

LLOREDA & CIA. S. A.
ABOGADOS

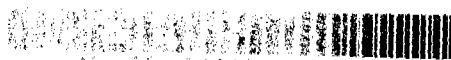
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Señor

SUPERINTENDENTE DE INDUSTRIA Y C
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____

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Nº 06-129.228-00001-0000

RECIBO DE PAGO DE LA TASA DE 2020 NULCRLACIONE
LAW 378 FASE NACIONAL
PAGOS 2

Re: P1.-ASTRAZENECA AB.-Solicitud de Patente de Invención en
Fase Nacional PCT para "COMPUESTOS NOVEDOSOS
DERIVADOS DE HIDANTOINA PARA EL TRATAMIENTO DE
ENFERMEDADES OBSTRUCTIVAS DE LAS VIAS AÉREAS".-
Clase C07D 401/14.-Expediente número 06-129.228.-

1. Me refiero a mi solicitud de patente de 26 de Diciembre de 2006.
2. De conformidad con lo dispuesto en el Artículo 5.2.12 de la Circular Externa No. 03 de 28 de Abril de 2003, y estando dentro del plazo de seis meses contados desde la fecha de la publicación de la solicitud en la Gaceta de la Propiedad Industrial número **578** de 31 de Julio de 2007, solicito a ese Despacho proceder a realizar el examen de patentabilidad de la presente invención.
3. Me permito recordar a usted, que tal como se informó en el Petitorio de la invención, la presente solicitud corresponde a Capítulo **I**.
4. Anexo me permito acompañar recibo número 08-4.852, expedido por la Superintendencia de Industria y Comercio, que acredita el pago de la tasa que dicho examen causa.

Señor Superintendente,

ALICIA LLOREDA RICAURTE

T.P. 53.215

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-129228-00001-0000

Dep. 2020 NUECREACIONI
Lva. 378 FASENACIONALI

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 500170009-2

RECORrido OFICIAL DE CAJA . 00 - 4,801
FECHA : CHORO 21 DE 2008

***** CONSIGNACION *****

DISPOSITIVO	Tipo COTO	BANCO	CUENTA	No. PASO	FECHA PDI	VAL. PASO
ALICORNIA Y CIA S. A	CONSIGNACION	BANCO DE BOGOTA	002134307	3452410	21/01/2008	5,734,000.00

***** C E X C E P T O *****

CANT. REQUISITOS	CONCEPTO	TOTAL CONCEPTO
1 36008-01-01 SOLICITUDES	DE EXAMEN DE PATENTABILIDAD DE INVEN	400,000.00
	TOTAL	400,000.00

SOM: CUATROCIENTOS VEINTE MIL PESOS

RESPONSABLE : _____

RECIBO DE CASH APLICADO AL EXPEDIENTE No. _____

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-129228

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **578** DE

FECHA **31 DE JULIO DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **26 DE OCTUBRE DE 2007**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X

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(19) World Intellectual Property Organization
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A61P 35/00, 11/00, 19/00, 29/00

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(72) Inventors; and

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

Declarations under Rule 4.17:

as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

- of inventorship (Rule 4.17(iv)) for US only
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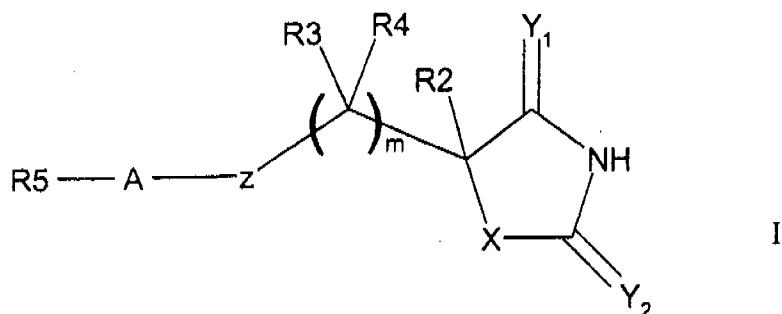


WO 02/074767 A1

(54) Title: **METALLOPROTEINASE INHIBITORS**

(57) Abstract: Compounds of the formula (I) wherein z is SO₂ or SO, useful as metalloproteinase inhibitors, especially as inhibitors of MMP12.

In a first aspect of the invention we now provide compounds of the formula I



wherein

5 X is selected from NR1, O, S;

Y1 and Y2 are independently selected from O, S;

Z is selected from SO, SO₂;

m is 1 or 2;

A is selected from a direct bond, (C1-6)alkyl, (C1-6)haloalkyl, or (C1-6)heteroalkyl
 10 containing a hetero group selected from N, O, S, SO, SO₂ or containing two hetero groups
 selected from N, O, S, SO, SO₂ and separated by at least two carbon atoms;

R1 is selected from H, (C1-3)alkyl, haloalkyl;

Each R2 and R3 is independently selected from H, halogen (preferably fluorine),
 alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkylaryl, alkyl-
 15 heteroaryl, heteroalkyl-aryl, heteroalkyl-heteroaryl, aryl-alkyl, aryl-heteroalkyl, heteroaryl-
 alkyl, heteroaryl-heteroalkyl, aryl-aryl, aryl-heteroaryl, heteroaryl-aryl, heteroaryl-
 heteroaryl, cycloalkyl-alkyl, heterocycloalkyl-alkyl, alkyl-cycloalkyl, alkyl-
 heterocycloalkyl;

Each R4 is independently selected from H, halogen (preferably fluorine), (C1-3)alkyl
 20 or haloalkyl;

Each of the R2 and R3 radicals may be independently optionally substituted with one
 or more (preferably one) groups selected from alkyl, heteroalkyl, aryl, heteroaryl, halo,
 haloalkyl, hydroxy, alkoxy, haloalkoxy, thiol, alkylthiol, arylthiol, alkylsulfon,
 haloalkylsulfon, arylsulfon, aminosulfon, N-alkylaminosulfon, N,N-dialkylaminosulfon,

arylamino-sulfon, amino, N-alkylamino, N,N-dialkylamino, amido, N-alkylamido, N,N-dialkylamido, cyano, sulfonamino, alkylsulfonamino, arylsulfonamino, amidino, N-aminosulfon-amidino, guanidino, N-cyano-guanidino, thioguanidino, 2-nitro-ethene-1,1-diamin, carboxy, alkyl-carboxy, nitro, carbamate;

5 Optionally **R2** and **R3** may join to form a ring comprising up to 7 ring atoms, or **R2** and **R4** may join to form a ring comprising up to 7 ring atoms, or **R3** and **R4** may join to form a ring comprising up to 7 ring atoms;

R5 is a monocyclic, bicyclic or tricyclic group comprising one, two or three ring structures each of up to 7 ring atoms independently selected from cycloalkyl, aryl, heterocycloalkyl or heteroaryl, with each ring structure being independently optionally substituted by one or more substituents independently selected from halogen, hydroxy, alkyl, alkoxy, haloalkoxy, amino, N-alkylamino, N,N-dialkylamino, alkylsulfonamino, alkylcarboxyamino, cyano, nitro, thiol, alkylthiol, alkylsulfonyl, haloalkylsulfonyl, alkylaminosulfonyl, carboxylate, alkylcarboxylate, aminocarboxy, N-alkylamino-carboxy, N,N-dialkylamino-carboxy, wherein any alkyl radical within any substituent may itself be optionally substituted with one or more groups selected from halogen, hydroxy, alkoxy, haloalkoxy, amino, N-alkylamino, N,N-dialkylamino, N-alkylsulfonamino, N-alkylcarboxyamino, cyano, nitro, thiol, alkylthiol, alkylsulfonyl, N-alkylaminosulfonyl, carboxylate, alkylcarboxy, aminocarboxy, N-alkylaminocarboxy, N,N-dialkylaminocarboxy, carbamate;

20 when **R5** is a bicyclic or tricyclic group, each ring structure is joined to the next ring structure by a direct bond, by -O-, by (C1-6)alkyl, by (C1-6)haloalkyl, by (C1-6)heteroalkyl, by (C1-6)alkenyl, by (C1-6)alkynyl, by sulfone, by CO, by NCO, by CON, by NH, by S, by C(OH) or is fused to the next ring structure;

25 Any heteroalkyl group outlined above is a hetero atom-substituted alkyl containing one or more hetero groups independently selected from N, O, S, SO, SO₂, (a hetero group being a hetero atom or group of atoms);

Any heterocycloalkyl or heteroaryl group outlined above contains one or more hetero groups independently selected from N, O, S, SO, SO₂;

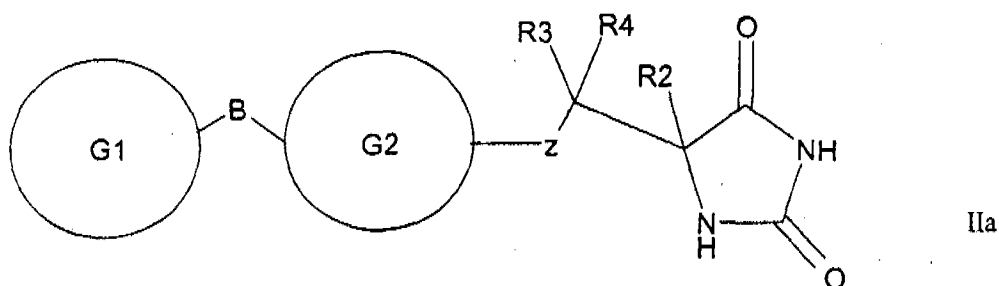
Any heteroalkyl group outlined above is a hetero atom-substituted alkyl containing one or more hetero groups independently selected from N, O, S, SO, SO₂, (a hetero group being a hetero atom or group of atoms);

Any heterocycloalkyl or heteroaryl group outlined above contains one or more hetero groups independently selected from N, O, S, SO, SO₂;

Any alkyl, alkenyl or alkynyl groups outlined above may be straight chain or branched; unless otherwise stated, any alkyl group outlined above is preferably (C1-7)alkyl and most preferably (C1-6)alkyl.

Preferred compounds of the formula II include those wherein R₂ is alkyl, aminoalkyl, alkyl-heteroaryl, alkyl-heterocycloalkyl or heteroaryl-alkyl.

The invention further provides compounds of the formula IIa



wherein

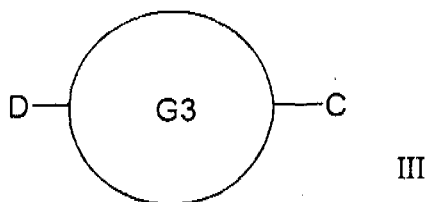
each of G1 and G2 is a monocyclic ring structure comprising each of up to 7 ring atoms independently selected from cycloalkyl, aryl, heterocycloalkyl or heteroaryl, with each ring structure being independently optionally substituted by one or two substituents independently selected from halogen, hydroxy, haloalkoxy, amino, N-alkylamino, N,N-dialkylamino, cyano, nitro, alkyl, alkoxy, alkyl sulfone, haloalkyl sulfone, alkylcarbamate, alkylamide, wherein any alkyl radical within any substituent may itself be optionally substituted with one or more groups selected from halogen, hydroxy, amino, N-

alkylamino, N,N-dialkylamino, cyano, nitro, alkoxy, haloalkoxy, aryloxy, heteroaryloxy, carbamate;

Z is SO₂;

B is selected from a direct bond, O, (C1-6)alkyl, (C1-6)heteroalkyl, CO, NCO, CON, NH, S, alkynyl;

R₂ is selected from H, (C1-6)alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, (N-alkylamino)alkyl, (N,N-dialkylamino)alkyl, amidoalkyl, thioalkyl, or R₂ is a group of formula III



C and D are independently selected from a direct bond, H, (C1-C6)alkyl, (C1-C6)haloalkyl, or (C1-C6)heteroalkyl containing one or two hetero atoms selected from N, O or S such that when two hetero atoms are present they are separated by at least two carbon atoms;

G₃ is a monocyclic ring structure comprising up to 7 ring atoms independently selected from cycloalkyl, aryl, heterocycloalkyl or heteroaryl, optionally substituted by one or two substituents independently selected from halogen, hydroxy, amino, N-alkylamino, N,N-dialkylamino, cyano, nitro, alkyl, alkoxy, alkyl sulfone, haloalkyl sulfone, or alkyl substituted with one or more groups selected from halogen, hydroxy, amino, N-alkylamino, N,N-dialkylamino, cyano, nitro, alkoxy, haloalkoxy;

Optionally R₂ is substituted with halo, haloalkyl, hydroxy, alkoxy, haloalkoxy, amino, aminoalkyl, N-alkylamino, N,N-dialkylamino, (N-alkylamino)alkyl, (N,N-dialkylamino)alkyl, alkylsulfone, aminosulfone, N-alkylamino-sulfone, N,N-dialkylamino-sulfone, amido, N-alkylamido, N,N-dialkylamido, cyano, sulfonamino, alkyl-sulfonamino, amidino, N-aminosulfone-amidino, guanidino, N-cyano-guanidino, thioguanidino, 2-nitroguanidino, carboxy, alkylcarboxy, carbamate;

R₃ and R₄ are independently selected from H or (C1-3)alkyl;

Optionally R2 and R3 may join to form a ring comprising up to 7 ring atoms, or R2 and R4 may join to form a ring comprising up to 7 ring atoms, or R3 and R4 may join to form a ring comprising up to 7 ring atoms;

Any heteroalkyl group outlined above is a hetero atom-substituted alkyl containing one or more hetero groups independently selected from N, O, S, SO, SO₂, (a hetero group being a hetero atom or group of atoms);

Any heterocycloalkyl or heteroaryl group outlined above contains one or more hetero groups independently selected from N, O, S, SO, SO₂;

Any alkyl, alkenyl or alkynyl groups outlined above may be straight chain or branched; unless otherwise stated, any alkyl group outlined above is preferably (C1-7)alkyl and most preferably (C1-6)alkyl.

Preferred compounds of the formula IIa are those wherein one or more of the following apply:

B is selected from a direct bond, O, CO, S, alkynyl; especially B is a direct bond, O, S, or alkynyl;

R2 is selected from H, (C1-6)alkyl, aryl-(C1-6)alkyl or heteroaryl-(C1-6)alkyl optionally substituted with halo, haloalkyl, hydroxy, alkoxy, haloalkoxy, amino, aminoalkyl, N-alkylamino, N,N-dialkylamino, (N-alkylamino)alkyl, (N,N-dialkylamino)alkyl, alkylsulfone, aminosulfone, N-alkylamino-sulfone, N,N-dialkylamino-sulfone, amido, N-alkylamido, N,N-dialkylamido, carbamate, cyano, sulfonamino, alkyl-sulfonamino, amidino, N-aminosulfone-amidino, guanidino, N-cyano-guanidino, thioguanidino, 2-nitroguanidino, 2-nitro-ethene-1,1-diamino, carboxy, alkylcarboxy, carbamate;

Each of R3 and R4 is H;

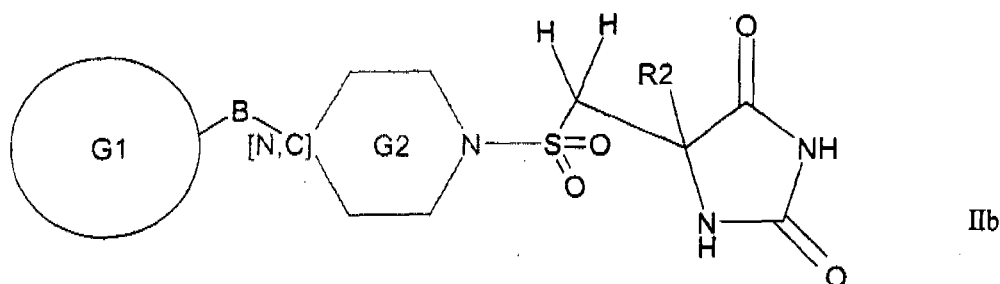
G2 is a nitrogen containing six-membered ring;

G1 is para substituted.

Particularly preferred compounds of formula IIa are those wherein each of R3 and R4 is H.

For example, particular compounds of the invention include compounds of formula IIa wherein B is a direct bond, O, S or alkynyl; and R2 is selected from H, (C1-6)alkyl, aryl-
 (C1-6)alkyl or heteroaryl-(C1-6)alkyl optionally substituted with cycloalkyl, heterocycloalkyl, halo, haloalkyl, hydroxy, alkoxy, aryloxy, haloalkoxy, amino, aminoalkyl, N-alkylamino, N,N-dialkylamino, (N-alkylamino)alkyl, (N,N-dialkylamino)alkyl, alkylsulfonyl, aminosulfonyl, N-alkylamino-sulfonyl, N,N-dialkylamino-sulfonyl, amido, N-alkylamido, N,N-dialkylamido, cyano, sulfonamino, alkyl-sulfonamino, amidino, N-aminosulfone-amidino, guanidino, N-cyano-guanidino, thioguanidino, 2-nitroguanidino, carbamate, carboxy, alkylcarboxy; and each of R3 and R4 is H.

Particularly preferred compounds of the invention are those of Formula IIb:



wherein G2 is optionally substituted piperidine or piperazine, and G1, B, and R2 are as described for Formula IIa.

In a compound of Formula IIb, preferably G2 is unsubstituted and G1 is optionally substituted, preferably G1 is para substituted. ✓

maleate salts and salts formed with phosphoric and sulphuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium or potassium, an alkaline earth metal salt for example calcium or magnesium, or organic amine salt for example triethylamine.

5 They may also be provided as *in vivo* hydrolysable esters. These are pharmaceutically acceptable esters that hydrolyse in the human body to produce the parent compound. Such esters can be identified by administering, for example intravenously to a test animal, the compound under test and subsequently examining the test animal's body fluids. Suitable *in vivo* hydrolysable esters for carboxy include methoxymethyl and for hydroxy include
10 formyl and acetyl, especially acetyl.

In order to use a metalloproteinase inhibitor compound of the invention (a compound of the formula I or II, IIa or IIb) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof for the therapeutic treatment (including prophylactic treatment) of mammals including humans, it is normally formulated in accordance with standard
15 pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the invention (a compound of the formula I or II, IIa or IIb) or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester and pharmaceutically acceptable carrier.

20 The pharmaceutical compositions of this invention may be administered in standard manner for the disease or condition that it is desired to treat, for example by oral, topical, parenteral, buccal, nasal, vaginal or rectal administration or by inhalation. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions, suspensions,
25 emulsions, creams, ointments, gels, nasal sprays, suppositories, finely divided powders or aerosols for inhalation, and for parenteral use (including intravenous, intramuscular or infusion) sterile aqueous or oily solutions or suspensions or sterile emulsions.

In addition to the compounds of the present invention the pharmaceutical composition of this invention may also contain, or be co-administered (simultaneously or sequentially)
30 with, one or more pharmacological agents of value in treating one or more diseases or conditions referred to hereinabove.

For example we provide a method of treating a metalloproteinase mediated disease or condition which comprises administering to a warm-blooded animal a therapeutically effective amount of a compound of the formula II, IIa or IIb (or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof). We also provide the use of a compound of the formula II, IIa or IIb (or a pharmaceutically acceptable salt or *in vivo* hydrolysable precursor thereof) in the preparation of a medicament for use in the treatment of a disease or condition mediated by one or more metalloproteinase enzymes.

Metalloproteinase mediated diseases or conditions include asthma, rhinitis, chronic obstructive pulmonary diseases (COPD), arthritis (such as rheumatoid arthritis and osteoarthritis), atherosclerosis and restenosis, cancer, invasion and metastasis, diseases involving tissue destruction, loosening of hip joint replacements, periodontal disease, fibrotic disease, infarction and heart disease, liver and renal fibrosis, endometriosis, diseases related to the weakening of the extracellular matrix, heart failure, aortic aneurysms, CNS related diseases such as Alzheimer's disease and Multiple Sclerosis (MS), hematological disorders.

Preparation of the compounds of the invention

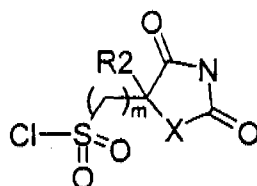
In another aspect the present invention provides a process for preparing a compound of the formula I or II, IIa, IIb or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as described in (a) to (d) below. It will be appreciated that many of the relevant starting materials are commercially or otherwise available or may be synthesised by known methods or may be found in the scientific literature.

(a) Compounds of formula I in which Y1 and Y2 are each O, Z is SO₂, R2 is as defined in formula I, A is a direct bond and R5 comprises a nitrogen directly attached to Z, or A is (C1-6) N-alkyl, may be prepared by reacting a compound of the formula IV in which R5 is defined as in formula I with the known compounds of the formula V in which X and m are as defined in formula I:

25



IV

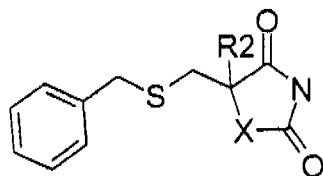


V

The reaction is preferably performed in suitable solvent optionally in the presence of base for 1 to 24h at ambient to reflux temperature. Preferably, solvents such as pyridine, dimethylformamide, tetrahydrofuran, acetonitrile or dichlorometane are used with bases like triethylamine, N-methylmorpholine, pyridine or alkali metal carbonates at ambient temperature for 2-16 h reaction time, or until end of reaction is achieved as detected by chromatographic or spectroscopic methods. Reactions of sulfonyl chlorides of formula V with various primary and secondary amines are previously described in the literature, and the variations of the conditions will be evident for those skilled in the art.

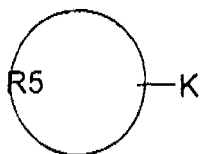
Synthesis of compounds of formula V is described in the literature and can be prepared from e.g. cystein or homocystein (Mosher, J.: J. Org. Chem. **23**, 1257 (1958)).

Sulfonylchlorides of formula V, in which m=1, X=NR₁ (R₁=H) and R₂ is as described in formula I, are conveniently prepared by oxidative chlorination of compounds of formula Va, in which R₂ is as described in formula I (Griffith, O.: J. Biol. Chem., 1983, 258, 3, 1591).

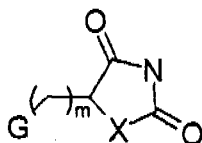


Va

(b) Compounds of formula I in which Y1 and Y2 are each O, Z is S, and X and R5 are as described in formula I may be prepared by reacting a compound of formula VI in which K is a leaving group (e.g chloride, or sulfonate ester) and R5 as described in formula I,



VI



VII

with a compound of formula VII, in which G is a sulfhydryl (SH), X and m as described in formula I. The reaction is preferably performed in the presence of base such as diethyl isopropyl amine or cesium carbonate and in the presence of a suitable solvent e.g DMF.

Alternatively, the compounds under process (b) may be prepared in the same manner as in process (b), by reacting the compounds of formula VI and VII, but in which K in compound VI is the sulfhydryl (SH) or a hydroxyl group and G in formula VII represents a leaving group.

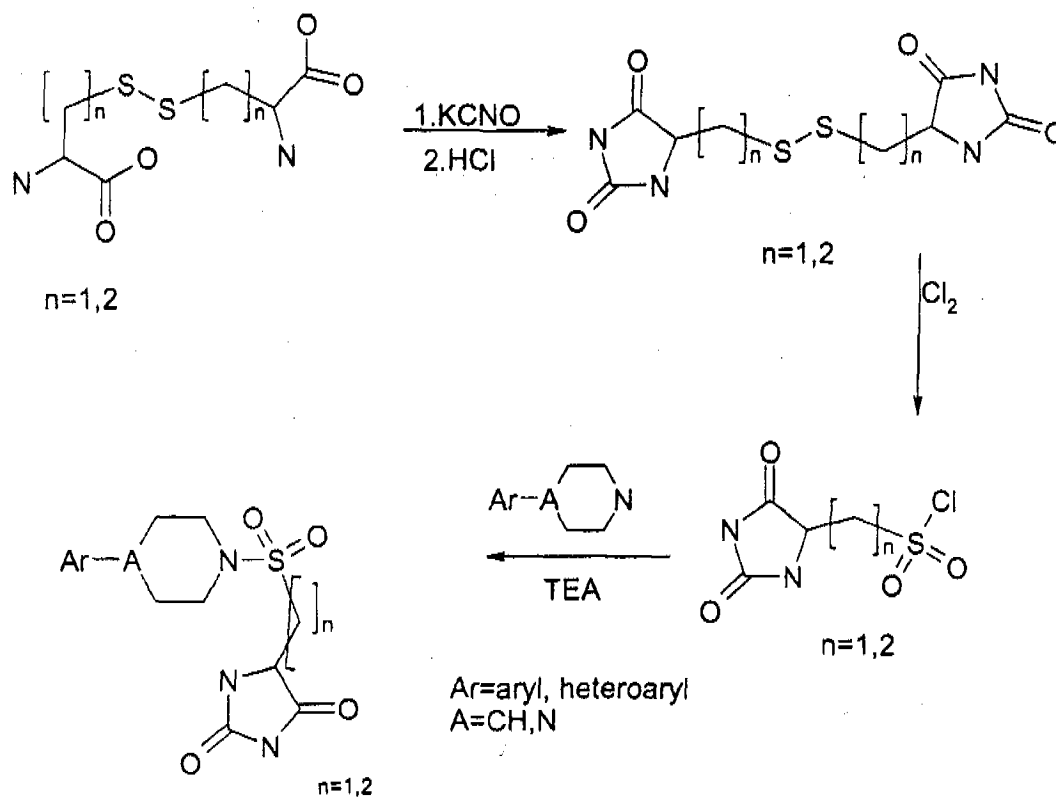
(c) Compounds of the formula I in which Y1 and Y2 are each O, Z is SO₂ or S(O), and X, A, and R5 are as described in formula I, may be prepared by oxidizing the final products described under process (b) and in which Z is S, with oxidizing agents like peroxide reagents, preferably m-chloroperbenzoic acid or oxone.

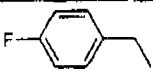
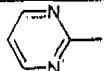
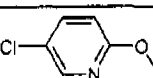
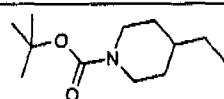
(d) Compounds of the formula I in which Y1 and Y2 are each O, X is NR₁ (R₁=H), m is 1, and R₂, R₃, R₄, R₅ are as described in formula I may be prepared by reacting a compound of formula XI in which R₂, R₃, R₄, R₅ and A are as described in formula I,

with sat. NaHCO₃ (ca 25 ml), then with 10% sodium thiosulfate, dried, evaporated, crystallised from THF-hexane (Lora-Tamayo, M. *et al*, 1968, An. Quim., 64(6):591-606);
¹H NMR : δ 2.55m (1.1H), 2.65m (1.8H), 2.70m (1H), 4.55m (1H).

- 5 **5-(2-([2-(2,5-dioxo-4-imidazolidinyl)ethyl]disulfanyl)ethyl)-2,4-imidazolidinedione**
 Commercially available RS homocysteine (0.18 mol) was suspended in 25 ml water and of potassium cyanate 1.5 g (0.2 mol) was added and the mixture was stirred at 100°C for 45 min. Then it was allowed to cool partially and 10 ml of 10% HCl were added at once and the mixture was stirred at 100°C again for 50 min. It was placed in the fridge
 10 overnight, crystals were filtered and washed successively with water and dried in vacuo.
 LC-MS (APCI) m/z 319.1 (MH⁺).

The overall generalised reaction scheme is shown below:



R	E	R2	Analysis
	N	Me	m/z 315 (MH ⁺) ⁽¹⁾
	N	Me	m/z 285 (MH ⁺) ⁽¹⁾
	CH		m/z 517 (MH ⁺) ⁽¹⁾

⁽¹⁾: crude products, no NMR available, mtrl. used directly in next synthetic step.

1-[4-(4-Fluoro-phenyl)-piperidine-1-sulfonyl]-propan-2-one.

4-(4-Fluoro-phenyl)-1-methanesulfonyl-piperidine (100mg; 0.39mmol) was dissolved in dry THF (3mL) under a protective nitrogen atmosphere. Lithium bis(trimethylsilyl)amide
 5 as a 1.0 M solution in THF (1.0mL; 1.0mmol) was added in one portion at room temperature, the resulting yellow solution was stirred for 45 min. Methylacetate (50mg; 0.68mmol) dissolved in dry THF (0.5mL) was added, the mixture was stirred at room temperature for 40 min. The reaction was quenched by adding NH₄Cl (sat.) (2mL). The
 10 mixture was evaporated and the resulting solid was dissolved in a mixture of DCM and H₂O. The organic phase was separated and washed with brine, dried (MgSO₄), filtrated and evaporated. The crude product was purified on 20g of Si-60 gel using a gradient of 100%Heptane to 50%EtOAc, a flow of 20mL/min was used and UV=254nm was used for detection. The fractions containing the product was evaporated and this gave the title
 15 compound as a colourless solid.

Obtained 70mg (59% yield).

TLC(Si-60; EtOAc:Heptane (2:1)): R_f=0.65

LC-MS (APCI) m/z 300.1 (MH⁺).

¹H-NMR(CDCl₃): δ 7.17 (m, 2H), 7.01 (m, 2H), 4.02 (s, 2H), 3.93 (m, 2H), 2.94 (dt, 2H),
 20 2.63 (m, 1H), 2.46 (s, 3H), 1.91 (m, 2H), 1.77 (m, 2H).

5-[(1,1'-biphenyl-4-ylsulfonyl)methyl]-5-methylimidazolidine-2,4-dioneLC-MS(APCI) m/z 345 (MH⁺).¹H NMR (DMSO-d₆): δ 1.27 (3H, s); 3.72, 3.81 (2H, abq, J=15.3 Hz); 7.45 (1H, t); 7.52 (2H, t); 7.76 (2H, d); 7.82 (1H, s); 7.88, 7.94 (4H, abq, J=8.9 Hz); 10.80 (1H, bs).

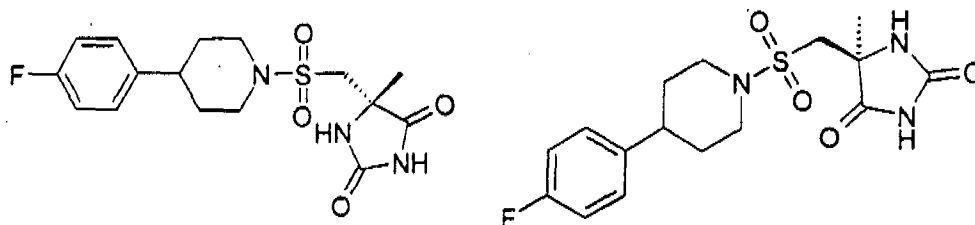
5

4'-{[(4-methyl-2,5-dioxoimidazolidin-4-yl)methyl]sulfonyl}-1,1'-biphenyl-4-carbonitrileLC-MS(APCI) m/z very weak 370 (MH⁺).¹H NMR (DMSO-d₆): δ 1.26 (3H, s); 3.74, 3.84 (2H, abq, J=16.0 Hz); 7.81 (1H, s); 7.91-8.03 (8H, m); 10.81 (1H, s).

10

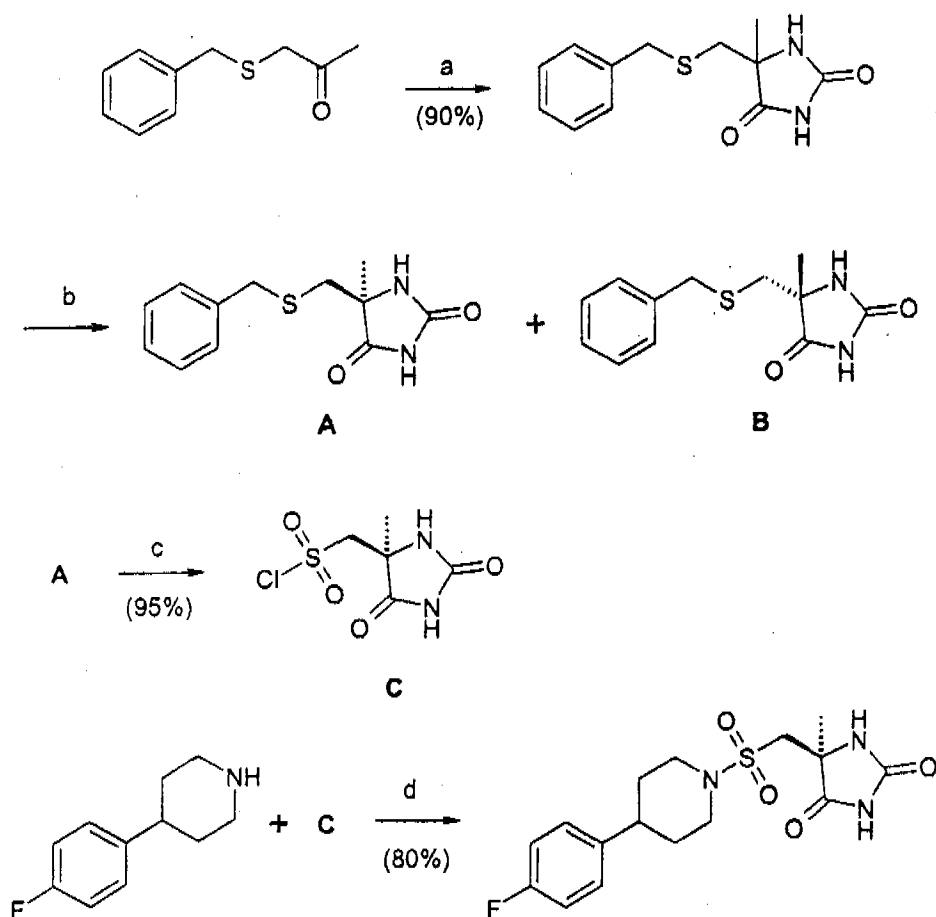
EXAMPLE 12**Synthesis of enantiomeric pure hydantoins**

15

Representative synthetic route is shown overleaf.

20

87



Reagents and conditions: a) KCN, NH_4CO_3 , EtOH/ H_2O , $+90^\circ\text{C}$, 3h. b) Chiral separation, CHIRALPAK AD, Methanol as eluent. c) Cl_2 (g), AcOH/ H_2O , $<+15^\circ\text{C}$, 25min. d) Diisopropylethylamine, THF, -20°C , 30 min.

5

Experimental procedures

(5S)-5-({[4-(4-fluorophenyl)piperidin-1-yl]sulfonyl}methyl)-5-methylimidazolidine-2,4-dione

4-(4-Fluorophenyl)piperidine hydrochloride (63 mg, 0.29 mmol) was taken up in 3 mL of dry THF, neutralized with diisopropylethylamine (50 μL , 0.29 mmol) and cooled on an ice-water bath. [(4S)-4-methyl-2,5-dioxo-imidazolidin-4-yl]methanesulfonyl chloride (80 mg, 0.35 mmol) was added and after stirring for 10 min, diisopropylethylamine (50 μL , 0.29 mmol) was added and the reaction mixture was stirred at ambient temperature until LC-MS (APCI) indicated consumption of the amine. The reaction mixture was evaporated

[(4R)-4-methyl-2,5-dioxoimidazolidin-4-yl]methanesulfonyl chloride

Following the procedure described for [(4S)-4-methyl-2,5-dioxoimidazolidin-4-yl]methanesulfonyl chloride.

Starting from (5R)-5-methyl-5-[[[(phenylmethyl)thio]methyl]imidazolidine-2,4-dione

(10.0g, 40mmol).

Obtained 8.78g (96% yield) of the title compound.

Purity by NMR > 98%.

$[\alpha]_D^{20} = +12.8^\circ$ (c=0.01g/mL, THF, T=20°C).

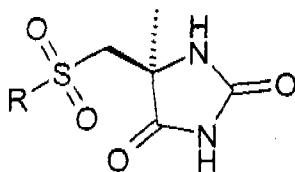
^1H NMR (THF- d_8): δ 9.91 (1H, brs); 7.57 (1H, s); 4.53, 4.44 (1H each, ABq, $J=14.6\text{Hz}$);

1.52 (s, 3H, CH_3).

^{13}C NMR (THF- d_8): δ 174.96; 155.84; 70.97; 61.04; 23.66.

EXAMPLE 13

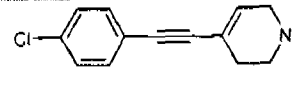
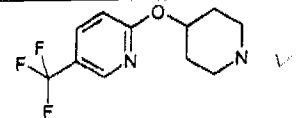
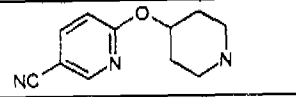
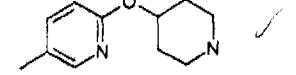
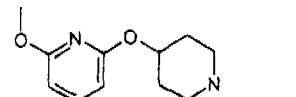
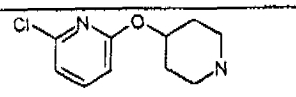
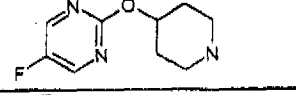
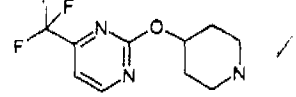
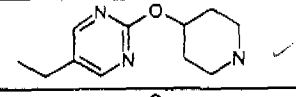
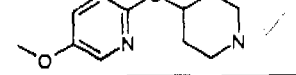
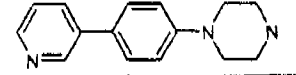
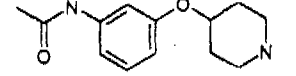
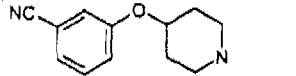
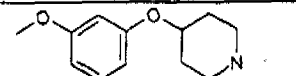
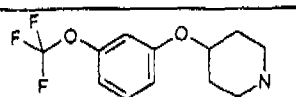
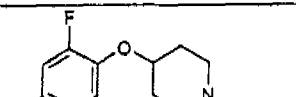
Compounds with the general formula

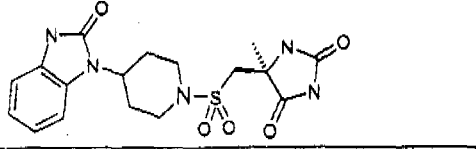
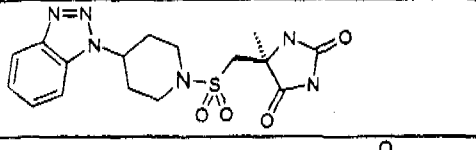
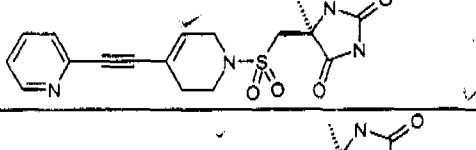
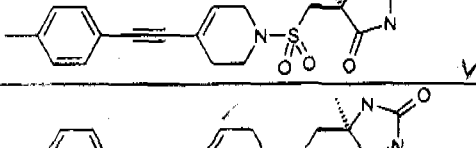
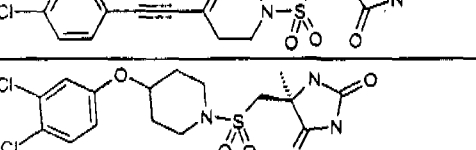
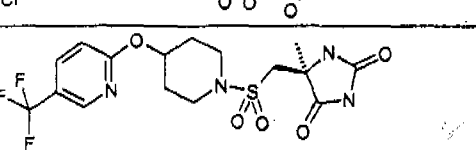
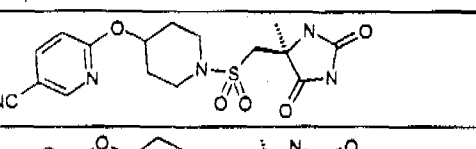
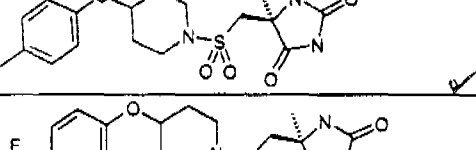
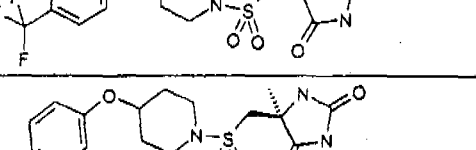
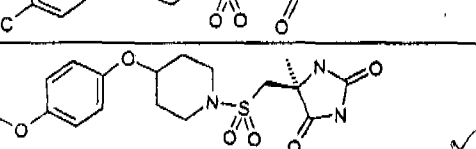
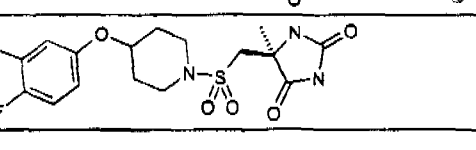


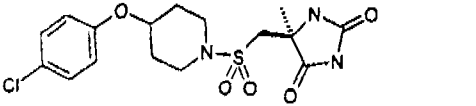
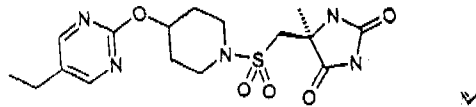
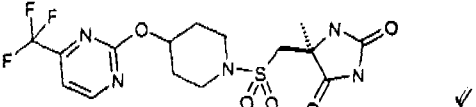
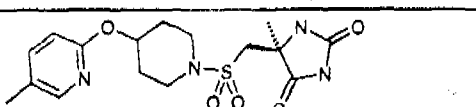
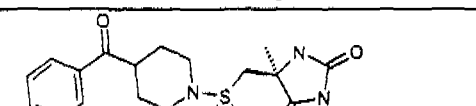
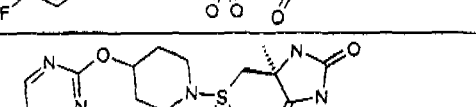
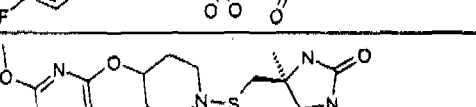
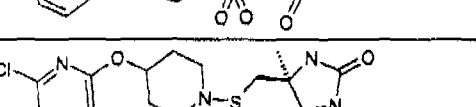
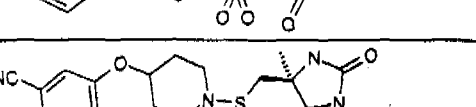
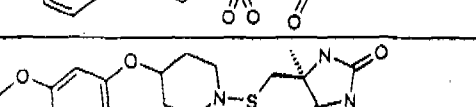
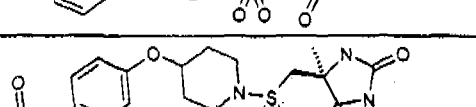
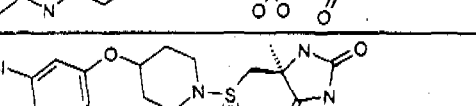
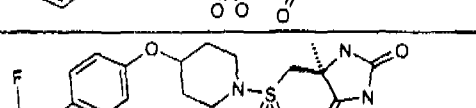
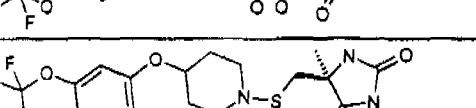
were synthesised according to the method described in Example 12.

AMINE INTERMEDIATES

Amine	Analysis
	m/z 246 (MH+); ^1H NMR data
	m/z 185 (MH+); ^1H NMR data
	m/z 198 (MH+); ^1H NMR data

	m/z 218/220 3:1 (MH+); ¹ H NMR data
	m/z 247 (MH+); ¹ H NMR data
	m/z 204 (MH+); ¹ H NMR data
	¹ H NMR data
	¹ H NMR data
	¹ H NMR data
	¹ H NMR data
	¹ H NMR data
	¹ H NMR data
	m/z 225 (MH+)
	m/z 240 (MH+)
	m/z 235 (MH+)
	m/z 203 (MH+)
	m/z 208 (MH+)
	m/z 262 (MH+)
	m/z 214 (MH+)

	m/z 408 (MH+)
	m/z 393 (MH+)
	m/z 375 (MH+)
	m/z 388 (MH+)
	m/z 408 (MH+)
	m/z 436 (MH+)
	m/z 437 (MH+)
	m/z 394 (MH+)
	m/z 382 (MH+)
	m/z 436 (MH+)
	m/z 393 (MH+)
	m/z 398 (MH+)
	m/z 404 (MH+)

	m/z 402 (MH+)
	m/z 398 (MH+) ✓
	m/z 438 (MH+) ✓
	m/z 383 (MH+)
	m/z 398 (MH+)
	m/z 388 (MH+)
	m/z 399 (MH+)
	m/z 403 (MH+)
	m/z 393 (MH+)
	m/z 398 (MH+)
	m/z 425 (MH+)
	m/z 402 (MH+)
	m/z 452 (MH+)
	m/z 452 (MH+)

84 94

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCION DE NUEVAS CREACIONES

2020
Bogotá, D.C.

Abogado
ALICIA LLOREDA RICAURTE

ASUNTO	Radicación	06-129228
	Trámite	011
	Evento	378
	Actuación	411
	Oficio	
	Folios	025

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap. I	☒
		Cap. II	☐
No. Sol. Internacional	<u>PCT/SE2005/001092</u>		
Fecha de Presentación Internal.	<u>04-07-2005</u>		

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

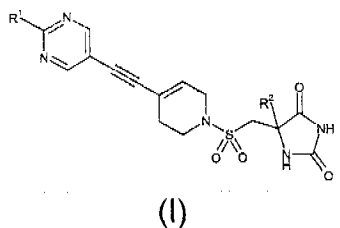
<u>Descripción:</u>	Folios <u>27-61</u> como se radicó inicialmente
<u>Reivindicaciones:</u>	Folios <u>62-66</u> como se radicó inicialmente
<u>Prioridad:</u>	Folio <u>1</u> SE, 0401762-0, 05-07-2004

2. Objeto de la invención

Título de la solicitud: COMPUESTOS NOVEDOSOS DERIVADOS DE HIDANTOINA PARA EL TRATAMIENTO DE ENFERMEDADES OBSTRUCTIVAS DE LAS VIAS AÉREAS (folio 1)

El problema técnico planteado en la solicitud está relacionado con la necesidad de obtener nuevos compuestos derivados de hidantoína como inhibidores de MMP (enzimas metaloproteinasas), útiles en condiciones respiratorias como asma, epoc, rinitis, entre otras (folio 28, 32 y 36; pág. 2, 6 y 10).

Para solucionar este problema técnico la solicitud en estudio proporciona en: Reivindicaciones 1-8 y 12: un compuesto de fórmula (I) ó una sal farmacéuticamente aceptable del mismo.



Reivindicación 9: un proceso para la preparación de un compuesto de formula (I).

Reivindicación 10: una composición farmacéutica que comprende un compuesto de formula (I) en asociación con un adyuvante, diluyente o portador farmacéuticamente aceptables.

Reivindicación 11: un proceso para preparar la composición farmacéutica de la reivindicación 10.

Reivindicaciones 13-14: relacionadas con el uso de un compuesto.

Reivindicaciones 15-16: relacionada con un método de tratamiento.

Clasificación Internacional de Patentes (IPC): C07D401/14, A61K31/506, A61P11/00.

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D 486)

La reivindicación 12 caracteriza inadecuadamente un compuesto por su uso en terapia, ya que un compuesto debe caracterizarse por su formula o estructura química.

4. Excepción a la patentabilidad (artículo 20 D486 literal d)

Las reivindicaciones 15-16, relacionadas con un método de tratamiento, están exceptuadas de patentabilidad de acuerdo con el artículo anterior; por lo que es necesario eliminarlas del alcance de la solicitud.

5. Reivindicaciones relativas a un uso o a un segundo uso (artículos 14 y 21 D 486)

De acuerdo con los artículos anteriores, las reivindicaciones 13-14 relacionadas con el uso de compuestos, no se consideran objeto de protección porque el uso no es un producto o un procedimiento tecnológico. Por lo que es necesario eliminarlas del alcance de la invención.

6. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la que se reivindica prioridad es 05-07-2004, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a ésta.

N°	Documento	Título	Fecha de Publicación
D1	WO02074767	Metalloproteinase inhibitors	26-09-2002

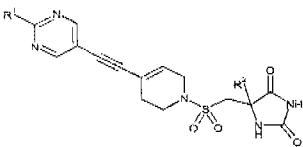
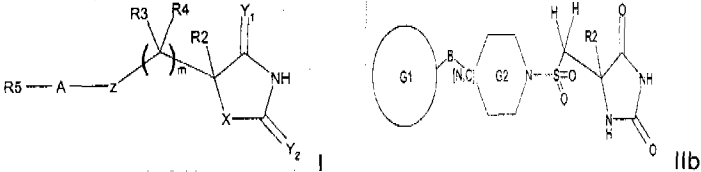
Anterioridad D1 en folios 74-93.

7. Análisis de patentabilidad (artículo 14 D486)

7.1. Novedad (artículo 16 D486)

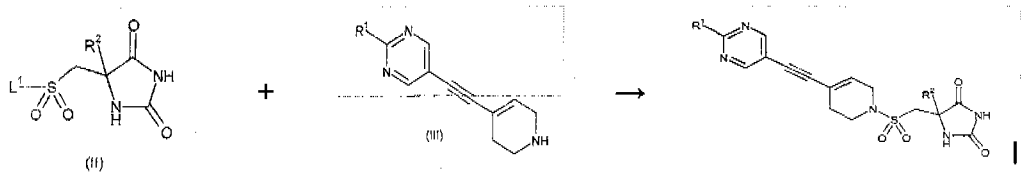
- Se solicita en las 1-8 y 12: un compuesto de fórmula (I) ó una sal farmacéuticamente aceptable del mismo y en la 10 una composición farmacéutica que lo contiene en asociación con un adyuvante, diluyente o portador farmacéuticamente aceptables.

Al comparar elemento por elemento el objeto de la presente solicitud con el estado de la técnica más cercano, se encuentra que:

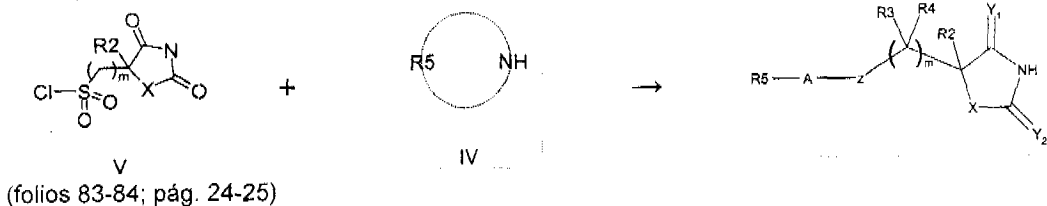
SOLICITUD	D1
Un compuesto de fórmula (I)  con radicales R¹ y R² según capítulo reivindicatorio.	Un compuesto de formula I, que incluye especialmente uno de formula IIb, donde:  G2: piperidina G1: heteroarilo (como pirimidinilo) opcionalmente sustituido por alquilo, alcoxi, haloalcoxi ó alquiltio B: alquinilo R2: alquiloC₁₋₆ (folios 75-76, 77-81; pág. 11-12, 15-19)

D1 enseña un compuesto de formula (I) y especialmente uno de formula IIb que ya encierra el compuesto de formula (I) solicitado, tal como se muestra en el cuadro comparativo. Por consiguiente, la materia solicitada (un compuesto de formula (I) y composiciones farmacéuticas que lo contienen) no cumple el requisito de novedad.

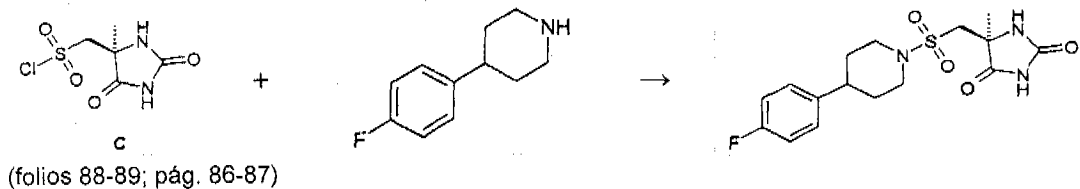
- Se solicita en la reivindicación 9 un proceso para preparar un compuesto de formula (I) que comprende:



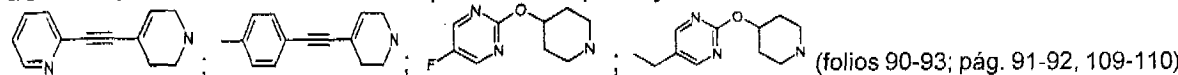
Al comparar el objeto de la presente solicitud con el estado de la técnica más cercano, se encuentra que D1 ya divulga el proceso solicitado al señalar un proceso de preparación de un compuesto de formula I o IIb que comprende:



Ejemplificando dicho proceso así:



Y señalando que de igual forma se obtienen otros compuestos de formula I ó IIb, donde le intermediario amino puede ser por ej:



Lo que significa que el proceso solicitado no es nuevo acorde con la divulgación del proceso señalado en D1.

➤ Se solicita en la reivindicación 11 un proceso para preparar una composición farmacéutica que comprende mezclar un compuesto de formula (I) o una sal farmacéuticamente aceptable del mismo con un adyuvante, diluyente o portador farmacéuticamente aceptable.

No obstante, D1 (folio 82; pág. 22) señala que composiciones farmacéuticas que comprenden un compuesto de formula I ó una sal farmacéuticamente aceptable y un vehículo farmacéuticamente aceptable, se formulan y realizan normalmente de acuerdo a la práctica farmacéutica estándar (*es decir tienen que haber una mezcla del activo con los excipientes*); por lo que el proceso solicitado no es nuevo.

8. Conclusión

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así

N°	Documento N°	Reivindicaciones Afectadas	Requisito que Afecta
D1	WO02074767	1-12	Novedad

98 98

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el artículo 8 de la resolución reglamentaria No. 00210 del 15 de enero de 2001, advirtiéndole que contra él no procede recurso alguno en la vía gubernativa.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha

CONCEPTO TECNICO No. 274	EXAMINADOR TECNICO Código No. 202079
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