hidroxi-benzamidina</u>

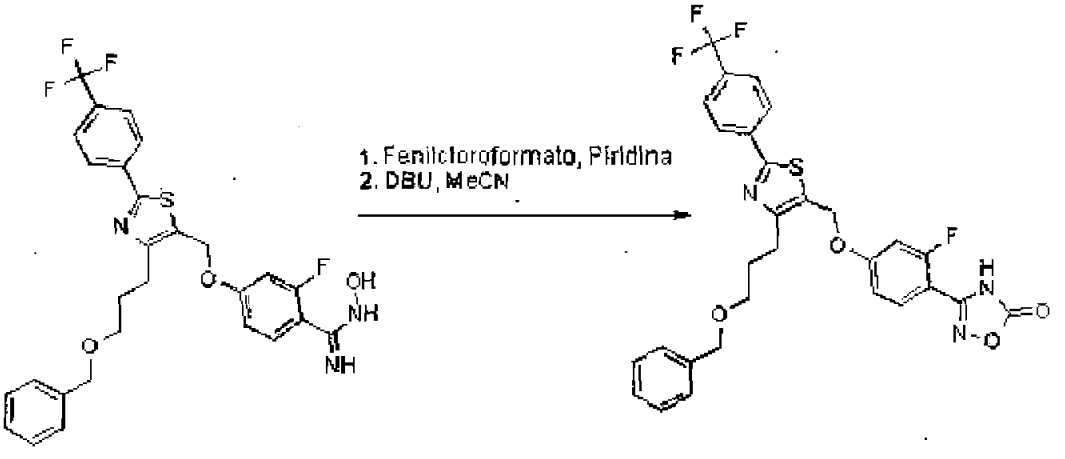


A una disolución agitada de 0,84 g de 4-[4-(3-benciloxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-fluoro-benzonitrilo en 5 mL de tetrahidrofurano y 5,6 mL de metanol se le añadió 1,14 g de hidrocloruro de hidroxilamina seguido de 1,8 mL de trietilamina. La mezcla de reacción se agitó a temperatura ambiente durante 2 horas y luego a temperatura ambiente. La mezcla de reacción se sometió a reflujo durante 2h adicionales y luego se

concentró a presión reducida. El residuo se absorbió en diclorometano, luego se añadió agua. La capa acuosa se separó y se extrajo tres veces con diclorometano. Las capas orgánicas combinadas se lavaron con agua, se secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida para producir 0,840 g de producto bruto como una goma amarilla. La precipitación en heptano produjo 620 mg de 4-[4-(3-benciloxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-fluoro-N-hidroxi-benzamidina como un polvo beis.

C28H25F4N3O3S (559,59), MS(ESI): 560 ($M+H^+$).

3-{4-[4-(3-Benciloxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-fluoro-fenil}-4H-[1,2,4]oxadiazol-5-ona

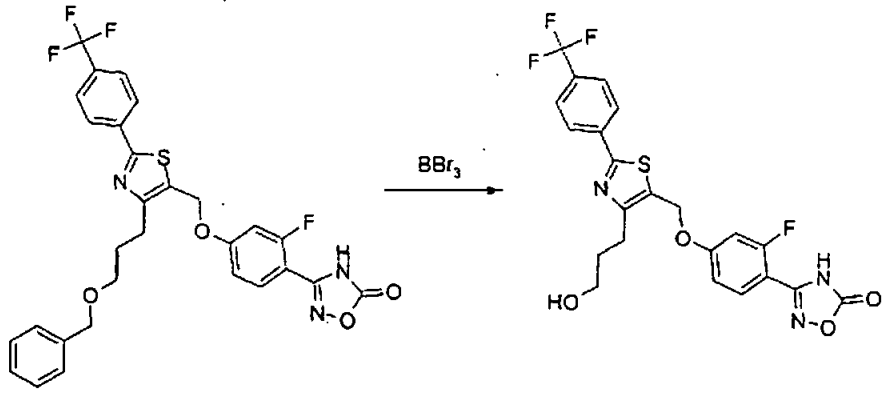


A una suspensión agitada de 0,62 g de 4-[4-(3-benciloxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-fluoro-N-hidroxi-benzamidina en 17 mL de diclorometano a 0°C, bajo argón, se le añadieron 0,23mL de piridina y 154 µL de cloroformato de fenilo. La mezcla de reacción se agitó durante 10 min a 0°C seguida de 1h a temperatura ambiente. La mezcla de reacción se concentró a presión reducida y el residuo resultante se absorbió en 10 mL de acetonitrilo bajo argón y se añadió 0,165 mL de 1,4-diazabiciclo[5.4.0]undec-7-eno (DBU). La mezcla de reacción se agitó a temperatura ambiente durante toda la noche, luego se calentó hasta 40°C durante 2h. La mezcla de reacción se concentró a presión reducida. El residuo se absorbió en diclorometano y se añadió una disolución acuosa 1M de NaH_2PO_4. La capa acuosa se separó y se extrajo tres veces con diclorometano. Las capas orgánicas combinadas se lavaron con agua, se secaron sobre sulfato magnésico, se filtraron y se concentraron a

presión reducida para producir 770 g de producto bruto como un polvo amarillo. La purificación por cromatografía en columna sobre gel de sílice (heptano 1/ acetato de etilo 1) produjo 150 mg seguidos por lavado en columna con 100% MeOH que produjo 320 mg del compuesto del título. En total, se obtuvieron 470 mg de 3-{4-[4-(3-benciloxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-fluoro-fenil}-4H-[1,2,4]oxadiazol-5-ona como un polo blanco.

C29H23F4N3O4S (585,58), MS(ESI): 586 ($M+H^+$).

3-{2-Fluoro-4-[4-(3-hidroxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona

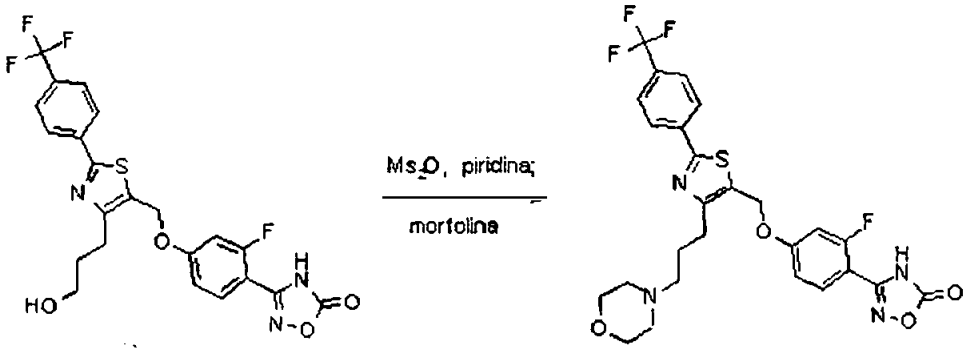


A una disolución agitada de 100 mg de 3-{4-[4-(3-benciloxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-fluoro-fenil}-4H-[1,2,4]oxadiazol-5-ona en 3 mL de diclorometano a –70°C se le añadió 0,34 mL de una disolución 1M de tribromuro de boro en diclorometano. Después de 1h a –60°C, el monitoreo TLC (diclorometano / acetona 8 / 2) demostró material de partida restante, de modo que se añadió 1 mL de una disolución 1M de tribromuro de boro en diclorometano. Después de 10 min, la mezcla de reacción se vertió en 30 mL de metanol y se neutralizó con 5 mL de disolución saturada acuosa de NaHCO3. La suspensión se filtró y el filtrado se concentró a presión reducida. El residuo se absorbió en diclorometano, luego se añadió agua. La capa acuosa se separó y se extrajo tres veces con diclorometano. Las capas orgánicas combinadas se secaron sobre sulfato magnésico, se filtraron y se concentraron a presión reducida para producir 60 g de producto bruto. La purificación por cromatografía en columna sobre gel de sílice (diclorometano 1/ acetona 1) produjo 13 mg de una primera partida del compuesto del título (pureza > 95%) y 50 mg de una segunda partida del compuesto del título

(pureza > 90%). La segunda partida se repurificó por cromatografía en columna sobre gel de sílice (diclorometano 90/metanol 10). Se obtuvo un total de 48 mg de 3-{2-fluoro-4-[4-(3-hidroxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-[1,2,4]oxadiazol-5-ona.

C22H17F4N3O4S (495,46), MS(ESI): 496 ($M+H^+$).

3-{2-Fluoro-4-[4-(3-morfolin-4-il-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona

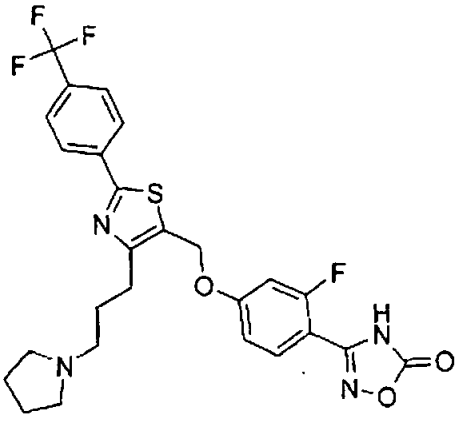


De acuerdo con el método descrito 3-{2-metoxi-4-[4-(3-perhidro-azepin-1-il-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona, se obtuvo 3-{2-fluoro-4-[4-(3-morfolin-4-il-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona a partir de 3-{2-fluoro-4-[4-(3-hidroxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona y morfolina.

C26H24F4N4O4S (564,56), MS(ESI): 565 ($M+H^+$).

Ejemplo 110

3-{2-Fluoro-4-[4-(3-pirrolidin-1-il-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona

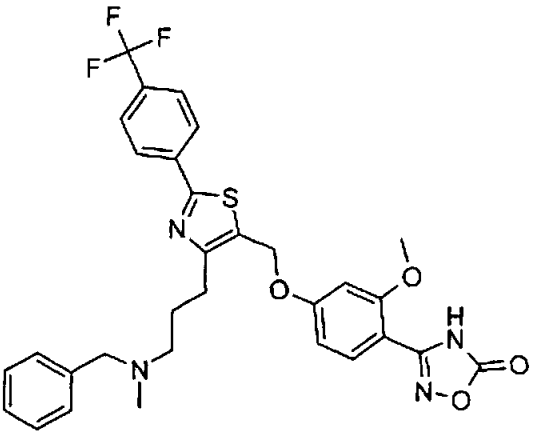


De acuerdo con el método descrito 3-{2-metoxi-4-[4-(3-perhidro-azepin-1-il-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona, se obtuvo 3-{2-fluoro-4-[4-(3-pirrolidin-1-il-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona a partir de 3-{2-fluoro-4-[4-(3-hidroxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona y pirrolidina.

C26H24F4N4O3S (548,56), MS(ESI): 549 ($M+H^+$).

Ejemplo 111

3-{4-[4-[3-(Bencil-metil-amino)-propil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona

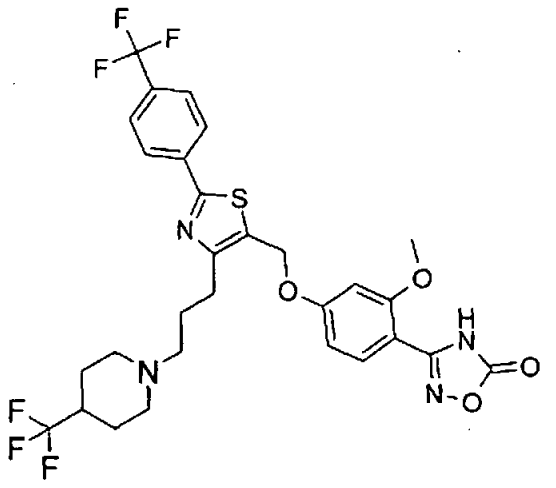


De acuerdo con el método descrito 3-{2-metoxi-4-[4-(3-perhidro-azepin-1-il-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona, se obtuvo 3-{4-[4-[3-(bencil-metil-amino)-propil]-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 3-{4-[4-(3-hidroxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona y bencil-metil-amina.

C31H29F3N4O4S (610,66), MS(ESI): 611 ($M+H^+$).

Ejemplo 112

3-(2-Metoxi-4-{2-(4-trifluorometil-fenil)-4-[3-(4-trifluorometil-piperidin-1-il)-propil]-tiazol-5-ilmetoxi}-fenil)-4H-[1,2,4]oxadiazol-5-ona

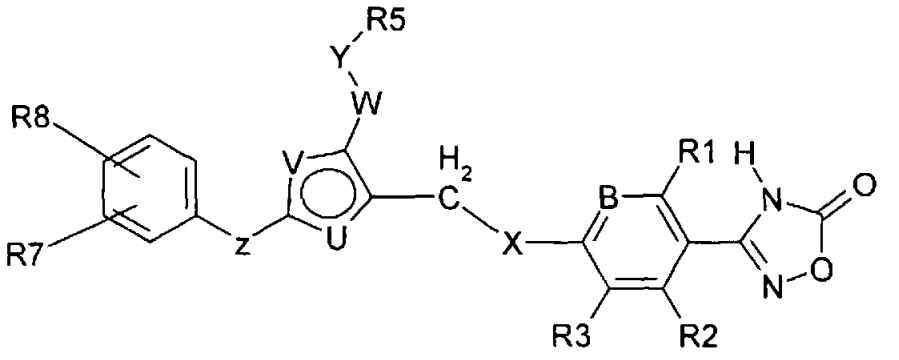


De acuerdo con el método descrito 3-{2-metoxi-4-[4-(3-perhidro-azepin-1-il-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-4H-1,2,4-oxadiazol-5-ona, se obtuvo 3-(2-metoxi-4-{2-(4-trifluorometil-fenil)-4-[3-(4-trifluorometil-piperidin-1-il)-propil]-tiazol-5-ilmetoxi}-fenil)-4H-[1,2,4]oxadiazol-5-ona a partir de 3-{4-[4-(3-hidroxi-propil)-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-metoxi-fenil}-4H-[1,2,4]oxadiazol-5-ona y 4-trifluorometil-piperidina.

C29H28F6N4O4S (642,63), MS(ESI): 643 ($M+H^+$).

REIVINDICACIONES

1. Compuestos de fórmula I:



fórmula I

en la que

B es C(R4) o N;

R1 es H, halógeno, alquilo (C1-C8), alquilen (C0-C4)-O-alquilen (C0-C4)-H, alquilen (C0-C2)-O-alquilen (C0-C2)-cicloalquilo (C3-C6), SCH3, CN, en el que alquilo y alquileno no están sustituidos o están mono, bi o trisustituidos con F;

R2, R3, R4 son independientemente

H, halógeno, alquilo (C1-C8), alquilen (C0-C4)-O-alquilen (C0-C4)-H, SCH3, CN, en los que alquilo y alquileno no están sustituidos o están mono, bi o trisustituidos con F;

X es O, S, S(O), S(O)2, O-CH2, S-CH2, CH2-O, CH2-S;

uno de U y V es N, el otro es S u O;

W es un enlace, alquileno (C1-C8), alquenileno (C2-C8), alquilen (C0-C6)-cicloalquileno (C3-C6), cicloalquilen (C3-C6) alquileno (C1-C6), en el que alquileno y alquenileno no están sustituidos o están mono, di o trisustituidos con OH y F;

Y es un enlace, O, S, S(O), S(O)2, N(R6) y

R5 es H, alquilo (C1-C8), alquilen (C0-C4)-cicloalquilo (C3-C13), alquilen (C0-C4)-arilo (C6-C14), alquenilo (C2-C8), alquilen (C0-C4)-heterocicloalquilo (C3-C15), alquilen (C0-C4)-heterocicloalquenilo (C3-C15), alquilen (C0-C4)-heteroarilo (C5-C15), alquilen (C0-C4)-CO-alquilo (C1-C4), alquilen (C0-C4)-CO-alquilen (C0-C4)-cicloalquilo (C3-C13), alquilen (C0-C4)-CO-alquilen (C0-

C4)-arilo (C6-C10), alquilen (C0-C4)- CO-alquilen (C0-C4)-heterocicloalquilo (C3-C15), alquilen (C0-C4)- CO-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), alquilen (C0-C4)-CO-alquilen (C0-C4)-heteroarilo (C5-C15), SO2-alquilo (C1-C4), SO2-alquilen (C0-C4)-cicloalquilo (C3-C13), SO2-alquilen (C0-C4)-arilo (C6-C10), SO2-alquilen (C0-C4)-heterocicloalquilo (C3-C15), SO2-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), SO2-alquilen (C0-C4)-heteroarilo (C5-C15), CO-O-alquilen (C0-C4)-arilo (C6-C10), CO-O-alquilo (C1-C4), CO-O-alquilen (C0-C4)-cicloalquilo (C3-C13), CO-O-alquileno (C0-C4)-heterocicloalquilo (C3-C15), CO-O-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), CO-O-alquilen (C0-C4)-heteroarilo (C5-C15), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-arilo (C6-C10), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-cicloalquilo (C3-C13), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)- heterocicloalquilo (C3-C15), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heteroarilo (C5-C15), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-arilo (C6-C10), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-cicloalquilo (C3-C13), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquilo (C3-C15), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heteroarilo (C5-C15) en el que alquilo y alquileno no están sustituidos o están mono, di o trisustituidos con F, S-alquilo (C1-C4), SO-alquilo (C1-C4), SO2-alquilo (C1-C4), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, CO-O alquilo (C1-C4), alquilo (C1-C4) y O-alquilen (C0-C4)-H y en los que cicloalquilo, arilo, heterocicloalquilo, heterocicloalquenilo y heteroarilo no están sustituidos o están mono, di o trisustituidos con F, Cl, Br, CF3, alquilo (C1-C4) y alquilen (C0-C4)-O-alquilen (C0-C4)-H,

con la salvedad que,

si Y es S, S(O) o S(O)2, entonces

R5 no es igual SO2-alquilo (C1-C4), SO2-alquilen (C0-C4)-cicloalquilo (C3-C13), SO2-alquilen (C0-C4)-arilo (C6C10), SO2-alquilen (C0-C4)-heterocicloalquilo (C3-C15), SO2-alquilen (C0-C4)-heterocicloalquenilo (C3-

C15), SO2-alquilen (C0-C4)-heteroarilo (C5-C15), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-arilo (C6-C10), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-cicloalquilo (C3-C13), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquilo (C3-C15), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heteroarilo (C5-C15);

con la salvedad que,

si Y es un enlace u O, entonces

Z no es igual un enlace o

o

Y es un enlace,

con la salvedad que

R5 es CN, alquilo (C1-C8) mono, di o trisustituido con F, CO-alquilo (C1-C4), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, SO2-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, N(alquilen (C0-C4)-H)-CO-alquilen (C0-C4)-H, alquilen (C1-C6)-cicloalquilo (C3-C13), heterocicloalquilo (C3-C15), heterocicloalquenilo (C3-C15), heteroarilo (C5-C15);

o

Y es O,

con la salvedad que

R5 es alquilo (C1-C8) mono, di o trisustituido con F, CO-alquilo (C1-C4), CO-O-alquilen (C0-C4)-arilo (C6-C10), CO-O-alquilen (C0-C4)-cicloalquilo (C3-C13), CO-O-alquilen (C0-C4)-heterocicloalquilo (C3-C15), CO-O-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), CO-O-alquilen (C0-C4)-heteroarilo (C5-C15), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-arilo (C6-C10), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-cicloalquilo (C3-C13), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquilo (C3-C15), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-cicloalquilo (C3-C13), CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heteroarilo (C5-C15), alquilen (C0-C4) cicloalquilo (C3-C13), alquilen (C0-C4) heterocicloalquilo (C3-C15), alquilen (C0-C4) heterocicloalquenilo (C3-C15),

alquilen (C0-C4)-heteroarilo (C5-C15), alquilen (C0-C4)-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, alquilen (C0-C4)-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-cicloalquilo (C3-C13), alquilen (C0-C4)-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-arilo (C6-C10), alquilen (C0-C4)-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquilo (C3-C15), alquilen (C0-C4)-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), alquilen (C0-C4)-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heteroarilo (C5-C15);

R6 es H, alquilo (C1-C8), alquenilo (C2-C8), alquilen (C0-C4)-cicloalquilo (C3-C6), en el que alquilo y alquenilo no están sustituidos o están mono, di o trisustituidos con F y O-alquilen (C0-C4)-H;

R5 y R6 junto con el átomo de nitrógeno al que están unidos (Y = N(R6)) forman un heterocicloalquilo (C3-C15), un heterocicloalquenilo (C3-C15) o un heteroarilo (C5-C15) que puede adicionalmente contener 1 a 3 heteroátomos N, O, S en el que además se pueden oxidar heteroátomos y que puede no estar sustituido o estar mono, di o trisustituido con halógeno, CN, CF3, alquilo (C1-C4), alquilen (C0-C4)-cicloalquilo (C3-C6), alquilen (C0-C4)-O-alquilen (C0-C4)-H, alquilen (C0-C4)-O-alquilen (C0-C4)-cicloalquilo (C3-C6), alquilen (C0-C4)-O-alquilen (C0-C4)-arilo (C6-C10), alquilen (C0-C4)-O-alquilen (C0-C4)-heterocicloalquilo (C3-C15), alquilen (C0-C4)-O-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), alquilen (C0-C4)-O-alquilen (C0-C4)-heteroarilo (C5-C15), alquilen (C0-C4)-S-alquilo (C1-C4), alquilen (C0-C4)-SO-alquilo (C1-C4), alquilen (C0-C4)-SO2-alquilo (C1-C4), alquilen (C0-C4)-CO-alquilo (C1-C4), alquilen (C0-C4)-CO-arilo (C6-C10), alquilen (C0-C4)-CO-heterocicloalquilo (C3-C15), alquilen (C0-C4)-CO-heterocicloalquenilo (C3-C15), alquilen (C0-C4)-CO-heteroarilo (C5-C15), alquilen (C0-C4)-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-H, alquilen (C0-C4)-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-cicloalquilo (C3-C6), alquilen (C0-C4)-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-arilo (C6-C10), alquilen (C0-C4)-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquilo (C3-C15), alquilen (C0-C4)-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), alquilen (C0-C4)-CO-N(alquilen (C0-C4)-H)-alquilen (C0-C4)-heteroarilo (C5-C15),

alquilen (C0-C4)-N(alquilen (C0-C4)-H)-CO-alquilo (C1-C4), alquilen (C0-C4)-N(alquilen (C0-C4)-H)-CO-alquilen (C0-C4)-cicloalquilo (C3-C6), alquilen (C0-C4)-N(alquilen (C0-C4)-H)-CO-alquilen (C0-C4)-arilo (C6-C10), alquilen (C0-C4)-N(alquilen (C0-C4)-H)-CO-alquilen (C0-C4)-heterocicloalquilo (C3-C15), alquilen (C0-C4)-N(alquilen (C0-C4)-H)-CO-alquilen (C0-C4)-heterocicloalquenilo (C3-C15), alquilen (C0-C4)-N(alquilen (C0-C4)-H)-CO-alquilen (C0-C4)-heteroarilo (C5-C15), alquilen (C0-C4)-arilo (C6-C14) y alquilen (C0-C4) heterocicloalquilo (C3-C15), alquilen (C0-C4)-heterocicloalquenilo (C3-C15), alquilen (C0-C4)-heteroarilo (C5-C15) en los que heteroarilo, heterocicloalquilo y heterocicloalquenilo pueden estar mono o disustituidos con residuo oxo y en los que alquilo puede no estar sustituido o estar mono, di o trisustituido con F;

Z es un enlace, alquileno (C1-C8), alquenileno (C2-C8), alquilideno (C2-C8), alquilen (C1-C6)-O-alquileno (C1-C6);

R7, R8 se seleccionan independientemente entre el grupo que consiste en H, halógeno, alquilo (C1-C8), alquilen (C0-C4)-O-alquilen (C0-C4)-H, SCF3, SF5, S(O)2CF3, alquilen (C0-C4)-O-arilo (C6-C12), alquilen (C0-C4)-arilo (C6-C12), NO2, en los que alquilo y alquileno no están sustituidos o están mono, di o trisustituidos con F y arilo no está sustituido o está mono, di o trisustituido con halógeno, alquilo (C1-C4) u O-alquilo (C1-C4);

en todas sus formas estereoisoméricas, formas enantioméricas y mezclas en cualquier relación, y sus sales farmacéuticamente aceptables y formas tautoméricas.

2. Compuestos de la fórmula I según la reivindicación 1, en los que

R2, R3 son independientemente

H, halógeno, alquilo (C1-C8), alquilen (C0-C4)-O-alquilen (C0-C4)-H, SCH3, CN, en los que alquilo y alquileno no están sustituidos o están mono, di o trisustituidos con F;

R4 es H, alquilo (C1-C8), alquilen (C0-C4)-O-alquilen (C0-C4)-H, en el que alquilo y alquileno no están sustituidos o están mono, di o trisustituidos con F.

3. Compuestos de fórmula I según las reivindicaciones 1 ó 2, en los que
B es C(R4) y
R4 es H.

4. Compuestos de la fórmula I según las reivindicaciones 1 a 3, en los que
R1 es halógeno, alquilo (C1-C4), alquilen (C0-C4)-O-alquilen (C0-C2)-H, O-alquilen (C0-C2) -cicloalquilo (C3-C6), en el que alquilo y alquileno no están sustituidos o están mono, di o trisustituidos con F.

5. Compuestos de la fórmula I según las reivindicaciones 1 a 4, en los que
W es alquileno (C1-C3);
Y es N(R6) y
R5 y R6, junto con el átomo de nitrógeno al que están unidos (Y = N(R6)), forman un heterocicloalquilo (C3-C7), un heterocicloalquenilo (C4-C7) o un heteroarilo (C5-C8) que puede contener adicionalmente 1 a 2 heteroátomos N, O, S y que no está sustituido o está mono o disustituido con F, CF3, alquilo (C1-C3), alquilen (C0-C3)-O-alquilen (C0-C3)-H, SO2-alquilo (C1-C3), CO-alquilo (C1-C3), CO-NH2, NH-CO-alquilo (C1-C3), fenilo, heteroarilo (C5-C6), heterocicloalquilo (C3-C7) y heterocicloalquenilo (C4-C7), en los que heterocicloalquilo, heterocicloalquenilo y heteroarilo pueden estar mono o disustituidos con un residuo oxo.

6. Compuestos de la fórmula I según las reivindicaciones 1 a 5, en los que
W es alquileno (C1-C3);
Y es N(R6) y
R5 es H, alquilo (C1-C4), alquilen (C0-C3)-cicloalquilo (C3-C7), alquilen (C0-C3)-fenilo, alquilen (C0-C3)-heterocicloalquilo (C3-C7), alquilen (C0-C4)-heterocicloalquenilo (C4-C7), alquilen (C0-C3)-heteroarilo (C5-C6), CO-alquilo (C0-C3), CO-O-fenilo, en el que alquilo y alquileno pueden estar mono, di o

trisustituidos con F, S-alquilo (C1-C3), SO-alquilo (C1-C3), SO2-alquilo (C1-C3), N(alquilen (C0-C3)-H)-alquilen (C0-C3)-H, CO-O alquilo (C1-C3) y O-alquilen (C0-C3)-H y en los que cicloalquilo, fenilo, heterocicloalquilo, heterocicloalquenilo y heteroarilo están mono, di o trisustituidos con F y alquilen (C0-C4)-O-alquilen (C0-C4)-H;

R6 es H, alquilo (C1-C3) o alquilen (C0-C3)-cicloalquilo (C3-C6), en el que alquilo no está sustituido o está mono, di o trisustituido con O-alquilen (C0-C4)-H; o

Y es S, S(O), S(O)2 y

R5 es alquilo (C1-C3) o alquilen (C0-C3)-cicloalquilo (C3-C6), en el que alquilo no está sustituido o está mono, di o trisustituido con F; o

Y es O y

R5 es alquilo (C1-C4) mono, di o trisustituido con F, CO-alquilo (C1-C3), alquilen (C0-C3)-cicloalquilo (C3-C6), alquilen (C0-C3)-heterocicloalquilo (C3-C7), alquilen (C0-C3)-heteroarilo (C5-C8); o

Z es –CH2-, -CH2-CH2-, -CH2-O-CH2-, -CH=CH-.

7. Compuestos de la fórmula I según las reivindicaciones 1 a 6, en los que

V es N y U es O; o

V es N y U es S.

8. Compuestos de la fórmula I según las reivindicaciones 1 a 7, en los que

X es O u O-CH2.

9. Compuestos de la fórmula I según las reivindicaciones 1 a 8, en los que

W es un enlace o –CH2-.

10. Compuestos de la fórmula I según las reivindicaciones 1 a 9, en los que

R7 está en la posición para.

11. Compuestos de la fórmula I según las reivindicaciones 1 a 10, en los que

R8 es H.

12. Compuestos de la fórmula I según las reivindicaciones 1 a 11, en los que

R1 es halógeno, alquilo (C1-C4), alquilen (C0-C4)-O-alquilen (C0-C2)-H, O-alquilen (C0-C2) -cicloalquilo (C3-C6), en el que alquilo y alquileno no están sustituidos o están mono, di o trisustituidos con F;

W es alquileno (C1-C3);

Y es N(R6) y

R5 y R6, junto con el átomo de nitrógeno al que están unidos (Y = N(R6)), forman un heterocicloalquilo (C3-C7), un heterocicloalquenilo (C4-C7) o un heteroarilo (C5-C8) que puede contener adicionalmente 1 a 2 heteroátomos N, O, S y que no está sustituido o está mono o disustituido con F, CF3, alquilo (C1-C3), alquilen (C0-C3)-O-alquilen (C0-C3)-H, SO2-alquilo (C1-C3), CO-alquilo (C1-C3), CO-NH2, NH-CO-alquilo (C1-C3), fenilo, heteroarilo (C5-C6), heterocicloalquilo (C3-C7) y heterocicloalquenilo (C4-C7), en los que heterocicloalquilo, heterocicloalquenilo y heteroarilo pueden estar mono o disustituidos con un residuo oxo;

W es alquileno (C1-C3);

Y es N(R6) y

R5 es H, alquilo (C1-C4), alquilen (C0-C3)-cicloalquilo (C3-C7), alquilen (C0-C3)-fenilo, alquilen (C0-C3)-heterocicloalquilo (C3-C7), alquilen (C0-C4)-heterocicloalquenilo (C4-C7), alquilen (C0-C3)-heteroarilo (C5-C6), CO-alquilo (C0-C3), CO-O-fenilo, en el que alquilo y alquileno pueden estar mono, di o trisustituidos con F, S-alquilo (C1-C3), SO-alquilo (C1-C3), SO2-alquilo (C1-C3), N(alquilen (C0-C3)-H)-alquilen (C0-C3)-H, CO-O alquilo (C1-C3) y O-alquilen (C0-C3)-H y en los que cicloalquilo, fenilo, heterocicloalquilo,

heterocicloalquenilo y heteroarilo están mono, di o trisustituidos con F y alquilen (C0-C4)-O-alquilen (C0-C4)-H;

R6 es H, alquilo (C1-C3) o alquilen (C0-C3)-cicloalquilo (C3-C6), en el que alquilo no está sustituido o está mono, di o trisustituido con O-alquilen (C0-C4)-H;

Y es S, S(O), S(O)2 y

R5 es alquilo (C1-C3) o alquilen (C0-C3)-cicloalquilo (C3-C6), en el que alquilo no está sustituido o está mono, di o trisustituido con F;

Y es O y

R5 es alquilo (C1-C4) mono, di o trisustituido con F, CO-alquilo (C1-C3), alquilen (C0-C3)-cicloalquilo (C3-C6), alquilen (C0-C3)-heterocicloalquilo (C3-C7), alquilen (C0-C3)-heteroarilo (C5-C8); o

Z es –CH2-, -CH2-CH2-, -CH2-O-CH2-, -CH=CH-.

13. Compuestos de la fórmula I según las reivindicaciones 1 a 12, en los que

B es C(R4) y

R4 es H,

R1 es F, Cl, alquilo (C1-C4), alquilen (C0-C4)-O-alquilen (C1-C4)-H, alquilen (C0-C2)-O-alquilen (C0-C2)-cicloalquilo (C3-C6), en el que alquilo y alquileno no están sustituidos o están mono, bi o trisustituidos con F;

R2 es H;

R3 es H, F, Br;

R4 es H;

X es O, O-CH2;

U es S, O y

V es N

o

U es N y

V es O;

W es un enlace, alquileno (C1-C4);

Y es N(R6) y

R5 se selecciona del grupo que consiste en alquilo (C1-C8), alquilen (C0-C4)-cicloalquilo (C3-C13), alquilen (C0-C4)-arilo (C6-C12), alquilen (C0-C4)-heterocicloalquilo (C3-C15) CO-alquilo (C0-C4), CO-O-arilo (C6-C10), en el que alquilo y alquileno pueden estar mono, di o trisustituidos con S-alquilo (C1-C4), SO-alquilo (C1-C4), N(alquilen(C0-C4)-H)-alquilen (C0-C4) -H y O-alquilen (C0-C4)-H y en el que arilo y heterocicloalquilo están mono, di o trisustituidos con F y alquilen (C0-C4)-O-alquilen (C0-C4)-H;

Y es O y

R5 es alquilo (C1-C8) mono, di o trisustituido con F, CO-alquilo (C1-C4), alquilen (C0-C4)-cicloalquilo (C3-C6); o

Z es –CH2-, -CH2-CH2-, -CH2-O-CH2-, -CH=CH-;

Y es S, S(O), S(O)2 y

R5 es alquilo (C1-C3);

R6 es H, alquilo (C1-C8) o alquilen (C0-C4)-cicloalquilo (C3-C6), en el que alquilo no está sustituido o está mono, di o trisustituido con O-alquilen (C0-C4)-H;

R5 y R6, junto con el átomo de nitrógeno al que están unidos (Y = N(R6)), pueden formar un heterocicloalquilo (C3-C8), un heterocicloalquenilo (C3-C10) que puede contener adicionalmente 1 a 3 heteroátomos N, O, S y que puede no estar sustituido o estar mono, di o trisustituido con F, CF3, alquilo (C1-C4), alquilen (C0-C4)-O-alquilen (C0-C4)-H, SO2-alquilo (C1-C4), CO-alquilo (C1-C4), en los que el heterocicloalquilo puede estar mono o disustituido con un residuo oxo;

Z es un enlace, alquileno (C1-C2), alquenileno (C2), alquilen (C1-C2)-O-alquileno (C1-C2);

R7 es H, O-alquilo (C1-C4), CF3;

R8 es H.

14. Compuestos de la fórmula I según las reivindicaciones 1 a 13, en los que:

R1 es halógeno, alquilo (C1-C4), OH, O-alquilo (C1-C3), en el que alquilo no está sustituido o está mono, di o trisustituido con F;

R2 es H;

R3 es H, F;

B es C(R4) o N, y

R4 es H;

X es O;

uno de U y V es N, el otro es S u O;

W es alquileno (C1-C3);

Y es N(R6) y

R5 y R6, junto con el átomo de nitrógeno al que están unidos (Y = N(R6)), forman un heterocicloalquilo (C3-C7), un heterocicloalquenilo (C4-C7) o un heteroarilo (C5-C8) que puede contener adicionalmente 1 a 2 heteroátomos N, O, S y que no está sustituido o está mono o disustituido con F, CF3, alquilo (C1-C3), alquilen (C0-C3)-O-alquilen (C0-C3)-H, SO2-alquilo (C1-C3), CO-alquilo (C1-C3), CO-NH2, NH-CO-alquilo (C1-C3), fenilo, heteroarilo (C5-C6), heterocicloalquilo (C3-C7) y heterocicloalquenilo (C4-C7), en los que heterocicloalquilo, heterocicloalquenilo y heteroarilo pueden estar mono o disustituidos con un residuo oxo;

Y es N(R6) y

R5 es H, alquilo (C1-C4), alquilen (C0-C3)-cicloalquilo (C3-C7), alquilen (C0-C3)-fenilo, alquilen (C0-C3)-heterocicloalquilo (C3-C7), alquilen (C0-C4)-heterocicloalquenilo (C4-C7); alquilen (C0-C3)-heteroarilo (C5-C6), CO-alquilo (C0-C3), CO-O-fenilo, en el que alquilo y alquileno pueden estar mono, di o trisustituidos con F, S-alquilo (C1-C3), SO-alquilo (C1-C3), SO2-alquilo (C1-C3), N(alquilen (C0-C3)-H)-alquilen (C0-C3)-H, CO-O alquilo (C1-C3) y O-alquilen (C0-C3)-H y en los que cicloalquilo, fenilo, heterocicloalquilo, heterocicloalquenilo y heteroarilo están mono, di o trisustituidos con F y alquilen (C0-C4)-O-alquilen (C0-C4)-H;

R6 es H, alquilo (C1-C3) o alquilen (C0-C3)-cicloalquilo (C3-C6), en el que alquilo no está sustituido o está mono, di o trisustituido con O-alquilen (C0-C4)-H;

Y es S, S(O), S(O)2 y

R5 es alquilo (C1-C3) o alquilen (C0-C3)-cicloalquilo (C3-C6), en el que alquilo no está sustituido o está mono, di o trisustituido con F;

Y es O y

R5 es alquilo (C1-C4) mono, di o trisustituido con F, CO-alquilo (C1-C3), alquilen (C0-C3)-cicloalquilo (C3-C6), alquilen (C0-C3)-heterocicloalquilo (C3-C7), alquilen (C0-C3)-heteroarilo (C5-C8); o

Z es –CH2-, -CH2-CH2-, -CH2-O-CH2-, -CH=CH-.

Z es un enlace, alquileno (C1-C2), alquenileno (C2), alquilen (C1-C2)-O-alquileno (C1-C2);

R7 es H, halógeno, alquilo (C1-C3), O-alquilo (C1-C3), en el que alquilo no está sustituido o está mono, di o trisustituido con F;

R8 es H.

15. Compuestos de la fórmula I según las reivindicaciones 1 a 14, en los que:

R1 es F, OH, OCH3, OCHF2, OCH2CF3;

R2 es H;

R3 es H, F;

B es C(R4) o N, y

R4 es H;

X es O;

uno de U y V es N, el otro es S u O;

W es CH2, CH2CH2CH2;

Y es N(R6) y

R5 y R6, junto con el átomo de nitrógeno al que están unidos (Y = N(R6)), forman piperidina, pirrolidina, azetidina, azepina, morfolina, tiomorfolina, tiomorfolina-S-óxido, tiomorfolina-S-dióxido, piperazina, piperazinona, isoindolina, no sustituida o mono o disustituida con F, CF3, alquilo (C1-C3), O-alquilo (C1-C3), OH, CH2OH, SO2CH3, COCH3, fenilo;

Y es S, S(O), S(O)2 y

R5 es CH3;

Z es un enlace;

R7 es CF3;

R8 es H.

16. Compuestos de la fórmula I según las reivindicaciones 1 a 15, en los que:

R1 es H, F, Cl;

R2 es H;

R3 es H;

B es C(R4) o N, y

R4 es H;

X es O;

U es S, O y

V es N;

W es CH2;

Y es un enlace u O;

Z es un enlace;

R5 es alquilo (C1-C6) mono, di o trisustituido con F;

R7 está en la posición para y es alquilo (C1-C4), alquilen (C0-C4)-O-alquilen (C0-C4)-H, SF5, alquilen (C0-C4)-O-fenilo, en el que alquilo, alquileno y fenilo están mono, di o trisustituidos con F;

R8 es H.

17. Un producto farmacéutico que comprende uno o más compuestos de la fórmula I según una o más de las reivindicaciones 1 a 16.

18. Un producto farmacéutico que comprende uno o más compuestos de fórmula I según una o más de las reivindicaciones 1 a 16, y una o más sustancias activas que tienen efectos beneficiosos en las alteraciones metabólicas o trastornos asociados frecuentemente con éstas.

19. Un producto farmacéutico que comprende uno o más compuestos de la fórmula I según una o más de las reivindicaciones 1 a 16, y uno o más antidiabéticos.

20. Un producto farmacéutico que comprende uno o más compuestos de la fórmula I según una o más de las reivindicaciones 1 a 16, y uno o más moduladores de lípidos.

21. El uso de los compuestos de la fórmula I según una o más de las reivindicaciones 1 a 16, para el tratamiento y/o la prevención de trastornos del metabolismo de ácidos grasos y trastornos de uso de la glucosa.

22. El uso de los compuestos de la fórmula I según una o más de las reivindicaciones 1 a 16, para el tratamiento y/o la prevención de trastornos en los que está implicada la resistencia a la insulina.

23. El uso de los compuestos de la fórmula I según una o más de las reivindicaciones 1 a 16, para el tratamiento y/o la prevención la diabetes mellitus, incluyendo la prevención de secuelas asociadas con ésta.

24. El uso de los compuestos de la fórmula I según una o más de las reivindicaciones 1 a 16, para el tratamiento y/o la prevención de dislipidemias y sus secuelas.

25. El uso de los compuestos de la fórmula I según una o más de las reivindicaciones 1 a 16, para el tratamiento y/o la prevención de afecciones que pueden estar asociadas al síndrome metabólico.

26. El uso de compuestos de la fórmula I según una o más de las reivindicaciones 1 a 16, para el tratamiento y/o la prevención del trastorno de desmielinización u otros trastornos de los sistemas nerviosos central y periférico.

27. El uso de compuestos según una o más de las reivindicaciones 1 a 16, combinados con por lo menos un compuesto activo adicional, para tratar trastornos del metabolismo de ácidos grasos y trastornos de uso de la glucosa.

28. El uso de compuestos según una o más de las reivindicaciones 1 a 16, combinados con por lo menos un compuesto activo adicional, para tratar trastornos en los que está implicada la resistencia a la insulina.

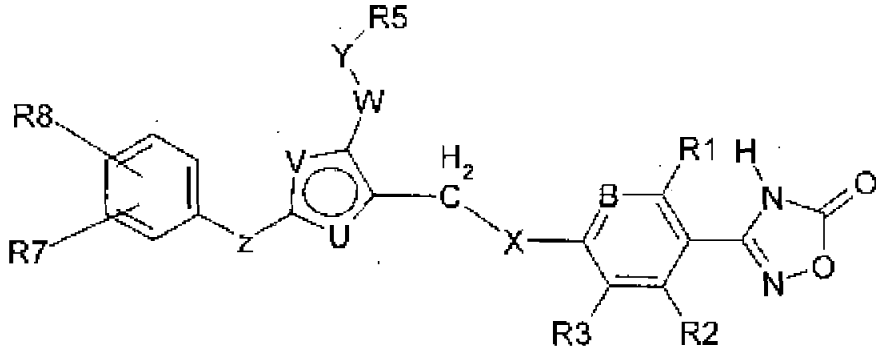
29. Un procedimiento para preparar un producto farmacéutico que comprende uno o más compuestos según una o más de las reivindicaciones 1 a 16, que comprende mezclar el compuesto activo con un vehículo farmacéuticamente aceptable, y poner esta mezcla en una forma de administración adecuada.

Resumen

DERIVADOS DE FENIL-1,2,4- Y PIRIDIL-1,2,4-OXADIAZOLONA CON GRUPO FENILO, PROCEDIMIENTOS PARA SU PREPARACIÓN Y SU USO COMO PRODUCTOS FARMACÉUTICOS

La invención se refiere a derivados de fenil-1,2,4-oxadiazolona con grupo fenilo y a sus sales fisiológicamente aceptables y derivados fisiológicamente funcionales que muestran actividad agonista de PPARdelta.

Se describen compuestos de fórmula (I),



(I)

en la que los radicales son como se han definido, y sus sales fisiológicamente aceptables, y procedimientos para sus preparaciones. Los compuestos son adecuados para el tratamiento y/o la prevención de trastornos del metabolismo de ácidos grasos y uso de la glucosa como también de trastornos en los que está implicada la resistencia a la insulina y otros trastornos de desmielinización y neurodegenerativos de los sistemas nerviosos central y periférico.

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO PROPIETARIOS

PATENTE DE INVENCION ___ PCT X MODELO DE UTILIDAD ___ DISEÑO INDUSTRIAL ___

(21) Nº de solicitud: (22) Fecha de solicitud:
(51) Clasificación Internacional :

(71)Solicitante(s) **SANOFI-AVENTIS**

(72) Inventor(es) **DR. PATRICK BERNADELLI, DR. STEFANIE KEIL, DR. MATHIAS URMANN, DR. HANS MATTER, DR. WOLFGANG WENDLER, DR. MAIKE GLIEN, DR. KAREN CHANDROSS, LAN LEE, DR. CORINNE TERRIER, DR. HERVÉ MINOUX**

(74) Apoderado: **DR. LUIS PATIÑO LEYVA**

(30) Prioridad	(31) Nº Prioridad	32) Fecha	(33) País
	05021235.6	29/09/2005	EP

(85) Fecha inicio fase nacional: 22 de julio de 2007
(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: **26/09/2006**
Nº de solicitud **PCT/EP2006/009298**

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Fecha: **12/04/2007**
Nº publicación: **WO 2007/039172 A1**

(54) Titulo: **DERIVADOS DE FENIL- Y PIRIDIL-1,2,4-OXADIAZOLONA CON GRUPO FENILO, PROCEDIMIENTOS PARA SU PREPARACION Y SU USO COMO PRODUCTOS FARMACEUTICOS**

Sanofi-Aventis Deutschland GmbH
Patentabteilung K 801
Vorg.
Eing.: 08. Aug. 2007
WV
Ablegen
Vert. wie Vorg./angegeben

PATENT COOPERATION TREATY

PCT/EP2006/009298

434

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From the INTERNATIONAL BUREAU

To:

SANOFI-AVENTIS DEUTSCHLAND GMBH
Patentabteilung
Industriepark Höchst, Geb. K801
65926 Frankfurt am Main
ALLEMAGNE

NOTIFICATION OF THE RECORDING OF A CHANGE

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

Date of mailing *(day/month/year)* 25 July 2007 (25.07.2007)	
Applicant's or agent's file reference DE2005/043	IMPORTANT NOTIFICATION
International application No. PCT/EP2006/009298	International filing date *(day/month/year)* 26 September 2006 (26.09.2006)

1. The following indications appeared on record concerning:

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

Name and Address	State of Nationality	State of Residence
SANOFI-AVENTIS DEUTSCHLAND GMBH Brüningstrasse 50 65929 Frankfurt am Main Germany	DE	DE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

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

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

Name and Address	State of Nationality	State of Residence
SANOFI-AVENTIS 54, avenue de France F-75013 Paris France	FR	FR
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

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

☒ the receiving Office
☐ the International Searching Authority
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Blanc Veronique e-mail Veronique.Blanc@wipo.int Telephone No. +41 22 338 96 66

Form PCT/IB/306 (October 2005)

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43

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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Act. 411 PRESENTACION Folios: 434

Industria y Comercio
SUPERINTENDENCIA

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRÁMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION (X) 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 presenta la solicitud	(X)	( )
- Descripción de la invención	(X)	( )
- Dibujos de ser estos pertinentes	( )	( )
- Comprobante de pago de las tasas establecidas	(X)	( )

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 ( )

EZQUEMA DE TRAZADO ( )

- 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 del Esquema de Trazado	( )	( )
- Comprobante de pago de las tasas establecidas	( )	( )

COMPLETA ( ) INCOMPLETA ( )

Firma responsable: Claudia M Nova Cortes

Fecha: _____

436

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
PATIÑO LEYVA LUIS
Apoderado(a) y/o Representante de
SANOFI-AVENTIS

REFERENCIA	Radicación No.	8 30803
	Solicitud internacional	PCT/EP2006/009298
	Fecha inicio fase nacional	29/04/2008
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	5944

Como resultado del examen de forma, realizado con fundamento en 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:

1. 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 Unica 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 09 MAYO 2008
adpall