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DELEGATURA DE PROPIEDAD INDUSTRIAL  
DIVISIÓN DE NUEVAS CREACIONES

08-105789

SOLICITUD DE PATENTE DE  
INVENCION

TITULO: PROCEDIMIENTO PARA PREPARAR DERIVADOS  
HETEROCICLICOS

SOLICITANTE: GLAXO GROUP LIMITED

DIRECCIÓN: Glaxo Wellcome House, Berkeley Avenue, Greenford,  
Middlesex UB6 ONN Inglaterra

APODERADO: CARLOS R. OLARTE

BOGOTÁ 01 de Octubre de 2008

# OLARTERAISBECK



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-105789- -00000-0000

Fecha: 2008-10-03 16:54:47 Dep. 2020 NUECREACION  
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI  
Act. 411 PRESENTACION Folios: 48

## PETITORIO - FORMULARIO ÚNICO DE SOLICITUD PATENTE PCT

ENTRADA EN FASE NACIONAL 3 Nov 2008 P2008/000166

### SOLICITUD DE:

1

☒

Patente de Invención.

☐

Patente de Modelo de Utilidad.

☒

Capítulo I.

☐

Capítulo II.

2

**SOLICITANTE  
(71)**

**Nombre:** GLAXO GROUP LIMITED

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**Nacionalidad o Domicilio:** Estadounidense

**Lugar de Constitución:** Estados Unidos de America.

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C.E. ☐ Otro ☐

Cual \_\_\_\_\_

Número \_\_\_\_\_

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### IDENTIFICACIÓN

C.C. ☒ NIT ☐

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Número 79.782.747Bta  
TP 74.295

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5

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Marzo 30, 2007

Publicación Internacional No. WO 2007/113261

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Octubre 11, 2007

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**Título (54) PROCEDIMIENTO PARA PREPARAR DERIVADOS HETEROCICLICOS**

**Clasificación Internacional (51)** C07D 401/04, C07D 403/04, C07D 413/04, C07D 417/04

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0607899.2

9

Comprobante de pago No. 08-76,069

Fecha Septiembre 24, 2008

10

**ANEXOS**

☒

Comprobante de pago de la tasa de presentación de la solicitud.

☒

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

☒

Poderes, si fuere el caso. Adjunto copia simple Ver Expediente No. 06-002.051

☐

Documento de cesión del inventor al solicitante o a su causante.

☐

Declaraciones.

☒

Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).

☒

Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).

☐

Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).

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Traducción del examen preliminar internacional efectuado por la IPEA.

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De ser el caso, copia del contrato de acceso.

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De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.

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De ser el caso, certificado de depósito del material biológico.

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Arte final 12 x 12.

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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.

☐

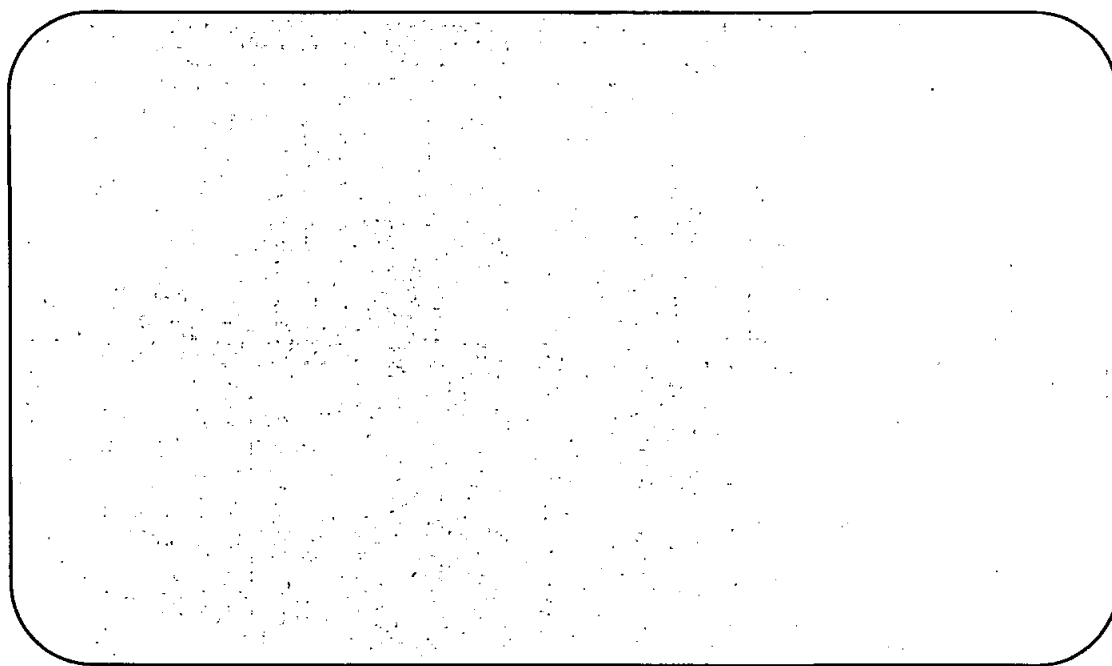
De ser el caso, modificaciones efectuadas a la solicitud internacional.

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Otros. Búsqueda Internacional

11

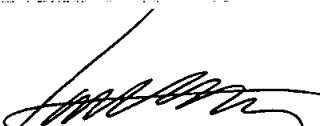
**FIGURA CARACTERÍSTICA:**



12

Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

FIRMA: 

C.C. 79.782.747 Btá T.P. 74.295

3

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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FECHA : SEPTIEMBRE 24 DE 2008

\*\*\*\*\* CONSIGNACION \*\*\*\*\*

| DEPOSITANTE    | TIPO PAGO    | BANCO           | CUENTA    | No. PAGO | FECHA PGO  | Vr. PAGO     |
|----------------|--------------|-----------------|-----------|----------|------------|--------------|
| OLARTE RAISBEK | CONSIGNACION | BANCO DE BOGOTA | 062754387 | 81234145 | 24/09/2008 | 6,692,000.00 |

\*\*\*\*\* CONCEPTO \*\*\*\*\*

| CANT. | RENTISTICO              | CONCEPTO                            | TOTAL CONCEPTO |
|-------|-------------------------|-------------------------------------|----------------|
| 1     | 50005-01-01 SOLICITUDES | 1 TRAMITES DE SOL. DE PATENTE DE IN | 501,000.00     |
|       |                         | TOTAL :                             | \$ 501,000.00  |

SON: QUINIENTOS UN MIL PESOS

RESPONSABLE : \_\_\_\_\_

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. \_\_\_\_\_

APOSTILLA EN PODER DE REPRESENTACIÓN DE

GLAXO GROUP LIMITED

PODER DE REPRESENTACION

Bilingüe inglés- español otorgado en Brentford, Middlesex, Inglaterra el 13 de agosto de 2003 y firmado por Peter John Giddings, Apoderado y Funcionario autorizado.

Certificado de Notario De Pinna en español firmado por James Kerr Milligan

APOSTILLA

(Convención de la Haya del 5 de octubre de 1961)

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte  
- Este documento Público
2. ha sido firmado por James Kerr Milligan
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5. En Londres
6. El 14 agosto 2003
7. Por el Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la Mancomunidad
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9. Gran Sello de la Oficina de Asuntos exteriores y de la Mancomunidad
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Si el documento se usa en un país que no pertenece a la Convención de la Haya del 5 de octubre de 1961 debe pasar por la sección consular de la Misión que representa el país.

Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 21 agosto-03.

Marlen Neira C

*Marlen Neira C*

MARLEN NEIRA CASTRO

Traductor e Intérprete Oficial

Inglés - Español - Inglés

Resolución No. 2117 del 7 O

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## Power of Attorney

The undersigned,

domiciled in

Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN, GB  
by means of these presents hereby grants to **Carlos R. Olarte, J. Ian Raisbeck and Ana María Frieri** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's Patents, Utility Models and Industrial Designs in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, appeals, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

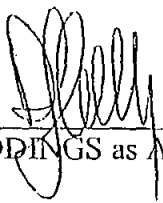
## Poder

El suscrito,

domiciliado en

por medio del presente otorga a **Carlos R. Olarte, J. Ian Raisbeck y Ana María Frieri** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de Patentes, Modelos de Utilidad y Diseños Industriales de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, apelaciones, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma:

  
Peter John GIDDINGS as Attorney and Authorised Official

Date/Fecha: 13 August 2003

City/Country/Ciudad,País: Brentford, Middlesex, England

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(72) Inventor; and

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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, BH, 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, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, 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.

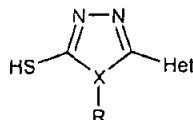
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SI, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, 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).

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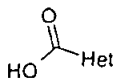
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR PREPARING HETEROCYCLIC DERIVATIVES



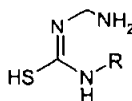
(I)

Scheme 1



(IIA)

step a



(II)

(57) Abstract: The present invention relates to a novel process, useful for preparing key intermediates of formula (I) in the synthesis of various compounds, among them compounds which are potent and specific antagonists of D3 receptors, Formula (I) in which X may be Nitrogen or Sulfur; Het means aryl or heteroaryl; each of which may be substituted by 1 to 4 groups J selected from: halogen, C1 -C6 alkyl, C1 -C6 alkoxy, halo C1 -C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, halo C1 -C6 alkoxy, -C(O)R1, nitro, hydroxy, -NR2R3, cyano or a group Z; R1 is a C1 -C4 alkyl, -OR3 Or -NR3R4; R2 is hydrogen or C1 -C6 alkyl; R3 is hydrogen or C1 -C6 alkyl; R is H, C1 -C6 alkyl, aryl, benzyl; each of which may be substituted by 1 to 4 groups J; according to the following Scheme 1: Scheme 1, in which step a means a reaction in basic conditions of compounds (NA) with 3- thiosemicarbazide derivatives, followed by a treatment with an inorganic base and n-propane phosphonic cyclic anhydride and final pH adjustment with inorganic acids to give compounds of formula (II).

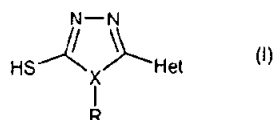
WO 2007/113261 A1

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## Process for preparing heterocyclic derivatives

The present invention relates to a novel process, useful for preparing key intermediates in the synthesis of various compounds, among them compounds which are potent and specific antagonists of D3 receptors.

The present invention relates to a novel process for preparing thiazole or triazole derivatives of formula (I)



in which

X may be Nitrogen or Sulfur;

Het means aryl or heteroaryl; each of which may be substituted by 1 to 4 groups J selected from:

halogen, C1-C6 alkyl, C1-C6 alkoxy, halo C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, halo C1-C6 alkoxy, -C(O)R<sub>1</sub>, nitro, hydroxy, -NR<sub>2</sub>R<sub>3</sub>, cyano or a group Z;

R<sub>1</sub> is a C1-C4 alkyl, -OR<sub>2</sub> or -NR<sub>3</sub>R<sub>4</sub>;

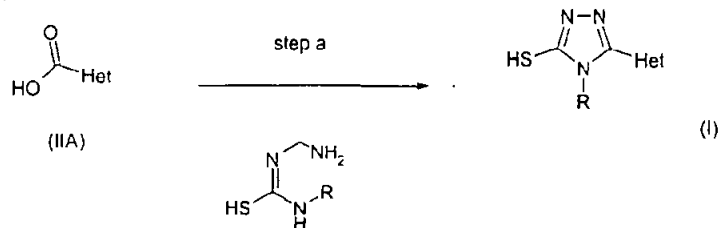
R<sub>2</sub> is hydrogen or C1-C6 alkyl;

R<sub>3</sub> is hydrogen or C1-C6 alkyl;

R is H, C1-C6 alkyl, aryl, benzyl; each of which may be substituted by 1 to 4 groups J;

according to the following Scheme 1:

Scheme 1



in which

step a means a reaction in basic conditions of compounds (IIA) with 3-thiosemicarbazide derivatives, followed by a treatment with an inorganic base and n-propane phosphonic cyclic anhydride and final pH adjustment with inorganic acids to give compounds of formula (II).

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The term C1-C6 alkyl as used herein as a group or a part of the group refers to a linear or branched alkyl group containing from 1 to 6 carbon atoms; examples of such groups include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert butyl, pentyl or hexyl.

- 5 The term halogen refers to a fluorine, chlorine, bromine or iodine atom.

The term halo C1-C6 alkyl, means an alkyl group having one or more carbon atoms and wherein at least one hydrogen atom is replaced with halogen such as for example a trifluoromethyl group and the like.

10

The term C1-C6 thioalkyl may be a linear or a branched chain thioalkyl group, for example thiomethyl, thioethyl, thiopropyl, thioisopropyl, thiobutyl, thiosec-butyl, thiotert-butyl and the like.

- 15 The term C2-C6 alkenyl defines straight or branched chain hydrocarbon radicals containing one or more double bond and having from 2 to 6 carbon atoms such as, for example, ethenyl, 2-propenyl, 3-butenyl, 2-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl or 3-hexenyl and the like.

- 20 The term C1-C6 alkoxy group may be a linear or a branched chain alkoxy group, for example methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy or methylprop-2-oxy and the like.

- 25 The term halo C1-C6 alkoxy group may be a C1-C6 alkoxy group as defined before substituted with at least one halogen, preferably fluorine, such as  $\text{OCHF}_2$ , or  $\text{OCF}_3$ .

The term C2-C6 alkynyl defines straight or branched chain hydrocarbon radicals containing one or more triple bond and having from 2 to 6 carbon atoms including acetylenyl, propynyl, 1-butyne, 1-pentyne, 3-methyl-1-butyne and the like.

30

The term aryl means an aromatic carbocyclic moiety such as phenyl, biphenyl or naphthyl.

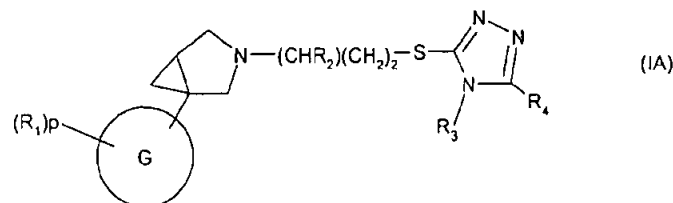
- 35 The term heteroaryl means an aromatic heterocycle ring of 5 to 10 members and having at least one heteroatom selected from nitrogen, oxygen and sulfur, and containing at least 1 carbon atom, including both mono- and bicyclic ring systems.

- 40 Representative heteroaryls include (but are not limited to) furyl, benzofuranyl, thiophenyl, benzothiophenyl, pyrrolyl, indolyl, isoindolyl, azaindolyl, pyridyl, quinolyl, isoquinolyl, oxazolyl, isooxazolyl, benzoxazolyl, pyrazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, cinnolyl, phthalazinyl, triazolyl, tetrazolyl, quinazolinyl, and benzodioxolyl.

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The term 5-6 membered heterocycle means, according to the above definition, a 5-6 monocyclic heterocyclic ring which is either saturated, unsaturated or aromatic, and which contains from 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen heteroatom may be optionally quaternized. Heterocycles include heteroaryls as defined above. The heterocycle may be attached via any heteroatom or carbon atom. Thus, the term includes (but is not limited to) morpholinyl, pyridinyl, pyrazinyl, pyrazolyl, thiazolyl, triazolyl, imidazolyl, oxadiazolyl, oxazolyl, isoxazolyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

Compounds of formula (I) can be useful, but are not limited to, for the preparation of D3 antagonists of formula (IA), as disclosed in WO2005/080382:



wherein

- G is selected from a group consisting of: phenyl, pyridyl, benzothiazolyl, indazolyl;
- p is an integer ranging from 0 to 5;
- $R_1$  is independently selected from a group consisting of: halogen, hydroxy, cyano,  $C_{1-4}$ alkyl, halo $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, halo $C_{1-4}$ alkoxy,  $C_{1-4}$ alkanoyl; or corresponds to a group  $R_5$ ;
- $R_2$  is hydrogen or  $C_{1-4}$ alkyl;
- $R_3$  is  $C_{1-4}$ alkyl;
- $R_4$  is hydrogen, or a phenyl group, a heterocyclyl group, a 5- or 6-membered heteroaromatic group, or a 8- to 11-membered bicyclic group, any of which groups is optionally substituted by 1, 2, 3 or 4 substituents selected from the group consisting of: halogen, cyano,  $C_{1-4}$ alkyl, halo $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy,  $C_{1-4}$ alkanoyl;
- $R_5$  is a moiety selected from the group consisting of: isoxazolyl,  $-CH_2-N$ -pyrrolyl, 1,1-dioxido-2-isothiazolidinyl, thienyl, thiazolyl, pyridyl, 2-pyrrolidinonyl, and such a group is optionally substituted by one or two substituents selected from: halogen, cyano,  $C_{1-4}$ alkyl, halo $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy,  $C_{1-4}$ alkanoyl;

and when  $R_1$  is chlorine and p is 1, such  $R_1$  is not present in the ortho position with respect to the linking bond to the rest of the molecule; and when  $R_1$  corresponds to  $R_5$ , p

is 1.

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Compounds of formula (I), as intermediates for the preparation of other compounds, may be conveniently functionalised, as disclosed in WO2005/080382. An example is reported in the present Experimental Section.

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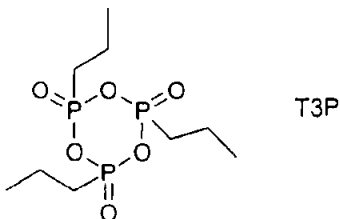
The preparation of compounds of formula (I) described in WO2005/080382 employed 1-hydroxybenzotriazole (HOBt) together with 1,3-dicyclohexylcarbodiimide (DCC).

The disadvantages of this reagents at an industrial level may be summarised as follows:

10

HOBt and its by-products have an explosive nature and DCC and its by-product are always difficult to fully remove.

The process solves the above problems by using n-propane phosphonic cyclic anhydride, T3P, as condensation agent.

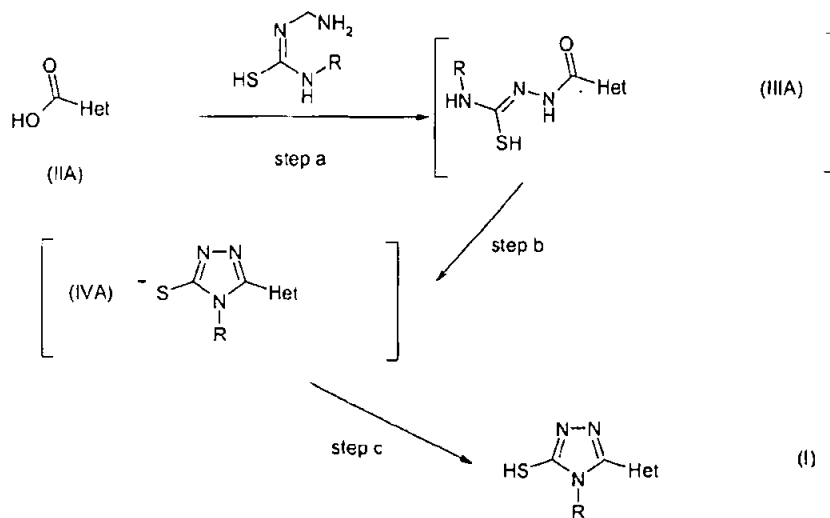


15 The T3P was first used in the peptide synthesis in 1980 by H. Wissmann (Angew. Chem., 1980, 92, 129) and is steadily gaining importance in organic synthesis because is less toxic and safer compared to other common condensation agents, such as DCC.

The reagent does not afford any water insoluble by-product. T3P is used as 50% solution in ethyl acetate in the process of the present invention and does not need the isolation of the intermediate hydrazine-carbothiamide. Similarly, T3P is available as 50% solution in  
20 DMF (dimethylformamide) and may be employed in the process of the present invention.

The process of the present invention can be depicted in more details as follows:

PB61926



The starting material, the heterocyclic carboxylic acid, generally commercially available or which may be prepared according to known methods in the literature, in an amount of 1 equivalent may be conveniently dissolved in the appropriate solvent (for example dimethylformamide; ethyl acetate; acetonitrile and tetrahydrofuran and other polar aprotic solvent) and treated with a slightly excess of derivatives of 3-thiosemicarbazide (1.10eq.), such as 4-methyl derivative. Then an organic base (e.g. triethylamine, diisopropylethylamine and possibly other aliphatic or aromatic amines) is added at RT.

N-propane phosphonic cyclic anhydride (50% w/w in ethyl acetate) may be then added at a temperature ranging from 0 to 40 degrees dropwise. In case the addition is made at about 0°C, the temperature is then maintained below 15°C over 20-60 minutes. The resulting mixture was then stirred at 20°C for 2-16 hours.

The mixture is then diluted with an aqueous solution of an appropriate inorganic base until basic pH was reached. The suitable base may be selected among: potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide.

The resulting bi-phasic mixture (when observed) is then allowed separating and the upper organic layer discarded. The aqueous layer is then heated to 50-90°C (internal temperature) for half an hour to several hours until reaction completion.

After cooling down to 20°C, an appropriate mineral acid, (e.g HCl 37%) is then slowly added to adjust the pH as needed. (4 to 8).

The suspension is then generally stirred for 2-16 hours, then the solid was filtered, washed with pure water and dried in a vacuum oven at 40-60°C until dryness. The final product is isolated from the aqueous mixture uncontaminated by phosphorous derivatives.

#### EXAMPLES

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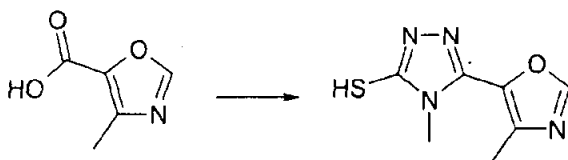
In the Examples unless otherwise stated:

All temperatures refers to °C. Infrared spectra were measured on a FT-IR instrument.

- 5 Compounds were analysed by direct infusion of the sample dissolved in acetonitrile into a mass spectra operated in positive electro spray (ES<sup>+</sup>) ionisation mode. Proton Magnetic Resonance (<sup>1</sup>H-NMR) spectra were recorded at 400 MHz, chemical shifts are reported in ppm downfield (d) from Me<sub>4</sub>Si, used as internal standard, and are assigned as singlets (s), broad singlets (bs), doublets (d), doublets of doublets (dd), triplets (t), quartets (q) or
- 10 multiplets (m). Column chromatography was carried out over silica gel (Merck AG Darmstadt, Germany). The following abbreviations are used in the text: T3P = N-propane Phosphonic Cyclic Anhydride, EtOAc = ethyl acetate, DIPEA = N,N-diisopropylethylamine.

15 EXAMPLE 1

Preparation of 4-Methyl-5-(4-methyl-1,3-oxazol-5-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione



20

4-Methyl-1,3-oxazole-5-carboxylic acid (commercially available) (12.9g, 101.5mmol) was dissolved in DMF (60mL) and treated with 4-methyl-3-thiosemicarbazide (11.61g, 1.10eq). Then DIPEA (31.0mL, 1.75eq) was added at 20°C. Under ice bath cooling, T3P 50% w/w in EtOAc (90mL) was added dropwise, maintaining the temperature below 15°C over 20

25 minutes. The resulting mixture was then stirred at 20°C for 6 hours.

25

The mixture was diluted with NaOH 4 M (120.0mL). The resulting bi-phasic mixture was allowed separating and the upper organic layer discarded. The aqueous layer (pH = 8) was adjusted to pH = 11 with additional NaOH 4 M (60mL) and then heated to 70°C (internal temperature) for 30min. After cooling down over night, HCl 37% was slowly

30 added until pH=5 was reached.

30

The suspension was stirred for 8 hours, then the solid was filtered and washed with water (60mL), and it was dried in a vacuum oven at 40°C overnight.

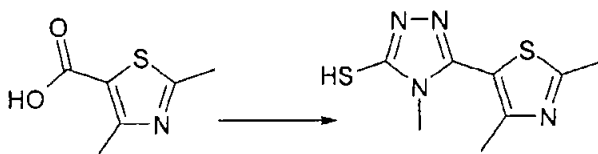
Yield: 10.48g, 53.4mmol, 53% th

35

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 600 MHz, δ ppm): 14.11 (bs, 1H), 8.60 (s, 1H), 3.61 (s, 3H), 2.33 (s, 3H)

MH<sup>+</sup> = 197

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EXAMPLE 2Preparation of 5-(2,4-dimethyl-1,3-thiazol-5-yl)-4-methyl-2,4-dihydro-3H-1,2,4-triazole-3-thione

5

2,4-Dimethyl-1,3-oxazole-5-carboxylic acid (commercially available) (5g, 31.8mmol) and 4-methyl-3-thiosemicarbazide (3.68g, 1.10eq) were dissolved in DMF (15mL). Then DIPEA (10.0mL, 1.80eq) was added at 20°C. Under ice bath cooling, T3P 50% w/w in EtOAc (35mL, 1.50eq) was added dropwise, maintaining the temperature below 10°C. The resulting mixture was then stirred at 20°C for 2h.

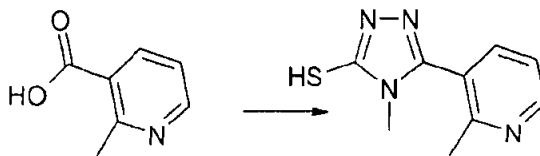
The mixture was diluted with water (20mL), then NaOH 4 M was added (20.0mL). The organic phase was discarded and the aqueous phase was heated to 70°C (internal temperature) for 90min. After cooling down to 50°C, HCl 37% was slowly added until pH=6.5 was reached.

The suspension was cooled to 5°C and the solid was filtered and washed with water, and it was then dried in a vacuum oven at 40°C overnight.

Yield: 5.45g, 24.4mmol, 77% th

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 600 MHz, δ ppm): 14.02 (bs, 1H), 3.39 (s, 3H), 2.69 (s, 3H), 2.34 (s, 3H)

MH<sup>+</sup> = 227

EXAMPLE 3Preparation of 4-methyl-5-(2-methyl-3-pyridinyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione

2-Methylnicotinic acid (commercially available) (5g, 36.5mmol) and 4-methyl-3-thiosemicarbazide (4.22g, 1.10eq) were dissolved in EtOAc (15mL). Then DIPEA (14.5mL, 2.28eq) was added at 20°C. Under ice bath cooling, T3P 50% w/w in EtOAc (32.5mL, 1.50eq) was added drop wise, maintaining the temperature below 15°C. The resulting mixture was then stirred at 20°C for 90min. The mixture was diluted with water (10mL), then NaOH 4 M was added (18.5mL). The organic layer was discarded and the remaining aqueous layer was heated to 70°C (internal temperature) for 2h 45min. After

16

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cooling down to ambient temperature, a suspension was obtained, which had a pH of about 7.5 to 8.0.

HCl 37% was slowly added until pH=5 was reached.

The solid was filtered and it was then dried in a vacuum oven at 40°C overnight.

5

Yield: 7.04g, 34.1mmol, 93% th

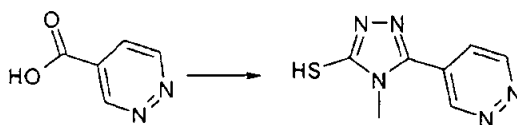
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 600 MHz, δ ppm): 14.01 (bs, 1H), 8.66 (dd, 1H), 7.96 (dd, 1H), 7.42 (dd, 1H), 3.29 (s, 3H), 2.42 (s, 3H)

MH<sup>+</sup> = 207

10

#### EXAMPLE 4

Preparation of 4-methyl-5-(4-pyridazinyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione



15

4-Pyridazinecarboxylic acid (commercially available) (5g, 40.3mmol) and 4-methyl-3-thiosemicarbazide (4.66g, 1.10eq) were dissolved in DMF (15mL). Then DIPEA (12.5mL, 1.78eq) was added at 20°C. Under ice bath cooling, T3P 50% w/w in EtOAc (36mL, 1.50eq) was added dropwise, maintaining the temperature below 20°C. The resulting mixture was then stirred at 20°C for 30min.

20

The mixture was diluted with water (20mL), then NaOH 4 M was added (20.0mL). The organic layer was discarded and the remaining aqueous phase was heated to 70°C (internal temperature) for 5h. After cooling down to ambient temperature, a suspension was obtained, which had a pH of about 7.5 to 8.0. HCl 37% was slowly added until pH=5

25

was reached. The solid was filtered and washed with water (3 times with 20mL), and it was then dried in a vacuum oven at 40°C overnight.

Yield: 6.37g, 33.0 mmol, 82% th

30

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 600 MHz, δ ppm): 14.29 (bs, 1H), 9.58 (d, 1H), 9.47 (d, 1H), 8.09 (d, 1H), 3.64 (s, 3H)

MH<sup>+</sup> = 194

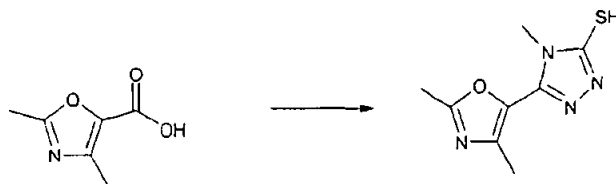
#### EXAMPLE 5

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Preparation of 5-(2,4-dimethyl-1,3-oxazol-5-yl)-4-methyl-2,4-dihydro-3H-1,2,4-triazole-3-thione



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4-methyl-3-thiosemicarbazide (4.5g, 42.8mmol) was dissolved in DMF (12.5mL, 2.5vol) under stirring. Commercially available 2,4-dimethyl-1,3-oxazole-5-carboxylic acid (5g, 35.4mmol) and DIPEA (15.5mL, 89mmol) were added. Mixture was cooled down to 5°C with an ice-water bath and a solution of T3P 50% w/w in ethyl acetate (45.5mL, 76.4mmol) was added drop wise in 15 minutes maintaining temperature below 10°C. At the end of the addition, mixture was allowed to reach ambient temperature and stirred for 2 hours under nitrogen. The mixture was diluted with 22.5mL of water and 22.5mL of a solution of NaOH 32% w/w under stirring (final pH = 12). After separation, the upper organic layer was discarded while the water phase was heated to 70°C (65°C internal). The pH of the mixture was checked over time and pH adjusted to 12 if necessary. The heating was kept for a total amount of 3 hours.

After cooling down to ambient temperature, 2.5 mL of a solution of HCl 37% w/w were added until pH was 8. A solid started precipitating and the suspension was stirred over night.

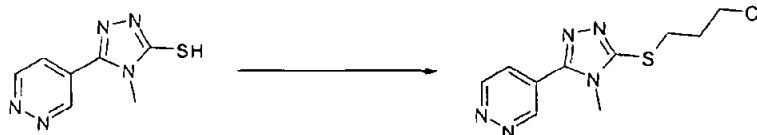
The mixture was filtered, the cake washed with 22.5mL of water and the collected solid dried under vacuum oven at 40°C for 5 hours.

Yield 4.28g; 57% theoretical

<sup>1</sup>H-NMR  
600 MHz, DMSO-d<sub>6</sub>: 2.26 (3H, s), 2.48 (3H, s), 3.59 (3H, s), 14.07 (1H, br. s.)  
MH<sup>+</sup> [211]

#### EXAMPLE 6

Preparation of a derivative of 4-methyl-5-(4-pyridazinyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione: 4-{5-[(3-chloropropyl)thio]-4-methyl-4H-1,2,4-triazol-3-yl}pyridazine



4-methyl-5-(4-pyridazinyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (5g; 1eq, 0.026mmol) and K<sub>2</sub>CO<sub>3</sub> 325 mesh (1.2eq, 4.3g) were suspended in a mixture of acetone (17.5mL) and methanol (7.5mL). The suspension was heated to 40°C and 1-bromo-3-chloropropane (1.1eq, 2.8mL) was added all at once. The suspension was stirred at 40°C for 3h, and then allowed to cool down to ambient. Ethyl acetate (25mL) was added and the mixture distilled to ca. 20mL. The mixture was diluted with ethyl acetate (20mL) and it was

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washed with water (15mL each). The solution was dried on Na<sub>2</sub>SO<sub>4</sub>; filtered and distilled down to ca. 20mL. The resulting solution was allowed to cool down to ambient temperature under stirring over 30 minutes and it was stirred an additional 30 minutes. During this time, part of the product crashed out of the solution. Heptane (40mL) was added drop wise over 30 minutes and the resulting suspension was stirred for at least 6 hour. The suspension was filtered and the cake washed with a mixture of EtOAc/Heptane 1/2 (15mL). The title compound 4-{5-[(3-chloropropyl)thio]-4-methyl-4*H*-1,2,4-triazol-3-yl}pyridazine, was dried in the oven at 40°C until constant weight achieved.

10 Yield: 61%th, 4.27g

MS: [MH]<sup>+</sup> 270

NMR (DMSO-d<sub>6</sub>, 600MHz; δ ppm): 9.61 (dd, 1H); 9.43 (dd, 1H); 8.07 (dd, 1H); 3.78 (t, 2H); 3.73 (s, 3H); 3.31 (t, 2H); 2.17 (m, 2H)

15

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

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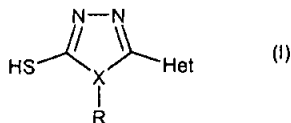
It is to be understood that the present invention covers all combinations of particular and preferred groups described herein above.

25 The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims:

1a

## Claims

1. Process for preparing thiazole or triazole derivatives of formula (I)



5

in which

X may be Nitrogen or Sulfur;

Het means aryl or heteroaryl; each of which may be substituted by 1 to 4 groups J selected from:

10 halogen, C1-C6 alkyl, C1-C6 alkoxy, halo C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, halo C1-C6 alkoxy, -C(O)R<sub>1</sub>, nitro, hydroxy, -NR<sub>2</sub>R<sub>3</sub>, cyano or a group Z;

R<sub>1</sub> is a C1-C4 alkyl, -OR<sub>3</sub> or -NR<sub>3</sub>R<sub>4</sub>;

R<sub>2</sub> is hydrogen or C1-C6 alkyl;

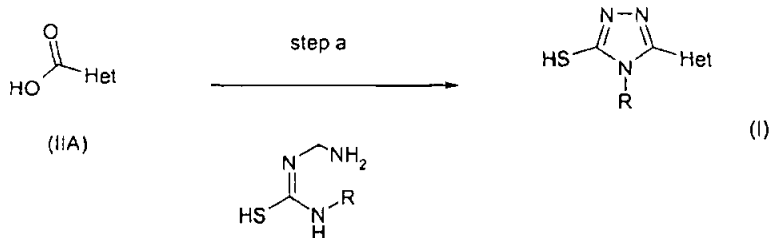
15 R<sub>3</sub> is hydrogen or C1-C6 alkyl;

R is H, C1-C6 alkyl, aryl, benzyl; each of which may be substituted by 1 to 4 groups J;

according to the following Scheme 1:

20

Scheme 1



in which

step a

25

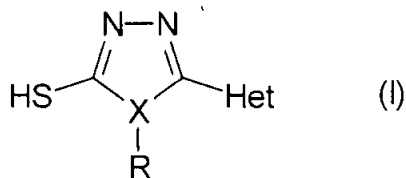
means a reaction in basic conditions of compounds (IIA) with 3-thiosemicarbazide derivatives, followed by a treatment with an inorganic base and n-propane phosphonic cyclic anhydride and finally pH adjustment with inorganic acids to give compounds of formula (II).

## PROCEDIMIENTO PARA PREPARAR DERIVADOS HETEROCICLICOS

### MEMORIA DESCRIPTIVA

5 La presente invención se refiere a un novedoso procedimiento, útil para preparar intermediarios clave en la síntesis de diversos compuestos, entre ellos, compuestos que son antagonistas potentes y específicos de los receptores D3.

La presente invención se refiere a un novedoso procedimiento  
10 para preparar derivados de tiazol o triazol de fórmula (I)



15 en la cual

X puede ser nitrógeno o azufre;

Het significa arilo o heteroarilo; cada uno de los cuales puede estar sustituido por uno 1 a 4 grupos J seleccionados de:

halógeno, alquilo de C1-C6, alcoxi de C1-C6, haloalquilo de C1-  
20 C6, alquenilo de C2-C6, alquinilo de C2-C6, haloalcoxi de C1-C6, -C(O)R<sub>1</sub>, nitro, hidroxilo, -NR<sub>2</sub>R<sub>3</sub>, ciano o un grupo Z;

R<sub>1</sub> es un alquilo de C1-C4, -OR<sub>3</sub> o -NR<sub>3</sub>R<sub>4</sub>;

R<sub>2</sub> es hidrógeno o alquilo de C1-C6;

$R_3$  es hidrógeno o alquilo de C1-C6;

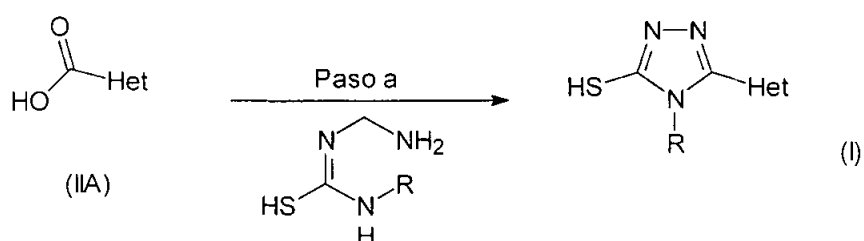
$R$  es H, alquilo de C1-C6, arilo, bencilo; cada uno de los cuales puede estar sustituido por 1 a 4 grupos J;

de acuerdo con el siguiente esquema 1:

5

### ESQUEMA 1

10



en el cual

paso a significa una reacción en condiciones básicas de los compuestos (IIA) con derivados de 3-tiosemicarbazida seguido por un tratamiento con un base inorgánica y anhídrido cíclico fosfónico de n-propano y ajuste final de pH con ácidos inorgánicos para dar compuestos de fórmula (II).

El término de alquilo de C1-C6 como se utiliza en la presente como un grupo o parte del grupo, se refiere a un grupo alquilo lineal o ramificado que contiene de 1 a 6 átomos de carbono; ejemplos de dichos grupos incluyen metilo, etilo, propilo, isopropilo, n-butilo, isobutilo, tert butilo, pentilo o hexilo.

El término halógeno se refiere a un átomo de flúor, cloro, bromo o yodo.

El término haloalquilo de C1-C6, significa un grupo alquilo que tiene uno o más átomos de carbono y en donde por lo menos un átomo de hidrógeno es reemplazado por halógeno como por ejemplo un grupo trifluorometilo y similares.

El término tioalquilo de C1-C6 puede ser un grupo tioalquilo de cadena lineal ramificada, por ejemplo tiometilo, tioetilo, tiopropilo, tioisopropilo, tiobutilo, tiosec-butilo, tiote-butilo y similares.

El término alqueno de C2-C6 define radicales hidrocarburo de cadena recta o ramificada que contienen uno o más enlaces dobles y que tienen de 2 a 6 átomos de carbono, como por ejemplo etenilo, 2-propenilo, 3-butenilo, 2-butenilo, 2-pentenilo, 3-pentenilo, 3-metil-2-butenilo o 3-hexenilo y similares.

El término grupo alcoxi de C1-C6 puede ser un grupo alcoxi de cadena lineal o ramificada, por ejemplo metoxi, etoxi, propoxi, prop-2-oxi, butoxi, but-2-oxi o metilprop-2-oxi y similares.

El término grupo haloalcoxi de C1-C6 puede ser un grupo alcoxi de C1-C6 como se definió anteriormente sustituido con al menos un halógeno, de preferencia flúor, tal como  $\text{OCHF}_2$ , u  $\text{OCF}_3$ .

El término de alquino de C2-C6 define radicales hidrocarburo de cadena recta o ramificada que contienen uno o más enlaces triples y que



tienen de 2 a 6 átomos de carbono incluyendo acetilenilo, propinilo, 1-butinilo, 1-pentinilo, 3-metil-1-butinilo y similares.

El término arilo significa una porción carbocíclica aromática tal como fenilo, bifenilo o naftilo.

- 5 El término heteroarilo significa un anillo heterociclo aromático de 5 a 10 elementos y que tiene por lo menos un heteroátomo seleccionado de nitrógeno, oxígeno y azufre, y que contiene por lo menos 1 átomo de carbono, incluyendo sistemas de anillo tanto mono como bicíclicos.

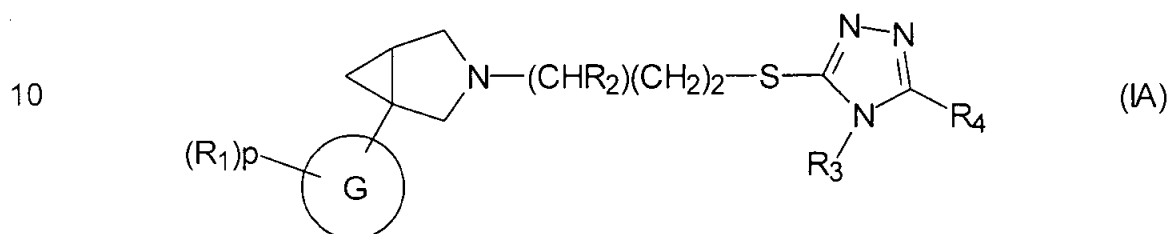
- 10 Los heteroarilos representativos incluyen (pero no se limitan a) furilo, benzofuranilo, tiofenilo, benzotiofenilo, pirrolilo, indolilo, isoindolilo, azaindolilo, piridilo, quinolinilo, isoquinolinilo, oxazolilo, isooxazolilo, benzoxazolilo, pirazolilo, imidazolilo, bencimidazolilo, tiazolilo, benzotiazolilo, isotiazolilo, piridazinilo, pirimidinilo, pirazinilo, triazinilo, cinnolinilo, ftalazinilo, triazolilo, tetrazolilo, quinazolinilo, y benzodioxolilo.

- 15 El término heterociclo de 5-6 elementos significa, de acuerdo con la definición anterior, un anillo heterocíclico monocíclico de 5 a 6 que es ya sea saturado, insaturado o aromático, y el cual contiene de 1 a 4 heteroátomos independientemente seleccionados de nitrógeno, oxígeno y azufre, y en donde los heteroátomos de nitrógeno y azufre pueden estar  
20 opcionalmente oxidados, y el heterátomo de nitrógeno puede estar opcionalmente cuaternizado. Los heterociclos incluyen heteroarilos como se definió anteriormente. El heterociclo se puede unir a través de cualquier heteroátomo o átomo de carbono. De esta manera, el término incluye (pero no

24

se limita a) morfolinilo, piridinilo, pirazinilo, pirazolilo, tiazolilo, triazolilo, imidazolilo, oxadiazolilo, oxazolilo, isoxazolilo, pirrolidinonilo, pirrolidinilo, piperidinilo, hidantoinilo, valerolactamilo, oxiranilo, oxetanilo, tetrahidrofuranilo, tetrahidropiranilo, tetrahidropiridinilo, tetrahidropirimidinilo, tetrahidrotiofenilo, 5 tetrahidrotiopiranilo, y similares.

Los compuestos de fórmula (I) pueden ser útiles, pero no están limitados, a la preparación de antagonistas de D3 de fórmula (IA), como se describe en el documento WO2005/080382:



en donde

- G se selecciona de un grupo que consiste en: fenilo, piridilo, 15 benzotiazolilo, indazolilo;
- p es un entero que varía de 0 a 5;
- R<sub>1</sub> se selecciona independientemente de un grupo que consiste en: halógeno, hidroxilo, ciano, alquilo de C<sub>1-4</sub>, haloalquilo de C<sub>1-4</sub>, alcoxi de C<sub>1-4</sub>, haloalcoxi de C<sub>1-4</sub>, 20 alcanoilo de C<sub>1-4</sub>; o corresponde a un grupo R<sub>5</sub>;
- R<sub>2</sub> es hidrógeno o alquilo de C<sub>1-4</sub>;
- R<sub>3</sub> es alquilo de C<sub>1-4</sub>;



- $R_4$  es hidrógeno, o un grupo fenilo, un grupo heterociclilo, un grupo heteroaromático de 5 o 6 elementos, o un grupo bicíclico de 8 a 11 elementos, cualquiera de dichos grupos está opcionalmente sustituido con 1, 2, 3 o 4 sustituyentes seleccionados del grupo que consiste en: halógeno, ciano, alquilo de  $C_{1-4}$ , haloalquilo de  $C_{1-4}$ , alcoxi de  $C_{1-4}$ , alcanilo de  $C_{1-4}$ ;
  - $R_5$  es una porción seleccionada del grupo que consiste en: isoxazolilo,  $-CH_2-N$ -pirrolilo, 1-1-dioxido-2-isotiazolidinilo, tienilo, tiazolilo, piridilo, 2-pirrolidinonilo, y dicho grupo está opcionalmente sustituido con uno o dos sustituyentes seleccionados de: halógeno, ciano, alquilo de  $C_{1-4}$ , haloalquilo de  $C_{1-4}$ , alcoxi de  $C_{1-4}$ , alcanilo de  $C_{1-4}$ ;
- y en donde  $R_1$  es cloro y  $p$  es 1, de manera que  $R_1$  no está presente en la posición orto con respecto al enlace de unión con el resto de la molécula; y en donde  $R_1$  corresponde a  $R_5$ ,  $p$  es 1.

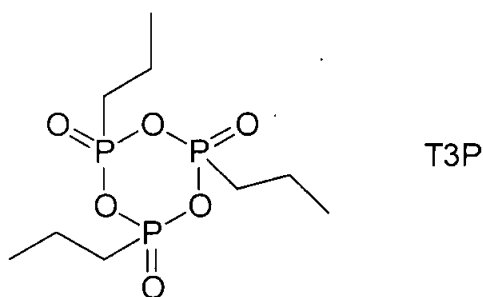
Los compuestos de fórmula (I), como intermediarios para la preparación de otros compuestos, se pueden funcionalizar de manera conveniente, según lo descrito en el documento WO2005/080382. Un ejemplo se reporta en la Sección Experimental de la presente.

La preparación de compuestos de fórmula (I) que se describe en el documento WO2005/080382 empleó 1-hidroxibenzotriazol (HOBt) junto con 1,3-diciclohexilcarbodiimida (DCC). Las desventajas de estos reactivos a nivel



industrial se pueden resumir de la siguiente manera: HOBt y sus productos secundarios tienen una naturaleza explosiva y DCC y su producto secundario siempre son difíciles de eliminar totalmente.

El procedimiento resuelve los problemas anteriores al utilizar  
5 anhídrido cíclico fosfónico de N-propano, T3P, como agente de condensación.

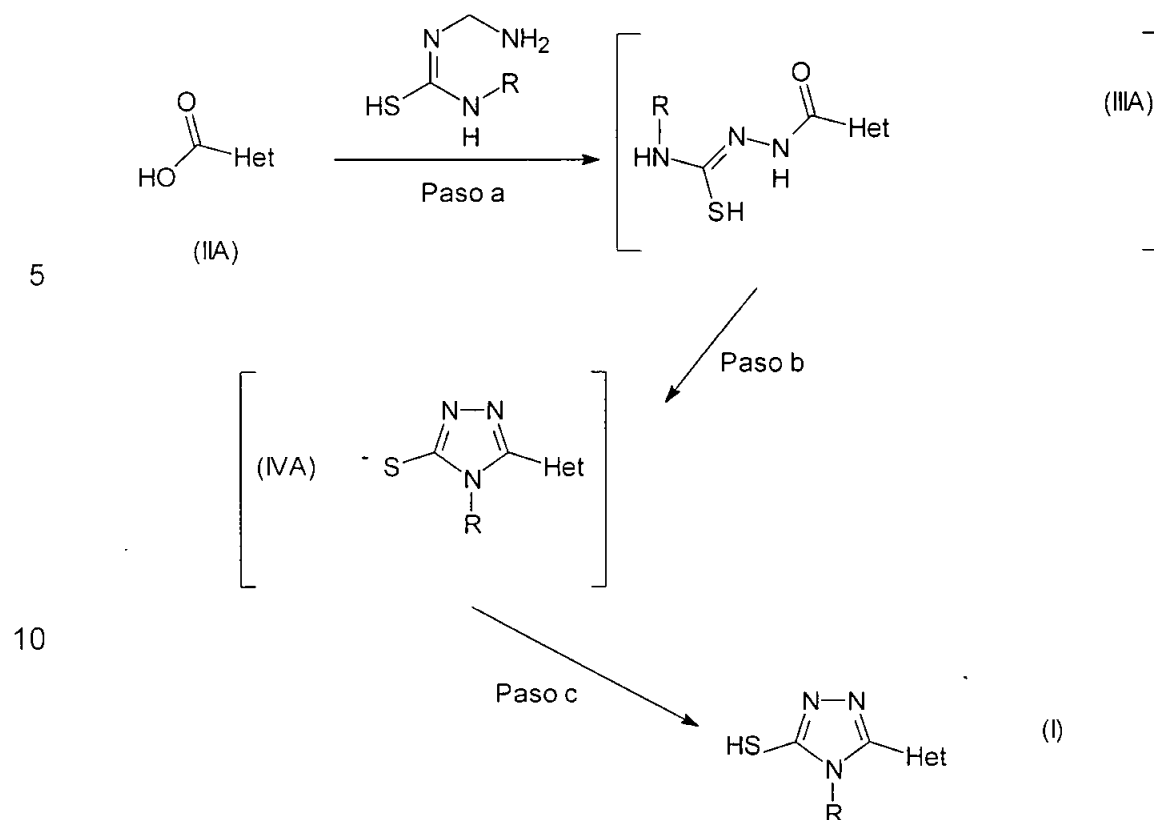


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T3P se utilizó primero en la síntesis peptídica en 1980 por H. Wissmann (Angew. Chem., 1980, 92, 129) y constantemente está ganando importancia en síntesis orgánica debido a que es menos tóxico y más seguro en comparación con otros agentes de condensación comunes, tales como  
15 DCC. El reactivo no proporciona ningún producto secundario insoluble en agua. T3P se utiliza como solución al 50% en acetato de etilo en el procedimiento de la presente invención y no necesita el aislamiento del intermediario hidrazina-carbotiamida. De manera similar, T3P está disponible como solución al 50% en DMF (dimetilformamida) y se puede emplear en el  
20 procedimiento de la presente invención.

El procedimiento de la presente invención se puede ilustrar con más detalle de la siguiente manera:

29



El material de partida, el ácido carboxílico heterocíclico, disponible generalmente a nivel comercial o el cual se puede preparar de acuerdo con métodos conocidos en la bibliografía, en una cantidad de 1 equivalente se puede disolver de manera adecuada en el solvente apropiado (por ejemplo dimetilformamida; acetato de etilo; acetonitrilo y tetrahidrofurano y otro solvente aprótico polar) y tratar con un ligero excedente de derivados de 3-tiosemicarbazida (1.10 eq.), tal como el derivado de 4-metilo. Luego se agrega a RT una base orgánica (por ejemplo, trietilamina, diisopropiletilamina y posiblemente otras aminas alifáticas o aromáticas).



Después se puede añadir de forma gradual anhídrido cíclico fosfónico de N-propano (50% p/p en acetato de etilo) a una temperatura que varía de 0 a 40 grados. En caso de que la adición se realice aproximadamente a 0°C, la temperatura se mantiene entonces por debajo de 15°C durante 20-  
5 60 minutos. La mezcla resultante luego se agitó a los 20°C durante 2-16 horas.

Luego la mezcla se diluye con una solución acuosa de una base inorgánica adecuada hasta alcanzar el pH básico, La base adecuada se puede seleccionar entre: carbonato de potasio, carbonato de sodio, hidróxido  
10 de sodio, hidróxido de potasio.

La mezcla bifásica resultante (cuando se observa) luego se deja separar y se descarta la capa orgánica superior. La capa acuosa luego se calienta a 50-90°C (temperatura interna) durante media hora hasta varias horas hasta terminar la reacción.

15 Después de enfriamiento a 20°C, se añade lentamente un ácido mineral adecuado (por ejemplo HCl al 37%) para ajustar el pH según sea necesario (4 a 8).

La suspensión luego se agita generalmente durante 2-16 horas, posteriormente se filtra el sólido, se lava con agua pura y se seca en un horno  
20 al vacío a 40-60°C hasta secar. El producto final se aísla de la mezcla acuosa no contaminada por derivados de fósforo.

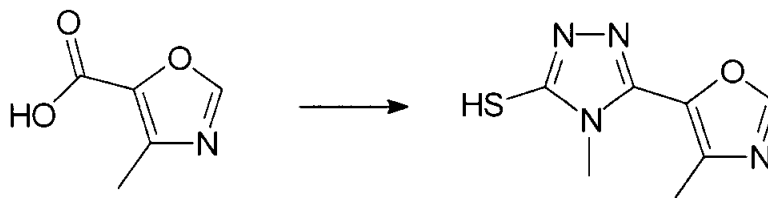
## EJEMPLOS

En los ejemplos, a menos que se establezca lo contrario:

Todas las temperaturas se refieren a °C. Los espectros  
5 infrarrojos se midieron en un instrumento FT-IR. Los compuestos se  
analizaron mediante infusión directa de la muestra disuelta en acetonitrilo en  
espectros de masa operados en modo de ionización de electroaspersión (ES<sup>+</sup>)  
positiva. Los espectros de Resonancia Magnética Protónica (<sup>1</sup>H-RMN) se  
registraron a 400 MHz, los cambios químicos se reportan en ppm de campo  
10 descendente (d) a partir de Me<sub>4</sub>Si, utilizado como estándar interno, y se  
asignan como singuletes (s), singuletes anchos (bs), dobletes (d), dobletes de  
dobletes (dd), tripletes (t), cuartetos (q) o multipletes (m). La cromatografía de  
columna se llevó a cabo sobre gel de sílice (Merck AG Darmstadt, Alemania).  
Las siguientes abreviaturas se utilizan en el texto: T3P = Anhídrido Cíclico  
15 Fosfónico de N-propano, EtOAc = acetato de etilo, DIPEA = N,N-  
diisopropiletilamina.

### EJEMPLO 1

#### Preparación de 4-metil-5-(4-metil-1,3-oxazol-5-il)-2,4-dihidro-3H-1,2,4- 20 triazol-3-tiona



30

Acido 4-metil-1,3-oxazol-5-carboxílico (comercialmente disponible) (12.9 g, 101.5 mmoles) se disolvió en DMF (60 mL) y se trató con 4-metil-3-tiosemicarbazida (11.61g, 1.10 eq). Luego se añadió DIPEA 5 (31.0mL, 1.75eq) a 20°C. Bajo enfriamiento en baño de hielo, se añadió por goteo T3P 50% p/p en EtOAc (90 mL) manteniendo la temperatura por debajo de 15°C durante 20 minutos. La mezcla resultante luego se agitó a 20°C durante 6 horas.

La mezcla se diluyó con NaOH 4 M (120.0mL). La mezcla 10 bifásica resultante se dejó separar y se descartó la capa orgánica superior. La capa acuosa (pH = 8) se ajustó pH = 11 con NaOH 4 M adicional (60 mL) y luego se calentó a 70°C (temperatura interna) durante 30 minutos. Después de enfriamiento durante la noche, se añadió lentamente HCl al 37% hasta alcanzar pH=5.

15 La suspensión se agitó durante 8 horas, luego el sólido se filtró y se lavó con agua (60 mL) y se secó en un horno al vacío a 40°C durante la noche.

Rendimiento: 10.48g, 53.4mmoles, 53% teor

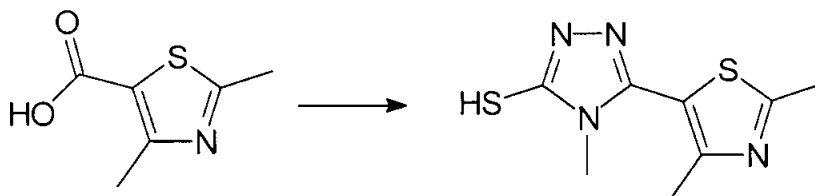
1H RMN (DMSO-d<sub>6</sub>, 6000 MHz,  $\delta$  ppm): 14.11 (bs, 1H), 8.60 (s, 20 1H), 3.61 (s, 3H), 2.33 (s, 3H)

MH<sup>+</sup> = 197

31

**EJEMPLO 2****Preparación de 5-(2,4-dimetil-1,3-tiazol-5-il)-4-metil-2,4-dihidro-3H-1,2,4-triazol-3-tiona**

5



Acido 2,4-dimetil-1,3-oxazol-5-carboxílico (comercialmente disponible) (5g, 31.8 mmoles) y 4-metil-3-tiosemicarbazida (3.68g, 1.10 eq) se disolvieron en DMF (15 mL). Luego se añadió DIPEA (10.0mL, 1.80eq) a 20°C. Bajo enfriamiento en baño de hielo, se añadió por goteo T3P 50% p/p en EtOAc (35mL, 1.50eq), manteniendo la temperatura por debajo de 10°C. La mezcla resultante luego se agitó a 20°C durante 2 horas.

La mezcla se diluyó con agua (20 mL), luego se agregó NaOH 4 M (20.0 mL). La fase orgánica se descartó y la fase acuosa se calentó a 70°C (temperatura interna) durante 90 minutos. Después de enfriamiento a 50°C, se añadió lentamente HCl al 37% hasta alcanzar pH=6.5.

La suspensión se enfrió a 5°C y el sólido se filtró y lavó con agua, y luego se secó a un horno al vacío a 40°C durante la noche.

20 Rendimiento: 5.45g, 24.4mmoles, 77% teor

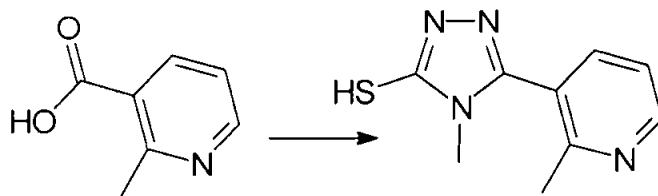
<sup>1</sup>H RMN (DMSO-d<sub>6</sub>, 600 MHz, δ ppm): 14.02 (bs, 1H), 3.39 (s, 3H), 2.69 (s, 3H), 2.34 (s, 3H)

MH<sup>+</sup> = 227

32

**EJEMPLO 3****Preparación de 4-metil-5-(2-metil-3-piridinil)-2,4-dihidro-3H-1,2,4-triazol-3-tianona**

5



Acido 2-metilnicotínico (comercialmente disponible) (5g,  
10 36.5mmoles) y 4-metil-3-tiosemicarbazida (4.22g, 1.10eq) se disolvieron en EtOAc (15 mL). Luego se añadió DIPEA (14.5mL, 2.28eq) a 20°C. Bajo enfriamiento en baño de hielo, se añadió por goteo T3P 50% p/p en EtOAc (32.5mL, 1.50eq), manteniendo la temperatura por debajo de 15°C. La mezcla resultante luego se agitó a 20°C durante 90 minutos. La mezcla se diluyó con  
15 agua (10mL), luego se añadió NaOH 4 M (18.5 mL). La capa orgánica se descartó y la capa acuosa restante se calentó a 70°C (temperatura interna) durante 2 horas 45 minutos. Después de enfriamiento a temperatura ambiente, se obtuvo una suspensión, la cual tenía un pH de aproximadamente 7.5 a 8.0.

20 Se añadió lentamente HCl al 37% hasta alcanzar pH =5.

El sólido se filtró y luego se secó en un horno al vacío a 40°C durante la noche.

Rendimiento: 7.04 g, 34.1 mmoles, 93% teor



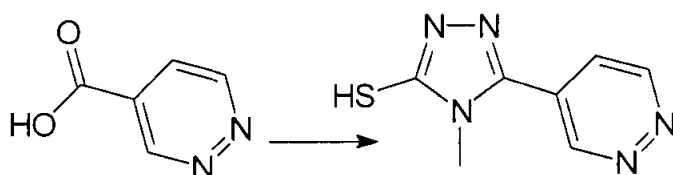
$^1\text{H}$  RMN (DMSO- $d_6$ , 600 MHz,  $\delta$  ppm): 14.01 (bs, 1H), 8.66 (dd, 1H), 7.96 (dd, 1H), 7.42 (dd, 1H), 3.29 (s, 3H), 2.42 (s, 3H)

$\text{MH}^+ = 207$

5

#### EJEMPLO 4

#### Preparación de 4-metil-5-(4-piridazinil)-2,4-dihidro-3H-1,2,4-triazol-3-tiona



10

Acido 4-piridazincarboxílico (comercialmente disponible) (5 g, 40.3 mmoles) y 4-metil-3-tiosemicarbazida (4.66 g, 1.10 eq) se disolvieron en DMF (15 mL). Luego se añadió DIPEA (12.5 mL, 1.78 eq) a 20°C. Bajo enfriamiento en baño de hielo, se añadió por goteo T3P 50% p/p en EtOAc (36 mL, 1.50 eq), manteniendo la temperatura por debajo de 20°C. La mezcla resultante luego se agitó a 20°C durante 30 minutos.

La mezcla se diluyó con agua (20 mL), luego se añadió NaOH 4 M (20.0 mL). La capa orgánica se descartó y la fase acuosa restante se calentó a 70°C (temperatura interna) durante 5 horas. Después de enfriamiento a temperatura ambiente, se obtuvo una suspensión, la cual tenía un pH de aproximadamente 7.5 a 8.0. Se añadió lentamente HCl al 37% hasta alcanzar pH=5.

El sólido se filtró y lavó con agua (3 veces con 20 mL), y luego se secó en un horno al vacío a 40°C durante la noche.

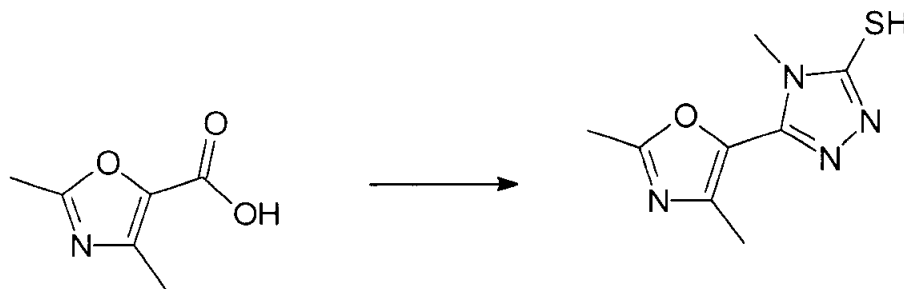
Rendimiento: 6.37 g, 33.0 mmoles, 82% teor

1H RMN (DMSO-d<sub>6</sub>, 600 MHz,  $\delta$  ppm): 14.29 (bs, 1H), 9.58 (d, 1H), 9.47 (d, 1H), 8.09 (d, 1H), 3.64 (s, 3H)

MH<sup>+</sup>=194

### EJEMPLO 5

#### Preparación de 5-(2,4-dimetil-1,3-oxazol-5-il)-4-metil-2,4-dihidro-3H-1,2,4-triazol-3-tiona



15

4-metil-3-tiosemicarbazida (4.5 g, 42.8 mmoles) se disolvió en DMF (12.5 mL, 2.5 vol) bajo agitación. Se agregó ácido 2,4-dimetil-1,3-oxazol-5-carboxílico comercialmente disponible (5g, 35.4 mmoles) y DIPEA (15.5 mL, 89 mmoles). La mezcla se enfrió a 5°C con un baño de agua helada y una solución de T3P 50% p/p en acetato de etilo (45.5 mL, 76.4 mmoles) se añadió por goteo en 15 minutos manteniendo la temperatura por debajo de 10°C. Al final de la adición, se dejó que la mezcla alcanzara la temperatura ambiente y se agitó durante 2 horas bajo nitrógeno. La mezcla se diluyó con

20

22.5 mL de agua y 22.5 mL de una solución de NaOH 32% p/p bajo agitación (pH final = 12). Después de separación, se descartó la capa orgánica superior mientras la fase acuosa se calentó a 70°C (65°C internos). El pH de la mezcla se verificó con el tiempo y el pH se ajustó a 12 en caso de ser necesario. El calentamiento se mantuvo durante un total de 3 horas.

Después de enfriamiento a temperatura ambiente, se añadieron 2.5 mL de una solución de HCl 37% p/p hasta que el pH fue de 8. Un sólido empezó a precipitarse y la suspensión se agitó durante la noche.

La mezcla se filtró, la torta se lavó con 22.5 mL de agua y el sólido recolectado se secó en un horno al vacío a 40°C durante 5 horas.

Rendimiento: 4.28 g, 57% teórico

<sup>1</sup>H RMN (600 MHz, DMSO-d<sub>6</sub>: 2.26 (3H, s), 2.48 (3H, s), 3.59 (3H, s), 14.07 (1H, br, s)

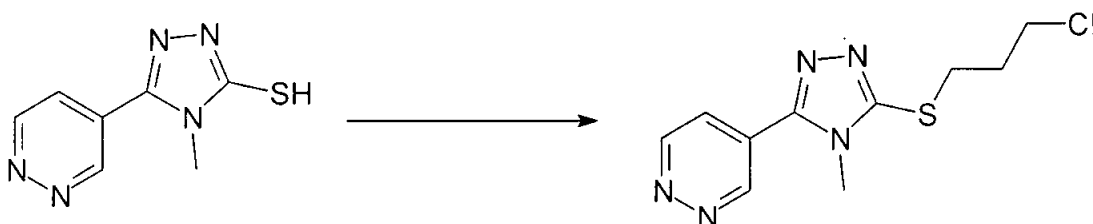
MH<sup>+</sup>=[211]

15

### EJEMPLO 6

Preparación de un derivado de 4-metil-5-(4-piridazinil)-2,4-dihidro-3H-1,2,4-triazol-3-tiona: 4-{5-[(3-cloropropil)tio]-4-metil-4H-1,2,4-triazol-3-il}piridazina

20



26

4-metil-5-(4-piridazinil)-2,4-dihidro-3H-1,2,4-triazol-3-ona (5g; 1eq 0.026 mmoles) y malla 325 de  $K_2CO_3$  (1.2eq, 4.3g) se suspendieron en una mezcla de acetona (17.5 mL) y metanol (7.5 mL). La suspensión se calentó a 40°C y 1-bromo-3-cloropropano (1.1eq, 2.8mL) se añadió todo al mismo tiempo. La suspensión se agitó a 40°C durante 3 horas, y luego se dejó enfriar a temperatura ambiente. Se agregó acetato de etilo (25 mL) y la mezcla se destiló a aproximadamente 20 mL. La mezcla se diluyó con acetato de etilo (20 mL) y se lavó con agua (15 mL cada uno). La solución se secó en  $Na_2SO_4$ ; se filtró y destiló a aproximadamente 20 mL. La solución resultante se dejó enfriar a temperatura ambiente bajo agitación durante 30 minutos y se agitó 30 minutos adicionales. Durante este tiempo, parte del producto se escapó de la solución. Se añadió por goteo heptano (40 mL) durante 30 minutos y la suspensión resultante se agitó durante al menos 6 horas. La suspensión se filtró y la torta se lavó con una mezcla de EtOAc/Heptano 1/2 (15 mL). El compuesto del título 4-{5-[(3-cloropropil)tio]-4-metil-4H-1,2,4-triazol-3-il}piridazina se secó en el horno a 40°C hasta lograr un peso constante.

Rendimiento: 61% teor, 4.27g

MS:  $[MH]^+ 270$

RMN (DMSO- $d_6$ , 600 MHz;  $\delta$  ppm): 9.61 (dd, 1H), 9.43 (dd, 1H); 8.07 (dd, 1H); 3.78 (t, 2H); 3.73 (s, 3H); 3.31 (t, 2H); 2.72 (m, 2H)

Todas las publicaciones, incluyendo sin límite las patentes y solicitudes de patente, citadas en esta especificación se incorporan como



referencia como si se indicara específica e individualmente que cada publicación individual se incorpore como referencia a la presente como si se expusieran en su totalidad.

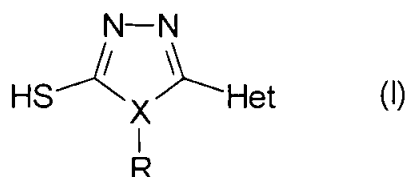
Se entenderá que la presente invención abarca todas las  
5 combinaciones de grupos preferidos y particulares anteriormente descritos.

La solicitud de la cual esta descripción y reivindicaciones forman parte, se puede utilizar como una base para prioridad con respecto a cualquier solicitud posterior. Las reivindicaciones de dicha solicitud posterior pueden ser dirigidas a cualquier característica o combinación de características aquí  
10 descritas. Pueden tener forma de reivindicaciones de producto, composición, procedimiento o uso y pueden incluir a manera de ejemplo, y sin límite, las siguientes reivindicaciones:

## NOVEDAD DE LA INVENCION

### REIVINDICACIONES

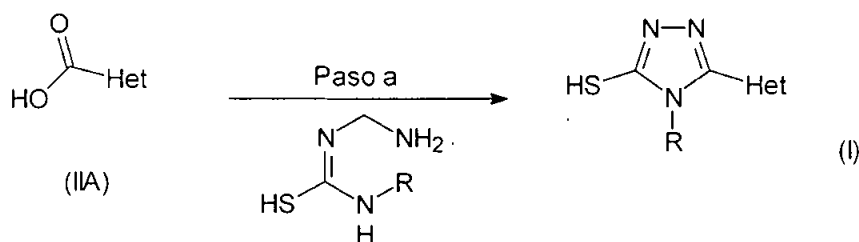
- 5 1.- Un procedimiento para preparar derivados de tiazol o triazol de fórmula (I)



en la cual X puede ser nitrógeno o azufre; Het significa arilo o heteroarilo; cada uno de los cuales puede estar sustituido por uno 1 a 4 grupos J seleccionados de: halógeno, alquilo de C1-C6, alcoxi de C1-C6, haloalquilo de C1-C6, alquenilo de C2-C6, alquinilo de C2-C6, haloalcoxi de C1-C6, -C(O)R<sub>1</sub>, 15 nitro, hidroxilo, -NR<sub>2</sub>R<sub>3</sub>, ciano o un grupo Z; R<sub>1</sub> es un alquilo de C1-C4, -OR<sub>3</sub> o -NR<sub>3</sub>R<sub>4</sub>; R<sub>2</sub> es hidrógeno o alquilo de C1-C6; R<sub>3</sub> es hidrógeno o alquilo de C1-C6; R es H, alquilo de C1-C6, arilo, bencilo; cada uno de los cuales puede estar sustituido por 1 a 4 grupos J; de acuerdo con el siguiente esquema 1:

Esquema 1

20



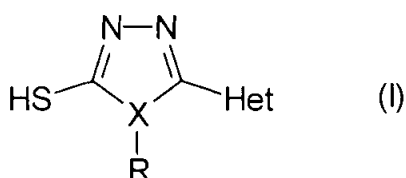


en el cual: *paso a* significa una reacción en condiciones básicas de los compuestos (IIA) con derivados de 3-tiosemicarbazida seguido por un tratamiento con un base inorgánica y anhídrido cíclico fosfónico de n-propano y finalmente ajuste de pH con ácidos inorgánicos para dar compuestos de

5 fórmula (II).

## RESUMEN DE LA INVENCION

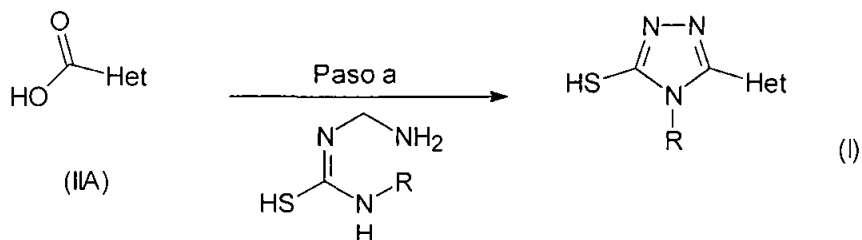
La presente invención se refiere a un novedoso procedimiento, útil para preparar intermediarios clave de fórmula (I) en la síntesis de diversos  
5 compuestos, entre ellos, compuestos que son antagonistas potentes y específicos de los receptores D3



10

en la cual X puede ser nitrógeno o azufre; Het significa arilo o heteroarilo; cada uno de los cuales puede estar sustituido por uno 1 a 4 grupos J seleccionados de: halógeno, alquilo de C1-C6, alcoxi de C1-C6, haloalquilo de C1-C6, alquenilo de C2-C6, alquinilo de C2-C6, haloalcoxi de C1-C6, -C(O)R<sub>1</sub>,  
15 nitro, hidroxilo, -NR<sub>2</sub>R<sub>3</sub>, ciano o un grupo Z; R<sub>1</sub> es un alquilo de C1-C4, -OR<sub>3</sub> o -NR<sub>3</sub>R<sub>4</sub>; R<sub>2</sub> es hidrógeno o alquilo de C1-C6; R<sub>3</sub> es hidrógeno o alquilo de C1-C6; R es H, alquilo de C1-C6, arilo, bencilo; cada uno de los cuales puede estar sustituido por 1 a 4 grupos J; de acuerdo con el siguiente esquema 1:

20



en el cual: *paso a* significa una reacción en condiciones básicas de los compuestos (IIA) con derivados de 3-tiosemicarbazida, seguido por un tratamiento con un base inorgánica y anhídrido cíclico fosfónico de n-propano y ajuste final de pH con ácidos inorgánicos para dar compuestos de fórmula

5 (II).

10

15

20

4A/ouf\*mmf\*aom\*

P08/1619F

# PATENT COOPERATION TREATY

*Handwritten initials*

From the INTERNATIONAL SEARCHING AUTHORITY

## PCT

|                                                                                                                                                                          |  |                                                                                                  |  |                                                                                                                                                              |  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--------------------------------------------------------------------------------------------------|--|--------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| <b>To:</b><br>GLAXOSMITHKLINE<br>Attn: Giddings, Peter John<br>Corp. Intel. Prop. (CN925.1)<br>980 Great West Road<br>Brentford, Middlesex<br>TW8 9GS<br>GRANDE BRETAGNE |  | <b>GlaxoSmithKline</b><br><b>Corporate IP</b><br><b>Received BRENTFORD</b><br><b>05 JUL 2007</b> |  | NOTIFICATION OF TRANSMITTAL OF<br>THE INTERNATIONAL SEARCH REPORT AND<br>THE WRITTEN OPINION OF THE INTERNATIONAL<br>SEARCHING AUTHORITY, OR THE DECLARATION |  |
|                                                                                                                                                                          |  | ATTY: <i>TG-V/NR</i> ADMIN: <i>08/Jul</i> (PCT Rule 44.1)                                        |  |                                                                                                                                                              |  |
|                                                                                                                                                                          |  | IPM: N/A ON UPDATED ON <i>05/07/2007</i> (day/month/year)                                        |  | Date of mailing<br>(day/month/year) <b>05/07/2007</b>                                                                                                        |  |
| Applicant's or agent's file reference<br><b>PB61926</b>                                                                                                                  |  | <b>CORPORATE INTELLECTUAL PROPERTY</b> <b>FOR FURTHER ACTION</b> See paragraphs 1 and 4 below    |  |                                                                                                                                                              |  |
| International application No.<br><b>PCT/EP2007/053118</b>                                                                                                                |  | Received <b>6 LUG 2007</b>                                                                       |  | International filing date<br>(day/month/year) <b>30/03/2007</b>                                                                                              |  |
| Applicant<br><b>GLAXO GROUP LIMITED</b>                                                                                                                                  |  | <b>VERONA</b> <b>File</b>                                                                        |  |                                                                                                                                                              |  |

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

**Filing of amendments and statement under Article 19:**  
 The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

**When?** The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

**Where?** Directly to the International Bureau of WIPO, 34 chemin des Colombettes  
 1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70

**For more detailed instructions, see the notes on the accompanying sheet.**

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO internet site.

|                                                                                                                                                                                                                                                                                                        |                                               |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Name and mailing address of the International Searching Authority<br> European Patent Office, P.B. 5818 Patentlaan 2<br>NL-2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Authorized officer<br><b>Emmanuel Cherqui</b> |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|

## NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

### INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

#### What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

#### When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

#### Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

#### How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

**The amendments must be made in the language in which the international application is to be published.**

#### What documents must/may accompany the amendments?

##### Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

**The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.**

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

|                                                    |                                                                                                  |                                                         |
|----------------------------------------------------|--------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| Applicant's or agent's file reference<br>PB61926   | <b>FOR FURTHER ACTION</b><br>see Form PCT/ISA/220<br>as well as, where applicable, Item 5 below. |                                                         |
| International application No.<br>PCT/EP2007/053118 | International filing date (day/month/year)<br>30/03/2007                                         | (Earliest) Priority Date (day/month/year)<br>03/04/2006 |
| Applicant<br><br>GLAXO GROUP LIMITED               |                                                                                                  |                                                         |

This International search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International search report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

a. With regard to the **language**, the International search was carried out on the basis of:

- ☒ the international application in the language in which it was filed  
☐ a translation of the international application into \_\_\_\_\_, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☐ **Unity of invention is lacking** (see Box No. III)

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant  
☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant  
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. \_\_\_\_\_  
☐ as suggested by the applicant  
☐ as selected by this Authority, because the applicant failed to suggest a figure  
☐ as selected by this Authority, because this figure better characterizes the invention  
b. ☐ none of the figures is to be published with the abstract

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2007/053118

## A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/04 C07D403/04 C07D413/04 C07D417/04

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

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, WPI Data, BEILSTEIN Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                           | Relevant to claim No. |
|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| A         | WO 2005/080382 A (GLAXO GROUP LTD [GB];<br>ARISTA LUCA [IT]; BONANOMI GIORGIO [IT];<br>CAPELLI) 1 September 2005 (2005-09-01)<br>cited in the application<br>preparation 77                                                                                  | 1                     |
| A         | US 2002/032238 A1 (PRIEPKE HENNING [DE] ET<br>AL) 14 March 2002 (2002-03-14)<br>example 16                                                                                                                                                                   | 1                     |
| A         | ECH-CHAHAD A ET AL: "An expeditious<br>hydroxyamidation of carboxylic acids"<br>TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM,<br>NL,<br>vol. 46, no. 31,<br>1 August 2005 (2005-08-01), pages<br>5113-5115, XP004963778<br>ISSN: 0040-4039<br>the whole document | 1                     |



Further documents are listed in the continuation of Box C.



See patent family annex.

## \* Special categories of cited documents:

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

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

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

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

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

\*G\* document member of the same patent family

Date of the actual completion of the international search

28 June 2007

Date of mailing of the international search report

05/07/2007

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

De Jong, Bart

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2007/053118

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|-------------------------------------------|---------------------|----------------------------|---------------------|
| WO 2005080382 A                           | 01-09-2005          | AR 047890 A1               | 01-03-2006          |
|                                           |                     | AU 2005215918 A1           | 01-09-2005          |
|                                           |                     | CA 2557115 A1              | 01-09-2005          |
|                                           |                     | EP 1745040 A1              | 24-01-2007          |
|                                           |                     | KR 20060127991 A           | 13-12-2006          |
|                                           |                     | US 2007142438 A1           | 21-06-2007          |
| <hr/>                                     |                     |                            |                     |
| US 2002032238 A1                          | 14-03-2002          | NONE                       |                     |
| <hr/>                                     |                     |                            |                     |

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2007/053118

## A. CLASSIFICATION OF SUBJECT MATTER

INV.: C07D401/04 C07D403/04 C07D413/04 C07D417/04

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

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, WPI Data, BEILSTEIN Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                   | Relevant to claim No. |
|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| A         | WO 2005/080382 A (GLAXO GROUP LTD [GB]; ARISTA LUCA [IT]; BONANOMI GIORGIO [IT]; CAPELLI) 1 September 2005 (2005-09-01) cited in the application preparation 77                                                                      | 1                     |
| A         | US 2002/032238 A1 (PRIEPKE HENNING [DE] ET AL) 14 March 2002 (2002-03-14) example 16                                                                                                                                                 | 1                     |
| A         | ECH-CHAHAD A ET AL: "An expeditious hydroxyamidation of carboxylic acids" TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 46, no. 31, 1 August 2005 (2005-08-01), pages 5113-5115, XP004963778 ISSN: 0040-4039 the whole document | 1                     |

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

## \* Special categories of cited documents:

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the International filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

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

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

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

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

\*Z\* document member of the same patent family

Date of the actual completion of the international search

28 June 2007

Date of mailing of the international search report

05/07/2007

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel: (+31-70) 340-2040, Tx. 31 651 epo nl,  
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Authorized officer

De Jong, Bart

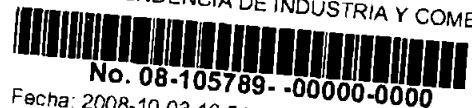
# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2007/053118

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|-------------------------------------------|---------------------|----------------------------|---------------------|
| WO 2005080382 A                           | 01-09-2005          | AR 047890 A1               | 01-03-2006          |
|                                           |                     | AU 2005215918 A1           | 01-09-2005          |
|                                           |                     | CA 2557115 A1              | 01-09-2005          |
|                                           |                     | EP 1745040 A1              | 24-01-2007          |
|                                           |                     | KR 20060127991 A           | 13-12-2006          |
|                                           |                     | US 2007142438 A1           | 21-06-2007          |
| <hr/>                                     |                     |                            |                     |
| US 2002032238 A1                          | 14-03-2002          | NONE                       |                     |
| <hr/>                                     |                     |                            |                     |



No. 08-105789- -00000-0000

Fecha: 2008-10-03 16:54:47  
Tra. 11 PATENTE IYII  
Act. 411 PRESENTACION

Dep. 2020 NUECREACION  
Eve: 378 FASE NACIONAL I  
Folios: 48

REQUISITOS MINIMOS PARA ADMISION A TRAMITE  
PCT

PATENTE DE INVENCION

[X]

MODELO DE UTILIDAD [ ]

- ◆ 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 [X]
- ◆ 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 [ ]

ESQUEMA DE TRAZADO [ ]

- ◆ Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- ◆ Representación gráfica del esquema trazado [ ]
- ◆ Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ]

INCOMPLETA [ ]

Felici Navarro

Firma Responsable

Fecha 3-10-09

Carrera 13 No. 27-00 Piso 5, 7 y 10  
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REPUBLICA DE COLOMBIA  
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,  
2020

Doctor(a)  
OLARTE GARCIA CARLOS REYNALDO  
Apoderado(a) y/o Representante de  
GLAXO GROUP LIMITED

|            |                            |                   |
|------------|----------------------------|-------------------|
| REFERENCIA | Radicación No.             | 8 105789          |
|            | Solicitud internacional    | PCT/EP2007/053118 |
|            | Fecha inicio fase nacional | 03/11/2008        |
|            | Trámite                    | 11                |
|            | Evento                     | 378               |
|            | Actuación                  | 430               |
|            | Oficio No.                 |                   |

No 14085

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 51bis 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, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

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 07 NOV. 2008  
jfernand