PETITORIO

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-030802- -00000-0000
Fecha: 2008-03-28 14:12:49 Dep: 2020 NUECREACION
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 169

FORMULARIO UNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

SOLICITUD DE:

(1)

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

[X] Capítulo I [ ] Capítulo II

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Lugar de Constitución: FRANCIA

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C.C. [ ] NIT [ ]
C.E. [ ] Otro [ ] Cual
Número

(3)

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C.E. [ ] Otro [ ] Cual
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(4)

INVENTOR (ES) (72)

VER ANEXO # 1

PCT (86)

Solicitud Internacional No. PCT/EP2006/009302 Fecha 26/09/2006

Publicación Internacional No. WO 2007/039176 A1 Fecha 12/04/2007

(6) Título (54)

DERIVADOS DE 2-AMINOTIAZOLES Y 2-AMINOOXAZOLES, PROCESOS PARA SU PREPARACIÓN Y SU USO COMO COMPUESTOS FARMACÉUTICOS

(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	05021279.4

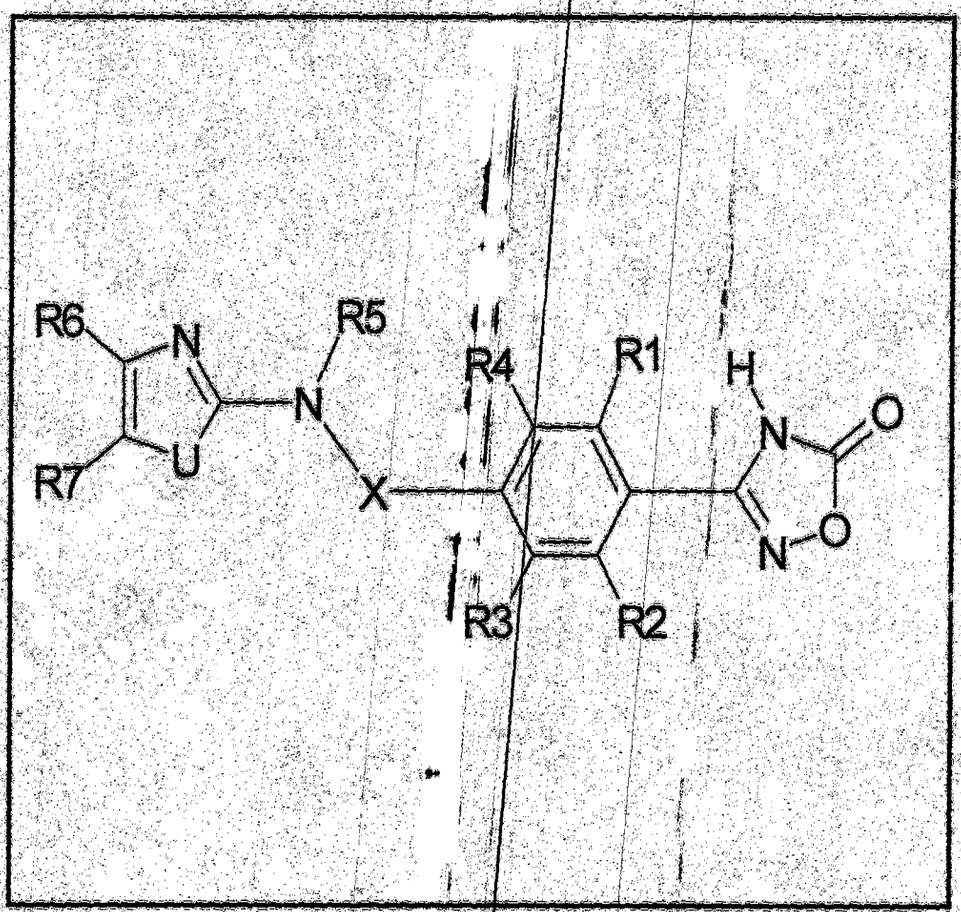
(9) Comprobante de pago No. 08-24.532 Fecha 26 de marzo de 2008

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,**

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 - P20193

G. HOLLMANN RESTREPO
ABOGADOS LTDA.

ANEXO # 1

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P20934
4

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 24,852
FECHA : MARZO 26 DE 2008

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No. 08-030802- -00000-0000
Fecha: 2008-03-28 14:12:49 Dep: 2020 NUEVACREACION
Tra: 11 PATENTE!YII Eve: 378 FASENACIONAL!
Act: 411 PRESENTACION Folios: 169

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
SHOLLMANN	CONSIGNACION	BANCO DE BOGOTA	042754387	4538722	26/03/2008	3,021,000.00

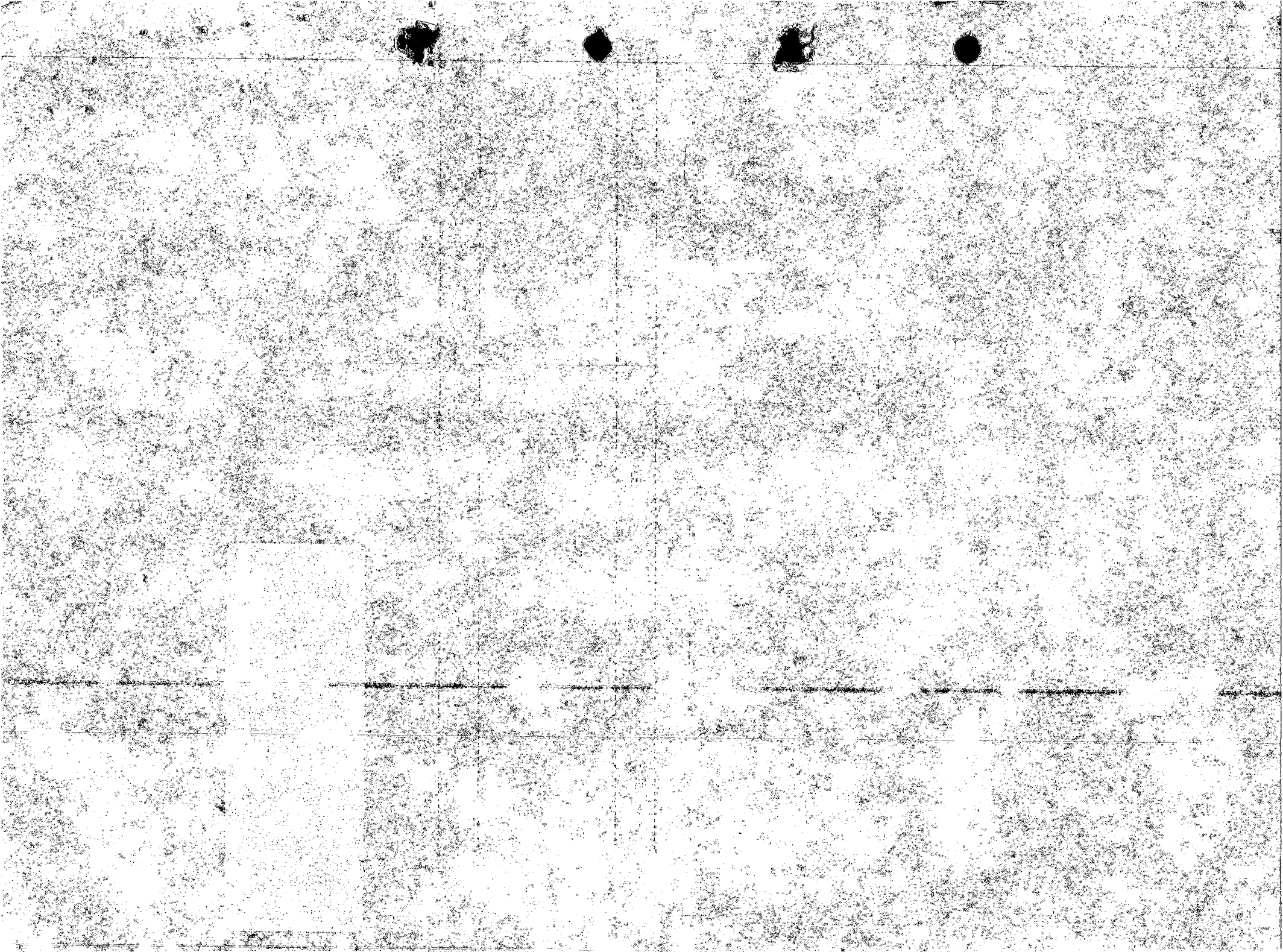
**** C O N C E P T O ****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	90005-01-01 SOLICITUDES	1	TRAMITES DE SOL. DE PATENTE DE IN	301,000.00
			TOTAL :	$ 301,000.00

SON: QUINIENTOS UN MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____



Un cuarto xa poder. 5
P.8008 G3
Dr. PATIÑO

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

H. POMMERY, Notaire Associé à PA

Esta copia coincide con el original que tuve a la vista
10 MAR 2008
ARGENTINA MORALES RIVEIRA
NOTARIO CIUDADANA YUNO

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. *République française*

Le présent acte public

2. a été signé par Maître PONCERY

3. agissant en qualité de Notaire

4. est revêtu du sceau/timbre de Me... Etude

Attesté

5. à PARIS

6. le 20/12/06

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

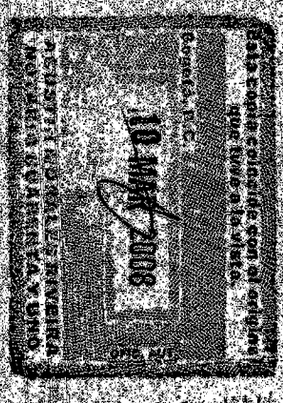
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6

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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 [illegible] of [illegible], he (they) is (are) empowered to grant this power; and that said company exists, accomplishes its social object and is organized in [illegible] 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 of 2007.

Hervé POMMERY
NOTAIRE

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

CERTIFICACIÓN

SOCIEDADES

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Todos los hechos anteriores le constan, por haber examinado los documentos respectivos y de todo ello da fe.

Firmado en _____ el _____ de _____ de _____.

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

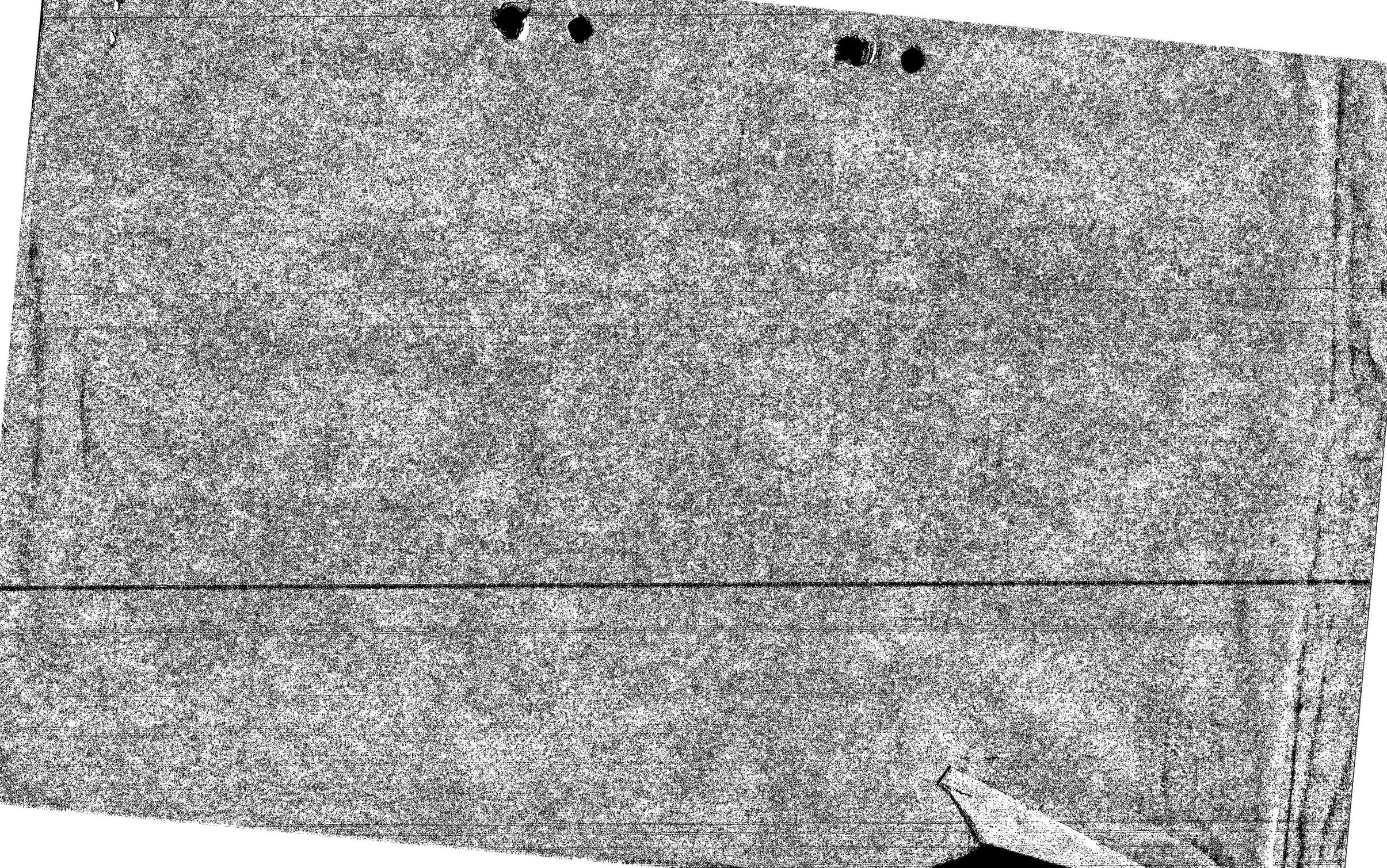
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5. à PARIS
6. le 22/02/2007
7. *par le Procureur général près la Cour d'appel de* PARIS
8. sous n° 17350
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Traductor oficial - Traducteur assermenté

Español - Francés
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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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BOGOTA D.C.

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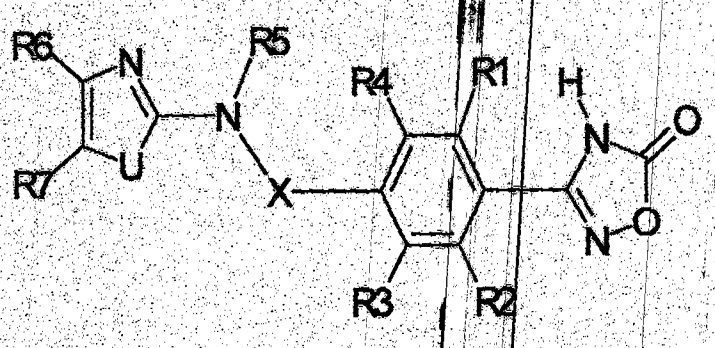
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, 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*

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:** DERIVATIVES OF 2 -AMINTHIAZOLES AND 2-AMINOOXAZOLES, PROCESSES FOR THEIR PREPARATION AND THEIR USE AS PHARMACEUTICALS



(I)

(57) **Abstract:** The invention relates to derivatives of 2-aminothiazoles and 2-aminooxazoles in all its stereoisomeric forms, enantiomeric forms and mixtures in any ratio, and its physiologically acceptable salts and tautomeric forms 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 2007/039176 A1

Description

DERIVATIVES OF 2-AMINTHIAZOLES AND 2-AMINOOXAZOLES, PROCESSES FOR THEIR PREPARATION AND THEIR USE AS PHARMACEUTICALS

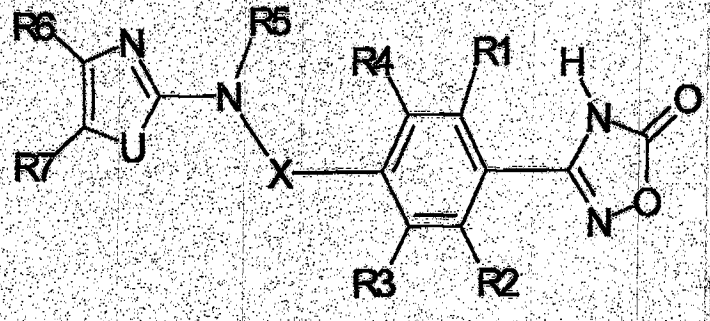
The invention relates to oxadiazolones and to their physiologically acceptable salts and physiologically functional derivatives showing PPARdelta agonist activity.

PPARdelta agonists have been described in the prior art (e.g. WO 01/00603, WO 02/092590, WO2003/074495, WO2004/093879, 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. Phenyl derivatives as agents for the therapy of thromboembolic disorders are known from WO 02/057236. Benzene derivatives as inhibitors of squalene synthase and protein farnesyltransferase are described in WO96/34851.

The invention was 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 and PPARalpha, however it is possible that the relative activation varies depending on the specific compounds.

Compounds of the present invention are described by formula I:



formula I

wherein

R1 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 trisubstituted 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 trisubstituted by F;

X –CH2-, -CH2-CH2-;

U is S or O;

R5 is H, (C1-C8) alkyl, (C1-C4) alkylene-O-(C1-C4) alkyl, (C1-C4) alkylene-O-(C0-C4) alkylene-(C6-C10) aryl, (C0-C4) alkylene-(C3-C12) cycloalkyl, (C2-C8) alkenyl, (C0-C4) alkylene-(C3-C15) heterocycloalkyl, (C0-C4) alkylene-(C3-C15) heterocycloalkenyl, (C0-C4) alkylene-(C5-C15) heteroaryl, wherein alkyl and alkylene are unsubstituted or mono-, di- or trisubstituted by F, N((C0-C4) alkylene-H)-(C0-C4) alkylene-H 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, CO-(C1-C4) alkyl and (C0-C4)-alkylen-O-(C0-C4) alkylene-H;

R6, R7 H, (C6-C14) aryl, which is unsubstituted or mono-, di- or trisubstituted by F, Cl, Br, CF3, (C1-C4) alkyl and (C0-C4)-alkylen-O-(C0-C4) alkylene-H; or

R6 and R7 together with the oxazole or thiazole ring form a benzothiazole or benzoxazole ring, which is unsubstituted or mono- di- or trisubstituted by F, Cl, Br, CF3, (C1-C4) alkyl and (C0-C4)-alkylen-O-(C0-C4) alkylene-H;

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 where one or more substituents have the following meaning:

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

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

R2,R3,R4 are H;

X is -CH2-CH2-;

X is CH2;

U is S;

R5 is (C1-C4) alkyl, (C1-C4) alkylene-O-(C1-C4) alkyl, (C1-C4) alkylene-O-CH2-phenyl, (C1-C4) alkylene-(C5-C6) heterocycloalkyl wherein alkyl and alkylene can be mono-, di- or trisubstituted by N((C1-C4) alkyl)-(C1-C4) alkyl and wherein heterocycloalkyl is unsubstituted or monosubstituted by (C1-C4) alkyl or CO-(C1-C4) alkyl;

R6 is phenyl monosubstituted by Cl or methoxy;

R6 and R7 together with the thiazole ring denote benzothiazole substituted by CF3 or Cl.

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

R1 is H, F, CH3 or CF3.

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

R1 is F, CH3 or CF3.

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

R6 and R7 together with the thiazole ring denote 6-trifluoromethyl-benzothiazole.

Another embodiment according to the invention are the compounds:

3-{4-[2-(Benzooxazol-2-yl-butyl-amino)-ethyl]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{4-[2-(Benzothiazol-2-yl-butyl-amino)-ethyl]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-(4-{2-[Butyl-(6-methoxy-benzothiazol-2-yl)-amino]-ethyl}-phenyl)-4H-[1,2,4]oxadiazol-5-one

3-(4-{2-[Butyl-(6-chloro-benzothiazol-2-yl)-amino]-ethyl}-phenyl)-4H-[1,2,4]oxadiazol-5-one

3-(4-{2-[Butyl-(6-chloro-benzothiazol-2-yl)-amino]-ethyl}-2-methyl-phenyl)-4H-[1,2,4]oxadiazol-5-one

3-(4-{2-[Butyl-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-2-methyl-phenyl)-4H-[1,2,4]oxadiazol-5-one

3-(2-Methyl-4-{2-[[2-(tetrahydro-pyran-4-yl)-ethyl]-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-phenyl)-4H-[1,2,4]oxadiazol-5-one

3-(2-Methyl-4-{2-[(tetrahydro-pyran-3-ylmethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-phenyl)-4H-[1,2,4]oxadiazol-5-one

3-(2-Methyl-4-{2-[(tetrahydro-pyran-4-ylmethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-phenyl)-4H-[1,2,4]oxadiazol-5-one

3-(4-{2-[[2-(1-Acetyl-piperidin-4-yl)-ethyl]-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-2-methyl-phenyl)-4H-[1,2,4]oxadiazol-5-one

3-{4-[(Benzooxazol-2-yl-butyl-amino)-methyl]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-{4-[(Benzothiazol-2-yl-butyl-amino)-methyl]-phenyl}-4H-[1,2,4]oxadiazol-5-one

3-(4-{[Butyl-(6-chloro-benzothiazol-2-yl)-amino]-methyl}-phenyl)-4H-[1,2,4]oxadiazol-5-one

3-(4-{2-[(3-Methoxy-propyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-2-methyl-phenyl)-4H-[1,2,4]oxadiazol-5-one

3-(4-{2-[[2-(2-Methoxy-ethoxy)-ethyl]-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-2-methyl-phenyl)-4H-[1,2,4]oxadiazol-5-one

3-(4-{2-[(2-Benzyloxy-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-2-methyl-phenyl)-4H-[1,2,4]oxadiazol-5-one

3-(4-{2-[(2-Methoxy-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-2-methyl-phenyl)-4H-[1,2,4]oxadiazol-5-one

3-[4-(2-{Butyl-[4-(4-methoxy-phenyl)-thiazol-2-yl]-amino}-ethyl)-phenyl]-4H-[1,2,4]oxadiazol-5-one

3-[4-(2-{Butyl-[4-(4-chloro-phenyl)-thiazol-2-yl]-amino}-ethyl)-phenyl]-4H-[1,2,4]oxadiazol-5-one

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

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

3-[4-(2-{(2-Benzyloxy-ethyl)-[4-(4-chloro-phenyl)-thiazol-2-yl]-amino}-ethyl)-phenyl]-4H-[1,2,4]oxadiazol-5-one

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

3-(4-{[Butyl-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-2-fluoro-phenyl)-4H-[1,2,4]oxadiazol-5-one

3-(4-{[Butyl-(6-chloro-benzothiazol-2-yl)-amino]-methyl}-2-fluoro-phenyl)-4H-[1,2,4]oxadiazol-5-one

3-(2-Fluoro-4-{[(2-pyrrolidin-1-yl-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-phenyl)-4H-[1,2,4]oxadiazol-5-one trifluoroacetate

3-(4-{[(2-Dimethylamino-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-2-fluoro-phenyl)-4H-[1,2,4]oxadiazol-5-one trifluoroacetate

3-(2-Fluoro-4-{[(2-methoxy-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-phenyl)-4H-[1,2,4]oxadiazol-5-one

3-(2-Fluoro-4-{[(2-piperidin-1-yl-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-phenyl)-4H-[1,2,4]oxadiazol-5-one trifluoroacetate

3-(2-Fluoro-4-{[(2-morpholin-4-yl-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-phenyl)-4H-[1,2,4]oxadiazol-5-one trifluoroacetate

3-(2-Fluoro-4-{[[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-phenyl)-4H-[1,2,4]oxadiazol-5-one trifluoroacetate

3-(4-{[(2-Pyrrolidin-1-yl-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-2-trifluoromethyl-phenyl)-4H-[1,2,4]oxadiazol-5-one

3-(4-{[(2-Dimethylamino-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-2-trifluoromethyl-phenyl)-4H-[1,2,4]oxadiazol-5-one trifluoroacetate

3-(4-{[(2-Methoxy-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-2-trifluoromethyl-phenyl)-4H-[1,2,4]oxadiazol-5-one

3-(4-{[(2-Piperidin-1-yl-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-2-trifluoromethyl-phenyl)-4H-[1,2,4]oxadiazol-5-one trifluoroacetate

3-(4-{[(2-Morpholin-4-yl-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-2-trifluoromethyl-phenyl)-4H-[1,2,4]oxadiazol-5-one trifluoroacetate

3-(4-{[[2-(1-Methyl-pyrrolidin-2-yl)-ethyl]-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-2-trifluoromethyl-phenyl)-4H-[1,2,4]oxadiazol-5-one trifluoroacetate

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

3-(4-{[[4-(4-Chloro-phenyl)-thiazol-2-yl]-(3-methoxy-propyl)-amino]-methyl}-2-fluoro-phenyl)-4H-[1,2,4]oxadiazol-5-one

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

3-[4-({[4-(4-Chloro-phenyl)-thiazol-2-yl]-[2-(2-methoxy-ethoxy)-ethyl]-amino}-methyl)-2-fluoro-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)heterocyclewhere 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 ringand, in particular, phenyl ringare 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 "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, 5306-5311). 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 demyelinating 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): 318 (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.

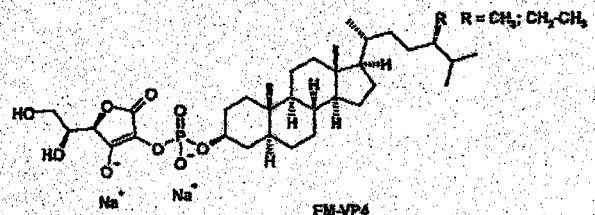
In one embodiment of the invention, the compound of the formula I is administered in combination with NRIs (norepinephrine reuptake inhibitors) as described, for example, in WO2002053140.

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.

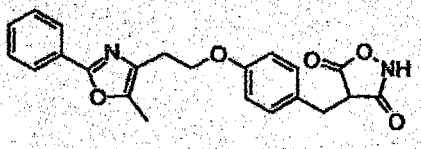
In one embodiment of the invention, the compound of the formula I is administered in combination with antithrombotic active ingredients, such as, for example, clopidrogel.

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.

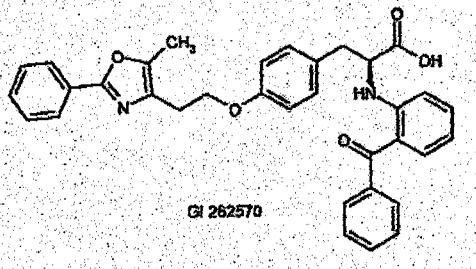
The formulae for some of the development codes mentioned above are given below.



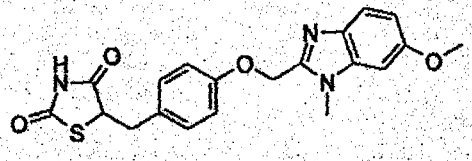
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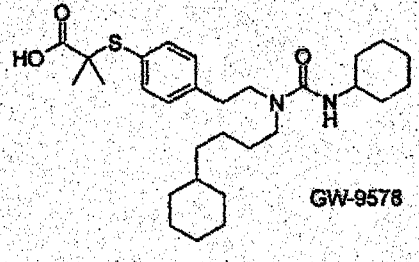
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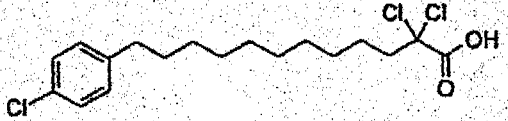
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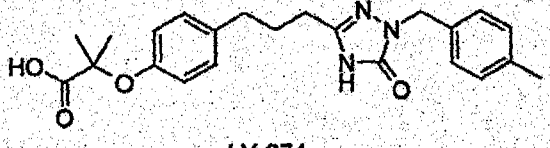
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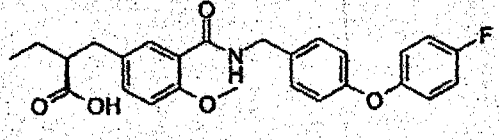
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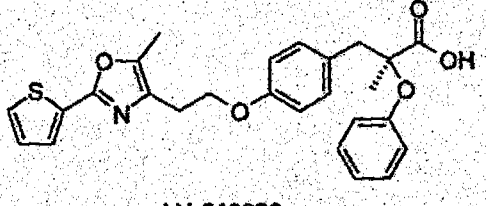
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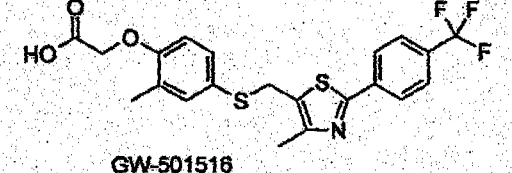
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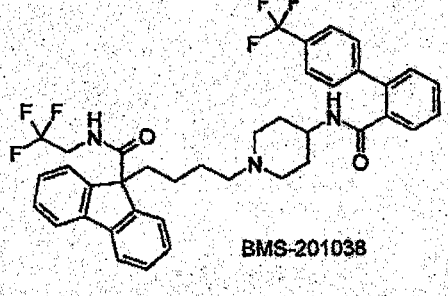
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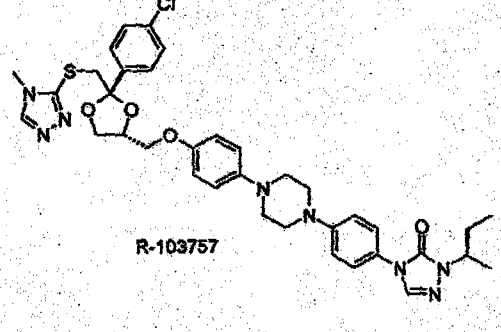
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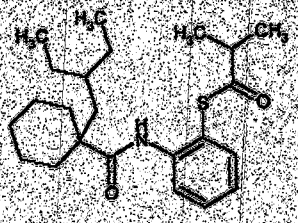
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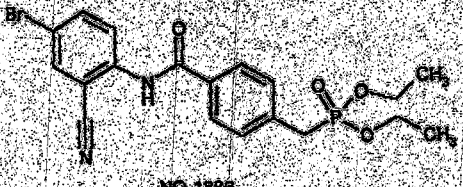
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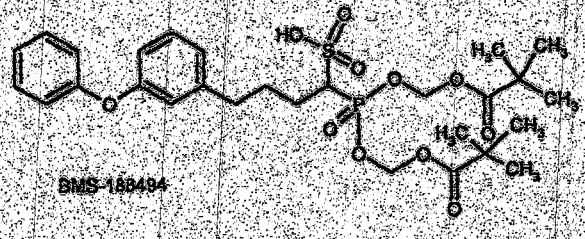
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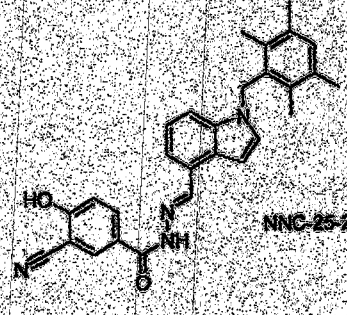
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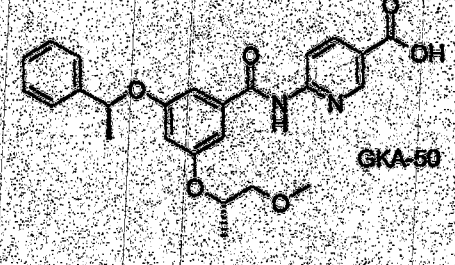
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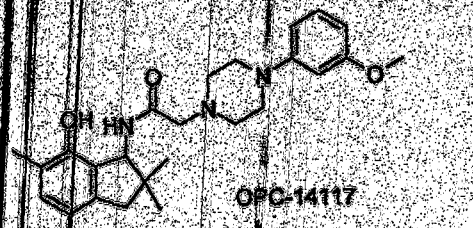
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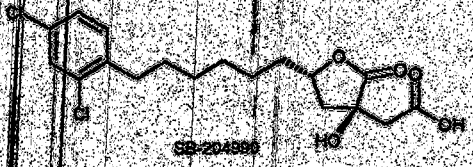
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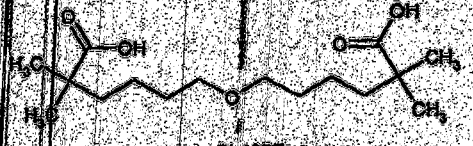
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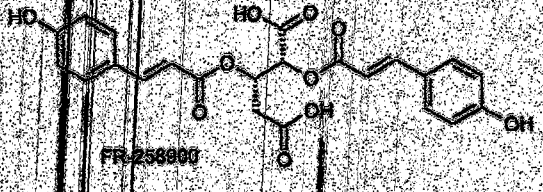
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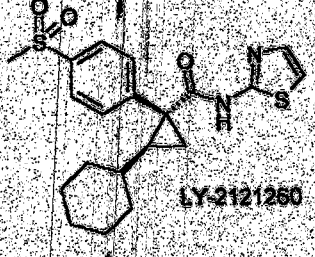
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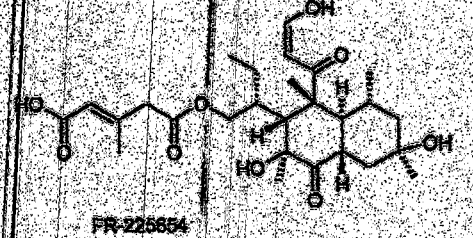
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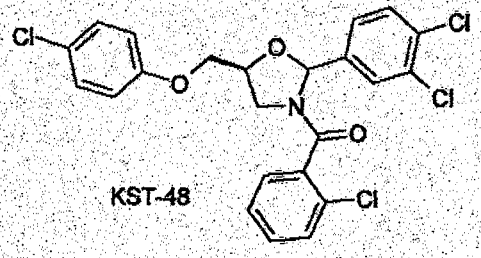
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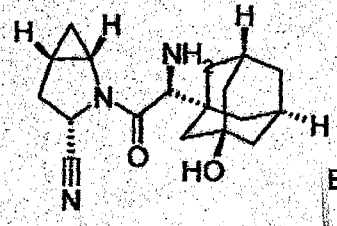
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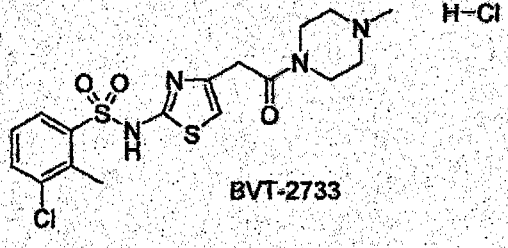
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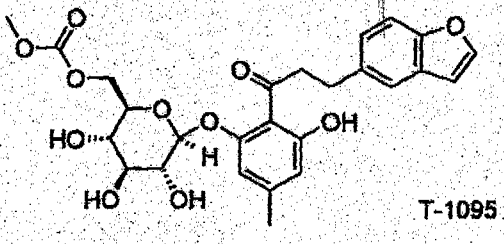
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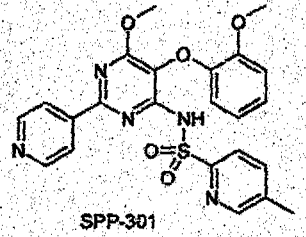
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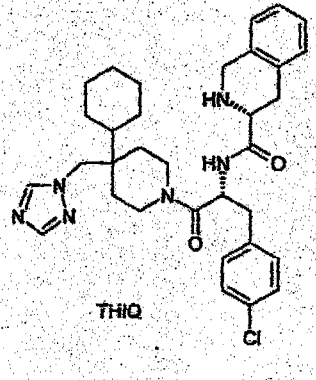
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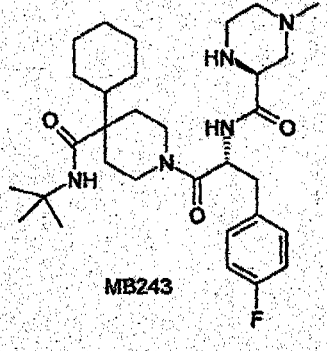
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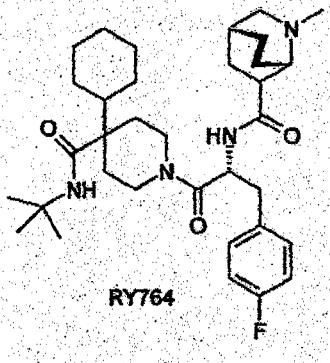
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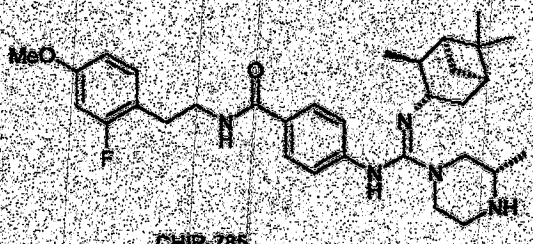
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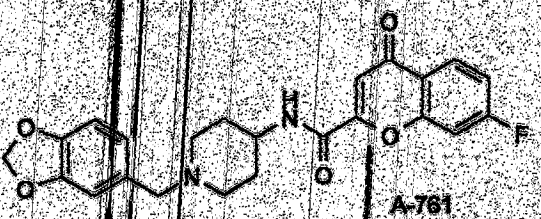
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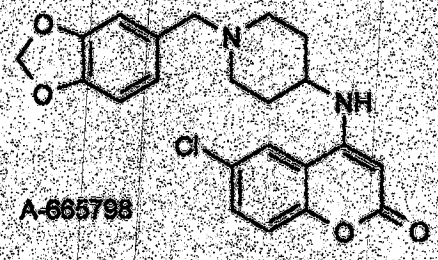
RY764



CHIR-785



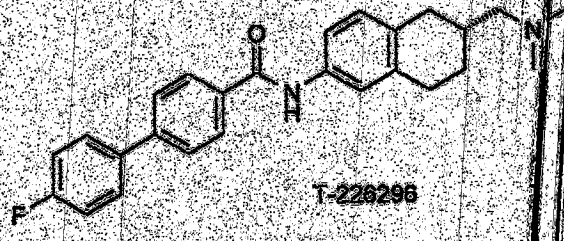
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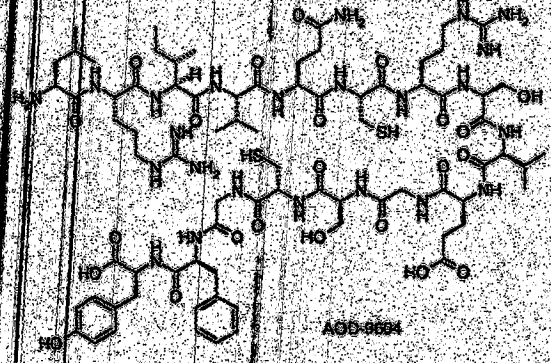
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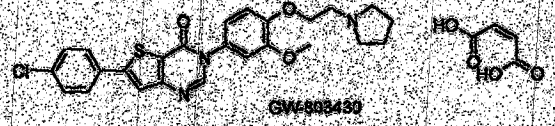
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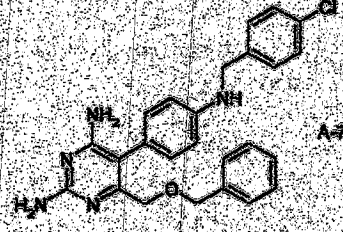
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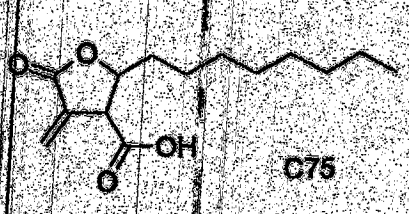
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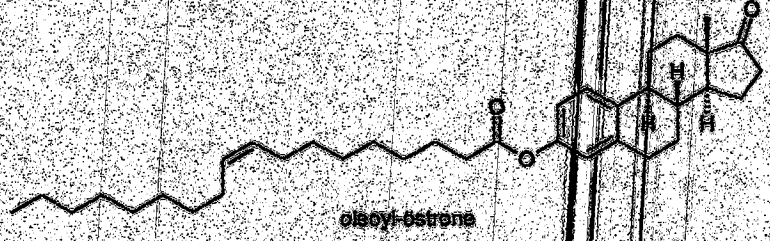
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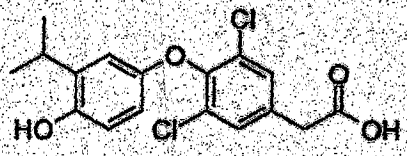
A-778193



C75



oleoyl-estrone



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 (#10131-027, 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 (# 353112, 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 41 in this assay are in the range from 50 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).

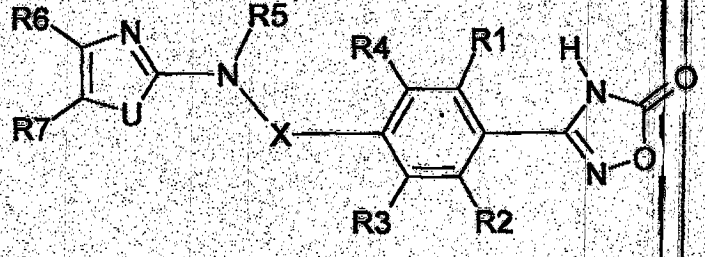
Assay procedure and evaluation

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.

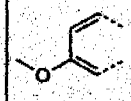
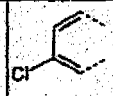
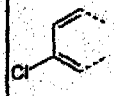
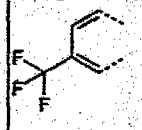
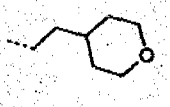
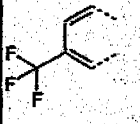
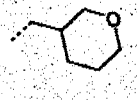
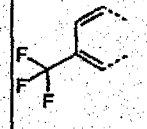
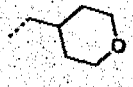
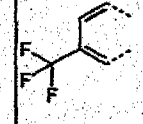
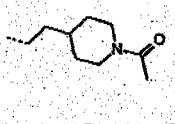
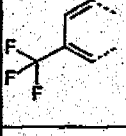
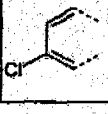
PPARdelta EC50 values in the range from 1 nM to >10 µM were measured for the PPAR agonists of Examples 1 to 41 described in this application. Compounds of the invention of the formula I activate the PPARdelta receptor.

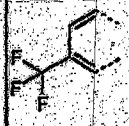
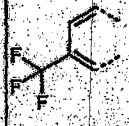
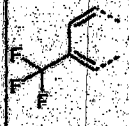
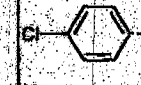
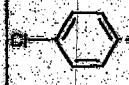
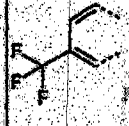
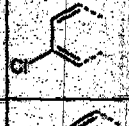
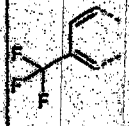
The examples given in Table II serve to illustrate the invention, but without limiting it.

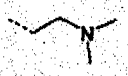
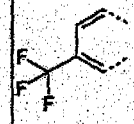
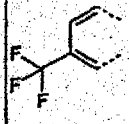
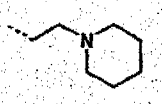
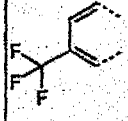
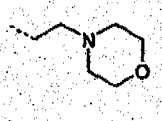
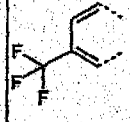
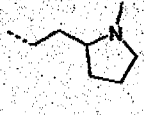
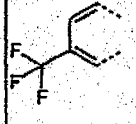
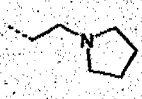
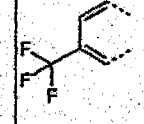
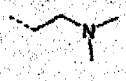
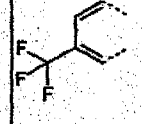
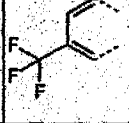
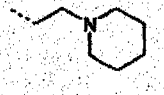
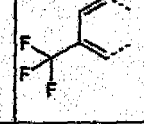
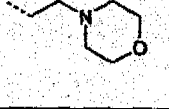
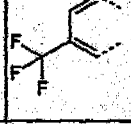
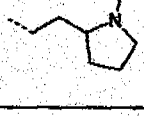
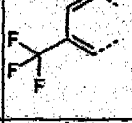
Table I



where R2, R3, R4 = H ,
a dotted line means the point of attachment
If R6 and R7 are bonded to form an annelated ring together with the oxazole respectively the thiazole ring, the upper dotted line means the point of attachment for R6 and the lower dotted line the point of attachment for R7.

Example	X	U	R1	R5	R6	R7
1	-CH2CH2-	O	H	-(CH2)3CH3		
2	-CH2CH2-	S	H	-(CH2)3CH3		
3	-CH2CH2-	S	H	-(CH2)3CH3		
4	-CH2CH2-	S	H	-(CH2)3CH3		
5	-CH2CH2-	S	-CH3	-(CH2)3CH3		
6	-CH2CH2-	S	-CH3	-(CH2)3CH3		
7	-CH2CH2-	S	-CH3			
8	-CH2CH2-	S	-CH3			
9	-CH2CH2-	S	-CH3			
10	-CH2CH2-	S	-CH3			
11	-CH2-	O	H	-(CH2)3CH3		
12	-CH2-	S	H	-(CH2)3CH3		
13	-CH2-	S	H	-(CH2)3CH3		

Example	X	U	R1	R5	R6	R7
14	-CH2CH2-	S	-CH3	-(CH2)3-O-CH3		
15	-CH2CH2-	S	-CH3	-(CH2)2-O-(CH2)2-O-CH3		
16	-CH2CH2-	S	-CH3			
17	-CH2CH2-	S	-CH3	-(CH2)2-O-CH3		
18	-CH2CH2-	S	H	-(CH2)3CH3		H
19	-CH2CH2-	S	H	-(CH2)3CH3		H
20	-CH2CH2-	S	H	-(CH2)3-O-CH3		H
21	-CH2CH2-	S	H	-(CH2)2-O-(CH2)2-O-CH3		H
22	-CH2CH2-	S	H			H
23	-CH2CH2-	S	H	-(CH2)2-O-CH3		H
24	-CH2-	S	F	-(CH2)3CH3		
25	-CH2-	S	F	-(CH2)3CH3		
26	-CH2-	S	F			

Example	X	U	R1	R5	R6	R7
27	-CH2-	S	F			
28	-CH2-	S	F	-(CH2)2-O-CH3		
29	-CH2-	S	F			
30	-CH2-	S	F			
31	-CH2-	S	F			
32	-CH2-	S	-CF3			
33	-CH2-	S	-CF3			
34	-CH2-	S	-CF3	-(CH2)2-O-CH3		
35	-CH2-	S	-CF3			
36	-CH2-	S	-CF3			
37	-CH2-	S	-CF3			
38	-CH2-	S	H	-(CH2)3CH3		H

Example	X	U	R1	R5	R6	R7
39	-CH2-	S	F	-(CH2)3-O-CH3		H
40	-CH2-	S	F	-(CH2)2-O-CH3		H
41	-CH2-	S	F	-(CH2)2-O-(CH2)2-O-CH3		H

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

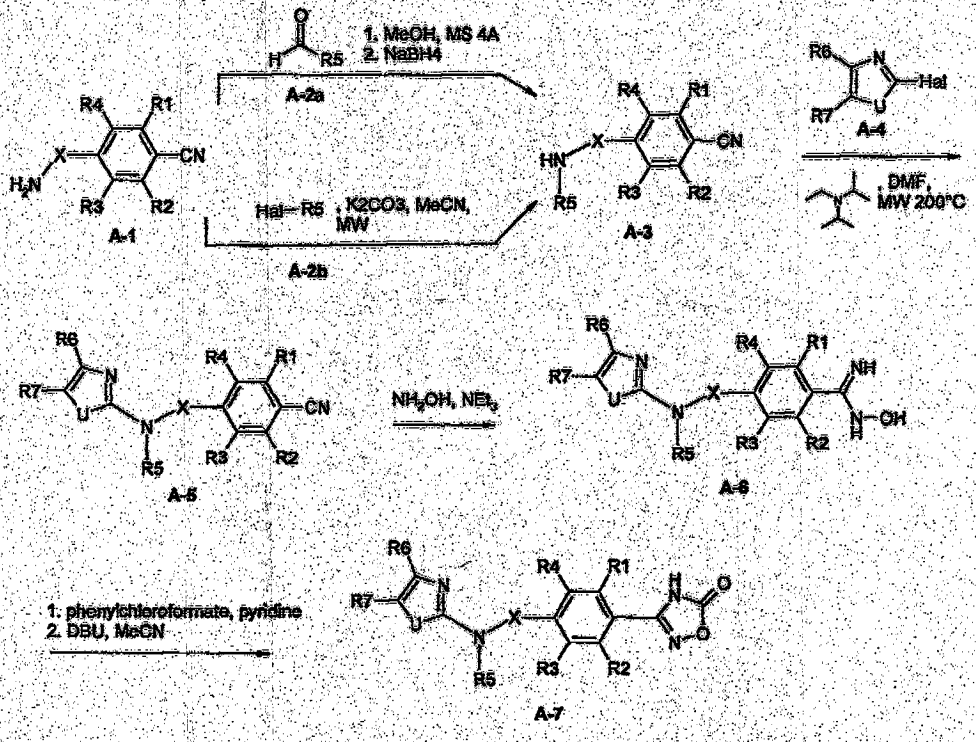
Example	PPARalpha EC50 (μM)	PPARdelta EC50 (μM)
9	0.06	0.02
14	0.07	0.004
23	0.82	0.65
24	1.35	0.27
28	1.02	0.06
33	1.10	1.80
39	0.36	0.20

Processes

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

Process A

This process is used for synthesizing compounds of general formula A-7, where X, U, R1, R2, R3, R4, R5, R6, and R7 are as defined.



A reductive amination with a primary amine of the general formula A-1 where X , R1, R2, R3 and R4 are as defined and an aldehyde of general formula A-2a where R5 is as defined is performed in a solvent as methanol in the presence of molecular sieves 4 Angström and by addition of a reducing agent as sodium borohydride to give a secondary amine of the general formula A-3. Alternatively the primary amine of the general formula A-1 can be alkylated with an halide of general formula A-2b, where R5 is as defined in a solvent as acetonitrile in presence of a base as potassium carbonate under microwave irradiation to give the secondary amine of the general formula A-3. The amine of general formula A-3 is reacted with an in two position halogenated thiazole, where U is S and R6 and R7 are as defined, or oxazole, where U is O and R6 and R7 are as defined in general formula A-4 under microwave irradiation at elevated temperature, e.g. 200°C, in a solvent as dimethylformamide in the presence of a base as N,N-diisopropylethylamine to give a compound of general formula A-5. The compound of the general formula A-5 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 A-6. A compound of the general formula

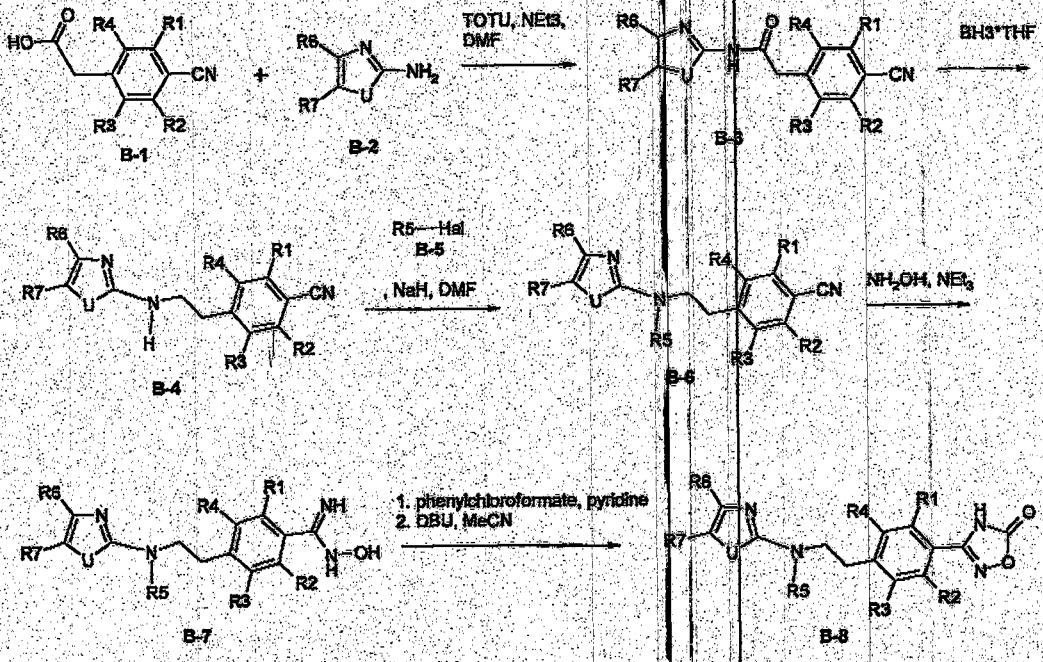
A-6 is converted to the product of general formula A-7 by reaction with phenylchloroformate in the presence of a base as pyridine and treating this intermediate with a base as 1,8-diazabicyclo[5.4.0]undec-7-ene in a solvent as acetonitrile.

Examples 1-17 were obtained according to process A.

Other compounds can be obtained accordingly or by known processes.

Process B:

This process is used for synthesizing compounds of general formula B-8, where X is -CH2CH2- and U, R1, R2, R3, R4, R5, R6, and R7 are as defined.



A carboxylic acid of general formula B-1 where R1, R2, R3 and R4 are as defined is condensed with a primary amine of general formula B-2 where R6 and R7 are as defined with a coupling reagent as O-((Ethoxycarbonyl)cyanomethyleneamino)-N,N,N',N'-tetramethyluronium tetrafluoroborat in a solvent as dimethylformamide in the presence of a base as triethylamine to give an amide of the general formula B-3. The amide of general formula B-3 is reduced with a reducing agent as borane tetrahydrofuran complex in a polar aprotic solvent as tetrahydrofuran to obtain a secondary amine of general formula B-4. The secondary amine of general formula B-4 is alkylated with a halide of general formula B-5, where R5 is as defined, in the

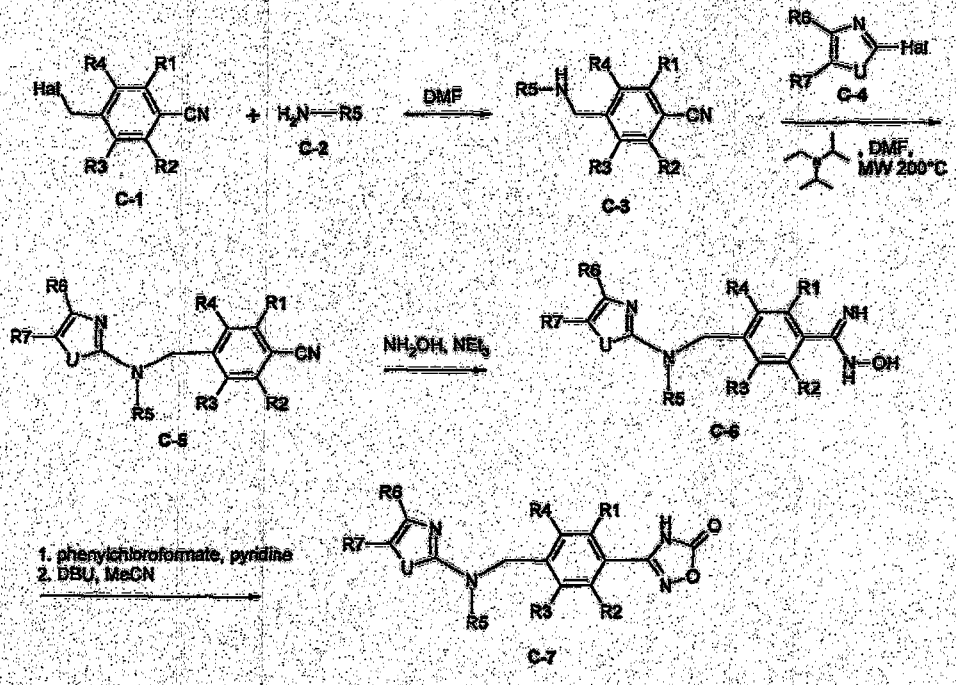
presence of a base as sodium hydride in a solvent as dimethylformamide to give a tertiary amine of general formula B-6. The compound of the general formula B-6 is reacted with hydroxylamine hydrochloride in the presence of a base as triethylamine in a solvent as tetrahydrofuran and methanol to obtain a compound of the general formula B-7. A compound of the general formula B-7 is converted to the product of general formula B-8 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 18-23 were obtained according to process B.

Other compounds can be obtained accordingly or by known processes.

Process C:

This process is used for synthesizing compounds of general formula C-7, where X is -CH2- and U, R1, R2, R3, R4, R5, R6, and R7 are as defined.



A benzylic halide of general formula C-1 where R1, R2, R3 and R4 are as defined is reacted with a primary amine of general formula C-2 where R5 is as defined in a solvent as dimethylformamide to give a secondary amine of the general formula C-3. The secondary amine of general formula C-3 is reacted with a in two position halogenated thiazole, where U is S and R6 and R7 are as defined or oxazole, where U

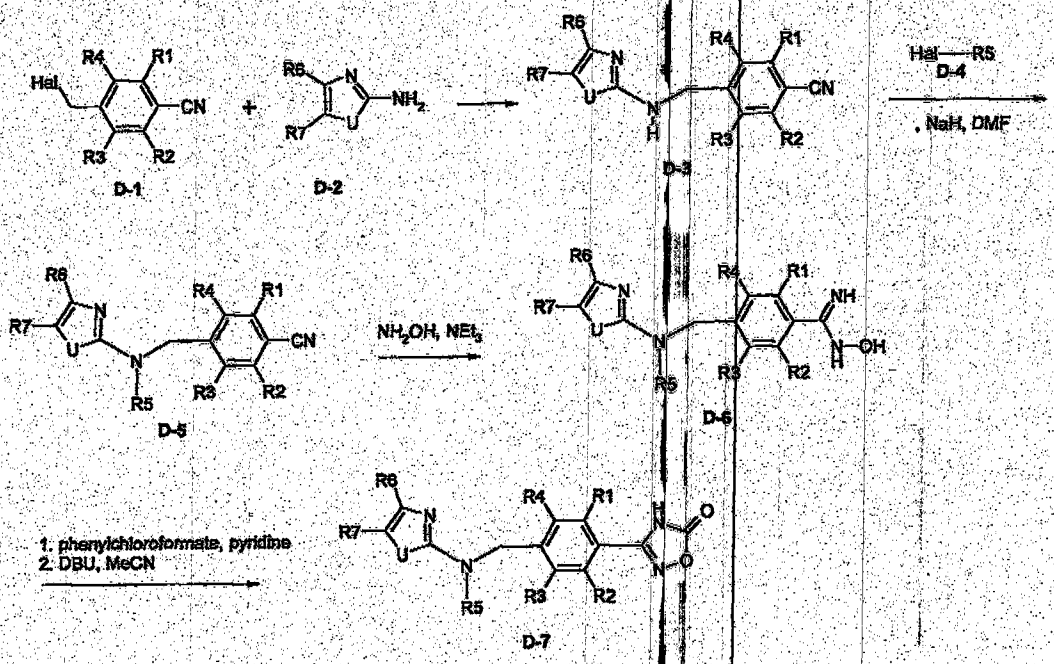
is O and R6 and R7 are as defined of general formula C-4 under microwave irradiation at elevated temperature, e.g. 200°C, in a solvent as dimethylformamide in the presence of a base as N,N-diisopropylethylamine to give a compound of general formula C-5. The compound of the general formula C-5 is reacted 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 C-6. A compound of the general formula C-6 is converted to the product of general formula C-7 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 24-37 were obtained according to process C.

Other compounds can be obtained accordingly or by known processes.

Process D:

This process is used for synthesizing compounds of general formula D-7, where X is -CH2- and U, R1, R2, R3, R4, R5, R6, and R7 are as defined.



A benzylic halide of general formula D-1 where R1, R2, R3 and R4 are as defined is reacted with a 2-amino-thiazole of general formula D-2, where U is S and R6 and R7

are with a 2-amino-oxazole, where U is O and R6 and R7 are as defined of general formula D-2 to give a secondary amine of the general formula D-3.

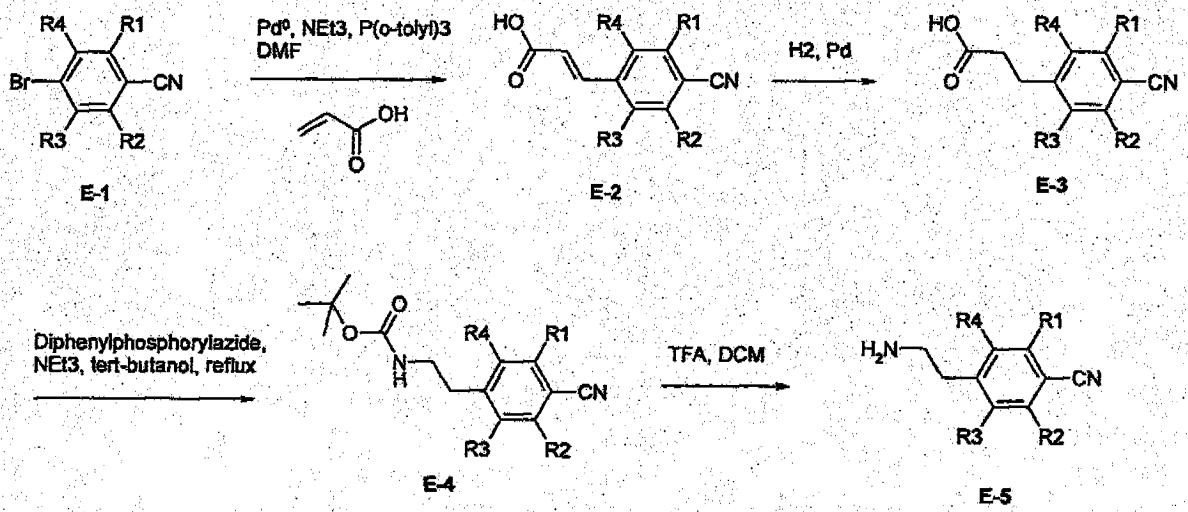
The secondary amine of general formula D-3 is alkylated with a halide of general formula D-4, where R5 is as defined, in the presence of a base as sodium hydride in a solvent as dimethylformamide to give a tertiary amine of general formula D-5. The compound of the general formula D-5 is reacted with 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 D-6. A compound of the general formula D-6 is converted to the product of general formula D-7 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 38-41 were obtained according to process D.

Other compounds can be obtained accordingly or by known processes.

Process E:

This process is used for synthesizing building blocks of general formula E-5, which correspond to general formula A-1 of process A, where X is -CH2CH2- and R1, R2, R3 and R4 are as defined.

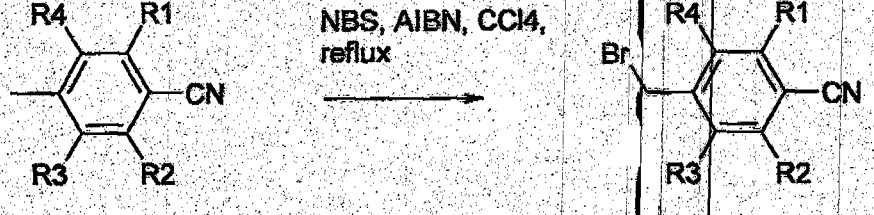


A Bromobenzonitrile of general formula E-1 is cross coupled with acrylic acid under Heck reaction conditions, in the presence of a palladium source as palladium(II)acetate, a ligand as Tri-o-tolyl-phosphine, a base as triethylamine in a solvent as acetonitrile to give a substituted acrylic acid of general formula E-2. The acrylic acid of general formula E-2 is hydrogenated in the presence of a palladium catalyst as palladium on charcoal (10%) in a solvent as methanol or a mixture of solvents as methanol and tetrahydrofuran under a hydrogen atmosphere to give a carboxylic acid of general formula E-3. The carboxylic acid of general formula E-3 is rearranged to the BOC protected amine of general formula E-4 by treatment with diphenylphosphorylazide in refluxing tert-butanol in the presence of a base as triethylamine. The BOC protecting group of the amine of general formula E-4 is removed by treatment with a base as trifluoroacetic acid in a solvent as dichloromethane to give the primary amine of general formula E-5.

Other compounds can be obtained accordingly or by known processes.

Process F:

This process is used for synthesizing building blocks of general formula F-2, which correspond to general formula C-1 of process C, where Hal is bromine and R1, R2, R3 and R4 are as defined and D-1 of process D, Hal is bromine and R1, R2, R3 and R4 are as defined.



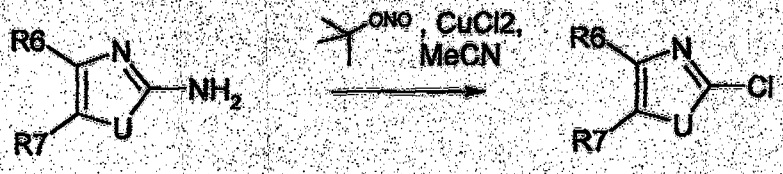
F-1 F-2

A 4-methyl-benzonitrile of general formula F-1 is brominated by treatment with N-bromosuccinimide in the presence of a radical initiator as 2,2´-azobis(2-methylpropionitrile) in a solvent as tetrachloromethane to give the benzylbromide of general formula F-2.

Other compounds can be obtained accordingly or by known processes.

Process G:

This process is used for synthesizing building blocks of general formula G-2, which correspond to general formula A-4 of process A, where Hal is chlorine, U is S and R6 and R7 are as defined and C-4 of process C, where Hal is chlorine, U is S and R6 and R7 are as defined.



G-1 G-2

A 2-amino-thiazole of general formula G-1, where U is S and R6 and R7 are as defined or a 2-amino-oxazole, where U is O and R6 and R7 are as defined is reacted with tert-butyl-nitrite and copper(II)chloride in a solvent as acetonitrile to give a 2-halogenated compound of general formula G-2.

Other compounds can be obtained accordingly or by known processes.

List of abbreviation:

Ac	acetyl
AIBN	2,2'-azobis(2-methylpropionitrile)
Bn	benzyl
BOC	tert-butyl-oxy-carbonyl
iBu	isobutyl
tBu	tert-Butyl
BuLi	n-butyllithium
Bz	benzoyl
Cy	cyclohexyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCI	direct chemical ionization (MS)
DCM	dichloromethane
DMAP	N,N-dimethylaminopyridine
DMF	N,N-dimethylformamide

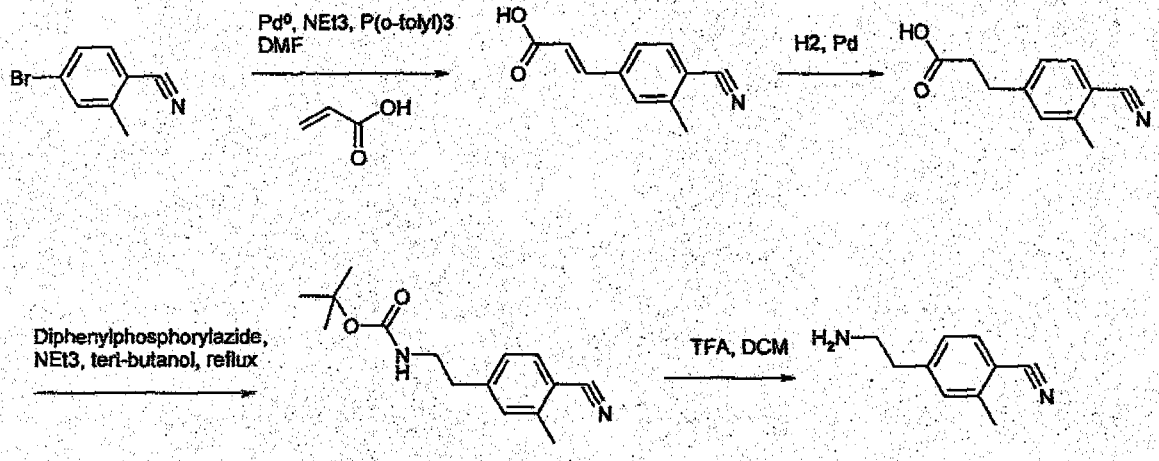
DMSO	dimethylsulfoxide
EE	ethyl acetate
eq	equivalents
ESI	electrospray-Ionisation (MS)
FG	leaving group
GC	gas chromatography
Hal	halogen
HPLC	high performance liquid chromatography
LC-MS	liquid chromatography coupled with mass-spectroscopy
Me	methyl
MeCN	acetonitrile
MS	mass-spectroscopy
MS 4A	molecular sieves four angström
MsCl	methansulfonylchloride
MW	micro wave
NBS	N-bromosuccinimide
NMR	nuclear magnetic resonance
p	para
Pd/C	palladium on carbon
iPr	isopropyl
nPr	n-propyl
Rf	retention factor (TLC)
tert	tertiary
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TOTU	O-((Ethoxycarbonyl)cyanomethyleneamino)-N,N,N',N'-tetramethyluronium tetrafluoroborat

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

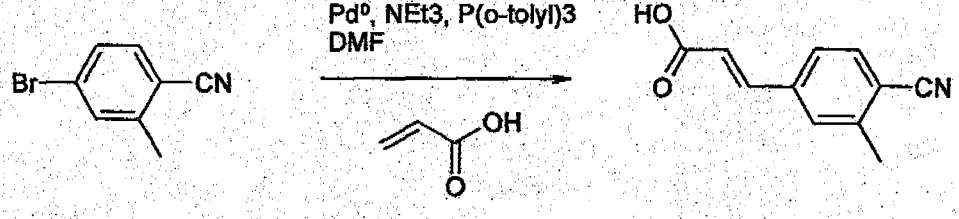
The experimental procedures for preparing the examples mentioned above are described below:

Building block synthesis according to process E:

4-(2-Amino-ethyl)-2-methyl-benzonitrile



(E)-3-(4-Cyano-3-methyl-phenyl)-acrylic acid

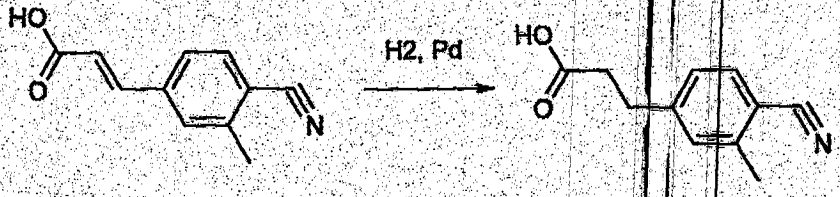


9.0 g 4-bromo-2-methylbenzonitrile, 2.76 g tri-o-tolylphosphine, 3.11 ml acrylic acid and 25.1 ml triethylamine are dissolved in 80 ml acetonitrile. The reaction mixture is degassed , then 2.0 g palladium (II)acetate were added and the mixture stirred two hours under microwave irradiation at 200°C. The cooled reaction mixture was diluted by addition of 50 ml ethylacetate. Thereby (E)-3-(4-Cyano-3-methyl-phenyl)-acrylic acid precipitated as a white solid. The precipitate was filtered off and dried in vacuo to obtain 2.5g (E)-3-(4-Cyano-3-methyl-phenyl)-acrylic acid. The filtrate was washed with 1N HCl, thereby (E)-3-(4-Cyano-3-methyl-phenyl)-acrylic acid precipitated again as a white solid. The precipitate was filtered off and dried in vacuo to obtain 2.0g (E)-3-(4-

Cyano-3-methyl-phenyl)-acrylic acid. The filtrate was reduced in vacuo to one third of its volume, 150 ml diethylether were added, thereby (E)-3-(4-Cyano-3-methyl-phenyl)-acrylic acid precipitated again as a white solid. The precipitate was filtered off and dried in vacuo to obtain 840 mg (E)-3-(4-Cyano-3-methyl-phenyl)-acrylic acid.

C11H9NO2 (187.20), MS(ESI): 188.1 ($M+H^+$), Rf(ethyl acetate : methanol = 9:1) = 0.16.

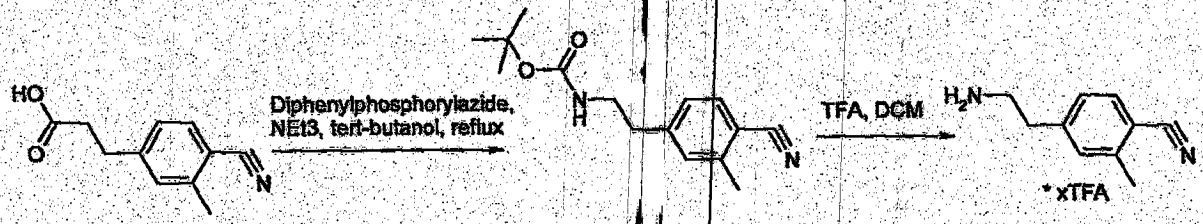
3-(4-Cyano-3-methyl-phenyl)-propionic acid



5.15 g (E)-3-(4-Cyano-3-methyl-phenyl)-acrylic acid were dissolved in a mixture of 250 ml tetrahydrofuran and 125 ml methanol. 510 mg palladium on charcoal (10%) were added and the reaction mixture was stirred under a hydrogen atmosphere overnight. The catalyst was filtered off over a celite pad. The solvent was removed in vacuo to obtain 5.2 g 3-(4-Cyano-3-methyl-phenyl)-propionic acid as a white solid.

C11H11NO2 (189.22), MS(ESI): 190.2 ($M+H^+$).

4-(2-Amino-ethyl)-2-methyl-benzonitrile



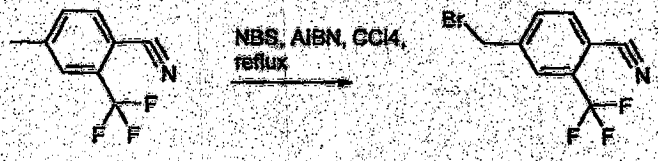
To a solution of 5.20 g 3-(4-Cyano-3-methyl-phenyl)-propionic acid and 4.57 ml triethylamine in 100 ml tert-butanol 9.10 g diphenylphosphorylazide were given and the mixture heated under reflux overnight. The cooled reaction mixture was evaporated in vacuo. The resulting residue was dissolved in 150 ml ethyl acetate, washed with 50 ml citric acid/brine = 1:1 and 50 ml saturated NaHCO3 solution and then dried over MgSO4. The residue was dissolved in 50 ml dichloromethane and 20 ml trifluoroacetic acid were added. The reaction mixture was stirred at room temperature for two hours.

The solvent was removed in vacuo. The residue was coevaporated four times with portions of 100 ml toluene. The resulting brown residue was taken up in 50 ml acetonitrile and stirred at room temperature. The solid material was filtered off and dried in vacuo to obtain 2.45g 4-(2-Amino-ethyl)-2-methyl-benzonitrile as its trifluoroacetate salt. The filtrate was evaporated in vacuo, the resulting residue was taken up in 100 ml diethylether and stirred at room temperature. The solid material was filtered off and dried in vacuo to obtain 1.17 g 4-(2-Amino-ethyl)-2-methyl-benzonitrile as its trifluoroacetate salt.

$C_{10}H_{12}N_2 \cdot x$TFA (160.22 + xTFA), MS(ESI): 161.1 ($M+H^+$).

Building block synthesis according to process F:

4-Bromomethyl-2-trifluoromethyl-benzonitrile

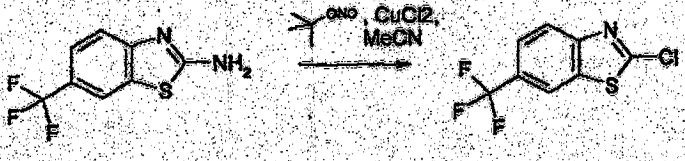


To a refluxing mixture of 5.0 g 4-Methyl-2-(trifluoromethyl)benzonitrile in 50 ml tetrachloromethane were added a mixture of 5.77 g N-bromosuccinimide and 1.77 g 2,2'-azobis(2-methylpropionitrile). The reaction mixture was heated under reflux for three hours. The reaction mixture was filtered throuph a pad of celite and the solvent was removed in vacuo to obtain 11.2 g crude 4-Bromomethyl-2-trifluoromethyl-benzonitrile (impurified with the dibromo product) as a white solid. This material was used without further purification.

$C_9H_5BrF_3N$ (264.05), MS(ESI): 264.0, 266.0 ($M+H^+$), Rf(n-heptane :ethyl acetate = 4:1) = 0.25 .

Building block synthesis according to process G:

2-Chloro-6-trifluoromethyl-benzothiazole

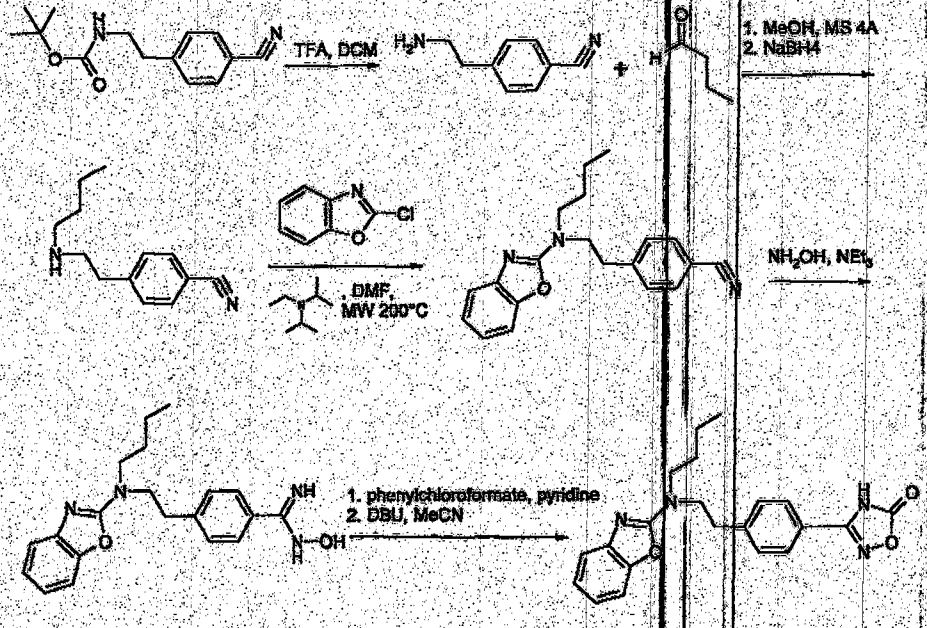


8.25 ml tert-butyl nitrite were added to a solution of 7.40 g copper (II) chloride in 120 ml acetonitrile. The reaction mixture was stirred ten minutes at room temperature. Then a solution of 10.0 g 2-Amino-6-(trifluoromethyl)benzonitrile were added. Then 100 ml 1N HCl were added to the cooled reaction mixture. The reaction mixture was extracted five times with portions of 50 ml ethyl acetate. The combined organic layers were washed with water and the dried over MgSO4. The solvent was removed in vacuo to obtain 9.79 g crude 2-Chloro-6-trifluoromethyl-benzothiazole as a red oil which solidifies upon standing. This material was used without further purification. C8H3ClF3NS (237.63), MS(GC): 237.0 ($M+H^+$), Rf(n-heptane :ethyl acetate = 1:1) = 0.72 .

The following examples were prepared according to process A:

Example 1

3-{4-[2-(Benzooxazol-2-yl-butyl-amino)-ethyl]-phenyl}-4H-[1,2,4]oxadiazol-5-one

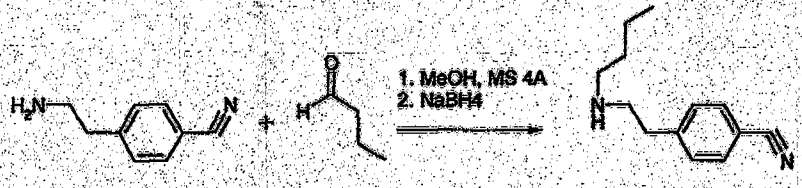


4-(2-Amino-ethyl)-benzonitrile



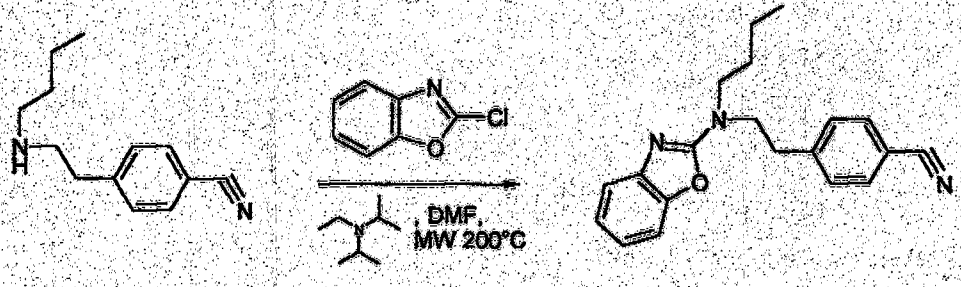
1.90 g commercially available [2-(4-Cyano-phenyl)-ethyl]-carbamic acid tert-butyl ester were dissolved in 100 ml dichloromethane. 10 ml trifluoroacetic acid were added and the reaction mixture was stirred at room temperature for one hour. 250 ml ethyl acetate were added and the mixture was washed three times with saturated NaHCO3 solution. The organic layer was dried over MgSO4 and then the solvent was removed in vacuo to obtain 700 mg 4-(2-Amino-ethyl)-benzonitrile as pale yellow solid.
C9H10N2 (146.19), MS(ESI): 147.1 ($M+H^+$).

4-(2-Butylamino-ethyl)-benzonitrile



700 mg 4-(2-Amino-ethyl)-benzonitrile and 63 µl Butyraldehyde were dissolved in 20 ml methanol. 1.0 g molecular sieves 4 Angström were added the mixture was stirred at room temperature for two hours. Then 270 mg sodium borohydride were added and the mixture was stirred for an additional hour at room temperature. 100 ml ethyl acetate were added, and the reaction was quenched by addition of 1 ml water. The reaction mixture was filtered through a pad of celite and MgSO4. The filtrate was evaporated in vacuo to provide 750 mg crude 4-(2-Butylamino-ethyl)-benzonitrile. This material was used without further purification.
C13H18N2 (202.30), MS(ESI): 203.2 ($M+H^+$).

4-[2-(Benzooxazol-2-yl-butyl-amino)-ethyl]-benzonitrile

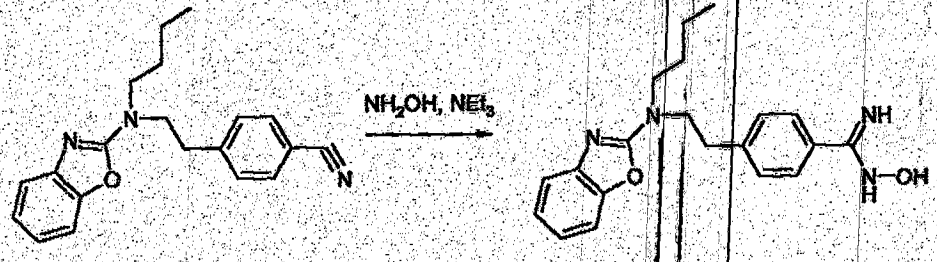


A solution of 750 mg 4-(2-Butylamino-ethyl)-benzonitrile, 854 mg 2-chlorobenzooxazole and 0.95 ml N,N-diisopropylethylamine in 10 ml

dimethylformamide were stirred under microwave irradiation at 200°C for thirty minutes. The cooled reaction mixture was diluted by the addition of 60 ml ethyl acetate, then washed three times with 40 ml brine. The organic layer was dried over MgSO4, then the solvent was removed in vacuo. The residue was purified by RP-HPLC to obtain 290 mg 4-[2-(Benzooxazol-2-yl-butyl-amino)-ethyl]-benzonitrile as pale yellow amorphous solid.

C20H21N3O (319.41), MS(ESI): 320.2 ($M+H^+$).

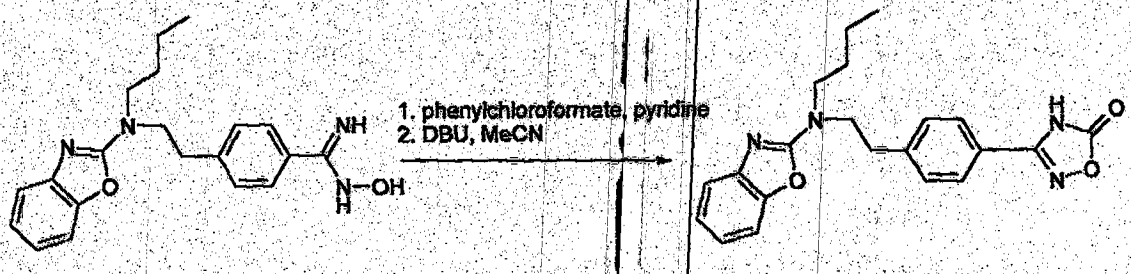
4-[2-(Benzooxazol-2-yl-butyl-amino)-ethyl]-N-hydroxy-benzamidine



290 mg 4-[2-(Benzooxazol-2-yl-butyl-amino)-ethyl]-benzonitrile were dissolved in a mixture of 10 ml tetrahydrofuran and 20 ml methanol. 930 mg hydroxylamine hydrochloride were added followed by the addition of 2.24 ml triethylamine. The reaction mixture was stirred at 65°C for two hours. The cooled reaction mixture was diluted by the addition of 100 ml ethyl acetate, then washed three times with 40 ml water. The organic layer was dried over MgSO4, then the solvent was removed in vacuo to obtain 280 mg 4-[2-(Benzooxazol-2-yl-butyl-amino)-ethyl]-N-hydroxy-benzamidine as a pale yellow oil.

C20H24N4O2 (352.44), MS(ESI): 353.2 ($M+H^+$).

3-{4-[2-(Benzooxazol-2-yl-butyl-amino)-ethyl]-phenyl}-4H-[1,2,4]oxadiazol-5-one



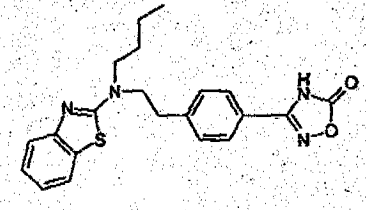
280 mg 4-[2-(Benzooxazol-2-yl-butyl-amino)-ethyl]-N-hydroxy-benzamidine were dissolved in 5 ml dichloromethane. 78 µl pyridine and 120 µl phenylchloroformate were

added and the mixture stirred at room temperature for ten minutes. The mixture was diluted by the addition of 15 ml acetonitrile and 115 µl 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 105 mg 3-{4-[2-(Benzooxazol-2-yl-butyl-amino)-ethyl]-phenyl}-4H-[1,2,4]oxadiazol-5-one as an amorphous lyophilisate.

$C_{21}H_{22}N_4O_3$ (378.43), MS(ESI): 379.2 ($M+H^+$).

Example 2

3-{4-[2-(Benzothiazol-2-yl-butyl-amino)-ethyl]-phenyl}-4H-[1,2,4]oxadiazol-5-one

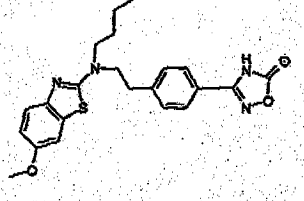


According to the method described in Example 1 3-{4-[2-(Benzothiazol-2-yl-butyl-amino)-ethyl]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 4-(2-Butylamino-ethyl)-benzonitrile and commercially available 2-chlorobenzothiazole.

$C_{21}H_{22}N_4O_2S$ (394.50), MS (ESI): 395.2 ($M+H^+$).

Example 3

3-(4-{2-[Butyl-(6-methoxy-benzothiazol-2-yl)-amino]-ethyl}-phenyl)-4H-[1,2,4]oxadiazol-5-one

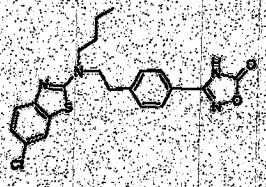


According to the method described in Example 1 3-(4-{2-[Butyl-(6-methoxy-benzothiazol-2-yl)-amino]-ethyl}-phenyl)-4H-[1,2,4]oxadiazol-5-one was obtained from 4-(2-Butylamino-ethyl)-benzonitrile and commercially available 2-Chloro-6-methoxy-benzothiazole.

$C_{22}H_{24}N_4O_3S$ (424.53), MS (ESI): 425.2 ($M+H^+$).

Example 4

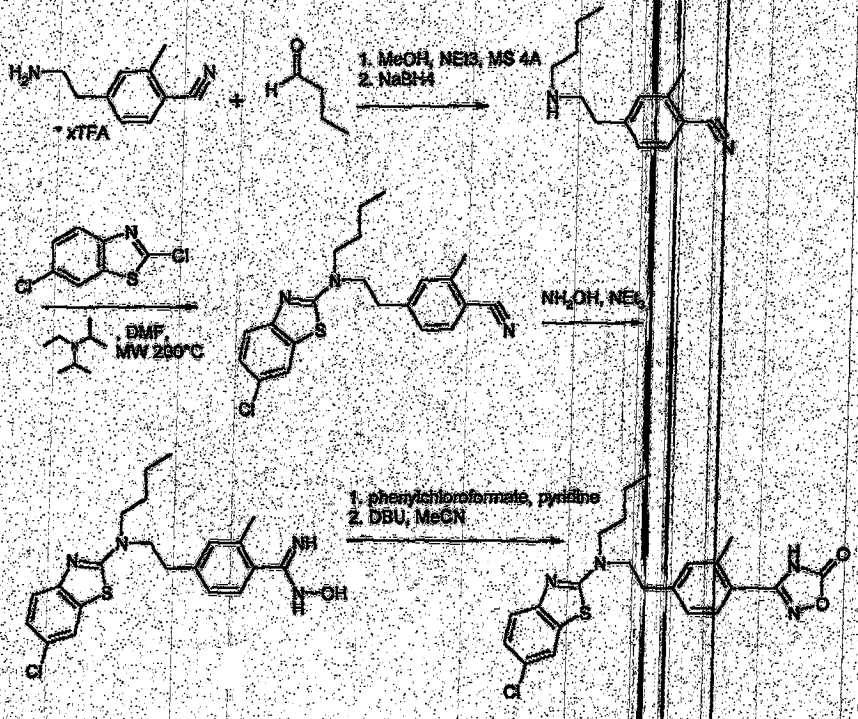
3-(4-{2-[Butyl-(6-chloro-benzothiazol-2-yl)-amino]-ethyl}-phenyl)-4H-[1,2,4]oxadiazol-5-one



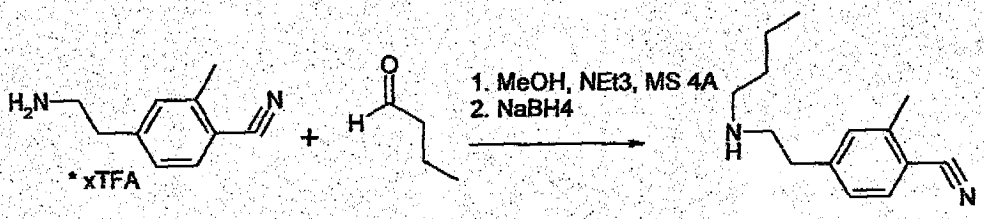
According to the method described in Example 1, 3-(4-{2-[Butyl-(6-chloro-benzothiazol-2-yl)-amino]-ethyl}-phenyl)-4H-[1,2,4]oxadiazol-5-one was obtained from 4-(2-Butylamino-ethyl)-benzonitrile and commercially available 2,6-dichlorobenzothiazole. $C_{21}H_{21}ClN_4O_2S$ (428.94), MS (ESI): 429.2 ($M+H^+$).

Example 5

3-(4-{2-[Butyl-(6-chloro-benzothiazol-2-yl)-amino]-ethyl}-2-methyl-phenyl)-4H-[1,2,4]oxadiazol-5-one



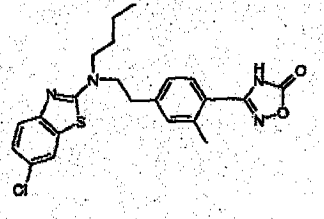
4-(2-Butylamino-ethyl)-2-methyl-benzonitrile



138 mg 4-(2-Amino-ethyl)-2-methyl-benzonitrile trifluoro acetate, 210 µl triethylamine and 50 µl Butyraldehyde were dissolved in 5 ml methanol. 150 mg molecular sieves 4 Angström were added and the mixture was stirred at room temperature overnight. Then 21 mg sodium borohydride were added and the mixture was stirred for an additional hour at room temperature. 50 ml ethyl acetate were added, and the reaction was quenched by addition of 0.5 ml water. The reaction mixture was filtered through a pad of celite and MgSO4. The filtrate was evaporated in vacuo to provide 230 mg crude 4-(2-Butylamino-ethyl)-2-methyl-benzonitrile, impurified with salts. This material was used without further purification.

C14H20N2 (216.33), MS(ESI): 217.2 ($M+H^+$).

3-(4-{2-[Butyl-(6-chloro-benzothiazol-2-yl)-amino]-ethyl}-2-methyl-phenyl)-4H-[1,2,4]oxadiazol-5-one

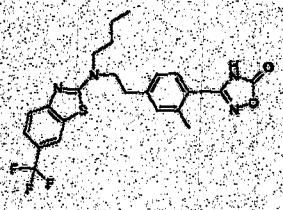


According to the method described in Example 1 3-(4-{2-[Butyl-(6-chloro-benzothiazol-2-yl)-amino]-ethyl}-2-methyl-phenyl)-4H-[1,2,4]oxadiazol-5-one was obtained from 4-(2-Butylamino-ethyl)-2-methyl-benzonitrile and commercially available 2,6-dichlorobenzothiazole.

C22H23ClN4O2S (442.97), MS (ESI): 443.1 ($M+H^+$).

Example 6

3-(4-{2-[Butyl-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-2-methyl-phenyl)-4H-[1,2,4]oxadiazol-5-one

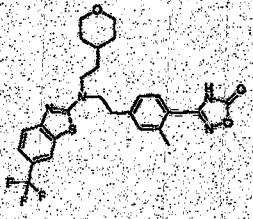


According to the method described in Example 1 3-(4-{2-[Butyl-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-2-methyl-phenyl)-4H-[1,2,4]oxadiazol-5-one was obtained from 4-(2-Butylamino-ethyl)-2-methyl-benzonitrile and 2-Chloro-6-trifluoromethyl-benzothiazole.

$C_{23}H_{23}F_3N_4O_2S$ (476.52), MS (ESI): 477.2 ($M+H^+$).

Example 7

3-(2-Methyl-4-{2-[[2-(tetrahydro-pyran-4-yl)-ethyl]-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-phenyl)-4H-[1,2,4]oxadiazol-5-one

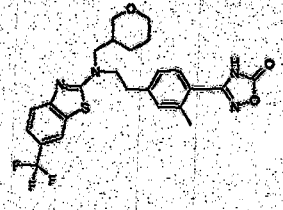


According to the method described in Example 1 and 5 3-(2-Methyl-4-{2-[[2-(tetrahydro-pyran-4-yl)-ethyl]-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-phenyl)-4H-[1,2,4]oxadiazol-5-one was obtained from 4-(2-Amino-ethyl)-2-methyl-benzonitrile trifluoro acetate, (tetrahydro-pyran-4-yl)-acetaldehyde and 2-Chloro-6-trifluoromethyl-benzothiazole.

$C_{26}H_{27}F_3N_4O_3S$ (532.59), MS (ESI): 533.1 ($M+H^+$).

Example 8

3-(2-Methyl-4-{2-[(tetrahydro-pyran-3-ylmethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-phenyl)-4H-[1,2,4]oxadiazol-5-one

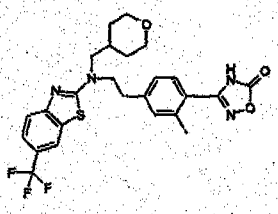


According to the method described in Example 1 and 5 3-(2-Methyl-4-{2-[(tetrahydro-pyran-3-ylmethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-phenyl)-4H-[1,2,4]oxadiazol-5-one was obtained from 4-(2-Amino-ethyl)-2-methyl-benzonitrile trifluoro acetate, tetrahydropyranyl-3-carboxaldehyde and 2-Chloro-6-trifluoromethyl-benzothiazole.

$C_{25}H_{25}F_3N_4O_3S$ (518.56), MS (ESI): 519.1 ($M+H^+$).

Example 9

3-(2-Methyl-4-{2-[(tetrahydro-pyran-4-ylmethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-phenyl)-4H-[1,2,4]oxadiazol-5-one

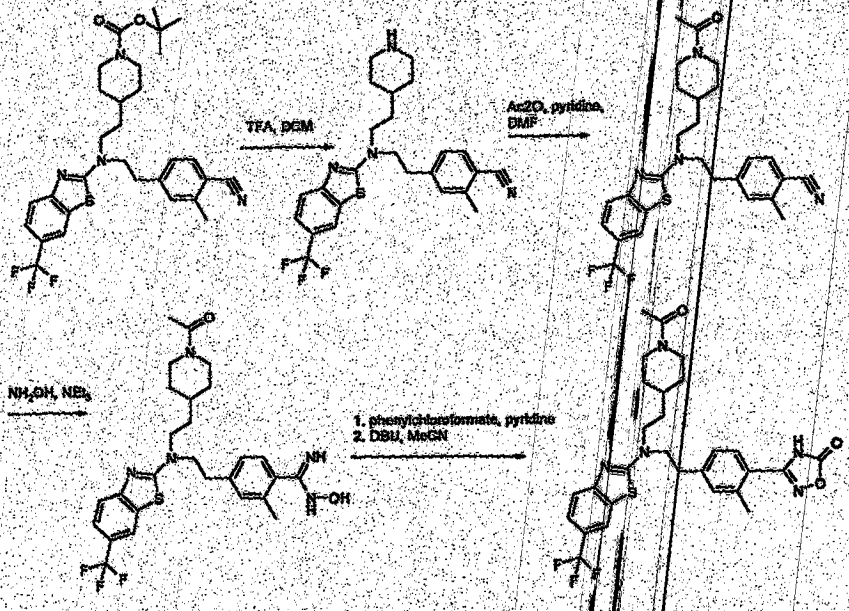


According to the method described in Example 1 and 5 3-(2-Methyl-4-{2-[(tetrahydro-pyran-4-ylmethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-phenyl)-4H-[1,2,4]oxadiazol-5-one was obtained from 4-(2-Amino-ethyl)-2-methyl-benzonitrile trifluoro acetate, tetrahydropyranyl-4-carboxaldehyde and 2-Chloro-6-trifluoromethyl-benzothiazole.

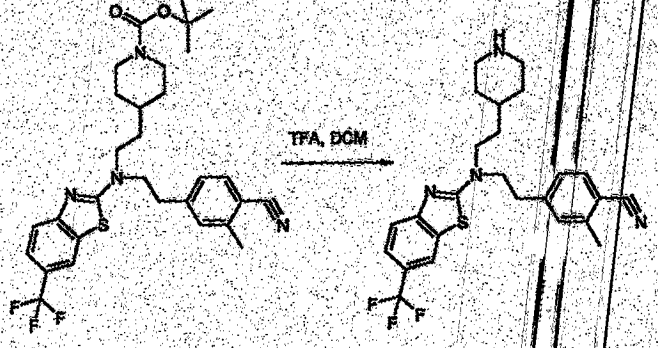
$C_{25}H_{25}F_3N_4O_3S$ (518.56), MS (ESI): 519.1 ($M+H^+$).

Example 10

3-(4-{2-[[2-(1-Acetyl-piperidin-4-yl)-ethyl]-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-2-methyl-phenyl)-4H-[1,2,4]oxadiazol-5-one



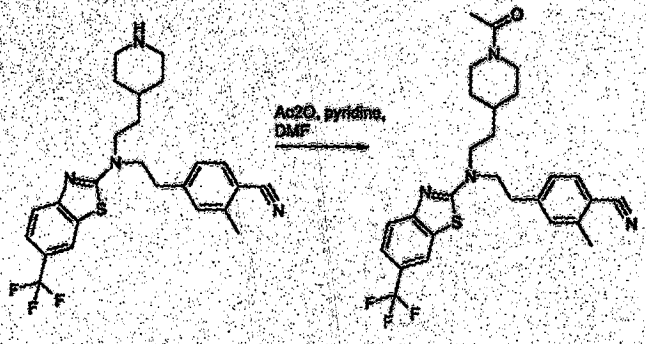
2-Methyl-4-{2-[(2-piperidin-4-yl-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-benzonitrile



1.1 g 4-{2-[[2-(4-Cyano-3-methyl-phenyl)-ethyl]-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-piperidine-1-carboxylic acid tert-butyl ester [prepared according to the method described in Example 1 and 5 from 4-(2-Amino-ethyl)-2-methyl-benzonitrile trifluoro acetate, N-boc-piperidinyl-4-acetaldehyde and 2-Chloro-6-trifluoromethyl-benzothiazole] were dissolved in 50 ml dichloromethane. 5 ml trifluoroacetic acid were added and the reaction mixture was stirred at room temperature for one hour. 150 ml ethyl acetate were added and the mixture was washed three times with saturated NaHCO3 solution. The organic layer was dried over MgSO4 and then the solvent was removed in vacuo. The residue was purified by RP-HPLC to obtain 325 mg 2-Methyl-4-{2-[(2-piperidin-4-yl-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-benzonitrile.

C25H27F3N4S (472.58), MS(ESI): 473.2 ($M+H^+$).

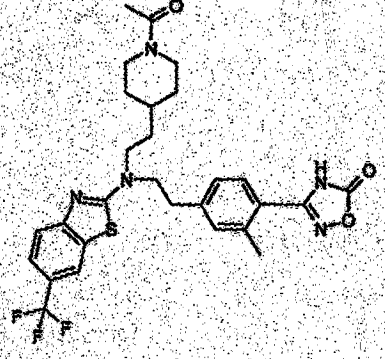
4-{2-[[2-(1-Acetyl-piperidin-4-yl)-ethyl]-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-2-methyl-benzonitrile



160 mg 4-{2-[[2-(1-Acetyl-piperidin-4-yl)-ethyl]-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-2-methyl-benzonitrile were dissolved in 2.5 ml dimethylformamide, 5 ml pyridine and 26 µl acetic acid anhydride were added. After being stirred at room temperature for thirty minutes, the reaction mixture was evaporated in vacuo to obtain 140 mg crude 4-{2-[[2-(1-Acetyl-piperidin-4-yl)-ethyl]-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-2-methyl-benzonitrile which was used in the next step without further purification.

C27H29F3N4OS (514.62), MS(ESI): 515.2 ($M+H^+$).

3-(4-{2-[[2-(1-Acetyl-piperidin-4-yl)-ethyl]-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-2-methyl-phenyl)-4H-[1,2,4]oxadiazol-5-one

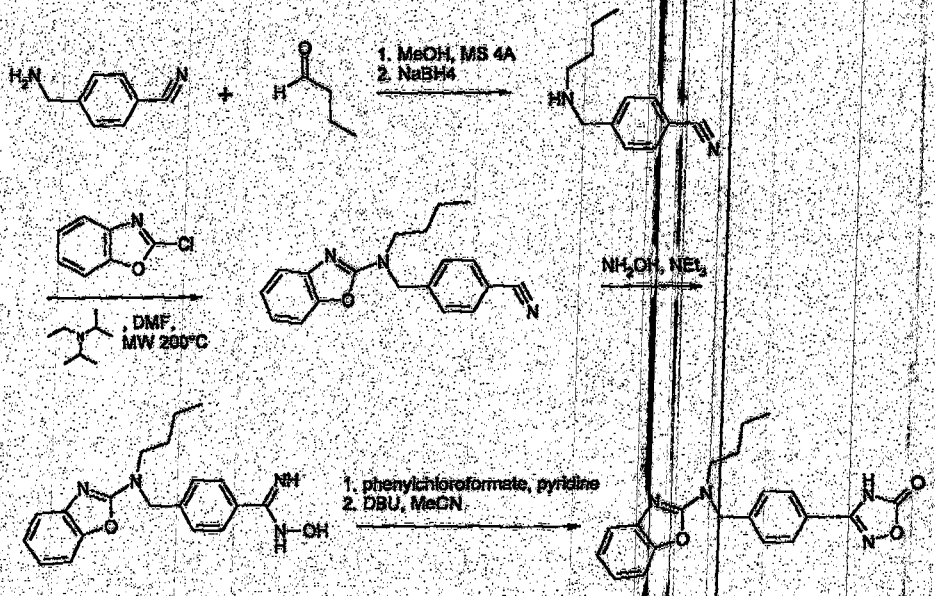


According to the method described in Example 1 3-(4-{2-[[2-(1-Acetyl-piperidin-4-yl)-ethyl]-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-2-methyl-phenyl)-4H-[1,2,4]oxadiazol-5-one was obtained from 4-{2-[[2-(1-Acetyl-piperidin-4-yl)-ethyl]-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-2-methyl-benzonitrile.

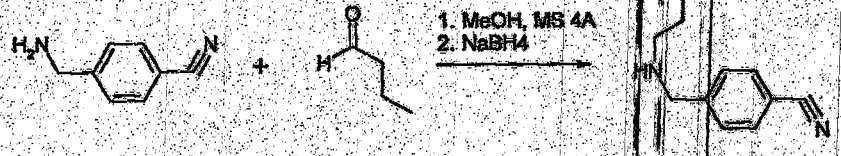
C28H30F3N5O3S (573.64), MS (ESI): 574.2 ($M+H^+$).

Example 11

3-{4-[(Benzooxazol-2-yl-butyl-amino)-methyl]-phenyl}-4H-[1,2,4]oxadiazol-5-one



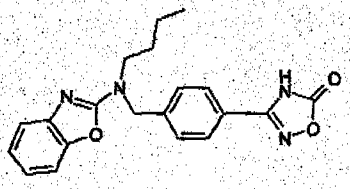
4-Butylaminomethyl-benzonitrile



5.0 g 4-Aminomethyl-benzonitrile and 3.75 ml Butyraldehyde were dissolved in 40 ml methanol. 3.0 g molecular sieves 4 Angström were added and the mixture was stirred at room temperature for two hours. Then 2.2 g sodium borohydride were added and the mixture was stirred for an additional hour at room temperature. 250 ml ethyl acetate were added, and the reaction was quenched by addition of 4 ml water. The reaction mixture was filtered through a pad of celite and MgSO4. The filtrate was evaporated in vacuo to provide 3.7 g crude 4-Butylaminomethyl-benzonitrile. This material was used without further purification.

C12H16N2 (188.27), MS(ESI): 189.2 ($M+H^+$).

3-{4-[(Benzooxazol-2-yl-butyl-amino)-methyl]-phenyl}-4H-[1,2,4]oxadiazol-5-one

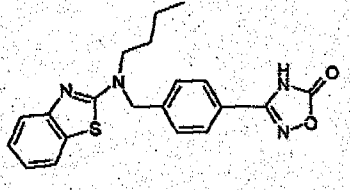


According to the method described in Example 1 3-{4-[(Benzooxazol-2-yl-butyl-amino)-methyl]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 4-butylaminomethyl-benzonitrile and 2-chlorobenzoxazole.

$C_{20}H_{20}N_4O_3$ (364.41), MS (ESI): 365.2 ($M+H^+$).

Example 12

3-{4-[(Benzothiazol-2-yl-butyl-amino)-methyl]-phenyl}-4H-[1,2,4]oxadiazol-5-one

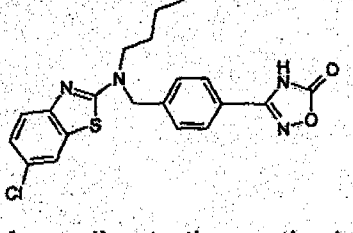


According to the method described in Example 1 3-{4-[(Benzothiazol-2-yl-butyl-amino)-methyl]-phenyl}-4H-[1,2,4]oxadiazol-5-one was obtained from 4-butylaminomethyl-benzonitrile and 2-chlorobenzothiazole.

$C_{20}H_{20}N_4O_2S$ (380.47), MS (ESI): 381.2 ($M+H^+$).

Example 13

3-(4-{[Butyl-(6-chloro-benzothiazol-2-yl)-amino]-methyl}-phenyl)-4H-[1,2,4]oxadiazol-5-one

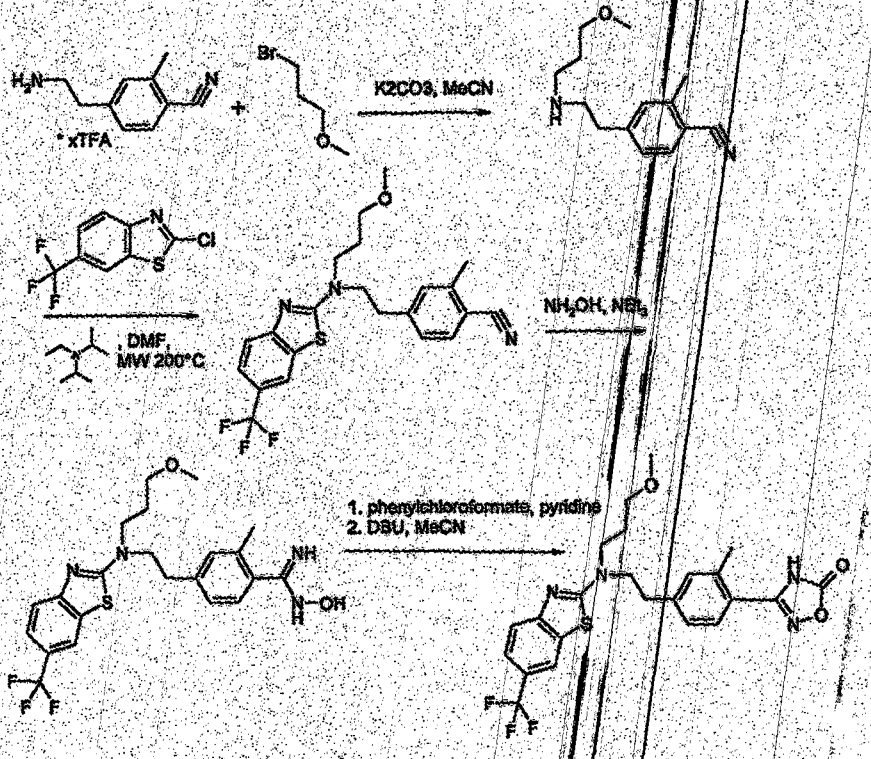


According to the method described in Example 1 3-(4-{[Butyl-(6-chloro-benzothiazol-2-yl)-amino]-methyl}-phenyl)-4H-[1,2,4]oxadiazol-5-one was obtained from 4-butylaminomethyl-benzonitrile and 2,6-dichlorobenzothiazole.

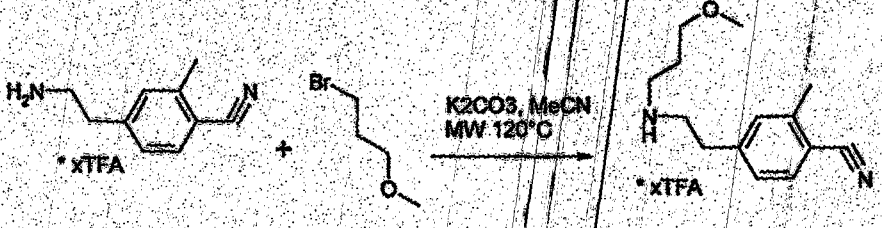
$C_{20}H_{19}ClN_4O_2S$ (414.92), MS (ESI): 415.1 ($M+H^+$).

Example 14

3-(4-[2-[(3-Methoxy-propyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-2-methyl-phenyl)-4H-[1,2,4]oxadiazol-5-one



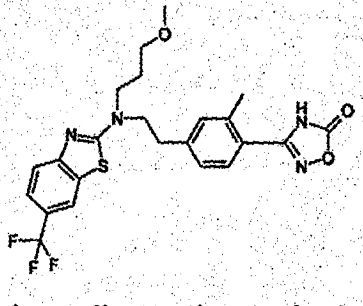
4-[2-(3-Methoxy-propylamino)-ethyl]-2-methyl-benzonitrile



A mixture of 500 mg 4-(2-Amino-ethyl)-2-methyl-benzonitrile trifluoro acetate and 756 mg potassium carbonate were stirred in 10 ml acetonitrile at 80°C for fifteen minutes. Then 279 mg 1-bromo-3-methoxypropane, dissolved in 5 ml acetonitrile, were added dropwise at 80°C. The reaction mixture was stirred under micro wave irradiation at 120°C for one hour. The cooled reaction mixture was filtered through a pad of celite to remove the salt. Then the solvent was removed in vacuo. The residue was purified by RP-HPLC to obtain 268 mg 4-[2-(3-Methoxy-propylamino)-ethyl]-2-methyl-benzonitrile as its trifluoroacetate salt.

C14H20N2O ·xTFA (232.16+ xTFA), MS(ESI): 233.2 (M+H+).

3-(4-{2-[(3-Methoxy-propyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-2-methyl-phenyl)-4H-[1,2,4]oxadiazol-5-one

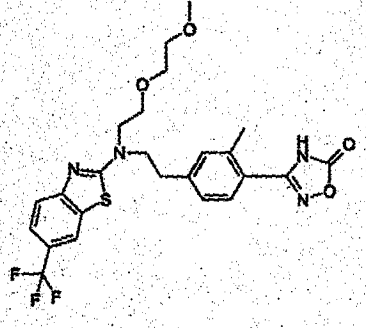


According to the method described in Example 1 3-(4-{2-[(3-Methoxy-propyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-2-methyl-phenyl)-4H-[1,2,4]oxadiazol-5-one was obtained from 4-[2-(3-Methoxy-propylamino)-ethyl]-2-methyl-benzonitrile trifluoroacetate and 2-Chloro-6-trifluoromethyl-benzothiazole.

C23H23F3N4O3S (492.52), MS (ESI): 493.0 ($M+H^+$).

Example 15

3-(4-{2-[[2-(2-Methoxy-ethoxy)-ethyl]-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-2-methyl-phenyl)-4H-[1,2,4]oxadiazol-5-one

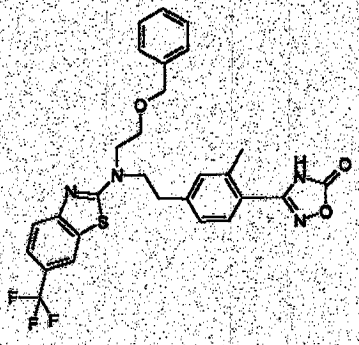


According to the method described in Example 1 and 14 3-(4-{2-[[2-(2-Methoxy-ethoxy)-ethyl]-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-2-methyl-phenyl)-4H-[1,2,4]oxadiazol-5-one was obtained from 4-(2-Amino-ethyl)-2-methyl-benzonitrile trifluoro acetate, 1-bromo-2-(2-methoxyethoxy)ethane and 2-Chloro-6-trifluoromethyl-benzothiazole.

C24H25F3N4O4S (522.55), MS (ESI): 523.0 ($M+H^+$).

Example 16

3-(4-{2-[(2-Benzyloxy-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-2-methyl-phenyl)-4H-[1,2,4]oxadiazol-5-one

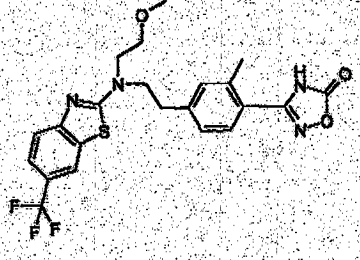


According to the method described in Example 1 and 14 3-(4-{2-[(2-Benzyloxy-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-2-methyl-phenyl)-4H-[1,2,4]oxadiazol-5-one was obtained from 4-(2-Amino-ethyl)-2-methyl-benzonitrile trifluoro acetate, benzyl 2-bromoethylether and 2-Chloro-6-trifluoromethyl-benzothiazole.

C28H25F3N4O3S (554.60), MS (ESI): 555.0 ($M+H^+$).

Example 17

3-(4-{2-[(2-Methoxy-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-2-methyl-phenyl)-4H-[1,2,4]oxadiazol-5-one



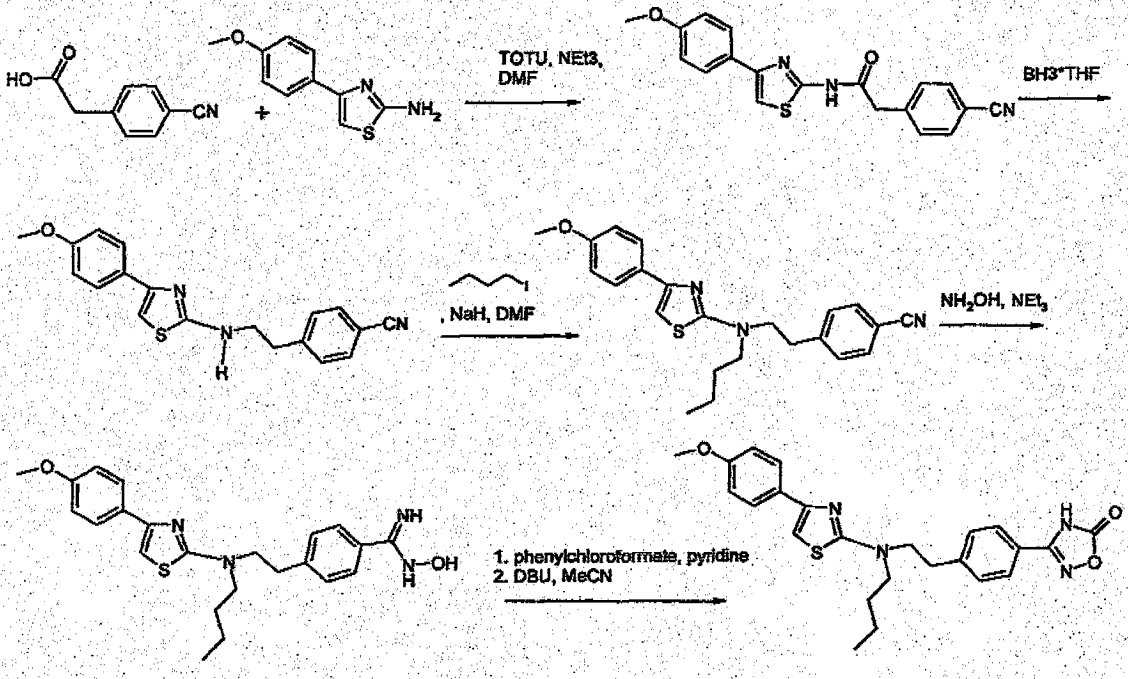
According to the method described in Example 1 and 14 3-(4-{2-[(2-Methoxy-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-ethyl}-2-methyl-phenyl)-4H-[1,2,4]oxadiazol-5-one was obtained from 4-(2-Amino-ethyl)-2-methyl-benzonitrile trifluoro acetate, 2-bromoethyl methylether and 2-Chloro-6-trifluoromethyl-benzothiazole.

C22H21F3N4O3S (478.50), MS (ESI): 479.0 ($M+H^+$).

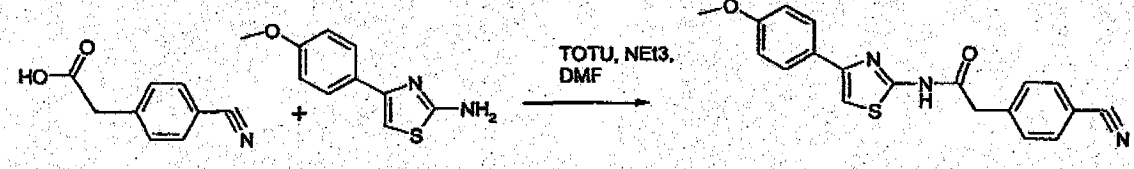
The following examples were prepared according to process B:

Example 18

3-[4-(2-{Butyl-[4-(4-methoxy-phenyl)-thiazol-2-yl]-amino}-ethyl)-phenyl]-4H-[1,2,4]oxadiazol-5-one



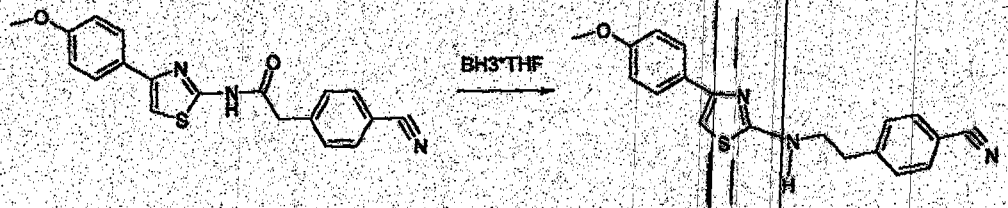
2-(4-Cyano-phenyl)-N-[4-(4-methoxy-phenyl)-thiazol-2-yl]-acetamide



1.41 g 4-(4-Methoxyphenyl)-1,3-thiazol-2-amine was dissoveld in 2 ml dimethylformamide. 3.0 ml N,N-Diisopropylethylamine, 1.0 g commercially available (4-Cyano-phenyl)-acetic acid and 2.25 g O-((Ethoxycarbonyl)cyanomethyleneamino)-N,N,N',N'-tetramethyluronium tetrafluoroborat were added. The reaction mixture was stirred at room temperature overnight. Then 200 ml ethylacetate were added and the mixture was washed three times with portions of 50 ml saturated NaHCO3 solution and then dried over MgSO4. The solvents were removed in vacuo and the residue purified by RP-HPLC to obtain 610 mg 2-(4-Cyano-phenyl)-N-[4-(4-methoxy-phenyl)-thiazol-2-yl]-acetamide as yellow solid.

C19H15N3O2S (349.41), MS (ESI): 350.1 ($M+H^+$).

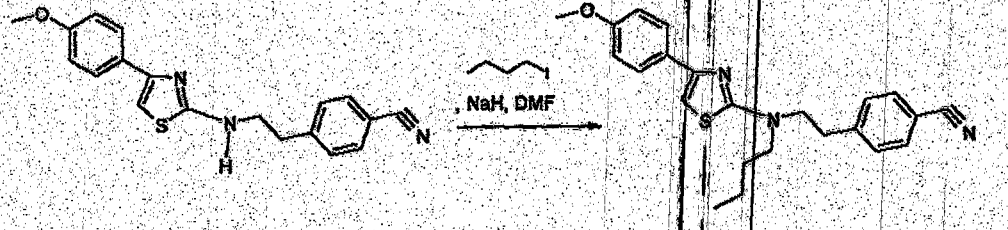
4-{2-[4-(4-Methoxy-phenyl)-thiazol-2-ylamino]-ethyl}-benzonitrile



610 mg 2-(4-Cyano-phenyl)-N-[4-(4-methoxy-phenyl)-thiazol-2-yl]-acetamide were suspended in 20 ml tetrahydrofuran. 2.1 ml of a one molar solution of borane tetrahydrofuran complex were added at room temperature. The reaction mixture was stirred at room temperature for two hours and then at 50°C for two hours. The cooled reaction mixture was poured on 50 ml water and extracted five times with portions of 50 ml ethyl acetate. The combined organic layers were dried over MgSO4. Then the solvents were removed in vacuo to obtain 600 mg 4-{2-[4-(4-Methoxy-phenyl)-thiazol-2-ylamino]-ethyl}-benzonitrile.

C19H17N3OS (335.43), MS (ESI): 336.2 ($M+H^+$).

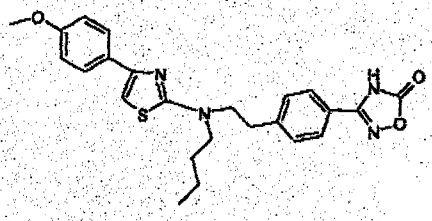
4-(2-{Butyl-[4-(4-methoxy-phenyl)-thiazol-2-yl]-amino}-ethyl)-benzonitrile



600 mg 4-{2-[4-(4-Methoxy-phenyl)-thiazol-2-ylamino]-ethyl}-benzonitrile were dissolved in 30 ml dimethylformamide. 85.9 mg sodium hydride (24% in mineral oil) were added and the reaction mixture stirred at room temperature for thirty minutes. Then 245 µl 1-Iodobutane were added and the reaction mixture stirred at room temperature for two hours. Then 100 ml ethylacetate were added and the mixture was washed three times with portions of 50 ml water and then dried over MgSO4. The solvents were removed in vacuo and the residue purified by RP-HPLC to obtain 279 mg 4-(2-{Butyl-[4-(4-methoxy-phenyl)-thiazol-2-yl]-amino}-ethyl)-benzonitrile.

C23H25N3OS (391.54), MS (ESI): 392.2 ($M+H^+$).

3-[4-(2-{Butyl-[4-(4-methoxy-phenyl)-thiazol-2-yl]-amino}-ethyl)-phenyl]-4H-[1,2,4]oxadiazol-5-one

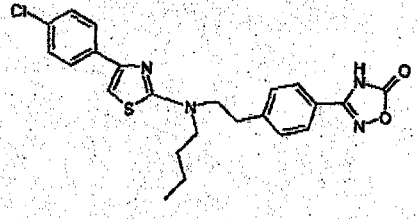


According to the method described in Example 1 3-[4-(2-{Butyl-[4-(4-methoxy-phenyl)-thiazol-2-yl]-amino}-ethyl)-phenyl]-4H-[1,2,4]oxadiazol-5-one was obtained from 4-(2-{Butyl-[4-(4-methoxy-phenyl)-thiazol-2-yl]-amino}-ethyl)-benzonitrile.

$C_{24}H_{26}N_4O_3S$ (450.56), MS (ESI): 451.2 ($M+H^+$).

Example 19

3-[4-(2-{Butyl-[4-(4-chloro-phenyl)-thiazol-2-yl]-amino}-ethyl)-phenyl]-4H-[1,2,4]oxadiazol-5-one

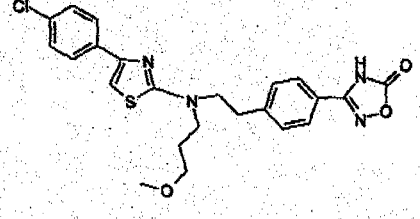


According to the method described in Example 1 and 18 3-[4-(2-{Butyl-[4-(4-chloro-phenyl)-thiazol-2-yl]-amino}-ethyl)-phenyl]-4H-[1,2,4]oxadiazol-5-one was obtained from (4-Cyano-phenyl)-acetic acid, 4-(4-Chloro-phenyl)-thiazol-2-ylamine and 1-Iodobutane.

$C_{23}H_{23}ClN_4O_2S$ (454.98), MS (ESI): 455.0 ($M+H^+$).

Example 20

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

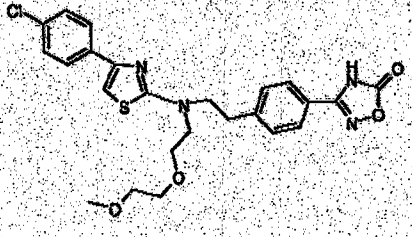


According to the method described in Example 1 and 18 3-(4-{2-[[4-(4-Chloro-phenyl)-thiazol-2-yl]-(3-methoxy-propyl)-amino]-ethyl}-phenyl)-4H-[1,2,4]oxadiazol-5-one was obtained from (4-Cyano-phenyl)-acetic acid, 4-(4-Chloro-phenyl)-thiazol-2-ylamine and 1-bromo-3-methoxypropane.

C23H23ClN4O3S (470.98), MS (ESI): 471.0 ($M+H^+$).

Example 21

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

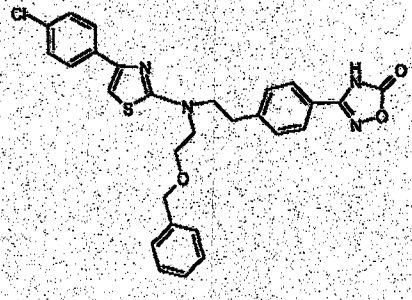


According to the method described in Example 1 and 18 3-[4-(2-{[4-(4-Chloro-phenyl)-thiazol-2-yl]-[2-(2-methoxy-ethoxy)-ethyl]-amino}-ethyl)-phenyl]-4H-[1,2,4]oxadiazol-5-one was obtained from (4-Cyano-phenyl)-acetic acid, 4-(4-Chloro-phenyl)-thiazol-2-ylamine and 1-bromo-2-(methoxyethoxy)ethane.

C24H25ClN4O4S (501.01), MS (ESI): 501.0 ($M+H^+$).

Example 22

3-[4-(2-{(2-Benzyloxy-ethyl)-[4-(4-chloro-phenyl)-thiazol-2-yl]-amino}-ethyl)-phenyl]-4H-[1,2,4]oxadiazol-5-one

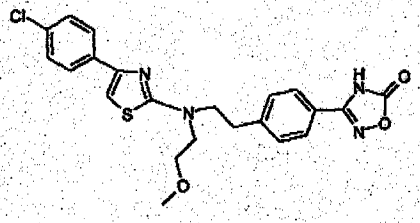


According to the method described in Example 1 and 18 3-[4-(2-{(2-Benzyloxy-ethyl)-[4-(4-chloro-phenyl)-thiazol-2-yl]-amino}-ethyl)-phenyl]-4H-[1,2,4]oxadiazol-5-one was obtained from (4-Cyano-phenyl)-acetic acid, 4-(4-Chloro-phenyl)-thiazol-2-ylamine and benzyl 2-bromoethylether.

$C_{28}H_{25}ClN_4O_3S$ (533.05), MS (ESI): 533.1 ($M+H^+$).

Example 23

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



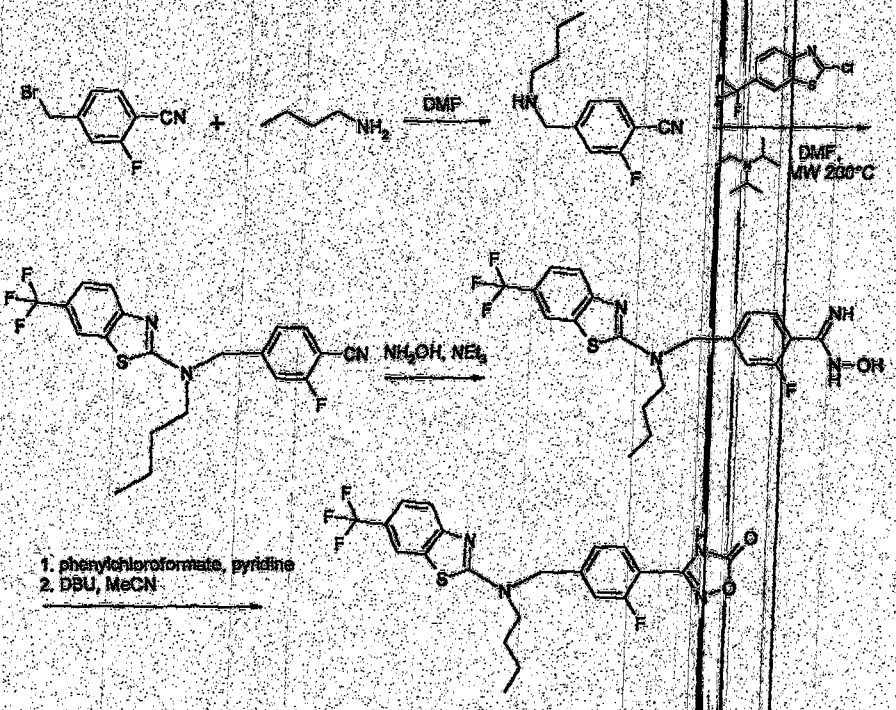
According to the method described in Example 1 and 18 3-(4-{2-[[4-(4-Chloro-phenyl)-thiazol-2-yl]-(2-methoxy-ethyl)-amino]-ethyl}-phenyl)-4H-[1,2,4]oxadiazol-5-one was obtained from (4-Cyano-phenyl)-acetic acid, 4-(4-Chloro-phenyl)-thiazol-2-ylamine and 2-bromoethylmethylether.

$C_{22}H_{21}ClN_4O_3S$ (456.95), MS (ESI): 457.0 ($M+H^+$).

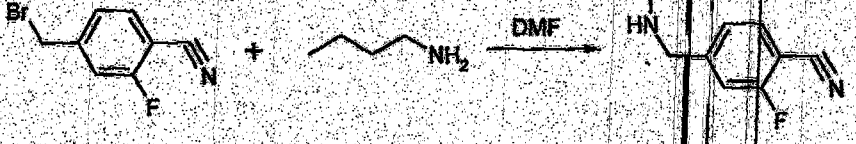
The following examples were prepared according to process C:

Example 24

3-(4-{[Butyl-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-2-fluoro-phenyl)-4H-[1,2,4]oxadiazol-5-one

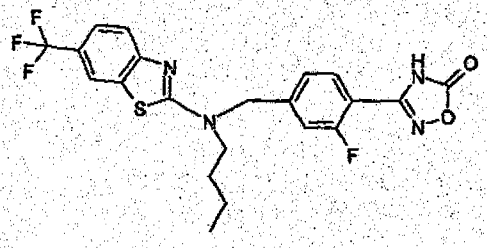


4-Butylaminomethyl-2-fluoro-benzonitrile



4.64 ml n-butylamine was dissolved in 30 ml dimethylformamide. 667 mg commercially available 4-cyano-3-fluorobenzylbromide, dissolved in 10 ml dimethylformamide was added dropwise. The reaction mixture was stirred at room temperature for thirty minutes. The solvent was removed in vacuo and the residue prurified by chromatography on silica gel with the eluent n-heptane:ethyl acetate = 1:4 => ethyl acetate : methanol = 4:1 to obtain 360 mg 4-Butylaminomethyl-2-fluoro-benzonitrile. C12H15FN2 (206.27), MS (ESI): 207.2 ($M+H^+$), Rf(ethyl acetate : methanol = 9:1) = 0.29 .

3-(4-{[Butyl-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-2-fluoro-phenyl)-4H-[1,2,4]oxadiazol-5-one

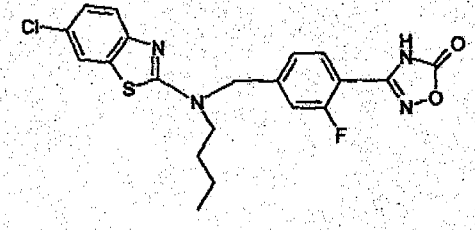


According to the method described in Example 1 3-(4-{[Butyl-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-2-fluoro-phenyl)-4H-[1,2,4]oxadiazol-5-one was obtained from 4-Butylaminomethyl-2-fluoro-benzonitrile and 2-Chloro-6-trifluoromethyl-benzothiazole.

$C_{21}H_{18}F_4N_4O_2S$ (466.46), MS (ESI): 467.0 ($M+H^+$).

Example 25

3-(4-{[Butyl-(6-chloro-benzothiazol-2-yl)-amino]-methyl}-2-fluoro-phenyl)-4H-[1,2,4]oxadiazol-5-one

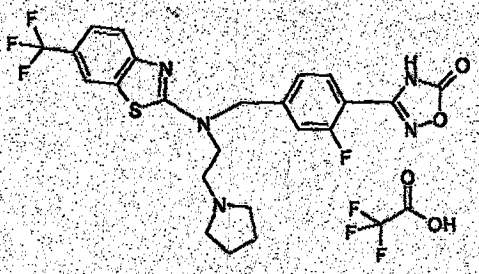


According to the method described in Example 1 3-(4-{[Butyl-(6-chloro-benzothiazol-2-yl)-amino]-methyl}-2-fluoro-phenyl)-4H-[1,2,4]oxadiazol-5-one was obtained from 4-Butylaminomethyl-2-fluoro-benzonitrile and 2,6-dichloro-benzothiazole.

$C_{20}H_{18}ClFN_4O_2S$ (432.91), MS (ESI): 433.0 ($M+H^+$).

Example 26

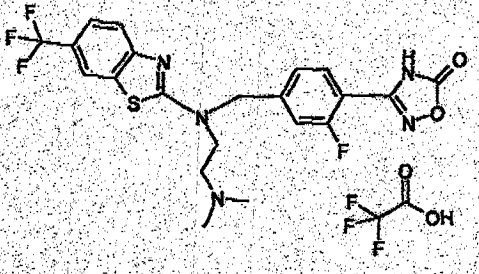
3-(2-Fluoro-4-{[(2-pyrrolidin-1-yl-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-phenyl)-4H-[1,2,4]oxadiazol-5-one trifluoroacetate



According to the method described in Example 1 3-(2-Fluoro-4-{[(2-pyrrolidin-1-yl-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-phenyl)-4H-[1,2,4]oxadiazol-5-one was obtained from commercially available 4-cyano-3-fluorobenzylbromide, N-(2-aminoethyl)pyrrolidine and 2-Chloro-6-trifluoromethyl-benzothiazole. After RP-HPLC the compound was obtained as its trifluoroacetate salt.
$C_{23}H_{21}F_4N_5O_2S$ * $C_2HF_3O_2$ (507.51+114.02), MS (ESI): 508.2 ($M+H^+$).

Example 27

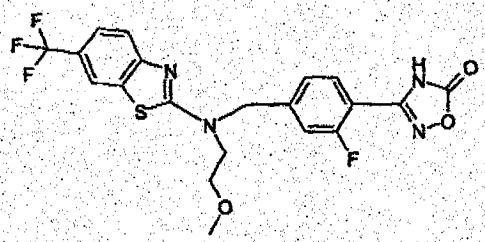
3-(4-{[(2-Dimethylamino-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-2-fluoro-phenyl)-4H-[1,2,4]oxadiazol-5-one trifluoroacetate



According to the method described in Example 1 3-(4-{[(2-Dimethylamino-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-2-fluoro-phenyl)-4H-[1,2,4]oxadiazol-5-one was obtained from commercially available 4-cyano-3-fluorobenzylbromide, N,N-dimethylethylenediamine and 2-Chloro-6-trifluormethyl-benzothiazole. After RP-HPLC the compound was obtained as its trifluoroacetate salt.
$C_{21}H_{19}F_4N_5O_2S$* $C_2HF_3O_2$ (481.48+114.02), MS (ESI): 482.2 ($M+H^+$).

Example 28

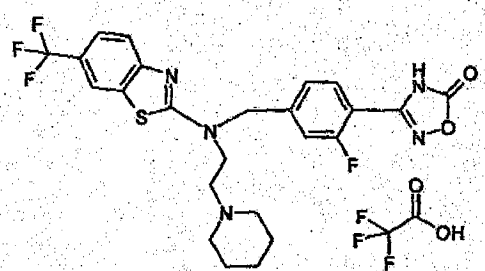
3-(2-Fluoro-4-{[(2-methoxy-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-phenyl)-4H-[1,2,4]oxadiazol-5-one



According to the method described in Example 1 3-(2-Fluoro-4-{[(2-methoxy-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-phenyl)-4H-[1,2,4]oxadiazol-5-one was obtained from commercially available 4-cyano-3-fluorobenzylbromide, 2-methoxyethylamine and 2-Chloro-6-trifluoromethyl-benzothiazole.
C20H16F4N4O3S (468.43), MS (ESI): 469.1 ($M+H^+$).

Example 29

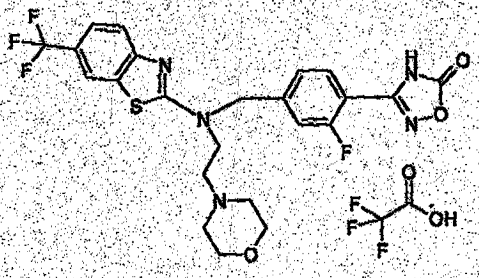
3-(2-Fluoro-4-{[(2-piperidin-1-yl-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-phenyl)-4H-[1,2,4]oxadiazol-5-one trifluoroacetate



According to the method described in Example 1 3-(2-Fluoro-4-{[(2-piperidin-1-yl-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-phenyl)-4H-[1,2,4]oxadiazol-5-one was obtained from commercially available 4-cyano-3-fluorobenzylbromide, 1-(2-aminoethyl)piperidine and 2-Chloro-6-trifluoromethyl-benzothiazole. After RP-HPLC the compound was obtained as its trifluoroacetate salt.
C24H23F4N5O2S* C2HF3O2 (521.54+114.02), MS (ESI): 522.2 ($M+H^+$).

Example 30

3-(2-Fluoro-4-{[(2-morpholin-4-yl-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-phenyl)-4H-[1,2,4]oxadiazol-5-one trifluoroacetate

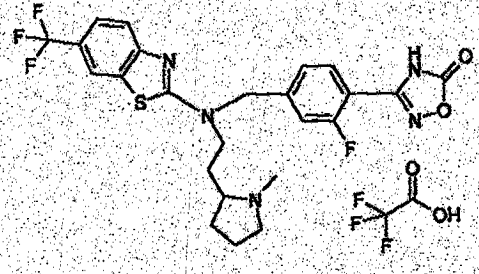


According to the method described in Example 1 3-(2-Fluoro-4-[[(2-morpholin-4-yl-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl]-phenyl)-4H-[1,2,4]oxadiazol-5-one was obtained from commercially available 4-cyano-3-fluorobenzylbromide, N-(2-aminoethyl)morpholine and 2-Chloro-6-trifluoromethyl-benzothiazole. After RP-HPLC the compound was obtained as its trifluoroacetate salt.

$C_{23}H_{21}F_4N_5O_3S^* C_2HF_3O_2$ (523.51+114.02), MS (ESI): 524.2 ($M+H^+$).

Example 31

3-(2-Fluoro-4-[[[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl]-phenyl)-4H-[1,2,4]oxadiazol-5-one trifluoroacetate

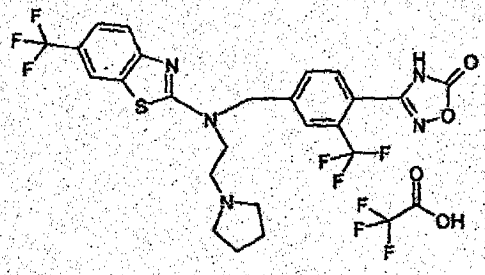


According to the method described in Example 1 3-(2-Fluoro-4-[[[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl]-phenyl)-4H-[1,2,4]oxadiazol-5-one was obtained from commercially available 4-cyano-3-fluorobenzylbromide, 2-(2-aminoethyl)-1-methylpyrrolidine and 2-Chloro-6-trifluoromethyl-benzothiazole. After RP-HPLC the compound was obtained as its trifluoroacetate salt.

$C_{24}H_{23}F_4N_5O_2S^* C_2HF_3O_2$ (521.54+114.02), MS (ESI): 522.2 ($M+H^+$).

Example 32

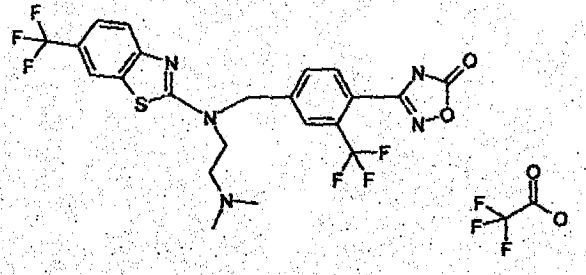
3-(4-[[(2-Pyrrolidin-1-yl-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl]-2-trifluoromethyl-phenyl)-4H-[1,2,4]oxadiazol-5-one



According to the method described in Example 1 3-(4-{[(2-Pyrrolidin-1-yl-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-2-trifluoromethyl-phenyl)-4H-[1,2,4]oxadiazol-5-one was obtained from 4-Bromomethyl-2-trifluoromethyl-benzonitrile, N-(2-aminoethyl)pyrrolidine and 2-Chloro-6-trifluoromethyl-benzothiazole. After RP-HPLC the compound was obtained as its trifluoroacetate salt. C24H21F6N5O2S * C2HF3O2 (557.52+114.02), MS (ESI): 558.0 ($M+H^+$).

Example 33

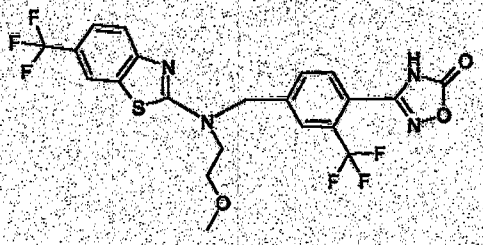
3-(4-{[(2-Dimethylamino-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-2-trifluoromethyl-phenyl)-4H-[1,2,4]oxadiazol-5-one trifluoroacetate



According to the method described in Example 1 3-(4-{[(2-Dimethylamino-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-2-trifluoromethyl-phenyl)-4H-[1,2,4]oxadiazol-5-one was obtained from 4-Bromomethyl-2-trifluoromethyl-benzonitrile, N,N-dimethylethylenediamine and 2-Chloro-6-trifluoromethyl-benzothiazole. After RP-HPLC the compound was obtained as its trifluoroacetate salt. C22H19F6N5O2S* C2HF3O2 (531.48+114.02), MS (ESI): 532.1 ($M+H^+$).

Example 34

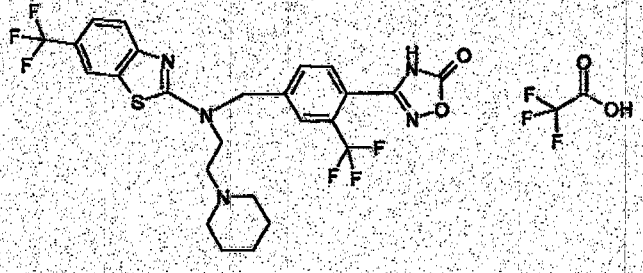
3-(4-{[(2-Methoxy-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-2-trifluoromethyl-phenyl)-4H-[1,2,4]oxadiazol-5-one



According to the method described in Example 1 3-(4-[[(2-Methoxy-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-2-trifluoromethyl-phenyl)-4H-[1,2,4]oxadiazol-5-one was obtained from 4-Bromomethyl-2-trifluoromethyl-benzonitrile, 2-methoxyethylamine and 2-Chloro-6-trifluoromethyl-benzothiazole. $C_{21}H_{16}F_6N_4O_3S$ (518.44), MS (ESI): 519.2 ($M+H^+$).

Example 35

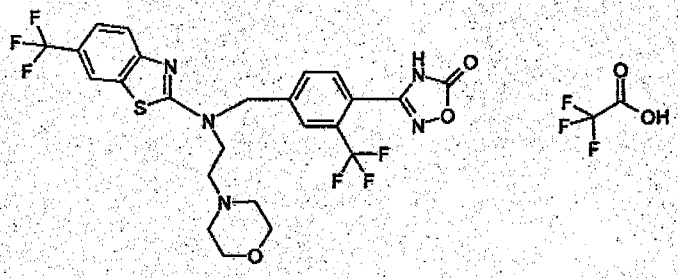
3-(4-[[(2-Piperidin-1-yl-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-2-trifluoromethyl-phenyl)-4H-[1,2,4]oxadiazol-5-one trifluoroacetate



According to the method described in Example 1 3-(4-[[(2-Piperidin-1-yl-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-2-trifluoromethyl-phenyl)-4H-[1,2,4]oxadiazol-5-one was obtained from 4-Bromomethyl-2-trifluoromethyl-benzonitrile, 1-(2-aminoethyl)piperidine and 2-Chloro-6-trifluoromethyl-benzothiazole. After RP-HPLC the compound was obtained as its trifluoroacetate salt. $C_{25}H_{23}F_6N_5O_2S * C_2HF_3O_2$ (571.55+114.02), MS (ESI): 572.2 ($M+H^+$).

Example 36

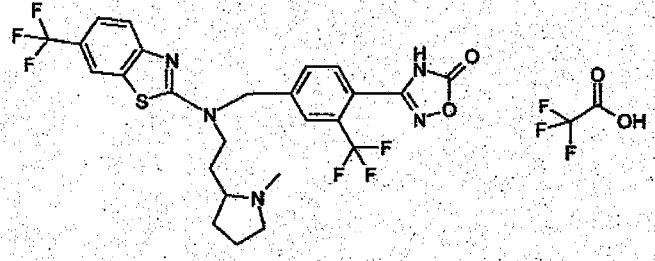
3-(4-[[(2-Morpholin-4-yl-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-2-trifluoromethyl-phenyl)-4H-[1,2,4]oxadiazol-5-one trifluoroacetate



According to the method described in Example 1 3-(4-{[(2-Morpholin-4-yl-ethyl)-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-2-trifluoromethyl-phenyl)-4H-[1,2,4]oxadiazol-5-one was obtained from 4-Bromomethyl-2-trifluoromethyl-benzonitrile, N-(2-aminoethyl)morpholine and 2-Chloro-6-trifluoromethyl-benzothiazole. After RP-HPLC the compound was obtained as its trifluoroacetate salt. C24H21F6N5O3S * C2HF3O2 (573.52+114.02), MS (ESI): 574.2 ($M+H^+$).

Example 37

3-(4-{[[2-(1-Methyl-pyrrolidin-2-yl)-ethyl]-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-2-trifluoromethyl-phenyl)-4H-[1,2,4]oxadiazol-5-one trifluoroacetate

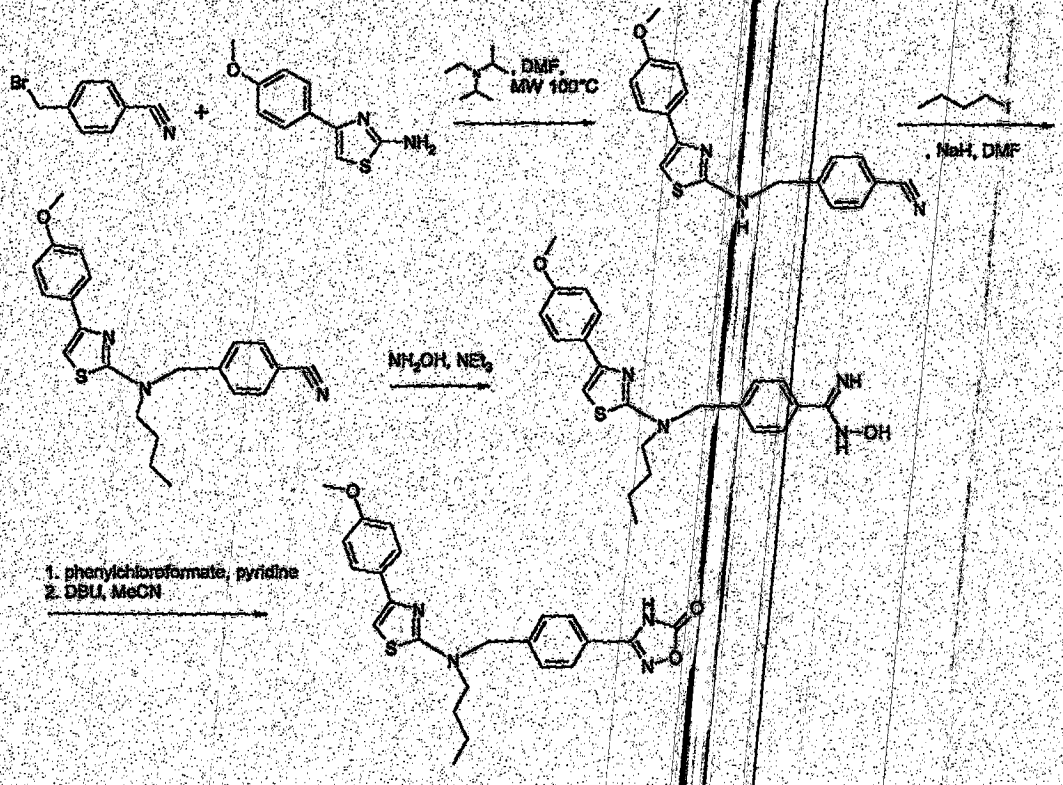


According to the method described in Example 1 3-(4-{[[2-(1-Methyl-pyrrolidin-2-yl)-ethyl]-(6-trifluoromethyl-benzothiazol-2-yl)-amino]-methyl}-2-trifluoromethyl-phenyl)-4H-[1,2,4]oxadiazol-5-one was obtained from 4-Bromomethyl-2-trifluoromethyl-benzonitrile, 2-(2-aminoethyl)-1-methylpyrrolidine and 2-Chloro-6-trifluoromethyl-benzothiazole. After RP-HPLC the compound was obtained as its trifluoroacetate salt. C25H23F6N5O2S * C2HF3O2 (571.55+114.02), MS (ESI): 572.2 ($M+H^+$).

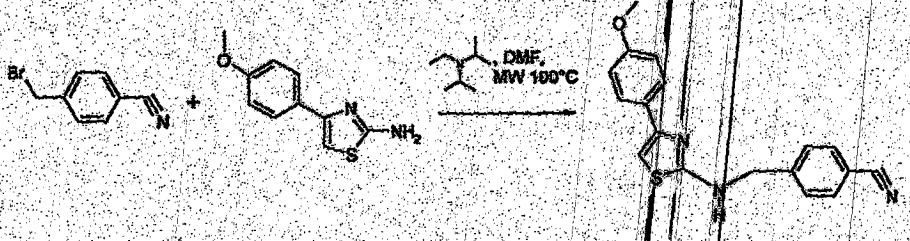
The following examples were prepared according to process D:

Example 38

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



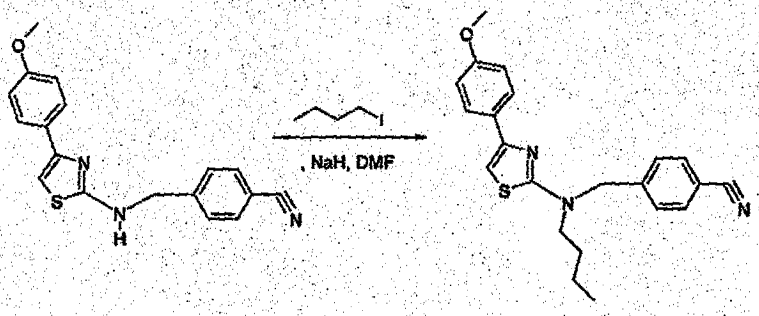
4-[[4-(4-Methoxy-phenyl)-thiazol-2-ylamino]-methyl]-benzonitrile



5.0 g 4-(4-Methoxyphenyl)-1,3-thiazol-2-amine, 4.29 g 4-bromomethyl-benzonitrile and 6.0 ml N,N.Diisopropylethylamine were suspended in 20 ml dimethylformamide. The reaction mixture was stirred under microwave irradiation at 100°C for thirty minutes. The cooled reaction mixture was diluted by the addition of 100 ml ethylacetate and washed 50 ml saturated NaHCO3 solution and the dried over MgSO4. The solvent was removed in vacuo and the resulting residue was purified by chromatography on silica gel with the eluent petroleum ether: ethyl acetate = 3 : 2 to obtain 2.41 g 4-[[4-(4-Methoxy-phenyl)-thiazol-2-ylamino]-methyl]-benzonitrile.

C18H15N3OS (321.40), MS (ESI): 322.1 ($M+H^+$), Rf(n-heptane : ethyl acetate = 1:1) = 0.29 .

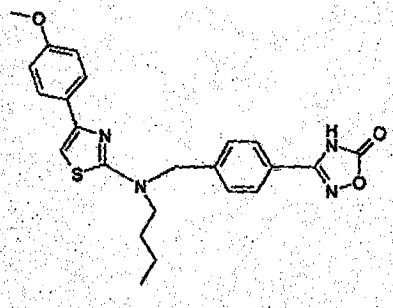
4-({Butyl-[4-(4-methoxy-phenyl)-thiazol-2-yl]-amino}-methyl)-benzonitrile



1.0 g 4-{[4-(4-Methoxy-phenyl)-thiazol-2-ylamino]-methyl}-benzonitrile was dissolved in 150 ml dimethylformamide. 150 mg sodium hydride (24% in mineral oil) were added and the reaction mixture stirred at room temperature for thirty minutes. Then 0.43 ml 1-Iodobutane were added and the reaction mixture stirred at room temperature for two hours. Then 100 ml ethylacetate were added and the mixture was washed three times with portions of 50 ml water and then dried over MgSO4. The solvents were removed in vacuo to obtain 1.2 g 4-({Butyl-[4-(4-methoxy-phenyl)-thiazol-2-yl]-amino}-methyl)-benzonitrile.

C22H23N3OS (377.51), MS (ESI): 378.2 ($M+H^+$).

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

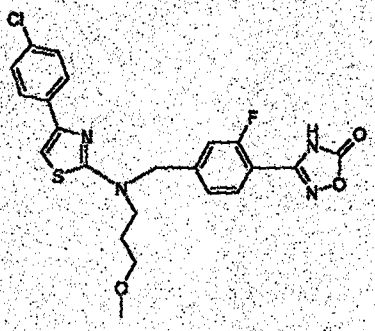


According to the method described in Example 1 3-[4-({Butyl-[4-(4-methoxy-phenyl)-thiazol-2-yl]-amino}-methyl)-phenyl]-4H-[1,2,4]oxadiazol-5-one was obtained from 4-({Butyl-[4-(4-methoxy-phenyl)-thiazol-2-yl]-amino}-methyl)-benzonitrile.

C23H24N4O3S (436.54), MS (ESI): 437.4 ($M+H^+$).

Example 39

3-(4-{[[4-(4-Chloro-phenyl)-thiazol-2-yl]-(3-methoxy-propyl)-amino]-methyl}-2-fluoro-phenyl)-4H-[1,2,4]oxadiazol-5-one

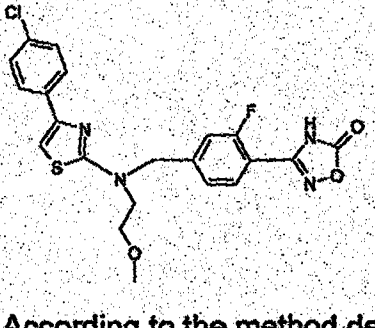


According to the method described in Example 1 and 38 3-(4-{[[4-(4-Chloro-phenyl)-thiazol-2-yl]-(3-methoxy-propyl)-amino]-methyl}-2-fluoro-phenyl)-4H-[1,2,4]oxadiazol-5-one was obtained from 2-amino-4-(4-chlorophenyl)thiazole, 4-cyano-3-fluorobenzylbromide and 1-bromo-3-methoxypropane .

$C_{22}H_{20}ClFN_4O_3S$ (474.95), MS (ESI): 475.0 ($M+H^+$).

Example 40

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



According to the method described in Example 1 and 38 3-(4-{[[4-(4-Chloro-phenyl)-thiazol-2-yl]-(2-methoxy-ethyl)-amino]-methyl}-2-fluoro-phenyl)-4H-[1,2,4]oxadiazol-5-one was obtained from 2-amino-4-(4-chlorophenyl)thiazole, 4-cyano-3-fluorobenzylbromide and 2-bromoethylmethylether.

$C_{21}H_{18}ClFN_4O_3S$ (460.92), MS (ESI): 461.0 ($M+H^+$).

wherein alkyl and alkylene are unsubstituted or mono-, di- or trisubstituted by F, N((C0-C4) alkylene-H)-(C0-C4) alkylene-H 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, CO-(C1-C4) alkyl and (C0-C4)-alkylen-O-(C0-C4) alkylene-H;

R6, R7 H, (C6-C14) aryl, which is unsubstituted or mono-, di- or trisubstituted by F, Cl, Br, CF3, (C1-C4) alkyl and (C0-C4)-alkylen-O-(C0-C4) alkylene-H; or

R6 and R7 together with the oxazole or thiazole ring form a benzothiazole or benzoxazole ring, which is unsubstituted or mono-, di- or trisubstituted by F, Cl, Br, CF3, (C1-C4) alkyl and (C0-C4)-alkylen-O-(C0-C4) alkylene-H;

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

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

R2,R3,R4 are H;

X is -CH2-CH2-;

U is S;

R5 is (C1-C4) alkyl, (C1-C4) alkylene-O-(C1-C4) alkyl, (C1-C4) alkylene-O-CH2-phenyl, (C1-C4) alkylene-(C5-C6) heterocycloalkyl, wherein alkyl and alkylene can be mono-, di- or trisubstituted by N((C1-C4) alkyl)-(C1-C4) alkyl and wherein heterocycloalkyl is unsubstituted or monosubstituted by (C1-C4) alkyl or CO-(C1-C4) alkyl;

R6 is phenyl monosubstituted by Cl or methoxy;

R6 and R7 together with the oxazole or thiazole ring denote benzothiazole substituted by CF3.

3. Compounds of the formula I as claimed in claim 1, wherein

R1 is 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 H;

X is -CH2-;

U is S;

R5 is (C1-C4) alkyl, (C1-C4) alkylene-O-(C1-C4) alkyl, (C1-C4) alkylene-O-CH2-phenyl, (C1-C4) alkylene-(C5-C6) heterocycloalkyl, wherein alkyl and alkylene can be mono-, di- or trisubstituted by N((C1-C4) alkyl)-(C1-C4) alkyl and wherein heterocycloalkyl is unsubstituted or monosubstituted by (C1-C4) alkyl or CO-(C1-C4) alkyl;

R6 is phenyl monosubstituted by Cl or methoxy;

R6 and R7 together with the oxazole or thiazole ring denote benzothiazole substituted by CF3.

4. Compounds of the formula I as claimed in claims 1 to 3, wherein

R1 is H, F, Cl, (C1-C4) alkyl which is unsubstituted or mono-, di- or trisubstituted by F.

5. Compounds of the formula I as claimed in claims 1 to 3, wherein

R1 is H, F, CH3 or CF3.

6. Compounds of the formula I as claimed in claims 1 to 3, wherein

R1 is F, CH3 or CF3.

7. Compounds of the formula I as claimed in claims 1 to 6, wherein

R6 and R7 together with the thiazole ring denote 6-trifluoromethyl-benzothiazole.

8. A pharmaceutical comprising one or more compounds of the formula I as claimed in one or more of claims 1 to 7.

9. A pharmaceutical comprising one or more compounds of the formula I as claimed in one or more of claims 1 to 7 and one or more active substances which have favorable effects on metabolic disturbances or disorders frequently associated therewith.

10. A pharmaceutical comprising one or more compounds of the formula I as claimed in one or more of claims 1 to 7 and one or more antidiabetics.

11. A pharmaceutical comprising one or more compounds of the formula I as claimed in one or more of claims 1 to 7 and one or more lipid modulators.

12. The use of the compounds of the formula I as claimed in one or more of claims 1 to 7for the treatment and/or prevention of disorders of fatty acid metabolism and glucose utilization disorders.

13. The use of the compounds of the formula I as claimed in one or more of claims 1 to 7 or the treatment and/or prevention of disorders in which insulin resistance is involved.

14. The use of the compounds of the formula I as claimed in one or more of claims 1 to 7 for the treatment and/or prevention of diabetes mellitus including the prevention of the squelae associated therewith.

15. The use of the compounds of the formula I as claimed in one or more of claims 1 to 7 for the treatment and/or prevention of dyslipidemias and their squelae.

16. The use of the compounds of the formula I as claimed in one or more of claims 1 to 7 for the treatment and/or prevention of conditions which may be associated with the metabolic syndrome.

17. The use of the compounds of the formula I as claimed in one or more of claims 1 to 7 for the treatment and/or prevention of demyelinating and other neurodegenerative disorders of the central and peripheral nervous system.

18. The use of compounds as claimed in one or more of claims 1 to 7 in combination with at least one further active compound for the treatment of disorders of fatty acid metabolism and glucose utilization disorders.

19. The use of compounds as claimed in one or more of claims 1 to 7 in combination with at least one further active compound for the treatment of disorders in which insulin resistance is involved.

20. A process for preparing a pharmaceutical comprising one or more of the compounds as claimed in one or more of claims 1 to 7, which comprises mixing the active compound with a pharmaceutically suitable carrier and bringing this mixture into a form suitable for administration.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/009302

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/12 C07D419/12 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.
Y	WO 03/074495 A (SMITHKLINE BEECHAM CORPORATION; CADILLA, RODOLFO; HENKE, BRAD, RICHARD) 12 September 2003 (2003-09-12) the whole document	1-20
Y	WO 01/12612 A (ASTRAZENECA AB; ASTRAZENECA LIMITED; HARGREAVES, RODNEY, BRIAN; WHITTA) 22 February 2001 (2001-02-22) the whole document	1-20
P,Y	EP 1 586 573 A (AVENTIS PHARMA DEUTSCHLAND GMBH) 19 October 2005 (2005-10-19) the whole document	1-20
Y	US 6 653 334 B1 (YAMAZAKI YUKIYOSHI ET AL.) 25 November 2003 (2003-11-25) the whole document	1-20

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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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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 December 2006	27/12/2006

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/009302

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 641 796 A (DOMINIANNI ET AL) 24 June 1997 (1997-06-24) the whole document	1-20

Descripción

DERIVADOS DE 2-AMINOTIAZOLES Y 2-AMINOOXAZOLES, PROCESOS PARA SU PREPARACIÓN Y SU USO COMO COMPUESTOS FARMACÉUTICOS

La invención se refiere a oxadiazolonas y a sus sales fisiológicamente aceptables y a derivados fisiológicamente funcionales que muestran actividad agonista de PPARdelta.

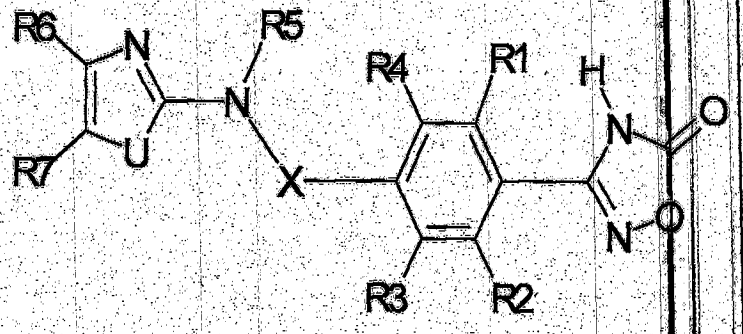
En la técnica anterior se han descrito agonistas de PPARdelta (por ejemplo, en los documentos WO 01/00603, WO 02/092590, WO2003/074495, WO2004/093879, WO2004/080943, WO2005/054213 y WO2005/097786). En el documento DE 10112768 A1 se describieron compuestos que comprenden un rasgo de oxadiazolona como inhibidores del factor Xa y en el documento WO 96/13264 agentes hipoglucemiantes. Por el documento WO 97/40017, se conocen compuestos que tienen un grupo fenilo unido a heterociclos como moduladores de moléculas con unidades de reconocimiento de fosfotirosina. Por el documento WO 02/057236 se conocen derivados de fenilo como agentes para la terapia de trastornos tromboembólicos. En el documento WO96/34851 se describen derivados de benceno como inhibidores de la escualeno sintasa y la proteína farnesiltransferasa.

La invención se basa en el objetivo de proporcionar compuestos que permitan el uso terapéutico de la modulación del metabolismo de lípidos y/o hidratos de carbono, y por lo tanto sean adecuados para prevenir y/o tratar enfermedades tales como la diabetes de tipo 2 y la aterosclerosis y sus diversas secuelas. Otro fin de la invención es tratar trastornos desmielinizantes y otros trastornos neurodegenerativos del sistema nervioso 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 y PPARalfa, sin embargo, es posible que la activación relativa varíe

dependiendo de los compuestos específicos.

Los compuestos de la presente invención se describen con la fórmula I:



fórmula I

en la que

R1 H, halógeno, alquilo (C1-C8), alquileno (C0-C4)-O-alquileno (C0-C4)-H, SCH3 o CN, donde los grupos alquilo y alquileno están sin sustituir o mono, di- o trisustituidos con F;

R2, R3, R4 son independientemente
H, halógeno, alquilo (C1-C8), alquileno (C0-C4)-O-alquileno (C0-C4)-H, SCH3 o CN, donde los grupos alquilo y alquileno están sin sustituir o mono, di- o trisustituidos con F;

X –CH2- o -CH2-CH2-;

U es S u O;

R5 es H, alquilo (C1-C8), alquileno (C1-C4)-O-alquilo (C1-C4), alquileno (C1-C4)-O-alquileno (C0-C4)-arilo (C6-C10), alquileno (C0-C4)-cicloalquilo (C3-C12), alquenilo (C2-C8), alquileno (C0-C4)-heterocicloalquilo (C3-C15), alquileno (C0-C4)-heterocicloalquenilo (C3-C15), alquileno (C0-C4)-heteroarilo (C5-C15), donde los grupos alquilo y alquileno están sin sustituir o mono-, di- o trisustituidos con F, N(alquileno (C0-C4)-H)-alquileno (C0-C4)-H y O-alquileno (C0-C4)-H y

donde los grupos cicloalquilo, arilo, heterocicloalquilo, heterocicloalquenilo y heteroarilo están sin sustituir o mono-, di- o trisustituidos con F, Cl, Br, CF3, alquilo (C1-C4), CO-alquilo (C1-C4) y alquileno (C0-C4)-O-alquileno (C0-C4)-H;

R6, R7 H, arilo (C6-C14), que está sin sustituir o mono-, di- o trisustituido con F, Cl, Br, CF3, alquilo (C1-C4) y alquileno (C0-C4)-O-alquileno (C0-C4)-H; o

R6 y R7 junto con el anillo oxazol o tiazol forman un anillo benzotiazol o benzoxazol, que está sin sustituir o mono- di- o trisustituido con F, Cl, Br, CF3, alquilo (C1-C4) y alquileno (C0-C4)-O-alquileno (C0-C4)-H;

en todas sus formas estereoisoméricas, formas enantioméricas y mezclas en cualquier relación, y sus sales fisiológicamente aceptables y formas tautoméricas.

Otra realización de acuerdo con la invención son compuestos de la fórmula I en la que uno o más sustituyentes tienen los siguientes significados:

R1 halógeno, alquilo (C1-C8), alquileno (C0-C4)-O-alquileno (C0-C4)-H, SCH3 o CN, donde los grupos alquilo y alquileno están sin sustituir o mono, di- o trisustituidos con F;

R1 es H, F, Cl, alquilo (C1-C4), O-alquilo (C1-C4), donde los grupos alquilo y alquileno están sin sustituir o mono, bi- o trisustituidos con F;

R2, R3, R4 son H;

X es -CH2-CH2-;

X es CH2;

U es S;

R5 es alquilo (C1-C4), alquileno (C1-C4)-O-alquilo (C1-C4), alquileno (C1-

C4)-O-CH2-fenilo, alquileno (C1-C4)-heterocicloalquilo (C5-C6) donde los grupos alquilo y alquileno pueden estar mono-, di- o trisustituidos con N(alquil (C1-C4))-alquilo (C1-C4) y donde el grupo heterocicloalquilo está sin sustituir o monosustituido con alquilo (C1-C4) o CO-alquilo (C1-C4);

R6 es fenilo monosustituido con Cl o metoxi;

R6 y R7 junto con el anillo tiazol indican benzotiazol sustituido con CF3 o Cl.

Otra forma de realización de acuerdo con la invención son compuestos de la fórmula I, en donde

R1 es H, F, CH3 o CF3.

Otra forma de realización de acuerdo con la invención son compuestos de la fórmula I, en donde

R1 es F, CH3 o CF3.

Otra forma de realización de acuerdo con la invención son compuestos de la fórmula I, en donde

R6 y R7 junto con el anillo tiazol se refieren a 6-trifluorometil-benzotiazol.

Otra forma de realización de acuerdo con la invención son los compuestos:

3-{4-[2-(Benzooxazol-2-il-butil-amino)-etil]-fenil}-4H-[1.2.4]oxadiazol-5-ona

3-{4-[2-(Benzotiazol-2-il-butil-amino)-etil]-fenil}-4H-[1.2.4]oxadiazol-5-ona

3-(4-{2-[Butil-(6-metoxi-benzotiazol-2-il)-amino]-etil}-fenil)-4H-[1.2.4]oxadiazol-5-ona

3-(4-{2-[Butil-(6-cloro-benzotiazol-2-il)-amino]-etil}-fenil)-4H-[1.2.4]oxadiazol-5-ona

3-(4-{2-[Butil-(6-cloro-benzotiazol-2-il)-amino]-etil}-2-metil-fenil)-4H-[1.2.4]oxadiazol-5-ona

3-(4-{2-[Butil-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-2-metil-fenil)-4H-[1.2.4]oxadiazol-5-ona

3-(2-Metil-4-{2-[[2-(tetrahidro-piran-4-il)-etil]-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-fenil)-4H-[1.2.4]oxadiazol-5-ona

3-(2-Metil-4-{2-[(tetrahidro-piran-3-ilmetil)-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-fenil)-4H-[1.2.4]oxadiazol-5-ona

3-(2-Metil-4-{2-[(tetrahidro-piran-4-ilmetil)-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-fenil)-4H-[1.2.4]oxadiazol-5-ona

3-(4-{2-[[2-(1-Acetil-piperidin-4-il)-etil]-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-2-metil-fenil)-4H-[1.2.4]oxadiazol-5-ona

3-{4-[(Benzooxazol-2-il-butil-amino)-metil]-fenil}-4H-[1.2.4]oxadiazol-5-ona

3-{4-[(Benzotiazol-2-il-butil-amino)-metil]-fenil}-4H-[1.2.4]oxadiazol-5-ona

3-(4-{[Butil-(6-cloro-benzotiazol-2-il)-amino]-metil}-fenil)-4H-[1.2.4]oxadiazol-5-ona

3-(4-{2-[(3-Metoxi-propil)-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-2-metil-fenil)-4H-[1.2.4]oxadiazol-5-ona

3-(4-{2-[[2-(2-Metoxi-etoxi)-etil]-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-2-metil-fenil)-4H-[1.2.4]oxadiazol-5-ona

3-(4-{2-[(2-Benciloxi-etil)-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-2-metil-fenil)-4H-[1.2.4]oxadiazol-5-ona

3-(4-{2-[(2-Metoxi-etil)-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-2-metil-fenil)-4H-

[1.2.4]oxadiazol-5-ona

3-[4-(2-{Butil-[4-(4-metoxi-fenil)-tiazol-2-il]-amino}-etil)-fenil]-4H-[1.2.4]oxadiazol-5-ona

3-[4-(2-{Butil-[4-(4-cloro-fenil)-tiazol-2-il]-amino}-etil)-fenil]-4H-[1.2.4]oxadiazol-5-ona

3-(4-{2-[[4-(4-Cloro-fenil)-tiazol-2-il]-(3-metoxi-propil)-amino]-etil}-fenil)-4H-[1.2.4]oxadiazol-5-ona

3-[4-(2-{[4-(4-Cloro-fenil)-tiazol-2-il]-[2-(2-metoxi-etoxi)-etil]-amino}-etil)-fenil]-4H-[1.2.4]oxadiazol-5-ona

3-[4-(2-{(2-Benciloxi-etil)-[4-(4-cloro-fenil)-tiazol-2-il]-amino}-etil)-fenil]-4H-[1.2.4]oxadiazol-5-ona

3-(4-{2-[[4-(4-Cloro-fenil)-tiazol-2-il]-(2-metoxi-etil)-amino]-etil}-fenil)-4H-[1.2.4]oxadiazol-5-ona

3-(4-{[Butil-(6-trifluorometil-benzotiazol-2-il)-amino]-metil}-2-fluoro-fenil)-4H-[1.2.4]oxadiazol-5-ona

3-(4-{[Butil-(6-cloro-benzotiazol-2-il)-amino]-metil}-2-fluoro-fenil)-4H-[1.2.4]oxadiazol-5-ona

Trifluoroacetato de 3-(2-fluoro-4-{[(2-pirrolidin-1-il-etil)-(6-trifluorometil-benzotiazol-2-il)-amino]-metil}-fenil)-4H-[1.2.4]oxadiazol-5-ona

Trifluoroacetato de 3-(4-{[(2-dimetilamino-etil)-(6-trifluorometil-benzotiazol-2-il)-amino]-metil}-2-fluoro-fenil)-4H-[1.2.4]oxadiazol-5-ona

3-(2-fluoro-4-{[(2-metoxi-etil)-(6-trifluorometil-benzotiazol-2-il)-amino]-metil}-fenil)-4H-[1.2.4]oxadiazol-5-ona

Trifluoroacetato de 3-(2-fluoro-4-{[(2-piperidin-1-il-etil)-(6-trifluorometil-benzotiazol-2-

il)-amino]-metil}-fenil)-4H-[1.2.4]oxadiazol-5-ona

Trifluoroacetato de 3-(2-fluoro-4-{[(2-morfolin-4-il-etil)-(6-trifluorometil-benzotiazol-2-il)-amino]-metil}-fenil)-4H-[1.2.4]oxadiazol-5-ona

Trifluoroacetato de 3-(2-fluoro-4-{[[2-(1-metil-pirrolidin-2-il)-etil]-(6-trifluorometil-benzotiazol-2-il)-amino]-metil}-fenil)-4H-[1.2.4]oxadiazol-5-ona

3-(4-{[(2-Pirrolidin-1-il-etil)-(6-trifluorometil-benzotiazol-2-il)-amino]-metil}-2-trifluorometil-fenil)-4H-[1.2.4]oxadiazol-5-ona

Trifluoroacetato de 3-(4-{[(2-dimetilamino-etil)-(6-trifluorometil-benzotiazol-2-il)-amino]-metil}-2-trifluorometil-fenil)-4H-[1.2.4]oxadiazol-5-ona

3-(4-{[(2-Metoxi-etil)-(6-trifluorometil-benzotiazol-2-il)-amino]-metil}-2-trifluorometil-fenil)-4H-[1.2.4]oxadiazol-5-ona

Trifluoroacetato de 3-(4-{[(2-piperidin-1-il-etil)-(6-trifluorometil-benzotiazol-2-il)-amino]-metil}-2-trifluorometil-fenil)-4H-[1.2.4]oxadiazol-5-ona

Trifluoroacetato de 3-(4-{[(2-morfolin-4-il-etil)-(6-trifluorometil-benzotiazol-2-il)-amino]-metil}-2-trifluorometil-fenil)-4H-[1.2.4]oxadiazol-5-ona

Trifluoroacetato de 3-(4-{[[2-(1-metil-pirrolidin-2-il)-etil]-(6-trifluorometil-benzotiazol-2-il)-amino]-metil}-2-trifluorometil-fenil)-4H-[1.2.4]oxadiazol-5-ona

3-[4-({Butil-[4-(4-metoxi-fenil)-tiazol-2-il]-amino}-metil)-fenil]-4H-[1.2.4]oxadiazol-5-ona

3-(4-{[[4-(4-Cloro-fenil)-tiazol-2-il]-(3-metoxi-propil)-amino]-metil}-2-fluoro-fenil)-4H-[1.2.4]oxadiazol-5-ona

3-(4-{[[4-(4-Cloro-fenil)-tiazol-2-il]-(2-metoxi-etil)-amino]-metil}-2-fluoro-fenil)-4H-[1.2.4]oxadiazol-5-ona

3-[4-({[4-(4-Cloro-fenil)-tiazol-2-il]-[2-(2-metoxi-etoxi)-etil]-amino}-metil)-2-fluoro-fenil]-4H-[1.2.4]oxadiazol-5-ona

Esta invención también abarca todas las combinaciones de aspectos preferidos de la invención descritos en esta memoria.

Como se usa en este documento, se entiende que el término alquilo se refiere, en el sentido más amplio, a restos de hidrocarburo que pueden ser lineales, es decir, de cadena lineal, o ramificados. Si no se define otra cosa, el término alquilo tiene de 1 a 8 átomos de carbono. Ejemplos de "-alquilo (C1-C8)" son residuos de alquilo que contienen 1, 2, 3, 4, 5, 6, 7 u 8 átomos de carbono y son metilo, etilo, propilo, butilo, pentilo, hexilo, heptilo u octilo, los n-isómeros de estos residuos, isopropilo, isobutilo, 1-metilbutilo, isopentilo, neopentilo, 2,2-dimetilbutilo, 2-metilpentilo, 3-metilpentilo, isohexilo, sec-butilo, terc-butilo o terc-pentilo. El término "-alquilo (C0-C8)" es un residuo de hidrocarburo que contiene 1, 2, 3, 4, 5, 6, 7 u 8 átomos de carbono, en el que el término "-CO-alquilo" es un enlace covalente. Todas estas declaraciones se aplican también al término alquileno.

Como se usa en este documento, se entiende que el término alquenilo se refiere, en el sentido más amplio, a restos de hidrocarburo que tienen de 1 a 4 dobles enlaces y pueden ser lineales, es decir, de cadena lineal, o ramificados. Si no se define otra cosa, el término alquenilo tiene de 2 a 8 átomos de carbono. Ejemplos de "-alquenilo (C2-C8)" son residuos de alquenilo que contienen 2, 3, 4, 5, 6, 7 u 8 átomos de carbono, 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. Todas estas declaraciones se aplican también al término alquenileno.

Como se usa en este documento, se entiende que el término alquinilo se refiere, en el sentido más amplio, a restos de hidrocarburo, que tienen de 1 a 4 triples enlaces y pueden ser lineales, es decir, de cadena lineal, o ramificados. Si no se define otra cosa, el término alquinilo tiene de 2 a 8 átomos de carbono. Ejemplos de "-alquinilo (C2-C8)" son residuos de alquinilo que contienen 2, 3, 4, 5, 6, 7 u 8 átomos de carbono, por ejemplo, etinilo, 1-propinilo, 2-propinilo (= propargilo) o 2-butinilo. Todas estas declaraciones se aplican también al término alquilideno.

Todos estos enunciados se aplican también si aparece un grupo alquilo como sustituyente en otro resto, por ejemplo en un resto alquiloxi, un resto alquiloxicarbonilo o un resto arilalquilo.

Si no se define otra cosa, los grupos alquilo, alquileno, alquenilo, alquenileno, alquinilo y alquinileno están sin sustituir o mono, di- o trisustituidos independientemente entre sí con grupos adecuados tales como, por ejemplo: F, Cl, Br, I, CF3, NO2, CN, COOH, CO-O-alquileno (C0-C4)-arilo (C6-C10), CO-O-alquilo (C1-C4), CO-O-alquileno (C0-C4)-cicloalquilo (C3-C13), CO-O-alquileno (C0-C4)-heterociclo (C3-C15), CO-N(alquileno (C0-C4)-H)-alquileno (C0-C4)-arilo (C6-C10), CO-N(alquileno (C0-C4)-H)-alquileno (C0-C4)-H, CO-N(alquileno (C0-C4)-H)-alquileno (C0-C4)-cicloalquilo (C3-C13), CO-N(alquileno (C0-C4)-H)-alquileno (C0-C4)-heterociclo (C3-C15), alquileno (C0-C4)-cicloalquilo (C3-C6), alquileno (C0-C4)-arilo (C6-C10), alquileno (C0-C4)-heterociclo (C3-C15), alquenilo (C2-C6), alquinilo (C2-C6), O-alquilo (C0-C6), O-alquileno (C0-C4)-arilo (C6-C10), O-alquileno (C0-C4)-cicloalquilo (C3-C12), O-alquileno (C0-C4)-heterociclo (C3-C15), O-CO-O-alquileno (C0-C4)-arilo (C6-C10), O-CO-O-alquilo (C1-C4), O-CO-O-alquileno (C0-C4)-cicloalquilo (C3-C13), O-CO-O-alquileno (C0-C4)-heterociclo (C3-C15), S-alquilo (C1-C4), S-alquileno (C0-C4)-cicloalquilo (C3-C13), S-alquileno (C0-C4)-arilo (C6-C10), S-alquileno (C0-C4)-heterociclo (C3-C15), SO-alquilo (C1-C4), SO-alquileno (C0-C4)-cicloalquilo (C3-C13), SO-alquileno (C0-C4)-arilo (C6-C10), SO-alquileno (C0-C4)-heterociclo (C3-C15), SO2-alquilo (C1-C4), SO2-alquileno (C0-C4)-cicloalquilo (C3-C13), SO2-alquileno (C0-C4)-arilo (C6-C10), SO2-alquileno (C0-C4)-heterociclo (C3-C15), SO2-N(alquileno (C0-C4)-H)-alquileno (C0-C4)-arilo (C6-C10), SO2-N(alquileno (C0-C4)-H)-alquileno (C0-C4)-H, SO2-N(alquileno (C0-C4)-H)-alquileno (C0-C4)-cicloalquilo (C3-C13), SO2-N(alquileno (C0-C4)-H)-alquileno (C0-C4)-heterociclo (C3-C15) donde el anillo arilo o el anillo heterocíclico está sin sustituir o mono- o disustituido con F, Cl, Br, OH, CF3, NO2, CN, OCF3, O-alquilo (C1-C6), alquilo (C1-C6), N(alquileno (C0-C4)-H)-alquileno (C0-C4)-H; N(alquileno (C0-C4)-H)-alquileno (C0-C4)-H, N(alquileno (C0-C4)-H)-alquileno (C0-C4)-H)-cicloalquilo (C1-C6), N(alquileno (C0-C4)-H)-alquileno (C0-C4)-arilo (C6-C12), N(alquileno (C0-C4)-H)-alquileno (C0-C4)-heterociclo (C3-C15), N(alquileno (C0-C4)-H)-CO-alquileno (C0-C4)-arilo (C6-C12), N(alquileno (C0-C4)-H)-CO-alquilo (C0-C4), N(alquileno (C0-C4)-H)-CO-alquileno (C0-C4)-cicloalquilo (C3-C13), N(alquileno (C0-C4)-H)-CO-alquileno (C0-C4)-heterociclo (C3-C15),

N(alquileno (C0-C4)-H)-CO-O-alquileno (C0-C4)-arilo (C6-C12), N(alquileno (C0-C4)-H)-CO-O-alquilo (C0-C4), N(alquileno (C0-C4)-H)-CO-O-alquileno (C0-C4)-cicloalquilo (C3-C13), N(alquileno (C0-C4)-H)-CO-O-alquileno (C0-C4)-heterociclo (C3-C15), N(alquileno (C0-C4)-H)-CO-N(alquileno (C0-C4)-H)-alquileno (C0-C4)-arilo (C6-C12), N(alquileno (C0-C4)-H)-CO-N(alquileno (C0-C4)-H)-alquilo (C0-C4), N(alquileno (C0-C4)-H)-CO-N(alquileno (C0-C4)-H)-alquileno (C0-C4)-cicloalquilo (C3-C13), N(alquileno (C0-C4)-H)-CO-N(alquileno (C0-C4)-H)-alquileno (C0-C4)-heterociclo (C3-C15), donde el anillo arilo o el anillo heterocíclico está sin sustituir o mono- o disustituido con F, Cl, Br, I, OH, CF3, NO2, CN, OCF3, O-alquilo (C1-C6), alquilo (C1-C6), N(alquileno (C0-C4)-H)-alquileno (C0-C4)-H, SO2-CH3, COOH, COO-alquilo (C1-C6), SF5, CONH2.

Se entiende que el término cicloalquilo se refiere a un hidrocarburo cíclico saturado que contiene de 3 a 13 átomos de carbono en un anillo mono- o bicíclico, condensado, enlazado o espirocíclico. Son ejemplos de restos cicloalquilo (C3-C13) restos alquilo cíclicos tales como restos cicloalquilo que contienen 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 ó 13 átomos de carbono de anillo tales como ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo, ciclononilo, ciclodecilo, cicloundecilo o ciclododecilo. El término cicloalquilo también incluye grupos bicíclicos donde cualquiera de los anillos cicloalquilo anteriores está condensado con un anillo benceno, por ejemplo indano y 1,2,3,4-tetrahidronaftaleno.

Se entiende que el término cicloalquenilo se refiere a un hidrocarburo cíclico insaturado que contiene de 3 a 8 átomos de carbono en un anillo mono- o bicíclico, condensado o enlazado, donde uno, dos o tres dobles enlaces no se encuentran dentro de un grupo alquilo cíclico de tal forma que se produzca un sistema aromático. Son ejemplos de grupos cicloalquenilo insaturados ciclopentenilo o ciclohexenilo, que pueden unirse mediante cualquier átomo de carbono. El término cicloalquenilo también incluye grupos bicíclicos donde cualquiera de los anillos cicloalquenilo anteriores está condensado con un anillo benceno, por ejemplo 1,2-dihidronaftaleno, 1,4-dihidronaftaleno y 1H-indeno.

Si no se define otra cosa, los grupos cicloalquilo o cicloalquenilo están sin sustituir o mono, di- o trisustituidos independientemente entre sí con grupos adecuados tales como, por ejemplo: F, Cl, Br, I, CF3, NO2, CN, COOH, CO-O-alquileno (C0-C4)-

arilo (C6-C10), CO-O-alquilo (C1-C4), CO-O-alquileno (C0-C4)-cicloalquilo (C3-C13), CO-O-alquileno (C0-C4)-heterociclo (C3-C15), CO-N(alquileno (C0-C4)-H)-alquileno (C1-C6)-H, CO-N(alquileno (C0-C4)-H)-cicloalquilo (C1-C6), CON(alquileno (C0-C4)-H)-alquileno (C0-C4)-arilo (C6-C12), alquileno (C0-C4)-cicloalquilo (C3-C6), alquilo (C3-C6), alquenilo (C2-C6), alquinilo (C2-C6), alquileno (C0-C4)-arilo (C6-C10), alquileno (C0-C4)-heterociclo (C3-C15), O-alquilo (C0-C6), alquileno (C0-C4)-O-alquilo (C0-C4), alquileno (C0-C4)-O-alquileno (C0-C4)-cicloalquilo (C3-C13), alquileno (C0-C4)-O-alquileno (C0-C4)-arilo (C6-C10), alquileno (C0-C4)-O-alquileno (C0-C4)-heterociclo (C3-C15), O-CO-O-alquileno (C0-C4)-arilo (C6-C10), O-CO-O-alquilo (C1-C4), O-CO-O-alquileno (C0-C4)-cicloalquilo (C3-C13), O-CO-O-alquileno (C0-C4)-heterociclo (C3-C15), O-CO-N(alquileno (C0-C4)-H)-alquileno (C0-C4)-arilo (C6-C10), O-CO-N(alquileno (C0-C4)-H)-alquileno (C0-C4)-H, O-CO-N(alquileno (C0-C4)-H)-alquileno (C0-C4)-cicloalquilo (C3-C13), O-CO-N(alquileno (C0-C4)-H)-alquileno (C0-C4)-heterociclo (C3-C15),S-alquilo (C1-C4), S-alquileno (C0-C4)-cicloalquilo (C3-C13), S-alquileno (C0-C4)-arilo (C6-C10), S-alquileno (C0-C4)-heterociclo (C3-C15), SO-alquilo (C1-C4), SO-alquileno (C0-C4)-cicloalquilo (C3-C13), SO-alquileno (C0-C4)-arilo (C6-C10), SO-alquileno (C0-C4)-heterociclo (C3-C15), SO2-alquilo (C1-C4), SO2-alquileno (C0-C4)-cicloalquilo (C3-C13), SO2-alquileno (C0-C4)-arilo (C6-C10), SO2-alquileno (C0-C4)-heterociclo (C3-C15), SO2-N(alquileno (C0-C4)-H)-alquileno (C0-C4)-arilo (C6-C10), SO2-N(alquileno (C0-C4)-H)-alquileno (C0-C4)-H, SO2-N(alquileno (C0-C4)-H)-alquileno (C0-C4)-cicloalquilo (C3-C13), SO2-N(alquileno (C0-C4)-H)-alquileno (C0-C4)-heterociclo (C3-C15), donde el anillo arilo o el anillo heterocíclico está sin sustituir o mono- o disustituido con F, Cl, Br, OH, CF3, NO2, CN, OCF3, O-alquilo (C1-C6), alquilo (C1-C6), N(alquileno (C0-C4)-H)-alquileno (C0-C4)-H;

N(alquileno (C0-C4)-H)-alquileno (C0-C4)-H, N(alquileno (C0-C4)-H)-alquileno (C0-C4)-H)-cicloalquilo (C1-C6), N(alquileno (C0-C4)-H)-alquileno (C0-C4)-arilo (C6-C12), N(alquileno (C0-C4)-H)-alquileno (C0-C4)-heterociclo (C3-C15), N(alquileno (C0-C4)-H)-CO-alquileno (C0-C4)-arilo (C6-C12), N(alquileno (C0-C4)-H)-CO-alquilo (C0-C4), N(alquileno (C0-C4)-H)-CO-alquileno (C0-C4)-cicloalquilo (C3-C13), N(alquileno (C0-C4)-H)-CO-alquileno (C0-C4)-heterociclo (C3-C15), N(alquileno (C0-C4)-H)-CO-O-alquileno (C0-C4)-arilo (C6-C12), N(alquileno (C0-C4)-H)-CO-O-alquilo (C0-C4), N(alquileno (C0-C4)-H)-CO-O-alquileno (C0-C4)-cicloalquilo (C3-C13), N(alquileno (C0-C4)-H)-CO-O-alquileno (C0-C4)-heterociclo

C4), SO-alquileno (C0-C4)-cicloalquilo (C3-C13), SO-alquileno (C0-C4)-arilo (C6-C10), SO-alquileno (C0-C4)-heterociclo (C3-C15), SO2-alquilo (C1-C4), SO2-alquileno (C0-C4)-cicloalquilo (C3-C13), SO2-alquileno (C0-C4)-arilo (C6-C10), SO2-alquileno (C0-C4)-heterociclo (C3-C15), SO2-N(alquileno (C0-C4)-H)-alquileno (C0-C4)-arilo (C6-C10), SO2-N(alquileno (C0-C4)-H)-alquileno (C0-C4)-H, SO2-N(alquileno (C0-C4)-H)-alquileno (C0-C4)-cicloalquilo (C3-C13), SO2-N(alquileno (C0-C4)-H)-alquileno (C0-C4)-heterociclo (C3-C15), donde el anillo arilo o el anillo heterocíclico está sin sustituir o mono- o disustituido con F, Cl, Br, OH, CF3, NO2, CN, OCF3, O-alquilo (C1-C6), alquilo (C1-C6), N(alquileno (C0-C4)-H)-alquileno (C0-C4)-H;
N(alquileno (C0-C4)-H)-alquileno (C0-C4)-H, N(alquileno (C0-C4)-H)-alquileno (C0-C4)-H)-cicloalquilo (C1-C6), N(alquileno (C0-C4)-H)-alquileno (C0-C4)-arilo (C6-C12), N(alquileno (C0-C4)-H)-alquileno (C0-C4)-heterociclo (C3-C15), N(alquileno (C0-C4)-H)-CO-alquileno (C0-C4)-arilo (C6-C12), N(alquileno (C0-C4)-H)-CO-alquilo (C0-C4), N(alquileno (C0-C4)-H)-CO-alquileno (C0-C4)-cicloalquilo (C3-C13), N(alquileno (C0-C4)-H)-CO-alquileno (C0-C4)-heterociclo (C3-C15), N(alquileno (C0-C4)-H)-CO-O-alquileno (C0-C4)-arilo (C6-C12), N(alquileno (C0-C4)-H)-CO-O-alquilo (C0-C4), N(alquileno (C0-C4)-H)-CO-O-alquileno (C0-C4)-cicloalquilo (C3-C13), N(alquileno (C0-C4)-H)-CO-O-alquileno (C0-C4)-heterociclo (C3-C15), N(alquileno (C0-C4)-H)-CO-N(alquileno (C0-C4)-H)-alquileno (C0-C4)-arilo (C6-C12), N(alquileno (C0-C4)-H)-CO-N(alquileno (C0-C4)-H)-alquilo (C0-C4), N(alquileno (C0-C4)-H)-CO-N(alquileno (C0-C4)-H)-alquileno (C0-C4)-cicloalquilo (C3-C13), N(alquileno (C0-C4)-H)-CO-N(alquileno (C0-C4)-H)-alquileno (C0-C4)-heterociclo (C3-C15), donde el anillo arilo o el anillo heterocíclico está sin sustituir o mono- o disustituido con F, Cl, Br, I, OH, CF3, NO2, CN, OCF3, O-alquilo (C1-C6), alquilo (C1-C6), N(alquileno (C0-C4)-H)-alquileno (C0-C4)-H,SO2-CH3, COOH, COO-alquilo (C1-C6), SF5, CONH2.

El término "residuo oxo" o "=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 de los compuestos de la fórmula I pueden tener independientemente entre sí la configuración R o la configuración S.

funcionales tal como se describe en esta memoria.

Uso

Esta invención se refiere además al uso de compuestos de la 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, PPARalfa, PPARgamma y PPARdelta (idéntica a PPARbeta), 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 PPARgamma existe en tres variantes, PPARgamma1, 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 funciones fisiológicas. Los PPAR tienen un papel principal en diferentes aspectos de la regulación de un gran número de genes, y estando los productos de dichos genes implicados de forma crucialmente directa o indirecta en el metabolismo de lípidos e hidratos de carbono. Así, por ejemplo, el receptor PPARalfa tiene un papel importante en la regulación del catabolismo de ácidos grasos o del metabolismo de lipoproteínas en el hígado, mientras que el PPARgamma 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 modularse por diferentes ácidos grasos, 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. y Berger, J.P, Int. J. Obes. Relat. Metab. Disord,

sigue sin descubrirse la mayor parte de su función en éste. Sin embargo, tiene un interés particular el descubrimiento de que el PPARdelta se expresaba 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 PPARdelta 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 PPARdelta se pueden usar para el tratamiento de la desmielinización y de otras enfermedades desmielinizantes. Puede mostrarse el uso de agonistas delta del receptor activado del proliferador de peroxisomas para el tratamiento de EM y otras enfermedades desmielinizantes como se describe en el documento 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 se proporcionan por la oligodendroglía 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 y McDonald, Demyelinating Diseases. In Greenfield's Neuropathology, 6ª ed. (Edward Arnold: New York, 1997) 813-811, Beers y Berkow, eds, The Merck Manual of Diagnosis y Therapy, 17ª 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 desmielinizantes primarias incluyen adrenoleucodistrofia (ALD), adrenomieloneuropatía, mielopatía vacuolar asociada al SIDA, mielopatía asociada a HTLV, atrofia óptica hereditaria de Leber, 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, también puede dar como resultado la desmielinización. También, los trastornos en los que las células gliales formadoras de mielina están dañadas, incluyendo lesiones de la médula espinal, neuropatías y lesión nerviosa.

La presente invención se refiere a compuestos de la fórmula I adecuados para modular la actividad de los PPAR, especialmente la actividad de los PPARdelta y PPARalfa. Dependiendo del perfil de modulación, los compuestos de la 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 pospandrial,
   - bajas concentraciones de colesterol HDL
   - bajas concentraciones de lipoproteína ApoA
   - altas concentraciones de colesterol LDL
   - partículas de colesterol LDL de baja densidad
   - altas concentraciones de lipoproteína ApoB

4. Diversos trastornos diferentes que se pueden asociar con el síndrome 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 éstas), 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 ulcerosa
   - 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 éstos), 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 desmielinizantes y otros trastornos neurodegenerativos de los sistemas nervioso central y periférico, incluyendo:

- enfermedad de Alzheimer
- esclerosis múltiple
- enfermedad de Parkinson
- adrenoleucodistrofia (ALD)
- adrenomieloneuropatía
- mielopatía vacuolar asociada con el SIDA
- mielopatía 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
- infecciones 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
- sabañones
- curación de heridas

9. Otros trastornos

- hipertensión arterial
- pancreatitis
- síndrome X
- síndrome de ovario poliquístico (SOP)
- asma
- osteoartritis
- 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 aguda (SDRA)

Formulaciones

La cantidad de un compuesto de la 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

inhibidores de glutamina:fructosa-6-fosfato amidotransferasa (GFAT),
agonistas de GLP-1,
agentes para abrir los canales de potasio, tales como, por ejemplo, los descritos en los documentos WO 97/26265 y WO 99/03861 por Novo Nordisk A/S,
inhibidores de dipeptidilpeptidasa IV (DPP-IV),
sensibilizadores a la insulina,
inhibidores de enzimas hepáticas implicadas en la estimulación de la gluconeogénesis y/o glucogenolisis,
moduladores de la captación de glucosa, transporte de glucosa y reabsorción de glucosa,
inhibidores de 11ß-HSD1,
inhibidores de la proteína tirosina fosfatasa 1B (PTP1B),
moduladores del cotransportador de sodio/glucosa 1 ó 2 (SGLT1, SGLT2),
compuestos que alteran el metabolismo de lípidos, tales como ingredientes activos antihiperlipidémicos 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 la HMGCoA-reductasa, tal 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 la reabsorción de colesterol tal como, por ejemplo, ezetimiba, tiquesida, pamaquesida, FM-VP4 (sitostanol/campesterol ascorbil fosfato; Forbes Medi-Tech, documento WO2005042692), MD-0727 (Microbia Inc, documento WO2005021497) o con compuestos como los descritos en el documento 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 PPARalfa, tal como, por ejemplo, GW9578, GW-590735, K-111, LY-674, KRP-101 o DRF-10945.

En una forma de realización de la invención, el compuesto de la fórmula I se administra en combinación con un agonista mixto de PPARalfa/gamma, tal como, por ejemplo, muraglitazar, tesaglitazar, naveglitazar, LY-510929, ONO-5129, E-3030 o como se describe en los documentos 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 los documentos 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 tal 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, tal como, por ejemplo, implitapida, BMS-201038, R-103757 o los descritos en el documento WO2005085226.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con un inhibidor de CETP, tal 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 la resorción de ácidos biliares (véanse, por ejemplo, los documentos US 6.245.744, US 6.221.897 o WO00/61568), tales como, por ejemplo, HMR 1741 o los descritos en los documentos 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 polimérico de ácidos biliares, tal 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 el documento US 6.342.512), tal como, por ejemplo, HMR1171, HMR1586 o los descritos en el documento WO2005097738.

En una realización, el compuesto de la fórmula I se administra en combinación con Omacor® (ácidos grasos omega-3; etil ésteres muy concentrados de ácido eicosapentaenoico y del ácido docosahexaenoico).

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con un inhibidor de ACAT tal como, por ejemplo, avasimiba.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con un antioxidante, tal 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 una vitamina, tal 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 la lipoproteína lipasa, tal 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 tal 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 la escualeno sintetasa, tal como, por ejemplo, BMS-188494 o como se describe en el documento WO2005077907.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con un antagonista de lipoproteína (a), tal como, por ejemplo, gemcabeno (CI-1027).

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con un agonista del receptor HM74A, tal 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, tal 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, tal 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, tal como, por ejemplo, metformina.

En otra realización de la invención, el compuesto de la fórmula I se administra en combinación con una meglitinida, tal como, por ejemplo, repaglinida o nateglinida.

En una realización de la invención, el compuesto de la fórmula I se administran en combinación con una tiazolidinodiona tal como, por ejemplo, troglitazona, ciglitazona, pioglitazona, rosiglitazona o los compuestos descritos en el documento WO 97/41097 de la Dr. Reddy's Research Foundation, en particular 5-[[4-[(3,4-dihidro-3-metil-4-oxo-2-quinazolinilmetoxi]fenil]metil]-2,4-tiazolidinodiona.

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 la proteína tirosina fosfatasa 1B (PTP1B), como se describe, por ejemplo, en los documentos 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 en combinación con moduladores del cotransportador de sodio/glucosa 1 ó 2 (SGLT1, SGLT2), tales como, por ejemplo, KGA-2727, T-1095 y SGL-0010 o como se describe, por ejemplo, en los documentos WO2004007517, WO200452903, WO200452902, WO2005121161, WO2005085237, JP2004359630 o por 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 los descritos, por ejemplo, en los documentos 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, por ejemplo los descritos en los documentos 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 carboxiquinasa (PEPCK), tal como, por ejemplo, los descritos en el documento WO2004074288.

En una realización de la invención, el compuesto de la fórmula I se administra en

combinación con un inhibidor de la glucógeno sintasa quinasa-3 beta (GSK-3 beta), tal como los descritos, por ejemplo, en los documentos 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 proteína quinasa C beta (PKC beta), tal 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, tal 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 la quinasa "I-kappaB quinasa" (inhibidores de la IKK), tales como los descritos, por ejemplo, en los documentos 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 como los descritos, por ejemplo, en el documento WO2005090336.

En una realización más de la invención, el compuesto de la fórmula I se administra en combinación con moduladores de CART (véase "Cocaine-anfetamina-regulated transcript influences energy metabolism, anxiety and gastric emptying in mice" Asakawa, A. et al.: Hormone y Metabolic Research (2001), 33(9), 554-558);
antagonistas de NPY tales como, por ejemplo, hidrocloruro de {4-[(4-aminoquinazolin-2-ilamino)metil]ciclohexilmetil}naftaleno-1-sulfonamida (CGP 71683A);
péptido YY 3-36 (PYY3-36) o compuestos análogos, tales como, por ejemplo, CJC-1682 (PYY3-36 conjugado con albúmina de suero humano a través de Cys34), CJC-1643 (obtenido a partir de PYY3-36 que se conjuga in vivo con albúmina de suero) o los descritos en el documento WO2005080424.

antagonistas del receptor 1 de cannabinoides tales como, por ejemplo, rimonabant, SR147778 o los descritos, por ejemplo, en los documentos 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; (documento WO 01/91752)) o LB53280, LB53279, LB53278 o THIQ, MB243, RY764, CHIR-785, PT-141 o los descritos en los documentos 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 los descritos, por ejemplo, en los documentos WO200196302, WO200185693, WO2004085403 o WO2005075458);

agonistas del receptor H3 de histamina (por ejemplo, sal del ácido oxálico de 3-ciclohexil-1-(4,4-dimetil-1,4,6,7-tetrahidroimidazo[4,5-c]piridin-5-il)-propan-1-ona (documento WO 00/63208) o los descritos en el documento WO200064884,

WO2005082893);

antagonistas de CRF (por ejemplo [2-metil-9-(2,4,6-trimetilfenil)-9H-1,3,9-triazafluoren-4-il]dipropilamina (documento WO 00/66585));

antagonistas de CRF BP (por ejemplo urocortina);

agonistas de urocortina;

agonistas de β3 (tales como, por ejemplo, hidrocloruro de 1-(4-cloro-3-metanosulfonilmetilfenil)-2-[2-(2,3-dimetil-1H-indol-6-iloxi)etilamino]etanol (documento WO 01/83451));

agonistas de MSH (hormona estimuladora de melanocitos);

antagonistas del receptor de MCH (hormona concentradora de melanina) (tales como, por ejemplo, NBI-845, A-761, A-665798, A-798, ATC-0175, T-226296, T-71, GW-803430 o los compuestos descritos en los documentos 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 de ácido trifluoroacético del ácido {2-[4-(4-cloro-2,5-dimetoxifenil)-5-(2-ciclohexiletil)-tiazol-2-ilcarbamoil]-5,7-dimetilindol-1-il}acético (documento WO 99/15525), SR-146131 (documento WO 0244150) o SSR-125180);

inhibidores de la recaptación de serotonina (por ejemplo dexfenfluramina);

compuestos serotoninérgicos y noradrenérgicos mixtos (por ejemplo, documento WO 00/71549);

agonistas del receptor 5-HT, por ejemplo sal de ácido oxálico de 1-(3-etilbenzofuran-7-il)piperazina (documento WO 01/09111);

agonistas del receptor 5-HT2C (tales como, por ejemplo, APD-356, BVT-933 o los descritos en los documentos WO200077010, WO20077001-02, WO2005019180, WO2003064423, WO200242304 o WO2005082859);

antagonistas del receptor 5-HT6, tales como los descritos, por ejemplo, en el documento WO2005058858;

agonistas del receptor de bombesina (agonistas de BRS-3);

antagonistas del receptor de galanina;

hormona del crecimiento (por ejemplo, hormona del crecimiento humana o AOD-9604);

compuestos de liberación de hormona del crecimiento (6-benciloxi-1-(2-

diisopropilamino-etilcarbamoil)-3,4-dihidro-1H-isoquinolina-2-carboxilato de terc-butilo (documento WO 01/85695));

antagonistas de receptores de secretagogos de hormona del crecimiento (antagonistas de grelina) tales como, por ejemplo, A-778193 o los descritos en el documento WO2005030734;

agonistas de TRH (véase, por ejemplo, el documento EP 0 462 884);

moduladores de proteína 2 ó 3 de desacoplamiento;

agonistas de leptina (véase, por ejemplo, Lee, Daniel W.; Leinung, Matthew C.; Rozhavskaya-Arena, Marina; Grasso, Patricia. "Leptin agonists as a potential procedimiento to the treatment of obesity". Drugs of the Future (2001), 26(9), 873-881);

agonistas de DA (bromocriptina o Doprexin);

inhibidores de lipasa/amilasa (como los descritos, por ejemplo, en el documento WO 00/40569);

inhibidores de diacilglicerol O-aciltransferasas (DGAT) tales como los descritos, por ejemplo, en los documentos US2004/0224997, WO2004094618, WO200058491, WO2005044250, WO2005072740, JP2005206492 o WO2005013907;

inhibidores de ácido graso sintasa (FAS) tales como, por ejemplo, C75 o los descritos en el documento WO2004005277;

oxintomodulina;

oleoil-estrona

o agonistas de receptores de hormonas tiroideas, tales como, por ejemplo, KB-2115 o los descritos en los documentos WO20058279, WO200172692, WO200194293, WO2003084915, WO2004018421 o WO2005092316,

En una realización de la invención, el ingrediente activo adicional 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 ingrediente activo adicional es dexanfetamina o anfetamina.

En una realización de la invención, el ingrediente activo adicional es fenfluramina o dexfenfluramina.

En otra realización de la invención, el ingrediente activo adicional es sibutramina.
En una realización de la invención, el ingrediente activo adicional es mazindol o fentermina.

En una realización de la invención, los compuestos de la fórmula I se administran en combinación con agentes que confieren volumen, preferiblemente agentes que confieren volumen insolubles (véase, por ejemplo, algarroba/Caromax® (Zunft H J; y otros, Carob pulp preparation for treatment of hypercholesterolemia, ADVANCES IN THERAPY (2001 Sep-Oct), 18 (5), 230-6). Caromax es un producto que contiene algarroba 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 la fórmula I y Caromax®. En relación con esto, Caromax® se puede administrar también en forma de productos alimentarios, 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), como los descritos, por ejemplo, en los documentos WO2003/077949 o WO2005012485.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con agonistas de NAR-1 (receptor de ácido nicotínico) como se describe, por ejemplo, en el documento WO2004094429.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con agonistas de CB2 (receptor de cannabinoides) como se describe, por ejemplo, en el documento US2005/143448.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con agonistas de histamina 1 como se describe, por ejemplo, en el documento WO2005101979.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con bupropión, como se describe en el documento WO2006017504.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con antagonistas de opiáceos como se describe, por ejemplo, en los documentos WO2005107806 o WO2004094429.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con inhibidores de la endopeptidasa neutra como se describe, por ejemplo, en los documentos 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) como se describe, por ejemplo, en el documento WO2002047670.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con inhibidores del intercambio de sodio/hidrógeno como se describe, por ejemplo, en el documento WO2003092694.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con moduladores del receptor de glucocorticoides como los descritos, por ejemplo, en el documento WO2005090336.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con agonistas del receptor de nicotina como se describe, por ejemplo, en el documento WO2004094429.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con inhibidores de NRI (inhibidores de la recaptación de norepinefrina) como se describe, por ejemplo, en el documento WO2002053140.

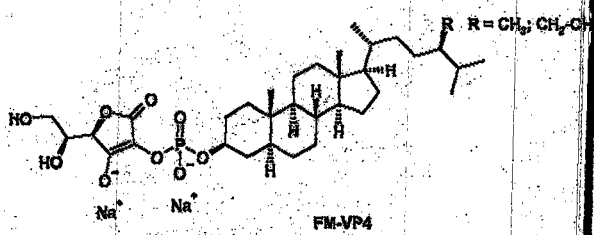
En una realización de la invención, el compuesto de la fórmula I se administra en combinación con MOA (E-beta-metoxiacrilato), tales como, por ejemplo, segelina, o como se describe, por ejemplo, en el documento WO2002053140.

En una realización de la invención, el compuesto de la fórmula I se administra en combinación con ingredientes activos antitrombóticos tales como, por ejemplo,

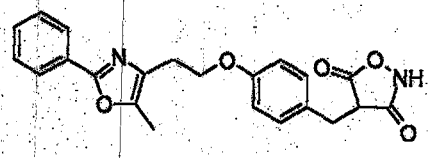
clopidrogel.

Debe entenderse que en el alcance de la presente invención se incluyen todas las combinaciones adecuadas de los compuestos de acuerdo con la invención con uno o más de los compuestos mencionados anteriormente y opcionalmente una o más sustancias farmacológicamente activas distintas.

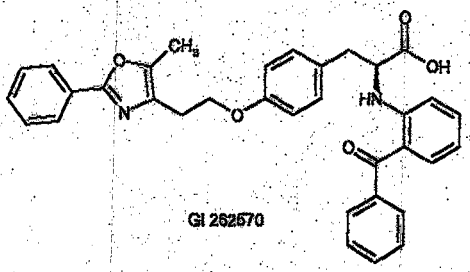
A continuación se proporcionan las fórmulas para algunos de los códigos de desarrollo mencionados anteriormente.



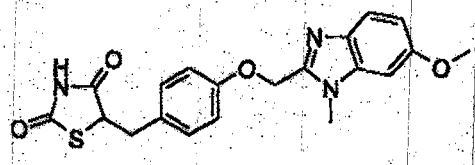
FM-VP4



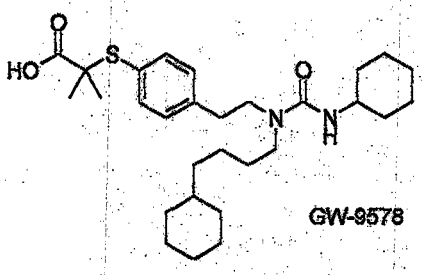
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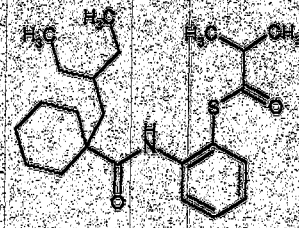
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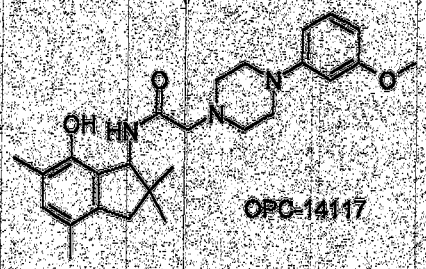
CS-011
Rivoglitazona



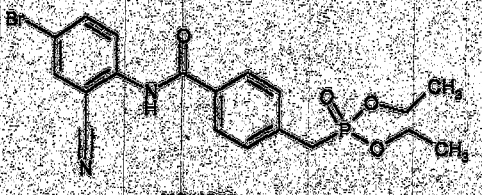
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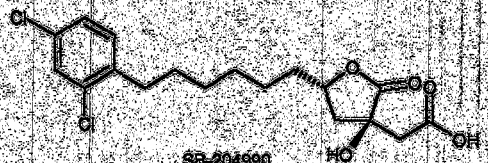
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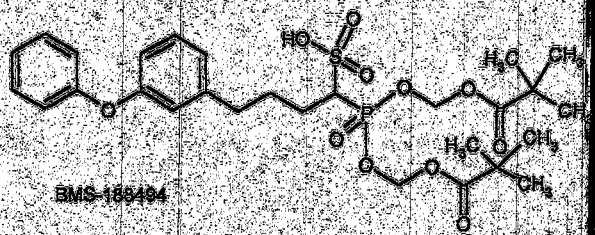
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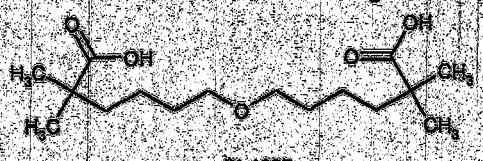
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SB-204990



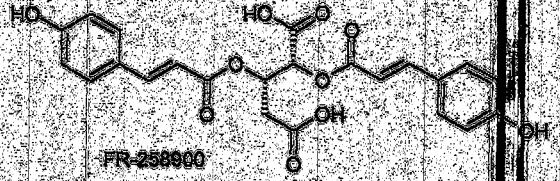
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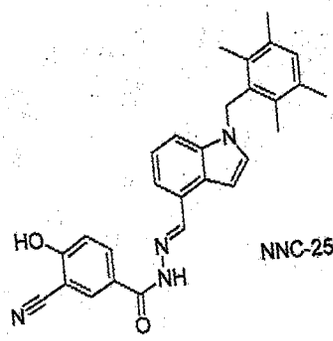
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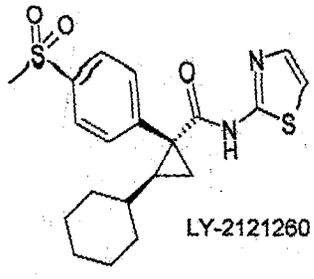
ATL-962



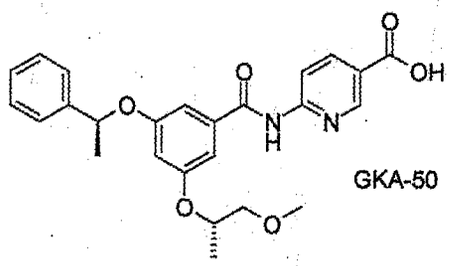
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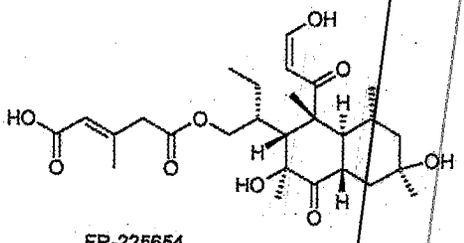
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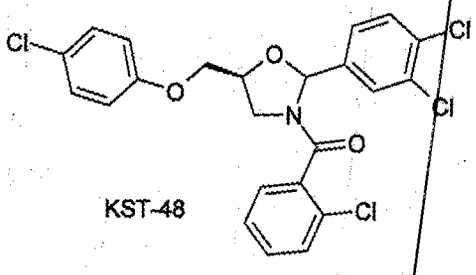
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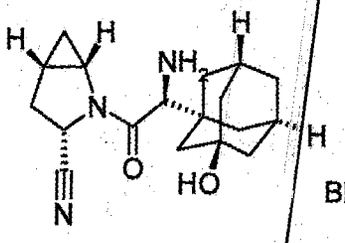
GKA-50



FR-225654

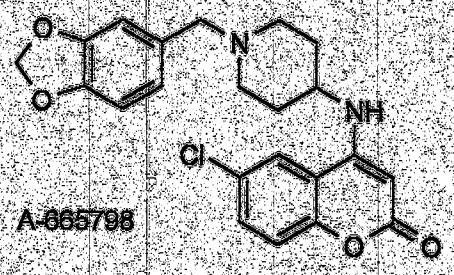


KST-48

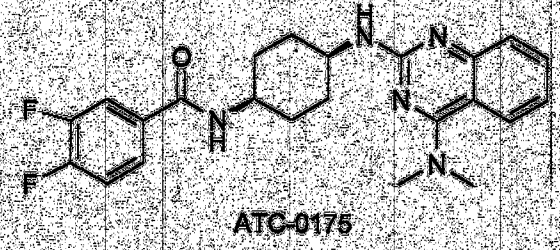


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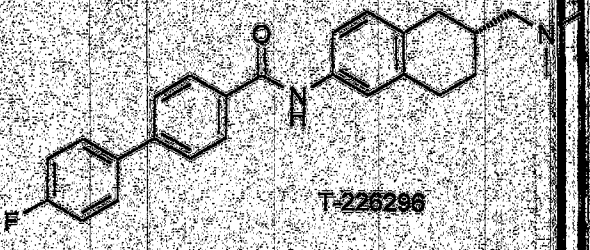
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SFP-1
T-1095
BVT-2733
46
H-Cl
THIL
MEB43
CHIR-265
A-761
5



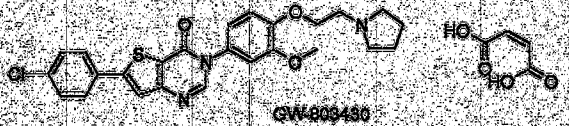
A-665798



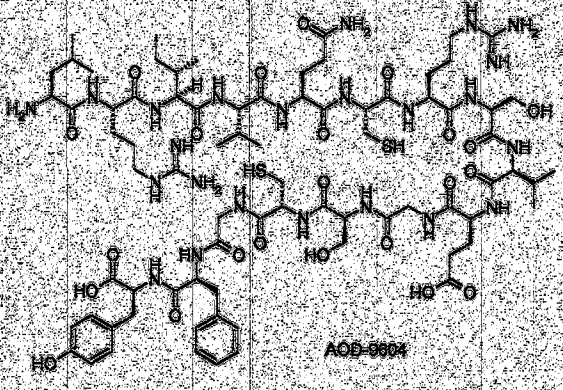
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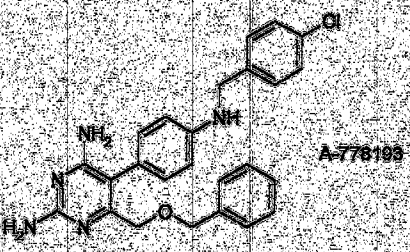
T-226296



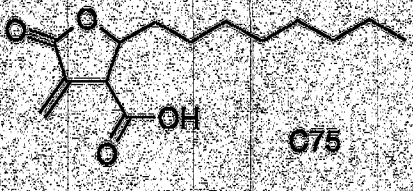
GW-803430



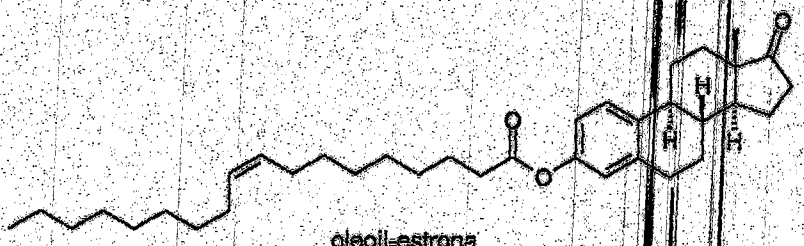
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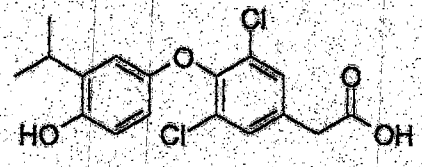
A-778193



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 PPARalfa celular

Principio

La potencia de las sustancias que se unen al PPARalfa humano y lo activan de forma agonista, se analiza usando una línea celular HEK transfectada de forma estable (HEK = riñón embrionario humano), que aquí se denomina línea celular de indicador de PPARalfa. Contiene dos elementos genéticos, un elemento indicador de luciferasa (pdeltaM-GAL4-Luc-Zeo) y una proteína de fusión de PPARalfa (GR-GAL4-PPARalfa-humano-LBD) que media en la expresión del elemento indicador de luciferasa que depende de un ligando del PPARalfa. 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 PPARalfa 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 está integrado establemente en el genoma de la línea celular. En ausencia de un ligando de PPARalfa 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 PPARalfa se unen y activan la proteína de fusión de PPARalfa, y así estimulan la expresión del gen indicador de luciferasa. La luciferasa que se forma se puede detectar por quimioluminiscencia mediante un sustrato adecuado.

Construcción de la línea celular de indicador de PPARalfa

La línea celular de indicador de PPARalfa se preparó en dos etapas. Primero, se construyó el elemento indicador de luciferasa y se introdujo establemente por transfección 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 Samprook J. et. al. (Molecular cloning, Cold Spring Harbor Laboratory Press, 1989). Después se clonó el gen de Photinus piralis (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 células estable adecuado que presentó muy poca expresión basal del gen de luciferasa.

En una segunda etapa, la proteína de fusión de PPARalfa (GR-GAL4-PPARalfa-humano-LBD) se introdujo en el clon de células 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 PPARalfa 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-PPARalfa-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 PPARalfa acabada que contiene un elemento indicador de luciferasa y expresa constitutivamente la proteína de fusión de PPARalfa (GR-GAL4-PPARalfa-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 PPARalfa se determina en un ensayo de 3 días que se describe a continuación.

Día 1

La línea celular de indicador de PPARalfa se cultiva hasta 80% de confluencia en DMEM (nº 41965-039, Invitrogen) que se mezcla con las siguientes adiciones: cs-FCS al 10% (suero de ternero fetal; #SH-30068.03, Hyclone), 0,5 mg/ml de zeocina (nº R250-01, Invitrogen), 0,5 mg/ml de G418 (nº 10131-027, Invitrogen), 1% de solución de penicilina-estreptomicina (nº 15140-122, Invitrogen) y L-glutamina 2 mM (nº 25030-024, Invitrogen). El cultivo se lleva a cabo en frascos de cultivo celular convencionales (nº 353112, Becton Dickinson) en un incubador de cultivo celular a 37ºC en presencia de CO_2 al 5%. Las células al 80% de confluencia se lavan una vez con 15 ml de PBS (nº 14190-094, Invitrogen), se tratan con 3 ml de solución de tripsina (nº 25300-054, Invitrogen) a 37ºC durante 2 min, se recogen en 5 ml del medio 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 37ºC 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 (nº 41965-039, Invitrogen) que se mezcla con cs-FCS al 5% (nº SH-30068.03, Hyclone), L-glutamina 2 mM (nº 25030-024, Invitrogen) y los antibióticos previamente descritos

Determinación de los valores de CE50 de los agonistas de PPAR en el ensayo de PPARdelta celular

Principio

La potencia de las sustancias que se unen al PPARdelta humano y lo activan de forma agonista, se analiza usando una línea celular HEK transfectada de manera estable (HEK = riñón embrionario humano), que aquí se denomina línea celular de indicador de PPARdelta. Análogamente al ensayo descrito para el PPARalfa, la línea celular de indicador de PPARalfa también contiene dos elementos genéticos, un elemento indicador de luciferasa (pdeltaM-GAL4-Luc-Zeo) y una proteína de fusión de PPARdelta (GR-GAL4-PPARdelta-humano-LBD) que media en la expresión del elemento indicador de luciferasa que depende de un ligando de PPARdelta. 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 PPARdelta 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 está integrado establemente en el genoma de la línea celular. En ausencia de un ligando de PPARdelta 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 PPARdelta se unen y activan la proteína de fusión de PPARdelta, y así estimulan la expresión del gen indicador de luciferasa. La luciferasa que se forma se puede detectar por quimioluminiscencia mediante un sustrato adecuado.

Construcción de la línea celular de indicador de PPARdelta

La producción de la línea celular de indicador de PPARdelta estable se basa en un clon de células 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 PPARdelta". En una segunda etapa, la proteína de fusión de PPARdelta (GR-GAL4-PPARdelta-humano-LBD) se introdujo establemente en este clon celular. Para este propósito, 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 PPARdelta (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-PPARdelta-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 PPARdelta que contiene un elemento indicador de luciferasa y expresa constitutivamente la proteína de fusión de PPARdelta (GR-GAL4-PPARdelta-humano-LBD) se aisló por selección con zeocina (0,5 mg/ml) y G418 (0,5 mg/ml).

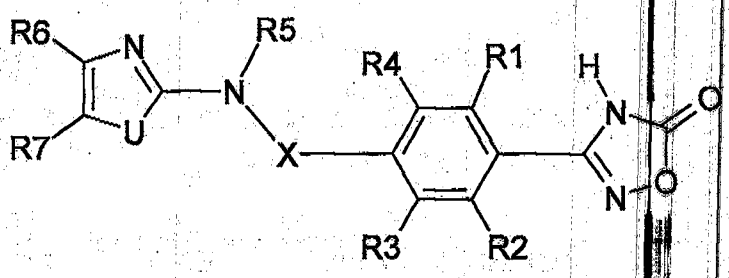
Procedimiento de ensayo y evaluación

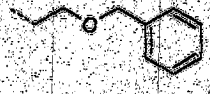
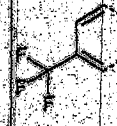
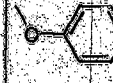
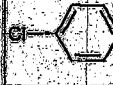
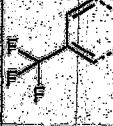
La actividad de los agonistas de PPARdelta se determina en un ensayo de 3 días de forma análoga al procedimiento descrito antes para la línea celular de indicador de PPARalfa, excepto que se usó la línea celular de indicador de PPARdelta y un agonista específico para PPARdelta, como patrón para controlar la eficacia del ensayo.

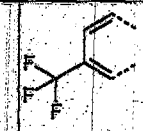
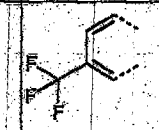
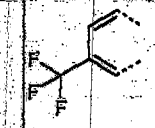
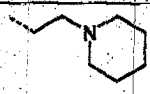
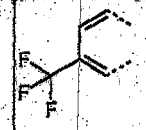
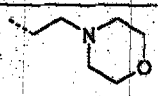
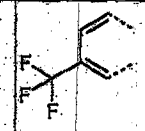
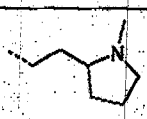
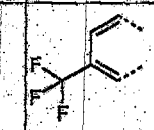
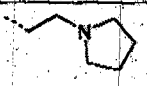
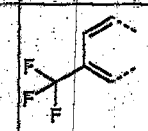
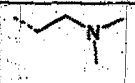
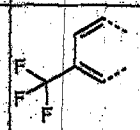
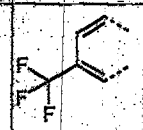
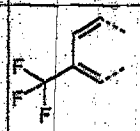
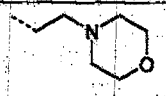
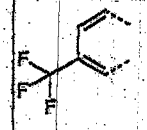
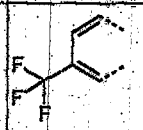
Se midieron los valores de CE50 para el PPARdelta en el intervalo de 1 nM a >10 µM para los agonistas de PPAR de los Ejemplos 1 a 41 descritos en esta solicitud. Los compuestos de la fórmula I de la invención activan al receptor PPARdelta.

Los ejemplos dados en la Tabla II sirven para ilustrar la invención, pero sin limitarla.

Tabla I



Ejemplo	X	U	R1	R5	R6	R7
12	-CH2-	S	H	-(CH2)3CH3		
13	-CH2-	S	H	-(CH2)3CH3		
14	-CH2CH2-	S	-CH3	-(CH2)3-O-CH3		
15	-CH2CH2-	S	-CH3	-(CH2)2-O-(CH2)2-O-CH3		
16	-CH2CH2-	S	-CH3			
17	-CH2CH2-	S	-CH3	-(CH2)2-O-CH3		
18	-CH2CH2-	S	H	-(CH2)3CH3		H
19	-CH2CH2-	S	H	-(CH2)3CH3		H
20	-CH2CH2-	S	H	-(CH2)3-O-CH3		H
21	-CH2CH2-	S	H	-(CH2)2-O-(CH2)2-O-CH3		H
22	-CH2CH2-	S	H			H
23	-CH2CH2-	S	H	-(CH2)2-O-CH3		H
24	-CH2-	S	F	-(CH2)3CH3		
25	-CH2-	S	F	-(CH2)3CH3		

Ejemplo	X	U	R1	R5	R6	R7
26	-CH2-	S	F			
27	-CH2-	S	F			
28	-CH2-	S	F	-(CH2)2-O-CH3		
29	-CH2-	S	F			
30	-CH2-	S	F			
31	-CH2-	S	F			
32	-CH2-	S	-CF3			
33	-CH2-	S	-CF3			
34	-CH2-	S	-CF3	-(CH2)2-O-CH3		
35	-CH2-	S	-CF3			
36	-CH2-	S	-CF3			
37	-CH2-	S	-CF3			

En la siguiente tabla se indica la potencia de algunos de los ejemplos descritos.

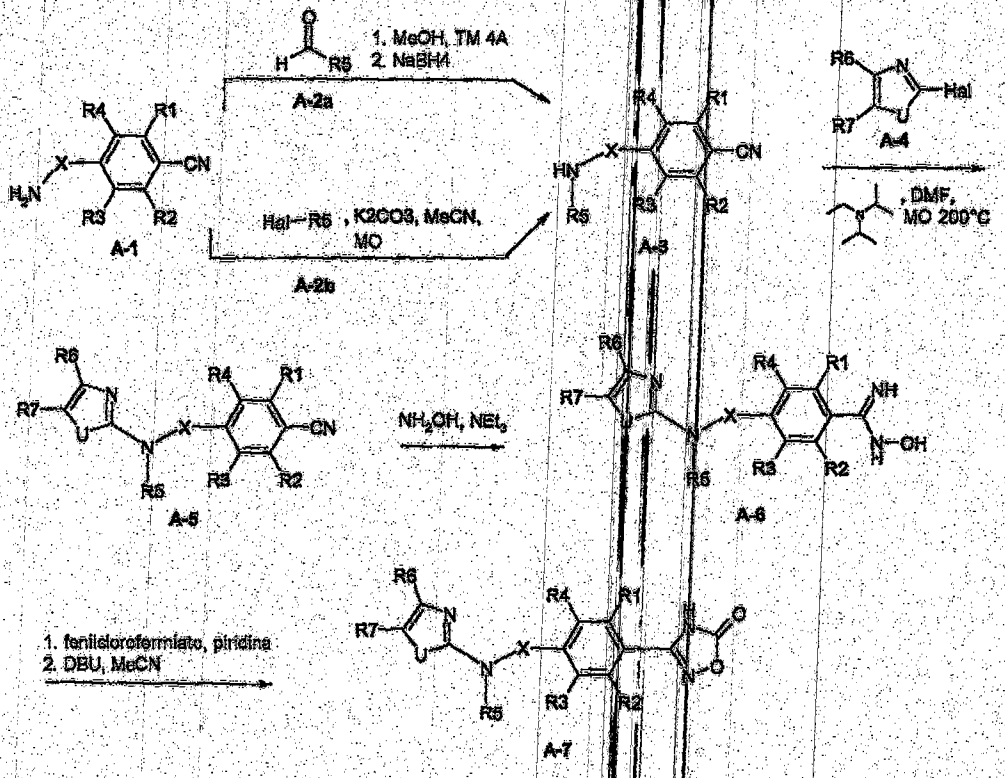
Ejemplo	PPARalfa CE50 (μM)	PPARdelta CE50 (μM)
9	0,06	0,02
14	0,07	0,004
23	0,82	0,65
24	1,35	0,27
28	1,02	0,06
33	1,10	1,80
39	0,36	0,20

Procesos

Los compuestos de la fórmula general I de acuerdo con la invención se pueden obtener como se indica en los siguientes esquemas de reacción.

Proceso A

Este proceso se usa para sintetizar compuestos de la fórmula general A-7, en la que X, U, R1, R2, R3, R4, R5, R6 y R7 son como se han definido.



Se realiza una aminación reductora con una amina primaria de la fórmula general A-1 en la que X, R1, R2, R3 y R4 son como se han definido y un aldehído de la fórmula general A-2a en la que R5 es como se ha definido en un disolvente tal como metanol en presencia de tamices moleculares 4 Angström y mediante la adición de un agente reductor tal como borohidruro sódico para dar una amina secundaria de la fórmula general A-3. Como alternativa, la amina primaria de la fórmula general A-1 puede alquilarse con un haluro de la fórmula general A-2b, en la que R5 es como se ha definido en un disolvente tal como acetonitrilo en presencia de una base tal como carbonato potásico con irradiación con microondas para dar la amina secundaria de la fórmula general A-3. La amina de la fórmula general A-3 se hace reaccionar con un tiazol halogenado en dos posiciones, donde U es S y R6 y R7 son como se han definido, u oxazol, donde U es O y R6 y R7 son como se han definido en la fórmula general A-4 con irradiación con microondas a temperatura elevada, por ejemplo 200°C, en un disolvente tal como dimetilformamida en presencia de una base tal como N,N-diisopropiletilamina para dar un compuesto de la fórmula general A-5. El compuesto de fórmula general A-5 se hace reaccionar con hidrocloruro de hidroxilamina en presencia de una base tal

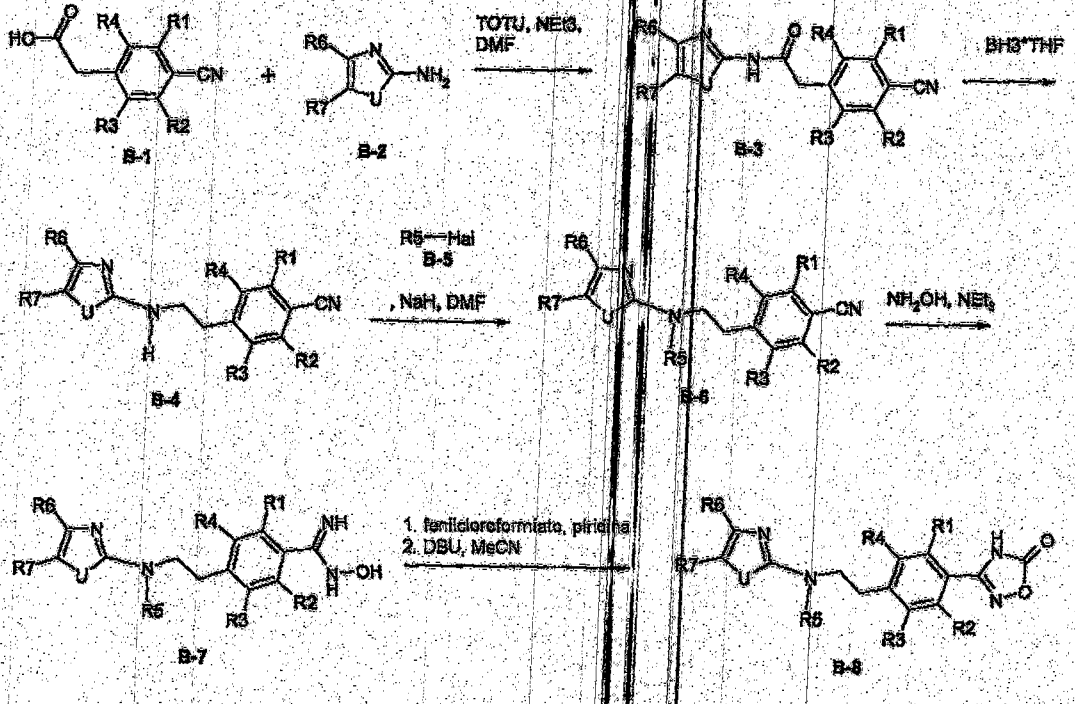
como trietilamina, en un disolvente tal como tetrahidrofurano y metanol para obtener un compuesto de fórmula general A-6. Un compuesto de fórmula general A-6 se convierte en el producto de fórmula general A-7, por reacción con cloroformiato de fenilo en presencia de una base tal como piridina y tratamiento de este producto intermedio con una base tal como 1,8-diazabiciclo[5.4.0]undec-7-eno en un disolvente tal como acetonitrilo.

Los Ejemplos 1-17 se obtuvieron de acuerdo con el proceso A.

Se pueden obtener otros compuestos de acuerdo con, o por procesos conocidos.

Proceso B:

Este proceso se usa para sintetizar compuestos de la fórmula general B-8, en la que X es -CH2CH2- y U, R1, R2, R3, R4, R5, R6 y R7 son como se han definido.



Un ácido carboxílico de la fórmula general B-1 en la que R1, R2, R3 y R4 son como se han definido se condensa con una amina primaria de la fórmula general B-2 en la que R6 y R7 son como se han definido con un reactivo de acoplamiento tal como tetrafluoroborato de O-((etoxicarbonil)cianometilenoamino)-N,N,N',N'-tetrametiluronio en un disolvente tal como dimetilformamida en presencia de una base tal como trietilamina para dar una amida de la fórmula general B-3. La amida de la fórmula general B-3 se reduce con un agente reductor tal como complejo de borano y tetrahidrofurano en un disolvente aprótico polar tal como tetrahidrofurano

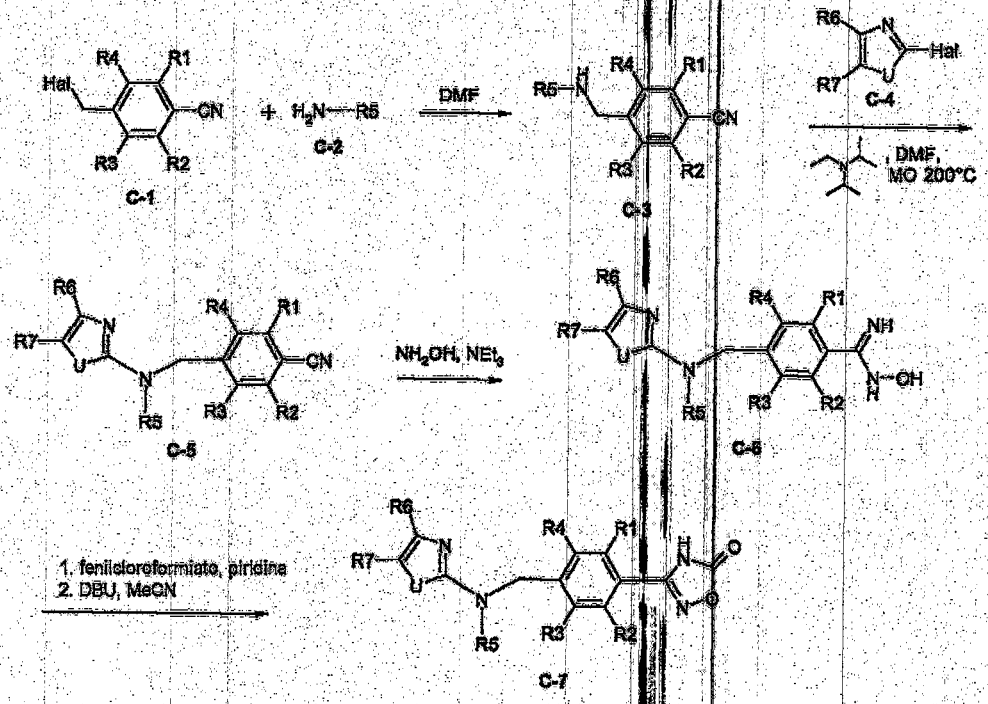
para obtener una amina secundaria de la fórmula general B-4. La amina secundaria de la fórmula general B-4 se alquila con un haluro de la fórmula general B-5, en la que R5 es como se ha definido, en presencia de una base tal como hidruro sódico en un disolvente tal como dimetilformamida para dar una amina terciaria de la fórmula general B-6. El compuesto de fórmula general B-6 se hace reaccionar con hidrocloruro de hidroxilamina en presencia de una base tal como trietilamina, en un disolvente tal como tetrahidrofurano y metanol para obtener un compuesto de fórmula general B-7. Un compuesto de fórmula general B-7 se convierte en el producto de fórmula general B-8, por reacción con cloroformiato de fenilo en presencia de una base tal como piridina y tratamiento de este producto intermedio con una base tal como 1,8-diazabiciclo[5.4.0]undec-7-eno en un disolvente tal como acetonitrilo.

Se obtuvieron los Ejemplos 18-23 de acuerdo con el proceso B.

Se pueden obtener otros compuestos de acuerdo con, o por procesos conocidos.

Proceso C:

Este proceso se usa para sintetizar compuestos de la fórmula general C-7, en la que X es -CH2- y U, R1, R2, R3, R4, R5, R6 y R7 son como se han definido.



Un haluro bencílico de la fórmula general C-1 en la que R1, R2, R3 y R4 son como se han definido se hace reaccionar con una amina primaria de la fórmula general C-

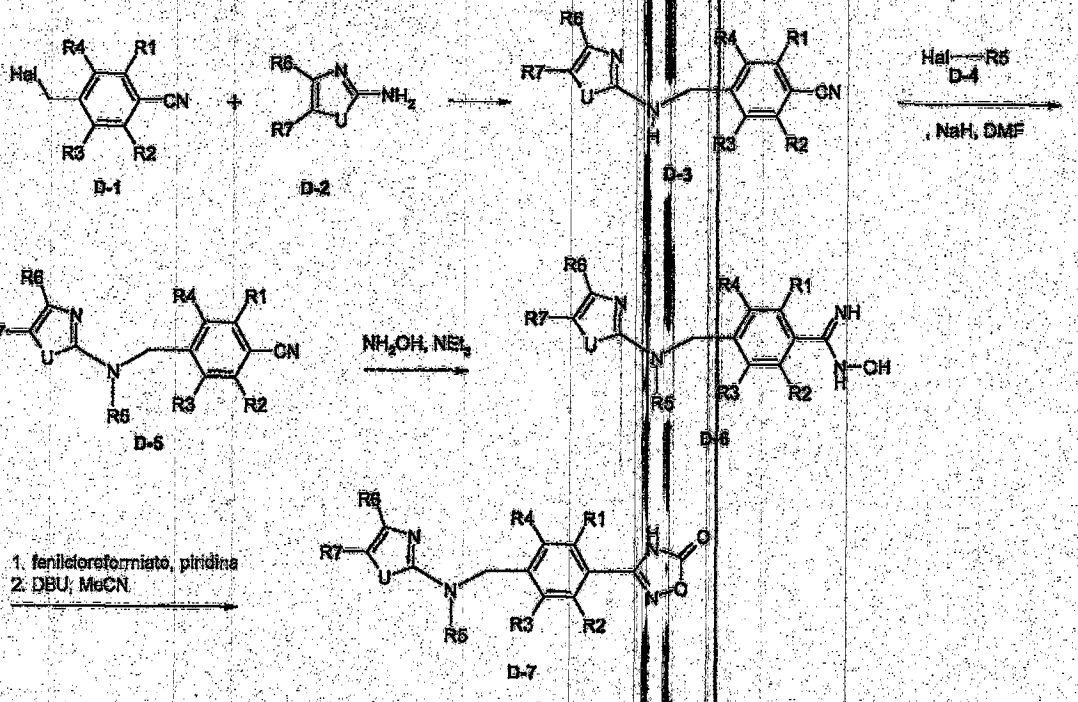
2 en la que R5 es como se ha definido en un disolvente tal como dimetilformamida para dar una amina secundaria de la fórmula general C-3. La amina secundaria de la fórmula general C-3 se hace reaccionar con un tiazol halogenado en dos posiciones, donde U es S y R6 y R7 son como se han definido u oxazol, donde U es O y R6 y R7 son como se han definido de la fórmula general C-4 con irradiación con microondas a temperatura elevada, por ejemplo 200ºC, en un disolvente tal como dimetilformamida en presencia de una base tal como N,N-diisopropilietilamina para dar un compuesto de la fórmula general C-5. El compuesto de la fórmula general C-5 se hace reaccionar con hidrocloruro de hidroxilamina en presencia de una base tal como trietilamina en un disolvente tal como tetrahidrofurano y metanol para obtener un compuesto de la fórmula general C-6. Un compuesto de la fórmula general C-6 se convierte en el producto de la fórmula general C-7 por reacción con fenilcloroformiato en presencia de una base tal como piridina y tratando este intermedio con una base tal como 1,8-diazabiciclo[5.4.0]undec-7-eno en un disolvente tal como acetonitrilo.

Los Ejemplos 24-37 se obtuvieron de acuerdo con el proceso C.

Se pueden obtener otros compuestos de acuerdo con, o por procesos conocidos.

Proceso D:

Este proceso se usa para sintetizar compuestos de la fórmula general D-7, en la que X es -CH2- y U, R1, R2, R3, R4, R5, R6 y R7 son como se han definido.



Un haluro bencílico de la fórmula general D-1 en la que R1, R2, R3 y R4 son como se han definido se hace reaccionar con un 2-amino-tiazol de la fórmula general D-2, en la que U es S y R6 y R7 están con un 2-amino-oxazol, donde U es O y R6 y R7 son como se han definido de la fórmula general D-2 para dar una amina secundaria de la fórmula general D-3.

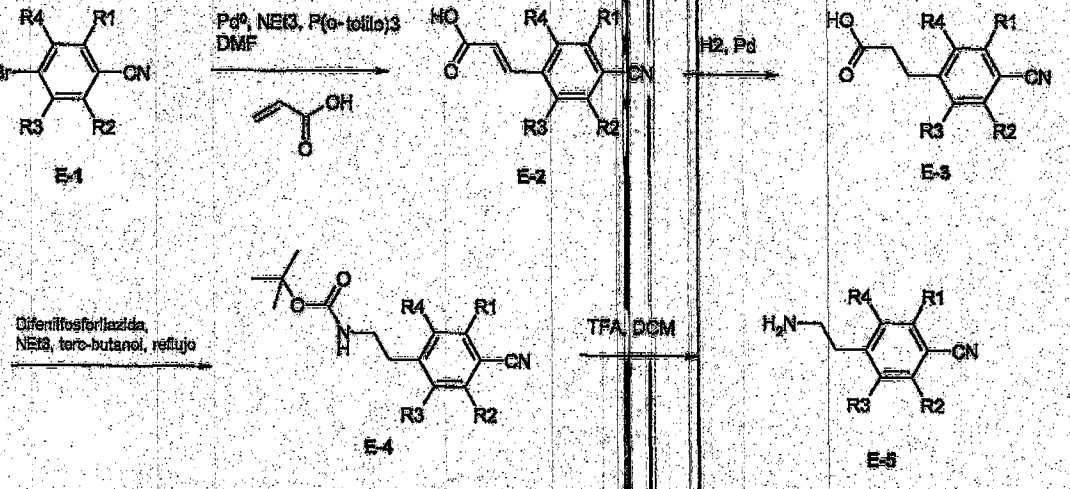
La amina secundaria de la fórmula general D-3 se alquila con un haluro de la fórmula general D-4, en la que R5 es como se ha definido, en presencia de una base tal como hidruro sódico en un disolvente tal como dimetilformamida para dar una amina terciaria de la fórmula general D-5. El compuesto de la fórmula general D-5 se hace reaccionar con hidrocloruro de hidroxilamina en presencia de una base tal como trietilamina en un disolvente tal como tetrahidrofurano y metanol para obtener un compuesto de la fórmula general D-6. Un compuesto de la fórmula general D-6 se convierte en el producto de la fórmula general D-7 por reacción con fenilcloroformiato en presencia de una base tal como piridina y tratando este intermedio con una base tal como 1,8-diazabiciclo[5.4.0]undec-7-eno en un disolvente tal como acetonitrilo.

Los ejemplos 38-41 se obtuvieron de acuerdo con el procedimiento D.

Se pueden obtener otros compuestos de acuerdo con, o por procesos conocidos.

Proceso E:

Este proceso se usa para sintetizar unidades estructurales de la fórmula general E-5, que se corresponden con la fórmula general A-1 del proceso A, donde X es -CH2CH2- y R1, R2, R3 y R4 son como se han definido.



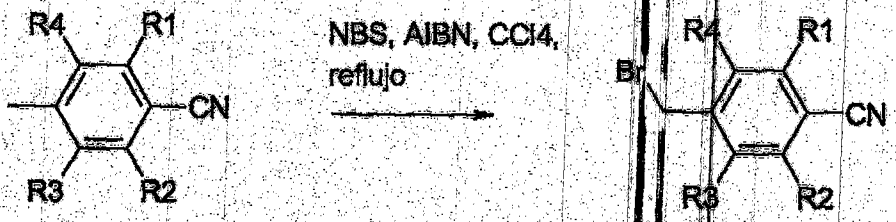
Un bromobenzonitrilo de la fórmula general E-1 se acopla de forma cruzada con ácido acrílico en condiciones de reacción de Heck, en presencia de una fuente de paladio tal como acetato de paladio (II), un ligando tal como Tri-o-tolil-fosfina, una base tal como trietilamina en un disolvente tal como acetonitrilo para dar un ácido acrílico sustituido de la fórmula general E-2. El ácido acrílico de la fórmula general E-2 se hidrogena en presencia de un catalizador de paladio tal como paladio sobre carbono (al 10%) en un disolvente tal como metanol o una mezcla de disolventes tal como metanol y tetrahidrofurano en una atmósfera de hidrógeno para dar un ácido carboxílico de la fórmula general E-3. El ácido carboxílico de la fórmula general E-3 se reorganiza en la amina protegida con BOC de la fórmula general E-4 por tratamiento con difenilfosforilazida en terc-butanol a la temperatura de reflujo en presencia de una base tal como trietilamina. El grupo protector de BOC de la amina de la fórmula general E-4 se retira por tratamiento con una base tal como ácido trifluoroacético en un disolvente tal como diclorometano para dar la amina primaria de la fórmula general E-5.

Se pueden obtener otros compuestos de acuerdo con, o por procesos conocidos.

Proceso F:

Este proceso se usa para sintetizar unidades estructurales de la fórmula general F-2, que corresponden a la fórmula general C-1 del proceso C, donde Hal es bromo y

R1, R2, R3 y R4 son como se han definido y D-1 del proceso D, Hal es bromo y R1, R2, R3 y R4 son como se han definido.



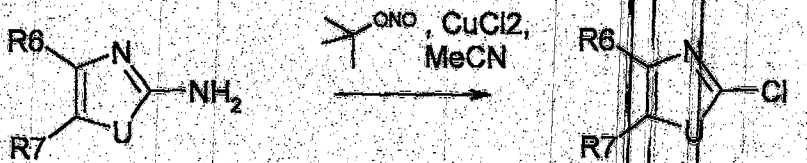
F-1 F-2

Un 4-metil-benzonitrilo de la fórmula general F-1 se broma por tratamiento con N-bromosuccinimida en presencia de un iniciador de radicales tal como 2,2'-azobis(2-metilpropionitrilo) en un disolvente tal como tetraclorometano para dar el bromuro de bencilo de la fórmula general F-2.

Se pueden obtener otros compuestos de acuerdo con, o por procesos conocidos.

Proceso G:

Este proceso se usa para sintetizar unidades estructurales de la fórmula general G-2, que corresponden a la fórmula general A-4 del proceso A, donde Hal es cloro, U es S y R6 y R7 son como se han definido y C-4 del proceso C, donde Hal es cloro, U es S y R6 y R7 son como se han definido.



G-1 G-2

Un 2-amino-tiazol de la fórmula general G-1, en la que U es S y R6 y R7 son como se han definido o un 2-amino-oxazol, donde U es O y R6 y R7 son como se han definido se hace reaccionar con nitrito de terc-butilo y cloruro de cobre (II) en un disolvente tal como acetonitrilo para dar un compuesto 2-halogenado de la fórmula general G-2.

Se pueden obtener otros compuestos de acuerdo con, o por procesos conocidos.

Lista de abreviaturas:

Ac	acetilo
AIBN	2,2'-azobis(2-metilpropionitrilo)
Bn	bencilo
BOC	terc-butil-oxi-carbonilo
iBu	isobutilo
tBu	terc-Butilo
BuLi	n-butil-litio
Bz	benzoílo
Cy	ciclohexilo
DBU	1,8-diazabiciclo[5.4.0]undec-7-eno
DCI	ionización química directa (MS)
DCM	diclorometano
DMAP	N,N-dimetilaminopiridina
DMF	N,N-dimetilformamida
DMSO	dimetilsulfóxido
EE	acetato de etilo
equiv.	equivalentes
ESI	electronebulización-ionización (MS)
FG	grupo lábil
GC	cromatografía gaseosa
Hal	halógeno
HPLC	cromatografía líquida de alta resolución
LC-MS	cromatografía líquida acoplada con espectrometría de masas
Me	metilo
MeCN	acetonitrilo
MS	espectrometría de masas
MS 4A	tamices moleculares 4 angström
MsCl	cloruro de metansulfonilo
MO	microondas
NBS	N-bromosuccinimida
RMN	resonancia magnética nuclear
p	para
Pd/C	paladio sobre carbono
iPr	isopropilo

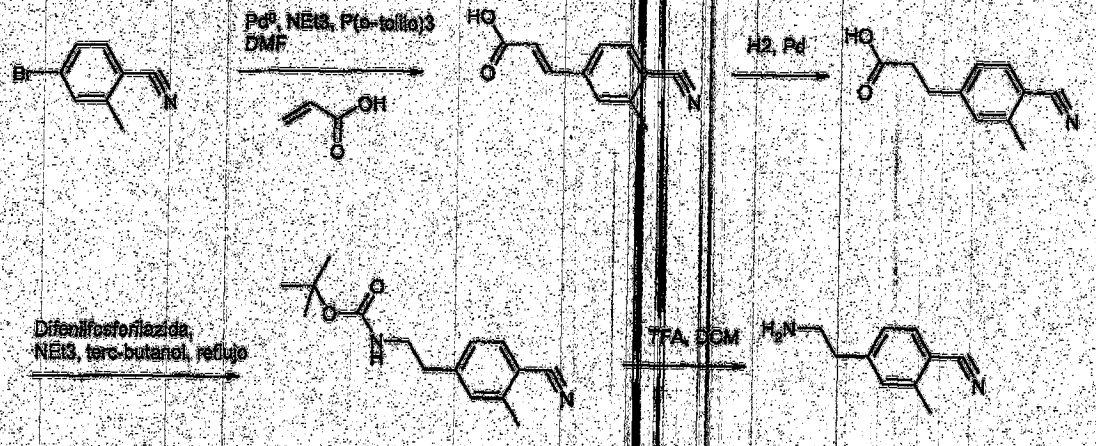
nPr	n-propilo
Rf	factor de retención (TLC)
terc	terciario
TFA	ácido trifluoroacético
THF	tetrahidrofurano
TLC	cromatografía de capa fina
TOTU	Tetrafluoroborato de O-((etoxicarbonil)cianometilenoamino)-N,N,N',N'-tetrametiluronio

Pueden prepararse otros compuestos de la fórmula I de forma correspondiente o por procesos conocidos.

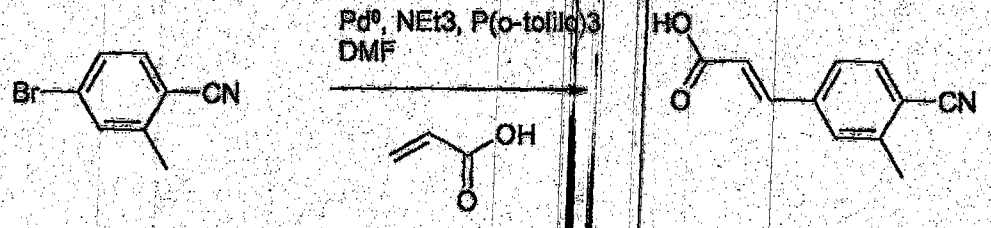
A continuación se describen los procedimientos experimentales para preparar los ejemplos mencionados anteriormente.

Síntesis de las unidades estructurales según el proceso E:

4-(2-Amino-etil)-2-metil-benzonitrilo



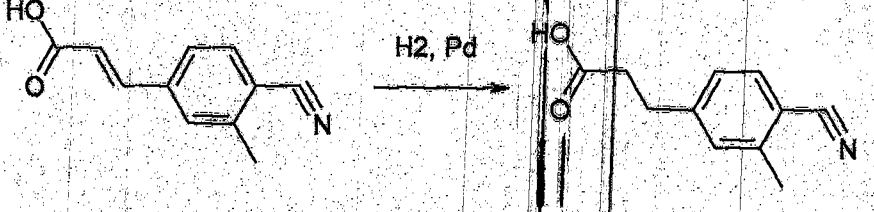
Ácido (E)-3-(4-ciano-3-metil-fenil)-acrílico



Se disolvieron 9,0 g de 4-bromo-2-metilbenzonitrilo, 2,76 g de tri-o-tolilfosfina, 3,11 ml de ácido acrílico y 25,1 ml de trietilamina en 80 ml de acetonitrilo. La mezcla de reacción se desgasificó, después se añadieron 2,0 g de acetato de paladio (II) y la mezcla se agitó durante dos horas con irradiación con microondas a 200°C. La mezcla de reacción enfriada se diluyó mediante la adición de 50 ml de acetato de etilo. De esta manera, precipitó ácido (E)-3-(4-ciano-3-metil-fenil)-acrílico en forma de un sólido blanco. El precipitado se retiró por filtración y se secó al vacío para obtener 2,5 g de ácido (E)-3-(4-ciano-3-metil-fenil)-acrílico. El filtrado se lavó con HCl 1 N, por lo que precipitó de nuevo ácido (E)-3-(4-ciano-3-metil-fenil)-acrílico en forma de un sólido blanco. El precipitado se retiró por filtración y se secó al vacío para obtener 2,0 g de ácido (E)-3-(4-ciano-3-metil-fenil)-acrílico. El filtrado se redujo al vacío hasta un tercio de su volumen y se añadieron 150 ml de éter dietílico, por lo que precipitó de nuevo ácido (E)-3-(4-ciano-3-metil-fenil)-acrílico en forma de un sólido blanco. El precipitado se retiró por filtración y se secó al vacío para obtener 840 mg de ácido (E)-3-(4-ciano-3-metil-fenil)-acrílico.

$C_{11}H_9NO_2$ (187,20), MS (ESI): 188,1 ($M+H^+$), Rf (acetato de etilo:metanol = 9:1) = 0,16.

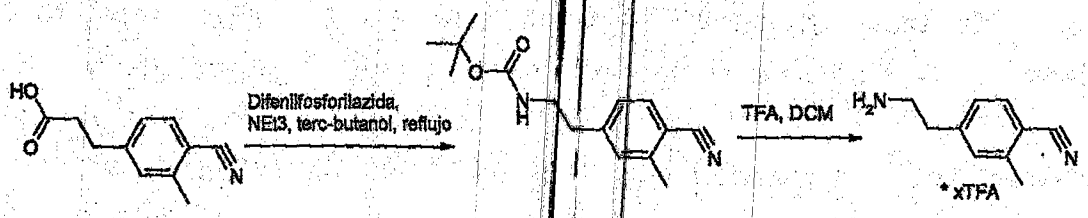
Ácido 3-(4-ciano-3-metil-fenil)-propiónico



Se disolvieron 5,15 g de ácido (E)-3-(4-ciano-3-metil-fenil)-acrílico en una mezcla de 250 ml de tetrahidrofurano y 125 ml de metanol. Se añadieron 510 mg de paladio sobre carbono (al 10%) y la mezcla de reacción se agitó en una atmósfera de hidrógeno durante una noche. El catalizador se retiró por filtración sobre una capa de celite. El disolvente se retiró al vacío para obtener 5,2 g de ácido 3-(4-ciano-3-metil-fenil)-propiónico en forma de un sólido blanco.

$C_{11}H_{11}NO_2$ (189,22), MS (ESI): 190,2 ($M+H^+$).

4-(2-Amino-etil)-2-metil-benzonitrilo

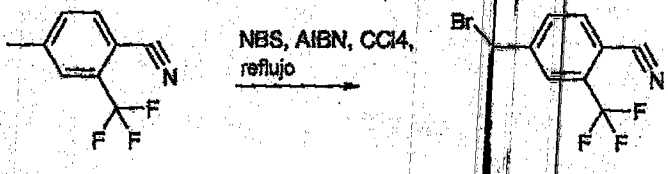


A una solución de 5,20 g de ácido 3-(4-ciano-3-metil-fenil)-propiónico y 4,57 ml de trietilamina en 100 ml de terc-butanol se le añadieron 9,10 g de difenilfosforilazida y la mezcla se calentó a reflujo durante una noche. La mezcla de reacción enfriada se evaporó al vacío. El residuo resultante se disolvió en 150 ml de acetato de etilo, se lavó con 50 ml de ácido cítrico/salmuera = 1:1 y 50 ml de una solución saturada de NaHCO3 y después se secó sobre MgSO4. El residuo se disolvió en 50 ml de diclorometano y se añadieron 20 ml de ácido trifluoroacético. La mezcla de reacción se agitó a temperatura ambiente durante dos horas. El disolvente se separó a vacío. El residuo se coevaporó cuatro veces con porciones de 100 ml de tolueno. El residuo pardo resultante se recogió en 50 ml de acetonitrilo y se agitó a temperatura ambiente. El material sólido se retiró por filtración y se secó al vacío para obtener 2,45 g de 4-(2-amino-etil)-2-metil-benzonitrilo en forma de su sal trifluoroacetato. El filtrado se evaporó al vacío y el residuo resultante se recogió en 100 ml de éter dietílico y se agitó a temperatura ambiente. El material sólido se retiró por filtración y se secó al vacío para obtener 1,17 g de 4-(2-amino-etil)-2-metil-benzonitrilo en forma de su sal trifluoroacetato.

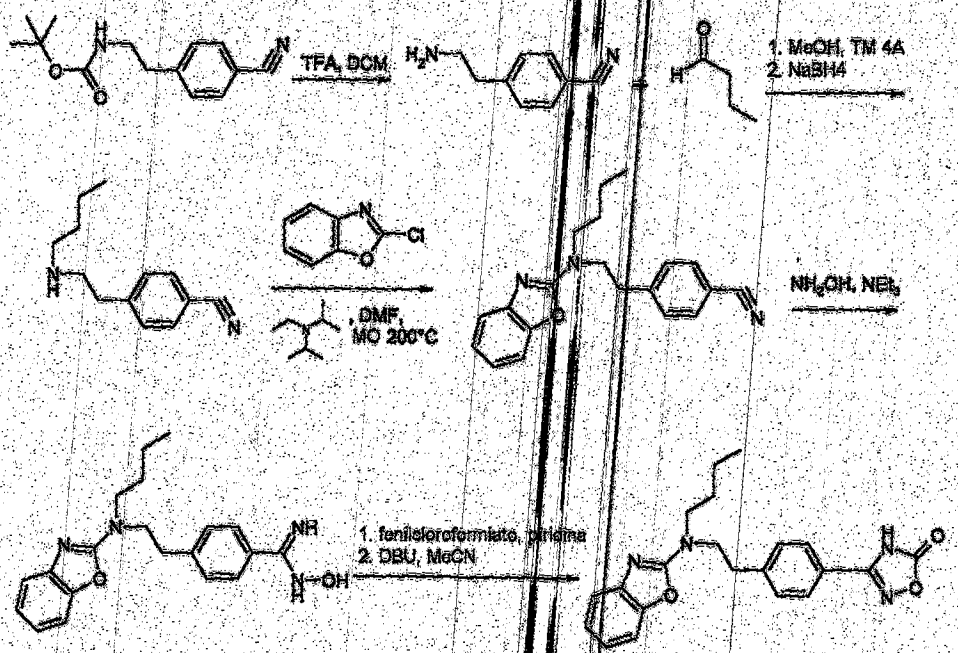
C10H12N2 .xTFA (160,22 + xTFA), MS (ESI): 161,1 (M+H+).

Síntesis de las unidades estructurales de acuerdo con el proceso F:

4-Bromometil-2-trifluorometil-benzonitrilo



A una mezcla a la temperatura de reflujo de 5,0 g de 4-metil-2-(trifluorometil)benzonitrilo en 50 ml de tetraclorometano se le añadieron una mezcla de 5,77 g de N-bromosuccinimida y 1,77 g de 2,2'-azobis(2-metilpropionitrilo). La



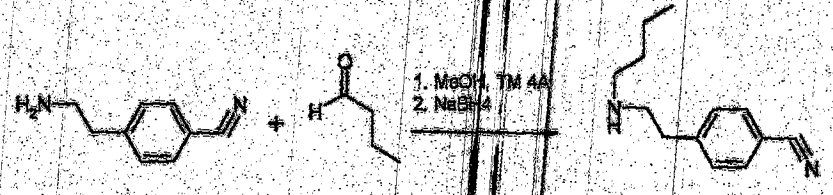
4-(2-Amino-etil)-benzonitrilo



Se disolvieron 1,90 g de éster terc-butílico del ácido [2-(4-ciano-fenil)-etil]-carbámico disponible en el mercado en 100 ml de diclorometano. Se añadieron 10 ml de ácido trifluoroacético y la mezcla de reacción se agitó a temperatura ambiente durante una hora. Se añadieron 250 ml de acetato de etilo y la mezcla se lavó tres veces con una solución saturada de $NaHCO_3$. La capa orgánica se secó sobre $MgSO_4$ y después el disolvente se retiró al vacío para obtener 700 mg de 4-(2-amino-etil)-benzonitrilo en forma de un sólido amarillo pálido.

$C_9H_{10}N_2$ (146,19), MS (ESI): 147,1 ($M+H^+$).

4-(2-Butilamino-etil)-benzonitrilo

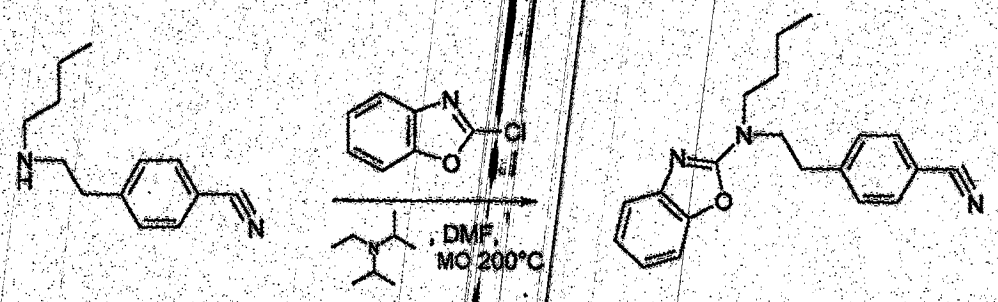


Se disolvieron 700 mg de 4-(2-amino-etil)-benzonitrilo y 63 µl de butiraldehído en 20 ml de metanol. Se añadió 1,0 g de tamices moleculares 4 Angström y la mezcla se

agitó a temperatura ambiente durante dos horas. Después, se añadieron 270 mg de borohidruro sódico y la mezcla se agitó durante una hora más a temperatura ambiente. Se añadieron 100 ml de acetato de etilo y la reacción se interrumpió mediante la adición de 1 ml de agua. La mezcla de reacción se filtró a través de una capa de celite y MgSO4. El filtrado se evaporó al vacío para proporcionar 750 mg de 4-(2-butilamino-etil)-benzonitrilo bruto. Este material se usó sin purificación adicional.

C13H18N2 (202,30), MS (ESI): 203,2 ($M+H^+$).

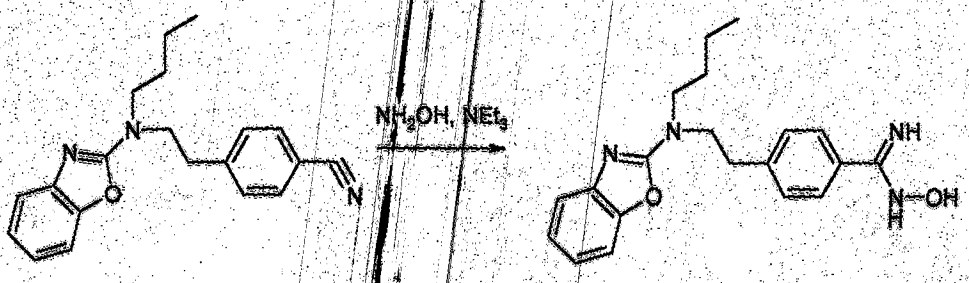
4-[2-(Benzooxazol-2-il-butil-amino)-etil]-benzonitrilo



Una solución de 750 mg de 4-(2-butilamino-etil)-benzonitrilo, 854 mg de 2-clorobenzooxazol y 0,95 ml de N,N-diisopropiletilamina en 10 ml de dimetilformamida se agitó con irradiación con microondas a 200°C durante treinta minutos. La mezcla de reacción enfriada se diluyó mediante la adición de 60 ml de acetato de etilo y después se lavó tres veces con 40 ml de salmuera. La capa orgánica se secó sobre MgSO4 y después el disolvente se retiró al vacío. El residuo se purificó por RP-HPLC para obtener 290 mg de 4-[2-(benzooxazol-2-il-butil-amino)-etil]-benzonitrilo en forma de un sólido amorfo amarillo pálido.

C20H21N3O (319,41), MS (ESI): 320,2 ($M+H^+$).

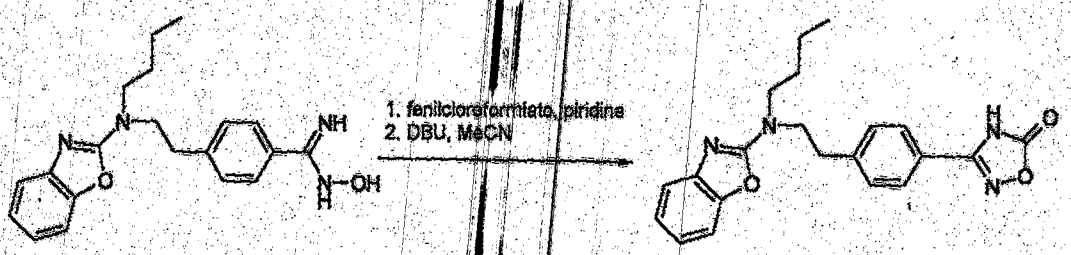
4-[2-(Benzooxazol-2-il-butil-amino)-etil]-N-hidroxi-benzamidina



Se disolvieron 290 mg de 4-[2-(benzooxazol-2-il-butil-amino)-etil]-benzonitrilo en una mezcla de 10 ml de tetrahidrofurano y 20 ml de metanol. Se añadieron 930 mg

de hidrocloruro de hidroxilamina seguido de la adición de 2,24 ml de trietilamina. La mezcla de reacción se agitó a 65ºC durante dos horas. La mezcla de reacción enfriada se diluyó mediante la adición de 100 ml de acetato de etilo y después se lavó tres veces con 40 ml de agua. La capa orgánica se secó sobre MgSO4 y después el disolvente se retiró al vacío para obtener 280 mg de 4-[2-(benzooxazol-2-il-butil-amino)-etil]-N-hidroxi-benzamidina en forma de un aceite amarillo pálido.
C20H24N4O2 (352,44), MS (ESI): 353,2 ($M+H^+$).

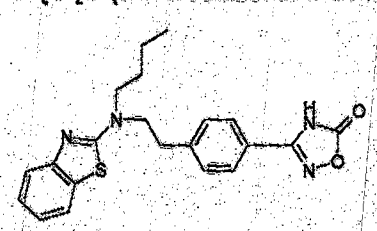
3-{4-[2-(Benzooxazol-2-il-butil-amino)-etil]-fenil}-4H-[1.2.4]oxadiazol-5-ona



Se disolvieron 280 mg de 4-[2-(benzooxazol-2-il-butil-amino)-etil]-N-hidroxi-benzamidina en 5 ml de diclorometano. Se añadieron 78 µl de piridina y 120 µl de fenilcloroformiato y la mezcla se agitó a temperatura ambiente durante diez minutos. La mezcla se diluyó mediante la adición de 15 ml de acetonitrilo y se añadieron 115 µl 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 al vacío y el material bruto resultante se purificó por HPLC de fase inversa para obtener 105 mg de 3-{4-[2-(benzooxazol-2-il-butil-amino)-etil]-fenil}-4H-[1.2.4]oxadiazol-5-ona en forma de un liofilizado amorfo.
C21H22N4O3 (378,43), MS (ESI): 379,2 ($M+H^+$).

Ejemplo 2

3-{4-[2-(Benzotiazol-2-il-butil-amino)-etil]-fenil}-4H-[1.2.4]oxadiazol-5-ona

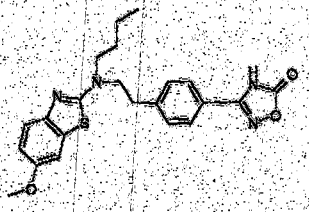


De acuerdo con el método descrito en el Ejemplo 1, se obtuvo 3-{4-[2-(benzotiazol-2-il-butil-amino)-etil]-fenil}-4H-[1,2,4]oxadiazol-5-ona a partir de 4-(2-butilamino-etil)-benzonitrilo y 2-clorobenzotiazol disponible en el mercado.

C21H22N4O2S (394,50), MS (ESI): 395,2 ($M+H^+$).

Ejemplo 3

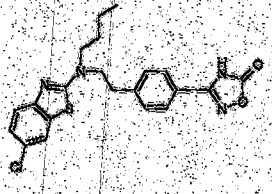
3-(4-{2-[Butil-(6-metoxi-benzotiazol-2-il)-amino]-etil}-fenil)-4H-[1.2.4]oxadiazol-5-ona



De acuerdo con el método descrito en el Ejemplo 1, se obtuvo 3-(4-{2-[butil-(6-metoxi-benzotiazol-2-il)-amino]-etil}-fenil)-4H-[1.2.4]oxadiazol-5-ona a partir de 4-(2-butilamino-etil)-benzonitrilo y 2-cloro-6-metoxi-benzotiazol disponible en el mercado. C22H24N4O3S (424,53), MS (ESI): 425,2 ($M+H^+$).

Ejemplo 4

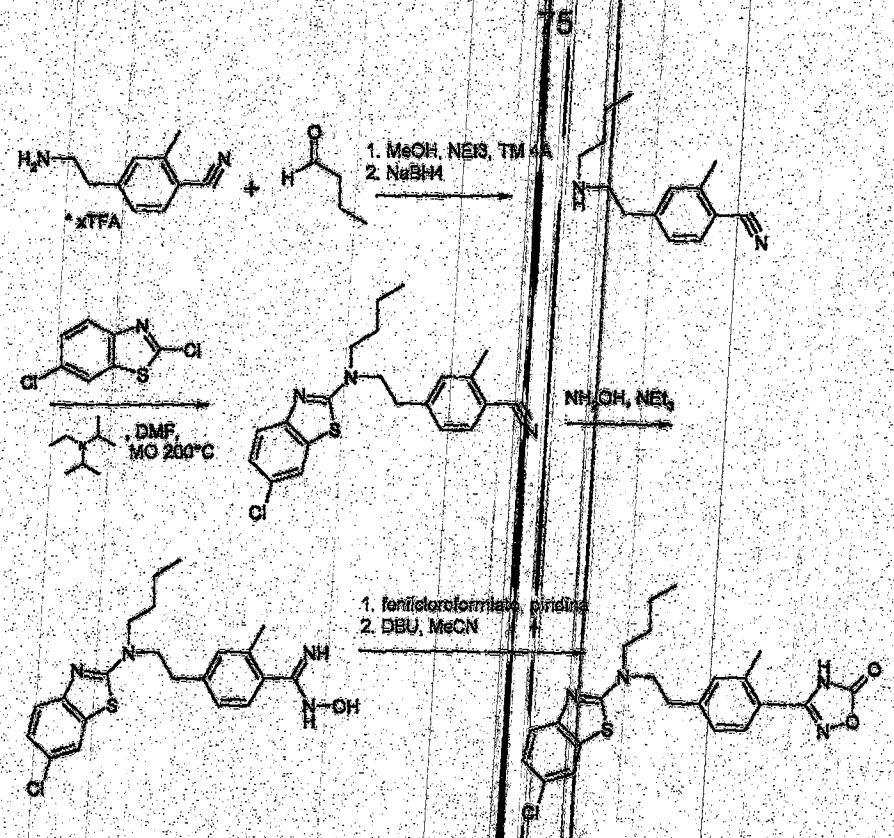
3-(4-{2-[Butil-(6-cloro-benzotiazol-2-il)-amino]-etil}-fenil)-4H-[1.2.4]oxadiazol-5-ona



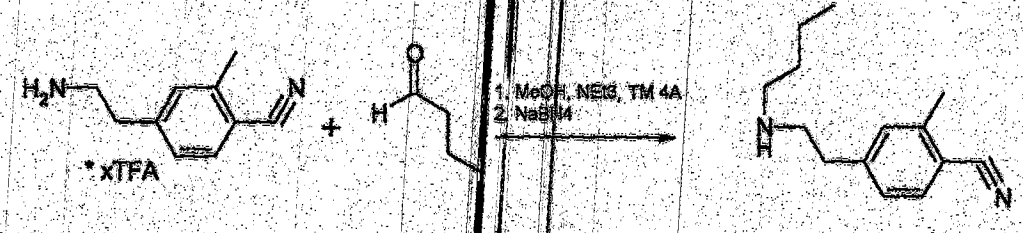
De acuerdo con el método descrito en el Ejemplo 1, se obtuvo 3-(4-{2-[butil-(6-cloro-benzotiazol-2-il)-amino]-etil}-fenil)-4H-[1.2.4]oxadiazol-5-ona a partir de 4-(2-butilamino-etil)-benzonitrilo y 2,6-diclorobenzotiazol disponible en el mercado. C21H21ClN4O2S (428,94), MS (ESI): 429,2 ($M+H^+$).

Ejemplo 5

3-(4-{2-[Butil-(6-cloro-benzotiazol-2-il)-amino]-etil}-2-metil-fenil)-4H-[1.2.4]oxadiazol-5-ona



4-(2-Butilamino-etil)-2-metil-benzonitrilo

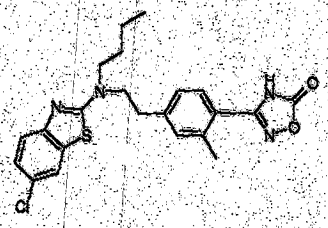


Se disolvieron 138 mg de trifluoroacetato de 4-(2-amino-etil)-2-metil-benzonitrilo, 210 µl de trietilamina y 50 µl de butiraldehído en 5 ml de metanol. Se añadieron 150 mg de tamices moleculares 4 Angstrom y la mezcla se agitó a temperatura ambiente durante una noche. Después, se añadieron 21 mg de borohidruro sódico y la mezcla se agitó durante una hora más a temperatura ambiente. Se añadieron 50 ml de acetato de etilo y la reacción se interrumpió mediante la adición de 0,5 ml de agua. La mezcla de reacción se filtró a través de una capa de celite y MgSO4. El filtrado se evaporó al vacío para proporcionar 230 mg de 4-(2-butilamino-etil)-2-metil-benzonitrilo bruto, impurificado con sales. Este material se usó sin purificación adicional.

C14H20N2 (216,33), MS (ESI): 217,2 ($M+H^+$).

3-(4-[2-[Butil-(6-cloro-benzotiazol-2-il)-amino]-etil]-2-metil-fenil)-4H-[1.2.4]oxadiazol-

5-ona

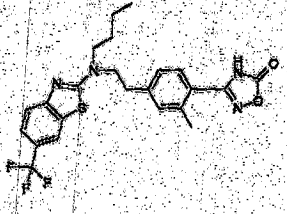


De acuerdo con el método descrito en el Ejemplo 1, se obtuvo 3-(4-{2-[butil-(6-cloro-benzotiazol-2-il)-amino]-etil}-2-metil-fenil)-4H-[1.2.4]oxadiazol-5-ona a partir de 4-(2-butilamino-etil)-2-metil-benzonitrilo y 2,6-diclorobenzotiazol disponible en el mercado.

$C_{22}H_{23}ClN_4O_2S$ (442,97), MS (ESI): 443,1 ($M+H^+$).

Ejemplo 6

3-(4-{2-[Butil-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-2-metil-fenil)-4H-[1.2.4]oxadiazol-5-ona

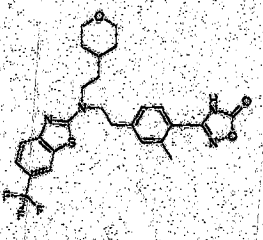


De acuerdo con el método descrito en el Ejemplo 1, se obtuvo 3-(4-{2-[butil-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-2-metil-fenil)-4H-[1.2.4]oxadiazol-5-ona a partir de 4-(2-butilamino-etil)-2-metil-benzonitrilo y 2-cloro-6-trifluorometil-benzotiazol.

$C_{23}H_{23}F_3N_4O_2S$ (476,52), MS (ESI): 477,2 ($M+H^+$).

Ejemplo 7

3-(2-Metil-4-{2-[[2-(tetrahidro-piran-4-il)-etil]-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-fenil)-4H-[1.2.4]oxadiazol-5-ona

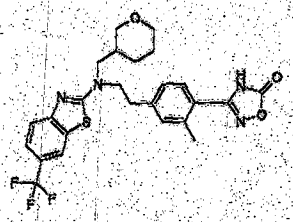


De acuerdo con el método descrito en los Ejemplos 1 y 5, se obtuvo 3-(2-metil-4-{2-[[2-(tetrahidro-piran-4-il)-etil]-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-fenil)-4H-[1.2.4]oxadiazol-5-ona a partir de trifluoroacetato de 4-(2-amino-etil)-2-metil-

benzonitrilo, (tetrahidro-piran-4-il)-acetaldehído y 2-cloro-6-trifluorometil-benzotiazol. C26H27F3N4O3S (532,59), MS (ESI): 533,1 ($M+H^+$).

Ejemplo 8

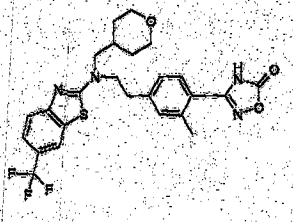
3-(2-Metil-4-{2-[(tetrahidro-piran-3-ilmetil)-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-fenil)-4H-[1.2.4]oxadiazol-5-ona



De acuerdo con el método descrito en los Ejemplos 1 y 5, se obtuvo 3-(2-metil-4-{2-[(tetrahidro-piran-3-ilmetil)-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-fenil)-4H-[1.2.4]oxadiazol-5-ona a partir de trifluoroacetato de 4-(2-amino-etil)-2-metil-benzonitrilo, tetrahidropiranil-3-carboxaldehído y 2-cloro-6-trifluorometil-benzotiazol. C25H25F3N4O3S (518,56), MS (ESI): 519,1 ($M+H^+$).

Ejemplo 9

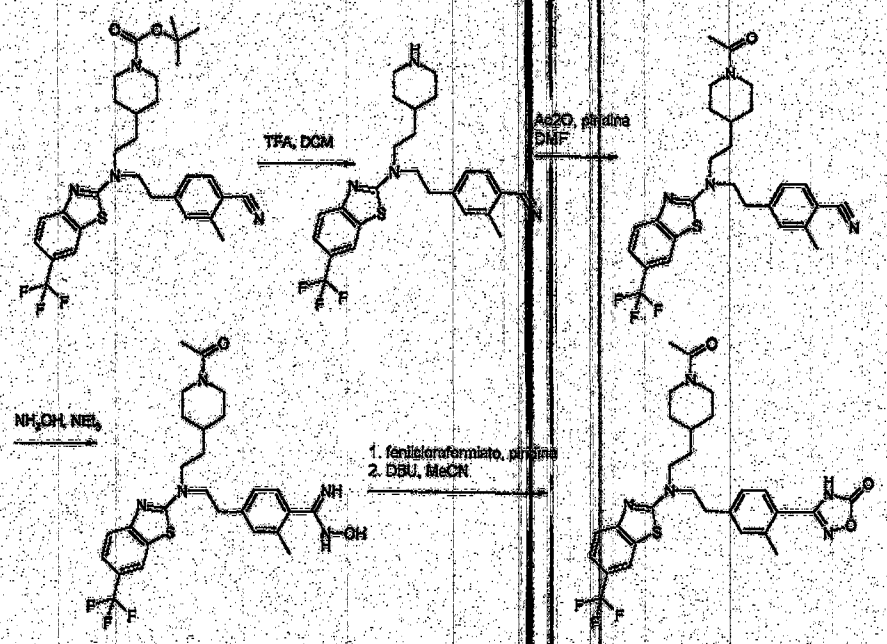
3-(2-Metil-4-{2-[(tetrahidro-piran-4-ilmetil)-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-fenil)-4H-[1.2.4]oxadiazol-5-ona



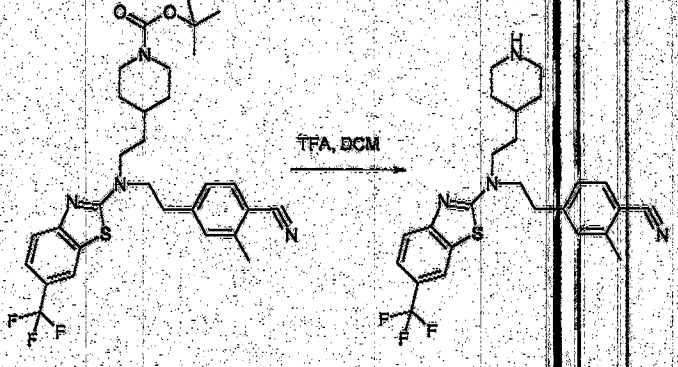
De acuerdo con el método descrito en los Ejemplos 1 y 5, se obtuvo 3-(2-metil-4-{2-[(tetrahidro-piran-4-ilmetil)-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-fenil)-4H-[1.2.4]oxadiazol-5-ona a partir de trifluoroacetato de 4-(2-amino-etil)-2-metil-benzonitrilo, tetrahidropiranil-4-carboxaldehído y 2-cloro-6-trifluorometil-benzotiazol. C25H25F3N4O3S (518,56), MS (ESI): 519,1 ($M+H^+$).

Ejemplo 10

3-(4-{2-[[2-(1-Acetil-piperidin-4-il)-etil]-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-2-metil-fenil)-4H-[1.2.4]oxadiazol-5-ona



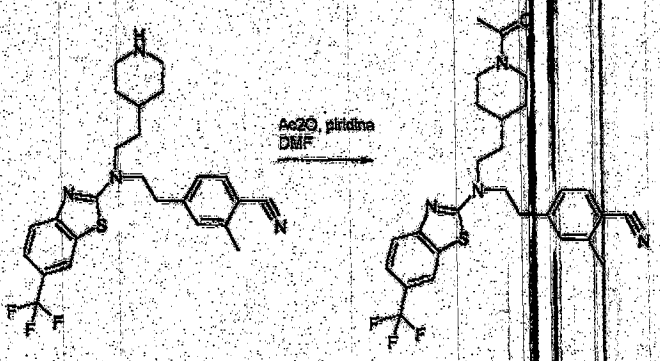
2-Metil-4-{2-[(2-piperidin-4-il-etil)-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-benzonitrilo



Se disolvieron 1,1 g de éster terc-butílico del ácido 4-{2-[[2-(4-ciano-3-metil-fenil)-etil]-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-piperidina-1-carboxílico [preparado de acuerdo con el método descrito en los Ejemplos 1 y 5 a partir de trifluoroacetato de 4-(2-amino-etil)-2-metil-benzonitrilo, N-boc-piperidinil-4-acetaldehído y 2-cloro-6-trifluorometil-benzotiazol] en 50 ml de diclorometano. Se añadieron 5 ml de ácido trifluoroacético y la mezcla de reacción se agitó a temperatura ambiente durante una hora. Se añadieron 150 ml de acetato de etilo y la mezcla se lavó tres veces con una solución saturada de NaHCO3. La capa orgánica se secó sobre MgSO4 y después el disolvente se retiró al vacío. El residuo se purificó por RP-HPLC para obtener 325 mg de 2-metil-4-{2-[(2-piperidin-4-il-etil)-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-benzonitrilo.

C25H27F3N4S (472,58), MS (ESI): 473,2 ($M+H^+$).

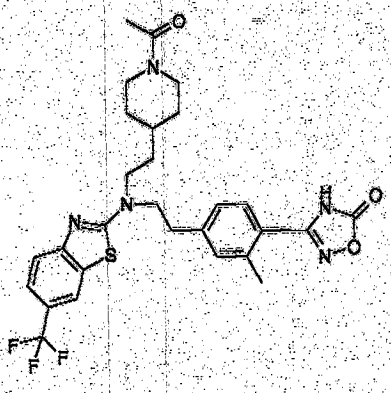
4-{2-[[2-(1-Acetil-piperidin-4-il)-etil]-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-2-metil-benzonitrilo



Se disolvieron 160 mg de 4-{2-[[2-(1-acetil-piperidin-4-il)-etil]-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-2-metil-benzonitrilo en 2,5 ml de dimetilformamida. Se añadieron 5 ml de piridina y 26 µl de anhídrido del ácido acético. Después de agitar a temperatura ambiente durante treinta minutos, la mezcla de reacción se evaporó al vacío para obtener 140 mg de 4-{2-[[2-(1-acetil-piperidin-4-il)-etil]-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-2-metil-benzonitrilo bruto que se usó en la siguiente etapa sin purificación adicional.

C27H29F3N4OS (514,62), MS (ESI): 515,2 ($M+H^+$).

3-(4-{2-[[2-(1-Acetil-piperidin-4-il)-etil]-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-2-metil-fenil)-4H-[1.2.4]oxadiazol-5-ona

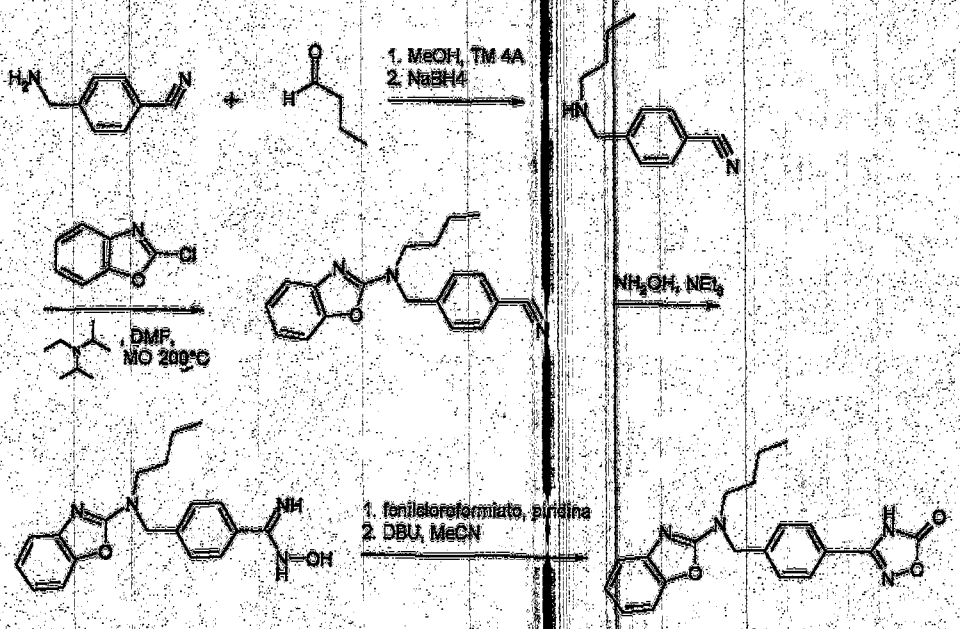


De acuerdo con el método descrito en el Ejemplo 1, se obtuvo 3-(4-{2-[[2-(1-acetil-piperidin-4-il)-etil]-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-2-metil-fenil)-4H-[1.2.4]oxadiazol-5-ona a partir de 4-{2-[[2-(1-acetil-piperidin-4-il)-etil]-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-2-metil-benzonitrilo.

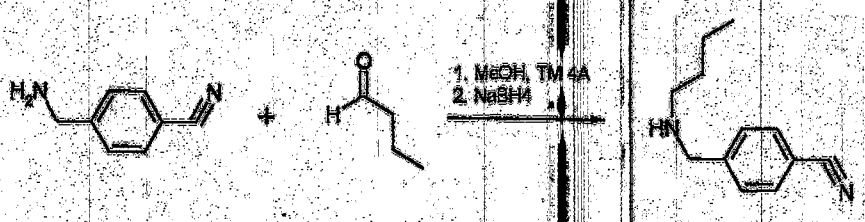
C28H30F3N5O3S (573,64), MS (ESI): 574,2 ($M+H^+$).

Ejemplo 11

3-[4-[(Benzooxazol-2-il-butil-amino)-metil]-fenil]-4H-[1.2.4]oxadiazol-5-ona

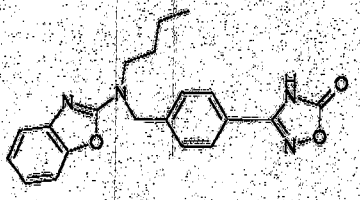


4-Butilaminometil-benzonitrilo



Se disolvieron 5,0 g de 4-aminometil-benzonitrilo y 3,75 ml de butiraldehído en 40 ml de metanol. Se añadieron 3,0 g de tamices moleculares 4 Angström y la mezcla se agitó a temperatura ambiente durante dos horas. Después, se añadieron 2,2 g de borohidruro sódico y la mezcla se agitó durante una hora más a temperatura ambiente. Se añadieron 250 ml de acetato de etilo y la reacción se interrumpió mediante la adición de 4 ml de agua. La mezcla de reacción se filtró a través de una capa de celite y MgSO4. El filtrado se evaporó al vacío para proporcionar 3,7 g de 4-butilaminometil-benzonitrilo bruto. Este material se usó sin purificación adicional. C12H16N2 (188,27), MS (ESI): 189,2 ($M+H^+$).

3-[4-[(Benzooxazol-2-il-butil-amino)-metil]-fenil]-4H-[1.2.4]oxadiazol-5-ona

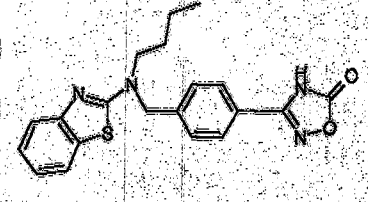


De acuerdo con el método descrito en el Ejemplo 1, se obtuvo 3-{4-[(benzooxazol-2-il-butil-amino)-metil]-fenil}-4H-[1.2.4]oxadiazol-5-ona a partir de 4-butilaminometil-benzonitrilo y 2-clorobenzoxazol.

C20H20N4O3 (364,41), MS (ESI): 365,2 ($M+H^+$).

Ejemplo 12

3-{4-[(Benzotiazol-2-il-butil-amino)-metil]-fenil}-4H-[1.2.4]oxadiazol-5-ona

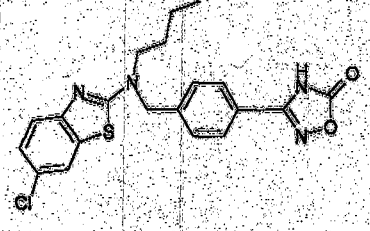


De acuerdo con el método descrito en el Ejemplo 1, se obtuvo 3-{4-[(benzotiazol-2-il-butil-amino)-metil]-fenil}-4H-[1.2.4]oxadiazol-5-ona a partir de 4-butilaminometil-benzonitrilo y 2-clorobenzotiazol.

C20H20N4O2S (380,47), MS (ESI): 381,2 ($M+H^+$).

Ejemplo 13

3-(4-{[Butil-(6-cloro-benzotiazol-2-il)-amino]-metil}-fenil)-4H-[1.2.4]oxadiazol-5-ona

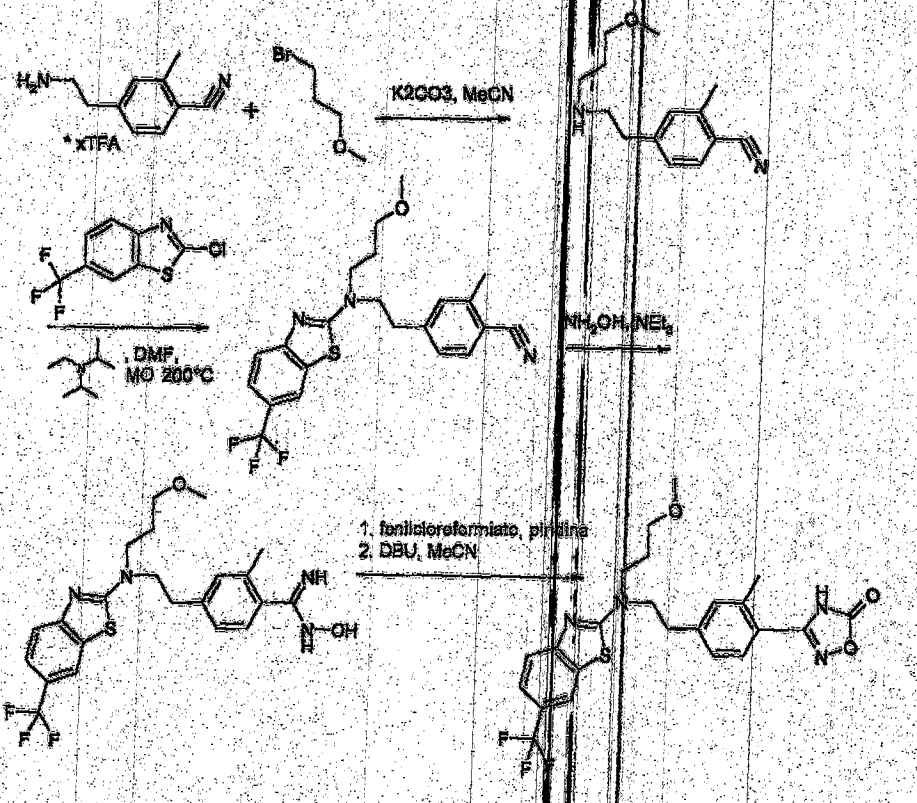


De acuerdo con el método descrito en el Ejemplo 1, se obtuvo 3-(4-{[butil-(6-cloro-benzotiazol-2-il)-amino]-metil}-fenil)-4H-[1.2.4]oxadiazol-5-ona a partir de 4-butilaminometil-benzonitrilo y 2,6-diclorobenzotiazol.

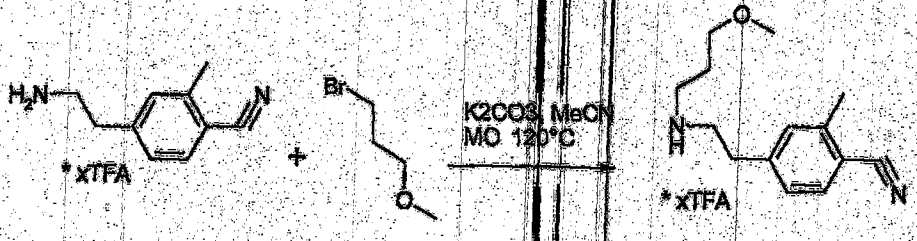
C20H19ClN4O2S (414,92), MS (ESI): 415,1 ($M+H^+$).

Ejemplo 14

3-(4-{2-[(3-Metoxi-propil)-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-2-metil-fenil)-4H-[1.2.4]oxadiazol-5-ona



4-[2-(3-Metoxi-propilamino)-etil]-2-metil-benzonitrilo

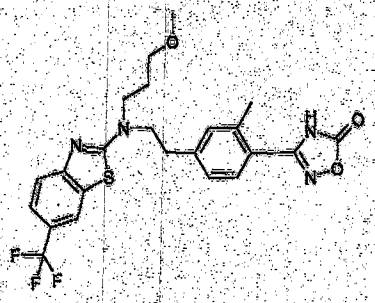


Una mezcla de 500 mg de trifluoroacetato de 4-(2-amino-etil)-2-metil-benzonitrilo y 756 mg de carbonato potásico se agitaron en 10 ml de acetonitrilo a 80ºC durante quince minutos. Después, se añadieron gota a gota 279 mg de 1-bromo-3-metoxipropano, disuelto en 5 ml de acetonitrilo, a 80ºC. La mezcla de reacción se agitó con irradiación con microondas a 120ºC durante una hora. La mezcla de reacción enfriada se filtró a través de una capa de celite para retirar la sal. Después el disolvente se eliminó al vacío. El residuo se purificó por RP-HPLC para obtener 268 mg de 4-[2-(3-metoxi-propilamino)-etil]-2-metil-benzonitrilo en forma de su sal trifluoroacetato.

C14H20N2O .xTFA (232,16+ xTFA), MS (ESI): 233,2 (M+H+).

3-(4-[2-[(3-Metoxi-propil)-(6-trifluorometil-benzotiazol-2-il)-amino]-etil]-2-metil-fenil)-

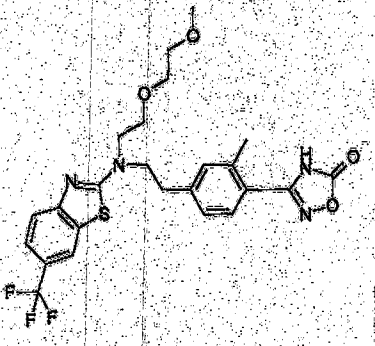
4H-[1.2.4]oxadiazol-5-ona



De acuerdo con el método descrito en el Ejemplo 1, se obtuvo 3-(4-{2-[(3-metoxi-propil)-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-2-metil-fenil)-4H-[1.2.4]oxadiazol-5-ona a partir de trifluoroacetato de 4-[2-(3-metoxi-propilamino)-etil]-2-metil-benzonitrilo y 2-cloro-6-trifluorometil-benzotiazol.
C23H23F3N4O3S (492,52), MS (ESI): 493,0 ($M+H^+$).

Ejemplo 15

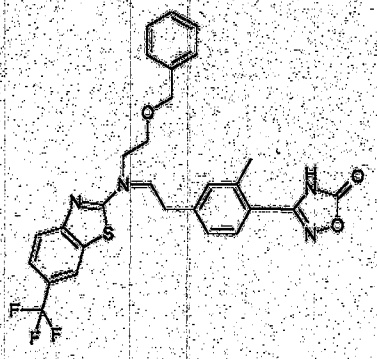
3-(4-{2-[[2-(2-Metoxi-etoxi)-etil]-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-2-metil-fenil)-4H-[1.2.4]oxadiazol-5-ona



De acuerdo con el método descrito en los Ejemplos 1 y 14, se obtuvo 3-(4-{2-[[2-(2-metoxi-etoxi)-etil]-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-2-metil-fenil)-4H-[1.2.4]oxadiazol-5-ona a partir de trifluoroacetato de 4-(2-amino-etil)-2-metil-benzonitrilo, 1-bromo-2-(2-metoxietoxi)etano y 2-cloro-6-trifluorometil-benzotiazol.
C24H25F3N4O4S (522,55), MS (ESI): 523,0 ($M+H^+$).

Ejemplo 16

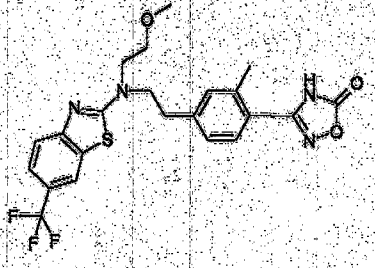
3-(4-{2-[(2-Benciloxi-etil)-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-2-metil-fenil)-4H-[1.2.4]oxadiazol-5-ona



De acuerdo con el método descrito en los Ejemplos 1 y 14, se obtuvo 3-(4-[2-[(2-benciloxi-etil)-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-2-metil-fenil)-4H-[1.2.4]oxadiazol-5-ona a partir de trifluoroacetato de 4-(2-amino-etil)-2-metil-benzonitrilo, bencil 2-bromoetiléter y 2-cloro-6-trifluorometil-benzotiazol. C28H25F3N4O3S (554,60), MS (ESI): 555,0 (M+H$^+$).

Ejemplo 17

3-(4-{2-[(2-Metoxi-etil)-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-2-metil-fenil)-4H-[1.2.4]oxadiazol-5-ona

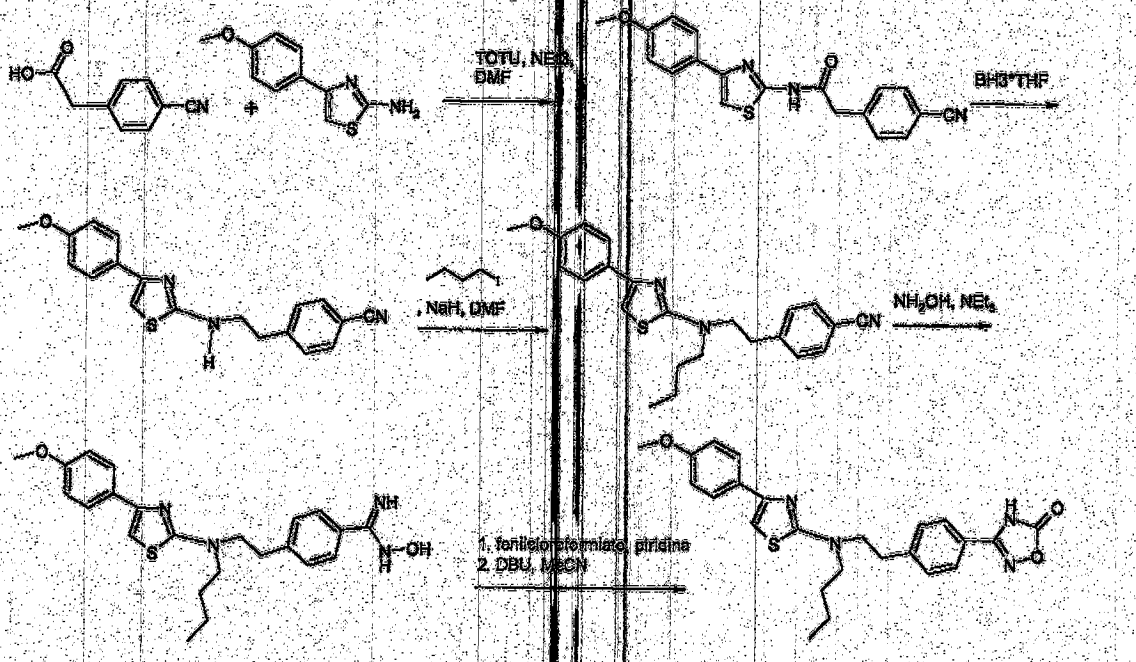


De acuerdo con el método descrito en los Ejemplos 1 y 14, se obtuvo 3-(4-{2-[(2-metoxi-etil)-(6-trifluorometil-benzotiazol-2-il)-amino]-etil}-2-metil-fenil)-4H-[1.2.4]oxadiazol-5-ona a partir de trifluoroacetato de 4-(2-amino-etil)-2-metil-benzonitrilo, 2-bromoetil metiléter y 2-cloro-6-trifluorometil-benzotiazol. C22H21F3N4O3S (478,50), MS (ESI): 479,0 (M+H$^+$).

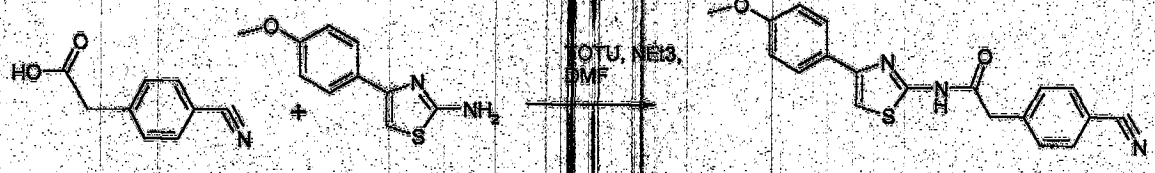
Se prepararon los siguientes ejemplos de acuerdo con el proceso B:

Ejemplo 18

3-[4-(2-{Butil-[4-(4-metoxi-fenil)-tiazol-2-il]-amino}-etil)-fenil]-4H-[1,2,4]oxadiazol-5-ona



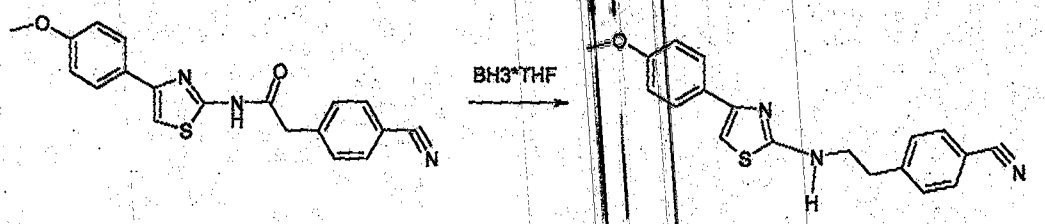
2-(4-Ciano-fenil)-N-[4-(4-metoxi-fenil)-tiazol-2-il]-acetamida



Se disolvieron 1,41 g de 4-(4-metoxifenil)-1,3-tiazol-2-amina en 2 ml de dimetilformamida. Se añadieron 3,0 ml de N,N-diisopropiletilamina, 1,0 g de ácido (4-ciano-fenil)-acético disponible en el mercado y 2,25 g de tetrafluoroborato de O-((etoxicarbonil)cianometilenoamino)-N,N,N',N'-tetrametiluronio. La mezcla de reacción se agitó a temperatura ambiente durante la noche. Después, se añadieron 200 ml de acetato de etilo y la mezcla se lavó tres veces con porciones de 50 ml de una solución saturada de NaHCO3 y después se secó sobre MgSO4. Los disolventes se retiraron al vacío y el residuo se purificó por RP-HPLC para obtener 610 mg de 2-(4-ciano-fenil)-N-[4-(4-metoxi-fenil)-tiazol-2-il]-acetamida en forma de un sólido amarillo.

C19H15N3O2S (349,41), MS (ESI): 350,1 (M+H$^+$).

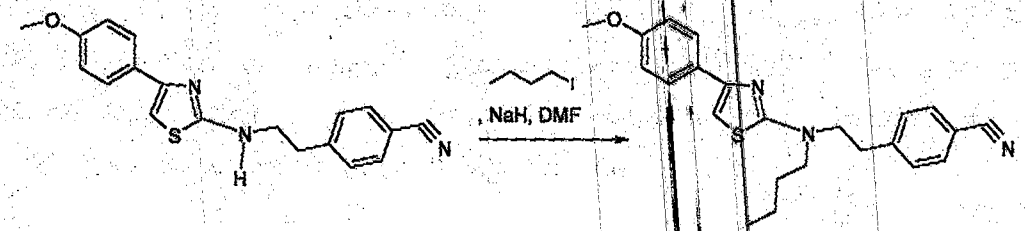
4-{2-[4-(4-Metoxi-fenil)-tiazol-2-ilamino]-etil}-benzonitrilo



Se suspendieron 610 mg de 2-(4-ciano-fenil)-N-[4-(4-metoxi-fenil)-tiazol-2-il]-acetamida en 20 ml de tetrahidrofurano. Se añadieron 2,1 ml de una solución uno molar de complejo de borano y tetrahidrofurano a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante dos horas y después a 50ºC durante dos horas. La mezcla de reacción enfriada se vertió sobre 50 ml de agua y se extrajo cinco veces con porciones de 50 ml de acetato de etilo. Las capas orgánicas combinadas se secaron sobre MgSO4. Después, los disolventes se retiraron al vacío para obtener 600 mg de 4-{2-[4-(4-metoxi-fenil)-tiazol-2-ilamino]-etil}-benzonitrilo.

C19H17N3OS (335,43), MS (ESI): 336,2 ($M+H^+$).

4-(2-{Butil-[4-(4-metoxi-fenil)-tiazol-2-il]-amino}-etil)-benzonitrilo

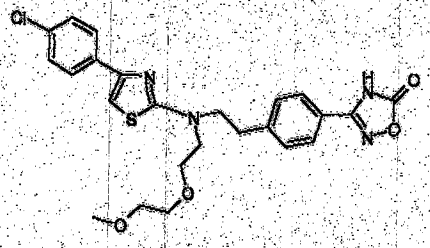


Se disolvieron 600 mg de 4-{2-[4-(4-metoxi-fenil)-tiazol-2-ilamino]-etil}-benzonitrilo en 30 ml de dimetilformamida. Se añadieron 85,9 mg de hidruro sódico (al 24% en aceite mineral) y la mezcla de reacción se agitó a temperatura ambiente durante treinta minutos. Después, se añadieron 245 µl de 1-yodobutano y la mezcla de reacción se agitó a temperatura ambiente durante dos horas. Después, se añadieron 100 ml de acetato de etilo y la mezcla se lavó tres veces con porciones de 50 ml de agua y después se secó sobre MgSO4. Los disolventes se retiraron al vacío y el residuo se purificó por RP-HPLC para obtener 279 mg de 4-(2-{butil-[4-(4-metoxi-fenil)-tiazol-2-il]-amino}-etil)-benzonitrilo.

C23H25N3OS (391,54), MS (ESI): 392,2 ($M+H^+$).

3-[4-(2-{Butil-[4-(4-metoxi-fenil)-tiazol-2-il]-amino}-etil)-fenil]-4H-[1.2.4]oxadiazol-5-ona

3-[4-(2-{[4-(4-Cloro-fenil)-tiazol-2-il]-[2-(2-metoxi-etoxi)-etil]-amino}-etil)-fenil]-4H-[1.2.4]oxadiazol-5-ona

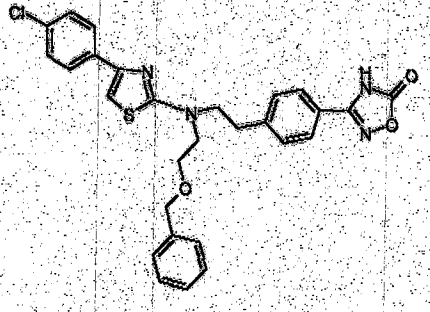


De acuerdo con el método descrito en los Ejemplos 1 y 18, se obtuvo 3-[4-(2-{[4-(4-cloro-fenil)-tiazol-2-il]-[2-(2-metoxi-etoxi)-etil]-amino}-etil)-fenil]-4H-[1.2.4]oxadiazol-5-ona a partir de ácido (4-ciano-fenil)-acético, 4-(4-cloro-fenil)-tiazol-2-ilamina y 1-bromo-2-(metoxietoxi)etano.

$C_{24}H_{25}ClN_4O_4S$ (501,01), MS (ESI): 501,0 ($M+H^+$).

Ejemplo 22

3-[4-(2-{(2-Benciloxi-etil)-[4-(4-cloro-fenil)-tiazol-2-il]-amino}-etil)-fenil]-4H-[1.2.4]oxadiazol-5-ona

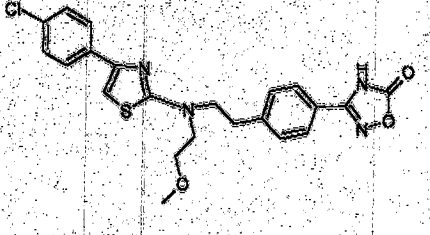


De acuerdo con el método descrito en los Ejemplos 1 y 18, se obtuvo 3-[4-(2-{(2-benciloxi-etil)-[4-(4-cloro-fenil)-tiazol-2-il]-amino}-etil)-fenil]-4H-[1.2.4]oxadiazol-5-ona a partir de ácido (4-ciano-fenil)-acético, 4-(4-cloro-fenil)-tiazol-2-ilamina y bencil 2-bromoetiléter.

$C_{28}H_{25}ClN_4O_3S$ (533,05), MS (ESI): 533,1 ($M+H^+$).

Ejemplo 23

3-(4-{2-[[4-(4-Cloro-fenil)-tiazol-2-il]-(2-metoxi-etil)-amino]-etil}-fenil)-4H-[1.2.4]oxadiazol-5-ona



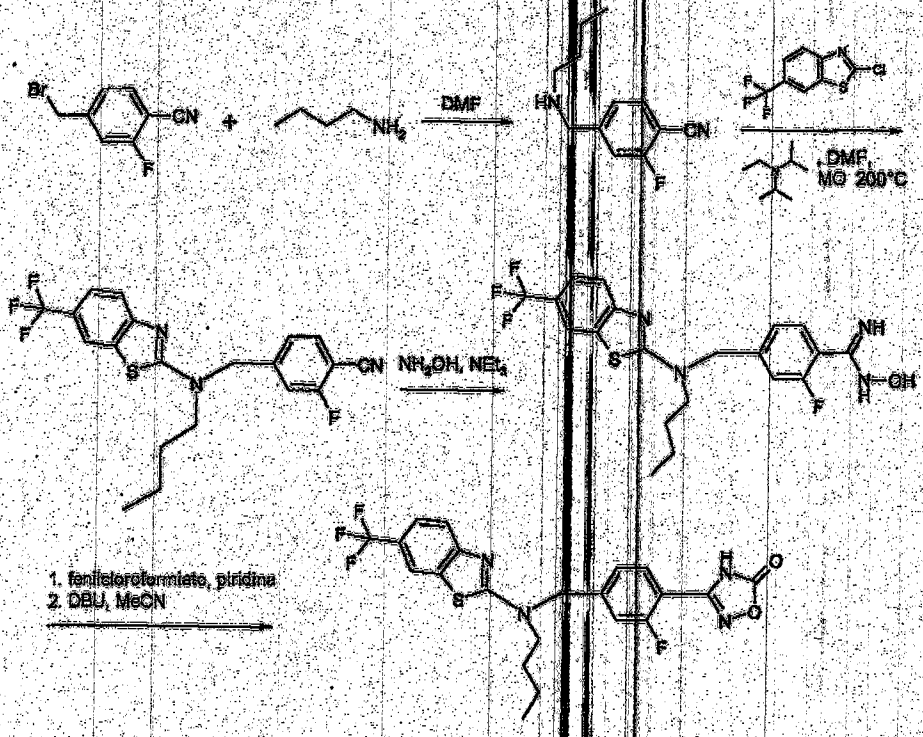
De acuerdo con el método descrito en los Ejemplos 1 y 18, se obtuvo 3-(4-{2-[[4-(4-cloro-fenil)-tiazol-2-il]-(2-metoxi-etil)-amino]-etil}-fenil)-4H-[1.2.4]oxadiazol-5-ona a partir de ácido (4-ciano-fenil)-acético, 4-(4-cloro-fenil)-tiazol-2-ilamina y 2-bromoetilmetiléter.

C22H21ClN4O3S (456,95), MS (ESI): 457,0 ($M+H^+$).

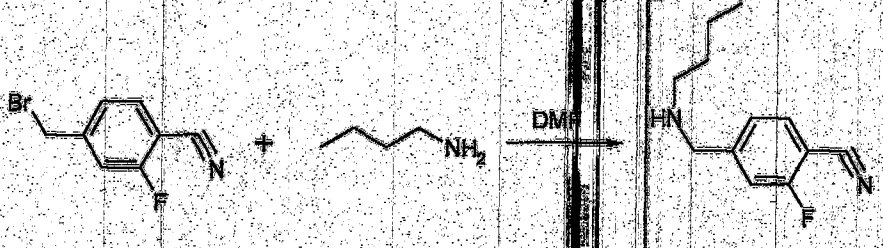
Los siguientes ejemplos se prepararon de acuerdo con el proceso C:

Ejemplo 24

3-(4-{[Butil-(6-trifluorometil-benzotiazol-2-il)-amino]-metil}-2-fluoro-fenil)-4H-[1.2.4]oxadiazol-5-ona



4-Butilaminometil-2-fluoro-benzonitrilo

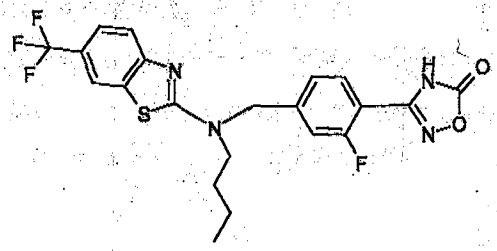


Se disolvieron 4,64 ml de n-butilamina en 30 ml de dimetilformamida. Se añadieron gota a gota 667 mg de bromuro de 4-ciano-3-fluorobencilo disponible en el

mercado, disuelto en 10 ml de dimetilformamida. La mezcla de reacción se agitó a temperatura ambiente durante 30 minutos. El disolvente se retiró al vacío y el residuo se purificó por cromatografía sobre gel de sílice con el eluyente n-heptano:acetato de etilo = 1:4 => acetato de etilo:metanol = 4:1 para obtener 360 mg de 4-butilaminometil-2-fluoro-benzonitrilo.

$C_{12}H_{15}FN_2$ (206,27), MS (ESI): 207,2 ($M+H^+$), R_f (acetato de etilo:metanol = 9:1) = 0,29.

3-(4-{[Butil-(6-trifluorometil-benzotiazol-2-il)-amino]-metil}-2-fluoro-fenil)-4H-[1.2.4]oxadiazol-5-ona

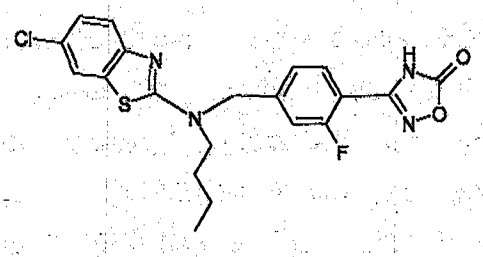


De acuerdo con el método descrito en el Ejemplo 1, se obtuvo 3-(4-{[butil-(6-trifluorometil-benzotiazol-2-il)-amino]-metil}-2-fluoro-fenil)-4H-[1.2.4]oxadiazol-5-ona a partir de 4-butilaminometil-2-fluoro-benzonitrilo y 2-cloro-6-trifluorometil-benzotiazol.

$C_{21}H_{18}F_4N_4O_2S$ (466,46), MS (ESI): 467,0 ($M+H^+$).

Ejemplo 25

3-(4-{[Butil-(6-cloro-benzotiazol-2-il)-amino]-metil}-2-fluoro-fenil)-4H-[1.2.4]oxadiazol-5-ona



De acuerdo con el método descrito en el Ejemplo 1, se obtuvo 3-(4-{[butil-(6-cloro-benzotiazol-2-il)-amino]-metil}-2-fluoro-fenil)-4H-[1.2.4]oxadiazol-5-ona a partir de 4-butilaminometil-2-fluoro-benzonitrilo y 2,6-dicloro-benzotiazol.

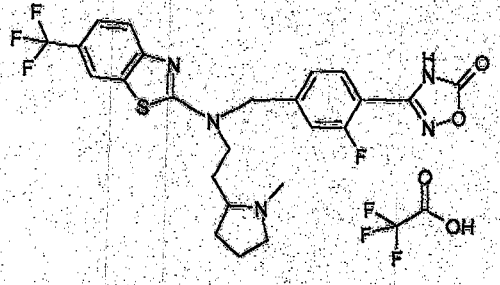
$C_{20}H_{18}ClFN_4O_2S$ (432,91), MS (ESI): 433,0 ($M+H^+$).

Ejemplo 26

De acuerdo con el método descrito en el Ejemplo 1, se obtuvo 3-(2-fluoro-4-{[(2-morfolin-4-il-etil)-(6-trifluorometil-benzotiazol-2-il)-amino]-metil}-fenil)-4H-[1.2.4]oxadiazol-5-ona a partir de bromuro de 4-ciano-3-fluorobencilo disponible en el mercado, N-(2-aminoetil)morfolina y 2-cloro-6-trifluorometil-benzotiazol. Después de la RP-HPLC, se obtuvo el compuesto en forma de su sal trifluoroacetato.
$C_{23}H_{21}F_4N_5O_3S \cdot C_2HF_3O_2$ (523,51+114,02), MS (ESI): 524,2 ($M+H^+$).

Ejemplo 31

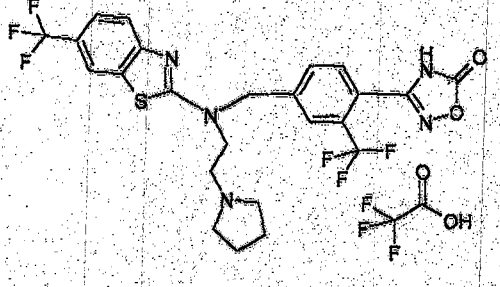
Trifluoroacetato de 3-(2-fluoro-4-{[[2-(1-metil-pirrolidin-2-il)-etil]-(6-trifluorometil-benzotiazol-2-il)-amino]-metil}-fenil)-4H-[1.2.4]oxadiazol-5-ona



De acuerdo con el método descrito en el Ejemplo 1, se obtuvo 3-(2-fluoro-4-{[[2-(1-metil-pirrolidin-2-il)-etil]-(6-trifluorometil-benzotiazol-2-il)-amino]-metil}-fenil)-4H-[1.2.4]oxadiazol-5-ona a partir de bromuro de 4-ciano-3-fluorobencilo disponible en el mercado, 2-(2-aminoetil)-1-metilpirrolidina y 2-cloro-6-trifluorometil-benzotiazol. Después de la RP-HPLC, se obtuvo el compuesto en forma de su sal trifluoroacetato.
$C_{24}H_{23}F_4N_5O_2S \cdot C_2HF_3O_2$ (521,54+114,02), MS (ESI): 522,2 ($M+H^+$).

Ejemplo 32

3-(4-{[(2-Pirrolidin-1-il-etil)-(6-trifluorometil-benzotiazol-2-il)-amino]-metil}-2-trifluorometil-fenil)-4H-[1.2.4]oxadiazol-5-ona

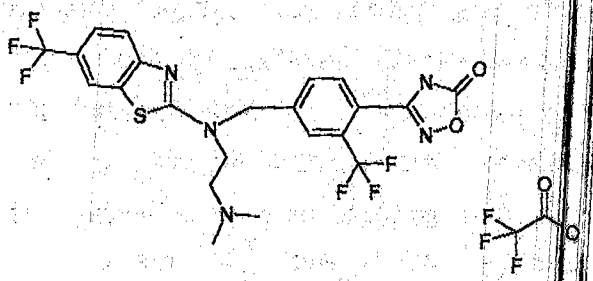


De acuerdo con el método descrito en el Ejemplo 1, se obtuvo 3-(4-{[(2-pirrolidin-1-il-etil)-(6-trifluorometil-benzotiazol-2-il)-amino]-metil}-2-trifluorometil-fenil)-4H-[1.2.4]oxadiazol-5-ona a partir de 4-bromometil-2-trifluorometil-benzonitrilo, N-(2-

aminoetil)pirrolidina y 2-cloro-6-trifluorometil-benzotiazol. Después de la RP-HPLC, se obtuvo el compuesto en forma de su sal trifluoroacetato.
C24H21F6N5O2S · C2HF3O2 (557,52+114,02), MS (ESI): 558,0 ($M+H^+$).

Ejemplo 33

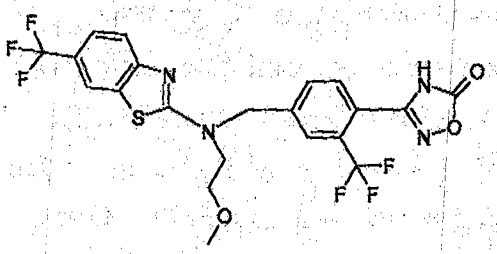
Trifluoroacetato de 3-(4-{[(2-dimetilamino-etil)-(6-trifluorometil-benzotiazol-2-il)-amino]-metil}-2-trifluorometil-fenil)-4H-[1.2.4]oxadiazol-5-ona



De acuerdo con el método descrito en el Ejemplo 1, se obtuvo 3-(4-{[(2-dimetilamino-etil)-(6-trifluorometil-benzotiazol-2-il)-amino]-metil}-2-trifluorometil-fenil)-4H-[1.2.4]oxadiazol-5-ona a partir de 4-bromometil-2-trifluorometil-benzonitrilo, N,N-dimetiletilendiamina y 2-cloro-6-trifluorometil-benzotiazol. Después de la RP-HPLC, se obtuvo el compuesto en forma de su sal trifluoroacetato.
C22H19F6N5O2S · C2HF3O2 (531,48+114,02), MS (ESI): 532,1 ($M+H^+$).

Ejemplo 34

3-(4-{[(2-Metoxi-etil)-(6-trifluorometil-benzotiazol-2-il)-amino]-metil}-2-trifluorometil-fenil)-4H-[1.2.4]oxadiazol-5-ona



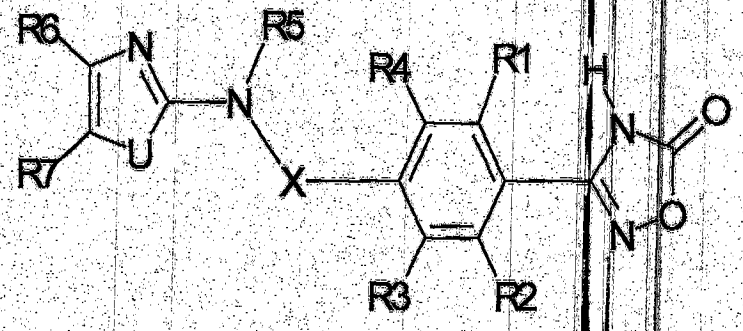
De acuerdo con el método descrito en el Ejemplo 1, se obtuvo 3-(4-{[(2-metoxi-etil)-(6-trifluorometil-benzotiazol-2-il)-amino]-metil}-2-trifluorometil-fenil)-4H-[1.2.4]oxadiazol-5-ona a partir de 4-bromometil-2-trifluorometil-benzonitrilo, 2-metoxietilamina y 2-cloro-6-trifluorometil-benzotiazol.
C21H16F6N4O3S (518,44), MS (ESI): 519,2 ($M+H^+$).

Ejemplo 35

Trifluoroacetato de 3-(4-{[(2-piperidin-1-il-etil)-(6-trifluorometil-benzotiazol-2-il)-

REIVINDICACIONES

1. Compuestos de fórmula I



fórmula I

en la que

R1 H, halógeno, alquilo (C1-C8), alquileno (C0-C4)-O-alquileno (C0-C4)-H, SCH3 o CN, donde los grupos alquilo y alquileno están sin sustituir o mono, di- o trisustituidos con F;

R2, R3, R4 son independientemente
H, halógeno, alquilo (C1-C8), alquileno (C0-C4)-O-alquileno (C0-C4)-H, SCH3 o CN, donde los grupos alquilo y alquileno están sin sustituir o mono, di- o trisustituidos con F;

X –CH2- o -CH2-CH2-;

U es S u O;

R5 es H, alquilo (C1-C8), alquileno (C1-C4)-O-alquilo (C1-C4), alquileno (C1-C4)-O-alquileno (C0-C4)-arilo (C6-C10), alquileno (C0-C4)-cicloalquilo (C3-C12), alquenilo (C2-C8), alquileno (C0-C4)-heterocicloalquilo (C3-C15), alquileno (C0-C4)-heterocicloalquenilo (C3-C15), alquileno (C0-C4)-heteroarilo (C5-C15), donde los grupos alquilo y alquileno están sin sustituir o mono-, di- o trisustituidos con F,

N(alquileno (C0-C4)-H)-alquileno (C0-C4)-H y O-alquileno (C0-C4)-H y donde los grupos cicloalquilo, arilo, heterocicloalquilo, heterocicloalquenilo y heteroarilo están sin sustituir o mono-, di- o trisustituidos con F, Cl, Br, CF3, alquilo (C1-C4), CO-alquilo (C1-C4) y alquileno (C0-C4)-O-alquileno (C0-C4)-H;

R6, R7 H, arilo (C6-C14), que está sin sustituir o mono-, di- o trisustituido con F, Cl, Br, CF3, alquilo (C1-C4) y alquileno (C0-C4)-O-alquileno (C0-C4)-H; o

R6 y R7 junto con el anillo oxazol o tiazol forman un anillo benzotiazol o benzoxazol, que está sin sustituir o mono-, di- o trisustituido con F, Cl, Br, CF3, alquilo (C1-C4) y alquileno (C0-C4)-O-alquileno (C0-C4)-H;

en todas sus formas estereoisoméricas, formas enantioméricas y mezclas en cualquier relación, y sus sales fisiológicamente aceptables y formas tautoméricas.

2. Compuestos de la fórmula I de acuerdo con la reivindicación 1, en los que

R1 es halógeno, alquilo (C1-C8), alquileno (C0-C4)-O-alquileno (C0-C4)-H, SCH3 o CN, donde los grupos alquilo y alquileno están sin sustituir o mono, bi- o trisustituidos con F;

R2, R3, R4 son H;

X es -CH2-CH2-;

U es S;

R5 es alquilo (C1-C4), alquileno (C1-C4)-O-alquilo (C1-C4), alquileno (C1-C4)-O-CH2-fenilo o alquileno (C1-C4)-heterocicloalquilo (C5-C6), donde los grupos alquilo y alquileno pueden estar mono-, di- o trisustituidos con N(alquil (C1-C4))-alquilo (C1-C4) y donde el grupo heterocicloalquilo está sin sustituir o monosustituido con alquilo (C1-C4) o CO-alquilo (C1-C4);

R6 es fenilo monosustituido con Cl o metoxi;

R6 y R7 junto con el anillo oxazol o tiazol se refieren a benzotiazol sustituido con CF3.

3. Compuestos de la fórmula I de acuerdo con la reivindicación 1, en los que

R1 es halógeno, alquilo (C1-C8), alquileno (C0-C4)-O-alquileno (C0-C4)-H, SCH3 o CN, donde los grupos alquilo y alquileno están sin sustituir o mono, bi- o trisustituidos con F;

R2, R3, R4 son H;

X es -CH2-;

U es S;

R5 es alquilo (C1-C4), alquileno (C1-C4)-O-alquilo (C1-C4), alquileno (C1-C4)-O-CH2-fenilo o alquileno (C1-C4)-heterocicloalquilo (C5-C6), donde los grupos alquilo y alquileno pueden estar mono-, di- o trisustituidos con N(alquil (C1-C4))-alquilo (C1-C4) y donde el grupo heterocicloalquilo está sin sustituir o monosustituido con alquilo (C1-C4) o CO-alquilo (C1-C4);

R6 es fenilo monosustituido con Cl o metoxi;

R6 y R7 junto con el anillo oxazol o tiazol se refieren a benzotiazol sustituido con CF3.

4. Compuestos de la fórmula I de acuerdo con las reivindicaciones 1 a 3, en los que

R1 es H, F, Cl o alquilo (C1-C4) que está sin sustituir o mono-, di- o trisustituido

con F.

5. Compuestos de la fórmula I de acuerdo con las reivindicaciones 1 a 3, en los que

R1 es H, F, CH3 o CF3.

6. Compuestos de la fórmula I de acuerdo con las reivindicaciones 1 a 3, en los que

R1 es F, CH3 o CF3.

7. Compuestos de la fórmula I de acuerdo con las reivindicaciones 1 a 6, en los que

R6 y R7 junto con el anillo tiazol se refieren a 6-trifluorometil-benzotiazol.

8. Un producto farmacéutico que comprende uno o más compuestos de fórmula I de acuerdo con una o más de las reivindicaciones 1 a 7.

9. Un producto farmacéutico que comprende uno o más compuestos de fórmula I de acuerdo con una o más de las reivindicaciones 1 a 7, y una o más sustancias activas que tienen efectos beneficiosos en las alteraciones metabólicas o trastornos asociados frecuentemente con éstas.

10. Un producto farmacéutico que comprende uno o más compuestos de fórmula I de acuerdo con una o más de las reivindicaciones 1 a 7, y uno o más antidiabéticos.

11. Un producto farmacéutico que comprende uno o más compuestos de fórmula I de acuerdo con una o más de las reivindicaciones 1 a 7, y uno o más moduladores de lípidos.

12. El uso de los compuestos de la fórmula I de acuerdo con una o más de las reivindicaciones 1 a 7, para tratar y/o prevenir trastornos del metabolismo de ácidos

grasos y trastornos de la utilización de la glucosa.

13. El uso de los compuestos de la fórmula I de acuerdo con una o más de las reivindicaciones 1 a 7 para tratar y/o prevenir trastornos en donde está implicada la resistencia a la insulina.

14. El uso de los compuestos de fórmula I de acuerdo con una o más de las reivindicaciones 1 a 7, para tratar y/o prevenir la diabetes mellitus, incluyendo la prevención de secuelas asociadas con ésta.

15. El uso de los compuestos de fórmula I de acuerdo con una o más de las reivindicaciones 1 a 7, para tratar y/o prevenir dislipidemias y sus secuelas.

16. El uso de los compuestos de la fórmula I de acuerdo con una o más de las reivindicaciones 1 a 7, para tratar y/o prevenir estados que pueden estar asociados con el síndrome metabólico.

17. El uso de los compuestos de la fórmula I de acuerdo con una o más de las reivindicaciones 1 a 7 para tratar y/o prevenir trastornos desmielinizantes y otros trastornos neurodegenerativos del sistema nervioso central y periférico.

18. El uso de compuestos de acuerdo con una o más de las reivindicaciones 1 a 7, en combinación con al menos un compuesto activo adicional, para tratar trastornos del metabolismo de ácidos grasos y trastornos de la utilización de la glucosa.

19. El uso de compuestos de acuerdo con una o más de las reivindicaciones 1 a 7, en combinación con al menos un compuesto activo adicional, para tratar trastornos en los que está implicada la resistencia a la insulina.

20.Un proceso para preparar un producto farmacéutico que comprende uno o más compuestos de acuerdo con una o más de las reivindicaciones 1 a 7, que comprende mezclar el compuesto activo con un vehículo farmacéuticamente aceptable, y poner esta mezcla en una forma de administración adecuada.

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Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO PROPIETARIOS

SUPERINTENDENCIA 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. STEFANIE KEIL, DR. MATHIAS URMANN, DR. MAIKE GLIEN, DR. WOLFGANG WENDLER, DR. KAREN CHANDROSS, LAN LEE**

(74) Apoderado: **DR. LUIS PATIÑO LEYVA**

(30) Prioridad	(31) **Nº Prioridad**	32) **Fecha**	(33) **País**
	05021279.4	**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/EP2006/009302**

(87) Publicación internacional
Fecha: **12/04/2007**
Nº publicación: **WO 2007/039176 A1**

(54) Título: **DERIVADOS DE 2-AMINOTIAZOLES Y 2-AMINOOXAZOLES, PROCESOS PARA SU PREPARACIÓN Y SU USO COMO COMPUESTOS FARMACÉUTICOS**

Sanofi-Aventis Deutschland GmbH
Patentabteilung K 801
Vorg.
Eing.: 08. Aug. 2007
○ WV
☒ ablegen
○ Vert. wie Vorg./angegeben

PATENT COOPERATION TREATY

PCT/EP2006/009302

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
DE2005/045

IMPORTANT NOTIFICATION

International application No.
PCT/EP2006/009302

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
SANOFI-AVENTIS DEUTSCHLAND GMBH
Brüningstrasse 50
65929 Frankfurt am Main
Germany

State of Nationality	State of Residence
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
SANOFI-AVENTIS
4, avenue de France
F-75013 Paris
France

State of Nationality	State of Residence
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

SUPERINTENDENCIA DE INDUSTRIA...

No. 08-030802- -00000-0000

Fecha: 2008-03-28 14:12:49 Dep: 2020 NUECREACIONE
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 169

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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 Nieto Cortes

Fecha: _____

REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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Bogotá,
2020

Doctor(a)
PATIÑO LEYVA LUIS
Apoderado(a) y/o Representante de
SANOFI AVENTIS

REFERENCIA	Radicación No.	8 30802
	Solicitud internacional	PCT/EP2006/009302
	Fecha inicio fase nacional	29/04/2008
	Trámite	21
	Evento	378
	Actuación	430
	Oficio No.	6255

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 16 MAYO 2008
adpa11