



Industria y Comercio

SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 02-109622-A-00000-0000

Fecha: 2002-12-03 00:00:00 Dep 2020 DIR NUEVASCR
Tra. 11 PATENTEIYII Eve 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 1

Delegatura de propiedad Indl

División de Nuevas Creaciones

PCT
SOLICITUD



PATENTE DE INVENCION

EXPEDIENTE No. **02-109622-A**

TÍTULO NOVEDOS COMPUESTOS DE
TRIAZOLO PIRIMIDINA

51. CLASIFICACIÓN INTERNACIONAL AGIK 3/SOS

71. SOLICITANTE JUAN PABLO CADENA SARMIENTO

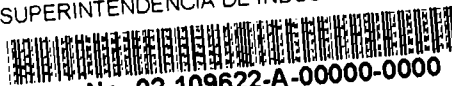
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74. APODERADO _____

22. BOGOTÁ, D. C., _____

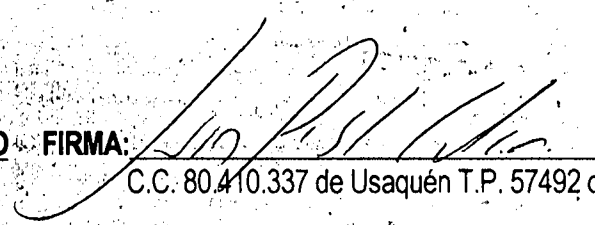
20 2038

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No. 02-109622-A-00000-0000

Fecha: 2002-12-03 00:00:00
Tra. 11 PATENTEIYII
Act. 411 PRESENTACIONDep. 2020 DIR.NUEVASCR
Eve. 379 FASENACIONALII
Folios: 1FORMULARIO ÚNICO DE CONVERSIÓN, DIVISIÓN Y FUSIÓN
DE SOLICITUDES

1 SOLICITUD DE:		
☐ Conversión. ☒ División. ☐ Fusión.		
2 SOLICITANTE	Nombre: ASTRAZENECA AB Dirección: S-1-51 85 Södertälje, Suecia Nacionalidad o Domicilio: Suecia Lugar de Constitución: Suecia Teléfono: _____ Fax: _____ E-mail: _____	IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número _____
3 REPRESENTANTE O APODERADO	Nombre: JUAN PABLO CADENA SARMIENTO Dirección: Cra. 7 No. 71-21, Torre B, Piso 4 Teléfono: 744-2200 Fax: 742-2200 E-mail: _____	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número <u>80 410.337</u> TP <u>57492</u>
4 CONVERSIÓN	5 DIVISIÓN	6 FUSIÓN
Expediente No.: _____ De: _____ A: _____	Expediente No.: <u>02-109622</u> No. de divisionales: <u>1</u>	Expediente No.: _____ Expediente No.: _____
7 Comprobante de pago No. <u>08-61.386</u> Fecha <u>26-08-2008</u>		
8 Anexos: ☒ Comprobante de pago de la tasa por \$ 501.000 ☒ Poderes, si fuere el caso. ☒ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas. ☒ Copia de la solicitud divisional.		
9 NOMBRE: JUAN PABLO CADENA SARMIENTO FIRMA:  C.C. 80.410.337 de Usaquén T.P. 57492 del C.S.J.		

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

23

PETITORIO

AS: 108.235



Espacio reservado para el adhesivo de radicación

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

1

SOLICITUD DE:



Patente de Invención.



Patente de Modelo de Utilidad.



Capítulo I.



Capítulo II.

2

SOLICITANTE
(71)

Nombre: **ASTRAZENECA AB**

Dirección: S-1-51 85 Södertälje, Suecia
Nacionalidad o Domicilio: Suecia
Lugar de Constitución: Suecia

Teléfono:

Fax:

E-mail:

IDENTIFICACIÓN

C.C.



NIT



C.E.



Otro



Cual

Número

3

REPRESENTANTE
O APODERADO

Nombre: **JUAN PABLO CADENA SARMIENTO**

Dirección: Cra. 7 No. 71-21 Torre B – Piso 4,
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Fax: 742-2200

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IDENTIFICACIÓN

C.C.



NIT



C.E.



Otro



Cual

Número 80.410.337 TP 57492

4

INVENTOR (ES)
(72)

Nombre: **Ulf LARSSON, Mattias MAGNUSSON, Tibor MUSIL, Andreas PALMGREN.**

Dirección: AstraZeneca R & D Södertälje S-151 85 Södertälje, SE; AstraZeneca R & D Södertälje S-151 85 Södertälje, SE; AstraZeneca Bulk Production S-151 85 Södertälje, SE; AstraZeneca R & D Södertälje S-151 85 Södertälje, SE (Respectivamente).

Nacionalidad o Domicilio: Suecia (Respectivamente).

5 PCT (86)

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PCT/SE01/001241

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31-05-2001

Publicación Internacional No

WO 2001/092263 A1

Fecha

06-12-2001

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NOVEDOSOS COMPUESTOS DE TRIAZOLO PIRIMIDINA

7 Clasificación Internacional (51):

8 Prioridad

SI ☒

NO ☐

(33) País de Origen

GB

(32) Fecha

02-06-2000

(31) Número de Solicitud

0013488.2

SE

06-06-2000

0002102-2

**ESTA ES UNA SOLICITUD DIVISIONAL O FRACCIONADA DEL
EXPEDIENTE No. 02-109.622**

9 Comprobante de pago No.

08 - 61,386

Fecha

26-08-2008

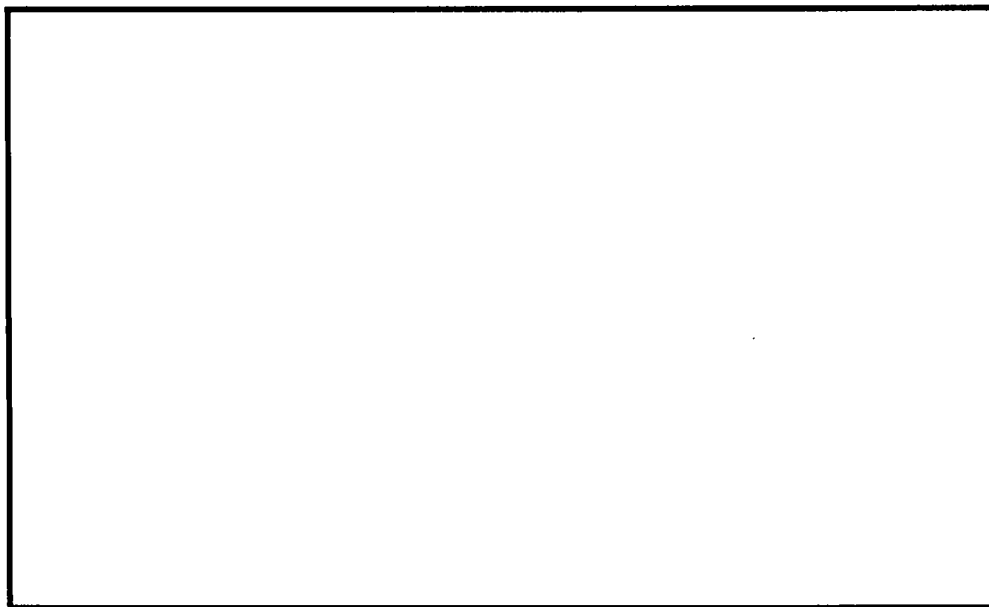
Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$ 501.000
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. **Fotocopia autenticada**
- ☒ 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 efectuado por la IPEA.
- ☒ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros: Extracto para Publicación y Tarjeta de Archivo Temático Listado de Secuencias
Tarjeta de Propietarios
Documentos PCT

11 FIGURA CARACTERÍSTICA:



12 Solicito la concesión de la patente,

NOMBRE: JUAN PABLO CADENA SARMIENTO

FIRMA: 
C.C. 80.410.337 de Usaquén TP 57492 del C.S.J.

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

108 235

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 02-109622- -00012-0000

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 61,386
FECHA : JULIO 31 DE 2008

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO DE BOGOTA	062754387	3257236	30/07/2008	21,542,000.00

***** 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: QUINTIENTOS UN MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

(21) No. de solicitud: 02-109622 A

(22) Fecha de solicitud: 03-12-2002

(51) Clasificación Internacional:

(71) Solicitante(s): ASTRAZENECA AB

(72) Inventor(es): Ulf LARSSON, Mattias MAGNUSSON, Tibor MUSIL, Andreas PALMGREN.

(74) Agente: JUAN PABLO CADENA SARMIENTO

(30) Prioridad	(31)	No. Prioridad	(32)	Fecha	(33)	País
		0013488.2		02-06-2000		GB
		0002102-2		06-06-2000		SE

FIGURA CARACTERÍSTICA
6 x 6 cm

(85) Fecha inicio fase nacional: 02-01-2003

(86) Datos relativos a la presentación de la solíc. PCT
Fecha de presentación de la solicitud: 31-05-2001
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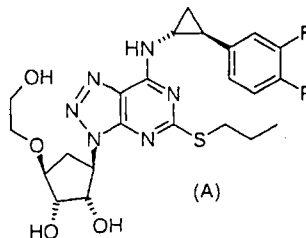
(87) Publicación internacional:

Fecha: 06-12-2001
No. Publicación: WO 01/92263 A1

(54) Título: NOVEDOSOS COMPUESTOS DE TRIAZOLO PIRIMIDINA

(55) Reivindicaciones:

1. Un proceso para preparar un compuesto de fórmula (A):



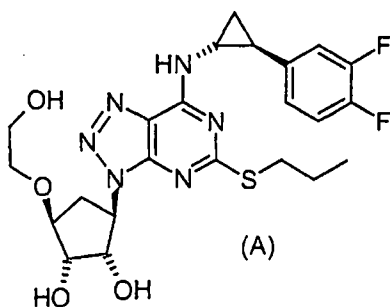
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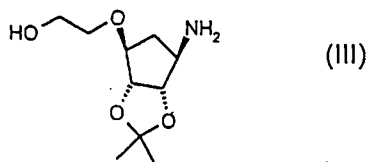
(21) No. de solicitud: 02-109622 A					(51) Int Cl:
(22) Fecha de solicitud: 03-12-2002					(71) Solicitante (s): ASTRAZENECA AB
(30) Prioridad	(31) No. Prioridad	(32) Fecha	(33) País	(72) Inventor(es): Ulf LARSSON, Mattias MAGNUSSON, Tibor MUSIL, Andreas PALMGREN.	
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(86) Datos relativos a la presentación de la solíc. PCT					(87) Publicación internacional
Fecha de presentación de la solicitud: 31-05-2001					Fecha: 06-12-2001
No. de solicitud: PCT/SE01/01241					No. publicación: WO 01/92263 A1
(54) Título: NOVEDOSOS COMPUESTOS DE TRIAZOLO PIRIMIDINA					

(55) Reivindicaciones:

- Un proceso para preparar un compuesto de fórmula (A):



- Un proceso para preparar una sal de un compuesto de fórmula (III):



con los intermediarios farmacéuticos usados en dichos procesos.

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a

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(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
6 December 2001 (06.12.2001)

PCT

(10) International Publication Number
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- (21) International Application Number: PCT/SE01/01241
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- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- (71) Applicant (*for all designated States except US*): ASTRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): LARSSON, Ulf [SE/SE]; AstraZeneca R & D Södertälje, S-151 85 Södertälje (SE). MAGNUSSON, Mattias [SE/SE]; AstraZeneca R & D Södertälje, S-151 85 Södertälje (SE). MUSIL, Tibor [SE/SE]; AstraZeneca Bulk Production, S-151 85 Södertälje (SE). PALMGREN, Andreas [SE/SE]; AstraZeneca R & D Södertälje, S-151 85 Södertälje (SE).

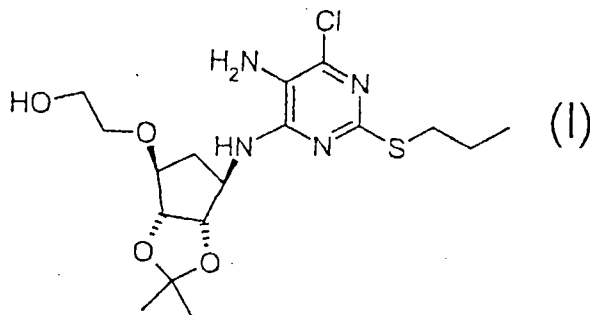
Published:

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

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

(54) Title: NOVEL TRIAZOLO PYRIMIDINE COMPOUNDS

WO 01/92263 A1

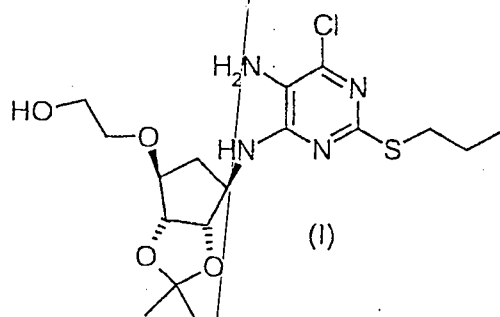


(57) Abstract: The present invention relates to a pyrimidine compound (I) useful as a pharmaceutical intermediate, to a process for preparing said pyrimidine compound, to intermediates used in said process, and to the use of said pyrimidine compound in the preparation of pharmaceuticals.

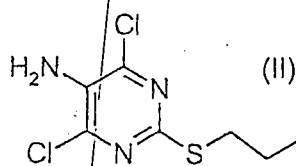
NOVEL TRIAZOLO PYRIMIDINE COMPOUNDS

The present invention relates to a pyrimidine compound useful as a pharmaceutical intermediate, to a process for preparing said pyrimidine compound, to intermediates used in said process, and to the use of said pyrimidine compound in the preparation of pharmaceuticals.

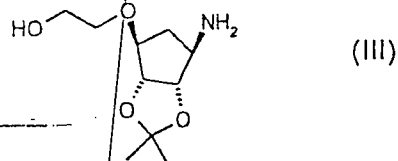
The present invention provides a compound of formula (I):



The present invention also provides a process for preparing a compound of formula (I), comprising reacting a compound of formula (II):



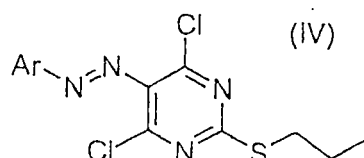
with a salt of a compound of formula (III):



in the presence of a suitable base (such as an alkali metal hydroxide (such as sodium or potassium hydroxide) a tertiary amine (such as a tri(C₁₋₆ alkyl)amine, for example triethylamine)), a suitable solvent (such as an alcohol, such as an aliphatic alcohol containing from 1 to 6 carbon atoms, for example ethanol), preferably at a temperature in the range 100-150°C and, where necessary (for example when the temperature exceeds the boiling point of the solvent), in a sealed system under autogenic pressure.

A suitable salt of a compound of formula (III) is a salt of a mineral or organic acid. Suitable mineral acids include hydrochloric, hydrobromic, hydroiodic, nitric or sulphuric acid. A suitable organic acid is, for example, an organic achiral acid such as acetic, trifluoroacetic, oxalic or p-toluenesulphonic acid, or an organic chiral acid such as L-tartaric acid, dibenzoyl-L-tartaric acid or di-p-toluoyl-L-tartaric acid.

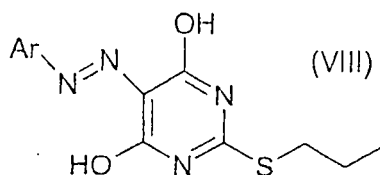
In another aspect the present invention provides a process for preparing a compound of formula (I) comprising hydrogenating a compound of formula (IV):



wherein Ar is phenyl optionally substituted by halogen, C₁₋₄ alkyl or C₁₋₄ alkoxy; to give a compound of formula (II), and reacting the compound of formula (II) with a compound of formula (III) (as described above) to provide the compound of formula (I).

The hydrogenation is preferably conducted using a heavy metal catalyst (such as platinum on carbon), in a suitable solvent (such as a C₁₋₆ aliphatic alcohol, for example 2-propanol (*iso*-propanol)), at a suitable temperature (such as 10-70°C, for example 20-50°C) and at a suitable pressure (such as 1-5 bar, for example about 3 bar).

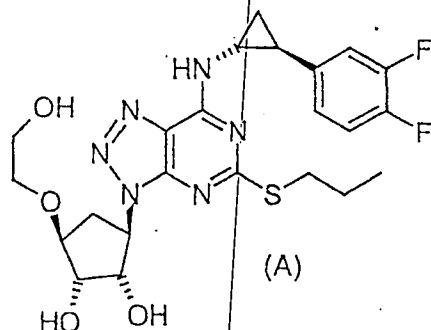
A compound of formula (IV) can be prepared by chlorinating a compound of formula (VIII):



wherein Ar is as defined above, with a suitable chlorinating agent (such as phosphorus oxychloride) in the presence of a suitable nitrogen containing base (such as triethylamine, especially pyridine) and at a suitable temperature (such as in the range 50°C to the boiling point of phosphorus oxychloride; for example 70 to 90°C). A compound of formula (VIII) can be prepared by routine adaptation of literature methods.

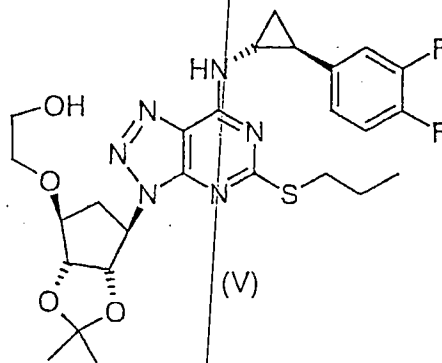
In a further aspect the present invention provides a process, as hereinbefore described, for the preparation of a compound of formula (II).

The compound of formula (I) can be used to prepare the pharmaceutical compound of formula (A):



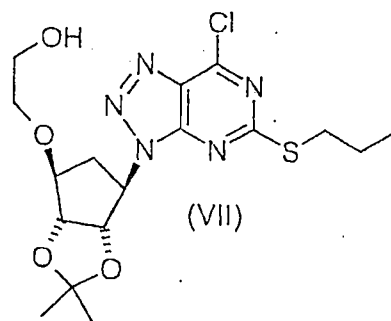
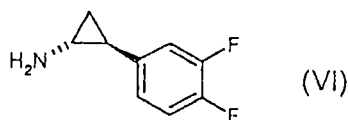
as described below.

Thus, a compound of formula (A) can be prepared by deprotecting a compound of formula (V):



for example using a strong mineral acid (such as hydrochloric acid) in a suitable solvent (such as methanol or ethanol).

A compound of formula (V) can be prepared by coupling a compound of formula (VI) {or a salt thereof (such as a mandelate salt) from which the compound of formula (VI) is generated *in situ*}, with a compound of formula (VII):



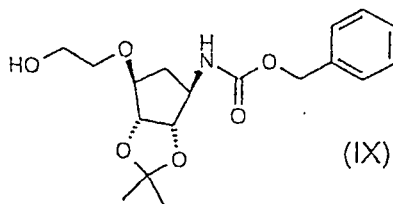
for example in the presence of a suitable base (such as a tertiary amine, such as a tri(C₁₋₆ alkyl)amine, for example triethylamine) and a suitable solvent (for example a polar solvent, such as an alcohol (such as an aliphatic alcohol containing from 1 to 6 carbon atoms, for example ethanol) or a nitrile (such as acetonitrile)) and at a suitable temperature (such as a temperature in the range 10-40°C, for example ambient temperature).

A compound of formula (VII) can be prepared by reacting a compound of formula (I) with an alkali metal nitrite (such as NaNO₂) or an organic nitrite (for example *iso*-amyl nitrite) in the presence of a suitable acid (such as acetic acid) and a suitable solvent (such as water or a mixture of water and acetic acid) and at a suitable temperature (such as a temperature in the range -10 to 15°C, for example -10 to 10°C).

Thus, in a further aspect the present invention provides the use of the compound of formula (I) in a process for the preparation of the compound of formula (A).

A salt of a compound of formula (III) can be prepared by reacting a compound of formula (III) with the necessary acid in a suitable solvent (such as water, an aliphatic alcohol containing 1 to 4 carbon atoms (for example ethanol) or a simple ester (such as ethyl acetate)) at a suitable temperature (such as from 10 to 60°C, for example 30 to 50°C).

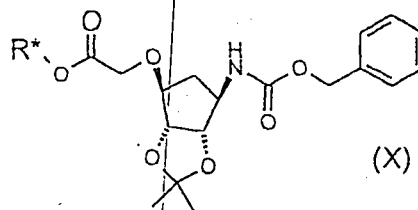
A compound of formula (III) can be prepared by deprotecting a compound of formula (IX):



for example by hydrogenation (such as with a heavy metal catalyst (such as palladium on carbon) in the presence of a solvent (such as an aliphatic alcohol containing 1 to 4 carbon

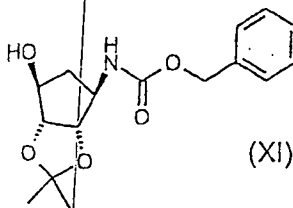
atoms, for example ethanol) at ambient temperature at a suitable pressure (such as 1 to 3 bar, for example 1.0 to 1.5 bar)).

A compound of formula (IX) can be prepared by reducing a compound of formula (X):



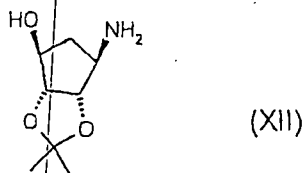
wherein R* is C₁₋₄ alkyl (preferably ethyl), such as with a suitable borohydride (for example an alkali metal borohydride, such as lithium borohydride), lithium aluminiumhydride or DIBAL-H in a suitable polar solvent (such as tetrahydrofuran).

A compound of formula (X) can be prepared by reacting a compound of formula (XI):



with a suitable compound L-CH₂CO₂R* {wherein R* is C₁₋₄ alkyl (especially ethyl); and L is a leaving group, especially halogen (for example bromo)}, in the presence of a suitable polar solvent (such as tetrahydrofuran) and in the presence of a suitable base (such as potassium *tert*-butoxide, sodium hydride or a C₁₋₆ alkyl lithium species).

A compound of formula (XI) can be prepared by reacting a compound of formula (XII):



with benzyl chloroformate in the presence of a suitable base (such as potassium carbonate) and a suitable solvent (such as a ketone (for example 4-methyl-2-pentanone) or a hydrocarbon (for example toluene)).

In a still further aspect the present invention provides a process for the preparation of a salt of a compound of formula (III) as hereinbefore described.

In further aspects the present invention provides an intermediate compound of formulae (II), (IV), (VII), (VIII), (X) or (XI), or a salt of a compound of formula (III).

5 The following Examples illustrate the invention.

EXAMPLE 1

This Example illustrates the preparation of 2-[(3aR,4S,6R,6aS)-6-amino-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]-dioxol-4-yl]oxy}-1-ethanol, L-tartaric acid salt (1:1).

10 Step a: Preparation of [3aS-(3a α ,4 α ,6 α ,6a α)]-[tetrahydro-6-hydroxy-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-yl]-carbamic acid, phenylmethyl ester.

Potassium carbonate (39.3g) was added to a suspension of [3aR-(3a α ,4 α ,6 α ,6a α)]-6-amino-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-ol, hydrochloride, (prepared as described in WO 9905142) (27.1g) in 4-methyl-2-pentanone (500ml). Water (150ml)
15 was then added followed by dropwise addition of benzyl chloroformate (23.1g). The reaction mixture was stirred at room temperature for 4 hours before the organic phase was separated. The aqueous phase was extracted with 4-methyl-2-pentanone (2x50ml). The combined organics were concentrated and the residue was purified (SiO₂, dichloromethane:methanol, 95:5 to 90:10 as eluant) to give the subtitle compound
20 (39.23g).

¹H NMR (CDCl₃) δ 7.32 (5H, m), 5.65 (1H, br s), 5.10 (2H, br s), 4.59 (1H, d), 4.48 (1H, d), 4.27 (1H, m), 4.19 (1H, br m), 2.24 (1H, br s), 1.69 (1H, d), 1.41 (3H, s), 1.26 (3H, s).

25 Step b: Preparation of [3aS-(3a α ,4 α ,6 α ,6a α)]-[2,2-dimethyl-6-(2-hydroxyethoxy)-tetrahydro-4H-cyclopenta-1,3-dioxol-4-yl]-carbamic acid, phenylmethyl ester.

Potassium tert-butoxide (3.6g) in tetrahydrofuran (20ml) was added over 5 minutes to a solution of the product from Step (a) (39.23g) in tetrahydrofuran (200ml). After 15 minutes, ethyl bromoacetate (3.7ml) in tetrahydrofuran (10ml) was added dropwise. The
30 mixture was stirred at 0°C for 10 minutes, then further ethyl bromoacetate was added (3.7ml x4). The reaction mixture was stirred at 0°C a further 2 hours.

Lithium borohydride (2.79g) was then added portionwise to the reaction mixture which was then stirred at $<5^{\circ}\text{C}$ for 16 hours. Glacial acetic acid (23g) was added dropwise to the cold mixture. After stirring for 30 minutes, water (100ml) was added dropwise and the resulting mixture was stirred for 30 minutes. The phases were then separated and the aqueous phase was extracted with ethyl acetate. The combined organics were washed with saturated sodium bicarbonate and brine, dried and concentrated. The residue was purified (SiO₂, ethyl acetate:hexane, 25:75 to 50:50 as eluant) to give the subtitle compound (38.6g).

MS (APCI) 218 ($\text{M}+\text{H}^{+}$, 100%).

Step c: Preparation of [3aR-(3a α ,4 α ,6 α ,6a α)]-2-[[6-amino-2,2-dimethyl-tetrahydro-4H-cyclopenta-1,3-dioxol-4-yl]oxy]-ethanol (alternatively named: 2-[[[(3aR,4S,6R,6aS)-6-amino-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]-dioxol-4-yl]oxy]-1-ethanol).

A slurry of 5% palladium on charcoal (4g) in ethanol was added to a solution of the product from Step (b) (39.96g) in ethanol (250ml) and the mixture was hydrogenated at 1.2 bar for 20 hours. The catalyst was filtered off and the filtrate was concentrated to give the subtitle compound (23.65g).

MS (APCI) 160 ($\text{M}+\text{H}^{+}$, 100%).

Step d: Preparation of [3aR-(3a α ,4 α ,6 α ,6a α)]-2-[[6-amino-2,2-dimethyl-tetrahydro-4H-cyclopenta-1,3-dioxol-4-yl]oxy]-ethanol L tartrate (alternatively named: 2-[[[(3aR,4S,6R,6aS)-6-amino-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]-dioxol-4-yl]oxy]-1-ethanol, L-tartaric acid salt (1:1)).

A stirred solution of the product obtained in Step (c) (545g) in ethanol (3.8l) was heated to 35°C . L-tartaric acid (352g) was added (temperature rise to 45°C) and the mixture was stirred at $40 - 45^{\circ}\text{C}$ for 1 h. The mixture was cooled to 20°C and the resulting thick slurry stirred for 16 h then filtered. The collected solid was washed with two portions of 2-propanol (300ml, then 500ml), sucked dry then dried *in vacuo* at 40°C to give the product as white crystals (728g).

EXAMPLE 2

This Example illustrates the preparation of *trans*-(1*R*,2*S*)-2-(3,4-difluorophenyl)-cyclopropylamine, R-mandate salt (alternatively named *trans*-(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropanaminium (2*R*)-2-hydroxy-2-phenylethanoate.

5 Step 1: Preparation of (E)-3-(3,4-difluorophenyl)-2-propenoic acid.

A stirred mixture of pyridine (15.5kg) and piperidine (0.72kg) were heated to 90°C. Malonic acid (17.6kg) was added, followed by slow addition, over 50 minutes, of 3,4-difluorobenzaldehyde (12.0kg). The reaction mixture was stirred at 90°C for a further 4 hours and 36 minutes. Water (58.5kg) was added and 32 litres of the pyridine/water
10 mixture then was distilled out of the reactor under reduced pressure. The reaction mixture was acidified to pH 1 with 37% hydrochloric acid (6.4kg) over a 40 minute period, then cooled to 25°C with strong stirring. The solids were collected by filtration, washed twice with 1% hydrochloric acid (34.8 L per wash), once with water (61 L) and then deliquored thoroughly in the filter. The product was then dried under vacuum at 40°C for 24 hours and
15 40 minutes, affording 13.7kg of the crystalline product.

Step 2: Preparation of (E)-3-(3,4-difluorophenyl)-2-propenoyl chloride.

A stirred mixture of (E)-3-(3,4-difluorophenyl)-2-propenoic acid (8.2 kg), toluene (7.4kg) and pyridine (0.18kg) was heated to 65°C and then thionyl chloride (7.4kg) was
20 added over 30 minutes. The reaction was stirred for a further 2h 15 minutes after the addition was complete, then diluted with toluene (8.7kg). Excess thionyl chloride, sulfur dioxide and hydrogen chloride were then distilled out, together with toluene (10 L), under reduced pressure, yielding a solution of the (E)-3-(3,4-difluorophenyl)-2-propenoyl chloride (approximately 9kg) in toluene.

25 Step 3: Preparation of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (E)-3-(3,4-difluorophenyl)-2-propenoate.

A solution of *L*-menthol (7.1kg) in toluene (8.5kg) was added over a 20 minute period to the solution of (E)-3-(3,4-difluorophenyl)-2-propenoyl chloride (prepared as in
30 Step 2) and pyridine (0.18kg, 2.28 mol) stirring at 65°C. The reaction mixture was stirred at 65°C for a further 4 hours and 40 minutes after the addition was complete, then cooled

to 25°C and stirred for a 14 hours. The solution was diluted with toluene (16kg), washed with 5% aqueous sodium chloride (6.4kg), then 6% sodium hydrogen carbonate (6.47kg), then water (6.1kg). The solution was dried azeotropically by distillation of the solvent (20 L) under reduced pressure. Dimethyl sulfoxide (33.9kg) was added and the remaining
5 toluene was distilled off under reduced pressure, affording 47.3kg of a solution of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (*E*)-3-(3,4-difluorophenyl)-2-propenoate (approx. 13.3kg) in dimethyl sulfoxide.

Step 4: Preparation of dimethylsulfoxonium methylide (dimethyl(methylene)oxo- λ^6 -
10 sulfane.

Sodium hydroxide powder (1.2kg), prepared by milling sodium hydroxide pellets in a rotary mill through a 1mm metal sieve, and trimethylsulfoxonium iodide (6.2kg) were stirred in dimethyl sulfoxide (25.2kg) under a nitrogen atmosphere at 25°C for 90 min. The solution was used directly in the preparation of (1*R*, 2*S*, 5*R*)-2-isopropyl-5-
15 methylcyclohexyl *trans*-2-(3,4-difluorophenyl)cyclopropanecarboxylate.

Step 5: Preparation of (1*R*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexyl *trans*-2-(3,4-difluorophenyl)cyclopropanecarboxylate.

A solution of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (*E*)-3-(3,4-
20 difluorophenyl)-2-propenoate (approximately 8.6kg) in dimethyl sulfoxide (approximately 27.9kg) was added with stirring over 20 minutes to a mixture of dimethylsulfoxonium methylide (approximately 2.6kg, prepared as described above), sodium iodide (approximately 4.2kg), water (approximately 500g) and sodium hydroxide (approximately 56g) in dimethylsulfoxide(27.7kg) at 25°C. The reaction mixture was stirred for a further 2
25 hours and 50 minutes at 25°C, then used directly for the preparation of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl *trans*-(1*R*,2*R*)-2-(3,4-difluorophenyl)cyclopropanecarboxylate.

Step 6: Preparation of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl *trans*-(1*R*,2*R*)-2-(3,4-difluorophenyl)cyclopropanecarboxylate
30

A crude solution of (1*R*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexyl *trans*-2-(3,4-difluorophenyl)cyclopropanecarboxylate produced as described in step 5 was heated with

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stirring from 25°C to 50°C over a 1 hour period and the temperature was maintained for a further hour. The mixture was then cooled with stirring from 50°C to 35°C over 4 hours, kept at 35°C for 1 hour, then cooled to 26°C over 4 hours, kept at 26°C for 1 hour, then cooled to 19°C over 3 hours and kept at 19°C for 5 hours and 10 minutes. The product was collected by filtration, affording a crystalline solid (2.7kg) which was shown to contain a mixture of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl *trans*-(1*R*,2*R*)-2-(3,4-difluorophenyl)cyclopropanecarboxylate (1.99 kg) and (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl *trans*-(1*S*,2*S*)-2-(3,4-difluorophenyl)cyclopropanecarboxylate (85g).

10 Step 7: Preparation of *trans*-(1*R*, 2*R*)-2-(3,4-difluorophenyl)cyclopropanecarboxylic acid.
(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl *trans*-(1*R*,2*R*)-2-(3,4-difluorophenyl)-cyclopropanecarboxylate (9.6kg, 91.8% diastereomeric excess) was dissolved in ethanol (13.8kg) and heated with stirring to 46°C. 45% aqueous sodium hydroxide (3.1kg) was added over a 20 minute period and the mixture was stirred for a further 2 hours and 27 minutes. Solvent (28 L) was distilled out of the mixture under reduced pressure, then the mixture was cooled to 24°C and diluted with water (29.3kg), after which the liberated menthol was extracted into toluene (3 washes of 3.3kg each). The remaining aqueous material was acidified to pH 2 with 37% hydrochloric acid (3.3 L) and the product was extracted into toluene (8.6kg, then 2 more washes of 4.2kg and 4.3kg). The combined toluene extracts were washed with 1% hydrochloric acid (4.9 L), then diluted with further toluene (4.2kg) and azeotropically dried by distillation of the solvent (25 L) under reduced pressure. A final dilution with toluene (24.2kg) was followed by distillation of the solvent under reduced pressure (10 L) affording a solution containing *trans*-(1*R*, 2*R*)-2-(3,4-difluorophenyl)cyclopropanecarboxylic acid (approximately 3.45kg) suitable for the production of *trans*-(1*R*, 2*R*)-2-(3,4-difluorophenyl)cyclopropanecarbonyl chloride.

Step 8: Preparation of *trans*-(1*R*, 2*R*)-2-(3,4-difluorophenyl)cyclopropanecarbonyl chloride.

Pyridine (70ml) was added to a solution of *trans*-(1*R*, 2*R*)-2-(3,4-difluorophenyl)cyclopropanecarboxylic acid (approximately 3.45kg) in toluene (approximately 12 -15kg), prepared as described above and the mixture was then heated to 65°C. Thionyl chloride (2.3kg) was added over a period of 1 hour and the mixture was

stirred at 70°C for 3 hours. Thionyl chloride (0.5kg) was added and the mixture was stirred a further 2 hours at 70°C. A final aliquot of thionyl chloride (0.5kg) was added and the reaction mixture was stirred for 1 hour at 70°C, then cooled to 40°C. Periodic additions of toluene (45kg, 3 additions of 15kg each) were made during distillation of solvent
5 (approximately 60 L) from the mixture under reduced pressure, then the solution of *trans*-(1*R*, 2*R*)-2-(3,4-difluorophenyl)cyclopropanecarbonyl chloride (approximately 3.8kg) in toluene (approximately 6-9 L) was cooled to 20°C.

Step 9: Preparation of *trans*-(1*R*, 2*R*)-2-(3,4-difluorophenyl)cyclopropanecarbonyl azide.

10 A solution of *trans*-(1*R*, 2*R*)-2-(3,4-difluorophenyl)cyclopropanecarbonyl chloride (approximately 3.8kg) in toluene (approximately 6-9 L), prepared in Step 8, at 1°C was added over a period of 74 minutes to a mixture of sodium azide (1.24kg), tetrabutylammonium bromide (56g) and sodium carbonate (922g) in water (6.2kg), stirring at 1.5°C. The mixture was stirred at 0°C for 1 hour and 55 minutes, then the aqueous layer
15 was diluted with cold water (3.8kg), stirred briefly, then separated. The toluene layer was washed once more at 0°C with water (3.8kg), then with 20% aqueous sodium chloride (3.8 L), then stored at 3°C for further use.

Step 10: Preparation of *trans*-(1*R*, 2*S*)-2-(3,4-difluorophenyl)cyclopropylamine.

20 A cold solution of *trans*-(1*R*, 2*R*)-2-(3,4-difluorophenyl)cyclopropanecarbonyl azide prepared as described in Step 9 was added over a period of 41 minutes to toluene (6.0kg) stirring at 100°C. The mixture was stirred for a further 55 minutes at 100°C, then cooled to 20°C and added over a period of 2 hours and 15 minutes to hydrochloric acid (3M, 18.2kg) stirring at 80°C. After 65 minutes the solution was diluted with water (34kg)
25 and cooled to 25°C. The toluene layer was removed and the aqueous layer was basified to pH 12 with 45% aqueous sodium hydroxide (3.8kg) and the product was then extracted into ethyl acetate (31kg) and washed twice with water (13.7kg per wash), affording a solution containing *trans*-(1*R*, 2*S*)-2-(3,4-difluorophenyl)cyclopropylamine (2.6kg, 91.8% enantiomeric excess) in ethyl acetate (29.5 L).

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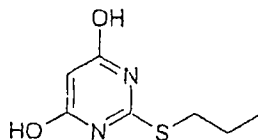
Step 11: Preparation of *trans*-(1*R*, 2*S*)-2-(3,4-difluorophenyl)cyclopropanaminium (2*R*)-2-hydroxy-2-phenylethanoate.

R-(-)-Mandelic acid (2.26kg) was added to a solution containing *trans*-(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropylamine (2.6kg, 91.8% enantiomeric excess), stirring at 17°C in ethyl acetate (45.3 L). The mixture was stirred at 25°C for 3 hours and 8 minutes, then filtered and washed twice with ethyl acetate (13.8kg total). The crystalline product was dried at 40°C under reduced pressure for 23 hours, affording *trans*-(1*R*,2*S*)-2-(3,4-difluorophenyl)-cyclopropanaminium (2*R*)-2-hydroxy-2-phenylethanoate (4.45kg).

EXAMPLE 3

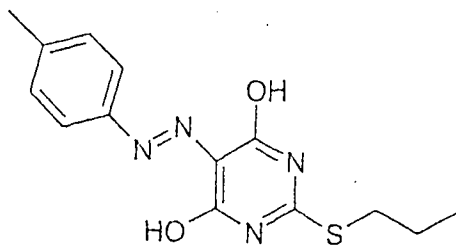
This Example illustrates the preparation of 4,6-dichloro-2-(propylsulfanyl)-5-pyrimidinamine.

Step 1: 4,6-Dihydroxy-2-(propylsulfanyl)pyrimidine.



Water (670ml) was added to 2-thiobarbituric acid (200 g). The resulting mixture was stirred and sodium hydroxide (126.3g) was added in portions. The mixture was stirred for 40 min. then diluted with water. 1-Methyl-2-pyrrolidinone (400 ml) and 1-iodopropane (140.9ml) were then added. The resulting slurry was stirred at 20°C for 22h. The pH of the mixture was then adjusted to 6.5 by addition of 1M HCl (600ml) over 30 min, then to pH 2.5 by the addition of 6 M HCl (180ml) over a further 30 min. The resulting slurry was stirred for 18h and the product was isolated by filtration and washed successively with water (4 X 100ml), ethanol (200ml) and water (2 X 200ml). The product was dried under reduced pressure overnight at 50°C to yield the title product as a white powder (185g).

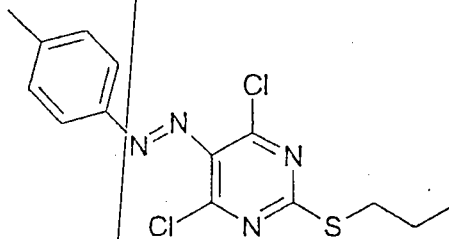
Step 2: 4,6-Dihydroxy-5-[(*E*)-2-(4-methylphenyl)diazenyl]-2-(propylsulfanyl)pyrimidine.



Ethanol (25ml), 4,6-dihydroxy-2-(propylsulfanyl)pyrimidine (Step 1; 5g) and water (25 ml) were stirred together at room temperature. Sodium hydroxide (1.02g) was added and a clear solution obtained. The resulting solution was cooled to 0°C and then sodium acetate (9.42g) was added to give Solution A.

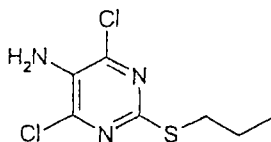
5 In a separate vessel, a solution of p-toluidine (3.01g) in water (10 ml) was prepared. To this was added concentrated hydrochloric acid (37% w/w aqueous solution; 8.45 ml). The resulting mixture was cooled to 0°C, and a solution of sodium nitrite (2.16g) in water (10ml) was cooled to 0°C and added dropwise to the toluidine – containing reaction mixture over 30 minutes. The temperature during the addition was kept between 0 and 5°C.
10 The resulting mixture was cooled to 0°C and added to the cold (0°C) Solution A (the temperature rose to 8°C). The resulting yellow suspension was stirred overnight and the pH of the mixture was adjusted to pH 1 by addition of 6 M HCl. The mixture was filtered and the collected product washed with water (25ml) ethanol (10ml). The product was dried under reduced pressure at 50°C over 24 h to give the product as a yellow solid (6.97g).

15 Step 3: 4,6-Dichloro-5-[(E)-2-(4-methylphenyl)diazanyl]-2-(propylsulfanyl)pyrimidine.



Pyridine (2.58ml) was added to a stirred, heated (70°C) slurry of 4,6-dihydroxy-5-[(E)-2-(4-methylphenyl)diazanyl]-2-(propylsulfanyl)pyrimidine (Step 2, 5g) in toluene
20 (15ml). Phosphorous oxychloride (18.7ml) was added dropwise to the mixture over 15 min (exotherm to 94°C). The reaction mixture was heated for a further 4.5 h then evaporated. The residue was azeotroped twice with toluene (2 x 30ml). The residue was dissolved in toluene (50 ml) and filtered to remove some solids. The collected solid was washed with toluene and the combined filtrates washed with water (30ml) and saturated aqueous sodium
25 bicarbonate solution (30ml). Evaporation gave the title product (4.98g) as a red oil that slowly crystallised on standing.

Step 4: Preparation of 4,6-dichloro-2-(propylsulfanyl)-5-pyrimidinamine.



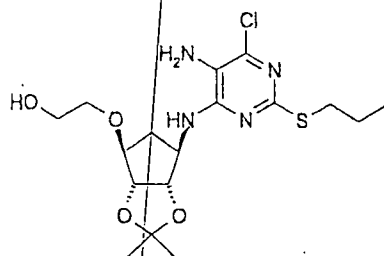
A stirred solution of 4,6-dichloro-5-[(E)-2-(4-methylphenyl)diazenyl]-2-(propylsulfanyl)pyrimidine (Step (3), 1.1kg) in 2-propanol (16.6kg) was hydrogenated for 1h at 40°C/3.2 bar over a platinum on carbon catalyst (0.81kg, 50% w/w Pt/C). The hydrogen gas pressure was released and the reactor flushed with nitrogen. The reaction mixture was filtered. The collected solid was washed with 2-propanol (1.7kg) and the combined filtrates were concentrated under reduced pressure. The residual oil was cooled to 20°C and dissolved in ethyl acetate (5kg) and water (5.5l) was added. The pH of the stirred mixture was adjusted to pH 2 by the addition of 3M aqueous hydrochloric acid (800ml). The phases were allowed to separate and the aqueous phase was discharged. Water (2.75l) was added to the organic phase and the pH was adjusted to 2 by the addition of a small amount of 3M HCl (45 ml). The aqueous phase was separated and the organic phase concentrated under reduced pressure at 30-50°C, to give 4,6-dichloro-2-(propylsulfanyl)-5-pyrimidinamine as a reddish viscous oil containing ethyl acetate that was dissolved in ethanol (8.5kg). Solvent (6.5l of ethanol/ethyl acetate) was then removed by distillation at reduced pressure. A further portion of ethanol (4.5kg) was added to the residue and the distillation repeated to remove 6.5 l of solvent. The ethanol solution of the product was used without further purification in the following step.

EXAMPLE 4

This Example illustrates the preparation of [1S-[1 α ,2 α ,3 β (1S*,2R*),5 β]]-3-[7-[2-(3,4-difluorophenyl)cyclopropyl-amino]-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol (alternatively named (1S,2S,3R,5S)-3-[7-([(1R,2S)-2-(3,4-difluorophenyl)cyclopropyl]amino)-5-(propylsulfanyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)-1,2-cyclopentanediol).

Step 1: Preparation of [3aR-(3 α ,4 α ,6 α ,6 α)]-2-[[6-[[5-amino-6-chloro-2-(propylthio)-4-pyrimidinyl]amino]tetrahydro-2,2-dimethyl-3aH-cyclopenta[d][1,3]dioxol-4-yl]oxy]ethanol (alternatively named 2-[[[(3aR,4S,6R,6aS)-6-[[5-amino-6-chloro-2-

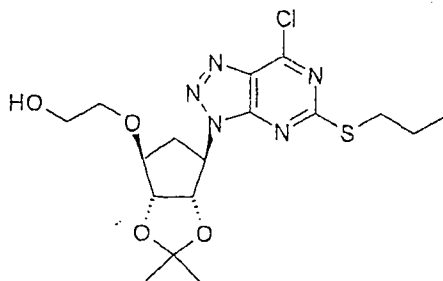
(propylsulfanyl)-4-pyrimidinyl]amino}-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-yl)oxy]-1-ethanol).



The ethanolic solution of 4,6-dichloro-2-(propylsulfanyl)-5-pyrimidinamine,
 5 (prepared as in Example 3, Step 4) was added to 2-(((3aR,4S,6R,6aS)-6-amino-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-yl)oxy)-1-ethanol, L-tartaric acid salt (1:1) (1.18kg). To the resulting stirred thick slurry was charged triethylamine (0.95kg) maintaining the temperature between 20 and 25°C. The reactor was sealed and the temperature increased to 120-125°C. The reaction mixture was kept within this
 10 temperature range for 30h, then cooled to 75°C, and the pressure released. The temperature of the mixture was adjusted to 50°C and the solvent distilled off under reduced pressure at 30 to 40°C. Ethyl acetate (4.95kg) and water (5.5l) were added, the pH of the mixture adjusted to pH 5 by the addition of 3M hydrochloric acid (100 ml), and the phases were separated. The organic phase was washed with 15% w/w brine (5.5l), then separated. The
 15 organic phase was concentrated under reduced pressure (4.8l of solvent removed) to give 2-(((3aR,4S,6R,6aS)-6-[[5-amino-6-chloro-2-(propylsulfanyl)-4-pyrimidinyl]amino]-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-yl)oxy)-1-ethanol as a brown-red viscous oil containing ethyl acetate. The product is used without further purification in the following step.

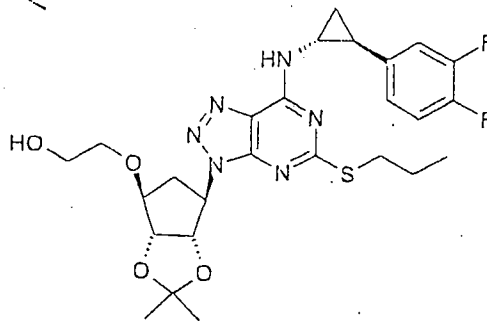
20

Step 2: Preparation of [3aR-(3a α ,4 α ,6 α ,6a α)]-2-[[6-[7-chloro-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]tetrahydro-2,2-dimethyl-3aH-cyclopenta[d][1,3]dioxol-4-yl]oxy]ethanol (alternatively named 2-(((3aR,4S,6R,6aS)-6-[7-chloro-5-(propylsulfanyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-yl)oxy)-1-ethanol).
 25



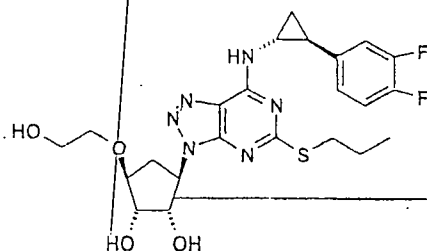
2-(((3aR,4S,6R,6aS)-6-({[5-Amino-6-chloro-2-(propylsulfanyl)-4-pyrimidinyl]amino}-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-yl)oxy)-1-ethanol, as obtained in Step 1 was dissolved in acetic acid (5.75kg) and water (650ml). The resulting solution was cooled to 2°C (with stirring) and a solution of sodium nitrite (232g) in water (1.25l) was added such that the mixture temperature was held below 7°C. The mixture was then allowed to warm to 7°C then ethyl acetate (8.9kg) was added. Aqueous potassium carbonate solution (4l, 37%w/w) was added. The mixture was separated and the organic phase washed with further aqueous potassium carbonate solution (3.8kg, 21% w/w). The aqueous phase was discarded and the organic phase concentrated under reduced pressure to give the sub-titled compound as a red-brown viscous oil used without further purification in the following step.

Step 3: Preparation of {3aR-[3aα,4α,6α(1R*,2S*),6aα]}-2-[6-({7-[2-(3,4-difluorophenyl)cyclopropyl]amino-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl}tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-yl)oxy]ethanol (alternatively named 2-(((3aR,4S,6R,6aS)-6-[7-({[1,2S]-2-(3,4-difluorophenyl)-cyclopropyl]amino)-5-(propylsulfanyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-yl)oxy)-1-ethanol).



trans-(1*R*,2*S*)-2-(3,4-Difluorophenyl)cyclopropanaminium (2*R*)-2-hydroxy-2-phenylethanoate (0.77kg) was charged to a vessel followed by a solution of 2-(((3*aR*,4*S*,6*R*,6*aS*)-6-[7-chloro-5-(propylsulfanyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-2,2-dimethyltetrahydro-3*aH*-cyclopenta-[*d*][1,3]dioxol-4-yl}oxy)-1-ethanol (prepared as in Step 2) dissolved in acetonitrile (3.85kg). To the resulting stirred mixture was added triethylamine (0.81kg) at such a rate that the reaction temperature was maintained between 20-25°C. The reaction mixture was stirred for 13 h then concentrated at reduced pressure at 30°C. To the residue was added ethyl acetate (8.1kg) and water (4.6l). The pH of the stirred two phase mixture was adjusted to pH 4 by the addition of 3M HCl (450ml). The mixture was then allowed to settle and separate. The aqueous phase was separated and the retained organic phase was washed with 15% w/w aqueous sodium chloride solution (4.15kg), the organic phase was concentrated under reduced pressure at 30-50°C giving the crude title compound as a red oil, that was used directly in the next step.

Step 4: Preparation of [1*S*-[1 α ,2 α ,3 β (1*S**,2*R**),5 β]]-3-[7-[2-(3,4-difluorophenyl)-cyclopropylamino]-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol (alternatively named (1*S*,2*S*,3*R*,5*S*)-3-[7-[[1*R*,2*S*)-2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-(propylsulfanyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyethoxy)-1,2-cyclopentenediol).



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Aqueous hydrochloric acid (3 M, 4.8l), was added to a stirred solution of 2-(((3*aR*,4*S*,6*R*,6*aS*)-6-[7-[[1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl]-amino]-5-(propylsulfanyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-2,2-dimethyltetrahydro-3*aH*-cyclopenta[*d*][1,3]dioxol-4-yl}oxy)-1-ethanol (1.931kg) in methanol (13.4kg), maintaining the temperature during the addition between 20 and 25°C. The mixture was then stirred for 24 h at 20°C. Sodium hydroxide (45% w/w aqueous solution; 780ml) was then added to adjust the pH of the mixture to pH 7.2. The methanol was then removed by distillation at

reduced pressure and ethyl acetate (14.3 kg) added. The mixture was heated to 45° and the aqueous layer separated. The organic phase was then washed 15% w/w aqueous sodium chloride solution (7.2kg). Ethyl acetate (10l) was removed by distillation at reduced pressure. Fresh ethyl acetate (7.2kg) was charged and the mixture filtered. The filter was washed with ethyl acetate (1.5kg). The combined filtrates were dried by repeated addition/distillation of ethyl acetate. When the solution was dry, the product content of the ethyl acetate solution was determined by a chromatographic assay technique and found to contain 1016g of product, the concentration of the ethyl acetate was adjusted until a concentration of 5ml ethyl acetate / g of the crude product was reached. The ethyl acetate solution was heated to 47°C and isooctane (2.5ml/g product, 2540ml) was then added over 15 min. The resulting slurry was stirred for 30 min. then more iso-octane (2540ml) was added over 5 mins. The resulting mixture was stirred at 48-50°C for 30 min then cooled to 20°C over 3h. The slurry was stirred at 20°C for 6.5 h then filtered and washed with a mixture consisting of iso-octane (1.25kg) and ethyl acetate (1.6kg). The collected solid was dried in vacuo to give the title compound (920g).

If desired, the crude product can be further purified by employing one of the following three methods.

Recrystallization from ethyl acetate / iso-octane

The crude product is dissolved in ethyl acetate (4.8 ml/g) at 55°C, then filtered to remove particles. The clear solution is taken back to the reactor for recrystallisation and the temperature is set at 50°C. iso-Octane is then added (4.8 ml/g) during 10 min. The slurry is allowed to stand for 30 minutes after which it is cooled to 20°C during 2-3 hours and finally the temperature is kept at 20°C for about 30 minutes. The product is then filtered and washed with iso-octane (2x1.5 ml/g). The product is dried under reduced pressure at 50°C giving pure product (>98% pure by h.p.l.c. analysis).

Slurry with n-butyl acetate

The crude product is suspended in n-butyl acetate 4 ml/g and stirred at room temperature for 10 hours. The slurry is cooled to 0°C during 3-4 hours and kept at 0°C for 1 hour. The product is filtered and washed with 2 ml/g of cold n-butyl acetate (<0°C). The

product is then dried in vacuo at 50°C, giving pure product (>98% pure by h.p.l.c. analysis).

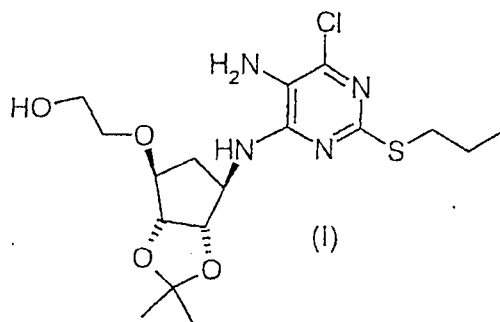
Slurry with iso-propanol

The crude product is suspended in iso-propanol 3 ml/g and stirred at 50°C for 72h.

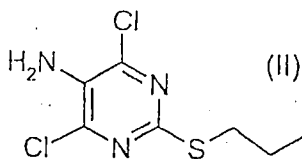
- s The slurry is then cooled to 20°C during 3 hours and the temperature is kept at 20°C for
> about 30 minutes. The product is then filtered and washed with 1 ml/g of cold iso-propanol
(<0°C). Finally, the product is dried under reduced pressure at 50°C giving pure product
(>98% pure by h.p.l.c. analysis).

CLAIMS

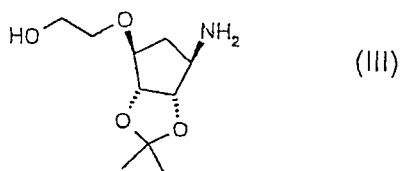
1. A compound of formula (I):



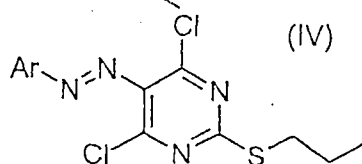
2. A process for preparing a compound of formula (I), comprising reacting a compound of formula (II):



with a salt of a compound of formula (III):



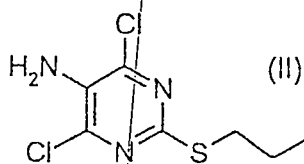
3. A process for preparing a compound of formula (I) as claimed in claim 2 comprising hydrogenating a compound of formula (IV):



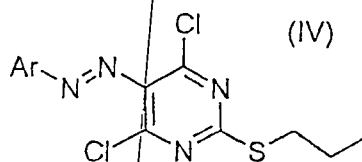
wherein Ar is phenyl optionally substituted by halogen, C₁₋₄ alkyl or C₁₋₄ alkoxy; to give a compound of formula (II), and reacting the compound of formula (II) with a compound of formula (III) to provide the compound of formula (I).

2^o gr

4. A process for preparing a compound of formula (II):



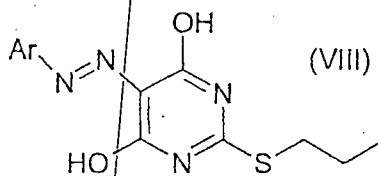
comprising hydrogenating a compound of formula (IV):



wherein Ar is phenyl optionally substituted by halogen, C₁₋₄ alkyl or C₁₋₄ alkoxy.

2^o gr

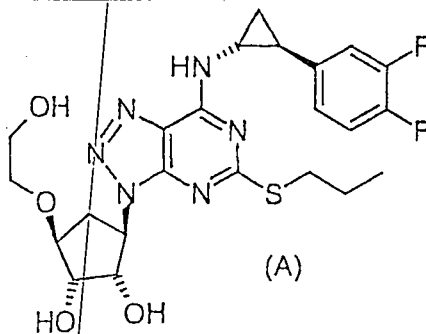
5. A process for preparing a compound of formula (II) as claimed in claim 2, comprising chlorinating a compound of formula (VIII):



wherein Ar is phenyl optionally substituted by halogen, C₁₋₄ alkyl or C₁₋₄ alkoxy, to provide a compound of formula (IV), and then hydrogenating the compound of formula (IV).

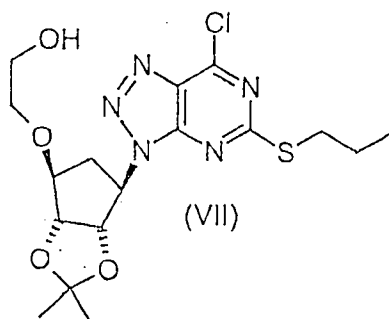
1^{er} gr

6. The use of a compound of formula (I) to prepare a compound of formula (A):

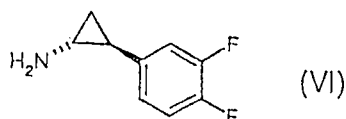


comprising:

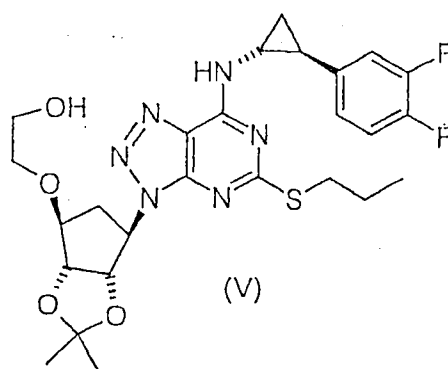
- (a) reacting a compound of formula (I) with an alkali metal nitrite in the presence of a suitable acid to prepare a compound of formula (VII):



- (b) coupling the compound of formula (VII) with a compound of formula (VI):



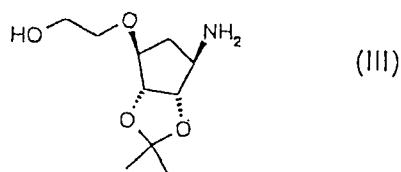
to provide a compound of formula (V):



and,

- (c) deprotecting a compound of formula (V) to provide the compound of formula (A).

7. A process for preparing a salt of a compound of formula (III):

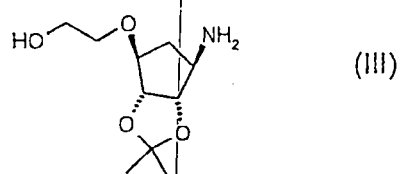


3er 9r

comprising reacting a compound of formula (III) with the necessary acid.

3 or

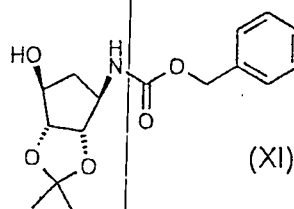
8. A process for preparing a salt of a compound of formula (III):



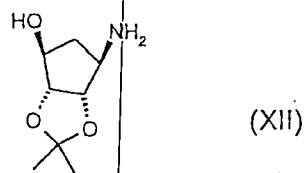
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comprising the steps:

- (a) preparing a compound of formula (XI):



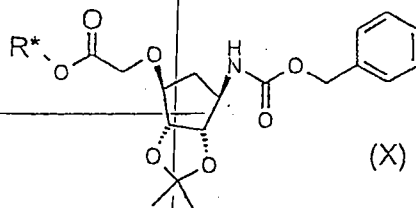
by reacting a compound of formula (XII):



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with benzyl chloroformate;

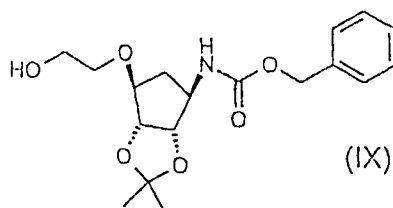
- (b) preparing a compound of formula (X):



by reacting a compound of formula (XI) with a compound $L-CH_2CO_2R^*$
{wherein R^* is C_{1-4} alkyl; and L is a leaving group};

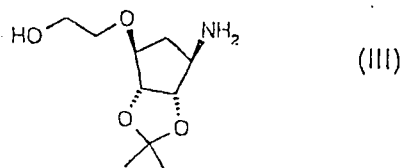
15

- (c) preparing a compound of formula (IX):



by reducing a compound of formula (X);

(d) preparing a compound of formula (III):



by deprotecting a compound of formula (IX); and,

(e) preparing a salt of a compound of formula (III) by reacting the compound of formula (III) with the necessary acid.

9. An intermediate compound of formula (II), (IV), (VII), (VIII), (X) or (XI) or a salt of a compound of formula (III).

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 01/01241

A. CLASSIFICATION OF SUBJECT MATTER		
IPC7: C07D 487/04 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)		
IPC7: C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
SE,DK,FI,NO classes as above		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9941254 A1 (ASTRA PHARMACEUTICALS LTD.), 19 August 1999 (19.08.99), page 8; page 9 --	1,2,6,9
A	US 5905085 A (DAVID R. BORCHERDING ET AL), 18 May 1999 (18.05.99) --	1,2,6
A	WO 9101317 A1 (GLAXO GROUP LIMITED), 7 February 1991 (07.02.91) --	1,2,6
E,A	WO 0034283 A1 (ASTRAZENECA UK LIMITED), 15 June 2000 (15.06.00) -- -----	1,2,6,9
☐ 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 application or patent 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 "I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
2 October 2001		04-10-2001
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86		Authorized officer Fernando Farieta/Eö Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT
Information on patent family members

03/09/01

International application No.

PCT/SE 01/01241

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9941254 A1	19/08/99	AU 723699 B	07/09/00
		AU 2650099 A	30/08/99
		AU 6430498 A	12/10/98
		BR 9811253 A	26/09/00
		BR 9907934 A	24/10/00
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		EP 1017439 A	12/07/00
		EP 1056749 A	06/12/00
		NO 994433 A	13/09/99
		NO 20004089 A	16/10/00
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		PL 342430 A	04/06/01
		SE 9800458 D	00/00/00
		SE 9803669 D	00/00/00
US 5905085 A	18/05/99	US 5723466 A	03/03/98
		US 5817660 A	06/10/98
		US 5817661 A	06/10/98
		US 5817672 A	06/10/98
		US 5916892 A	29/06/99
		US 5929079 A	27/07/99
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WO 0034283 A1	15/06/00	AU 2016500 A	26/06/00
		NO 20012725 D	00/00/00
		SE 9804211 D	00/00/00
		AU 5077599 A	07/02/00
		BR 9912104 A	02/05/01
		EP 1097139 A	09/05/01
		NO 20010210 A	15/03/01
		SE 9901271 D	00/00/00

INTERNATIONAL SEARCH REPORT

International application No.
SE01/01241

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)	
This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:	
1. ☐ Claims Nos.:	because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:	because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:	because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)	
This International Searching Authority found multiple inventions in this international application, as follows: see next sheet	
1. ☐	As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐	As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒	As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.: 1, 2, 6, 9
4. ☐	No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark on Protest	
☐	The additional search fees were accompanied by the applicant's protest.
☐	No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/01241

According to Article 34(3) (a-c) and Rule 13.2, an international application shall relate to one invention only or to a group of inventions linked by one or more of the same or corresponding "special technical features", i. e. features, that define a contribution which each of the inventions makes over the prior art.

The problem the claimed invention aims to solve is a compound I : 2-[(3aR, 4S, 6R, 6aS)-6-{[5-amino-6-chloro-2-(propylsulfanyl)- 4-pyrimidinyl] amino}-2,2 - dimethyltetrahydro-3aH-cyclopenta[d][1,3] oxy]-1-ethanol, a process for the preparation thereof and the use for the production of the compound (A). The process is performed in several steps where the essential step is the formation of a pyrimidinamine connected to a cyclopenta-dioxol (Claim 2) to form compound I (Claim 1).

Claims 3-9, which confers to process steps before the formation of compound I of claim 1, are formally associated with claim 1. However, the reaction described in claim 2 is not new and, as this step is to be considered as the unifying special technical feature, there is no such feature when the reaction of claim is known according to WO99/ 41254.

The reactions claimed in claims [3,7,8] and [4,5] are completely separated from the reaction described in claim 2. The application also contains a claim [9] concerning the intermediate and end products of the process. In order to fulfil the requirements of unity of invention it is necessary that the intermediate compounds are closely interconnected with the end products. Such close connection requires that the essential structural part of the end product is incorporated by the intermediate.

In the present invention the essential structural parts are a cyclopentanyl-amine directly attached to a pyrimidinamine. This structural parts are however not present in all the compounds claimed. Consequently the present application does not fulfil the requirements of unity of invention.

The application is found to contain the following three inventions:

Invention 1: Compounds I and VII, and a method for producing those compounds containing the same essential structural parts. As described in claims 1, 2, 6 and partly 9.

Invention 2: Compounds II, IV and VIII, and a method for producing those compounds. As described in claims 4, 5 and partly 9.

Invention 3: Compounds III, X and XI, and a method for producing those compounds. As described in claims 3, 7, 8 and partly 9.

As a consequence of the lack of unity of the application a complete search has not been performed. The search comprises only what is referred to as invention 1 above.

(12) SOLICITUD INTERNACIONAL PUBLICADA SEGÚN EL TRATADO DE COOPERACIÓN INTERNACIONAL
EN MATERIA DE PATENTES (PCT)

(19) Organización Mundial de Propiedad Intelectual
Oficina Internacional



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PCT

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(21) No. Solicitud Internacional: PCT/SE01/01241

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(72) Inventores, e

(75) Inventores/Solicitantes (para US únicamente):
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(SE).

(74) Agente: **GLOBAL INTELLECTUAL PROPERTY**;
AstraZeneca AB S-151 85 Södertälje (SE).

(81) Países designados (a menos que se indique lo
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SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG,
US, UZ, VC, VN, ZA, ZM, ZW.

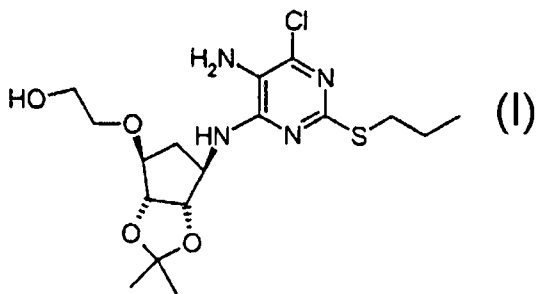
(84) Países designados (a menos que se indique lo
contrario para cada clase de protección disponible):
ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL,
SZ, TZ, UG, ZM, ZW), Eurasiática (AM, AZ, BY, KG,
KZ, MD, RU, TJ, TM), Europea (AT, BE,
BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR,
HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE,
SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN,
GQ, GW, ML, MR, NE, SN, TD, TG).

Publicado:

- con informe internacional de búsqueda
- antes del vencimiento del tiempo límite para modificar las
reivindicaciones y para volverse a publicar en el caso de
recibo de modificaciones.

Para códigos de dos letras y otras abreviaturas, remítase a las
"Notas Guía sobre Códigos y Abreviaturas" que aparece al
comienzo de cada edición regular del Boletín Oficial PCT.

(54) Título: NOVEDOSOS COMPUESTOS DE TRIAZOLO PIRIMIDINA



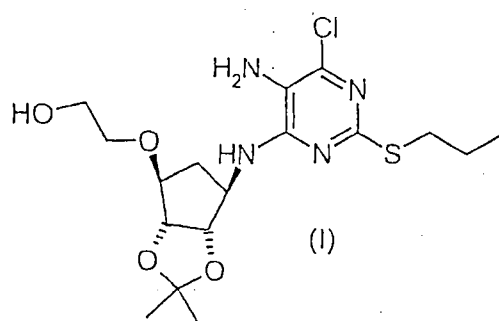
(57) Extracto: La presente invención se relaciona
con un compuesto de pirimidina (I) útil como un
intermediario farmacéutico, con un proceso para
preparar dicho compuesto de pirimidina, con
intermediarios usados en dicho proceso, y con el uso
de dicho compuesto de pirimidina en la preparación
de fármacos.

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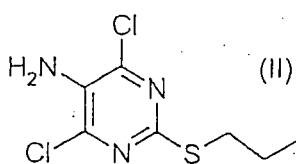
NOVEDOSOS COMPUESTOS DE TRIAZOLO PIRIMIDINA

La presente invención se relaciona con un compuesto de pirimidina útil como un intermediario farmacéutico, con un proceso para preparar dicho compuesto de pirimidina, con intermediarios usados en dicho proceso, y con el uso de dicho compuesto de pirimidina en la preparación de fármacos.

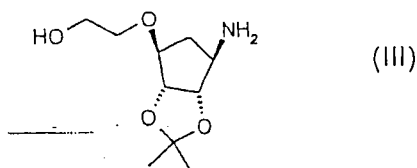
La presente invención proporciona un compuesto de fórmula (I):



La presente invención también proporciona un proceso para preparar un compuesto de fórmula (I), que comprende reaccionar un compuesto de fórmula (II):



con una sal de un compuesto de fórmula (III):

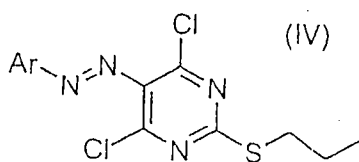


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en presencia de una base adecuada (tal como un hidróxido de metal alcalino (tal como hidróxido de sodio o potasio) una amina terciaria (tal como un tri(C₁₋₆ alquil)amina, por ejemplo trietilamina)), un solvente adecuado (tal como un alcohol, tal como un alcohol alifático que contiene desde 1 a 6 átomos de carbono, por ejemplo etanol), preferiblemente a una temperatura en el rango de 100-150°C y, donde sea necesario (por ejemplo cuando la temperatura excede el punto de ebullición del solvente), en un sistema sellado bajo presión autógena.

Una sal adecuada de un compuesto de fórmula (III) es una sal de un mineral o ácido orgánico. Ácidos minerales adecuados incluyen ácido clorhídrico, bromhídrico, yodídrico, nítrico o sulfúrico. Un adecuado ácido orgánico es, por ejemplo, un ácido orgánico aquiral tal como ácido acético, trifluoroacético, oxálico o p-tolueno ácido sulfónico, o un ácido orgánico quiral tal como L-ácido tartárico, dibenzoil-L-ácido tartárico o di-p-toluoil-L-ácido tartárico.

En otro aspecto la presente invención proporciona un proceso para preparar un compuesto de fórmula (I) que comprende hidrogenar un compuesto de fórmula (IV):

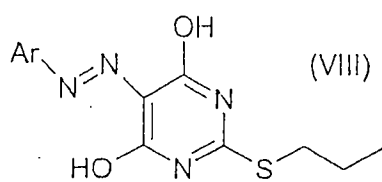


donde Ar es fenil opcionalmente sustituido por halógeno, C₁₋₄ alquil o C₁₋₄ alcoxi; para dar un compuesto de fórmula (H), y reaccionando el compuesto de fórmula (H) con un compuesto de fórmula (III) (como se describió arriba) para proporcionar el compuesto de fórmula (I).

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La hidrogenación se conduce preferiblemente usando un catalizador de metal pesado (tal como platino sobre carbono), en un solvente adecuado (tal como un C₁₋₆ alcohol alifático, por ejemplo 2-propanol (iso-propanol)), a una adecuada temperatura (tal como 10-70°C, por ejemplo 20-50°C) y a una adecuada presión (tal como 1-5 bar, por ejemplo alrededor de 3 bar).

Un compuesto de fórmula (IV) puede prepararse por clorinación de un compuesto de fórmula (VIII):

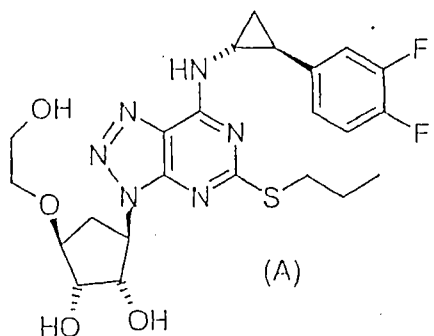


donde Ar es como se definió arriba, con un adecuado agente de clorinación (tal como oxi-cloruro fosforoso) en presencia de una adecuada nitrógeno que contiene base (tal como trietilamina, especialmente piridina) y a una adecuada temperatura (tal como en el rango de 50°C al punto de ebullición del oxi-cloruro fosforoso; por ejemplo 70 a 90°C). Un compuesto de fórmula (VIII) puede prepararse mediante adaptación de rutina de métodos de la literatura.

En un adicional aspecto la presente invención proporciona un proceso, como se describió aquí anteriormente, para la preparación de un compuesto de fórmula (II).

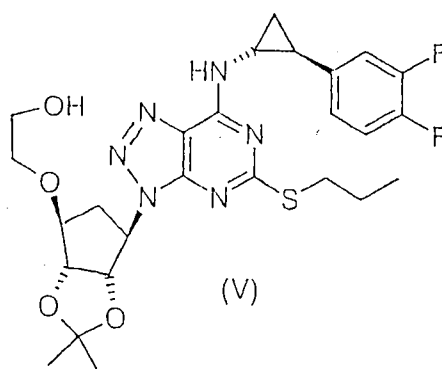
El compuesto de fórmula (I) puede usarse para preparar el compuesto farmacéutico de fórmula (A):

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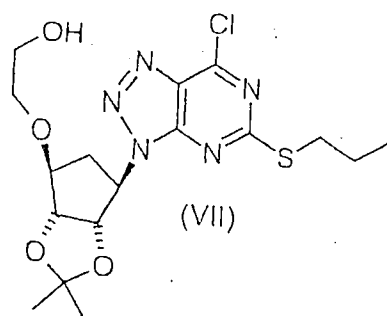
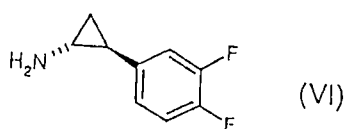
como se describió abajo.

Consecuentemente, un compuesto de fórmula (A) puede prepararse desprotegiendo un compuesto de fórmula (V):



por ejemplo usando un ácido de mineral fuerte (tal como ácido clorhídrico) en un adecuado solvente (tal como metanol o etanol).

Un compuesto de fórmula (V) puede prepararse acoplando un compuesto de fórmula (VI) {o su sal (tal como una sal de mandelato) a partir de la cual el compuesto de fórmula (VI) se genera in situ, con un compuesto de fórmula (VII):



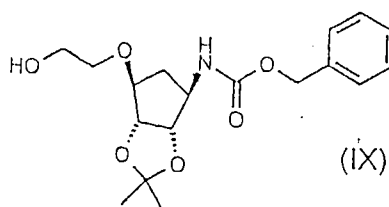
por ejemplo en presencia de una base adecuada (tal como una amina terciaria, tal como un tri(C₁₋₆ alquil)amina, por ejemplo trietilamina) y un solvente adecuado (por ejemplo un solvente polar, tal como un alcohol (tal como un alcohol alifático que contiene desde 1 a 6 átomos de carbono, por ejemplo etanol) o un nitrato (tal como acetonitrilo)) y a una adecuada temperatura (tal como una temperatura en el rango de 10-40°C, por ejemplo temperatura ambiente).

Un compuesto de fórmula (VII) puede prepararse reaccionando un compuesto de fórmula (I) con un nitrato de metal alcalino (tal como NaNO₂) o un nitrato orgánico (por ejemplo iso-amilo nitrato) en presencia de un ácido adecuado (tal como ácido acético) y un adecuado solvente (tal como agua o una mezcla de agua y ácido acético) y a una adecuada temperatura (tal como una temperatura en el rango de -10 a 15°C, por ejemplo -10 a 10°C).

Consecuentemente, en un adicional aspecto la presente invención proporciona el uso del compuesto de fórmula (1) en un proceso para la preparación del compuesto de fórmula (A).

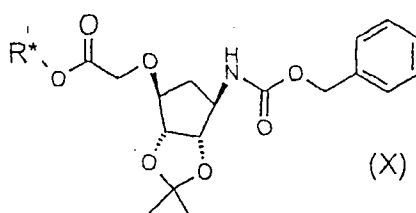
Una sal de un compuesto de fórmula (III) puede prepararse reaccionando un compuesto de fórmula (III) con el ácido necesario en un solvente adecuado (tal como agua, un alcohol alifático que contiene 1 a 4 átomos de carbono (por ejemplo etanol) o un simple éster (tal como acetato de etilo)) a una temperatura adecuada (tal como desde 10 a 60°C, por ejemplo 30 a 50°C).

Un compuesto de fórmula (III) puede presentarse desprotegiendo un compuesto de fórmula (IX):

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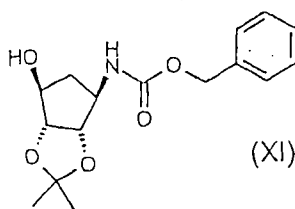
por ejemplo por hidrogenación (tal como con un catalizador de metal pesado (tal como paladio sobre carbono) en presencia de un solvente (tal como un alcohol alifático que contiene 1 a 4 átomos de carbono, por ejemplo etanol) a temperatura ambiente a una presión adecuada (tal como 1 a 3 bar, por ejemplo 1,0 a 1,5 bar).

Un compuesto de fórmula (IX) puede prepararse reduciendo un compuesto de fórmula (X):



donde R* es C₁₋₄ alquil (preferiblemente etilo), tal como con un adecuado borohidrido (por ejemplo un borohidrido de metal alcalino, tal como borohidrido de litio), aluminio hídrido de litio o DIBAL-H en un adecuado solvente polar (tal como tetrahidrofuran).

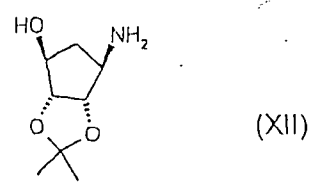
Un compuesto de fórmula (X) puede prepararse reaccionando un compuesto de fórmula (XI):



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con un compuesto adecuado $L-CH_2CO_2R^*$ {donde R^* es C_{1-4} alquil (especialmente etilo); y L es un grupo libre, especialmente halógeno (por ejemplo bromo)), en presencia de un adecuado solvente polar (tal como tetrahidrofuran) y en presencia de una base adecuada (tal como potasio tert-butóxido, hídrido de sodio o una especie de litio C_{1-6} alquil).

Un compuesto de fórmula (XI) puede prepararse reaccionando un compuesto de fórmula (XII):



con cloroformiato de bencilo en presencia de una base adecuada (tal como carbonato de potasio) y un solvente adecuado (tal como un quetona (por ejemplo 4-metil-2-pentanona) o un hidrocarburo (por ejemplo tolueno)).

En aún un adicional aspecto la presente invención proporciona un proceso para la preparación de una sal de un compuesto de fórmula (III) como se describió aquí anteriormente.

En adicionales aspectos la presente invención proporciona un compuesto intermediario de fórmulas (II), (IV), (VII), (VIII), (X) o (XI), o una sal de un compuesto de fórmula (III).

Los siguientes Ejemplos ilustran la invención.

EJEMPLO 1

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Este Ejemplo ilustra la preparación de 2-[[[(3aR,4S,6R,6aS)-6-amino-2,2-dimetiltetrahidro-3aH-ciclopenta[d][1,3]-dioxol-4-il]oxi}-1-
etanol, L-sal de ácido tartárico (1:1).

Paso a: Preparación de [3aS-(3aa,4a,6a,6aa)]-[tetrahidro-6-hidroxi-2,2-dimetil-4H-ciclopenta-1,3-dioxol-4-il]-ácido carbámico, fenil metil éster.

Carbonato de potasio (39,3g) se agregó a una suspensión de [3aR-(3aa,4a,6a,6aa)]6-amino-tetrahidro-2,2-dimetil-4H-ciclopenta-1,3-dioxol-4-ol, hidrocloreuro, (preparado como se describió en WO 9905142) (27,1g) en 4-metil-2-pentanona (500ml). Agua (150ml) se agregó entonces mediante adición gota a gota de cloroformiato de bencilo (23,1g). La mezcla de la reacción se agitó a temperatura ambiente durante 4 horas antes de que se separara la fase orgánica. La fase acuosa se extrajo con 4-metil-2-pentanona (2x50ml). Los orgánicos combinados se concentraron y el residuo se purificó (SiO₂, diclorometano: metanol, 95:5 a 90:10 como eluyente) para dar el compuesto titulado (39,23g).

¹H NMR (CDCl₃) δ 7,32 (5H, m), 5,65 (1H, br s), 5,10 (2H, br s), 4,59 (1H, d), (1H, d), 4,27 (1H, m), 4,19 (1H, br m), 2,24 (1H, br s), 1,69 (1H, d), 1m41 (3H, s), 1,26 (3H, s).

Paso b: Preparación de [3aS-(3aa, 4a, 6a, 6aa)]-[2,2-dimetil-6-(2-hidroxietoxi)tetrahidro-4H-ciclopenta-1,3-dioxol-4-il]-ácido carbámico, fenil-metil éster.

Potasio ter-butóxido (3,6g) en tetrahidrofuran (20ml) se agregó durante 5 minutos a una solución del producto del Paso (a) (39,23g) en tetrahidrofuran (200ml). Después de 15 minutos, bromo acetato de etilo

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(3,7ml) en tetrahidrofuran (10ml) se agregó gota a gota. La mezcla se agitó a 0°C durante 10 minutos, luego adicional bromo acetato de etilo se agregó (3,7ml x4). La mezcla de la reacción se agitó a 0°C 2 horas adicionales.

Boro hídrido de litio (2,79g) se agregó entonces en porciones a la mezcla de la reacción la cual se agitó entonces a <5°C durante 16 horas. Ácido acético glacial (23g) se agregó gota a gota a la mezcla fría. Después de agitar durante 30 minutos, se agregó agua (100ml) gota a gota y la mezcla resultante se agitó durante 30 minutos. Las fases se separaron entonces y la fase acuosa se extrajo con acetato de etilo. Los orgánicos comandos se lavaron con bicarbonato de sodio saturado y salmuera, se secaron y concentraron. El residuo se purificó (SiO₂, acetato de etilo: hexano, 25:75 a 50:50 como eluyente) para dar el compuesto titulado (38,6g).

MS (APCI) 218 (M+H⁺, 100%).

Paso c: Preparación de [3aR-(3aα, 4α, 6α, 6aα)]-2-[[6-amino-2,2-dimetil-tetrahidro-4Hciclopenta-1,3-dioxol-4-il]oxi]-etanol (alternativamente denominado: 2-{[(3aR,4S,6R,6aS)-6amino-2,2-dimetiltetrahidro-3aH-ciclo-penta[d][1,3]-dioxol-4-il]oxi}-l-etanol).

Un precipitado de 5% de paladio en carbón (4g) en etanol se agregó a una solución del producto del Paso (b) (39,96g) en etanol (250ml) y la mezcla se hidrogenó a 1,2 bar durante 20 horas. El catalizador se sacó por filtración y el filtrado se concentró para dar el compuesto titulado (23,65g).

MS (APCI) 160 (M+H⁺, 100%).

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Paso d: Preparación de [3aR-(3a α , 4 α , 6 α , 6a α)]-2-[[6-amino-2,2-dimetil-tetrahidro-4H-ciclopenta- 1,3 -dioxol-4-il] oxi]-etanol L tartrato (denominado alternativamente: 2-{[(3aR,4S,6R,6aS)-6-amino-2,2-dimetiltetrahidro-3aH-ciclopenta[d][1,3]-dioxol-4-il]oxi}-l-etanol, L-sal de ácido tartárico (1:1)).

Una solución agitada del producto obtenido en el Paso (c) (545g) en etanol (3,8l) se calentó a 35°C. se agregó L-ácido tartárico (352g) (la temperatura se elevó a 45°C) y la mezcla se agitó a 40 – 45°C durante 1 hora. La mezcla se enfrió a 20°C y el precipitado pegajoso resultante se agitó durante 16 horas y luego se filtró. El sólido recogido se lavó con dos porciones de 2-propanol (300ml, luego 500ml), se resumió seco y luego se secó en vacío a 40°C para dar el producto como cristales blancos (728g).

EJEMPLO 2

Este Ejemplo ilustra la preparación de trans-(1R, 2s)-2-(3,4-difluorofenil) ciclo propilamina, R-sal de mandelato (nombrada alternativamente trans-(1R, 2s)-2-(3,4difluorofenil)ciclo propanaminio (2R)-2-hidroxi-2-feniletanoato.

Paso 1: Preparación de (E)-3-(3,4-difluorofenil)-2-ácido propenóico

Una mezcla agitada de piridina (15,5kg) y piperidina (0,72kg) se calentó a 90°C. Se agregó ácido malónico (17,6kg), seguido por lenta adición, durante 50 minutos, de 3,4-difluorobenzaldehído (12,0kg). La mezcla de la reacción se agitó a 90°C durante adicionales 4 horas y 36 minutos. Se agregó agua (58,5kg) y 32 litros de la mezcla de

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piridina/agua se sacó entonces por destilación del reactor bajo presión reducida. La mezcla de la reacción se acidificó a pH 1 con 37% de ácido clorhídrico (6,4kg) durante un periodo de 40 minutos, luego se enfrió a 25°C con fuerte agitación. Los sólidos se recogieron por filtración, se lavaron dos veces con 1% de ácido clorhídrico (34,8 L por lavada), una vez con agua (61 L) y luego se sacó el licor a todo el través en el filtro. El producto se secó entonces bajo vacío a 40°C durante 24 horas y 40 minutos, logrando 13,7kg del producto cristalino.

Paso 2: Preparación de (E)-3-(3,4-difluorofenil)-2-propenoil cloruro.

Una mezcla agitada de (E)-3-(3,4-difluorofenil)-2-ácido propenóico (8,2 kg), tolueno (7,4kg) y piridina (0,18kg) se calentó a 65°C y luego cloruro de tionil (7,4kg) se agregó durante 30 minutos. La reacción se agitó durante adicionales 2 horas 15 minutos después de que se completó la adición, luego se diluyó con tolueno (8,7kg). El exceso de cloruro de tionil, dióxido de azufre y cloruro de hidrógeno se sacó por destilación conjuntamente con tolueno (10 L), bajo presión reducida, logrando una solución del (E)-3-(3,4-difluorofenil)-2-propenoil cloruro (9kg aproximadamente) en tolueno.

Paso 3: Preparación de (1R, 2S, 5R)-2-isopropil-5-metilciclohexil (E)-3-(3,4-difluorofenil)-2-propenoato.

Una solución de L-mentol (7,1kg) en tolueno (8,5kg) se agregó durante un periodo de 20 minutos a la solución de (E)-3-(3,4-difluorofenil)-2-propenoil cloruro (preparado como en el Paso 2) y piridina (0,18kg, 2,28 mol) agitando a 65°C. La mezcla de la reacción se agitó a 65°C durante adicionales 4 horas y 40 minutos después de que se completó la adición, luego se enfrió a 25°C y agitó durante 14 horas. La

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solución se diluyó con tolueno (16kg), se lavó con 5% de cloruro de sodio acuoso (6,4kg), luego 6% de carbonato de hidrógeno de sodio (6,47kg), luego agua (6,1 kg). La solución se secó azeotrópicamente por destilación del solvente (20 L) bajo presión reducida. Dimetil sulfóxido (33,9kg) se agregó y el restante tolueno se destiló fuera bajo presión reducida, logrando 47,3kg de una solución de (1R, 2S, 5R)-2-isopropil-5-metilciclohexil (E)-3-(3,4-difluorofenil)-2-propenoato (aproximadamente 13,3kg) en dimetil sulfóxido.

Paso 4: Preparación de dimetilsulfoxonio metilida (dimetil(metileno)oxo- λ^6 -sulfano).

Polvo de hidróxido de sodio (1,2kg), preparado moliendo tabletas de hidróxido de sodio en un molino rotativo a través de un tamiz de metal de 1mm, e ioduro trimetilsulfoxonio (6,2kg) se agitaron en dimetil sulfóxido (25,2kg) bajo una atmósfera de nitrógeno a 25°C durante 90 minutos. La solución se usó directamente en la preparación de (1R, 2R, 5R)-2-isopropil-5-metilciclohexil trans-2-(3,4-difluorofenil) ciclo propano carboxilato.

Paso 5: Preparación de (1R, 2S, 5R)-2-isopropil-5-metilciclohexil trans-2-(3,4-difluorofenil)ciclo propano carboxilato.

Una solución de (1R, 2S, 5R)-2-isopropil-5-metilciclohexil (E)-3-(3,4-difluorofenil)-2-propenoato (aproximadamente 8,6kg) en dimetil sulfóxido (aproximadamente 27,9kg) se agregó con agitación durante 20 minutos a una mezcla de dimetilsulfoxonio metilida (aproximadamente 2,6kg, preparada como se describió arriba), ioduro de sodio (aproximadamente 4,2kg), agua (aproximadamente 500g) e hidróxido de

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sodio (aproximadamente 56g) en dimetilsulfóxido (27,7kg). La mezcla de la reacción se agitó durante 2 horas y 50 minutos adicionales a 25°C, luego se usó directamente para la preparación de (1R, 2S, 5R)-2-isopropil-5-metilciclohexil trans-(1R, 2R)-2-(3,4-difluorofenil) ciclo propano carboxilato.

Paso 6: Preparación de (1R, 2S, 5R)-2-isopropil-5-metilciclohexil trans-(1R, 2R)-2-(3,4-difluorofenil)ciclo propano carboxilato

Una solución cruda de (1R, 2S, 5R)-2-isopropil-5-metilciclohexil trans-2-(3,4-difluorofenil)ciclo propano carboxilato producida como se describió en el Paso 5 se calentó con agitación desde 25°C a 50°C durante un periodo de 1 hora y la temperatura se mantuvo durante una hora adicional. La mezcla se enfrió luego con agitación de 50°C a 35°C durante 4 horas, se mantuvo a 35°C durante 1 hora, luego se enfrió a 26°C durante 4 horas, se mantuvo a 26°C durante 1 hora, luego se enfrió a 19°C durante 3 horas y se mantuvo a 19°C durante 5 horas y 10 minutos. El producto se recogió por filtración, logrando un sólido cristalino (2,7kg) el cual se muestra que contiene una mezcla de (1R,2S,5R)-2-isopropil-5-metilciclohexil trans-(1R,2R)-2-(3,4-difluorofenil) ciclo propano carboxilato (1,99kg) y (1R,2S,5R)-2-isopropil-5-metilciclohexil trans-(1R, 2S)-2-(3,4-difluorofenil) ciclo propano carboxilato (85g).

Paso 7: Preparación de trans-(1R, 2R)-2-(3,4-difluorofenil) ciclo propano ácido carboxílico.

(1R, 2S, 5R)-2-isopropil-5-metilciclohexil trans-(1R, 2R)-2-(3,4-difluorofenil) ciclo propano carboxilato (9,6kg, 91,8% de exceso

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diastereomérico) se disolvió en etanol (13,8kg) y se calentó con agitación a 46°C. Se agregó 45% de hidróxido de sodio acuoso (3,1kg) durante un periodo de 20 minutos y la mezcla se agitó durante adicionales 2 horas y 27 minutos. El solvente (28 L) se sacó por destilación de la mezcla bajo presión reducida, luego la mezcla se enfrió a 24°C y diluyó con agua (29,3kg), después de lo cual el mentol liberado se extrajo en tolueno (3 lavadas de 3,3kg cada una). El material acuoso restante se acidificó a pH 2 con 37% de ácido clorhídrico (3,3 L) y el producto se extrajo en tolueno (8,6kg, luego 2 más lavadas de 4,2kg y 4,3kg). Los extractos combinados de tolueno se lavaron con 1% ácido clorhídrico (4,9 L), luego se diluyeron con adicional tolueno (4,2kg) y se secó azeotrópicamente por destilación del solvente (25 L) bajo presión reducida. Una dilución final con tolueno (24,2kg) fue seguida por destilación del solvente bajo presión reducida (10 L) logrando una solución que contiene trans-(1R, 2R)-2-(3,4-difluorofenil)ciclo propano ácido carboxílico (aproximadamente 3,45kg) adecuado para la producción de trans-(1R, 2R)-2-(3,4-difluorofenil) ciclo propano cloruro carbonilo.

Paso 8: Preparación de trans-(1R, 2R)-2-(3,4-difluorofenil) ciclo propano cloruro carbonilo.

Piridina (70ml) se agregó a una solución de trans-(1R, 2R)-2-(3,4-difluorofenil)ciclo propano ácido carboxílico (aproximadamente 3,45kg) en tolueno (aproximadamente 12 -15kg)), preparado como se describió arriba y la mezcla se calentó luego a 65°C. Cloruro de tionil (2,3kg) se agregó durante un periodo de 1 hora y la mezcla se agitó a 70°C durante 3 horas. Cloruro de tionil se agregó (0,5kg) y la mezcla se agitó 2 horas adicionales a 70°C. Una alícuota final de cloruro de tionil (0,5kg) se

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agregó y la mezcla de la reacción se agitó durante 1 hora a 70°C, luego se enfrió a 40°C. Adiciones periódicas de tolueno (45kg, 3 adiciones de 15kg cada una) se hicieron durante la destilación de solvente (aproximadamente 60 L) de la mezcla bajo presión reducida, luego la solución de trans-(1R, 2R)-2-(3,4-difluorofenil)ciclo propano cloruro carbonilo (3,8kg aproximadamente) en tolueno (aproximadamente 6-9 L) se enfrió a 20°C.

Paso 9: Preparación de trans-(1R, 2R)-2-(3,4-difluorofenil) ciclo propano ázido carbonilo.

Una solución de trans-(1R, 2R)-2-(3,4-difluorofenil) ciclo propano carbonilo cloruro (aproximadamente 3,8kg) en tolueno (aproximadamente 6-9 L), preparado en el Paso 8, a 1°C se agregó durante un periodo de 74 minutos a una mezcla de ázido de sodio (1,24kg), bromuro de tetrabutilamonio (56g) y carbonato de sodio (922g) en agua (6,2kg), agitación a 1,5°C. La mezcla se agitó a 0°C durante 1 hora y 55 minutos, luego la capa acuosa se diluyó con agua fría (3,8kg), se agitó brevemente, luego se separó. La capa de tolueno se lavó una vez más a 0°C con agua (3,8kg), luego con 20% de cloruro de sodio acuoso (3,8 L), luego se almacenó a 3°C para adicional uso.

Paso 10: Preparación de trans-(1R, 2S)-2-(3,4-difluorofenil) ciclo propilamina.

Una solución fría de trans-(1R, 2R)-2-(3,4-difluorofenil)ciclo propano ázido carbonilo preparada como se describió en el Paso 9 se agregó durante un periodo de 41 minutos a tolueno (6,0kg), agitación a 100°C. La mezcla se agitó durante adicionales 5,5 minutos a 100°C,

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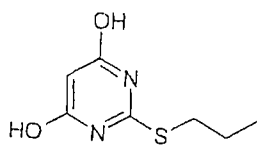
luego se enfrió a 20°C y se agregó durante un periodo de 2 horas y 15 minutos a ácido clorhídrico (3M, 18,2kg) con agitación a 80°C. Después de 65 minutos la solución se diluyó con agua (34kg) y se enfrió a 25°C. La capa de tolueno se retiró y la capa acuosa se basificó a pH 12 con 45% de hidróxido de sodio acuoso (3,8kg) y el producto se extrajo luego en acetato de etilo (3 kg) y se lavó dos veces con agua (13,7kg por lavada), logrando una solución que contiene trans-(1R, 2S)-2-(3,4-difluorofenil) ciclo propilamina (2,6kg, 91,8% de exceso enantiomérico) en acetato de etilo (29,5 L).

Paso 11: Preparación de trans-(1R,2,S)-2-(3,4-difluorofenil) ciclo propanaminio (2R)-2-hidroxi-2-feniletanoato

Se agregó R-(-)-ácido mandélico (2,26kg) a una solución que contiene trans-(1R, 2S)-2-(3,4-difluorofenil)ciclo-propilamina (2,6kg, 91.8% de exceso enantiomérico), agitación a 17°C en acetato de etilo (45,3 L). La mezcla se agitó a 25°C durante 3 horas y 8 minutos, luego se filtró y lavó dos veces con acetato de etilo (13,8kg total). El producto cristalino se secó a 40°C bajo presión reducida durante 23 horas, logrando trans-(2R,2,S)-2-(3,4-difluorofenil)-ciclo-propanaminio (2R)-2-hidroxi-2-feniletanoato (4,45kg).

EJEMPLO 3

Este Ejemplo ilustra la preparación de 4,6-dicloro-2-(propilsulfanil)-5-pirimidinamina

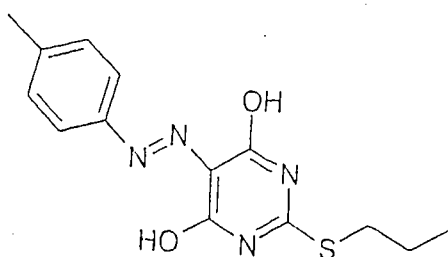


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Paso 1: 4,6-Dihidroxi-2-(propilsulfanil) pirimidina

Agua (670 ml) se agregó a 2-ácido tio-barbitúrico (200 g). La mezcla resultante se agitó y se agregó hidróxido de sodio (126,3g) se agregó en porciones. La mezcla se agitó durante 40 minutos y luego se diluyó con agua. 1-metil-2-pirrolidinona (400 ml) y 1-iodo propano (140,9ml) se agregaron luego. El precipitado resultante se agitó a 20°C durante 22 horas. El pH de la mezcla se ajustó luego a 6,5 por la adición de 1M HCl (600ml) durante 30 minutos, luego a pH 2,5 mediante la adición de 6 M HCl (190ml) durante 30 minutos adicionales. El precipitado resultante se agitó durante 18 horas y el producto se aisló por filtración y se lavó sucesivamente con agua (4 X 100ml), etanol (200ml) y agua (2 X 200ml). El producto se secó bajo presión reducida durante la noche a 50°C para lograr el producto titulado como un polvo blanco (185g).

Paso 2: 4,6-Dihidroxi-5-[(E)-2-(4-metilfenil)diazenil]-2-(propilsulfanil) pirimidina

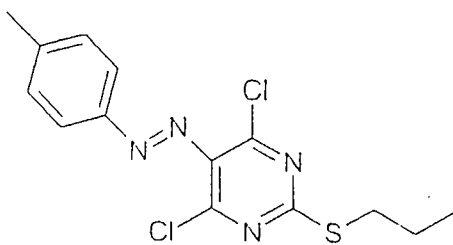


Etanol (25ml), 4,6-dihidroxi-2-(propilsulfanil)pirimidina (Paso 1; 5g) y agua (25ml) se agitaron conjuntamente a temperatura ambiente. Hidróxido de sodio (1,02g) se agregó y se obtuvo una solución clara. La solución resultante se enfrió a 0°C y luego acetato de sodio (9,42g) se agregó para dar la Solución A.

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K2

En un recipiente separado, se preparó una solución de p-toluidina (3,01 g) en agua (10 ml). A esto se agregó ácido clorhídrico concentrado (37% p/p de solución acuosa; 8,45 ml). La mezcla resultante se enfrió a 0°C, y una solución de nitrito de sodio (2,16g) en agua (10ml) se enfrió a 0°C y se agregó gota a gota a la mezcla de la reacción que contiene toluidina durante 30 minutos. La temperatura durante la adición se mantuvo entre 0 y 5°C. La mezcla resultante se enfrió a 0°C y se agregó a la Solución A fría (0°C) (la temperatura alcanzó los 8°C). La suspensión amarilla resultante se agitó durante la noche y el pH de la mezcla se ajustó a pH 1 mediante la adición de 6 M HCl. La mezcla se filtró y el producto recogido se lavó con agua (25ml) etanol (10ml). El producto se secó bajo presión reducida a 50°C durante 24 horas para dar el producto como un sólido amarillo (6,97g).

Paso 3: 4,6-Dicloro-5-[(E)-2-(4-metilfenil)diazenil]-2-(propilsulfanil) pirimidina

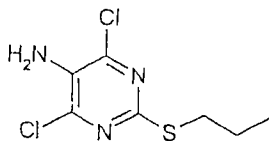


Piridina (2,58ml) se agregó a un precipitado agitado, calentado (70°C) de 4,6-dihidroxi-5-[(E)-2-(4-metilfenil)diazenil]-2-(propilsulfanil) pirimidina (Paso 2, 5g) en tolueno (15ml). Oxícloruro fosforoso (18,7ml) se agregó gota a gota a la mezcla durante 15 minutos (exoterma 94°C). La mezcla de la reacción se calentó durante adicionales 4,5 horas y luego se evaporó. El residuo se azeotropó dos veces con tolueno (2 x 30ml). El residuo se disolvió en tolueno (50 ml) y se filtró para retirar algunos sólidos. El sólido recogido se lavó con

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tolueno y los filtrados combinados se lavaron con agua (30ml) y solución saturada acuosa de bicarbonato de sodio (30ml). La evaporación dio el producto titulado (4,98g) como un aceite rojo el cual se cristalizó lentamente ante permanencia.

Paso 4: Preparación de 4,6-dicloro-2-(propilsulfanil)-5-pirinidinamina

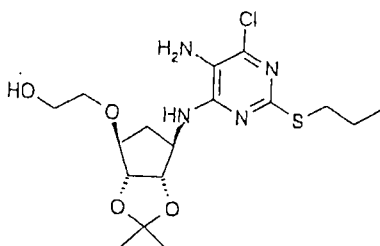


Una solución agitada de 4,6-dicloro-5-[(E)-2-(4-metilfenil) diazenil]-2(propilsulfanil)pirimidina (Paso (3), 1,1kg) en 2-propanol (16,6kg) se hidrógeno durante 1 hora a 40°C/3,2 bar sobre un catalizador de platino sobre carbón (0,81kg, 50% p/p Pt/C). La presión del gas hidrógeno se liberó y el reactor se destelló con nitrógeno. La mezcla de la reacción se filtró. El sólido recogido se lavó con 2-propanol (1,7kg) y los filtrados combinados se concentraron bajo presión reducida. El aceite residual se enfrió a 20°C y disolvió en acetato de etilo (5kg) y agua (5,5 l) se agregó. El pH de la mezcla agitada se ajustó a pH 2 por la adición de 3M ácido clorhídrico acuoso (800ml). Las fases se dejaron separar y la fase acuosa se descargó. Se agregó agua (2,75l) se agregó a la fase orgánica y el pH se ajustó a 2 mediante la adición de una pequeña cantidad de 3M HCl (45ml). La fase acuosa se separó y la fase orgánica se concentró bajo presión reducida a 30-50°C, para dar 4,6-dicloro-2-(propilsulfanil)-5-pirinidinamina como un aceite viscoso rojizo que contiene acetato de etilo que se disolvió en etanol (8,5kg). Solvente (6,5l de etanol/acetato de etilo) luego se retiró por destilación a presión reducida. Una adicional porción de etanol (4,5kg) se agregó al residuo y la destilación se repitió para retirar 6,5 l de solvente. La solución de etanol del producto se usó sin adicional purificación en el siguiente paso.

EJEMPLO 4

Este Ejemplo ilustra la preparación de [1S-[1 α , 2 α , 3 β (1S*, 2R*),5 β]]-3-[7-[2(3,4-difluorofenil)ciclopropil-amino]-5-(propiltio)-3H-1,2,3-triazolo[4,5-d]pirimidin-3-il]-5-(2-hidroxietoxi)ciclo-pentano-1,2-diol (nombrado alternativamente (1S, 2S, 3R, 5S)-3-[7-[[1R, 2S)-2-(3,4-difluorofenil)ciclopropil]amino]-5-(propilsulfanil)-3H[1,2,3]triazolo[4,5-d]pirimidin-3-il]-5-(2-hidroxietoxi)-1,2-ciclo-pentanodiol).

Paso 1: Preparación de [3aR-(3a α , 4 α , 6 α , 6a α)]-2-[[6-[[5-amino-6-cloro-2-(propiltio)-4pirimidinilamina]tetrahydro-2,2-dimetil-3aH-ciclo-penta[d] [1,3]dioxol-4yl]oxietanol (nombrado alternativamente 2-[[((3aR, 4S, 6R, 6aS)-6-1[5-amino-6-cloro-2-(propilsulfanil)-4-pirimidinil]amino)-2,2-dimetiltetrahydro-3aH-ciclopenta[d][1,3]dioxol-4-il)oxi]-1-etanol).

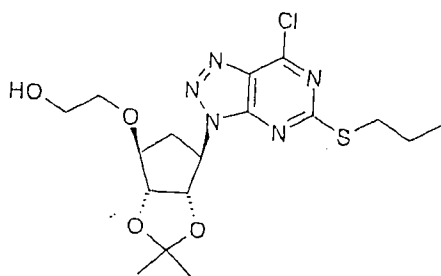


La solución etanólica de 4,6-dicloro-2-(propilsulfanil)-5-pirimidinamina, (preparada como en el Ejemplo 3, Paso 4) se agregó a 2-1[(3aR, 4S, 6R, 6aS)-6-amino-2,2dimetiltetrahydro-3aH-ciclopenta[d][1,3]-dioxol. 4-il]oxi}-1-etanol, L-sal de ácido tartárico (1:1) (1,18kg). Al precipitado espeso agitado resultante se cargó trietilamina (0,95kg) manteniendo la temperatura entre 20 y 25°C. El reactor se selló y la temperatura se incrementó a 120-125°C. La mezcla de la reacción se mantuvo dentro de este rango de temperatura durante

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30 horas, luego se enfrió a 75°C, y se liberó la presión. La temperatura de la mezcla se ajustó a 50°C y el solvente se retiró por destilación bajo presión reducida a 30 a 40°C. Acetato de etilo (4,95kg) y agua (5,51) se agregaron, el pH de la mezcla se ajustó a pH 5 mediante adición de 3M ácido clorhídrico (100 ml), y las fases se separaron. La fase orgánica se lavó con 15% p/p de salmuera (5,51), luego se separó. La fase orgánica se concentró bajo presión reducida (4,81 de solvente retirado) para dar 2-(((3aR, 4S, 6R, 6aS)-6-1[5-amino-6-cloro-2-(propilsulfanil)-4-pirimidinil]amino)-2,2di-metil tetrahidro-3aH-ciclopenta[d][1,3]dioxol-4-il)oxi]-1-etanol como un aceite viscoso castaño rojo que contiene acetato de etilo. El producto se usó sin adicional purificación en el siguiente paso.

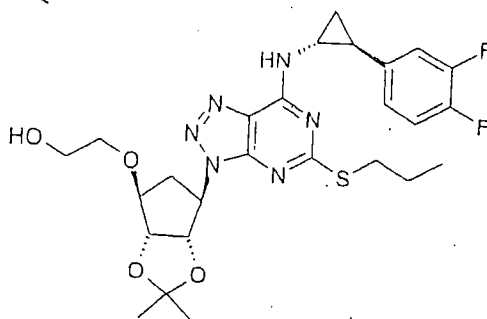
Paso 2: Preparación de [3aR-(3aα, 4α, 6aα)]-2-[[6-[7-cloro-5-(propiltio)-3H[1,2,3]triazolo[4,5-d]pirimidin-3-il]tetrahidro-2,2-dimetil-3aH-ciclopenta[d][1,3]dioxol-4-yl]oxi]etanol (alternativamente nombrado 2-(((3aR, 4S, 6R, 6aS)-6-[7cloro-5-(propilsulfanil)-3H-[1,2,3]triazolo[4,5-d]pirimidin-3-il]-2,2-dimetiltetrahidro-3aH-ciclopenta-[d][1,3]dioxol-4-il)oxi)-1-etanol).



2-(((3aR, 4S, 6R, 6aS)-6-{[5-Amino-6-cloro-2-(propilsulfanil)-4-pirimidinil]amino}-2,2-di-metil-tetrahidro-3aH-ciclopenta[d][1,3]dioxol-4-il)oxi]-1-etanol, como se obtuvo en el Paso 1 se disolvió en ácido acético (5,75kg) y agua (650ml). La solución resultante se enfrió a 2°C (con agitación) y una solución de nitrito de

sodio (232g) en agua (1,25 l) se agregó tal que la temperatura de la mezcla se sostuvo debajo de 7°C. La mezcla se dejó calentar entonces a 7°C luego acetato de etilo (8,9kg) se agregó. Se agregó una solución acuosa de carbonato de potasio (41,37% p/p) se agregó. La mezcla se separó y la fase orgánica se lavó con adicional solución acuosa de carbonato de potasio (3,8kg, 21% p/p). La fase acuosa se desechó y la fase orgánica se concentró bajo presión reducida para dar el compuesto subtitulado como un aceite viscoso rojo- castaño usado sin adicional purificación en el siguiente paso.

Paso 3: Preparación de {3aR-[3aα, 4α, 6α(1R*, 2S*),6aα]}-2-[6-(17-[2-(3,4-difluorofenil) ciclopropil]amino-5-(propiltio)-3H-1,2,3-triazolo[4,5-d]pirimidin-3-il)tetrahidro-2,2dimetil-4H-ciclopenta-1,3-dioxol-4-il)oxi] etanol (alternativamente denominado 2({(3aR, 4S, 6R, 6aS)-6-[7-{{[(IR,2S)-2-(3,4-difluorofenil)-ciclopropil]amino)-5(propilsulfanil)-3H-[1,2,3]triazolo[4,5-d]pirimidin-3-il]-2,2-dimetiltetrahidro-3aH-ciclopenta [d][1,3]dioxol-4-il}oxi)-l-etanol).

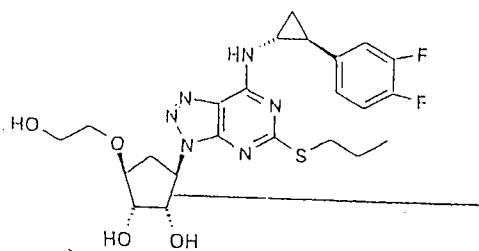


trans-(1R, 2S)-2-(3,4-Difluorofenil)ciclo propanaminio (2R)-2-hidroxi-2-feniletanoato (0,77kg) se cargó en un recipiente seguido por una solución de 2-({(3aR, 4S, 6R, 6aS)-6-[7-cloro-5-(propilsulfanil)-3H-[1,2,3]triazolo [4,5-d]pirimidin-3-il]-2,2-dimetiltetrahidro-3aH-ciclopenta-[d][1,3]dioxol-4-il)oxi)-l-etanol (preparado como en el Paso 2) disuelto en acetonitrilo (3,85kg). A la mezcla agitada resultante se agregó trietilamina (0,81kg) a una velocidad tal que la temperatura de la

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reacción se mantuvo entre 20-25°C. La mezcla de la reacción se agitó durante 13 horas y luego se concentró a presión reducida a 30°C. Al residuo se agregó acetato de etilo (8,1kg) y agua (4,6 l). El pH de la mezcla agitada de dos fases se ajustó a pH 4 mediante la adición de 3M HCl (450ml). La mezcla se dejó luego asentar y separar. La fase acuosa se separó y la fase orgánica retenida se lavó con 15% p/p de solución de cloruro de sodio acuoso (4,15kg), la fase orgánica se concentró bajo presión reducida a 30-50°C dando el compuesto crudo titulado como un aceite rojo, el cual se usó directamente en el siguiente paso.

Paso 4: Preparación de [1S-[1 α , 2 α , 3 β (1S*, 2R*),5 β]]-3-[7-[2-(3,4-difluorofenil)ciclo-propilamino]-5-(propiltio)-3H-1,2,3-triazolo[4,5-d]pirimidin-3-il]-5-(2hidroxietoxi)ciclo pentano-1,2-diol (alternativamente denominado (1S, 2S, 3R, 5S)-3-[7-1-[(1R,2s)2-(3,4-difluorofenil) ciclo-propilamino)-5-(propilsulfanil)-3H-[1,2,3]triazolo[4,5d]pirimidin-3-il]-5-(2-hidroxietoxi)-1,2-ciclopentanedio1).



Se agregó ácido clorhídrico acuoso (3 M, 4,81), a una solución agitada de 2-([(3aR, 4S, 6R, 6aS)-6-[7-{[(1R,2S)-2-(3,4-difluorofenil)ciclopropil]-amino)-5(propilsulfanil)-3H-[1,2,3]triazolo[4,5-d]pirimidin-3-il]-2,2-dimetil-tetrahidro-3aH-ciclopenta[d][1,3]dioxol-4-il)oxi)-1-etanol (1,931 kg) en metanol (13,4kg), manteniendo la temperatura durante la adición entre 20 y 25°C. La mezcla se agitó entonces durante 24 horas a 20°C. Hidróxido de sodio (45% p/p solución acuosa; 780ml) se agregó luego para ajustar el pH de

la mezcla a pH 7,2. El metanol se retiró luego por destilación a presión reducida y se agregó acetato de etilo (14,3 kg). La mezcla se calentó a 45° y la capa acuosa se separó. Luego se lavó la fase orgánica 15% p/p de solución acuosa de cloruro de sodio (7,2kg). Se retiró acetato de etilo (10 l) por destilación a presión reducida. Se cargó acetato de etilo fresco (7,2kg) y la mezcla se filtró. El filtro se lavó con acetato de etilo (1,5kg). Los filtrados combinados se secaron por repetida adición/destilación de acetato de etilo. Cuando la solución estaba seca, el contenido del producto de la solución de acetato de etilo se determinó mediante una técnica de ensayo de cromatografía y se encontró que contenía 1 016g del producto, la concentración del acetato de etilo se ajustó hasta una concentración de 5ml de acetato de etilo / g del producto crudo se alcanzó. La solución de acetato se calentó a 47°C e iso-octano (2,5ml/g de producto, 2540ml) se agregó luego durante 15 minutos. El precipitado resultante se agitó durante 30 minutos y luego iso-octano (2540ml) se agregó durante 5 minutos. La mezcla resultante se agitó a 48-50°C durante 30 minutos y luego se enfrió a 20°C durante 3 horas. El precipitado se agitó a 20°C durante 6,5 horas y luego se filtró y lavó con una mezcla que consiste de iso-octano (1,25kg) y acetato de etilo (1,6kg). El sólido recogido se secó en vacío para dar el compuesto titulado (920g). si se desea, el producto crudo puede purificarse adicionalmente empleando uno de los siguientes tres métodos.

Recristalización a partir de acetato de etilo / iso-octano

El producto crudo se disolvió en acetato de etilo (4,8 ml/g) a 55°C, luego se filtró para retirar partículas. La solución clara se devolvió al reactor para recristalización y la temperatura se establece a 50°C. Se agrega luego iso-octano (4,8 ml/g) durante 10 minutos. El precipitado se deja

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Xg

permanecer durante 30 minutos después de lo cual se enfría a 20°C durante 2-3 horas y finalmente la temperatura se mantiene a 20°C durante alrededor de 30 minutos. El producto se filtra luego y se lava con iso-octano (2x1,5 ml/g). El producto se secó bajo presión reducida a 50°C dando un producto puro (>98% puro por análisis h.p.l.c.).

Precipitado con n-butil acetato

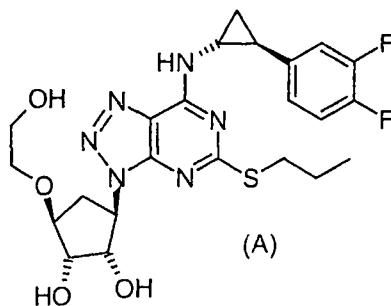
El producto crudo se suspende en n-butil acetato 4 ml/g y se agitó a temperatura ambiente durante 10 horas. El precipitado se enfrió a 0°C durante 3 a 4 horas y se mantuvo a 0°C durante 1 hora. El producto se filtró y lavó con 2 ml/g de n-butil acetato frío (<0°C). El producto se seca luego en vacío a 50°C, dando producto puro (>98% puro por análisis h.p.l.c.).

Precipitado con iso-propanol

El producto crudo se suspendió en iso-propanol 3 ml/g y se agitó a 50°C durante 72 horas. El precipitado luego se enfrió a 20°C durante 3 horas y la temperatura se mantuvo a 20°C durante alrededor de 30 minutos. El producto luego se filtró y lavó con 1 ml/g de iso-propanol frío (<0°C). Finalmente, el producto se secó bajo presión reducida a 50°C dando un producto puro (>98% puro por análisis h.p.l.c.).

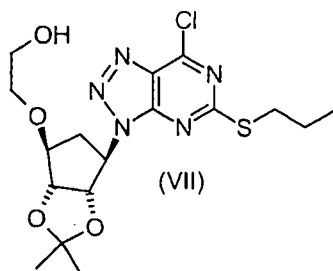
REIVINDICACIONES

1. Un proceso para preparar un compuesto de fórmula (A)

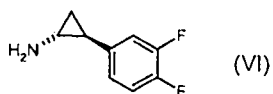


que comprende:

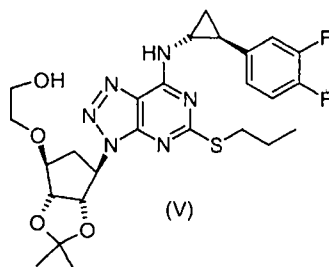
- a) reaccionar un compuesto de fórmula (I) con un nitrito de un metal alcalino en presencia de un ácido adecuado para preparar un compuesto de fórmula (VII):



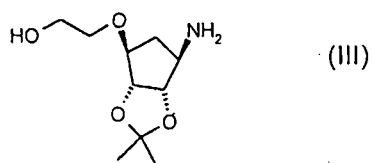
- b) acoplar el compuesto de fórmula (VII) con un compuesto de fórmula (VI):



para proporcionar un compuesto de fórmula (V):

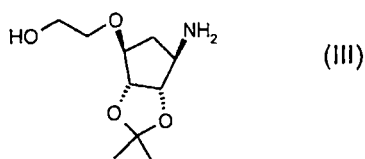


- c) desproteger un compuesto de fórmula (V) para proporcionar el compuesto de fórmula (A).
2. Un proceso para preparar una sal de un compuesto de fórmula (III):



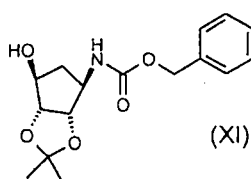
que comprende reaccionar un compuesto de fórmula (III) con el ácido necesario.

3. Un proceso para preparar una sal de un compuesto de fórmula (III):

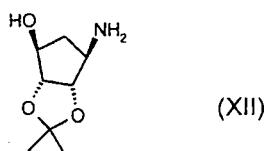


que comprende los pasos de:

a) preparar un compuesto de fórmula (XI):

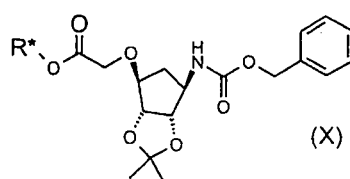


reaccionando un compuesto de fórmula (XII):



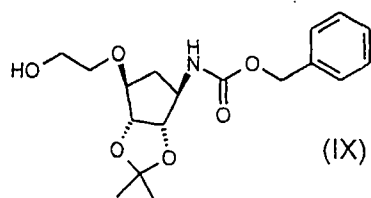
con bencilo cloroformiato;

b) preparar un compuesto de fórmula (X):



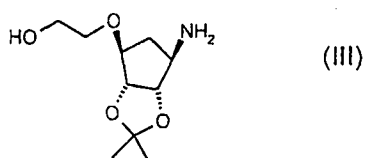
reaccionando un compuesto de fórmula (XI) con un compuesto de fórmula $L-CH_2-CO_2R^*$ donde R^* es C1-4alquilo, y L es un grupo libre;

c) preparar un compuesto de fórmula (IX):



reduciendo un compuesto de fórmula (X);

d) preparar un compuesto de fórmula (III):



desprotegiendo un compuesto de fórmula (IX); y

e) preparar una sal de un compuesto de fórmula (III) reaccionando el compuesto de fórmula (III) con el ácido necesario.

4. Un compuesto intermediario de fórmula (VII), (X) o (IX) o una sal de un compuesto de fórmula (III).

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 100081-1 WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IEA/416)	
International application No. PCT/SE01/01241	International filing date (day/month/year) 31.05.2001	Priority date (day/month/year) 02.06.2000
International Patent Classification (IPC) or national classification and IPC7 C07D 487/04		
Applicant AstraZeneca AB et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.	
2. This REPORT consists of a total of <u>6</u> sheets, including this cover sheet.	
☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).	
These annexes consist of a total of _____ sheets.	
3. This report contains indications relating to the following items:	
I ☒ Basis of the report	
II ☐ Priority	
III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability	
IV ☒ Lack of unity of invention	
V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement	
VI ☐ Certain documents cited	
VII ☐ Certain defects in the international application	
VIII ☐ Certain observations on the international application	

Date of submission of the demand 30.11.2001	Date of completion of this report 09.07.2002
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. 08-667 72 88	Authorized officer Fernando Farieta/BS Telephone No. 08-782 25 00

Form PCT/IEA/409 (cover sheet) (January 1998)

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6X

I. Basis of the report

1. With regard to the elements of the international application:*

- ☒ the international application as originally filed
- ☐ the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____
- ☐ the claims:
pages _____, as originally filed
pages _____, as amended (together with any statement) under article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____
- ☐ the drawings:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____
- ☐ the sequence listing part of the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheet/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2 (c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.

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IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
☐ paid additional fees.
☐ paid additional fees under protest.
☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with rules 13.1, 13.2 and 13.3 is

- ☐ complied with.
☒ not complied with for the following reasons:

According to Article 34(3) (a-c) and Rule 13.2, an international application shall relate to one invention only or to a group of inventions linked by one or more of the same or corresponding "special technical features", i. e. features, that define a contribution which each of the inventions makes over the prior art.

The problem the claimed invention aims to solve is a compound I : 2-(((3aR, 4S, 6R, 6aS)-6-([5-amino-6-chloro-2-(propylsulfanyl)-4-pyrimidinyl] amino)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3] oxy)-1-ethanol, a process for the preparation thereof and the use for the production of the compound (A). The process is performed in several steps where the essential step is the formation of a pyrimidinamine connected to a cyclopenta-dioxol (Claim 2) to form compound I (Claim 1).

Claims 3-9, which confers to process steps before the formation of compound I of claim 1, are formally associated with claim 1. However, the reaction described in claim 2 is not new and, as this step is to be considered as the unifying special technical feature, there is no such feature when the reaction of claim is known according to W099/ 41254.

.../.

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☐ all parts.
☒ the parts relating to claims Nos. 1, 2, 6 and partly 9.

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Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Box IV

The reactions claimed in claims [3,7,8] and [4,5] are completely separated from the reaction described in claim 2. The application also contains a claim [9] concerning the intermediate and end products of the process. In order to fulfil the requirements of unity of invention it is necessary that the intermediate compounds are closely interconnected with the end products. Such close connection requires that the essential structural part of the end product is incorporated by the intermediate.

In the present invention the essential structural parts are a cyclopentanyl-amine directly attached to a pyrimidinamine. This structural parts are however not present in all the compounds claimed. Consequently the present application does not fulfil the requirements of unity of invention.

The application is found to contain the following three inventions:

Invention 1: Compounds I and VII, and a method for producing those compounds containing the same essential structural parts. As described in claims 1, 2, 6 and partly 9.

Invention 2: Compounds II, IV and VIII, and a method for producing those compounds. As described in claims 4, 5 and partly 9.

Invention 3: Compounds III, X and XI, and a method for producing those compounds. As described in claims 3, 7, 8 and partly 9.

As a consequence of the lack of unity of the application a complete examination has not been performed.

The applicant decided not to pay the additional fees, thus the examination concerns only invention 1. Compounds I and VII, and a method for producing those compounds containing the same essential structural parts. As described in claims 1, 2, 6 and partly 9.

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V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	<u>1</u>	YES
	Claims	<u>2, 6 and partly 9</u>	NO
Inventive step (IS)	Claims		YES
	Claims	<u>1, 2, 6 and partly 9</u>	NO
Industrial applicability (IA)	Claims	<u>1, 2, 6 and partly 9</u>	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The applicant decided not to pay the additional fees, thus the examination concerns only invention 1. Invention 1 comprises compounds I and VII, and a method for producing those compounds containing the same essential structural parts. As described in claims 1, 2, 6 and partly 9.

The following documents have been found relevant:

D1: WO 99/41254 A1

Document D1 provides new triazolo[4, 5-d] pyrimidine compounds (formula I), their use as medicaments, compositions containing them and processes for their preparation.

D2: WO 97/03084 A1

New inhibitors of platelet aggregation are provided by document D2. The compounds accord to formula I as well as pharmaceutically acceptable salts and prodrugs thereof. D2 comprises furthermore the intermediate compositions in the scope of the protection.

.../.

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Box V

Novelty

Claims 1, 2, 6 and partly 9

Claims 1 relates to the compound of formula I (2-(((3aR, 4S, 6R, 6aS)-6-([5-amino-6-chloro-2-(propylsulfanyl)-4-pyrimidinyl] amino)-2,2 - dimethyltetrahydro- 3aH-cyclopenta[d] [1,3] oxy]-1-ethanol) and a process for preparing the compound of formula I. The compound of formula I works as an intermediate compound in the synthesis of triazolo pyrimidine compound (A) (see description page 3 line 2). Claim 2 has a cyclopentanyl-dioxol (compound III) and a pyridinamine (compound II) in order to prepare compound of formula I.

Document D1 discloses a pharmaceutical composition close enough the pyrimidine setting with the cyclopentanyl-ring in order to synthesise compound A. The process document D1 (page 8 and 9) is very like the same as described in the claim 2 of the application. The process of cyclization trough diazotization is known, as well as the step between compounds formula I and VII, according to document D2 (page 12 claim 6). With respect to the embodiment of Claim 1, 2, 6 and partly 9, the closest state of the art is represented by documents D1 and D2. It is considered obvious to a person skilled in the art to use the compounds and reactions of documents D1/D2. The invention according to claims 2, 6 and partly 9 does not fulfil the requirements of novelty and an inventive step.

Hoya
ex blanco

TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES

PCT

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL

(Artículo 36 y Regla 70 PCT)

No. de Expediente del Solicitante o Apoderado 100081-1 WO	PROCEDIMIENTO POSTERIOR Véase comunicación sobre el envío del informe de examen preliminar internacional (Formulario PCT/IPEA/416)	
No. Solicitud Internacional PCT/SE01/01241	Fecha Internacional de Presentación (día/mes/año) 31.05.2001	Fecha de Prioridad (día/mes/año) 02.06.2000
Clasificación Internacional de Patente (IPC) o Clasificación Nacional e IPC C07D 487/04		
Solicitante AstraZeneca AB y colaboradores		

1. Este informe de examen preliminar internacional fue elaborado por esta Oficina Encargada del Examen Preliminar Internacional y se envía al solicitante según Artículo 36.

2. Este INFORME comprende un total de 6 hojas, inclusive esta portada

☐ Además se adjuntan ANEXOS al informe, en este caso se trata de hojas con descripciones, reivindicaciones y/o dibujos, que se modificaron y que sirven de base para este informe, y/o hojas con correcciones efectuadas ante esta Oficina (véase Regla 70.16 y Sección 607 de las instrucciones administrativas bajo el PCT).

Estos anexos comprenden un total de ____ hojas.

3. Este informe contiene datos con respecto a los siguientes puntos:

- I ☒ Base del Informe
- II ☐ Prioridad
- III ☐ Sin elaboración de un dictamen sobre novedad, actividad inventiva y posibilidad de aplicación industrial
- IV ☒ Falta de unidad de la invención
- V ☒ Comprobación justificada según Artículo 35(2) con respecto a la novedad, la actividad inventiva y la posibilidad de aplicación industrial; documentos y explicaciones sustentando esta comprobación
- VI ☐ Ciertos documentos enumerados
- VII ☐ Ciertas deficiencias del registro internacional
- VIII ☐ Ciertas observaciones relacionadas con la solicitud internacional

Fecha de presentación de la petición 30.11.2001	Fecha de la conclusión de este informe 09.07.2002
--	--

Nombre y dirección postal de la (IPEA) Oficina de Patentes y Registros Apartado 5055 S-102 42 ESTOCOLMO Fax No. 08-667 72 88	Empleado Autorizado Fernando Farieta / BS Tel.: 08-782 25 00
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INFORME DE EXAMEN PRELIMINAR INTERNACIONAL

Solicitud Internacional No. PCT/SE01/01241

I. Bases del Informe

1. Con respecto a los elementos de la solicitud internacional*

☒ La solicitud original como presentada originalmente

☐ La descripción:

páginas _____ como presentadas originalmente
páginas _____ presentadas con la petición
páginas _____ presentadas con la carta de _____

☐ Las reivindicaciones:

páginas _____ como presentadas originalmente
páginas _____ modificadas (junto con cualquier declaración) bajo el Artículo 19
páginas _____ presentadas con la petición
páginas _____ presentadas con la carta de _____

☐ Los dibujos:

páginas _____ como presentadas originalmente
páginas _____ presentadas con la petición
páginas _____ presentadas con la carta de _____

☐ La parte del listado de secuencias de la descripción:

páginas _____ como presentadas originalmente
páginas _____ presentadas con la petición
páginas _____ presentadas con la carta de _____

2. En lo concerniente al idioma, todos los elementos indicados más arriba estuvieron a disposición de esta Oficina o le fueron enviados en el idioma en el cual se radicó la solicitud internacional, salvo indicación en contrario consignada bajo este punto.

Estos elementos estuvieron a disposición de esta Oficina o le fueron enviados en el idioma siguiente _____, que es:

- ☐ el idioma de una traducción enviada para efectos de la búsqueda internacional (según la regla 23.1 (b)).
- ☐ el idioma de publicación de la solicitud internacional (según la regla 48.3 (b)).
- ☐ el idioma de la traducción enviada para efectos del examen preliminar internacional (según la regla 55.2 y/o 55.3).

3. En lo que concierne a cualquier secuencia de nucleótidos y/o aminoácidos divulgada en la solicitud internacional, el examen preliminar internacional se llevó a cabo sobre la base del listado de secuencias:

- ☐ contenido en la solicitud internacional, por escrito.
- ☐ presentado con la solicitud internacional, en formato de lectura por computador.
- ☐ remitido posteriormente a esta Oficina, por escrito.
- ☐ remitido posteriormente a esta Oficina, en formato de lectura por computador.
- ☐ se ha rendido la declaración, según la cual el listado de secuencias por escrito y suministrado posteriormente no va más allá de la divulgación hecha en la solicitud tal como se radicó.
- ☐ se ha rendido la declaración, según la cual las informaciones registradas en formato de lectura por computador son idénticas a las de los listados de secuencias, presentados por escrito.

4. Las modificaciones han acarreado la anulación:

- ☐ de la descripción, páginas: _____
- ☐ de las reivindicaciones, Nos.: _____
- ☐ de los dibujos, hojas/fig: _____

5. ☐ El presente informe se preparó sin tener en cuenta (algunas de) las modificaciones, que se consideraron que van más allá de la exposición de la invención (regla 70.2 (c))**

* Las hojas intercambiables que se han suministrado a la Oficina receptora en respuesta a una invitación bajo Artículo 14 se mencionan en este informe como "presentadas originalmente" y no se anexan a este informe puesto que no contienen correcciones (Reglas 70.16 y 70.17)).

** Se debe citar cualquier hoja intercambiable conteniendo la citada modificación bajo el punto I y se debe anexar a este informe.

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL

Solicitud Internacional No. PCT/SE01/01241

IV Falta de unidad de la invención

1. En respuesta a la invitación de restringir o de cancelar unas tarifas adicionales, el solicitante ha:

- ☐ restringido las reivindicaciones
- ☐ pagado tarifas adicionales
- ☐ pagado tarifas adicionales bajo protesta
- ☒ ni restringió ni pagó tarifas adicionales

2. ☐ esta Oficina encontró que no se cumple el requerimiento de unidad de la invención, y escogió, de conformidad con la Regla 68 1, no invitar al solicitante a la restricción ni a pagar tarifas adicionales.

3. Esta Oficina considera que el requerimiento de unidad de invención de conformidad con las reglas 13.1, 13.2 y 13.3

- ☐ se cumple
- ☒ no se cumple por los siguientes motivos:

De conformidad con el Artículo 34 (3) (a-c) y la Regla 13.2, una solicitud internacional se relacionará únicamente con una invención o con un grupo de invenciones relacionadas entre sí por una o varias "características técnicas especiales" o que correspondan entre sí; es decir las características que definen una contribución que cada una de las invenciones hace sobre la anterioridad.

El problema que la invención reivindicada busca resolver es un compuesto I: 2-(((3aR, 4S, 6R, 6aS) -6- {[5-amino-6-cloro-2-propilosulfanilo-4 pirrimidinilo] amino}-2,2-dimetiltetrahidro-3aH-ciclopenta [d] [1,3] oxil)-1-etanol, un proceso de preparación del mismo y el uso para la producción del compuesto (A). El proceso se desarrolla en varias etapas donde la etapa esencial es la formación de una pirrimidinamina conectada a un ciclopenta-dioxol (Reivindicación 2) para formar el compuesto I (Reivindicación 1).

Las reivindicaciones 3-9 que tratan los pasos del proceso antes de la formación del compuesto I de la reivindicación están asociadas formalmente con la reivindicación 1. Sin embargo, la reacción descrita en la reivindicación 2 no es nueva, y puesto que este paso se debe considerar como la característica técnica especial de unidad, no existe la referida característica cuando la reacción de la reclamación se conoce de acuerdo con WO 099 / 41245.

4. Por lo tanto, las siguientes partes de la solicitud internacional se sometieron al examen internacional preliminar cuando se estableció este informe:

- ☐ todas las partes
- ☒ las partes relacionadas con las reivindicaciones No. 1, 2, 6 y parcialmente 9.

Las reacciones reivindicadas en las reivindicaciones [3, 7, 8] y [4, 5] están totalmente separadas de la reacción descrita en la reivindicación 2. Igualmente la solicitud contiene una reivindicación [9] concerniente a los productos intermedios y finales del proceso. Con el fin de cumplir los requerimientos de unidad de la invención, es necesario que los compuestos intermedios estén estrechamente interconectados con los productos finales. La referida estrecha conexión requiere que la parte estructural esencial del producto final esté incorporada por el intermedio.

En la presente invención, las partes estructurales esenciales son una ciclopentanila amina directamente ligada a una pirrimidinamina. Sin embargo estas partes estructurales no están presentes en todos los compuestos reivindicados. Por lo tanto, la presente solicitud no cumple los requisitos de unidad de invención.

**INFORME DE EXAMEN PRELIMINAR
INTERNACIONAL**

Solicitud Internacional No. PCT/SE01/01241

Casilla adicional

(Se puede utilizar cuando el espacio de cualquiera de las casillas anteriores no es suficiente).

Continuación de la Casilla IV

Se encontró que la solicitud contiene las tres siguientes invenciones:

Invención 1: Compuestos I y VII y un método para producir los compuestos que contengan las mismas partes estructurales esenciales. Como se describe en las reivindicaciones 1, 2, 6 y parcialmente en la 9.

Invención 2: Compuestos II, IV y VIII y un método para producir esos compuestos. Como se describe en las reivindicaciones 4, 5 y parcialmente en la 9.

Invención 3: Compuestos III, X y XI y un método para producir esos compuestos. Como se describe en las reivindicaciones 3, 7, 8 y parcialmente en la 9.

Como consecuencia de la falta de unidad de la solicitud, no se efectuó un examen completo.

El solicitante decidió no pagar las tarifas adicionales, por lo tanto el examen únicamente se relaciona con la invención 1. Los compuestos I y VII, y un método para producir esos compuestos conteniendo las mismas partes estructurales esenciales. Como se describió en las reivindicaciones 1, 2, 6 y parcialmente en la 9.

INFORME DE EXAMEN PRELIMINAR
INTERNACIONAL

Solicitud Internacional No. PCT/SE01/01241

V. Comprobación justificada bajo el Artículo 35(2) en cuanto a la novedad, la actividad inventiva y la posibilidad de aplicación industrial; citas y explicaciones sustentando esta declaración

1. Declaración

Novedad (N)	Reivindicaciones	1	SI
	Reivindicaciones	2, 6 y parcialmente 9	NO
Actividad Inventiva	Reivindicaciones		SI
	Reivindicaciones	1, 6 y parcialmente 9	NO
Aplicación Industrial	Reivindicaciones	1, 6 y parcialmente 9	SI
	Reivindicaciones		NO

2. Enumeraciones y Explicaciones (Regla 70.7)

El solicitante decidió no pagar las tarifas adicionales y por lo tanto la investigación se limita únicamente a la invención 1. La invención 1 comprende los compuestos I y VII, y un método para producir esos compuestos conteniendo las mismas partes estructurales esenciales. Como se describe en las reivindicaciones 1, 2, 6 y parcialmente la 9.

Se encontró que los siguientes documentos son relevantes:

D1: WO 99/41254 A1

El documento D1 dispone compuestos nuevos de triazolo [4, 5-d] pirridina (fórmula 1), su uso como medicamentos, composiciones que los contienen y procesos para su preparación.

D2: WO 97/03084 A1

El documento D2 dispone nuevos inhibidores de la agregación de plaquetas. Los compuestos acordes con la fórmula I al igual que las sales y prodrogas farmacéuticamente aceptables de la misma. Adicionalmente el D2 comprende las composiciones intermedias en el ámbito de la protección.

.../...

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**INFORME DE EXAMEN PRELIMINAR
INTERNACIONAL**

Solicitud Internacional No. PCT/SE01/01240

Casilla adicional

(Se puede utilizar cuando el espacio de cualquiera de las casillas anteriores no es suficiente).

Continuación de la Casilla V

Novedad

Reivindicaciones 1, 2, 6 y parcialmente la 9.

Reivindicación 1 se relaciona con el compuesto de fórmula I (2-(((3aR, 4S, 6R, 6aS)-6-([5-amino-6-cloro-2-(propilosulfanilo)-4-piridinolo] amino)-2, 2-dimetiltetrahydro-3aH-ciclopenta [d] [1,3] oxil)-1-etanol) y un proceso para preparar el compuesto de fórmula I. El compuesto de fórmula I actúa como un compuesto intermedio en la síntesis del compuesto (A) triazolo piridina (consulte la descripción en la página 3 línea 2). Reivindicación 2 tiene un ciclopentanilo-dioxol (compuesto III) y una pirridinamina (compuesto II) con el fin de preparar el compuesto de fórmula I.

El D1 divulga una composición farmacéutica lo suficientemente cerca del marco de la pirridina con el anillo de ciclopentanilo con el fin de sintetizar el compuesto A. El documento de proceso D1 (páginas 8 y 9) es muy similar al que se describe en la reivindicación 2 de la solicitud. El proceso de ciclación por medio de la diazoación es conocido, al igual que el paso entre los compuestos de fórmula I y VII, de acuerdo con el documento 2 (página 12, reivindicación 6). Con respecto a la incorporación de las Reivindicaciones 1, 2, 6 y parcialmente la 9, el estado de arte más cercano se representa en los documentos D1 y D2. Se considera obvio para una persona con conocimientos en el arte que se utilicen los compuestos y las reacciones de los documentos D1/D2. La invención, de conformidad con las reivindicaciones 2, 6 y la 9 parcialmente no cumple los requerimientos de novedad y de actividad inventiva.

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ SE

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only		
Identification of IPEA		Date of receipt of DEMAND
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 100081-1 WO
International application No. PCT/SE01/01241	International filing date (day/month/year) 31 May 2001 (31.05.2001)	(Earliest) Priority date (day/month/year) 2 June 2000 (02.06.2000)
Title of invention CHEMICAL COMPOUND		
Box No. II APPLICANT(S)		
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) AstraZeneca AB S-151 85 Södertälje Sweden		Telephone No. +46 8 553 260 00
		Facsimile No. +46 8 553 288 20
		Teleprinter No.
		Applicant's registration No. with the Office
State (that is, country) of nationality: SE		State (that is, country) of residence: SE
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) LARSSON, Ulf AstraZeneca R&D Södertälje S-151 85 Södertälje Sweden		
State (that is, country) of nationality: SE		State (that is, country) of residence: SE
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) MAGNUSSON, Mattias AstraZeneca R&D Södertälje S-151 85 Södertälje Sweden		
State (that is, country) of nationality: SE		State (that is, country) of residence: SE
☒ Further applicants are indicated on a continuation sheet.		

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

MUSIL, Tibor
AstraZeneca Bulk Production, Sweden
S-151 85 Södertälje
Sweden

State (that is, country) of nationality:

SE

State (that is, country) of residence:

SE

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

PALMGREN, Andreas
AstraZeneca R&D Södertälje
S-151 85 Södertälje
Sweden

State (that is, country) of nationality:

SE

State (that is, country) of residence:

SE

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality:

State (that is, country) of residence:

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality:

State (that is, country) of residence:

☐ Further applicants are indicated on another continuation sheet.

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representativeand ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.Name and address: (Family name followed by given name; for a legal entity, full official designation.
The address must include postal code and name of country.)Global Intellectual Property, Patents
AstraZeneca AB
S-151 85 Södertälje
Sweden

Telephone No.

+46 8 553 260 00

Facsimile No.

+46 8 553 288 20

Teleprinter No.

Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filedthe description ☐ as originally filed
☐ as amended under Article 34the claims ☐ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34the drawings ☐ as originally filed
☐ as amended under Article 342. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). (This check-box may be marked only where the time limit under Article 19 has not yet expired.)

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

☒ which is the language in which the international application was filed.☐ which is the language of a translation furnished for the purposes of international search.☐ which is the language of publication of the international application.☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States (that is, all States which have been designated and which are bound by Chapter II of the PCT)

excluding the following States which the applicant wishes not to elect:

67
69

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|--|---|--------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter | : | sheets |
| 6. other (specify) | : | sheets |

For International Preliminary Examining Authority use only

received	not received
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☐	☐
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐

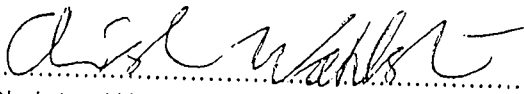
The demand is also accompanied by the item(s) marked below:

- | | |
|--|--|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listing in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ other (specify): |
| 4. ☒ copy of general power of attorney; reference number, if any: GF 3502/2001 | |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand)

Södertälje, 30 November 2001



Christer Wahlström
Global Intellectual Property, Patents, AstraZeneca AB

For International Preliminary Examining Authority use only

- Date of actual receipt of DEMAND:
- Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):
- ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.
 ☐ The applicant has been informed accordingly.
- ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
- ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) 100081-1 WO**Box No. I TITLE OF INVENTION**
CHEMICAL COMPOUND**Box No. II APPLICANT**

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

AstraZeneca AB
S-151 85 Södertälje
Sweden

☐ This person is also inventor.

Telephone No.

+46 8 553 260 00

Facsimile No.

+46 8 553 288 20

Teleprinter No.

State (that is, country) of nationality:

SE

State (that is, country) of residence:

SE

This person is applicant
for the purposes of:☐ all designated
States☒ all designated States except
the United States of America☐ the United States
of America only☐ the States indicated in
the Supplemental Box**Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)**

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

LARSSON, Ulf
AstraZeneca R&D Södertälje
S-151 85 Södertälje
Sweden

This person is:

☐ applicant only☒ applicant and inventor☐ inventor only (If this check-box
is marked, do not fill in below)

State (that is, country) of nationality:

SE

State (that is, country) of residence:

SE

This person is applicant
for the purposes of:☐ all designated
States☐ all designated States except
the United States of America☒ the United States
of America only☐ the States indicated in
the Supplemental Box☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.**Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE**

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☒ agent☐ common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

Global Intellectual Property
AstraZeneca AB
S-151 85 Södertälje
Sweden

Telephone No.

+46 8 553 260 00

Facsimile No.

+46 8 553 288 20

Teleprinter No.

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: (Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

MAGNUSSON, Mattias
AstraZeneca R&D Södertälje
S-151 85 Södertälje
Sweden

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

SE

State (that is, country) of residence:

SE

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

MUSIL, Tibor
AstraZeneca Bulk Production, Sweden
S-151 85 Södertälje
Sweden

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

SE

State (that is, country) of residence:

SE

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

PALMGREN, Andreas
AstraZeneca R&D Södertälje
S-151 85 Södertälje
Sweden

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

SE

State (that is, country) of residence:

SE

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

Regional Patent

- ☒ AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | |
|--|--|
| ☒ AE United Arab Emirates | ☒ LC Saint Lucia |
| ☒ AG Antigua and Barbuda | ☒ LK Sri Lanka |
| ☒ AL Albania | ☒ LR Liberia |
| ☒ AM Armenia | ☒ LS Lesotho |
| ☒ AT Austria | ☒ LT Lithuania |
| ☒ AU Australia | ☒ LU Luxembourg |
| ☒ AZ Azerbaijan | ☒ LV Latvia |
| ☒ BA Bosnia and Herzegovina | ☒ MA Morocco |
| ☒ BB Barbados | ☒ MD Republic of Moldova |
| ☒ BG Bulgaria | ☒ MG Madagascar |
| ☒ BR Brazil | ☒ MK The former Yugoslav Republic of Macedonia |
| ☒ BY Belarus | ☒ MN Mongolia |
| ☒ BZ Belize | ☒ MW Malawi |
| ☒ CA Canada | ☒ MX Mexico |
| ☒ CH and LI Switzerland and Liechtenstein | ☒ MZ Mozambique |
| ☒ CN China | ☒ NO Norway |
| ☒ CR Costa Rica | ☒ NZ New Zealand |
| ☒ CU Cuba | ☒ PL Poland |
| ☒ CZ Czech Republic | ☒ PT Portugal |
| ☒ DE Germany | ☒ RO Romania |
| ☒ DK Denmark | ☒ RU Russian Federation |
| ☒ DM Dominica | ☒ SD Sudan |
| ☒ DZ Algeria | ☒ SE Sweden |
| ☒ EE Estonia | ☒ SG Singapore |
| ☒ ES Spain | ☒ SI Slovenia |
| ☒ FI Finland | ☒ SK Slovakia |
| ☒ GB United Kingdom | ☒ SL Sierra Leone |
| ☒ GD Grenada | ☒ TJ Tajikistan |
| ☒ GE Georgia | ☒ TM Turkmenistan |
| ☒ GH Ghana | ☒ TR Turkey |
| ☒ GM Gambia | ☒ TT Trinidad and Tobago |
| ☒ HR Croatia | ☒ TZ United Republic of Tanzania |
| ☒ HU Hungary | ☒ UA Ukraine |
| ☒ ID Indonesia | ☒ UG Uganda |
| ☒ IL Israel | ☒ US United States of America |
| ☒ IN India | ☒ UZ Uzbekistan |
| ☒ IS Iceland | ☒ VN Viet Nam |
| ☒ JP Japan | ☒ YU Yugoslavia |
| ☒ KE Kenya | ☒ ZA South Africa |
| ☒ KG Kyrgyzstan | ☒ ZW Zimbabwe |
| ☒ KP Democratic People's Republic of Korea | |
| ☒ KR Republic of Korea | |
| ☒ KZ Kazakhstan | |

Check-box reserved for designating States which have become party to the PCT after issuance of this sheet:

- ☒ CO Colombia ☒ EC Ecuador

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

(day/month/year)		national application: country	regional application: regional Office	international application: receiving Office
item (1) 02.06.2000 (02 June 2000)	0013488.2	Great Britain (GB)		
item (2) 06.06.2000 (06 June 2000)	0002102-2	Sweden (SE)		
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): (2)

* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(h)(ii)). See Supplemental Box.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA)
(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA / SE

Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year)

29 Nov 2000

Number

SE00/00653

Country (or regional Office)

Sweden

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following number of sheets:

request : 4

description (excluding sequence listing part) : 19

claims : 5

abstract : 1

drawings :

sequence listing part of description :

Total number of sheets : 29

This international application is accompanied by the item(s) marked below:

- ☒ fee calculation sheet
- ☐ separate signed power of attorney
- ☒ copy of general power of attorney; reference number, if any: GF53/2001
- ☐ statement explaining lack of signature
- ☒ priority document(s) identified in Box No. VI as item(s): (1)
- ☐ translation of international application into (language):
- ☐ separate indications concerning deposited microorganism or other biological material
- ☐ nucleotide and/or amino acid sequence listing in computer readable form
- ☒ other (specify): ITS Report SE00/00653

Figure of the drawings which should accompany the abstract:

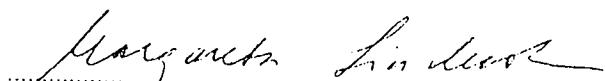
Language of filing of the international application:

English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Södertälje, 31 May 2001



Margareta Linderöth

Global Intellectual Property, AstraZeneca AB

For receiving Office use only	
1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	
6. ☐ Transmittal of search copy delayed until search fee is paid.	

For International Bureau use only	
Date of receipt of the record copy by the International Bureau:	

72
74

APOSTILLA

(Convention de La Haye du 5 octobre 1961)

1. Pais: -Suecia

El presente documento oficial

2. ha sido firmado por Sra. Anne-Marie Bonde

3. en su calidad de Notario Público

4. y lleva el timbre/sello de Notario Público en Estocolmo

Atestado

5. en Estocolmo

6. el 24 de octubre de 2003

7. de Ministerio de Asuntos Exteriores

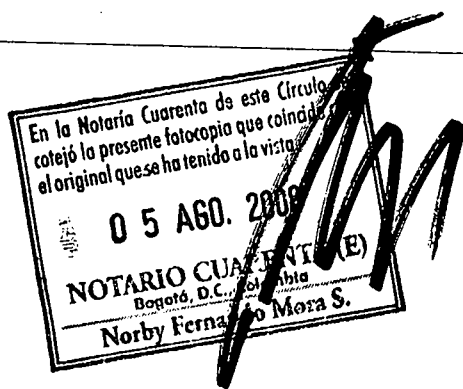
8. N° 7030

9. Timbre/Sello

10. Firma



Agenda Bonde



ASSIGNMENT

The undersigned,
LARSSON, Ulf
MAGNUSSON, Mattias
MUSIL, Tibor
PALMGREN, Andreas

domiciled in

AstraZeneca R&D Södertälje, S-151 85 Södertälje, Sweden;
AstraZeneca R&D Södertälje, S-151 85 Södertälje, Sweden;
AstraZeneca Bulk Production, S-151 85 Södertälje,
Sweden;
AstraZeneca R&D Södertälje, S-151 85 Södertälje, Sweden;

hereby state under oath to be the sole and true inventor of

NOVEL TRIAZOLO PYRIMIDINE COMPOUNDS

We state as well that we assign, without reservations or
limitation, in favor of

AstraZeneca AB

a corporation organized and existing under the laws of
Sweden

domiciled in

S-151 85 Södertälje, Sweden

all rights inherent to said invention, and that the above
mentioned corporation hereby is enabled to apply, in its
name, for the corresponding patent in the Republic of
Colombia.

Ulf Larsson

Tibor Musil

TRASPASO

abajo firmado

domiciliado en

decla bajo juramento ser único y verda-
dero inventor de.

Declaro asimismo que ced y
transf sin reserva ni limitación, a favor de
la sociedad

organizada y existente de conformidad con la ley de
de

domiciliada en

Todos los derechos inherentes a la invención
que la citada sociedad queda facultada para solicitar
en su nombre la patente correspondiente en la
República de Colombia.

Mattias Magnusson

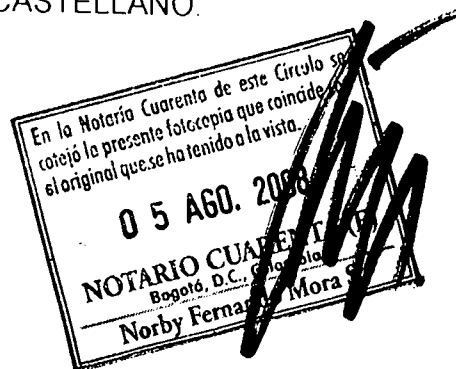
Andreas Palmgren



74
76

TRADUCCION DEL SELLO QUE SE ENCUENTRA EN EL
DOCUMENTO DE CESIÓN DE DERECHOS SOBRE LA INVENCION,
OTORGADO POR LOS INVENTORES: ULF LARSSON, MATTIAS
MAGNUSSON, TIBOR MUSIL Y ANDREAS PALMGREN A LA
SOCIEDAD **ASTRAZENECA AB**, DOMICILIADA EN S-151 85
SÖDERTÄLJE, SUECIA, DEL SUECO AL CASTELLANO.

ANNE-MARIE BONDE
NOTARIO PÚBLICO DE ESTOCOLMO



Brigard & Castro

BOGOTA - COLOMBIA

PODER

POWER OF ATTORNEY

Yo (nosotros)

I (We) ASTRAZENECA AB

domiciliado(s) en

domiciled in SE-151 Sodertalje, Sweden

Nombro(amos) a: **RAMIRO CASTRO DUQUE y/o JUAN PABLO CADENA SARMIENTO y/o BEATRIZ JARAMILLO S.**

de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales y enseñanzas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

A este efecto, lo(s) faculto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistir a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores, dando el descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeran conducentes al resguardo de mis (nuestros) intereses, con todas las demás facultades legales necesarias.

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistir, transigir, comprometer, y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a: **RAMIRO CASTRO DUQUE y/o JUAN PABLO CADENA SARMIENTO y/o BEATRIZ JARAMILLO S.**

domiciliado(s) en la Carrera 7 No. 16-56 Piso 9, Bogotá, Colombia, con facultades para recibir notificaciones y designar apoderados judiciales o extrajudiciales.

Otorgado y firmado en

hoy de de 200_

Firma

Nombre
Cargo

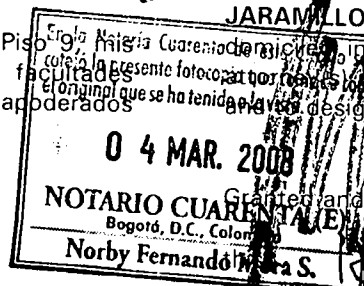
Hereby appoint **RAMIRO CASTRO DUQUE and/or JUAN PABLO CADENA SARMIENTO and/or BEATRIZ JARAMILLO S.**

of Bogotá, Colombia, my (our) true and lawful attorneys with special, ample and sufficient power to obtain from the Colombian administrative, judicial and police offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial designs and utility models; registration of commercial names and emblems, registration of copyright and contracts related thereto, certificates of obtainers of vegetables varieties, as well as extensions, renewals and recordal of assignments and changes of name and domicile related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as: oppositions to the registration of trademarks; caducity, cancellation and nullity actions; claim actions derived from the obtaining or exploitation of licenses, action of unfair competition; penal demands, actions of indemnities for damages; claims or observations on patent applications, models, industrial designs and utility models; in the exercise of preventive measures: and in other actions or similar proceedings.

To that effect they are hereby empowered to file applications, formulate descriptions, amendments, protests, declarations, oppositions, cancellations, nullities, appeals and claims; to pay taxes, quotas and assessments prescribed by law, renounce or waive the rights granted or in the process of granting; to receive all kind of documents and valuables, giving the respective release of receipt, and, in general, to take before said authorities the necessary steps to such effect, and any measures that they may deem pertinent to the safeguard of my (our) interest(s) with all the other necessary legal powers.

This power includes the faculty to ratify or confirm, desist, settle and compromise on my (our) behalf, and to substitute this power in whole or in part and to revoke substitutions. At the same time I (We) hereby appoint **RAMIRO CASTRO DUQUE and/or JUAN PABLO CADENA SARMIENTO and/or BEATRIZ JARAMILLO S.**

domiciled in Carrera 7 No. 16-56, Piso 9, my (our) attorneys with powers to receive notifications and designate judicial and extrajudicial attorneys.



Given and signed in Macclesfield, Cheshire, England day of July 2003

Signature

Name **KEVIN BILL**
Title **Director, IP Services**

120816

CERTIFICADO NOTARIAL (SOCIEDAD)

Hoy de de personalmente compareció ante mí

a quien conozco, y de quien me consta que firmó el anterior documento, debidamente juramentado declaró y dijo que él es

de

Sociedad legalmente constituida para un período de duración que aún no ha terminado; que el declarante está autorizado por dicha compañía para conferir este poder; que el sello estampado por él al pie de tal poder, en nombre y representación de la expresada compañía, es el sello oficial de ella; y que el objeto para el cual se confiere este instrumento está comprendido dentro del de la sociedad.

El suscrito Notario hace constar que tuvo a la vista las pruebas de la existencia de la sociedad.

Estado de con fecha

y que quien confiere el presente poder es su representante.

Notario Público (sello)

CERTIFICADO NOTARIAL
PERSONA NATURAL

Hoy de de ante mí

a quien (es) conozco y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede y quien(es) declara(n) que otorgan el mismo para los fines y propósitos que en él se expresan.

Notario Público (sello)

LEGALIZACION POR APOSTILLA ES REQUERIDA.

NOTARIAL CERTIFICATE (CORPORATION)

On this 18th day of July 2003 of personally appeared before me

KEVIN BILL to me known, and known to me to be the person who signed the foregoing instrument who being by me duly sworn did depose and say that he (she) is the

ATTORNEY
of
ATRAZENECA AB

Which is legally constituted for a term not yet expired, that deponent is authorized by said Company to confer this Power of Attorney: that the seal affixed hereun by the deponent in the name and on behalf of Corporation is the corporate seal thereof; and that purpose for which this instrument is granted included within the corporate purpose of company.

The undersigned Notary Public attests that he has seen the documents that prove the existence of the company.

State of Sweden under date of 1st January 2003

and that he (she) who grants the present power of attorney is its Representative.

Notary Public (Seal)

NOTARIAL CERTIFICATE
NATURAL PERSON

On this day of personally appeared before me of

who is(are) known to me and who I attest executed the foregoing document and he (they) declared he (they) grant(s) the document for the uses and purposes therein expressed.

Notary Public (Seal)

LEGALIZATION BY APOSTILLE IS REQUIRED.

APOSTILLE

(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

This public document / Le présent acte public

2. Has been signed by **J B Hodgson**
a été signé par
3. Acting in the capacity of **Notary Public**
agissant en qualité de
4. Bears the seal/stamp of **The Said Notary Public**
est revêtu du sceau/timbre de

Certified/Attesté

5. at London/à Londres
6. the/le **17 February 2004**
7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

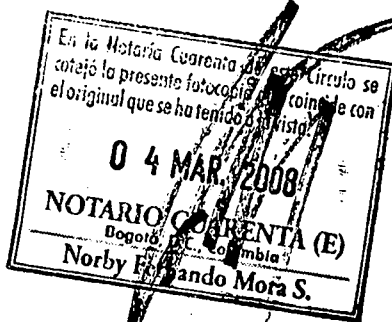
8. Number/sous No **G348987**

9. Stamp:
timbre:
10. Signature: **J. Ireland**



For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961,
it should be presented to the consular section of the mission representing that country.



TRADUCCIÓN SIMPLE AL ESPAÑOL del la Apostilla que vienen junto con el Certificado Notarial (Sociedad) y el **Poder** concedido por **ASTRAZENECA AB**, domiciliada en SE - 151 Sodertalje, Suecia a **Ramiro Castro Duque y/o Juan Pablo Cadena Sarmiento y/o Beatriz Jaramillo S**, domiciliados en la Carrera 7 #16-56, P. 9, Bogotá D.C., Colombia.

AUTENTICACIÓN

(Convención de La Haya del 5 de Octubre de 1961)

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

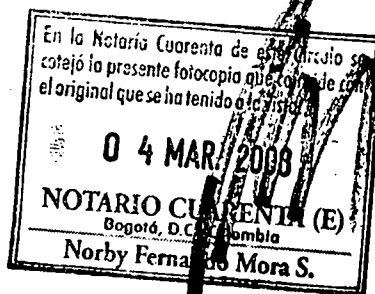
1. País: Reino Unido de Gran Bretaña e Irlanda del Norte
2. Este documento público
ha sido firmado por **J. B. Hodgson**
3. actuando en capacidad de **Notario Público**
4. lleva el sello de: **Dicho Notario Público**

CERTIFICADO

5. en Londres
6. el **17 de Febrero de 2004**
7. por El secretario de Estado Principal de Su Majestad para Asuntos Exteriores y de la Comunidad
8. No. **G348987**
9. Sello
10. Firma

J. Ireland (Firma)

Si este documento va a ser utilizado en un país que no es parte de la Convención de La Haya del 5 de Octubre de 1961, debe ser presentado a la sección consular de la misión que representa a ese país.





GAVIRI A

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88ORGANIZACIÓN ELECTORAL
REGISTRADURÍA NACIONAL DEL ESTADO CIVIL

REGISTRO CIVIL DE DEFUNCIÓN

Indicativo 5562241
Serial

Datos de la oficina de registro							
Clase de oficina:	Registraduría	Notaría	☒	Defunción	Corregimiento	Insp. de Policía	Código 9990
Pais: Departamento: Municipio: Corregimiento o Inspección de Policía:							
COLOMBIA CUNDINAMARCA BOGOTÁ D.C.					NOTARIA 32		

Datos del inscrito	
Apellidos y nombres completos	
CASTRO DUQUE RAMIRO	
Documento de identificación (Clase y número)	Sexo (en Letras)
C.C. No. 170322 DE BOGOTÁ	MASCULINO

Datos de la defunción	
Lugar de la Defunción País - Departamento - Municipio - Corregimiento o Inspección de Policía	
COLOMBIA CUNDINAMARCA BOGOTÁ D.C.	
Fecha de la defunción	Hora
Año 2004 Mes 10 Día 30 04:10 PM	Número de certificado de defunción
A- 2094375	
Presunción de muerte	
Juzgado que profiere la sentencia	
Fecha de la sentencia	
Documento presentado	
Autorización judicial	
Certificado Médico	
Nombre y cargo del funcionario	
ANDRES DIAZ CAMPOS	
R.M. No. 79982662	

Datos del denunciante	
Apellidos y nombres completos	
EDGAR DAVID REGINO H.	
Documento de identificación (Clase y número)	Firma
C.C. No. 15.030.154 DE LORICA CORDOBA	

Primer testigo	
Apellidos y nombres completos	
Documento de identificación (Clase y número)	Firma

Segundo testigo	
Apellidos y nombres completos	
Documento de identificación (Clase y número)	Firma

Fecha de inscripción	
Año 2004 Mes 10 Día 02	Nombre y firma del funcionario que autoriza
BLANCA LEONARDO RESTREPO	
NOTARIA 32	
PADRES: ALFONSO CASTRO	
MERCEDES DUQUE	
ESPACIO PARA NOTAS	

En la Notaría Cuarenta de este Circuito se
cotejó la presente fotocopia que coincide con
la copia que se ha tenido a la vista.

10 DIC, 2004

NOTARIO CUARENTA (B)
Bogotá, D.C., Colombia
Norby Fernando Mora S.

ORIGINAL PARA LA OFICINA DE REGISTRO

OTARIA 32

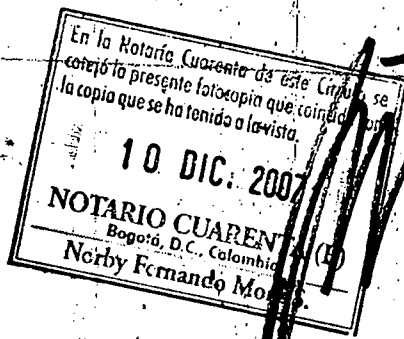
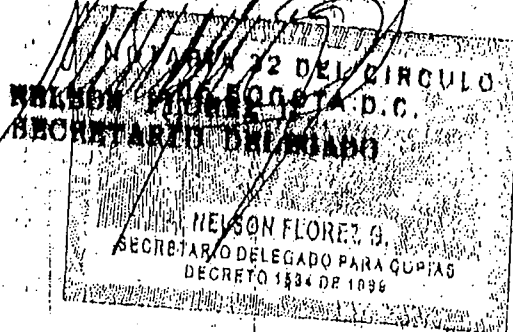
IRCULO DE SANTA FE DE BOGOTA, D.C.

German Eleazar Moreno L.
Notario

COMO SECRETARIO DELEGADO DE LA NOTARIA TREINTA Y DOS (32) DEL
CIRCULO DE BOGOTA

CERTIFICO QUE:

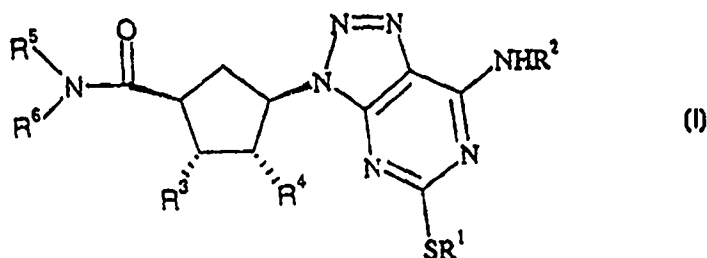
La presente acta es fiel copia del original tomada del registro
civil de defunciones serial indicativo número: 55.622.47
que expido en la ciudad de Bogotá D.C., hoy 17 NOV 2004




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

(51) International Patent Classification ⁶ : C07D 487/04, A61K 31/505, 31/44 // (C07D 487/04, 249:00, 239:00)		A1	(11) International Publication Number: WO 99/41254
			(43) International Publication Date: 19 August 1999 (19.08.99)
(21) International Application Number: PCT/SE99/00154		wood, Bakewell Road, Loughborough, Leics. LE11 5RH (GB).	
(22) International Filing Date: 5 February 1999 (05.02.99)		(74) Agent: ASTRA AKTIEBOLAG; Intellectual Property, Patents, S-151 85 Södertälje (SE).	
(30) Priority Data: 9800458-3 17 February 1998 (17.02.98) SE 9803669-2 26 October 1998 (26.10.98) SE		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, 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, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(71) Applicant (for all designated States except MG US): ASTRA PHARMACEUTICALS LTD. [GB/GB]; Home Park, Kings Langley, Herts. WD4 8DH (GB).			
(71) Applicant (for MG only): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE).			
(72) Inventors; and (75) Inventors/Applicants (for US only): BROWN, Roger [GB/GB]; Astra Charnwood, Bakewell Road, Loughborough, Leics. LE11 5RH (GB). PAIRAUDEAU, Garry [GB/GB]; Astra Charnwood, Bakewell Road, Loughborough, Leics. LE11 5RH (GB). SPRINGTHORPE, Brian [GB/GB]; Astra Charnwood, Bakewell Road, Loughborough, Leics. LE11 5RH (GB). THOM, Stephen [GB/GB]; Astra Charnwood, Bakewell Road, Loughborough, Leics. LE11 5RH (GB). WILLIS, Paul [GB/GB]; Astra Charn-		Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	

(54) Title: NOVEL TRIAZOLO(4,5-*d*)PYRIMIDINE COMPOUNDS

(57) Abstract

The invention provides new triazolo[4,5-*d*]pyrimidine compounds of formula (I), their use as medicaments, compositions containing them and processes for their preparation.

or a C₃₋₈-cycloalkyl group optionally substituted by phenyl which itself can be optionally substituted by halogen, OR⁸ or C₁₋₆-alkyl. More preferably R² is cyclopropyl optionally substituted by phenyl, 4-methoxyphenyl, 3-chlorophenyl, 4-methylphenyl or 4-fluorophenyl.

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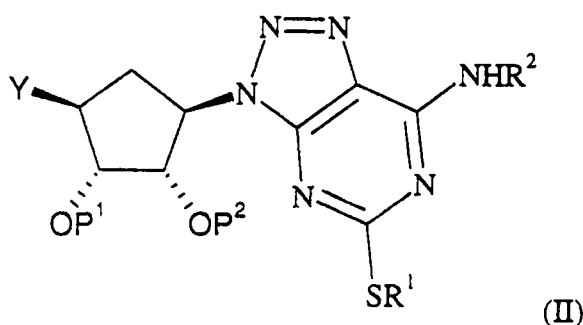
Suitably R⁵ is hydrogen or C₁₋₆ alkyl; R⁶ is C₁₋₆ alkyl, optionally substituted by one or more groups selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halogen, OR²¹, C₃₋₆ cycloalkyl, or R⁶ is C₃₋₆ cycloalkyl, or R⁶ is -A-phenyl or -A-pyridyl each of which may be optionally substituted by one or more groups selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halogen, OC₁₋₆ alkyl, C₃₋₆ cycloalkyl, or methylenedioxy; or R⁵ and R⁶ together with the nitrogen atom to which they are attached for a 5 to 7-membered saturated ring optionally substituted by C₁₋₆ alkyl. Preferably R⁵ is hydrogen and R⁶ is cyclopropyl, methylcyclopropyl, C₁₋₆ alkyl, C₁₋₆ alkyl substituted by halogen, preferably one or more fluoro atoms. More preferably R⁵ is ethyl, isopropyl or isobutyl, or R⁵ and R⁶ together with the nitrogen atom to which they are attached form a pyrrolidine ring. Most preferably R⁵ is hydrogen and R⁶ is methyl or 2-fluoroethyl.

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Particularly preferred compounds of the invention include those exemplified herein, both in **free** base form and as a pharmaceutically acceptable salt or solvate thereof.

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According to the invention there is further provided a process for the preparation of a compound of formula (I) which comprises reaction of a compound of formula (II):



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where R¹ and R² are as defined in formula (I) or are protected derivatives thereof, P¹ and P² are hydrogen or protecting groups and Y is CO₂H, with a compound of formula (III):



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where R^5 and R^6 are as defined in formula (I), and optionally thereafter in any order:

- converting one or more functional groups into a further functional groups
- removing any protecting groups
- forming a pharmaceutically acceptable salt or solvate.

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Examples of suitable groups which each P^1 and P^2 can independently represent are C_{1-6} -alkyl (preferably methyl), benzyl, $(C_{1-6}\text{-alkyl})_3\text{Si}$ (preferably trimethylsilyl) and a $C(O)C_{1-6}$ -alkyl group (preferably acetyl). Preferably the two groups P^1 and P^2 together with the atoms to which they are attached complete a ring, for example the two groups P^1 and P^2 together represent an alkylidene such as methylidene or, more preferably, isopropylidene, or an alkoxy methylidene such as ethoxymethylidene.

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The reaction of compounds of formula (II) and (III) is preferably carried out in the presence of a coupling agent using methods known from peptide synthesis (see M. Bodanszky and A. Bodanszky, *The Practice of Peptide Synthesis*, Springer-Verlag, 1984). Suitable coupling agents include 1,1'-carbonyldiimidazole and dicyclohexylcarbodiimide; the preferred coupling agent is bromo-tris-pyrrolidino-phosphonium hexafluorophosphate or benzotriazole-1-yl-oxy-tris-(dimethylamino)phosphoniumhexafluorophosphate, used in the presence of *N,N*-diisopropylethylamine. The reaction is preferably carried out in *N,N*-dimethylformamide (DMF) or tetrahydrofuran (THF) and preferably at a temperature of from -15° to 120°C , more preferably at a temperature of from 0°C to room temperature.

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Protecting groups can be added and removed using known reaction conditions. The use of protecting groups is fully described in 'Protective Groups in Organic Chemistry', edited by J W F McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 2nd edition, T W Greene & P G M Wutz, Wiley-Interscience (1991).

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Alternative methods of activating a compound of formula (II) wherein Y is CO_2H include formation of an acyl halide or an acetic anhydride. Acid anhydrides may be formed by treatment with an acyl halide, such as acetyl chloride in the presence of a base, such as pyridine or by treatment with a dehydrating agent such as acetic acid anhydride or phosphorus pentoxide in an inert solvent. Acyl halides may be formed by treatment of the acid with a halogenating agent, for example P(III), P(V) or S(IV) halides such as phosphorus trichloride. Acyl halides may also be prepared by an exchange reaction of the acid with an acyl halide such as oxalyl bromide. The reactions may be performed in the halogenating agent or acyl halide as solvent or in other inert solvents such as methylene

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chloride, at a temperature of from 0 to 150°C. Activation is preferably carried out by treatment with oxalyl chloride in dichloromethane at room temperature.

Deprotection can be carried out using methods generally known in the art. For example for groups P^1/P^2 deprotection is preferably carried out as follows:

(i) where one or both of P^1 and P^2 represent $C(O)C_{1-6}$ -alkyl, these groups can be removed by basic hydrolysis, for example by using a metal hydroxide, preferably an alkali metal hydroxide, such as sodium hydroxide or lithium hydroxide, or quaternary ammonium hydroxide in a solvent, such as aqueous ethanol or aqueous tetrahydrofuran, at a temperature of from 10° to 100°C, preferably the temperature is around room temperature; or by acidic hydrolysis using a mineral acid such as HCl or a strong organic acid such as trichloroacetic acid in a solvent such as aqueous 1,4-dioxane;

(ii) where one or both of P^1 and P^2 represent $(C_{1-6}$ -alkyl)₃Si, these can be removed by the use of, for example, a fluoride ion source, for example tetra-n-butylammonium fluoride or hydrogen fluoride;

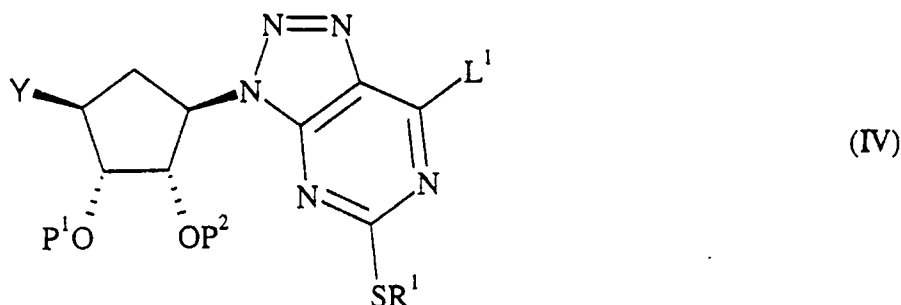
(iii) where one or both of P^1 and P^2 represent a C_{1-6} -alkyl group, these groups can be removed by the use of, for example, boron tribromide;

(iv) where one or both of P^1 and P^2 represent a benzyl group these can be removed by hydrogenolysis using a transition metal catalyst, for example palladium on charcoal, under an atmosphere of hydrogen, at a pressure of from 1 to 5 bar, in a solvent, such as acetic acid; and/or

(v) where both P^1 and P^2 together represent alkylidene or an alkoxy alkylidene, they can be removed by the use of, for example, a mineral or organic acid, preferably by using 2M aqueous hydrochloric acid in methanol/1,4-dioxane at room temperature.

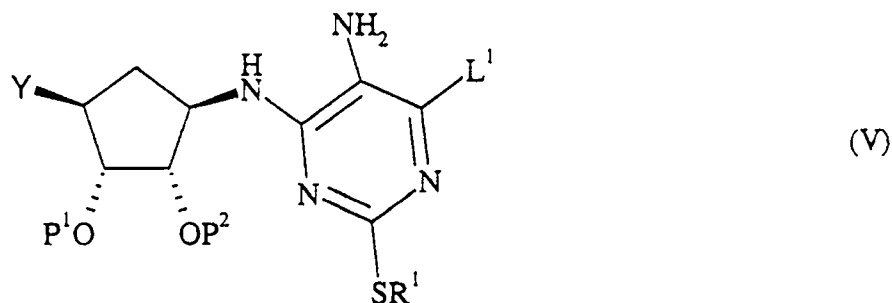
Compounds of formula (III) are commercially available or can be prepared by literature methods known to those skilled in the art.

A compound of formula (II) wherein Y is CO_2H , $CONR^5R^6$ or CO_2R' can be prepared by reacting a compound of formula (IV):



wherein R^1 , P^1 , P^2 , R^5 and R^6 are as defined above, L^1 is a leaving group, for example a halogen atom and R' is a C_{1-6} -alkyl or benzyl group, with an amine NH_2R^2 or a salt of NH_2R^2 wherein R^2 is as defined above, in the presence of a base. Suitable salts of NH_2R^2 include hydrochlorides. Suitable bases include an organic base such as triethylamine or an inorganic base such as potassium carbonate. The amines NH_2R^2 can be prepared using procedures described in H Nishiyama *et al*, Bull. Chem. Soc., Jpn., 1995, **68**, 1247, P. Newman, Optical Resolution Procedures for Chemical Compounds, Vol. 1, Amines and Related Compounds; Optical Resolution and Information Centre: Manhattan College, Riverdale, NY, 1978, p120, J. Vallgarda *et al*, J. Chem. Soc. Perkin 1, 1994, 461. Certain amines NH_2R^2 are novel compounds and form a further aspect of the invention.

A compound of formula (IV) can be prepared by diazotising a compound of formula (V):



wherein R^1 , Y , L^1 , P^1 and P^2 are as defined above, with a metal nitrite, for example an alkali metal nitrite, especially sodium nitrite in dilute aqueous acid, for example 2M HCl, or with a C_{1-6} -alkyl nitrite in an inert solvent, at a temperature of from -20 to 100°C; preferred conditions are isoamyl nitrite in acetonitrile at 80°C.

A compound of formula (V) where Y is CO_2H can be prepared by reducing and hydrolysing a compound of formula (VI):

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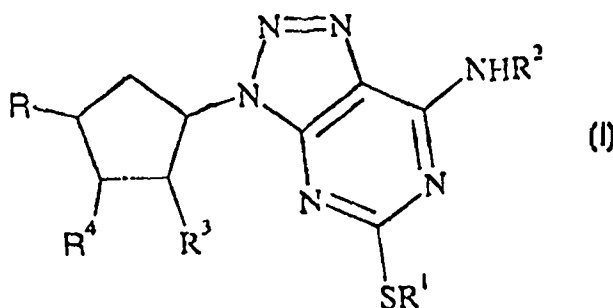
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 487/04, A61K 31/505, 31/41 // (C07D 487/04, 249:00, 239:00)		A1	(11) International Publication Number: WO 99/05143
			(43) International Publication Date: 4 February 1999 (04.02.99)
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(22) International Filing Date: 15 July 1998 (15.07.98)			
(30) Priority Data: 9702773-4 22 July 1997 (22.07.97) SE 9702775-9 22 July 1997 (22.07.97) SE		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
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(54) Title: NOVEL COMPOUNDS

(57) Abstract

The invention provides new triazolo[4,5-*d*]pyrimidine compounds of formula (I), their use as medicaments, compositions containing them and processes for their preparation.



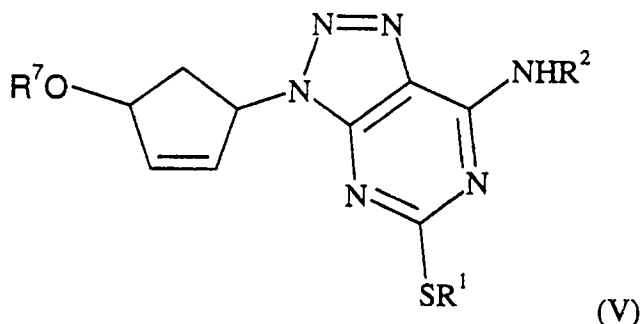
Suitably R^2 is C_{1-8} alkyl optionally substituted by one or more substituents selected from halogen, OR^8 , NR^9R^{10} , SR^{11} , C_{3-8} -cycloalkyl, aryl (optionally substituted by one or more alkyl groups and/or halogen atoms), or C_{1-6} -alkyl; or R^2 is a C_{3-8} -cycloalkyl group optionally substituted by one or more substituents selected from halogen, OR^8 , NR^9R^{10} , SR^{11} , C_{1-6} -alkyl or phenyl, the latter two groups being optionally substituted by one or more substituents selected from halogen, NO_2 , $C(O)R^8$, OR^8 , SR^{11} , $NR^{12}R^{13}$, a fused 5- or 6-membered saturated ring containing one or two oxygen atoms, phenyl or C_{1-6} -alkyl the latter two groups being optionally substituted by OR^8 , NR^9R^{10} or one or more halogen atoms. Aryl groups include phenyl and naphthyl groups. Acyl groups include $C(O)C_{1-6}$ alkyl such as acetyl and 1-oxopropyl. Preferably R^2 is C_{1-6} alkyl or a C_{3-8} -cycloalkyl group optionally substituted by phenyl. More preferably R^2 is butyl or cyclopropyl optionally substituted by phenyl, the phenyl group itself being optionally substituted by one or more halogen, C_{3-8} alkyl, alkoxy, phenoxy or phenyl groups.

Suitably one of R^3 and R^4 is hydroxy and the other is hydrogen, hydroxy or NR^9R^{10} . Preferably R^3 and R^4 are both hydroxy.

Suitably R is a group $(CR^5R^6)_mOR^7$ where m is 0 or 1, R^5 and R^6 are independently hydrogen, C_{1-6} alkyl or phenyl the latter two groups being optionally substituted by halogen, and R^7 is hydrogen, C_{1-6} alkyl or $(CR^5R^6)_nR^{14}$ where R^5 and R^6 are as defined above, n is 1 to 3 and R^{14} is $COOH$, OR^{15} , $NR^{16}R^{17}$ or $CONR^{16}R^{17}$; or R is a C_{1-4} alkyl or C_{2-4} alkenyl group, each of which is substituted by one or more groups selected from $=S$, $=O$, $=NR^{20}$ or OR^{21} and optionally substituted by one or more groups selected from halogen, C_{1-4} alkyl, phenyl, SR^{21} , NO_2 or $NR^{22}R^{23}$ (where R^{21} , R^{22} and R^{23} are independently hydrogen, C_{1-4} alkyl or phenyl; R^{20} is OR^{24} or $NR^{25}R^{26}$, where R^{24} is hydrogen, C_{1-4} alkyl or phenyl, and R^{25} and R^{26} are independently hydrogen, C_{1-4} alkyl, aryl, C_{1-6} acyl, arylsulphonyl or arylcarbonyl).

Preferred R groups include OH , CH_2OH , CH_2CH_2OH , OCH_2CH_2OH , $CH_2OCH_2C(CH_3)_2OH$ and $OCH_2C(CH_3)_2OH$.

Particularly preferred compounds of the invention include those exemplified herein both as free bases and as pharmaceutically acceptable salts and solvates.



where R^1 , R^2 and R^7 are as defined in formula (I) or are protected derivatives thereof, and optionally thereafter (a), (b) or (c) and in any order:

- converting one or more functional groups into a further functional groups
- removing any protecting groups
- forming a pharmaceutically acceptable salt or solvate.

Compounds of formula (II) can be reacted with amines of formula (III) in the presence of a base such as a tertiary organic amine in an inert solvent such as dichloromethane at ambient or elevated temperature. Other suitable bases include inorganic bases such as potassium carbonate.

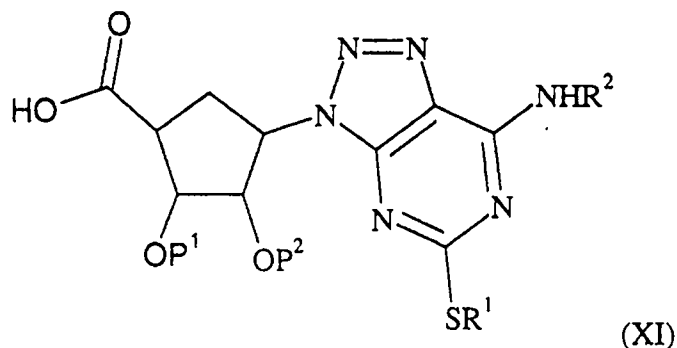
When one or both of R^3 and R^4 are hydroxy they can be protected as groups OP^1 and OP^2 where P^1 and P^2 are protecting groups. Examples of suitable protecting groups in compounds of formula (II) and (IV) are C_{1-6} alkyl (preferably methyl), benzyl, $(C_{1-6}alkyl)_3Si$ (preferably t-butyldimethylsilyl), and a $C(O)C_{1-6}alkyl$ group such as acetyl. When both of R^3 and R^4 are hydroxy preferably the two groups P^1 and P^2 together with the atoms to which they are attached form an alkylidene ring such as a methylenedioxy or isopropylidene ring. Alternatively P^1 and P^2 can form an alkoxymethylenedioxy ring such as ethoxymethylenedioxy.

Protecting groups can be added and removed using known reaction conditions. The use of protecting groups is fully described in 'Protective Groups in Organic Chemistry', edited by J W F McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 2nd edition, T W Greene & P G M Wuts, Wiley-Interscience (1991).

Ester protecting groups can be removed by basic hydrolysis, for example by using a metal hydroxide, preferably an alkali metal hydroxide, such as sodium hydroxide or lithium hydroxide, or quaternary ammonium hydroxide in a solvent, such as aqueous ethanol or aqueous tetrahydrofuran, at a temperature of from 10° to $100^\circ C$, preferably the temperature

compound of formula (I) where R is $\text{COCH}_2\text{OR}'$, or with light followed by a reducing agent (eg DIBAL-H) to give a compound of formula (I) where R is $\text{CH}_2\text{CH}_2\text{OH}$.

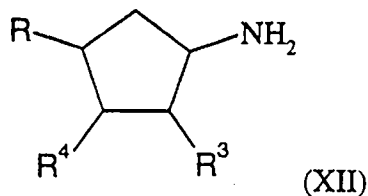
Compounds of formula (IV) can be prepared from compounds of formula (XI):



in which R^1 , R^2 , P^1 and P^2 are as defined above by treatment with an activating agent, such as an acyl chloride, followed by diazomethane. Compounds of formula (XI) can be prepared from compounds of formula (VII) as defined above by reduction of the nitro group followed by hydrolysis. Hydrolysis can be performed using a mineral acid such as HCl or a strong organic acid such as trifluoroacetic acid. Preferably the reduction and hydrolysis are carried out simultaneously using iron in an alcoholic solvent, for example ethanol, containing an alkaline earth halide such as calcium chloride at a temperature of about 80°C .

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Compounds of formula (VI) can also be prepared by treating a compound of formula (XII)



where R^3 and R^4 are as defined in formula (I) or are protected derivatives thereof or R^3 and R^4 together form a bond with a compound of formula (VIII) as defined above, followed by reduction of the nitro group. The reaction is carried out in an inert solvent such as dichloromethane or 1,4-dioxane in the presence of a non-nucleophilic base such as *N,N*-diisopropylamine at a temperature of about -20°C to about 150°C , preferably at ambient temperature.

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MS (APCI) 501 (M+H⁺, 100%)

NMR δ H (d₆-DMSO) 9.35 (1H, d), 7.33-7.16 (7H, m), 5.20 (2H, br m), 5.00-4.90 (1H, q), 4.55 (1H, m), 4.05 (1H, br s), 3.85 (2H, s), 3.80 (1H, m), 3.20 (1H, br m), 3.15 (1H, m), 3.00-2.90 (1H, m), 1.91 (1H, m), 1.51 (3H, m), 1.31 (1H, m), 0.81 (3H, t).

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Example 24

[1S-[1 α ,2 β ,3 β ,4 α (1S*,2R*)]]-4-[7-[[2-(3-Methoxyphenyl)cyclopropyl]amino]-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-cyclopentane-1,2,3-triol

- 10 a) **[3aR-(3aa,4a,6a,6aa)]-6-Amino-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-ol, hydrochloride**

The product from example 19, step (b) (17.37g) in 6M HCl (100ml) and methanol (500ml) was stirred for 18 hours. The mixture was evaporated and then azeotroped with toluene (4 x 200ml) to give a colourless powder (8.67g). This solid was suspended in acetone (250ml) containing 2,2-dimethoxypropane (25ml) and conc. HCl (0.2ml) then heated under reflux
15 for 2 hours. The mixture was cooled, evaporated and azeotroped with toluene (3 x 200ml). The residue was dissolved in 20% aqueous acetic acid and stirred for 2 hours. The mixture was evaporated and azeotroped with toluene (4 x 200ml) to afford the subtitle compound (10.1g).

- 20 MS (APCI) 174 (M+H⁺, 100%)

b) [3aR-(3aa,4a,6a,6aa)]-6-[[6-Chloro-5-nitro-2-(propylthio)-pyrimidin-4-yl]amino]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-ol

A solution of the product from step (a) (10.0g) and *N,N*-diisopropylethylamine (35ml) in THF (600ml) was stirred for 1 hour. The mixture was filtered and the solution was added
25 over 1 hour to a solution of 4,6-dichloro-5-nitro-2-(propylthio)-pyrimidine (prepared as described in WO 9703084) (25.57g) in THF (1000ml) and stirred for a further 2 hour. The solvent volume was reduced *in vacuo* and ethyl acetate was added (1000ml). The mixture was washed with water and the organic layers were dried (MgSO₄), evaporated and
30 purified (SiO₂, isohexane-ethyl acetate as eluant) to afford the sub-title compound (14.22g).

MS (APCI) 405 (M+H⁺, 100%)

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020
 Bogotá, D.C.,

Abogado
JUAN PABLO CADENA SARMIENTO
 Apoderado

ASUNTO	Radicación	02-109622-A
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	Nº 13755
	Folios	18

Patente de Invención	☐	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap. I	☐ Cap. II ☒
No. Sol. Internacional	<u>PCT/SE01/01241</u>		
Fecha de Presentación Internal.	<u>31 de Mayo de 2001</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:

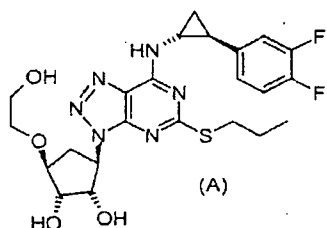
1. Documentos estudiados

- 1.1. Descripción: Folios: 24 a 48 como se radicó inicialmente
- 1.2. Reivindicaciones: Folios 49 a 51 como se radicó inicialmente
- 1.3. Prioridad: Folios: 01
 02 de Junio de 2000, GB, 0013488.2
 06 de Junio de 2000, SE, 0002102.2

2. Objeto de la invención

Título de la solicitud: **"NOVEDOSOS COMPUESTOS DE TRIAZOLO PIRIMIDINA"**

El objeto de la presente solicitud de patente de invención consiste en un proceso de producción para obtener un compuesto de fórmula (A):

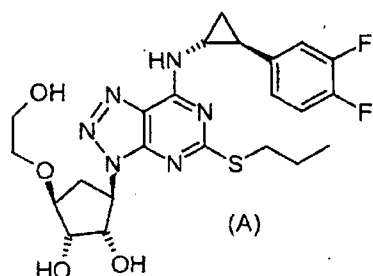


Compuesto de Fórmula A

Reivindicación 1-3: Un proceso

Reivindicación 4: Un compuesto intermediario de fórmula (VII), (X) o (XI) o una sal de un compuesto de fórmula (III)

El problema planteado en esta solicitud es la necesidad de proporcionar un proceso proporcionar un proceso de preparación para el compuesto de fórmula A



- **Clasificación Internacional de Patentes (IPC):** C07D 487/04, A61K31/505

3. De la solicitud de Patente

3.1. Descripción (artículo 28 D. 486)

- El solicitante no presenta las ventajas técnicas y el efecto superior de los procesos de preparación para la obtención del compuesto (A) a partir del compuesto (I) con lo previamente descrito en el estado de la técnica.

3.2. Reivindicaciones (artículo 30 D 486)

- El compuesto 1 no se encuentra descrito en las reivindicaciones
- La reivindicación 2 referente al "ácido necesario" se encuentra de forma general y amplia así mismo en el numeral e) reivindicación 3

El título de la solicitud no se encuentra acorde con la solicitud presentada.

4. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 02/06/2000, se encontraron los siguientes documentos del estado de la técnica relacionados, que pueden afectar la patentabilidad del objeto de la presente solicitud:

Nº	Documento	Título	Fecha de publicación
D1	WO99/41254	"Novel triazolo(4,5d) pyrimidine compounds"	19/08/1999
D2	WO 99/05143	"Novel compounds"	04/02/1999
D3	*Libro	"Química Orgánica-Fessenden and Fessenden"	1983
D4	Organic Chemistry Portal	"Carboxyl Protecting Groups Stability" Reference: Protective Groups in Organic Synthesis	1999

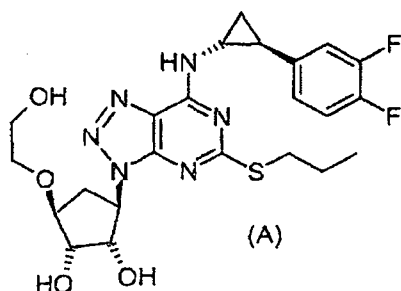
"Química Orgánica - Ralph J. Fessenden and Joan S. Fessenden- 2ª edición, 1983-Páginas 28-31 y 545-547"

4.1 Nivel inventivo (artículo 18 D486)

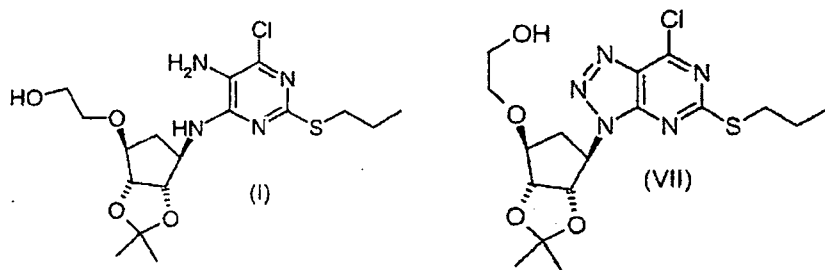
El nivel inventivo se realiza de acuerdo con la solicitud presentada como 02-109622 con lo ya planteado y expresado en el concepto técnico 0997.

Solicitud presentada

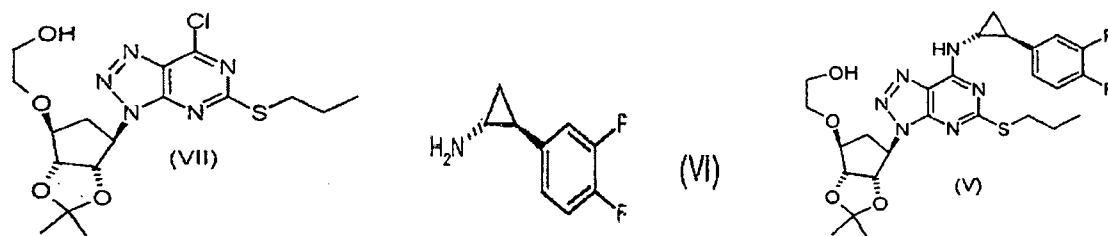
La reivindicación 1 de la solicitud presentada se refiere al proceso de preparación del compuesto de fórmula (A):



que comprende a) reaccionar un compuesto de fórmula (I) con un nitrito de un metal alcalino en presencia de un ácido para preparar un compuesto de fórmula (VII)

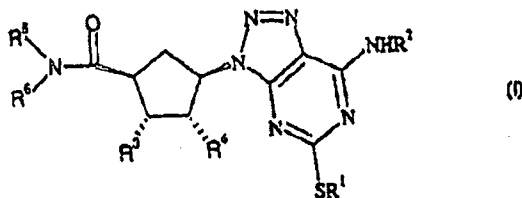


b) acoplar el compuesto de fórmula (VII) con un compuesto de fórmula (VI) para proporcionar un compuesto de fórmula (V):



c) desproteger el compuesto de fórmula (V) para proporcionar el compuesto de fórmula (A)

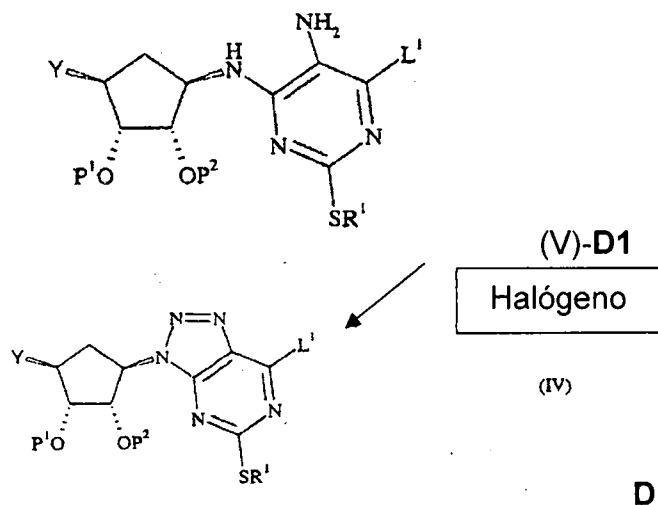
D1 enseña previamente novedosos compuestos triazolo [4,5-d] pirimidinas de fórmula I y sus procesos de preparación (Ver resumen):



Donde R^1 , R^2 son grupos protectores

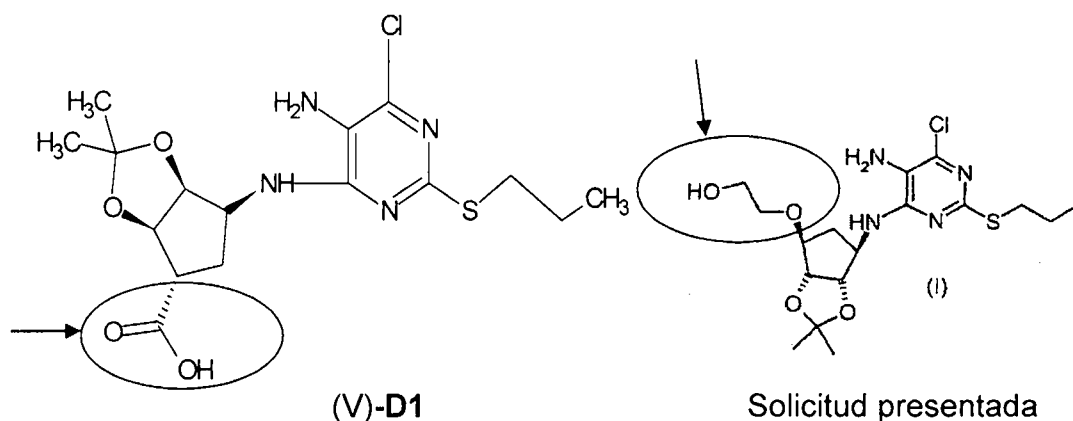
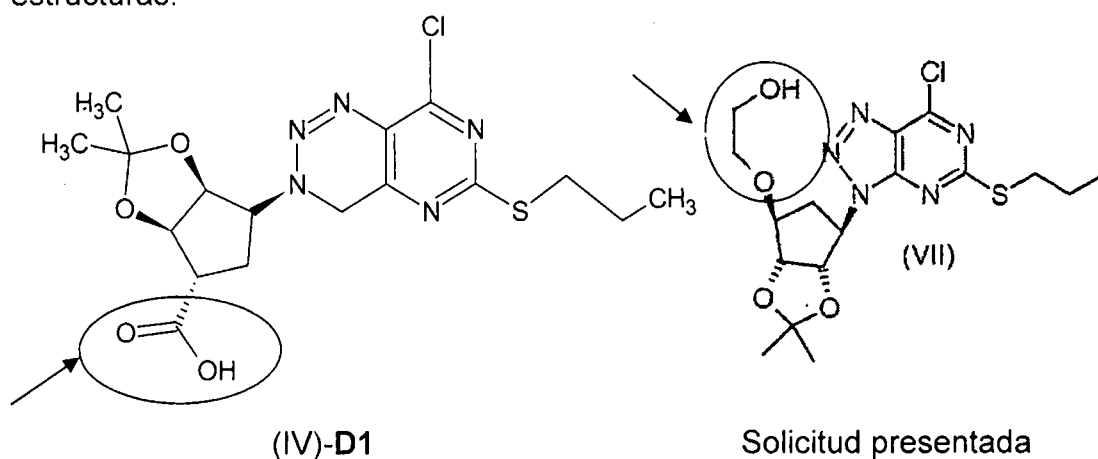
D1 enseña la preparación del compuesto de fórmula (IV) el cual puede ser preparado

por la diazotización del compuesto de fórmula (V) con un nitrito de metálico, por ejemplo **un nitrito de metal alcalino**, especialmente **nitrito de sodio** en ácido acuoso diluido por ejemplo ácido clorhídrico 2M (Ver página 7, líneas 14-21) :



Donde L^1 es un grupo saliente por ejemplo **halógeno**
 P^1 y P^2 junto a los átomos que se encuentran unidos **formar un anillo**, por ejemplo pueden representar un alquilideno, entre otros o un **alcoximetilideno** tal como **etoximetilideno** (Ver página 5, líneas 6-11)
 R^1 es C_{1-6} alquilo
 Y es CO_2H

Al realizar las sustituciones, los compuestos (IV) y (V) corresponden a las siguientes estructuras:

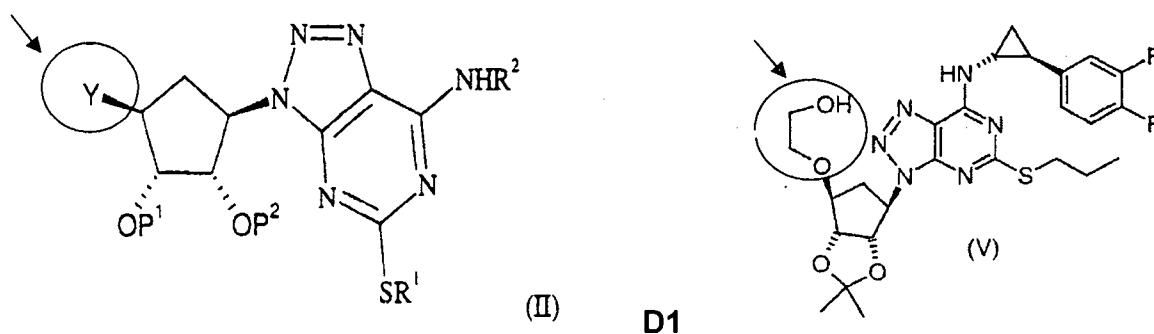
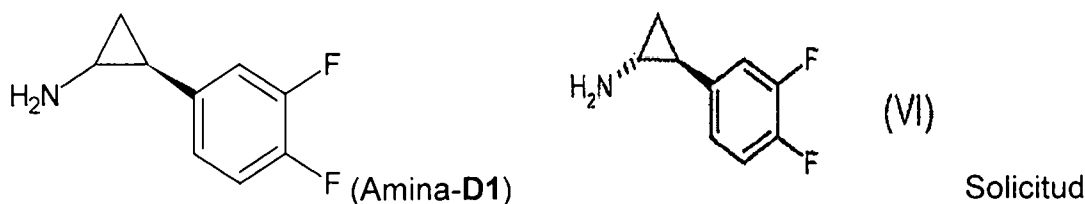
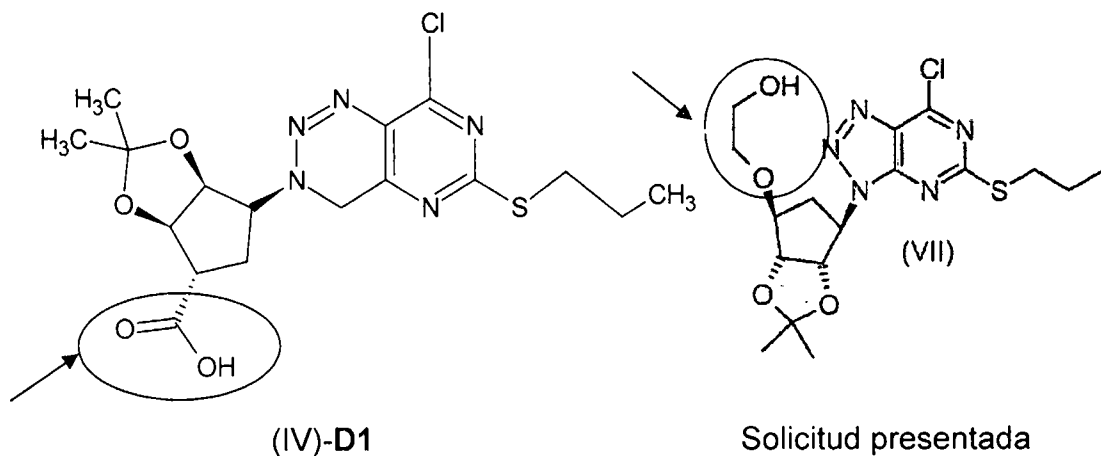


La única diferencia con la solicitud presentada es la presencia de un grupo CO_2H en la estructura del ciclopentano en **D1** (Y), mientras la solicitud presentada posee una

sustitución alcoxi alquil alcohol en el anillo pentano.

D1 ya sugería el empleo de un halógeno como grupo saliente, y la reacción de diazotización, con un nitrito alcalino, el cual con un grupo entrante tal como el **compuesto de fórmula (VI) se formaría el compuesto (V)** de la solicitud presentada.

Un compuesto de fórmula (II) en **D1** puede ser preparado por reacción de un compuesto de fórmula (IV) con una amina NH_2R^2 , donde R^2 puede ser un grupo cicloalquilo opcionalmente sustituido por fenilo y éste opcionalmente sustituido por halógeno. (Ver página 4, línea 1-4)



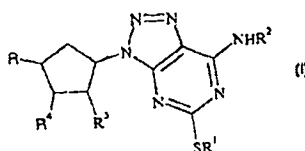
La única diferencia con la solicitud presentada es la presencia de un grupo CO_2H en la estructura del ciclopentano en **D1** (Y), mientras la solicitud presentada posee una sustitución alcoxi alquil alcohol en el anillo pentano.

El solicitante utiliza reacciones previamente descritas en el estado de la técnica para la preparación del compuesto (A) tal como la diazotización para obtener compuestos derivados triazolo pirimidina utilizando un nitrito de metal alcalino, partiendo de núcleos estructurales químicamente previamente conocidos, y cambiando un radical en la estructura; el cual al parecer no le concede un efecto técnico superior e inesperado a los procesos previamente conocidos, considerándose por lo tanto un proceso alternativo a los previamente divulgados.

D2 divulgaba compuestos novedosos de fórmula I, donde R puede ser del grupo preferido entre $\text{OCH}_2\text{CH}_2\text{OH}$ (Ver página 4, líneas 29-30) y cuyos productos

derivados también pueden ser preparados por **diazotización**. (Ver página 7, líneas 14-25).

R^3 y R^4 son grupos hidroxí y pueden estar protegidos como grupos OP^1 y OP^2 donde P^1 y P^2 son grupos protectores, los dos grupos P^1 y P^2 junto a los átomos a los cuales están unidos pueden formar un anillo alquilideno tal como metilideno o isopropilideno. (Ver página 6, líneas 14-21)

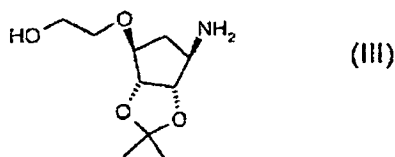


La única diferencia con la solicitud presentada es el grupo saliente el cual se encuentra de forma general en **D2**.

El solicitante utiliza reacciones previamente descritas en el estado de la técnica para tal como la diazotización para obtener compuestos derivados triazolo pirimidina utilizando un nitrito de metal alcalino, siendo evidente para el experto en la materia emplear compuestos con la sustitución **OCH₂CH₂OH en el anillo pentano (D2) y utilizar un grupo saliente como halógeno (D1)**, careciendo por lo tanto de habilidad inventiva.

Solicitud presentada

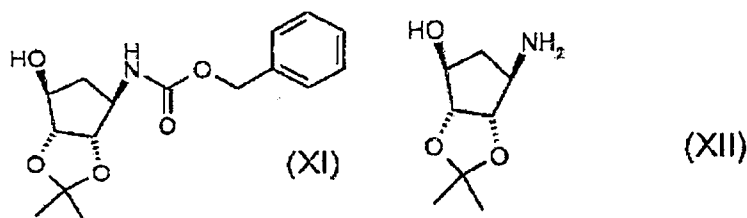
La reivindicación 2 se refiere a la preparación de una sal de un compuesto de fórmula (III)



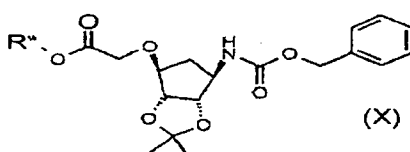
Que comprende reaccionar un compuesto de fórmula (III) con el ácido necesario.

La reivindicación 3 se refiere a la preparación de una sal de un compuesto de fórmula (III), que comprende los pasos de:

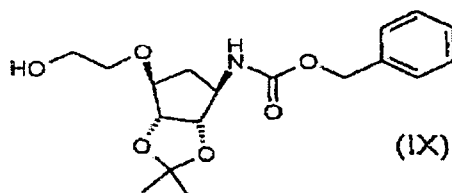
- preparar un compuesto de fórmula (XI) reaccionando un compuesto de fórmula (XII) con bencilo cloroformiato:



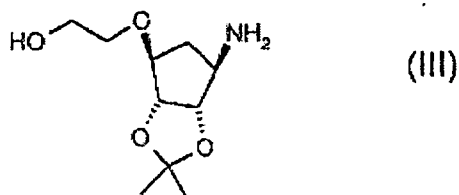
- preparar un compuesto de fórmula (X) reaccionando con un compuesto de fórmula (XI) con un compuesto de fórmula **L-CH₂-CO₂R*** donde R^* es C1-4 alquilo y L es un grupo libre



c) preparar un compuesto de fórmula (IX) reduciendo un compuesto de fórmula (X)



d) preparar un compuesto de fórmula (III) desprotegiendo el compuesto de fórmula (IX)

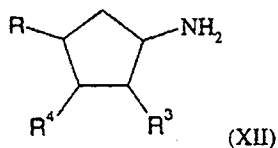


e) preparar una sal de un compuesto de fórmula (III).

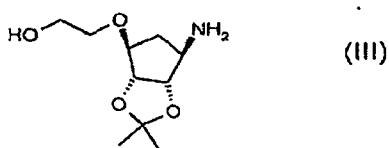
Anterioridades

Preparación de la sal del compuesto de fórmula III

D2 enseña previamente el compuesto (XII), donde al realizar los reemplazos en **R** como $\text{OCH}_2\text{CH}_2\text{OH}$ y los descritos para R^3 y R^4 los cuales pueden ser grupos hidroxilo los cuales pueden estar protegidos como grupos OP^1 y OP^2 y pueden formar un anillo alquilideno tal como metilideno o isopropilideno, se obtiene el compuesto de la solicitud presentada (III) (Ver página 10, línea 20):



D1



Solicitud presentada

En **D2** así mismo en el ejemplo 24, parte a) se reporta la formación de una sal como clorhidrato para el compuesto (3aR,4S,6R,6aS)-6-amino-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-ol. (Ver página 40, líneas 10-20). Por lo tanto sería evidente para el experto en la materia preparar la sal del compuesto (III) de acuerdo a lo previamente sugerido por **D2**.

D3 enseña la teoría de ácidos y bases de Bronsted-Lowry, donde la formación de sales para aminas con ácidos fuertes o con ácidos carboxílicos, ya se encontraba previamente divulgado en el estado de la técnica pues la reacción hace parte de las generalidades de Química Orgánica (Ver páginas 29-31)

El solicitante parte de compuestos previamente divulgados en el estado de la técnica cuya formación de sal con un ácido, es obvia para el experto en la materia de acuerdo con **D2** y **D3**.

Reducción de un compuesto de fórmula (X)

D3 enseña la reducción de ésteres usando hidruro de aluminio y litio, y hidruro de diisobutil-aluminio (DIBALH), como reacciones orgánicas genérica previamente divulgadas. (Ver páginas 545-547)

Preparar un compuesto de fórmula (III) desprotegiendo el compuesto de fórmula (IX) **D4** enseña el grupo protector bencil éster el cual se conoce como grupo protector dentro del campo de la química orgánica.

Compuestos intermediarios

Los compuestos intermediarios (VII), (X) o (IX) o la sal de un compuesto de fórmula (III) hacen parte de la estructura química principal de los compuestos en **D1** y **D2**. El solicitante parte de estructuras conocidas previamente, utilizando grupos protectores previamente divulgados en el estado del arte, sin que éstos concedan un efecto inesperado o superior.

El Problema Técnico Objetivo fundamental de la Invención Reivindicada que es: **“proporcionar un proceso de preparación para el compuesto de fórmula A”** sería solucionado fácilmente por el Experto en la Materia con base en los procesos divulgados en **D1** y **D2**, o **D2** y **D3** o **D2** y **D4** los cuales serían fácilmente logrados sin usar habilidad inventiva, partiendo de la molécula inicial con estructura (A).

5. Conclusión:

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

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	WO 99/41254	1-4	Nivel Inventivo
D2	WO 99/05143	1-4	Nivel Inventivo
D3	*Libro	1-4	Nivel Inventivo
D4	Organic Chemistry Portal	1-4	Nivel Inventivo

*“Química Orgánica - Ralph J. Fessenden and Joan S. Fessenden- 2ª edición, 1983-Páginas 28-31 y 545-547”

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 numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 31 OCT. 2008

CONCEPTO TÉCNICO No.02822	EXAMINADOR TÉCNICO Código No. 202070
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