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Señores

DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá, D.C.-

SUPERINTENDENCIA Y DEPARTAMENTO
Radicación: 00065.923 (00065.923) Folios: 13
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Trámite: 22 PAGINAS 1 REGISTRAR 29 OCTUBRE
Indicador: 222 CUESTA DE PAGO DE FOLIOS

Re.: Expediente No. 00065.923

Solicitud de Patente

SB PHARMCO PUERTO RICO INC.

Debidamente traducida, adjunto acompaño la copia oficial de la solicitud de patente básica británica No. GB 9920919.9, la cual le solicito agregar a este expediente para los fines legales respectivos.

De Usted atentamente,

GERMAN CASTILLO GRAU

C.C.#17.017.671 de Bogotá

T.P.#2978 del C.S.J



INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed

Dated 20 October 2000

An Executive Agency of the Department of Trade and Industry



Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference **AJB/PMS/P32412**

2. Patent application number

(The Patent Office will fill in this part)

03 SEP 1999

9920919.9

3. Full name, address and postcode of the or of each applicant (underline all surnames)

SB Pharmco Puerto Rico Inc
Road 172, KM 9.1/Bo Certenejas, Cidra, Puerto Rico 00639

Patents ADP number (*if you know it*)

If the applicant is a corporate body, give the country/state of its incorporation

7733249 001

4. Title of the invention

Novel Compound

5. Name of your agent (*if you have one*)

CORPORATE INTELLECTUAL PROPERTY

"Address for service" in the United Kingdom to which all correspondence should be sent (*including the postcode*)

SMITHKLINE BEECHAM PLC
TWO NEW HORIZONS COURT
BRENTFORD
MIDDLESEX TW8 9EP

Patents ADP number (*if you know it*)

5800 974003

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and (*if you know it*) the or each application number

Country	Priority application number (<i>if you know it</i>)	Date of filing (<i>day / month / year</i>)
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7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (<i>day / month / year</i>)
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8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (*Answer yes if:*

- a) any applicant named in part 3 is not an inventor, or
- b) there is an inventor who is named as an applicant, or
- c) any named applicant is a corporate body

See note (d)

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	0
Description	5 - 824
Claim(s)	2
Abstract	0
Drawings	0

10. If you are also filing any of the following, state how many against each item.

Priority Documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (Patents Form 1/77)

Request for preliminary examination and search (Patents Form 9/77)

Request for substantive examination (Patents Form 10/77)

Any other documents (please specify)

11.

We request the grant of a patent on the basis of this application

Signature A J Blakely Date 3-Sep-99

A J Blakely

12. Name and daytime telephone number of person to contact in the United Kingdom

A J Blakely 01279 644355

Warning

After an application for a Patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission unless an application has been filed at least six weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

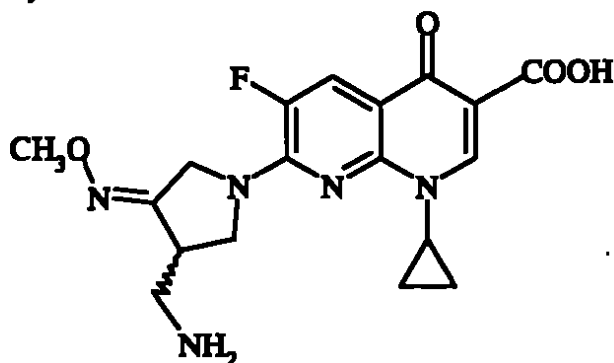
- If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505
- Write your answers in capital letters using black ink or you may type them.
- If there is not enough space for all relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.
- If you have answered 'Yes' Patents Form 7/77 will need to be filed.
- For details of the fee and ways to pay please contact the Patent Office.

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NOVEL COMPOUND

The present invention relates to novel compounds which are of use in the production of pharmaceutically active compounds, for example, quinoline carboxylic acid derivatives having antibacterial activity.

EP 688772 discloses novel naphthyridine carboxylic acid derivatives having antibacterial activity, including anhydrous (R,S)-7-(3-aminomethyl-4-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid of the formula:

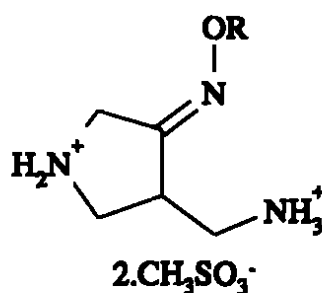


WO 98/42705 discloses (R,S)-7-(3-aminomethyl-4-*syn*-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate and hydrates thereof including the sesquihydrate.

PCT/KR99/00099 (published after the priority date of the present application) discloses a process for the production of 4-aminomethyl-3-alkoxyiminopyrrolidines and salts thereof from aminomethylpyrrolidin-3-one and the corresponding alkoxyamine. Suitable salts of the 4-aminomethyl-3-alkoxyiminopyrrolidines are described as the hydrochloride, trifluoroacetate and sulfate salts.

The present invention relates to novel 4-aminomethyl-3-alkoxyiminopyrrolidine salts which are of use in the synthesis of pharmaceutically active compounds.

According to the invention there is provided a compound of formula (I):

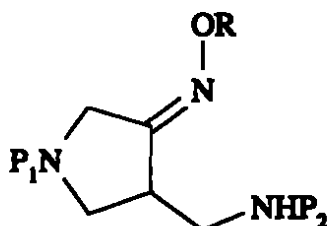


(I)

wherein R is C₁₋₄ alkyl or C₁₋₄ haloalkyl.

The compound of formula (I) is preferably 4-aminomethyl-3-methoxyiminopyrrolidinium dimethanesulfonate.

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



(II)

- 10 wherein R is as defined for formula (I) and P₁ and P₂, which may be the same or different, are amino protecting groups, with methanesulfonic acid.

Suitable protecting groups P₁ and P₂ include any suitable amino protecting groups which are removable by treatment with methanesulfonic acid. The preferred protecting group for both P₁ and P₂ is t-butoxycarbonyl.

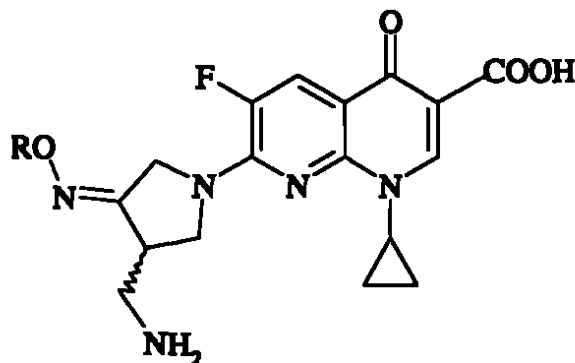
- 15 The reaction of the compound of formula (II) and methanesulfonic acid is suitably carried out at a temperature between about 10°C and about 50°C.

The amount of methanesulfonic acid used to effect the deprotection of the compound of formula (II) is suitably 2 to 4 equivalents. Preferably 2.4 equivalents, suitably used at a temperature of between 35°C and 40°C; or 3 equivalents, suitably used at ambient temperature.

- 20 The reaction is suitably carried out in a solvent, for example, an alcohol such as methanol, ethanol, isopropanol, or n-propanol, dichloromethane, acetonitrile, acetone, methyl iso-butyl ketone, DME, THF, tert-butylmethyl ether, dioxane or ethyl acetate. The solvent is preferably methanol.

- 25 The compounds of formula (II) may be prepared by the processes described in US 5,633,262, EP 688772A1 and PCT/KR99/00099.

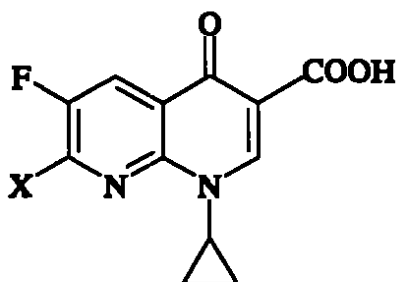
- 30 The compounds of formula (I) are useful as an intermediates for preparing quinolone antibacterials particularly those described in US 5,633,262 and EP 688772A1. Thus according to a further aspect of the invention there is provided a process for the production of a compound of formula (III), or a pharmaceutically acceptable salt and/or hydrate thereof:

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(III)

wherein R is as defined for formula (I), which comprises reaction of a compound of formula (I), with a compound of formula (IV):

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(IV)

wherein X is a leaving group, e.g. a halogen atom, preferably chlorine; and optionally forming a pharmaceutically acceptable salt and/or hydrate thereof.

Other suitable leaving groups X will be apparent to those skilled in the art.

The reaction of the compounds of formulae (I) and (IV) is preferably conducted in the presence of a base e.g. triethylamine. The reaction of the compounds of formulae (I) and (IV) is preferably conducted in a solvent, e.g. acetonitrile, an aqueous such as aqueous acetonitrile or an aqueous alcohol and more preferably water. When water is used as solvent for this process the resulting compound of formula (III) is of superior quality to that obtained using other solvents. This leads to an improvement in the quality of the resulting drug substance as well as a process that is more environmentally acceptable. Further details regarding the reaction of the compounds of formula (I) and (IV) can be found in US 5,633,262 and EP 688772A1.

The compounds of formula (IV) may be synthesised as described in US 5,633,262 and EP 688772A1.

The compound of formula (III) produced according to this aspect of the invention is preferably (R,S)-7-(3-aminomethyl-4-*syn*-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate or a hydrate thereof, preferably the sesquihydrate, as disclosed in WO 98/42705. The methanesulfonate and hydrates thereof may be synthesised from

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the free acid as described in WO 98/42705.

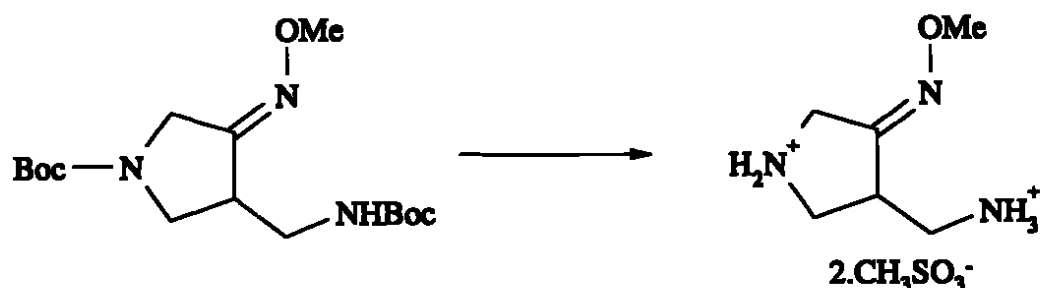
The compounds of the invention have the advantage that they are stable, i.e. not hygroscopic. They can be isolated from the reaction in higher yield and purity than the corresponding dihydrochloride or free base. The dimesylate salts can be recrystallised if necessary, whereas the corresponding dihydrochloride or free base has not been successfully recrystallised. The dimesylate salts can be used to produce quinolone antibacterials of high purity and several advantages result from using this intermediate. For example, when the resulting drug substance is (R,S)-7-(3-aminomethyl-4-*syn*-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate or a hydrate thereof, it has improved colour and significantly lower levels of high molecular weight impurities compared to the drug substance produced using the corresponding dihydrochloride or free base as intermediate.

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

The invention is illustrated by the following examples. However, it should be understood that the examples are intended to illustrate but not in any manner limit the scope of the invention.

Example 1

Synthesis of 4-aminomethyl-3-methoxyiminopyrrolidinium dimethanesulfonate



A solution of 1-(N-*t*-butoxycarbonyl)-4-(*t*-butoxycarbonylamino)methyl) pyrrolidin-3-methoxime (100g) in methanol (660mL) at 15-20°C under nitrogen was treated with methanesulfonic acid (56.4mL) over 5 min keeping the temperature below 30°C. The solution was stirred at 20-25°C for 16-20hrs. During this time the product precipitated forming a thick suspension. The product was isolated by filtration, washed with methanol (165ml) and dried under vacuo at 25°C to give the title compound 84g (86%).

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m.p. 189-193°C;

m/z: 144 (M+H)⁺;¹H NMR (400MHz, d₆-DMSO) δ: 9.27, (2H, brs), 7.95 (3H, brs), 4.01 (1H, d), 3.92 (1H, d), 3.87 (3H, s), 3.69 (1H, m), 3.26 (2H, m), 3.26 (2H, m), 3.15 (1H, m), 3.08 (1H, m),

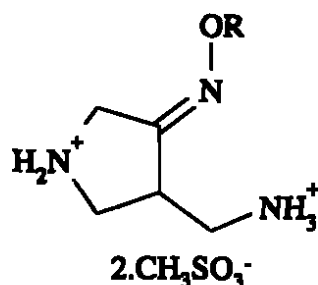
5 2.39 (6H, s);

Analysis: C, 28.64%, H, 6.25%, N, 12.46%; C₈H₂₁N₃O₇S₂ requires C, 28.65%, H, 6.31%, N, 12.53%.**Example 2**10 **Synthesis of (R,S)-7-(3-aminomethyl-4-syn-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid**

15 Triethylamine (5.1ml) was added to 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (3.05g) in water (25ml) at 15-20°C and the mixture stirred for 20 min. 4-Aminomethyl-3-methoxyimino-pyrrolidinium dimethanesulfonate (3.86g) was added, followed by water (5ml), and the mixture stirred at 20-25°C for 17½ hours. The resulting product was filtered and the cake washed with water (30ml) followed by ethanol (30ml) and dried under vacuum at 50°C to give the title compound as a white solid (4.23g). (102% as is, 86% on assay). Characterising data were consistent with a standard sample of the title compound.

CLAIMS

1. A compound of formula (I):



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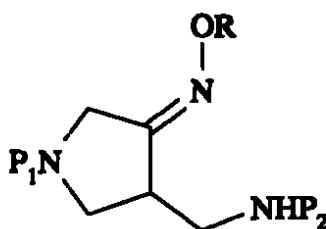
(I)

wherein R is C₁₋₄ alkyl or C₁₋₄ haloalkyl.

2. 4-Aminomethyl-3-methoxyiminopyrrolidinium dimethanesulfonate.

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3. A process for the production of a compound of formula (I) as defined in claim 1 which comprises reaction of a compound of formula (II):



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(II)

wherein R is as defined for formula (I) and P₁ and P₂, which may be the same or different, are amino protecting groups, with methanesulfonic acid.

4. The process according to claim 3 wherein P₁ and P₂ are both t-butyloxycarbonyl.

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5. The process according to claim 3 or 4 wherein the amount of methanesulfonic acid used to effect the deprotection of the compound of formula (II) is 2 to 4 equivalents.

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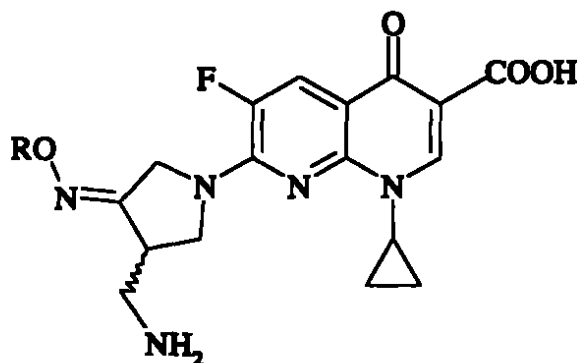
6. The process according to any one of claims 3 to 5 wherein the reaction is carried out at a temperature between about 10°C and about 50°C.

7. The process according to any one of claims 3 to 6 which is carried out in a

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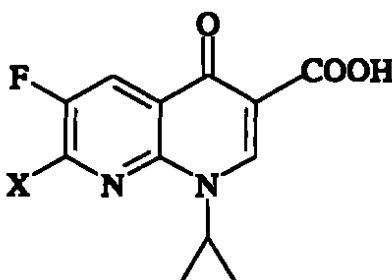
solvent selected from methanol, ethanol, isopropanol, n-propanol, dichloromethane, acetonitrile, acetone, methyl iso-butyl ketone, DME, THF, tert-butylmethyl ether, dioxane and ethyl acetate.

- 5 8. A process for the production of a compound of formula (III), or a pharmaceutically acceptable salt and/or hydrate thereof:



(III)

- 10 wherein R is as defined for formula (I) in claim 1, which comprises reaction of a compound of formula (I) as defined in claim 1, with a compound of formula (IV):



(IV)

- 15 wherein X is a leaving group; and optionally forming a pharmaceutically acceptable salt and/or hydrate thereof.

9. The process according to claim 8 wherein the reaction of the compound of formula (I) and the compound of formula (IV) is conducted in a solvent in the presence of a base.

10. The process according to claim 8 or 9 wherein the compound of formula (III) is (R,S)-7-(3-aminomethyl-4-*syn*-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate or a hydrate thereof.

Handwritten initials and signature in the top right corner.

LEGALIZACIONES

OFICINA DE PATENTES

Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

El suscrito, un funcionario debidamente autorizado conforme a los Artículos 74(1) y (4) de la Ley de Desreglamentación y Contratación de 1994 para firmar y expedir certificados en nombre del Contralor General, certifico que la copia adjunta es una copia correcta de los documentos archivados originalmente con respecto a la solicitud de patente que allí se identifica.

De acuerdo con las Reglamentaciones de Patentes de 1982 (Re-registro de Compañías), si una compañía nombrada en este certificado y en los documentos adjuntos se ha vuelto a registrar según la Ley de Compañías de 1980 con el mismo nombre con el que fue registrada inmediatamente antes del re-registro, salvo la sustitución o inclusión como la última parte del nombre de las palabras "sociedad anónima" o su equivalente en galés, las referencias al nombre de la compañía y sus documentos adjuntos serán tratadas como referencias al nombre con el cual fue re-registrada.

De acuerdo con las reglas, las palabras "sociedad anónima" (o en inglés *public limited company*) pueden ser reemplazadas por las letras p.l.c, plc. P.L.C ó PLC.

El re-registro bajo la Ley de Compañías no constituye una nueva entidad legal sino simplemente somete a la compañía a ciertas normas de ley adicionales.

(FIRMA) R. MAHONEY

FECHA: 20 de octubre de 2000

(SELLO DE LACRE)

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73

OFICINA DE PATENTES

SOLICITUD DE PATENTE

1. Su referencia: **AJB/PMS/P32412**

2. Solicitud No. **9920919.9** **6 de septiembre de 199**

3. Nombre completo y código postal de cada solicitante:

Dirección: **SB Pharmco Puerto Rico Inc
Road 172, KM 9.1/Bo Certenejas, Cidra,
Puerto Rico 00639**

No. APD 7733249001

Si el solicitante es una entidad, indique el país/estado de constitución:

4. TITULO DEL INVENTO:

COMPUESTO NOVEDOSO

5. NOMBRE DE SU AGENTE:

Nombre del Agente: **CORPORATE INTELLECTUAL PROPERTY**

Dirección para notificaciones: **SMITHKLINE BEECHAM PLC
TWO NEW HORIZONS COURT
BRENTFORD
MIDDLESEX TW8 9EP**

NO. ADP Patentes 5800974003

6. N/A

7. N/A

8. SI

9. Número de hojas radicadas (En inglés). Descripción: 5 Reivindicaciones: 2

Resumen : - Dibujos: -

10. Solicitud de examen preliminar y búsqueda:

9920919.9 - nov 00

11. Solicitamos se nos adjudique una patente con base en esta solicitud.

A J Blakey

3 de septiembre de 1999

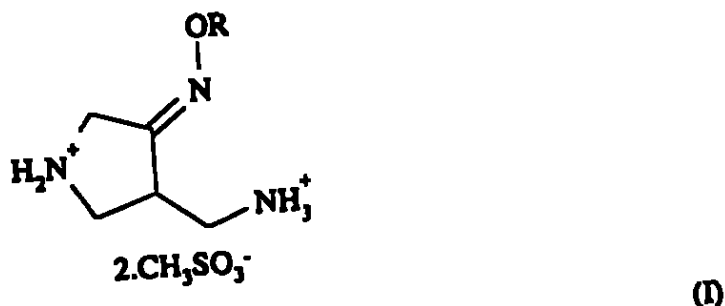
12. Nombre y teléfono del contacto en el Reino Unido Nombre y teléfono del contacto en el
Reino Unido (FIRMA) A J Blakey 01279 644355

33 X
85

COMPUESTO NOVEDOSO

REIVINDICACIONES:

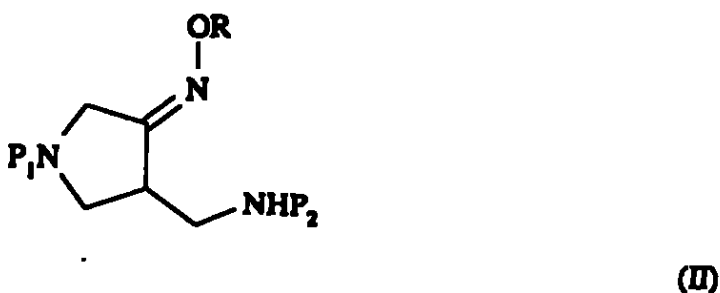
1. Un compuesto de la fórmula (I):



en donde R es alquil C₁₋₄ o haloalquil C₁₋₄.

2. dimetanosulfonato de 4-Aminometil-3-metoximinopirrolidinio.

3. Un proceso para la producción de un compuesto de la fórmula (I) según se define en la reivindicación 1, que comprende una reacción de un compuesto de la fórmula (II):



en donde R es según se define para la fórmula (I) y P₁ y P₂ que pueden ser el mismo o diferentes, son grupos protectores con ácido metnosulfónico.

4. El proceso según la reivindicación 3, en el cual P₁ y P₂ son ambos t-butiloxycarbonil.

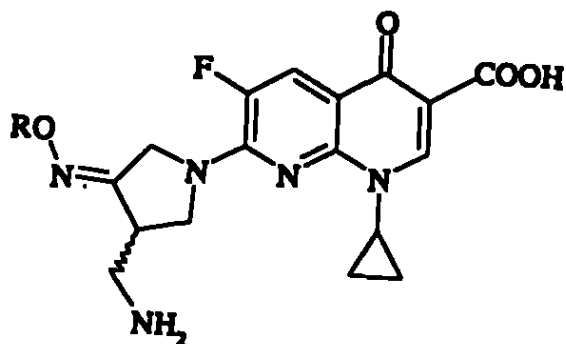
34 2
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5. El proceso según la reivindicación 3 ó 4, en el cual la cantidad de ácido metanosulfónico utilizado para efectuar la desprotección del compuesto de la fórmula (I)) es de 2 a 4 equivalentes.

6. El proceso según cualquiera de las reivindicaciones 3 a 5, en el cual la reacción se lleva a cabo a una temperatura entre aproximadamente 10°C y 50°C

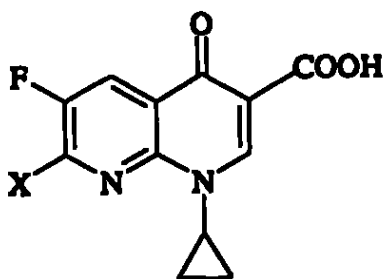
7. El proceso según cualquiera de las reivindicaciones 3 a 6 que se lleva a cabo en un solvente seleccionado de metanol, etanol, Isopropanol, n-propanol, diclorometano, acetonitrilo, acetona, metil Isobutil cetona, DME, THF, tert-butilmetil éter, dioxano y acetato etílico.

8. Un proceso para la producción de un compuesto de la fórmula (III), o una sal y/o hidrato farmacéuticamente aceptable de lo mismo:



(III)

en el cual R es según se define para la fórmula (I), que comprende la reacción de un compuesto de la fórmula (I) según se define en la reivindicación 1, con un compuesto de la fórmula (IV):



(IV)

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en el cual X es un grupo saliente; y opcionalmente formar una sal y/o hidrato farmacéuticamente aceptable de lo mismo.

9. El proceso según la reivindicación 8, en el cual la reacción del compuesto de la fórmula (I) y el compuesto de la fórmula (IV) se lleva a cabo en un solvente en la presencia de una base.

10. El proceso según la reivindicación 8 ó 9 en el cual el compuesto de la fórmula (III) es metanosulfonato de (R,S)-7-(3-aminometil-4-syn-metoxilmino-pirrolidin-1-il)-1-ciclopropil-6-fluoro-4-oxo-1,4-dihidro-1,8-naftiridina-3-ácido carboxílico o un hidrato de lo mismo.