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1

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Patente de Invención



Patente de Modelo de Utilidad



Capítulo I



Capítulo II

2

SOLICITANTE
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C.E.



Otro



Cual

Número

3

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4

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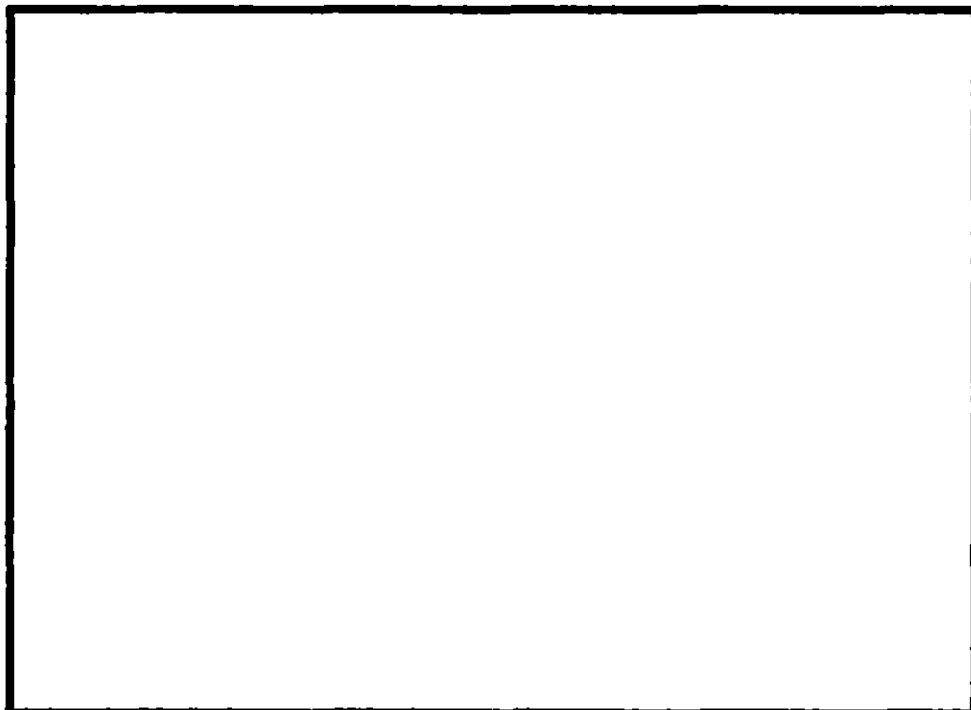
Instrucciones para el diligenciamiento del presente formulario ver reverso de esta página

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ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud \$378.000
- ☒ Comprobante de pago por reivindicación de prioridad \$212.000
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. Fotocopia Autenticada Anexa
- ☐ 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)
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- ☐ Otros

11 FIGURA CARACTERÍSTICA.



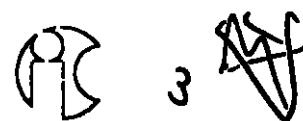
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NOMBRE. RAMIRO CASTRO DUQUE

FIRMA.

C.C 170.322 de Bogotá T.P 1003 del C.S.J

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(72) Inventors

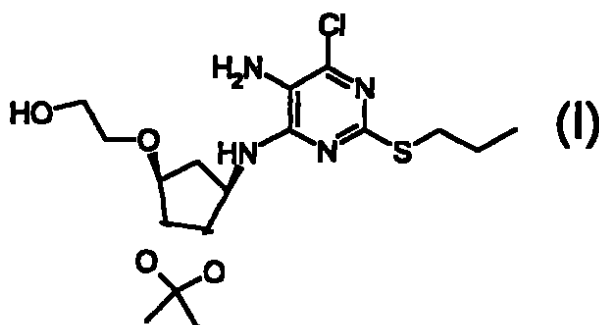
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(54) Title: NOVEL TRIAZOLO PYRIMIDINE COMPOUNDS

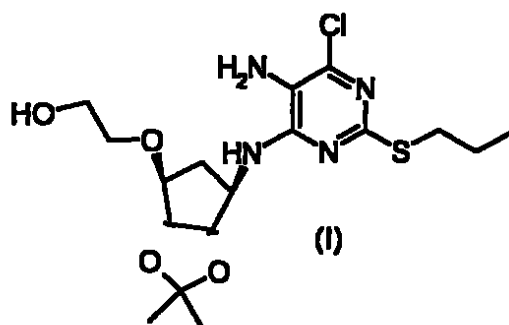


(57) Abstract The present invention relates to pyrimidine compound (I) useful as pharmaceutical intermediate, to process for preparing said pyrimidine compound in intermediates used in said process, and to the use of said pyrimidine compound in the preparation of pharmaceutical

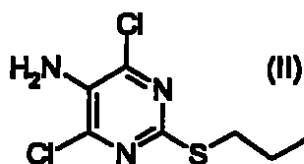
NOVEL TRIAZOLO PYRIMIDINE COMPOUNDS

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

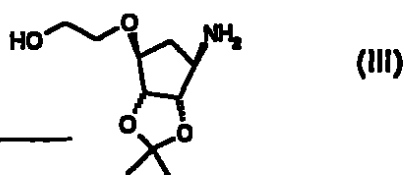
The present invention provides a compound of formula (I)



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(C₁₋₄ 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.

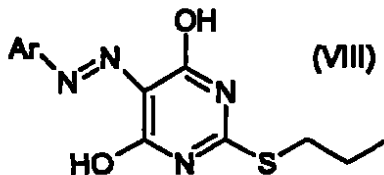
In another aspect the present invention provides a process for preparing a compound of formula (I) comprising hydrogenating a compound of formula (IV)



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 C₁₋₄ 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)

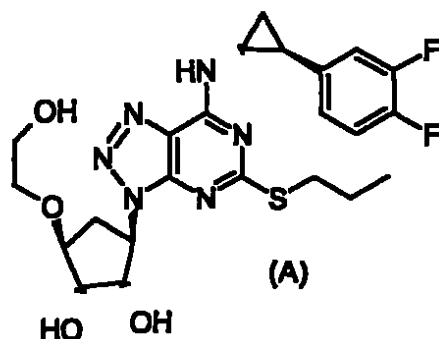
A compound of formula (IV) can be prepared by chlorinating a compound of formula (VIII)



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.

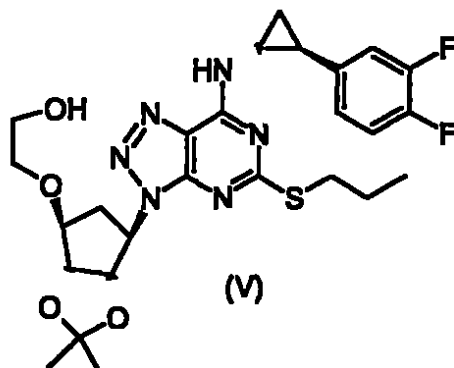
In a further aspect the present invention provides a process as hereinbefore described, for the preparation of a compound of formula (II)

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



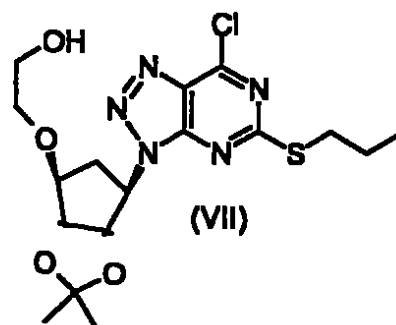
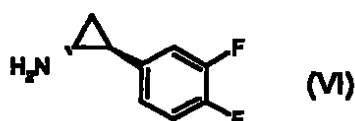
as described below

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)

10 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)



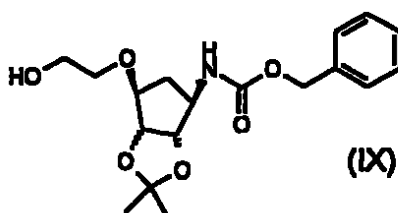
for example in the presence of a suitable base (such as a tertiary amine, such as a tri(C₁₋₄ alkyl)amine, for example triethylamine) and a suitable solvent (for example a polar solvent, such as an alcohol (such as an aliphatic alcohol containing from 1 to 6 carbon atoms, for example ethanol) or a nitrile (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)

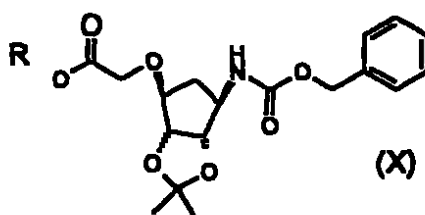
A compound of formula (III) can be prepared by deprotecting a compound of formula (IX)



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

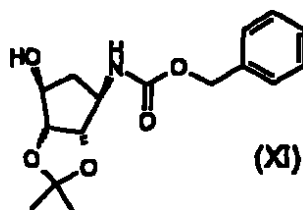
atoms, for example ethanol) at ambient temperature at a suitable pressure (such as 1 to 3 bar for example 1.0 to 1.5 bar))

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



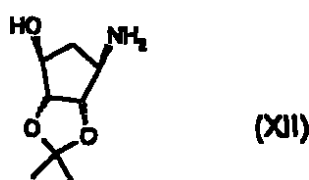
wherein R* is C₁₋₄ alkyl (preferably ethyl), such as with a suitable borohydride (for example an alkali metal borohydride, such as lithium borohydride) lithium aluminumhydride or DIBAL-H in a suitable polar solvent (such as tetrahydrofuran)

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 (XII) 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 (SiO_2 , 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*-mandelate 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 (15.5 kg) and piperidine (0.72 kg) were heated to 90°C. Malonic acid (17.6 kg) was added, followed by slow addition, over 50 minutes of 3,4-difluorobenzaldehyde (12.0 kg). The reaction mixture was stirred at 90°C for a further 4 hours and 36 minutes. Water (58.5 kg) 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 (6.4 kg) 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 13.7 kg 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 (7.4 kg) and pyridine (0.18 kg) was heated to 65°C and then thionyl chloride (7.4 kg) 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 (8.7 kg). 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 9 kg) 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 (7.1 kg) in toluene (8.5 kg) 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 (0.18 kg, 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-λ⁶
10 sulfone.

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

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 (0.5 kg) was added and the mixture was stirred a further 2 hours at 70 C. A final aliquot of thionyl chloride (0.5 kg) was added and the reaction mixture was stirred for 1 hour at 70 C, then cooled to 40 C. Periodic additions of toluene (45 kg, 3 additions of 15 kg 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 3.8 kg) 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 3.8 kg) 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 (1.24 kg) tetrabutylammonium bromide (56 g) and sodium carbonate (922 g) in water (6.2 kg) 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 (3.8 kg) stirred briefly then separated. The toluene layer was washed once more at 0 C with water (3.8 kg), 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 (6.0 kg) 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 (3*M*, 18.2 kg) stirring at 80 C. After 65 minutes the solution was diluted with water (34 kg)
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 (3.8 kg) and the product was then extracted into ethyl acetate (3.1 kg) and washed twice with water (13.7 kg per wash) affording a solution containing *trans*-(1*R*, 2*S*)-2-(3,4-difluorophenyl)cyclopropylamine (2.6 kg, 91.8% enantiomeric excess) in ethyl acetate (29.5 L).

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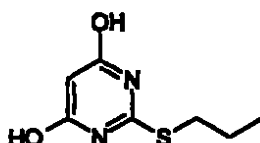
Step 11 Preparation of *trans*-(1*R*, 2*S*)-2-(3,4-difluorophenyl)cyclopropanaminium (2*R*)-2-hydroxy-2-phenylethanolate.

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

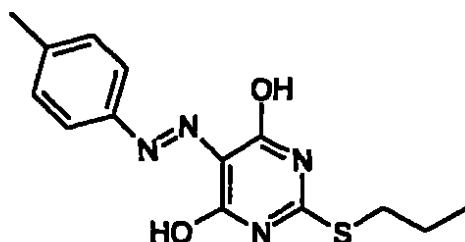
This Example illustrates the preparation of 4,6-dichloro-2-(propylsulfanyl)-5-pyrimidinamine.

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

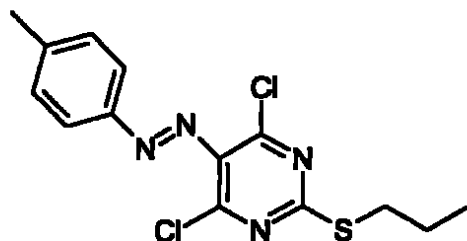


Ethanol (25ml) 4,6-dihydroxy-2-(propylsulfanyl)pyrimidine (Step 1 5g) and water (25 ml) were stirred together at room temperature. Sodium hydroxide (1.02g) was added and a clear solution obtained. The resulting solution was cooled to 0°C and then sodium acetate (9.42g) was added to give Solution A.

- 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 toluene – 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).

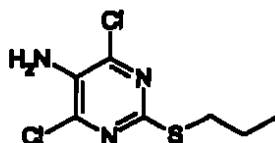
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Step 3. 4,6-Dichloro-5-[(E)-2-(4-methylphenyl)diazenyl]-2-(propylsulfanyl)pyrimidine.



- Pyridine (2.58ml) was added to a stirred, heated (70°C) slurry of 4,6-dihydroxy-5-[(E)-2-(4-methylphenyl)diazenyl]-2-(propylsulfanyl)pyrimidine (Step 2 5g) in toluene (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 bicarbonate solution (30ml). Evaporation gave the title product (4.98g) as a red oil that slowly crystallised on standing.
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Step 4. Preparation of 4,6-dichloro-2-(propylsulfanyl)-5-pyrimidinamine.



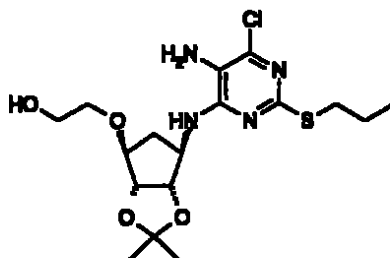
A stirred solution of 4,6-dichloro-5-[(E)-2-(4-methylphenyl)diazenyl]-2-(propylsulfanyl)pyrimidine (Step (3)) 1.1 kg in 2-propanol (16.6 kg) was hydrogenated for 1 h at 40°C/3.2 bar over a platinum on carbon catalyst (0.81 kg, 50% w/w Pt/C). The hydrogen gas pressure was released and the reactor flushed with nitrogen. The reaction mixture was filtered. The collected solid was washed with 2-propanol (1.7 kg) and the combined filtrates were concentrated under reduced pressure. The residual oil was cooled to 20°C and dissolved in ethyl acetate (5 kg) and water (5.5 l) was added. The pH of the stirred mixture was adjusted to pH 2 by the addition of 3M aqueous hydrochloric acid (800 ml). The phases were allowed to separate and the aqueous phase was discharged. Water (2.75 l) 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 (8.5 kg). Solvent (6.5 l of ethanol/ethyl acetate) was then removed by distillation at reduced pressure. A further portion of ethanol (4.5 kg) 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)cyclopropylamino]-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)



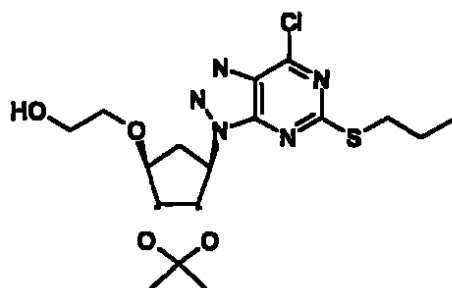
The ethanolic solution of 4,6-dichloro-2-(propylsulfanyl)-5-pyrimidinamine,
5 (prepared as in Example 3 Step 4) was added to 2 {[(3aR,4S,6R,6aS)-6-amino-2,2-
dimethyltetrahydro 3aH-cyclopenta[d][1,3]-dioxol-4-yl]oxy} 1-ethanol, L-tartaric acid salt
(1:1) (1.18 kg). To the resulting stirred thick slurry was charged triethylamine (0.95 kg)
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 (4.95 kg) and water (5.5 l) 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 (5.5 l), then separated. The
15 organic phase was concentrated under reduced pressure (4.8 l 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

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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-
25 dimethyltetrahydro-3aH-cyclopenta-[d][1,3]dioxol-4-yl]oxy)-1-ethanol)

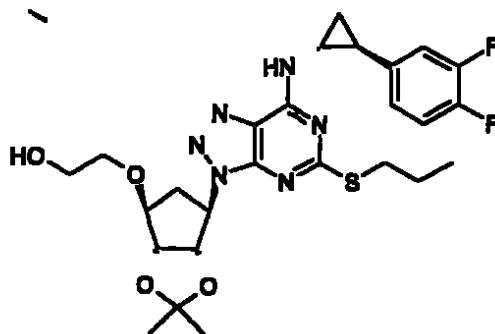
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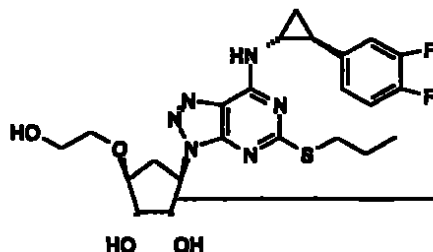
2-(((3aR,4S,6R,6aS)-6-([5-amino-6-chloro-2-(propylsulfanyl)-4-pyrimidinyl]amino)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-yl)oxy)-1-ethanol, as obtained in Step 1 was dissolved in acetic acid (5.75 kg) and water (650 ml). The resulting solution was cooled to 2°C (with stirring) and a solution of sodium nitrite (232 g) in water (1.25 l) 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 (8.9 kg) was added. Aqueous potassium carbonate solution (4 l, 37% w/w) was added. The mixture was separated and the organic phase washed with further aqueous potassium carbonate solution (3.8 kg, 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-(((1R,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-cyclopentanediol)



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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

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reduced pressure and ethyl acetate (14.3 kg) added. The mixture was heated to 45 °C 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 isooctane (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 isooctane (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 / isooctane

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. Isooctane 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 isooctane (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)

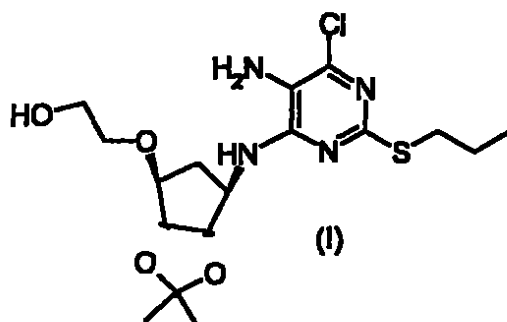
Slurry with iso-propanol

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

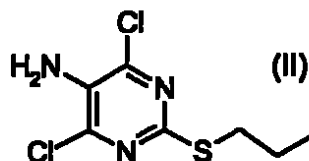
- 5 The slurry is then cooled to 20 °C during 3 hours and the temperature is kept at 20°C for about 30 minutes. The product is then filtered and washed with 1 ml/g of cold iso-propanol (<0°C). Finally the product is dried under reduced pressure at 50°C giving pure product (>98% pure by h.p l c. analysis)

CLAIMS

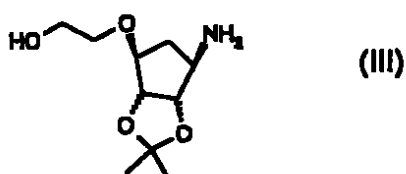
- 1 A compound of formula (I)



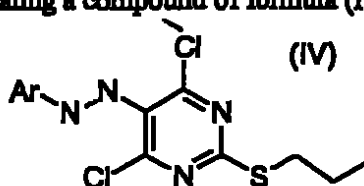
- 2 A process for preparing a compound of formula (I) comprising reacting a compound of formula (II)



with a salt of a compound of formula (III)

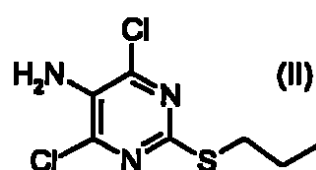


- 3 A process for preparing a compound of formula (I) as claimed in claim 2
comprising hydrogenating a compound of formula (IV)

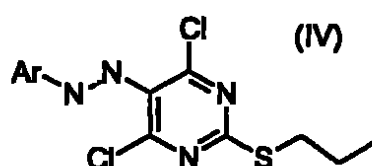


- 15 wherein Ar is phenyl optionally substituted by halogen, C₁₋₄ alkyl or C₁₋₄ alkoxy
to give a compound of formula (II) and reacting the compound of formula (II) with
a compound of formula (III) to provide the compound of formula (I)

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

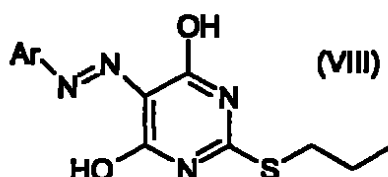


comprising hydrogenating a compound of formula (IV)



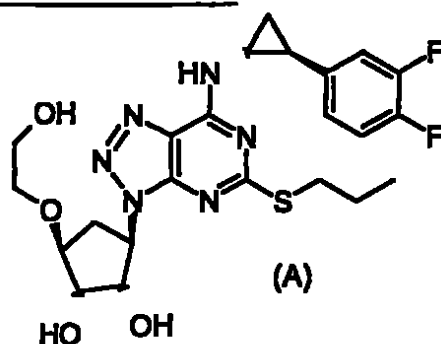
wherein Ar is phenyl optionally substituted by halogen, C₁₋₄ alkyl or C₁₋₄ alkoxy

- 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)

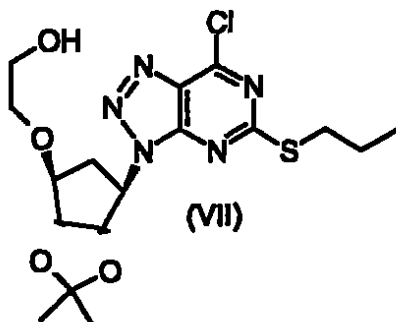
- 6 The use of a compound of formula (I) to prepare a compound of formula (A)



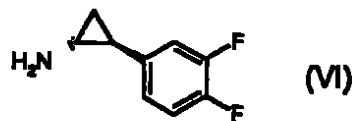
comprising

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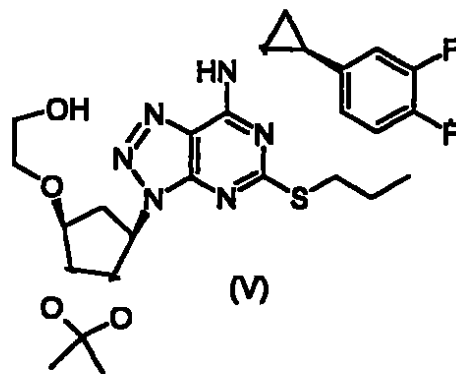
- (a) reacting a compound of formula (I) with an alkali metal nitrite in the presence of a suitable acid to prepare a compound of formula (VII)



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



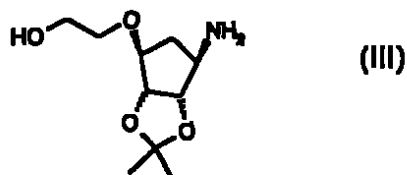
to provide a compound of formula (V)



and,

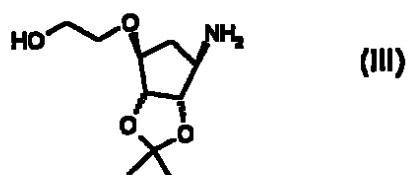
- (c) deprotecting a compound of formula (V) to provide the compound of formula (A)

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



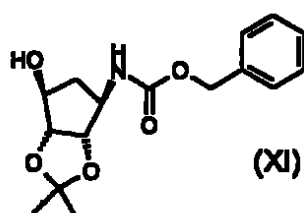
comprising reacting a compound of formula (III) with the necessary acid.

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

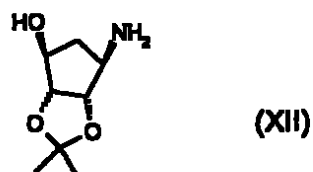


9 comprising the steps

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

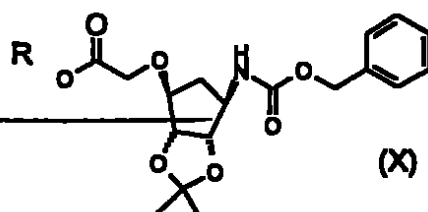


by reacting a compound of formula (XII)



10 with benzyl chloroformate;

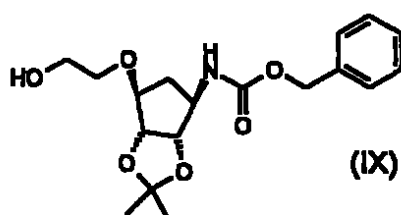
- (b) preparing a compound of formula (X)



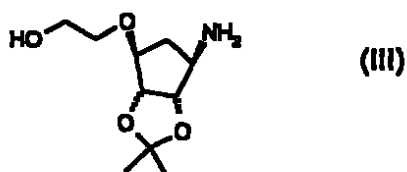
by reacting a compound of formula (XI) with a compound $L-CH_2CO_2R$
{wherein R^* is C_{1-4} alkyl and L is a leaving group}

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

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- by reducing a compound of formula (X)
(d) preparing a compound of formula (III)



- 3 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
10 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	T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	
E earlier application or patent not published on or after the international filing date	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	
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another claim or other special reason (as specified)	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	
O document referring to an oral disclosure, use, exhibition or other means	Z document number of the same patent family	
P document published prior to the international filing date but later than the priority date claimed		
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/EB Telephone No. +46 8 782 23 00	

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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
				CN	1291193 T	11/04/01
				EP	1017439 A	12/07/00
				EP	1056749 A	06/12/00
				NO	994433 A	13/09/99
				NO	20004089 A	16/10/00
				PL	335701 A	08/05/00
				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
				AT	194618 T	15/07/00
				AU	658698 B	27/04/95
				AU	2975292 A	10/06/93
				CA	2084222 A	07/06/93
				DE	69231242 D T	21/12/00
				DK	545413 T	09/10/00
				EP	0545413 A B	09/06/93
				SE	0545413 T3	
				ES	2149163 T	01/11/00
				FI	925520 A	07/06/93
				GR	3034586 T	31/01/01
				HU	217077 B	29/11/99
				HU	9203858 D	00/00/00
				IL	103962 A	10/01/97
				JP	6056835 A	01/03/94
				KR	251996 B	01/09/00
				MX	9206963 A	01/06/93
				NO	305207 B	19/04/99
				NO	924691 D	00/00/00
				NZ	245342 A	26/10/95
				PT	545413 T	31/10/00
				ZA	9209318 A	07/06/93
WO	9101317	A1	07/02/91	GB	8916477 D	00/00/00
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.
BR01/01241

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.

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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.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant or agent's file reference 100081-1 WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IP/EA/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 IPC C07D 487/04		
Applicant AstraZeneca AB et al		

1 The 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 sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/ 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 Postoch gata 1 g v e k t T 1 Box 5055 17 78 S 102 42 STOCKHOLM PATOREG S Facsimile No 08 667 72 88	Authorized officer Fernando Farieta/BS Telephone No 08 782 25 00

Form PCT/IP/EA/409 (cover sheet) (January 1998)

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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 _____

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 31(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 55.1 and/or 55.3)

3 With regard to any electronic and/or machine-readable 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 of 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 70.1(c))

Replacements of sheets which have been furnished to the receiving Office in response to an invitation under Article 17.14 are referred to in this report as originally filed and annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)

Any replacement sheets containing such amendments must be referred to and annexed as annexed to this report

IV Lack of unity

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

☐ 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 is 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 1 is known according to WO99/41254.

/

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 available 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.

V Reasoned statement under Article 35(2) with regard to novelty, inventive step, 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

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 specificity of the preceding boxes is not sufficient)

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Continuation of Box V

Novelty

Claims 1 2 6 and partly 9

Claim 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 to 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 through 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.

PCT

REQUEST

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

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and PCT International Application

Applicant or agent file reference
(if desired) (12 characters maximum) 1000811 WOBox No. I TITLE OF INVENTION
CHEMICAL COMPOUND

Box No. II APPLICANT

Name and address (Family name followed by given name for 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 inventorTelephone No.
+46 8 553 260 00Facsimile No.
+46 8 553 288 20

Teleprinter No.

State (that is, country) of nationality
SEState (that is, country) of residence
SEThis 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
the Supplemental Box

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

Name and address: (Family name followed by given name for 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
SEState (that is, country) of residence
SEThis 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
the Supplemental Box☒ Further applicants and/or (further) inventors are indicated on 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 legal entity, full official designation. The address must include postal code and name of country.)

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AstraZeneca AB
S-151 85 Södertälje
Sweden

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+46 8 553 260 00Facsimile No.
+46 8 553 288 20

Teleprinter No.

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

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Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
<i>If none of the following sub-boxes is used this sheet should not be included in the request.</i>	
Name and address (Family name followed by given name, for 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 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: ☐ 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 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 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: ☐ 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.	

B No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9 () (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 Contracting State of the Harare Protocol and of the PCT
- ☐ **EA** Eurasia 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 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 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 member State of OAPI and 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 CO Colombia | ☐ 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) other designations which would be permitted under the PCT except any designation () indicated in the Supplementary Box. The applicant declares that those additional designations as subject to withdrawal 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.)

Box No. VI PRIORITY CLAIM		☐ Further priority claim are indicated the Supplemental Box		
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is.		
		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() (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() (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(b)(iv)). 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)

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).

ISA / SE

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) 18

claims 5

abstract 1

drawings

sequence listing part of description

Total number of sheets 29

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

1 ☒ fee calculation sheet2 ☐ separate signed power of attorney3 ☒ copy of general power of attorney reference number (any GF53/2001)4 ☐ statement explaining lack of signature5 ☒ priority document() identified Box No. VI as item() (1)6 ☐ translation of international application into (language):7 ☐ separate indications concerning deposited microorganism or other biological material8 ☐ nucleotide and/or amino acid sequence listing computer readable form9 ☒ other (specify) ITS Report SE00/00653

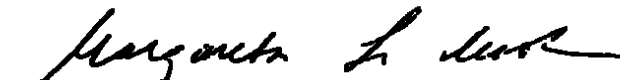
Figure of the drawings which should accompany the abstract

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 17(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
--

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

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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 or agent's file reference 100081 1 WO	
International application N 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 legal entity, full official designation. The address must include postal code and name of country) AstraZeneca AB S 151 85 Södertälje Sweden	Telephone N +46 8 553 260 00
	Facsimil 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 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 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 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 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 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 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 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() also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent()/common representative is hereby revoked.☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority in addition to the agent()/common representative appointed earlierName and address. (Family name followed by given name; for 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 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 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 copy of any amendments made under Article 19 or 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 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 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 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

34-35

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			For International Preliminary Examining Authority use only	
			received	not received
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	☐	☐

- 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 of ny 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

1 Date of actual receipt of DEMAND

2 Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b).

3 ☐ 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

4 ☐ 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

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

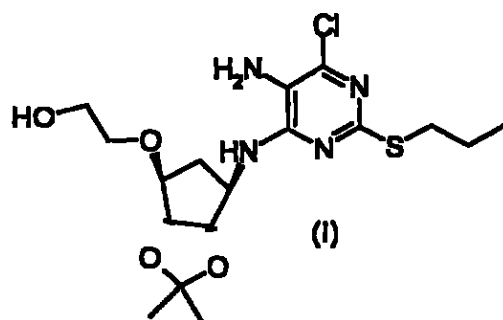
For International Bureau use only

Demand received from IPEA on

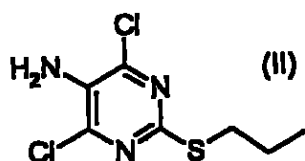
NOVEDOSOS COMPUESTOS DE TRIAZOLO PIRIMIDINA

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

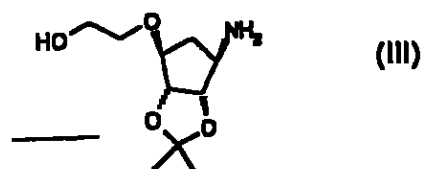
La presente invención proporciona un compuesto de fórmula (I)



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



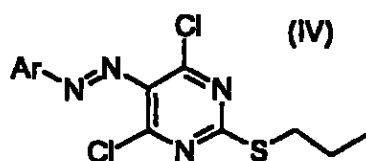
con una sal de un compuesto de fórmula (III)



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)



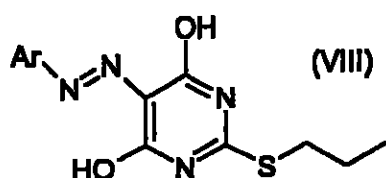
donde Ar es fenil opcionalmente sustituido por halógeno C₁₋₄ alquil o C₁₋₄ alcoxi para dar un compuesto de fórmula (H) y reaccionando el compuesto de fórmula (H) con un compuesto de fórmula (III) (como se describió arriba) para proporcionar el compuesto de fórmula (I)

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→ 37

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)

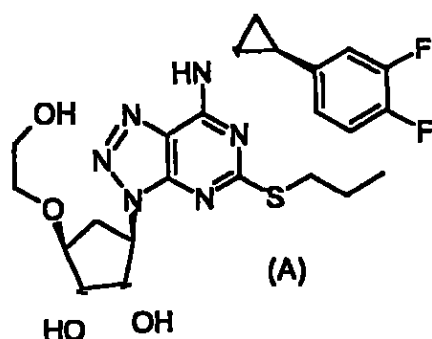
Un compuesto de fórmula (IV) puede prepararse por clorinación de un compuesto de fórmula (VIII)



donde Ar es como se definió arriba, con un adecuado agente de clorinación (tal como oxí cloruro fosforoso) en presencia de una adecuada nitrogeno 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 oxí cloruro fosforoso por ejemplo 70 a 90°C) Un compuesto de fórmula (VIII) puede prepararse mediante adaptacion de rutina de métodos de la literatura

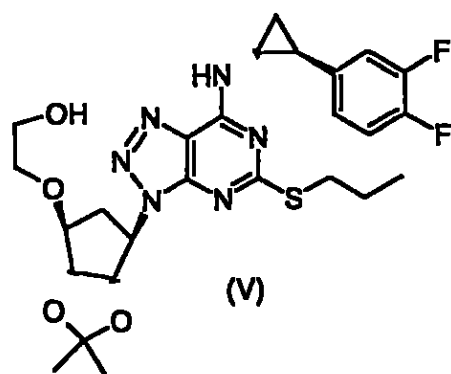
En un adicional aspecto la presente invencion proporciona un proceso como se describió aquí anteriormente para la preparación de un compuesto de fórmula (II)

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



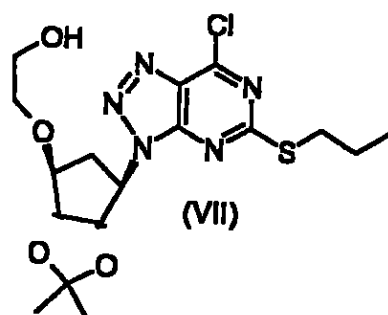
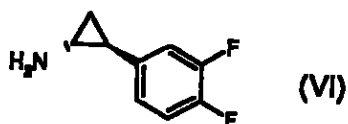
como se describio abajo

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 formula (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)



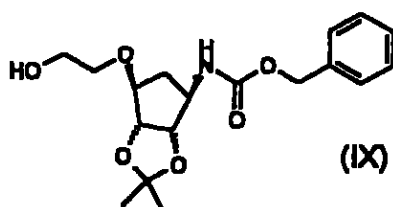
por ejemplo en presencia de una base adecuada (tal como una amina terciaria tal como un tri(C₁₋₆ alquil)amina, por ejemplo trietilamina) y un solvente adecuado (por ejemplo un solvente polar tal como un alcohol (tal como un alcohol alifático que contiene desde 1 a 6 átomos de carbono por ejemplo etanol)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

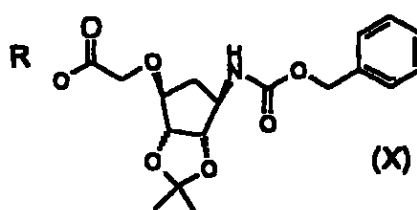
Una sal de un compuesto de fórmula (III) puede prepararse reaccionando un compuesto de fórmula (III) con el ácido necesario en un solvente adecuado (tal como agua un alcohol alifático que contiene 1 a 4 átomos de carbono (por ejemplo etanol) o un simple éster (tal como acetato de etilo)) a una temperatura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



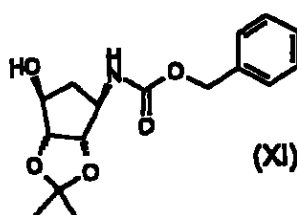
por ejemplo por hidrogenación (tal como con un catalizador de metal pesado (tal como paladio sobre carbono) en presencia de un solvente (tal como un alcohol alifático que contiene 1 a 4 átomos de carbono por ejemplo etanol) a temperatura ambiente a una presión adecuada (tal como 1 a 3 bar por ejemplo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

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



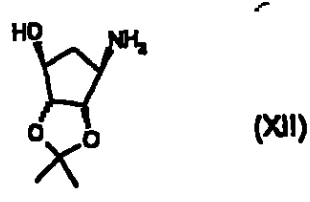
donde R* es C₁₋₄ alquil (preferiblemente etilo) tal como con un adecuado borohidrido (por ejemplo un borohidrido de metal alcalino tal como borohidrido de litio) aluminio hidrido de litio o DIBAL H en un adecuado solvente polar (tal como tetrahidrofuran)

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



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

Un compuesto de formula (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 aun un adicional aspecto la presente invencion proporciona un proceso para la preparaci3n de una sal de un compuesto de f3rmula (III) como se describio aqu3 anteriormente

En adicionales aspectos la presente invencion proporciona un compuesto intermediario de formulas (II) (IV) (VII) (VIII) (X) o (XI) o una sal de un compuesto de formula (III)

Los siguientes Ejemplos ilustran la invenci3n

EJEMPLO 1

Este Ejemplo ilustra la preparación de 2 {[(3aR 4S 6R,6aS) 6 amino 2 2 dimetiltetrahydro 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)] [tetrahydro 6 hidroxí 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 tetrahydro 2 2 dimetil-4H ciclopenta 1 3 dioxol 4 ol hidrócloruro (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)tetrahydro-4H ciclopenta 1 3 dioxol 4 il] ácido carbámico fenil metil éster

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

44
4

(3.7 ml) en tetrahydrofuran (10 ml) se agregó gota a gota. La mezcla se agitó a 0°C durante 10 minutos. Luego, adicional bromoacetato de etilo se agregó (3.7 ml x 4). La mezcla de la reacción se agitó a 0°C 2 horas adicionales.

Borohidruro de litio (2.79 g) 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 (23 g) se agregó gota a gota a la mezcla fría. Después de agitar durante 30 minutos se agregó agua (100 ml) 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 combinados 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 (38.6 g).

MS (APCI) 218 (M+H⁺ 100%)

Paso c Preparación de [3aR (3aα, 4α, 6α, 6aα)] 2 [[6-amino-2,2-dimetil-tetrahydro-4H-ciclopenta[1,3-dioxol-4-yl]oxi] etanol] (alternativamente denominado 2 {[(3aR,4S,6R,6aS)-6-amino-2,2-dimetiltetrahydro-3aH-ciclo-penta[d][1,3]-dioxol-4-yl]oxi} 1 etanol)

Un precipitado de 5% de paladio en carbono (4 g) en etanol se agregó a una solución del producto del Paso (b) (39.96 g) en etanol (250 ml) y la mezcla se hidrógeno a 1.2 bar durante 20 horas. El catalizador se sacó por filtración y el filtrado se concentró para dar el compuesto titulado (23.65 g).

MS (APCI) 160 (M+H⁺ 100%)

Paso d Preparación de [3aR (3aa 4a 6a 6aa)] 2 [[6 amino 2,2 dimetil tetrahidro-4Hciclopenta 1,3 dioxol 4 il] oxí] etanol L tartrato (denominado alternativamente 2 {[(3aR,4S 6R,6aS) 6 amino 2,2 dimetiltetrahidro 3aH ciclopenta[d][1,3] dioxol 4il]oxi} 1 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 propanamino (2R) 2 hidroxí 2 feniletanoato

Paso 1 Preparación de (E) 3 (3,4 difluorofenil) 2 ácido propenoico

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

11-45

piridina/agua se sacó entonces por destilacion del reactor bajo presión reducida. La mezcla de la reacción se acidifico 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 traves 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

solucion se diluyo 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 seco azeotropicamente por destilación del solvente (20 L) bajo presion reducida. Dimetil sulfoxido (33 9kg) se agrego y el restante tolueno se destilo fuera bajo presion 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 sulfoxido

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

Polvo de hidroxido de sodio (1 2kg) preparado moliendo tabletas de hidroxido de sodio en un molino rotativo a través de un tamiz de metal de 1mm e ioduro trimetilsulfoxonio (6 2kg) se agitaron en dimetil sulfoxido (25 2kg) bajo una atmósfera de nitrogeno a 25 C durante 90 minutos La solución se uso directamente en la preparación de (1R 2R 5R) 2 isopropil 5 metilcielo hexil trans 2 (3 4 difluorofenil) ciclo propano carboxilato

Paso 5 Preparacion 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 agitacion 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

48

73 43

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

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

Una solucion 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 agitacion de 50°C a 35 C durante 4 horas se mantuvo a 35 C durante 1 hora luego se enfrio a 26°C durante 4 horas se mantuvo a 26 C durante 1 hora luego se enfrio a 19°C durante 3 horas y se mantuvo a 19°C durante 5 horas y 10 minutos El producto se recogió por filtracion logrando un solido 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 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 acido carboxílico

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

49

48

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 período 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 seco 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)ciclopropano ácido carboxílico (aproximadamente 3 45kg) adecuado para la producción de trans (1R, 2R)-2-(3,4-difluorofenil)ciclopropano cloruro carbonilo.

Paso 8 Preparación de trans (1R, 2R)-2-(3,4-difluorofenil)ciclopropano cloruro carbonilo

Piridina (70ml) se agregó a una solución de trans (1R, 2R)-2-(3,4-difluorofenil)ciclopropano 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 período 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

agrego 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 azido 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 azido de sodio (1,24kg) bromuro de tetrabutilamonio (56g) y carbonato de sodio (922g) en agua (6,2kg) agitación a 15°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 azido 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.

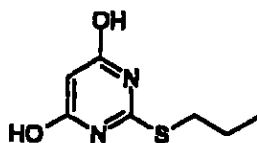
luego se enfrió a 20°C y se agregó durante un periodo de 2 horas y 15 minutos a ácido clorhídrico (3M 18 2kg) con agitación a 80 C Después de 65 minutos la solución se diluyó con agua (34kg) y se enfrió a 25°C La capa de tolueno se retiró y la capa acuosa se basificó a pH 12 con 45% de hidróxido de sodio 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 propanamino (2R) 2 hidroxil 2 feniletanoato (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 propanamino (2R) 2 hidroxil 2 feniletanoato

Se agregó R () ácido mandélico (2 26kg) a una solución que contiene trans (1R, 2S) 2 (3 4 difluorofenil)ciclo propanamino (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 propanamino (2R) 2 hidroxil 2 feniletanoato (4 45kg)

EJEMPLO 3

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

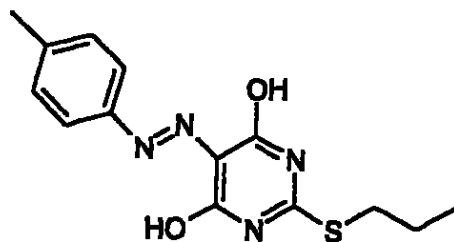


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Paso 1 4,6-Dihidroxi-2-(propilsulfanil)pirimidina

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 yodo 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).

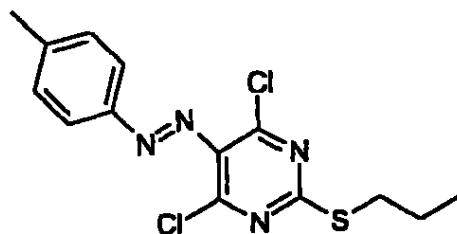
Paso 2 4,6-Dihidroxi-5-[(E)-2-(4-metilfenil)diazenil]-2-(propilsulfanil)pirimidina



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.

En un recipiente separado se preparo 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 agrego 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 alcanzo los 8°C) La suspensión amarilla resultante se agito durante la noche y el pH de la mezcla se ajusto 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 solido amarillo (6 97g)

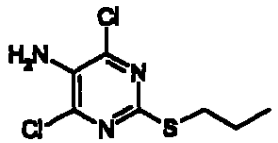
Paso 3 4 6 Diclono 5 [(E) 2 (4-metilfenil)diazetil] 2 (propilsulfanil) pirimidina



Piridina (2 58ml) se agregó a un precipitado agitado calentado (70°C) de 4 6 dihidroxí 5 [(E) 2 (4 metilfenil)diazetil] 2 (propilsulfanil) pirimidina (Paso 2 5g) en tolueno (15ml) Oxícloruro fosforoso (18 7ml) se agrego 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 evaporo El residuo se azeotropo dos veces con tolueno (2 x 30ml) El residuo se disolvio en tolueno (50 ml) y se filtró para retirar algunos sólidos El solido recogido se lavó con

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

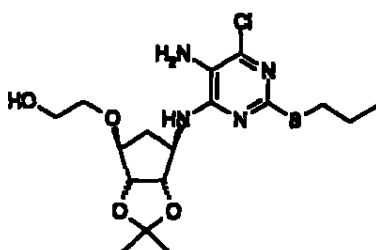


Una solución agitada de 4 6 dicloro 5 [(E)-2 (4 metilfenil) diazenil] 2(propilsulfanil)pirimidina (Paso (3) 1 1kg) en 2 propanol (16 6kg) se hidrógeno durante 1 hora a 40°C/3 2 bar sobre un catalizador de platino sobre carbon (0 81kg, 50% p/p Pt/C) La presión del gas hidrogeno se libero y el reactor se destelló con nitrógeno La mezcla de la reacción se filtro El sólido recogido se lavo con 2 propanol (1 7kg) y los filtrados combinados se concentraron bajo presión reducida El aceite residual se enfrio a 20 C y disolvió en acetato de etilo (5kg) y agua (5 5 l) se agrego El pH de la mezcla agitada se ajusto 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 separo y la fase organica se concentro 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 disolvio en etanol (8 5kg) Solvente (6 5l de etanol/acetato de etilo) luego se retiró por destilación a presión reducida Una adicional porcion 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 uso sin adicional purificación en el siguiente paso

EJEMPLO 4

Este Ejemplo ilustra la preparacion 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]pirimidin3 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]1 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]tetrahidro 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 dimetiltetrahidro 3aH ciclopenta[d][1 3]dioxol 4-il]oxi] 1 etanol)

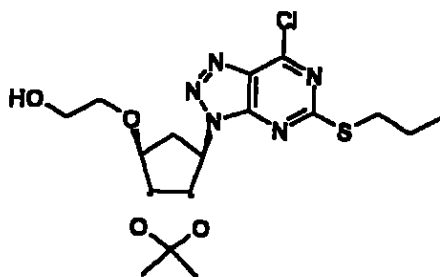


La solucion etanólica de 4 6 dicloro-2 (propilsulfanil) 5 pirimidinamina, (preparada como en el Ejemplo 3 Paso 4) se agrego a 2 1[[3aR, 4S 6R, 6aS) 6 amino 2 2dimetiltetrahidro 3aH ciclopenta[d][1 3] dioxol 4 il]oxi} 1 etanol L sal de acido tartarico (1

1) (1 18kg) Al precipitado espeso agitado resultante se cargo trietilamina (0 95kg) manteniendo la temperatura entre 20 y 25 C El reactor se sello y la temperatura se incrementó a 120 125°C La mezcla de la reaccion se mantuvo dentro de este rango de temperatura durante

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 (4.95 kg) y agua (5.5 l) 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 (5.5 l) luego se separó. La fase orgánica se concentró bajo presión reducida (4.8 l de solvente retirado) para dar 2 [((3aR, 4S, 6R, 6aS)-6-[5-amino-6-cloro-2-(propilsulfanil)-4-pirimidinil]amino)-2,2-dimetil-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.

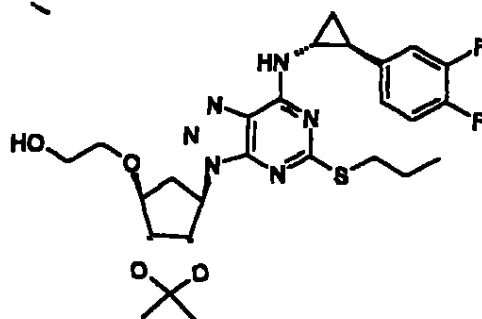
Paso 2 Preparación de [3aR (3aR, 4a, 6aR)]-2-[[6-[7-cloro-5-(propiltio)-3H-[1,2,3]triazolo[4,5-d]pirimidin-3-il]tetrahidro-2,2-dimetil-3aH-ciclopenta[d][1,3]dioxol-4-yl]oxi]etanol (alternativamente nombrado 2-(((3aR, 4S, 6R, 6aS)-6-[7-cloro-5-(propilsulfanil)-3H-[1,2,3]triazolo[4,5-d]pirimidin-3-il]-2,2-dimetiltetrahidro-3aH-ciclopenta[d][1,3]dioxol-4-il)oxi)-1-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



2 [((3aR, 4S, 6R, 6aS)-6-{{5-Amino-6-cloro-2-(propilsulfanil)-4-pirimidinil]amino}-2,2-dimetil-tetrahidro-3aH-ciclopenta[d][1,3]dioxol-4-il)oxi]-1-etanol como se obtuvo en el Paso 1 se disolvió en ácido acético (5.75 kg) y agua (650 ml). La solución resultante se enfrió a 2°C (con agitación) y una solución de nitrito de

sodio (232g) en agua (1 25 l) se agrego 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 agrego Se agrego una solución acuosa de carbonato de potasio (41 37% p/p) se agregó La mezcla se separó y la fase organica se lavo con adicional solucion 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

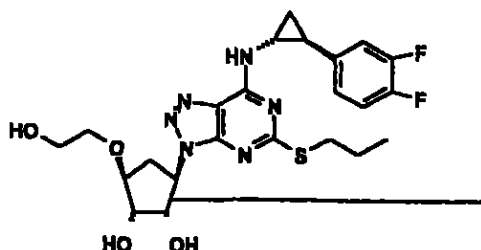
Paso 3 Preparacion de {3aR [3aa 4a 6a(1R* 2S*) 6aa]} 2 [6 (17 [2 (3 4 difluorofenil) ciclopropil]amino 5 (propiltio) 3H 1 2 3 triazolo[4 5 d]pirimidin 3 il)tetrahydro 2 2dimetil-4H ciclopenta 1 3 dioxol-4 il)oxi] etanol (alternativamente denominado 2({(3aR, 4S 6R 6aS) 6 [7 {(1R,2S) 2 (3 4 difluorofenil)-ciclopropil)amino)-5(propilsulfanil) 3H [1 2 3]triazolo[4 5 d]pirimidin 3 il] 2 2 dimetiltetrahydro-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 dimetiltetrahydro 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 agrego trietilamina (0 81kg) a una velocidad tal que la temperatura de la

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 (8.1 kg) 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 (450 ml). 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 (4.15 kg). 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)ciclopropilamino]-5-(propiltio)-3H-1,2,3-triazolo[4,5-d]pirimidin-3-yl]-5-(2-hidroxietoxi)ciclo-pentano-1,2-diol (alternativamente denominado (1S, 2S, 3R, 5S)-3-[7-[1-[(1R,2S)-2-(3,4-difluorofenil)ciclopropilamino]-5-(propilsulfanil)-3H-1,2,3-triazolo[4,5-d]pirimidin-3-yl]-5-(2-hidroxietoxi)-1,2-ciclopentanediol])



Se agregó ácido clorhídrico acuoso (3 M, 4.8 l) 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-yl]-2,2-dimetil-tetrahidro-3aH-ciclopenta[d][1,3]dioxol-4-yl]oxi]-1-etanol (1.931 kg) en metanol (13.4 kg) 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, 780 ml) 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 °C y la capa acuosa se separó. Luego se lavó la fase orgánica 15% p/p de solución acuosa de cloruro de sodio (7.2 kg). Se retiró acetato de etilo (10.1) por destilación a presión reducida. Se cargó acetato de etilo fresco (7.2 kg) y la mezcla se filtró. El filtro se lavó con acetato de etilo (1.5 kg). 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 1.016 g del producto. La concentración del acetato de etilo se ajustó hasta una concentración de 5 ml de acetato de etilo / g del producto crudo se alcanzó. La solución de acetato se calentó a 47°C e iso-octano (2.5 ml/g de producto 2540 ml) se agregó luego durante 15 minutos. El precipitado resultante se agitó durante 30 minutos y luego iso-octano (2540 ml) 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 (1.25 kg) y acetato de etilo (1.6 kg). El sólido recogido se secó en vacío para dar el compuesto titulado (920 g). 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

permanecer durante 30 minutos despues de lo cual se enfria 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 (2xl 5 ml/g) El producto se secó bajo presion reducida a 50°C dando un producto puro (>98% puro por analisis h p l c)

Precipitado con n butil acetato

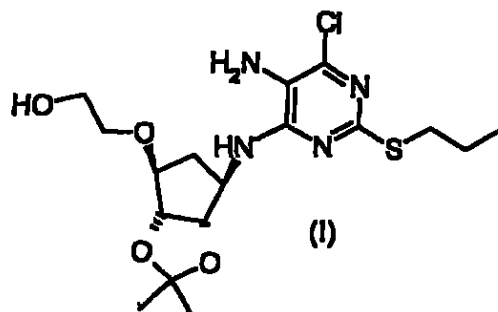
El producto crudo se suspende en n butil acetato 4 ml/g y se agito a temperatura ambiente durante 10 horas El precipitado se enfrio a 0°C durante 3 a 4 horas y se mantuvo a 0°C durante 1 hora El producto se filtro y lavo con 2 ml/g de n butil acetato frio (<0 C) El producto se seca luego en vacio a 50°C dando producto puro (>98% puro por análisis h p l c)

Precipitado con iso propanol

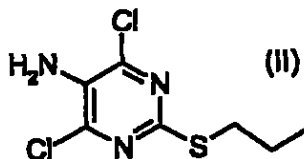
El producto crudo se suspendió en iso-propanol 3 ml/g y se agito a 50°C durante 72 horas El precipitado luego se enfrio a 20°C durante 3 horas y la temperatura se mantuvo a 20°C durante alrededor de 30 minutos El producto luego se filtro y lavo con 1 m/g de iso propanol frio (<0°C) Finalmente el producto se seco bajo presion reducida a 50°C dando un producto puro (>98% puro por analisis h p l c)

REIVINDICACIONES

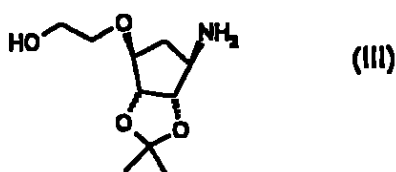
1 Un compuesto de formula (I)



2 Un proceso para preparar un compuesto de formula (I) que comprende reaccionar un compuesto de fórmula (II)



con una sal de un compuesto de formula (III)

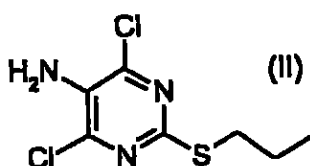


3 Un proceso para preparar un compuesto de formula (I) como se reivindica en la reivindicación 2 que comprende hidrogenar un compuesto de formula (IV)

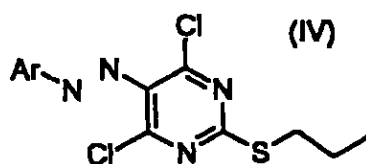


donde Ar es fenil opcionalmente sustituido por halogeno C₁₋₄ alquil o C₁₋₄ alcoxi para dar un compuesto de fórmula (II) y reaccionar el compuesto de formula (II) con un compuesto de formula (III) para proporcionar el compuesto de fórmula (I)

4 Un proceso para preparar un compuesto de formula (II)

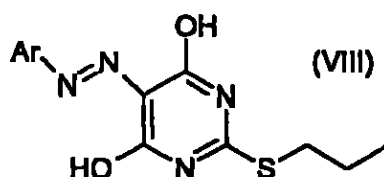


que comprende hidrogenar un compuesto de fórmula (IV)



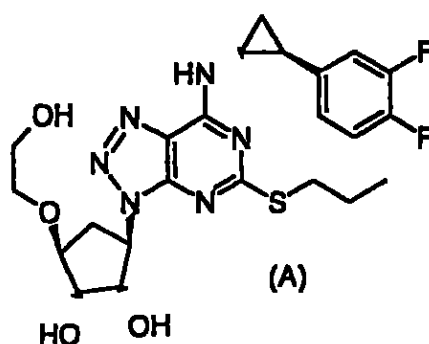
donde Ar es fenil opcionalmente sustituido por halógeno C₁₋₄ alquil o C₁₋₄ alcoxi

5 Un proceso para preparar un compuesto de fórmula (II) como se reivindica en la reivindicación 2 que comprende clorinar un compuesto de fórmula (VIII)



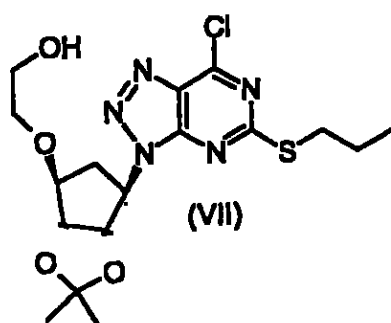
donde Ar es fenil opcionalmente sustituido por halogeno C_{1-4} alquil o C_{1-4} alcoxi para proporcionar un compuesto de formula (IV) y luego hidrogenar el compuesto de fórmula (IV)

6 El uso de un compuesto de formula (I) para preparar un compuesto de fórmula (A)



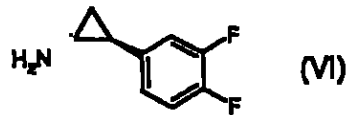
que comprende

- (a) reaccionar un compuesto de formula (1) con un nitrito de metal alcalino en presencia de un ácido adecuado para preparar un compuesto de formula (VII)

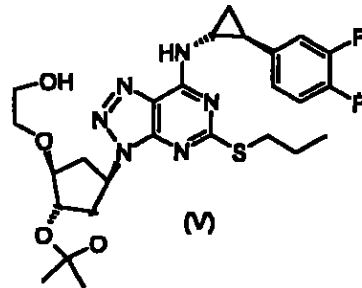


- (b) acoplar el compuesto de formula (VII) con un compuesto de fórmula (VI)

64
63

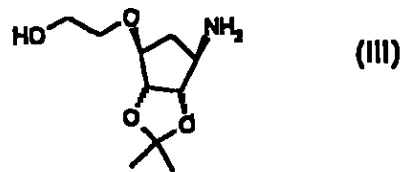


para proporcionar un compuesto de formula (V)



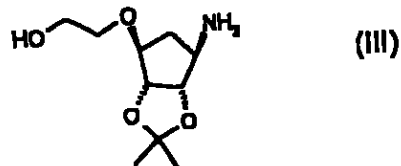
(c) desproteger un compuesto de formula (V) para proporcionar el compuesto de formula (A)

7 Un proceso para preparar una sal de un compuesto de formula (III)



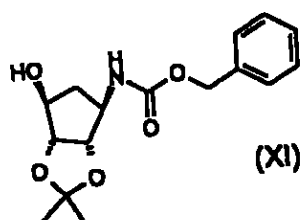
que comprende reaccionar un compuesto de fórmula (III) con el ácido necesario

8 Un proceso para preparar una sal de un compuesto de formula (III)

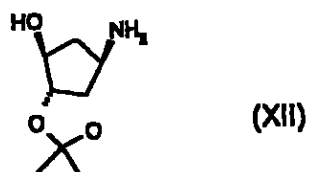


que comprende los pasos

(a) preparar un compuesto de fórmula (XI)

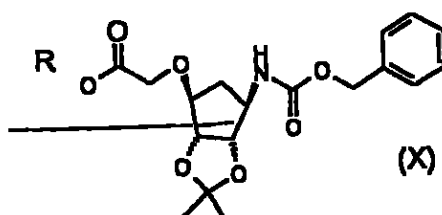


reaccionando un compuesto de formula (XII)



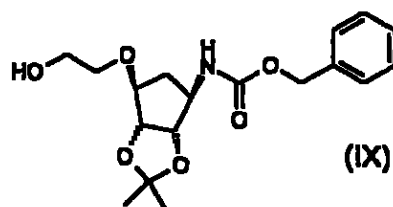
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- (b) preparar un compuesto de fórmula (X)



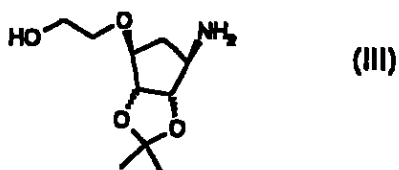
reaccionando un compuesto de fórmula (XI) con un compuesto $L-CH_2CO_2R^*$ donde R^* es C_{1-4} alquil y L es un grupo libre)

- (c) preparar un compuesto de formula (IX)



reduciendo un compuesto de formula (X)

- (d) preparar un compuesto de formula (III)



desprotegiendo un compuesto de formula (IX) y

(e) preparar una sal de un compuesto de formula (III) reaccionando el compuesto de formula (III) con el acido necesario

9 Un compuesto intermediario de fórmula (II) (IV) (VII) (VIII) (X) o (XI) o una sal de un compuesto de formula (III)



CONSULADO GENERAL DE COLOMBIA

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El suscrito Consul General de Colombia en Londres vistos los documentos presentados ante este Despacho

CERTIFICA

Que J B HODGSON Notario Publico de Macclesfield Cheshire Inglaterra legalizó la firma del documento precedente y su firma se encuentra certificada por J GARBRAH Oficial de del Ministerio de Relaciones Exteriores Britanico firma que se encuentra registrada en este Consulado General

Que AstraZeneca AB es una Sociedad constituida organizada y existente en Soderstje Suecia y que cumple con su objeto social de acuerdo con las leyes de ese pais

Que DAVID ERIC GILES en su calidad de Representante Legal de la mencionada Sociedad debidamente autorizado otorga el documento precedente y su firma se encuentra legalizada por J B HODGSON Notario Publico de Macclesfield Cheshire Inglaterra Gran Bretaña

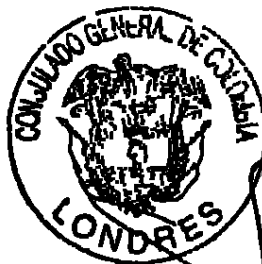
El Consul General no asume responsabilidad por el contenido del mencionado documento

Dado en Londres Inglaterra Gran Bretaña a los quince (15) dias del mes de Noviembre de dos mil (2000)

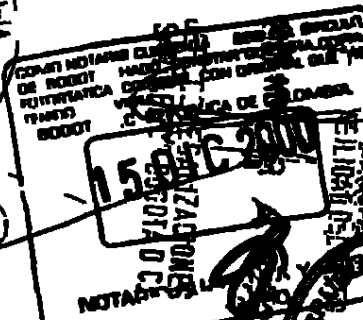
Certificacion No 11 /1722

Derechos, L \$ 106 00 CANCELADOS

JAIME H. BERRIO VILI ARREAI
Consul General



HUGO NAVARRO ALVAREZ
IRADUCTOR E INTERPRETE
Res. 1878 del 19 de mayo 1999



BRIGARD & CASTRO

SANTAFF DE BOGOTA COLOMBIA

PODER

Yo (nosotros) ASTRAZENECA AB

Domiciado(s) en S 151 85 Sodertalje
SUECIA

Nombro(amos) a RAMIRO CASTRO DUQUE y/o HECTOR GOMEZ MEJIA de Santafé 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 policia en cualquier instancia o recurso la obtención de patentes de invención registros de marcas diseños industriales modelos de utilidad depósitos de nombres comerciales y enseñas 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 policia 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 HECTOR GOMEZ MEJIA domiciliado(s) en la Carrera 7 No 18 56 Piso 9 mis (nuestros) apoderados en Colombia con facultades para recibir notificaciones y designar apoderados judiciales o extrajudiciales

Otorgado y firmado en

hoy de de 20

Firma

Nombre
Cargo

POWER OF ATTORNEY

I (We ASTRAZENECA AB

Domiciled in S 151 85 Sodertalje
SWEDEN

Hereby appoint RAMIRO CASTRO DUQUE and/or HECTOR GOMEZ MEJIA of Santafé de 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 copyright and emblems registration of copyright and contracts related thereto certificates of obtainers of vegetable 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 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 kinds 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. I (We) (my (our)) hereby appoint RAMIRO CASTRO DUQUE and/or HECTOR GOMEZ MEJIA domiciliado(s) en la Carrera 7 No 18 56 Piso 9 my (our) attorney(s) in and with powers to receive notifications and to designate judicial and extrajudicial attorneys

GRANTED AND SIGNED IN

NOTARY PUBLIC

GRANTED AND SIGNED IN

NOTARY PUBLIC

This 12 NOV 2001 day

Signature

Name
Title

DAVID ERIC GILES
DIRECTOR IP SERVICES

CERTIFICADO NOTARIAL (SOCIEDAD)

NOTARIAL CERTIFICATE (CORPORATION)

Hoy de de
Personalmente compareció ante mí

On this 10 day of November of 2000
Personally appeared before me

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

DAVID ERIC GILES
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

DIRECTOR IP SERVICES

De ASTRAZENECA AB

of ASTRAZENECA AB

10 NOV 2000
14:44:44 ALVAREZ
E - 46.000000

Sociedad legalmente constituida para un periodo 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

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 hereunto by
the deponent in the name and on behalf of said
Corporation is the corporate seal thereof and that the
purpose for which this instrument is granted is included
within the corporate purpose of company

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

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

Estado de
con fecha

State of Sweden
under date of 3rd JANUARY 2000

y que quien confiere el presente poder es su
representante

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

[Signature]
Notary Public (Seal)

Notario Público (sello)

**CERTIFICADO NOTARIAL
PERSONA NATURAL**

**NOTARIAL CERTIFICATE
NATURAL PERSON**

Hoy de de
compareció(eron) ante mí

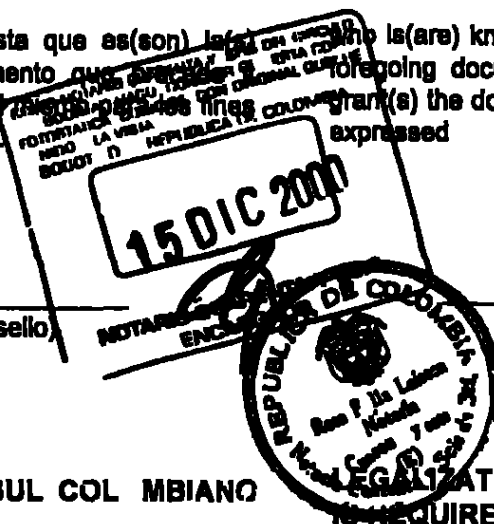
On this day of of
personally appeared before me

a quien (es) conozco y me consta que es(son) la(s)
persona(s) firmante(s) del documento que
quien(es) declara(n) que otorgan el presente poder
y propósitos que en él se expresan.

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

Notario Público (sello)

Notary Public (Seal)



LEGALIZACION ANTE CONSUL COL MBIANO
ES REQUERIDA

LEGALIZATION BEFORE COLOMBIAN CONSUL
IS REQUIRED



70
69

TRADUCCION OFICIAL No 432/2000 de las legalizaciones que se encuentran a continuación de un Poder otorgado ASTRAZENECA AB una compañía domiciliada en S 151 85 Sodertalje SUECIA al doctor RAMIRO CASTRO y HECTOR GOMEZ Santafé de Bogotá D C Colombia del Inglés al español las cuales para su identificación se sella con el Sello del Traductor al mismo tiempo que la presente

++++
ANEXOS El Poder arriba mencionado Certificación Notarial Certificación por el Secretario de Estado Principal de Su Majestad Para los Asuntos de la Comunidad y el Extranjero en Londres Inglaterra Certificación del Consulado General de Colombia en Londres Inglaterra Autenticación por el Ministerio de Relaciones Exteriores de Colombia

++++

**Firma ilegible (Firmado)
Notario Público
SELLO NOTARIAL EN RELIEVE**

++++

REINO UNIDO DE LA GRAN BRETAÑA E IRLANDA DEL NORTE

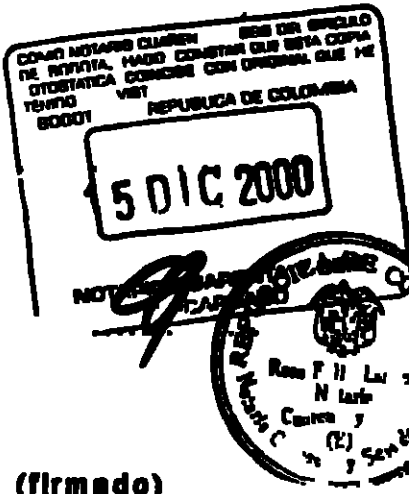
**No D644894
Fecha 14 de Noviembre del año 2000
Este documento porta
la firma/sello de J B Hodgeon

actuando en la capacidad de
Notario Público

Firmado por J Garbrah**

Firma ilegible (firmado)

**HUGO NAVARRO ALVAREZ
TRADUCCION E. INTERPRETE OFICIAL
Bm. 1476 M3 (válido 1995)**



Por el Secretario de Estado Principal de
Su Majestad para los Asuntos de la
Comunidad y el Extranjero

SELLO EN RELIEVE

**HAY SELLO DE LA COMUNIDAD
Y EL EXTRANJERO EN LONDRES
INGLATERRA**

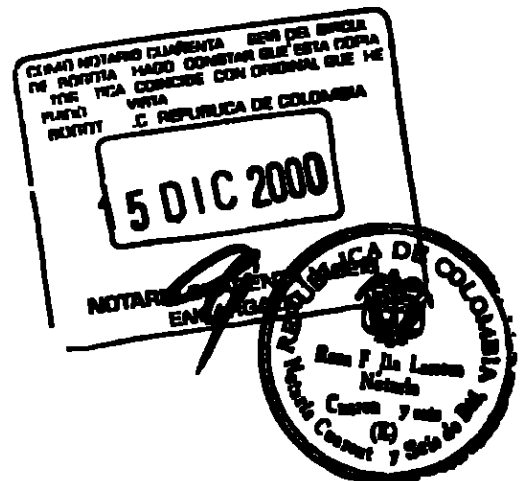
+++++
EN ESPAÑOL La Certificación del Consulado General de Colombia
en Londres Inglaterra bajo el Número de Certificación 11/1722 de
fecha 16 de Noviembre del año 2000 Autenticación Hasta por el
Ministerio de Relaciones Exteriores de Colombia bajo el Número
481834 de fecha 29 de Noviembre del año 2000

(Pagados Derechos por valor de \$106 00 Dólares)

+++++
**ES TRADUCCION FIEL Y COMPLETA DE LOS DOCUMENTOS
ADJUNTOS**


HUGO NAVARRO ALVAREZ
TRADUCTOR E. INTERPRETE OFICIAL
Boa. 1876 M. (aviliza 1979)

**Resolución Número 1876 del Ministerio de Justicia
Fecha 4 de Diciembre del año 2000**



47 JUL 24 1964

1 ALL INFORMATION CONTAINED HEREIN IS UNCLASSIFIED
DATE 11-14-2010 BY 60322 UCBAW

ADVERTENCIA

ES TRADUCCION FIEL Y COMPLETA DE LOS DOCUMENTOS
+ + + + +
(Para los Estados Unidos de América)

416 4 de fecha 1 de mayo de 1900

Ministerio de Relaciones Exteriores de Colombia

EN ESPANOL La Comision del Congreso de Colombia
+ + + + +

51.14

NOTARIO ENCARGADO
REPUBLICA DE COLOMBIA
15 DIC 2000

NOTARIO ENCARGADO
ENCABEZADO

433

My Dear Mr. [illegible]

SECRET

100-4-1-1 MEZ

175 111 4 4 11

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION	()	()
MODELO DE UTILIDAD	()	()
Indicación de que se solicita la concesión de una patente	()	()
Datos de identificación del solicitante o de la persona que se presenta la solicitud	()	()
Descripción de la invención.	()	()
Dibujos de ser estos pertinentes.	()	()
Comprobante de Pago de las tasas establecidas	()	()

COMPLETA	()	INCOMPLETA	()	()
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DISEÑO INDUSTRIAL ()

Indicación de que se solicita el registro de Diseño Industrial	()	()
Datos de identificación del solicitante o de la persona que presenta la solicitud	()	()
Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño	()	()
Comprobante de pago de las tasas establecidas	()	()

COMPLETA	()	INCOMPLETA	()	()
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● ESQUEMA DE TRAZADO ()

Indicación de que solicita el registro de un Esquema de trazado	()	()
Datos de identificación del solicitante o de la persona que presenta La solicitud	()	()
Representación gráfica del esquema de trazado	()	()
Comprobante de pago de las tasas establecidas	()	()

COMPLETA	()	INCOMPLETA	()	()
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Firma Responsable

Fecha

73
72



2020
Bogotá, D C

Doctor
Ramiro Castro Duque
Apoderado
ASTRAZENECA AB

Oficio N°
06847

ASUNTO	Radicación N°	02-109822
	Solicitud internacional	PCT/SE01/01241
	Fecha inicio fase nacional	02/01/2003
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT) regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que.

- ❑ La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante (Art. 26-k) Decisión 486)
- ❑ La solicitud no contiene la traducción de los anexos del reporte de examen preliminar internacional (Art. 36.2.b) del tratado PCT)

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486 se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2 literal e) del capítulo quinto del título primero de la Circular Única N° 10 de 2001


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

22 AGO 2020

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