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Señores

DIVISION DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

Ciudad.-

Re.: Expediente No. 00 - 65.924

Solicitud de Patente

Debidamente traducida, adjunto acompaño la copia oficial de la solicitud de patente básica inglesa No. GB 9920917.3, la cual le solicito agregar a este expediente para los efectos legales respectivos.

De Ud. atentamente,

GERMAN CASTILLO GRAU

T.P. 2978



INVENTOR IN PEOPLE

25
27

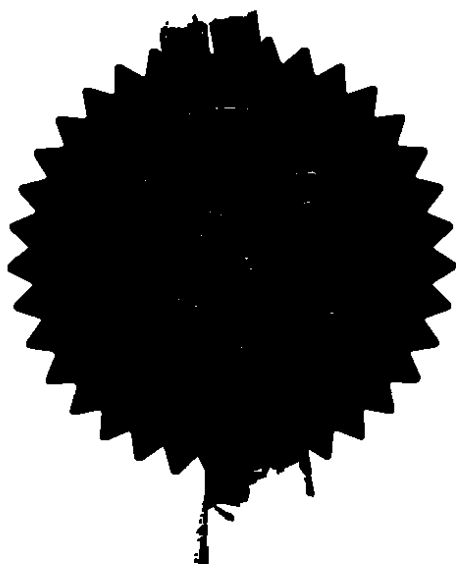
The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

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.



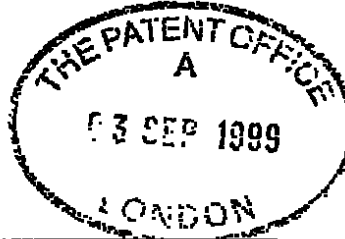
Signed *P. Mahoney*
Dated 20 October 2000

An Executive Agency of the Department of Trade and Industry

The
Patent
Office

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1/77 28

06SEP99 E474432-1 D02029
P01/7700 0.00 - 9920917.3



The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

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)

1. Your reference

AJB/PMS/P32411

2. Patent application number

03 SEP 1999

9920917.3

(The Patent Office will fill in this part)

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

7733249001

4. Title of the invention

Novel Process

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*)

5806974003

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)

Patents Form 1/77

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	1
Description	5
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 Alison Blakey Date 3-Sep-99
A J Blakey

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

A J Blakey 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.

Patents Form 1/77

CONTINUATION SHEET

Reference: AJB/PMS/P32411

Further Applicant (s)
LG Chemical Industries- LIMITED
Yoido-dong, Yongdungpo-ku, Seoul, Korea

PE 25/9/00

C7309800001

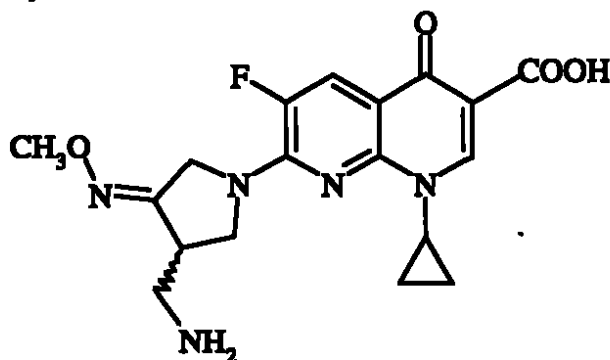
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NOVEL PROCESS

The present invention relates to a novel process for 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:



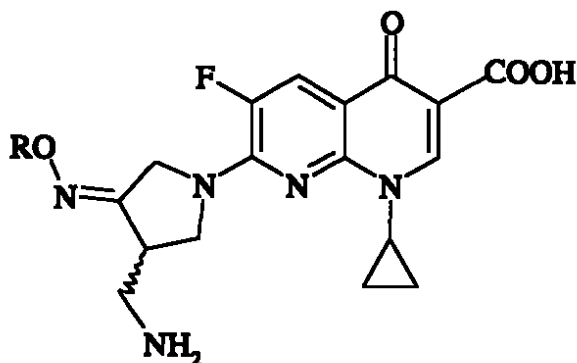
WO 98/42705 discloses (R,S)-7-(3-aminomethyl-4-*syn*-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate and hydrates thereof including the sesquihydrate.

EP 688772 discloses a process for the production 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 which comprises the reaction of 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid and 4-aminomethyl-3-methoxyiminopyrrolidinium ditrifluoroacetate in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene using dry acetonitrile as solvent.

PCT/KR99/00099 (published after the priority date of the present application) discloses the same process using 4-aminomethyl-3-methoxyiminopyrrolidinium dihydrochloride.

The present invention relates to an improved process for the production of quinoline carboxylic acid derivatives having antibacterial activity.

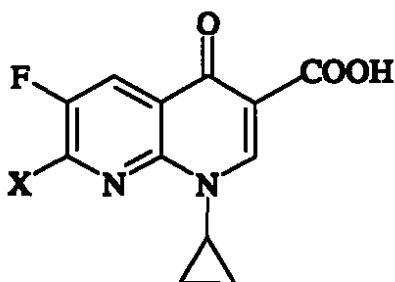
Thus according to the invention there is provided a process for the production of a compound of formula (I), or a pharmaceutically acceptable salt and/or hydrate thereof:



(I)

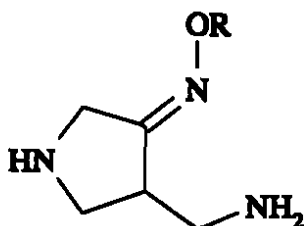
wherein R is C₁₋₄ alkyl or C₁₋₄ haloalkyl, which comprises reaction of a compound of formula (II):

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(II)

wherein X is a leaving group; with a compound of formula (III):



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(III)

wherein R is as defined for formula (I), or a salt thereof; in the presence of a base and an aqueous solvent;

and optionally forming a pharmaceutically acceptable salt and/or hydrate thereof.

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Suitable aqueous solvents for use in the process according to the invention include aqueous acetonitrile and aqueous alcohols, e.g. aqueous C₁₋₆alkyl alcohols such as aqueous ethanol; however the preferred solvent is water.

When the solvent used for the process is a mixed solvent any ratio of solvents may be used, for example when the solvent is aqueous acetonitrile a ratio of between 0.7 and 1.4 acetonitrile:water may be used, preferably 1:1 acetonitrile:water.

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The reaction is preferably performed in greater than 1 volume of solvent

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based on the compound of formula (II), for example 10 volumes of solvent.

The reaction is preferably performed using an excess of the compound of formula (III) to the compound of formula (II), for example between 1.01 and 1.08 mole equivalents of the compound of formula (III), preferably 1.05 mole equivalents.

5 The reaction is preferably performed at a temperature between ambient and 100°C, for example between ambient and about 60°C.

Suitable bases for use in the process of the invention include inorganic bases such as sodium and potassium hydrogen carbonate, sodium and potassium hydroxide and sodium and potassium carbonate, and organic bases such as triethylamine, diisopropylamine, pyridine, N,N-dimethylaniline, N,N-dimethylaminopyridine, 1,8-diazabicyclo[5.4.0]undec-7-ene and 1,4-diazabicyclo[2.2.2]octane.

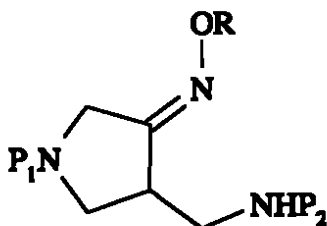
The base is preferably triethylamine.

Suitably between 3.2 and 3.8 mole equivalents of base are used based on the compound of formula (II), preferably 3.4 mole equivalents of base are used.

15 Suitable leaving groups X in the compound of formula (II) include halogens, particularly chloro, other suitable leaving groups will be apparent to those skilled in the art.

The compound of formula (III) is preferably in the form of the dimethanesulfonate salt, e.g. 4-aminomethyl-3-methoxyiminopyrrolidinium dimethanesulfonate

20 Dimethanesulfonate salts of the compound of formula (III) may be produced by a process comprising reaction of a compound of formula (IV):



25 (IV)
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.

30 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.

The reaction of the compound of formula (IV) 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 (IV) 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.

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

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

The compound of formula (I) produced according to 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 the free acid as described in WO 98/42705.

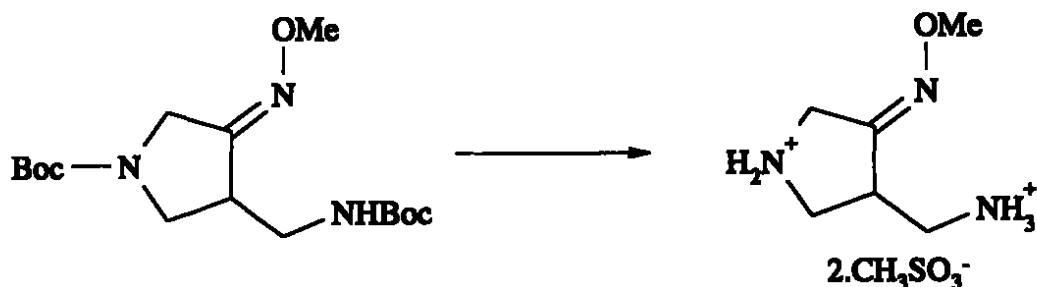
The process of the invention has the advantages that it produces drug substance of superior quality compared to the known process using dry acetonitrile as solvent. In addition the use of an aqueous solvent is more cost effective and also more environmentally friendly.

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-butoxycarbonylaminomethyl) pyrrolidin-3-methoxime (100g) in methanol (660mL) at 15-20°C under nitrogen was

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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%).

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), 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

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

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 17¼ 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.

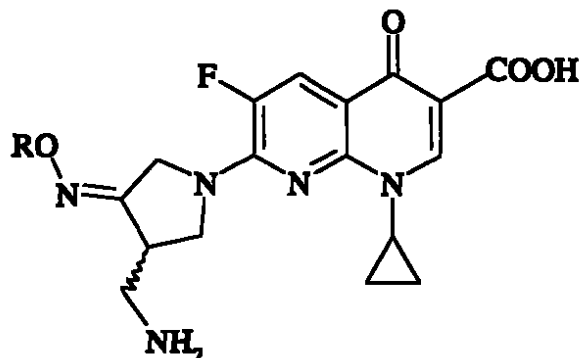
Example 3

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

Triethylamine (34ml) was added to 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (20.17g) in a mixture of acetonitrile (100ml) and water (100ml) at 15-20°C and the mixture stirred for 30 min. 4-Aminomethyl-3-methoxyiminopyrrolidinium dihydrochloride (18.9g) was added, followed by water (5ml), and the mixture stirred at 20-25°C for 23¼ hours. The resulting product was filtered and the cake washed with ice-cold 1:2 acetonitrile:water (100ml) followed by acetonitrile (100ml), air dried, then dried under vacuum, at ambient temperature, to give the title compound as a fawn solid (26g). (94% as is, 78.8% on assay). Characterising data were consistent with a standard sample of the title compound.

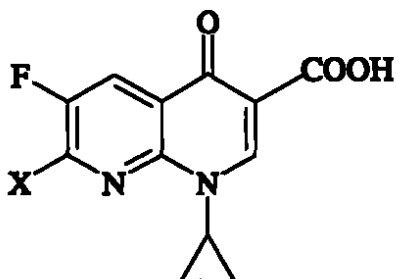
CLAIMS

1. A process for the production of a compound of formula (I), or a pharmaceutically acceptable salt and/or hydrate thereof:



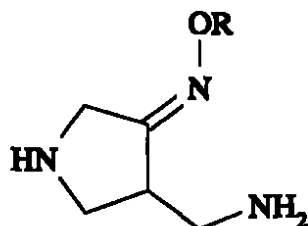
(I)

wherein R is C₁₋₄ alkyl or C₁₋₄ haloalkyl, which comprises reaction of a compound of formula (II):



(II)

wherein X is a leaving group; with a compound of formula (III):



(III)

wherein R is as defined for formula (I), or a salt thereof; in the presence of a base and an aqueous solvent;

and optionally forming a pharmaceutically acceptable salt and/or hydrate thereof.

2. The process according to claim 1 wherein the solvent is aqueous acetonitrile,

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an aqueous alcohol or water.

3. The process according to claim 2 wherein the solvent is water.
- 5 4. The process according to any one of the preceding claims wherein 10 volumes of solvent based on the compound of formula (II) are used.
5. The process according to any one of the preceding claims wherein between 1.01 and 1.08 mole equivalents of the compound of formula (III) based on the
10 compound of formula (II) are used.
6. The process according to any one of the preceding claims performed at a temperature between ambient and about 60°C.
- 15 7. The process according to any one of the preceding claims wherein the base is triethylamine.
8. The process according to any one of the preceding claims wherein between 3.2 and 3.8 mole equivalents of base is used based on the compound of formula (II).
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9. The process according to any one of the preceding claims wherein X is chloro.
- 25 10. The process according to any one of the preceding claims wherein the compound of formula (III) is 4-aminomethyl-3-methoxyiminopyrrolidinium dimethanesulfonate.
11. The process according to any one of the preceding claims wherein the
30 compound of formula (I) 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 sesquihydrate.

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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)

OFICINA DE PATENTES

SOLICITUD DE PATENTE

1. Su referencia: **AJB/PMSP32411**

2. Solicitud No. **9920917.3** **3 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:

PROCESO 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:

9920917.3 - nov 00

8533

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

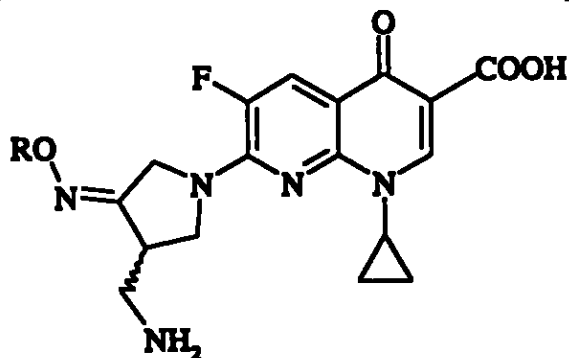
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PROCESO NOVEDOSO

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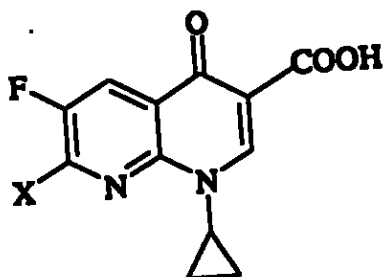
REIVINDICACIONES:

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



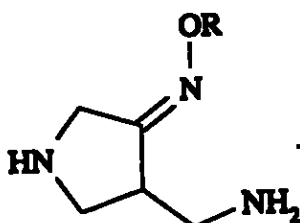
(I)

en la cual R es alquil C₁₋₄ o haloalquil C₁₋₄, que comprende la reacción de un compuesto de la fórmula (II):



(II)

en la cual X es un grupo saliente; con un compuesto de la fórmula (III):



(III)

en la cual R es según se define para la fórmula (I), o una sal de lo mismo; en la presencia de una base y un solvente acuoso;

y opcionalmente formar una sal y/o hidrato farmacéuticamente aceptable de lo mismo.

2. El proceso según la reivindicación 1, en el cual el solvente es acetonitrilo acuoso, un alcohol acuoso o agua.

3. El proceso según la reivindicación 2, en el cual el solvente es agua.

4. El proceso según cualquiera de las reivindicaciones anteriores, en el cual se utilizan 10 volúmenes de solvente basados en el compuesto de la fórmula (II).

5. El proceso según cualquiera de las reivindicaciones anteriores, en el cual se utilizan entre 1,01 y 1,08 equivalentes de mole del compuesto de la fórmula (III) basados en el compuesto de la fórmula (II).

6. El proceso según cualquiera de las reivindicaciones anteriores llevado a cabo a una temperatura entre temperatura ambiente y aproximadamente 60°C.

7. El proceso según cualquiera de las reivindicaciones anteriores en el cual la base es trietilamina.

8. El proceso según cualquiera de las reivindicaciones anteriores, en el cual se utilizan entre 3,2 y 3,8 equivalentes de mole en el compuesto de la fórmula (II).

9. El proceso según cualquiera de las reivindicaciones anteriores, en el cual X es cloro.

10. El proceso según cualquiera de las reivindicaciones anteriores, en el cual el compuesto de la fórmula (III) es dimetanosulfonato 4-aminometil-3-metoxilimopirrolidinio.

11. El proceso según cualquier de las reivindicaciones anteriores, en el cual el compuesto de la fórmula (I) es metanosulfonato de (R,S)-7-(3-aminometil-4-*syn*-metoxilimino-pirrolidino-1-il)-1-ciclopropil-6-fluoro-4-oxo-1,4-dihidro-1,8-naftiridina-3-ácido carboxílico o un hidrato de lo mismo.