

FORMULARIO ÚNICO DE CORRECCIONES Y MODIFICACIONES
2000-10

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SOLICITUD DE:

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Corrección de Error Material

☒

Modificación a una Solicitud.

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SOLICITANTE

Nombre: LG LIFE SCIENCES LIMITED
Dirección: LG Twin Tower, 20, Yoido-dong,
Youngdungpo-gu
Teléfono:
E-mail
Domicilio: Seúl, República de Korea

IDENTIFICACIÓN

C.C. ☐ NIT ☐
C.E. ☐ Otro ☐

Número _____

3

REPRESENTANTE
O APODERADO

Nombre: GERMAN CASTILLO GRAU
Dirección: Carrera 13 No. 37-43 Piso 12
Teléfono: 285 74 60 Fax: 285 92 67
E-mail info@castillograu.com

IDENTIFICACION

C.C. ☒ NIT ☐
C.E. ☐ Otro ☐

Número 17.017.671 T.P. 2.978 del
de Bogotá C.S.J.

4

Número de Expediente

00 65.923

5

Descripción de la corrección o modificación solicitada

MODIFICACION del nombre de la socie-

dad solicitante por TRASPASO a favor de

LG LIFE SCIENCES LIMITED

Dirección: LG Twin Tower, 20, Yoido-dong, Youngdungpo-gu

Domicilio: Seúl, República de Korea

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Comprobante de pago N°

04.095239

Fecha

Dic- 10/04

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Anexos:

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Comprobante de pago de la tasa

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Podemos, si fuere el caso

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Certificado de existencia y representación legal de las partes, cuando sean personas jurídicas.

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documento que respalde la modificación

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NOMBRE GERMAN CASTILLO GRAU

FIRMA

C.C. 17.017.671 de Bogotá T.P. 2.978 del C.S.J.

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

7165

SUPERINDUSTRIA Y COMERCIO
Radicacion : 00065923 00000004 Folios: 2
Fecha (IMP): 2004-12-10 11:39:20
Tramite : 002 PATENTES D 1 REGISTRO/ 329 COMPLEMEN
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

MIT : 800176089-2

RECIBO OFICIAL DE CAJA : 04 - 95,279
FECHA : DICIEMBRE 10 DE 2004

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
CASTILLO GRAU Y ASOCIADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	33602288	10/12/2004	932,000.

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICA	
		12 MARCAS Y LENAS COMERCIALES	87,000.00
		TOTAL :	87,000.00

SON: OCHENTA Y SIETE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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66

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020

Bogotá, DC, 04 de octubre de 2005

Apoderado: Germán Castillo Grau

Oficio: 9448

ASUNTO Radicación: 0-65923

Trámite 002

Evento 001

Actuación 430

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

Documentos estudiados:

- capítulo descriptivo, folios 4 a 11;
- capítulo reivindicatorio, folios 12 a 156;
- 1° examen de forma, folio 21;
- solicitud de la cual se reivindica prioridad, junto con la traducción requerida, folios 26 a 37;
- 2° examen de forma, folio 65;
- Solicitud del examen de patentabilidad, folio 67 y 68.

Objeto de la invención:

El título de la invención es: "PROCESO PARA LA PRODUCCIÓN DE COMPUESTOS FARMACEUTICAMENTE ACTIVOS, PARTICULARMENTE DERIVADOS DE QUINOLINCARBOXILICO CON ACTIVIDAD ANTIBACTERIANA".

El objeto de la presente solicitud se refiere a compuestos derivados de 4-amino-3-aminometil-3-metoxiiminopirrolidino, protegidos del mismo con t-butoxicarbonilo y un proceso para obtener los compuestos del estado de la técnica de formula (III).

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CX

Claridad de la solicitud:

En el artículo 30 de la Decisión 486 de la Comisión de la Comunidad Andina se establece: *"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción"*.

La reivindicación 3, no es clara, puesto que el encabezado no es congruente con el texto de la reivindicación, se encabeza como un proceso que no se sabe en que consiste, por que solo se indican genéricamente los sustituyentes como grupos protectores.

-La reivindicación 4 no define técnicamente ningún proceso, tal como lo indica el encabezado y un proceso no se puede caracterizar por el significado de un sustituyente.

-La reivindicación 6 define las cantidades con términos ambiguos como "aproximadamente", lo cual es inaceptable en las reivindicaciones.

-La reivindicación 9, no es clara, puesto que no se define el solvente, ni la base, ya que esos términos son solo propiedades químicas, de algunas sustancias, y no definen a ninguna sustancia inequívocamente, como tampoco delimitan claramente el alcance de la reivindicación.

Determinación del estado de la técnica:

El artículo 16 de la Decisión 486 de la Comisión establece: *"El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida."*

Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40."

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Item	Documento	Fecha de publicación	Título
D1	EP0688772	27- 12-1995	Novel quinoline carboxylic acid derivatives having 7-(4-amino-methyl-3-oxime)pyrroline substituents and processes for their preparation
D2	WO9842705	01-oct-1998	Salt of naphthyridine carboxylic acid derivatives

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece: *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial."*

En cumplimiento con este artículo, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación de la Novedad:

El art.16 de la Decisión 486 de la Comisión de la Comunidad Andina establece: *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida".*

-La anterioridad D1 enseña explícitamente los compuestos y la materia reclamada en las reivindicaciones 3 a 10, tanto los intermediarios protegidos con t-butoxido como el proceso para la obtención quinolinocarboxílicos derivados que están completamente definidos en esta anterioridad, por lo tanto las reivindicaciones 3 a 10 de la presente solicitud, no tienen novedad.

Por su parte D2 describe las sales y hidratos de los derivados quinolinocarboxílicos de las reivindicaciones 8 y 10, como también toda la materia contenida en la otra anterioridad, y el ejemplo 3, establece lo que se reclama como nuevo en las reivindicaciones 3 a 10.

Evaluación del Nivel Inventivo:

El art. 18 de la Decisión 486 de la Comisión de la Comunidad Andina establece:

"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica."

No se considera que la presente solicitud tenga nivel inventivo porque la solicitud en estudio reclama las sales de dimetano sulfonato, y la anterioridad D1, por ejemplo en la pagina 9, las sales de dimetano sulfonato de los 3-alcoxiimino-4-aminometilpirrolidinio. Las sales metanofulfónicas, son sales farmacéuticamente aceptables, típicamente no tóxicas y universalmente conocidas, y se indica en esta anterioridad como las mejores sales de 3-alcoxiimino-4-aminometilpirrolidinio las de trifluoro acéticas y las metanosulfónicas, que son las que se reclaman como nuevas e inventivas en la presente solicitud. El proceso puede ser considerado como una desprotección de un grupo protector específico con ácido trifluoro acético. Como es conocido esto por la persona del nivel medio en el área que las sales metanosulfonato son un equivalente de las sales trifluoroacetato, se considera que pueden ser intercambiadas de acuerdo con las circunstancias.

El documento D1 enseña la preparación de los compuestos llamados (III) en la solicitud en estudio, consistiendo en la reacción de una sal de metanosulfonato de un compuesto de fórmula (I) con uno de fórmula (IV) 3-alcoxiimino-4-aminometilpirrolidinio compuesto que puede ser usado en forma libre o como sal de halógena o sal de ácido trifluoroacetato como se muestra en la pag-10 como se muestra en especialmente en los renglones 30 a 35.

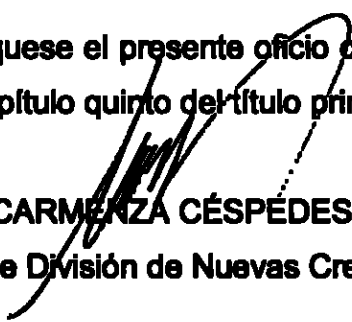
-Por otro lado la solicitud describe las ventajas exhibidas por los metano sulfonatos no podían haber sido predichas, pero en documento D2 en la pag-7, se enseñase que esta sal exhibe propiedades físicoquímicas deseables, así como la mayor facilidad de manipulación, control de calidad y formulación que otras sales. Entonces es obvio para persona experta en el campo técnico que cuando los resultados a obtener son conocidos, para el uso de sales metanosulfonato en el método acorde con el D1, de esa manera se llega al proceso de la reivindicación 8 de la presente solicitud, no hay ningún resultado inesperado.

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de

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sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la circular única No. 10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 13 OCT. 2005

CONCEPTO TÉCNICO N°	581	EXAMINADOR TÉCNICO Código 202012
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Europäisches Patentamt
European Patent Office
Office européen des brevets



Publication number: **0 688 772 A1**

⑫

EUROPEAN PATENT APPLICATION

⑪ Application number: 95250143.5

⑫ Date of filing: 14.06.95

⑪ Int. Cl.⁸: C07D 401/04, C07D 471/04,
A61K 31/47, //(C07D401/04,
215:00,207:00),(C07D471/04,
221:00,221:00)

⑬ Priority: 16.06.94 KR 9413604
30.12.94 KR 9439916
30.12.94 KR 9439930

⑭ Date of publication of application:
27.12.95 Bulletin 95/52

⑮ Designated Contracting States:
CH DE DK FR GB IT LI NL SE

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⑲ Novel quinoline carboxylic acid derivatives having 7-(4-amino-methyl-3-oxime) pyrrolidine substituents and processes for their preparation

⑲ The present invention relates to a novel quinolone compound having an excellent antibacterial activity. More specifically, the present invention relates to a novel quinoline(naphthyridine)carboxylic acid derivative represented by the following formula (I), which has an 4-aminomethyl-3-oximepyrrolidine substituent on 7-position of the quinolone nucleus and shows a superior antibacterial activity in contrast to the known quinolone antibacterial agents having a weak activity against gram-positive bacterial strains and also has a broad antibacterial spectrum and a highly improved pharmacokinetic property :

D1

EP 0 688 772 A1

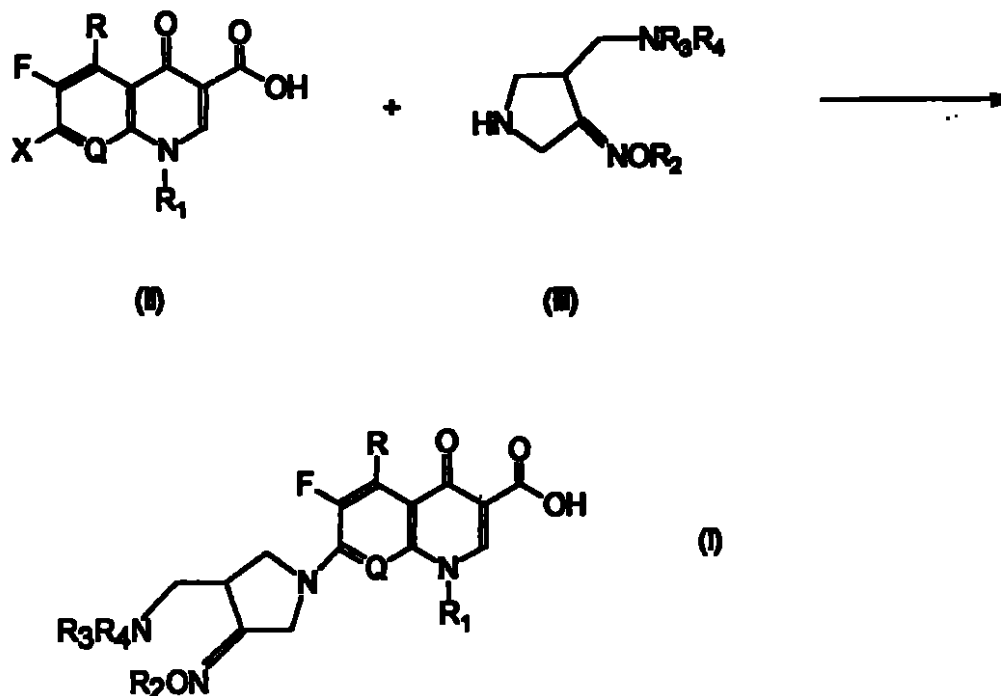
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x2

sulfuric acid, etc., a salt with organic carboxylic acids such as acetic acid, trifluoroacetic acid, citric acid, maleic acid, oxalic acid, succinic acid, benzoic acid, tartaric acid, fumaric acid, mandelic acid, ascorbic acid or malic acid or with sulfonic acids such as methanesulfonic acid, para-toluenesulfonic acid, etc., and a salt with other acids which are generally known and conventionally used in the technical field of quinolone-based compounds. These acid-addition salts can be prepared according to a conventional conversion method.

[0026] In the second aspect, the present invention also relates to a process for preparing the novel compound of formula (I).

[0027] According to the present invention, the compound of formula (I) can be prepared by reacting a compound of formula (II) with a compound of formula (III) or a salt thereof, as shown in the following reaction scheme 1.

Reaction Scheme 1



In the above scheme,

R, R₁, R₂, R₃, R₄ and Q are defined as previously described; and X represents a halogen atom, preferably chlorine, bromine or fluorine.

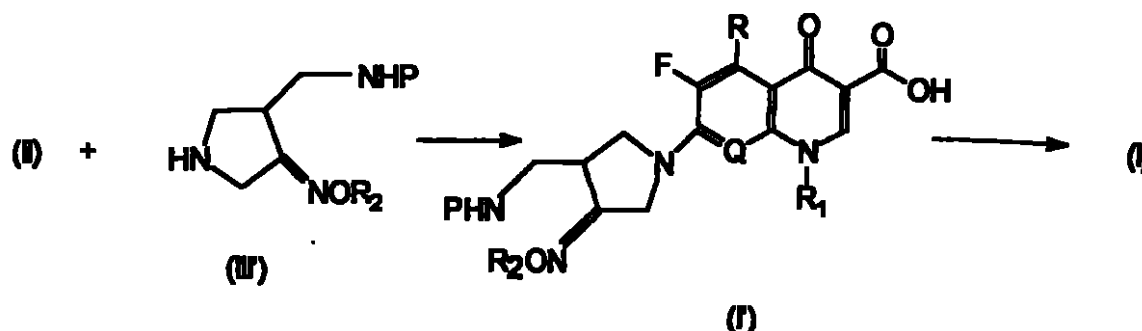
[0028] According to the above reaction scheme 1, the compound of formula (I) according to the present invention can be prepared by stirring the compound of formula (II) and the compound of formula (III) in the presence of a solvent for 1 to 20 hours at the temperature between room temperature and 200°C with the addition of a suitable base. In this reaction, the compound of formula (III) can be used in the form of a free compound or a salt with an acid such as hydrochloric acid, hydrobromic acid or trifluoroacetic acid.

[0029] As the solvent for the above reaction, any solvent which does not adversely affect the reaction can be used. Preferably, acetonitrile, dimethylformamide(DMF), dimethylsulfoxide(DMSO), pyridine or hexamethylphosphoramide(HMPA) can be used.

[0030] This reaction is generally conducted in the presence of an acid acceptor. In this case, to increase the reaction efficiency of the relatively expensive starting material (II) the reactant (III) is used in an excessive amount, for example, an equimolar amount to 10 times molar amount, preferably an equimolar amount to 5 times molar amount, with respect to the starting material (II). When the reactant (III) is used in an excessive amount, the unreacted compound of formula (III) which is retained after the reaction can be recovered and reused in another reaction. The acid acceptor which can be preferably used in this reaction includes inorganic bases such as sodium hydrogen carbonate, potassium carbonate, etc., and organic bases such as triethylamine, diisopropylethylamine, pyridine, N,N-dimethylaniline, N,N-dimethylaminopyridine, 1,8-diazabicyclo[5.4.0]undec-7-ene(DBU), 1,4-diazabicyclo[2.2.2]octane(DABCO), etc.

[0031] The compound of formula (I) according to the present invention can also be prepared by a method depicted in the following reaction scheme 2, in which a protecting group P is introduced into one of R₃ and R₄ of the compound of formula (II) wherein R₃ and R₄ are hydrogen to prepare the compound of formula (III) wherein the amino group is protected with P, the protected compound of formula (III) is reacted with the compound of formula (II) under the same condition as in the reaction scheme 1, and then the resulting compound of formula (I) is deprotected by removing the protecting group P to form the desired compound of formula (I).

Reaction Scheme 2



In the above reaction scheme,

R, R₁, R₂ and Q are defined as previously described; and P represents an amino-protecting group.

[0032] In the reaction of the above reaction scheme 2, the compound of formula (III) can be used in the form of a free compound or a salt with hydrochloric acid, hydrobromic acid or trifluoroacetic acid, as in the compound of formula (III) used in the reaction scheme 1.

[0033] Any protecting group which is conventionally used in the field of organic chemistry and can be readily removed after the reaction without decomposition of the structure of the desired compound can be used as the suitable amino-protecting group P in the compound of formula (III). The specific example of protecting groups which can be used for this purpose includes formyl, acetyl, trifluoroacetyl, benzoyl, para-toluenesulfonyl, methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, benzyloxycarbonyl, para-methoxybenzyloxycarbonyl, trichloroethoxycarbonyl, beta-ketoethoxycarbonyl, benzyl, para-methoxybenzyl, trityl, tetrahydropyranyl, etc.

[0034] After the reaction is completed, the amino-protecting group present in the resulting compound of formula (I) can be removed by hydrolysis, solvolysis or reduction depending on properties of the relevant protecting group. For example, the compound of formula (I) is treated in a solvent in the presence or absence of an acid or base at the temperature of 0 to 130°C to remove the protecting group. As the acid which can be used for this purpose, an inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, etc., an organic acid such as acetic acid, trifluoroacetic acid, formic acid, toluenesulfonic acid, etc., or a Lewis acid such as boron tribromide, aluminum chloride, etc., can be mentioned. As the base for this purpose, hydroxide of an alkali or alkaline earth metal such as sodium hydroxide, barium hydroxide, etc., an alkali metal carbonate such as sodium carbonate, calcium carbonate, etc., an alkali metal alkoxide such as sodium methoxide, sodium ethoxide, etc., or sodium acetate, and the like can be used. The reaction can be carried out in the presence of a solvent, for example, water or an organic solvent such as ethanol, tetrahydrofuran, dioxane, ethyleneglycol, acetic acid, etc., or a mixture of such organic solvent and water. If required, this reaction can also be practiced in the absence of any solvent.

[0035] In addition, when the protecting group is para-toluenesulfonyl, benzyl, trityl, para-methoxybenzyl, benzyloxycarbonyl, para-methoxybenzyloxycarbonyl, trichloroethoxycarbonyl, beta-ketoethoxycarbonyl and the like, such groups can be effectively removed by means of a reduction. Although the reaction condition of the reduction for removing protecting group may be varied with properties of the relevant protecting group, the reduction can be generally carried out with hydrogen gas stream in an inert solvent in the presence of a catalyst such as platinum, palladium, Raney nickel, etc., at the temperature of 10 to 100°C or with metal sodium or metal lithium in ammonia at the temperature of -50 to -10°C.

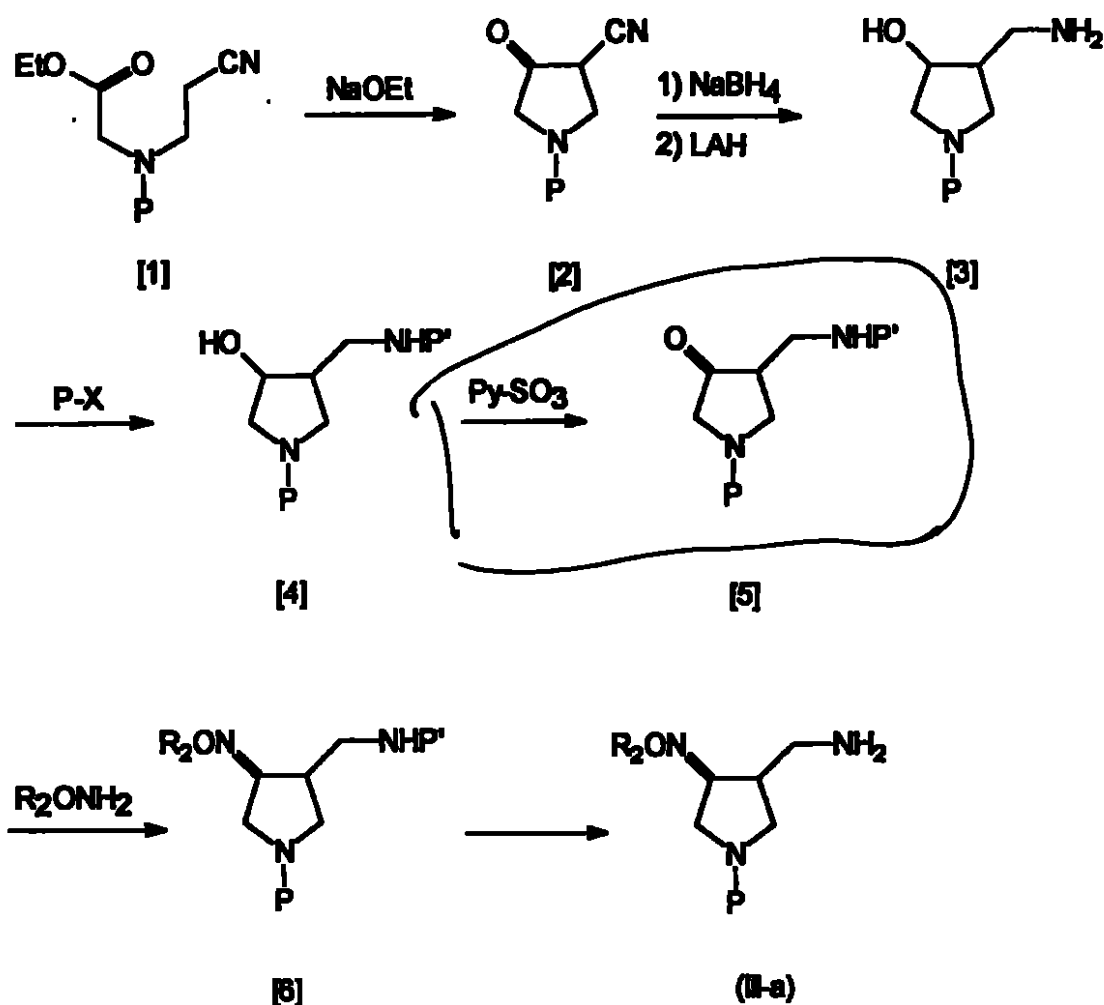
[0036] The compound of formula (II) used as the starting material in the present invention is a known compound and

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can be readily prepared according to a method known in the prior publication (see, J. M. Domagala, et al., J. Med. Chem. 34, 1142 (1991); J. M. Domagala, et al., J. Med. Chem. 31, 991 (1988); D. Bouzard, et al., J. Med. Chem. 35, 518 (1992)).

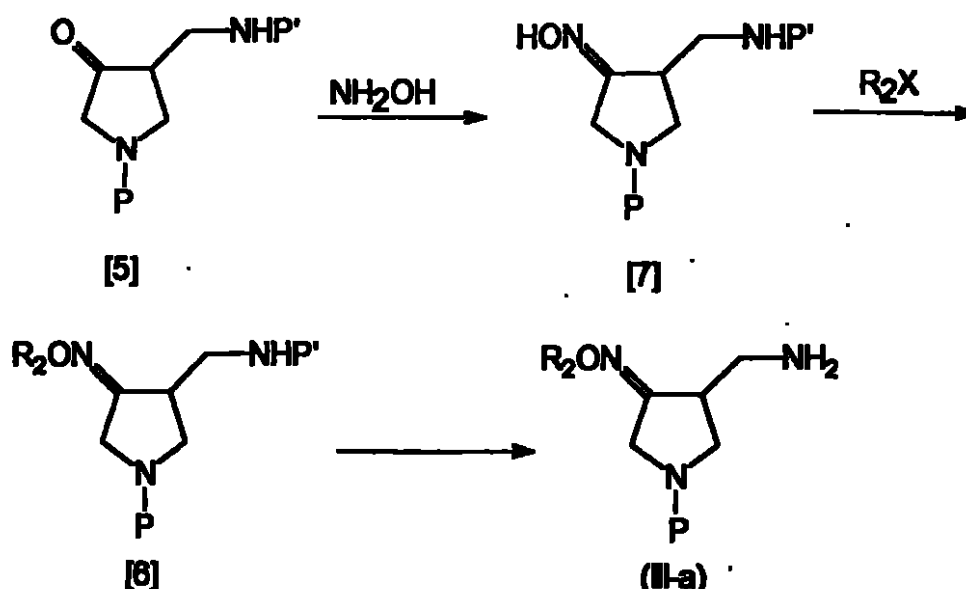
[0037] The compound of formula (II) used as another starting material in the present invention can be readily prepared according to the method as depicted in the following reaction schemes 3, 4 and 5.

Reaction Scheme 3



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Reaction Scheme 4



In the above reaction schemes 3 and 4, the protecting groups P and P' independently of one another represent the same amino-protecting group as defined for P in connection with the compound of formula (III) and can be identical with or different from each other; and

Py represents pyridine.

[0038] The process depicted in the reaction schemes 3 and 4 will be specifically explained hereinafter.

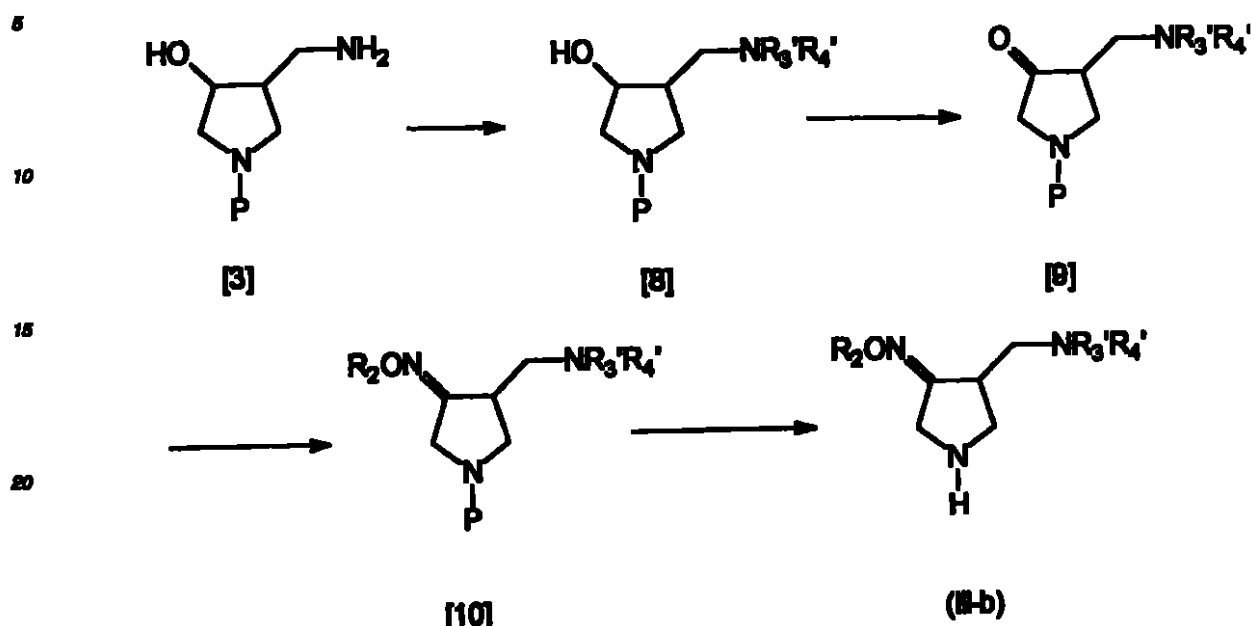
[0039] According to the reaction scheme 3, first a cyano ester [1] having a protected amino group can be reacted with sodium ethoxide in a solvent such as ethanol to obtain a 3-keto-4-cyanopyrrolidine [2]. The resulting cyanopyrrolidine [2] is reduced with hydrogen gas in the presence of a platinum catalyst to prepare an aminoalcohol [3]. In this case, the cyanopyrrolidine [2] may be reduced by means of other reductant to prepare the aminoalcohol [3]. For example, the ketone and cyano groups can be reduced with lithium aluminumhydride(LAH), sodium borohydride-cobalt chloride complex($\text{NaBH}_4\text{-CoCl}_2$) or lithium borohydride(LiBH_4). Alternatively, the aminoalcohol [3] can be synthesized by reducing first the ketone group to a hydroxyl group by means of sodium borohydride(NaBH_4) and then reducing the cyano group by lithium aluminum hydride(LAH). Then, the amino group of the aminoalcohol [3] thus prepared is selectively protected to obtain a protected amine [4], which is then treated with sulfur trioxide(SO_3)-pyridine mixture in dimethylsulfoxide solvent (see, Parikh, J.R. and Doering, W. v. E. J. Am. Chem. Soc. 1967, 89, 5505), or oxidized with other oxidant, to prepare a ketone compound [5]. The resulting ketone compound [5] is then reacted with a O-substituted hydroxylamine of formula R_2ONH_2 to obtain the desired substituted oxime compound [6], which can be deprotected by means of a suitable method selected depending on the kind of protecting group to obtain the desired oxime compound (III) wherein R_3 and R_4 are hydrogen, i.e. the compound of formula (III-a).

[0040] Alternatively, according to the method depicted in the reaction scheme 4, the ketone compound [5] is reacted with hydroxylamine to obtain the desired oxime compound [7] and the compound [7] is reacted with a suitable electrophilic compound of formula R_2X which can introduce the desired R_2 group, in the presence of a base to prepare the oxime derivative of formula [8], which is then deprotected by means of a suitable method selected depending on the kind of protecting group in the same manner as in the reaction scheme 3 to prepare the desired oxime compound (III-a).

[0041] The compound of formula (III) wherein R_3 and R_4 of aminomethyl group present on 4-position of pyrrolidine are other than hydrogen, i.e. the compound of formula (III-b), can be prepared by the following reaction scheme 5.

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Reaction Scheme 5



In the above reaction scheme,

R_3' and R_4' represent the same meaning as defined for R_3 and R_4 in connection with the compound of formula (I), provided that they cannot be hydrogen.

[0042] According to the method of reaction scheme 5, first the amine compound [3] is treated with C_1 - C_3 aldehyde and then reduced to obtain a substituted amine compound [8] and the resulting amine compound [8] is treated with sulfur trioxide (SO_3)-pyridine mixture in dimethylsulfoxide solvent, or oxidized with other oxidant, to obtain a ketone compound [9]. The resulting ketone compound [9] can be treated in the same manner as in the method for treating ketone compound [5] in the reaction schemes 3 and 4 to synthesize the desired compound of formula (II-b).

[0043] The synthetic methods as described above will be more specifically explained in the following preparation examples.

[0044] The present invention also provides an antibacterial composition comprising the novel compound of formula (I), as defined above, or a pharmaceutically acceptable salt thereof as an active component together with a pharmaceutically acceptable carrier. When such antibacterial composition is used for clinical purpose, it may be formulated into solid, semi-solid or liquid pharmaceutical preparations for oral, parenteral or topical administration by combining the compound of formula (I) with a pharmaceutically acceptable inert carrier. The pharmaceutically acceptable inert carrier which can be used for this purpose may be solid or liquid. The solid or semi-solid pharmaceutical preparation in the form of powders, tablets, dispersible powders, capsules, cachets, suppositories and ointments may be prepared in which case solid carriers are usually used. The solid carrier which can be used is preferably one or more substances selected from the group consisting of diluents, flavouring agents, solubilizing agents, lubricants, suspending agents, binders, swelling agents, etc. or may be encapsulating substances. In the case of powder preparation, the micronized active component is contained in an amount of 5 or 10 to 70% in the carrier. Specific example of the suitable solid carrier includes magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectine, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, low boiling wax, cocoa butter, etc. Because of their ease in administration, tablets, powders, cachets and capsules represent the most advantageous solid preparation for oral administration.

[0045] The liquid preparation includes solutions, suspensions and emulsions. For example, the injectable preparation for parenteral administration may be in the form of water or water-propyleneglycol solution, of which isotonicity, pH and the like can be adjusted to be suited for the physiological condition of living body. The liquid preparation can also be prepared in the form of a solution in aqueous polyethyleneglycol solution. The aqueous solution for oral administration

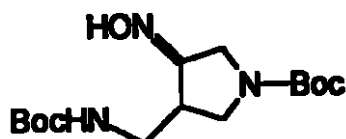
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EP 0 686 772 B1

Preparation 6

Synthesis of 1-(N-t-butoxycarbonyl)-4-(N-t-butoxycarbonyl)aminomethyl-pyrrolidin-3-one oxime

[0067]



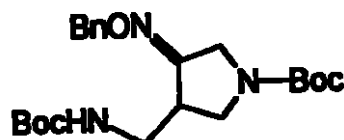
[0068] 300mg of the compound prepared in preparation 5 was dissolved in the mixture of 6ml of 95% ethanol and 3ml of tetrahydrofuran(THF) and this solution was introduced into a 30ml reaction vessel. 232mg (3.5 mole eq.) of hydroxylamine hydrochloride ($\text{NH}_2\text{OH} \cdot \text{HCl}$) was added thereto and then 281mg (3.5 mole eq.) of sodium hydrogen carbonate dissolved in 1.5ml of distilled water was added. The reaction mixture was stirred for 40 minutes at 40°C under oil bath to complete the reaction, cooled down and then concentrated under reduced pressure. The residue was diluted with methylene chloride, washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate and then filtered. The filtrate was concentrated and the residue was subjected to silica gel column chromatography eluting with hexane-ethyl acetate (1:1 by volume) to obtain 230mg (Yield: 73%) of the title compound.

^1H NMR (CDCl_3 , ppm) : δ 9.70(1H, bs), 5.05(1, bs), 4.2(2H, br), 3.83(1H, m), 3.5-3.2(3H,m), 3.0(1H, m), 1.42(18H, s)
Ms (FAB, m/e) : 330(M+H)

Preparation 7

Synthesis of 1-(N-t-butoxycarbonyl)-4-(N-t-butoxycarbonyl)aminomethyl-pyrrolidin-3-one-benzyl oxime

[0069]



[0070] 659mg of the compound prepared in Preparation 6, 193mg of tetra-n-butylammonium bromide and 855mg of benzyl bromide were added to 15ml of dichloromethane and then 5ml of 15% aqueous sodium hydroxide solution was added thereto. The reaction mixture was stirred for 30 minutes at room temperature. The organic layer was separated, dried over anhydrous magnesium sulfate and filtered. The filtrate was distilled under reduced pressure and the residue was purified with glass column chromatography to obtain 776mg (Yield: 92%) of the title compound.

^1H NMR (CDCl_3 , ppm) : δ 7.38(5H, m), 5.13(2H, s), 4.92(1H, m), 4.13(2H, m), 3.78(1H, m), 3.41(1H, m), 3.25(2H m), 3.02(1H, m), 1.50(9H, s), 1.49(9H, s)
MS (FAB, m/e) : 420(M+H)

Preparations 8 to 17

[0071] The amine compounds listed in the following Table 1 were prepared according to the same procedure as Preparation 7 except that the corresponding benzylbromide derivatives having R_2 structure as presented in the following Table 1 are used instead of benzylbromide.

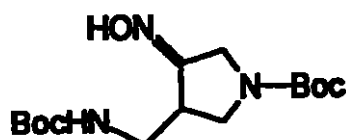
84
20

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Preparation 6

Synthesis of 1-(N-t-butoxycarbonyl)-4-(N-t-butoxycarbonyl)aminomethyl-pyrrolidin-3-one oxime

[0067]



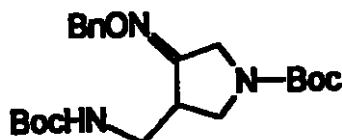
[0068] 300mg of the compound prepared in preparation 5 was dissolved in the mixture of 6ml of 95% ethanol and 3ml of tetrahydrofuran(THF) and this solution was introduced into a 30ml reaction vessel. 232mg (3.5 mole eq.) of hydroxylamine hydrochloride ($\text{NH}_2\text{OH} \cdot \text{HCl}$) was added thereto and then 281mg (3.5 mole eq.) of sodium hydrogen carbonate dissolved in 1.5ml of distilled water was added. The reaction mixture was stirred for 40 minutes at 40°C under oil bath to complete the reaction, cooled down and then concentrated under reduced pressure. The residue was diluted with methylene chloride, washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate and then filtered. The filtrate was concentrated and the residue was subjected to silica gel column chromatography eluting with hexane-ethyl acetate (1:1 by volume) to obtain 230mg (Yield: 73%) of the title compound.

^1H NMR (CDCl_3 , ppm) : δ 9.70(1H, bs), 5.05(1, bs), 4.2(2H, br), 3.83(1H, m), 3.5-3.2(3H, m), 3.0(1H, m), 1.42(18H, s)
Me (FAB, m/e) : 330(M+H)

Preparation 7

Synthesis of 1-(N-t-butoxycarbonyl)-4-(N-t-butoxycarbonyl)aminomethyl-pyrrolidin-3-one benzyl oxime

[0069]



[0070] 659mg of the compound prepared in Preparation 6, 193mg of tetra-n-butylammonium bromide and 855mg of benzyl bromide were added to 15ml of dichloromethane and then 5ml of 15% aqueous sodium hydroxide solution was added thereto. The reaction mixture was stirred for 30 minutes at room temperature. The organic layer was separated, dried over anhydrous magnesium sulfate and filtered. The filtrate was distilled under reduced pressure and the residue was purified with glass column chromatography to obtain 776mg (Yield: 92%) of the title compound.

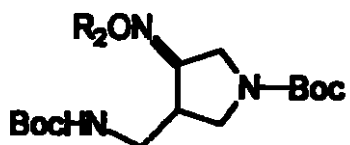
^1H NMR (CDCl_3 , ppm) : δ 7.38(5H, m), 5.13(2H, s), 4.92(1H, m), 4.13(2H, m), 3.76(1H, m), 3.41(1H, m), 3.25(2H m), 3.02(1H, m), 1.50(9H, s), 1.49(9H, s)
MS (FAB, m/e) : 420(M+H)

Preparations 8 to 17

[0071] The amine compounds listed in the following Table 1 were prepared according to the same procedure as Preparation 7 except that the corresponding benzylbromide derivatives having R_2 structure as presented in the following Table 1 are used instead of benzylbromide.

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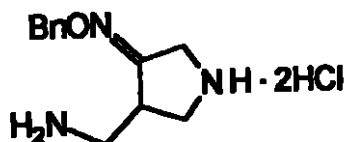
86
80

EP 0 688 772 B1

Preparation 18

Synthesis of 4-aminomethyl-pyrrolidin-3-one-benzoyloxime dihydrochloride

[0072]



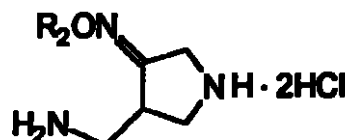
[0073] 20ml of methanol was cooled down to 5°C and then 10ml of acetyl chloride was slowly added thereto. This mixture was stirred for 30 minutes and 990mg of the compound prepared in Preparation 7, which is dissolved in 10ml of methanol, was added thereto. The reaction mixture was stirred for 50 minutes at room temperature and concentrated under reduced pressure. The residue was washed with ethyl acetate and dried to obtain 648mg (Yield: 94%) of the title compound as a yellow solid.

¹H NMR (DMSO-d₆, ppm) δ 10.0(1H, m), 8.35(2H, m), 7.40(5H, m), 5.18(2H, s), 4.00(2H, m), 3.69(1H, m), 3.40(2H, m), 3.12(2H, s)

MS (FAB, m/e) : 220(M+H)

Preparations 19 to 28

[0074] The compounds listed in the following Table 2 were prepared from the amine compounds prepared in Preparations 8 to 17 according to the same procedure as Preparation 18.

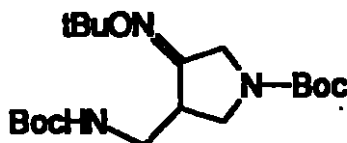


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81

Preparation 29

Synthesis of 1-(N-t-butoxycarbonyl)-4-(N-t-butoxycarbonyl)aminomethyl-pyrrolidin-3-one t-butylloxime

[0075]



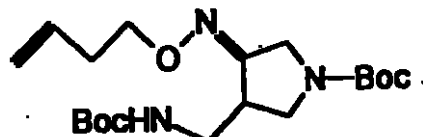
[0076] 300mg of the compound prepared in Preparation 5 was dissolved in the mixture of 8ml of 95% ethanol and 3ml of tetrahydrofuran(THF) and this solution was introduced into a 30ml reaction vessel. 487mg (3.5 mole eq.) of o-t-butylhydroxylamine hydrochloride was added thereto and then 281mg (3.5 mole eq.) of sodium hydrogen carbonate dissolved in 1.5ml of distilled water was added. The reaction mixture was stirred for 40 minutes at 40°C under oil bath to complete the reaction, and then cooled down, concentrated under reduced pressure, diluted with methylene chloride, washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate and then filtered. The filtrate was concentrated and the residue was subjected to silica gel column chromatography eluting with hexane-ethyl acetate (1:1 by volume) to obtain 285mg (Yield: 80%) of the title compound.

¹H NMR (CDCl₃, ppm) : δ 5.10(1H, bs), 4.05(2H, s), 3.71(1H, dd), 3.43(1H, br), 3.2(2H, m), 3.0(1H, m), 1.42(18H, s), 1.30(9H, s)
MS (FAB, m/e) : 386(M+H)

Preparation 30

Synthesis of 1-(N-t-butoxycarbonyl)-4-(N-t-butoxycarbonyl)aminomethyl-pyrrolidin-3-one 3-butynloxime

[0077]



A. Synthesis of 3-butynyl hydroxylamine

[0078] 0.35g (5 mmole) of 3-butynol, 0.86g (5.25 mmole) of N-hydroxyphthalimide and 1.44g (5.5 mmole) of triphenylphosphine were dissolved in 15ml of dry tetrahydrofuran, and then 1.05g (8 mmole) of diethylazodicarboxylate was added thereto over 30 minutes. The mixture was stirred for 10 minutes at room temperature and then distilled under reduced pressure to remove the solvent. To the residue was added 50ml of ethyl acetate-hexane (1:1 v/v). The precipitated solid material was filtered off and the filtrate was concentrated. The residue was purified with column chromatography (hexane-ethyl acetate 9:1 v/v). The resulting white solid [0.54g, Yield 50%, ¹H NMR (CDCl₃, ppm) : δ 7.85(2H, m), 7.75(2H, m), 4.2(2H, t), 2.8(2H, dd), 2.5(2H, dd), 2.1(1H, s), FAB MS(POS) : [M+H]⁺ = 216] was dissolved in 12ml of methylene chloride, and 0.25g (5 mmole) of hydrazine hydrate diluted with 4ml of methanol was added dropwise thereto. The solid precipitate was filtered off and the filtrate was concentrated at low temperature under reduced pressure to obtain 0.2g (Yield: 93%) of the title compound.

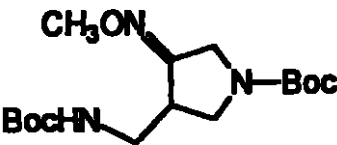
¹H NMR (CDCl₃, ppm) : δ 9.5(2H, br), 4.5(2H, t), 2.8(2H, m), 2.4(2H, m), 2.05(1H, s)

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Preparation 51

Synthesis of 4-(N-t-butoxycarbonyl)aminomethyl-1-(N-t-butoxycarbonyl)pyrrolidin-3-one O-methylidene

[0087]



[0088] 260mg (8.26×10^{-4} mole) of the compound prepared in Preparation 5 was dissolved in the mixture of 5ml of 95% ethanol and 2.5ml of tetrahydrofuran and this solution was introduced into a reaction vessel. Then, 256mg (3.7 mole eq.) of methoxyamine hydrochloride was added thereto and 257mg (3.7 mole eq.) of sodium hydrogen carbonate (NaHCO_3) dissolved in 2.5ml of distilled water was also added. The reaction mixture was stirred for 1 hour at 40°C under oil bath, concentrated under reduced pressure, washed successively with aqueous ammonium chloride solution and aqueous sodium chloride solution, dried over anhydrous magnesium sulfate and then filtered. The filtrate was concentrated to obtain 250mg (Yield: 88%) of the title compound.

^1H NMR (CDCl_3 , ppm) : δ 4.98(1H, bs), 3.81(3H, s), 3.75-2.80(7H, m), 1.40(18H, s)
MS (FAB, m/e) : 344(M+H)

Preparations 52 and 53

[0089] The compounds listed in the following Table 6 were prepared according to the same procedure as Preparation 51 except that phenoxyamine hydrochloride or ethoxyamine hydrochloride are used instead of methoxyamine hydrochloride.

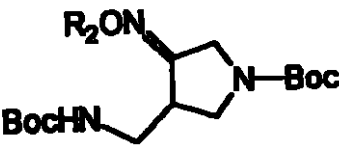


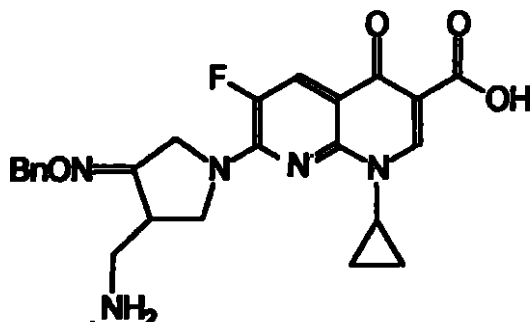
Table 6

Preparations 52 and 53			
Prep.	R ₂	^1H NMR(CDCl_3), δ (ppm)	FAB MS(M+H)
52	phenyl	7.3(5H,m), 4.97(1H,bs), 3.8-2.8(7H,m), 1.40(18H,s)	406
53	-CH ₂ CH ₃	5.0(1H,bs), 3.8-2.8(7H,m), 1.42(18H,s), 1.41(18H,s), 1.38(3H,t)	358

Example 1

Synthesis of 7-(4-aminomethyl-3-benzoyloxymino-pyrrolidin-1-yl)-1-cyclopropyl-8-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid

[0093]



[0094] 622mg of 7-chloro-1-cyclopropyl-8-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid and 643mg of the compound prepared in Preparation 18 were suspended in 15ml of acetonitrile. This suspension was cooled down under ice-water bath and then 1.0ml of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was slowly added thereto. The reaction mixture was stirred for 1.5 hours at room temperature and, after adding 15ml of water, was then concentrated. The concentrated suspension was filtered. The filtered solid product was washed with water and ethanol to obtain 584mg (Yield: 57%) of the title compound.

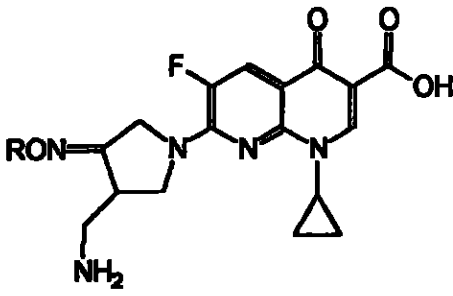
¹H NMR (DMSO-d₆, ppm) δ 8.59(1H, s), 8.03(1H, d), 7.40(5H, m), 5.14(2H, s), 4.75(2H, s), 4.18(1H, m), 3.94(1H, m), 3.83(1H, m), 3.35(2H, m), 3.05(1H, m), 2.81(1H, m), 2.73(1H, m), 1.25-1.05(4H, m)
MS (FAB, m/e) : 468(M+H)

Examples 2 to 11

[0095] The same starting material as Example 1 was reacted with each of the compounds prepared in Preparations 19 to 28 according to the same procedure as Example 1 to prepare the respective compounds listed in the following Table 8.

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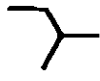
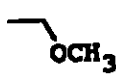
Table 16. Examples 97 to 106



Examp. No.	R	¹ H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (min)	Yield (%)
97		8.6(1H,s),8.0(1H,d),4.7(1H,m),4.6(2H,s),4.2(1H,m),3.9(1H,m),3.7(1H,m),3.0(1H,m),2.9-2.7(2H,m),1.2-1.0(4H,m),0.9(6H,d)	DMSO-d ₆	418	10	73
98		8.6(1H,s),8.05(1H,d),4.8(1H,m),4.7(2H,s),4.2(1H,m),4.0(1H,m),3.7(1H,m),3.0(1H,m),2.9-2.7(2H,m),2.2(2H,m),2.1(2H,m),1.7(1H,m),1.5(1H,m),1.2-1.0(4H,m)	DMSO-d ₆	430	10	63
99		8.6(1H,s),8.0(1H,d),4.7(1H,m),4.5(2H,s),4.2(1H,m),3.9(1H,m),3.7(1H,m),3.1(1H,m),2.9-2.8(2H,m),1.7(4H,s),1.6(2H,m),1.5(2H,m),1.2-1.0(4H,m)	DMSO-d ₆	444	50	77
100		8.6(1H,s),8.0(1H,d),4.8(1H,m),4.6(2H,s),4.2(1H,m),3.9(1H,m),3.8-3.6(5H,m),3.1(1H,m),2.9-2.7(2H,m),2.3-1.9(2H,m),1.2-1.0(4H,m)	DMSO-d ₆	446	30	61
101		8.65(1H,s),8.05(1H,d),4.6(2H,s),4.25(1H,m),3.9(1H,m),3.85(2H,dd),3.75(1H,m),3.1(1H,m),3.0-2.8(2H,m),1.3-1.0(5H,m),0.5(2H,m),0.3(2H,m)	DMSO-d ₆	430	30	84

91
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Table 16. (continued)

Examp. No.	R	¹ H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (min)	Yield (%)
102		8.6(1H,s),8.0(1H,d),4.6(2H,s),4.2(1H,m),3.95(1H,m),3.8(2H,d),3.7(1H,m),3.05(1H,m),2.9-2.7(2H,m),1.9(1H,m),1.2-1.0(4H,m),0.9(6H,d)	DMSO-d ₆	432	15	80
103		8.60(1H,s),8.05(1H,d),4.74(2H,s),4.60(2H,s),4.21(1H,m),3.97(1H,m),3.75(1H,m),3.50(1H,s),3.35(2H,s),3.08(1H,m),2.90-2.70(2H,m),1.30-1.05(4H,m)	DMSO-d ₆	414	90	63
104		8.6(1H,s),8.0(1H,d),4.6(2H,s),4.2(1H,m),4.1(2H,t),3.9(1H,m),3.7(1H,m),3.1(1H,m),2.9-2.7(2H,m),2.8(1H,s),2.5(2H,t),1.2-1.0(4H,m)	DMSO-d ₆	428	15	65
105		8.6(1H,s),8.0(1H,d),4.6(2H,s),4.2(1H,m),3.9(1H,m),3.7(1H,m),3.4(2H,s),3.3(3H,s),3.0(1H,m),2.8-2.6(2H,m),1.2-1.0(4H,m)	DMSO-d ₆	420	20	52
106		8.6(1H,s),8.05(1H,d),4.6(2H,s),4.3(2H,t),4.2(1H,m),3.9(1H,m),3.8(2H,t),3.7(1H,m),3.1(1H,m),2.9-2.7(2H,m),1.2-1.0(4H,m)	DMSO-d ₆	438	10	50

86 92

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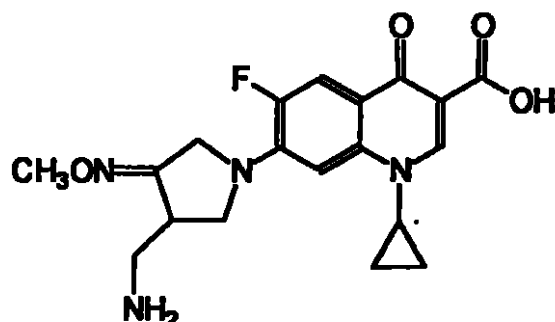
¹H NMR (DMSO-d₆, ppm) δ 8.7(1H, s), 7.85(1H, d), 4.4(1H, m), 3.75(3H, s), 3.7(3H, m), 3.4(2H, m), 3.0-2.7(2H, m), 1.25(2H, d), 1.0(2H, s)

FAB MS(POS) : [M+H] = 423

5 Example 179

Synthesis of 7-(4-aminomethyl-3-methoxypyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

10 [0138]



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[0139] 132mg (0.5 mmole) of 1-cyclopropyl-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and 205mg (0.55 mmole) of 4-aminomethylpyrrolidin-3-one O-methylxime ditrifluoroacetate were reacted for 3 hours according to the same manner as Example 177. Then, the reaction solution was concentrated and the residue was purified with preparative HPLC to obtain 73mg (Yield: 37%) of the title compound.

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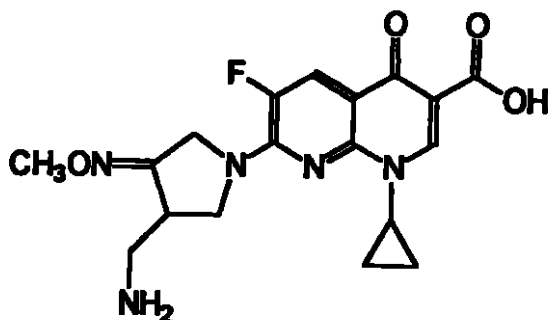
¹H NMR (DMSO-d₆, ppm) δ 8.6(1H, s), 7.85(1H, d), 7.2(1H, d), 4.4(2H, d), 3.9(1H, m), 3.65(3H, s), 3.3-3.65(2H, m), 3.0(1H, m), 2.9-2.7(2H, m), 1.3(2H, m), 1.1(2H, m)

FAB MS(POS) : [M+H] = 389

35 Example 180

Synthesis of 7-(4-aminomethyl-3-methoxypyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid

40 [0140]



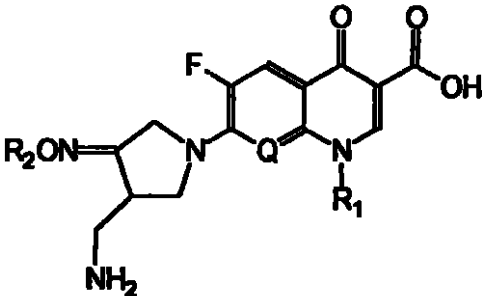
55

[0141] 141mg (0.5 mmole) of 1-cyclopropyl-7-chloro-6-fluoro-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid and 205mg (0.5 mmole) of 4-aminomethylpyrrolidin-3-one O-methylxime ditrifluoroacetate were reacted for 0.5 hour according to the same manner as Example 177 to obtain 167mg (Yield: 85%) of the title compound.

87 93

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Table 24. Examples 183 to 202



Ex. No.	Q	R ₁	R ₂	¹ H NMR(DMSO-d ₆) δ(ppm)	FAB MS (POS) [M+H]	Reac. Time (hr)	Yield (%)
183	CF		H	8.8(1H,s), 7.9(1H,d), 4.35(1H,m), 3.8(2H,m), 3.7(2H,m), 3.4(1H,m), 3.0(2H,m), 1.2-1.0(4H,m)	393	2.5	41
184	CF		Et	8.8(1H,s), 7.9(1H,d), 4.4(1H,m), 4.2(2H,q), 4.1-3.9(2H,m), 3.4(2H,m), 2.8(2H,m), 1.4(3H,t), 1.25-1.0(4H,m)	421	2	38
185	CF		Ph	8.8(1H,s), 7.9(1H,d), 7.3-7.1(5H,m), 4.3(1H,m), 3.9-3.7(3H,m), 3.4(2H,m), 2.8(2H,m), 1.2(2H,d), 1.05(2H,s)	469	4	29
186	CF		tBu	8.8(1H,s), 7.9(1H,d), 4.35(1H,d), 4.1-3.9(3H,m), 3.4(2H,m), 2.9-2.7(2H,m), 1.35(9H,s), 1.2-0.95(4H,m)	449	2	35
187	CCl		H	8.9(1H,s), 7.9(1H,d), 4.4(1H,m), 3.8(2H,m), 3.7(2H,m), 3.4(1H,m), 2.9(2H,m), 1.25(2H,m), 1.1(2H,s)	409	1.5	39
188	CCl		Et	8.9(1H,s), 7.9(1H,d), 4.35(1H,m), 4.2(2H,q), 3.95-3.75(3H,m), 3.7(2H,m), 3.4(2H,m), 2.85-2.7(2H,m), 1.4(3H,t), 1.3-1.15(4H,m)	437	1.5	37

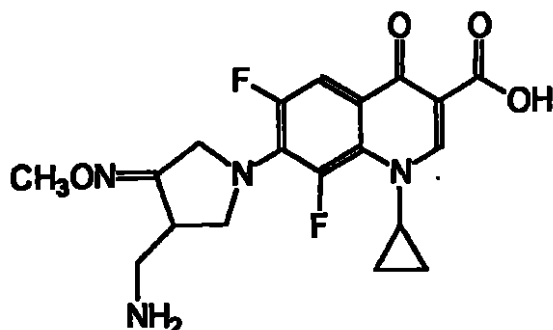
88 94

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Example 177

Synthesis of 7-(4-amino-3-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6,8-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

[0134]



[0135] 2.63g (10 mmole) of 1-cyclopropyl-6,7,8-trifluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and 4.27g (11.5 mmole) of 4-aminomethyl-pyrrolidin-3-one O-methyloxime ditrifluoroacetate were added to 23ml of dry acetonitrile. Then, 4.6g (30 mmole) of 1,8-diazabicyclo[5.4.0]undec-7-ene was added thereto and the mixture was refluxed for 1.5 hours under heating and then cooled down to room temperature. 15ml of distilled water was added to the reaction solution. The precipitated solid product was separated and dried to obtain 2.24g (Yield: 55%) of the title compound.

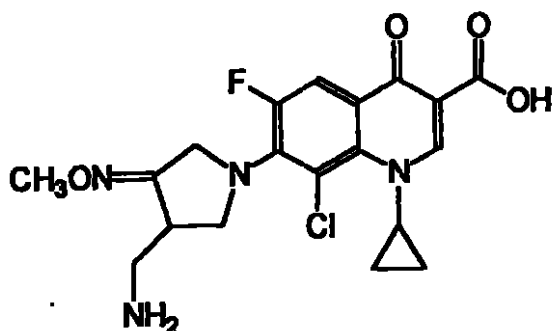
¹H NMR (DMSO-d₆, ppm) δ 8.8(1H, s), 7.75(1H, d), 4.35(2H, s), 4.1-3.9(2H, m), 3.8(3H, s), 3.7(1H, m), 3.35(1H, m), 2.9-2.6(2H, m), 1.25 (2H, d), 0.95(2H, s)

FAB MS (POS) : [M+H]⁺ = 407

Example 178

Synthesis of 7-(4-aminomethyl-3-methoxyimino-pyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

[0136]



[0137] 141mg (0.5 mmole) of 1-cyclopropyl-8-chloro-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and 205mg (0.55 mmole) of 4-aminomethylpyrrolidin-3-one O-methyloxime ditrifluoroacetate were reacted for one hour according to the same manner as Example 177. Then, the reaction solution was concentrated and the residue was purified with preparative HPLC to obtain 88mg (Yield: 42%) of the title compound.

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PCT

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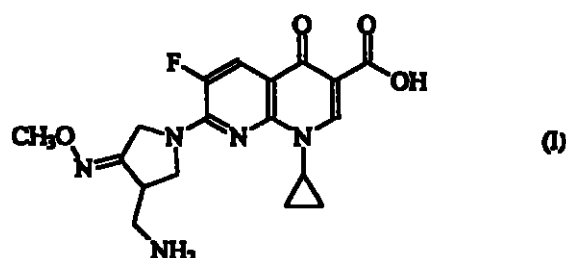
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(54) Title: SALT OF NAPHTHYRIDINE CARBOXYLIC ACID DERIVATIVE			
(57) Abstract			
7-(3-Aminomethyl-4-methoxyiminopyrrolidin-1-yl) -1-cyclopropyl-6-fluoro -4-oxo-1,4-dihydro-1,8 -naphthyridine-3-carboxylic acid methanesulfonate and hydrates thereof, processes for their preparation, pharmaceutical compositions comprising them, and their use in antibacterial therapy.			
DZ			

SALT OF NAPHTHYRIDINE CARBOXYLIC ACID DERIVATIVE**TECHNICAL FIELD**

The present invention relates to a salt and associated hydrates of racemic 7-(3-aminomethyl-4-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid, processes for their preparation, pharmaceutical compositions comprising them, and their use in antibacterial therapy.

BACKGROUND ART

EP 688772 (corresponding to Korean Patent Laid open Publication No 96-874) discloses novel quinoline(naphthyridine)carboxylic acid derivatives, including anhydrous 7-(3-aminomethyl-4-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid of formula I, having antibacterial activity.

**DISCLOSURE OF INVENTION**

According to the invention there is provided 7-(3-Aminomethyl-

4-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate.

7-(3-Aminomethyl-4-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate (hereinafter referred to as 'the methanesulfonate') may be obtained as an anhydrate or a hydrate i.e. methanesulfonate. $n\text{H}_2\text{O}$.

Hydrates of the methanesulfonate wherein n is in the range 1 to 4 are preferred. Particular hydrates of the methanesulfonate which may be mentioned are those in which n is 1, 1.5, 2, 2.5, 3, 3.5 and 4. Particular preferred compounds are those in which n is 1.5 or 3, with $n=1.5$ being most preferred.

The moisture content of the methanesulfonate hydrates varies with the hydration number (n) of the hydrated molecule. The methanesulfonate has a molecular weight of 485.5 thus the calculated moisture content of hydrates where n is 1, 1.5, 2, 2.5, 3, 3.5 and 4 is 3.6%, 5.0%, 6.9%, 8.5%, 10.0%, 11.5% and 12.9% respectively. However, the actual moisture content of the methanesulfonate hydrates may differ from the calculated value depending on various factors including recrystallization conditions and drying conditions. The observed moisture content for the methanesulfonate hydrates where n is 1, 1.5, 2, 2.5, 3, 3.5 and 4 is shown in Table 1:

Both the methanesulfonate anhydrate and $n=3$ hydrate undergo transition to the $n=1.5$ hydrate in aqueous suspension indicating that the latter is thermodynamically more stable. The $n=1.5$ hydrate is a sesquihydrate at 11 to 64% of relative humidity. Above 75% relative humidity, it takes up water over 10% and its X-ray diffraction pattern changes. The hydrate (another form of $n=3$ having different physiochemical properties from the $n=3$ hydrate of Example 2) obtained from $n=1.5$ hydrate at 93% relative humidity is not stable at lower relative humidity, it converts back to $n=1.5$ hydrate at a relative humidity below 75%.

Since the moisture content of the anhydrate changes readily depending on the environment e.g. relative humidity, formulation additives etc, it may require careful handling during storage or formulation, with operations such as quantifying procedures being performed in a dry room. The hydrates do not change in moisture content as easily and hence products which are stable to prolonged storage and formulation may be obtained. The hydrate can be tabletted without the addition of a binder since the water contained in the compound itself acts a binder, whereas it may not be possible to tablet the anhydrate at a similar pressure.

The present invention also provides a process for the preparation of 7-(3-aminomethyl-4-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate and hydrates thereof which comprises reacting 7-(3-aminomethyl-4-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid with methanesulfonic acid and crystallizing the resulting methanesulfonate from solution, and where desired or

necessary adjusting the hydration of the compound.

The methanesulfonate and its hydrates may be prepared by the addition of methanesulfonic acid to the free base which may be prepared as described in EP 688772. Preferably, 0.95 to 1.5 molar equivalents of methanesulfonic acid is added to the free base, or 1 molar equivalent of methanesulfonic acid dissolved in a suitable solvent is added to the free base. Suitable solvents for the preparation of the methanesulfonate and its hydrates include any solvent in which the methanesulfonate is substantially insoluble, suitable solvents include C₁-C₄ haloalkanes, C₁-C₃ alcohols and water, or mixtures thereof. Dichloromethane, chloroform, 1,2-dichloroethane, methanol, ethanol, propanol and water, or mixtures thereof, are preferred solvents. If necessary, the free base may be heated in the solvent to facilitate solution before methanesulfonic acid is added, alternatively the methanesulfonic acid may be added to a suspension, or partial suspension, of the free base in the solvent. Following addition of the methanesulfonic acid the reaction mixture is preferably allowed to stand or is stirred for 1 to 24 hours at a temperature of from about -10 to 40°C. The resulting methanesulfonate is obtained as a solid which can be isolated by filtration or by removal of the solvent under reduced pressure.

Different hydrates may be obtained by altering the recrystallization conditions used in the preparation of the methanesulfonate, such conditions may be ascertained by conventional methods known to those skilled in the art.

The present invention also provides a process for the preparation of a hydrate of 7-(3-aminomethyl-4-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid

methanesulfonate comprising exposing the methanesulfonate anhydrate or a solvate thereof to a high relative humidity.

The methanesulfonate anhydrate or solvate thereof is preferably exposed to a relative humidity of at least 75%.

The methanesulfonate anhydrate or solvate thereof may be exposed to high relative humidity by passing humidified nitrogen gas through the methanesulfonate anhydrate or solvate thereof or by standing the methanesulfonate anhydrate or solvates thereof under a high relative humidity.

The humidified nitrogen gas used in this process, for example nitrogen gas having a humidity of at least 75%, may be made by conventional methods. In this process it is desirable to maintain the temperature in the range above which moisture condensation could occur.

Also, particularly in large scale production, it is preferable to stir the sample thoroughly while the humidified nitrogen gas is passed through. When the hydrate is prepared by standing the methanesulfonate anhydrate or solvate thereof under a high relative humidity, for example a relative humidity of at least 75%, it is preferable to spread the sample as thinly as possible in order to raise the conversion efficiency.

The solvates of methanesulfonate anhydrate which may be used in the process according to this aspect of the present invention include solvates with one or more organic solvents. Preferred solvents include C₁-C₄ haloalkanes and C₁-C₃ alcohols, for example those selected from the group consisting of ethanol, dichloromethane, isopropanol and 2-methyl-2-propanol.

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Solvates of the methanesulfonate anhydrate are novel. Thus according to a further aspect of the invention there is provided a solvate of 7-(3-aminomethyl-4-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate with one or more organic solvents.

The solvates of the methanesulfonate are prepared by recrystallization and controlled by the condition of recrystallizing system.

The methanesulfonate and its hydrates exhibit the same potent antibacterial activity as the corresponding free base disclosed in EP 688772. The methanesulfonate and its hydrates also exhibit desirable physicochemical properties including improved solubility and constant moisture content regardless of the ambient relative humidity when compared to the free base and other salts thereof. The methanesulfonate and its hydrates thus exhibit greater ease of handling, quality control and formulation than the free base and other salts thereof.

As mentioned above the methanesulfonate and its hydrates exhibit antibacterial activity. The methanesulfonate and its hydrates may be formulated for administration in any convenient way for use in human or veterinary medicine, according to techniques and procedures *per se* known in the art with reference to other antibiotics, and the invention therefore includes within its scope a pharmaceutical composition comprising 7-(3-aminomethyl-4-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate or a hydrate thereof together with a pharmaceutically acceptable carrier or excipient.

Compositions comprising the methanesulfonate or hydrate thereof

the dried nitrogen introduced through the inlet was 20psi the relative humidity of the nitrogen exiting through the outlet was more than 93%. The anhydrate of Example 1 having a moisture content of 2.5% (1.0g) was introduced into a fritted filter and the humidified nitrogen produced as described above passed through the filter. Samples were taken after 0, 5, 10, 20, 30, and 60 minutes and the moisture content measured. From the results shown in Figure 8 it can be seen that a moisture content of about 10% is maintained when the humidifying procedure is carried out over about 30 minutes. The X-ray diffraction pattern of the humidified sample was identical to that of the n=3 hydrate obtained by recrystallization.

Example 3: Synthesis of 7-(3-aminomethyl-4-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate n=1.5 hydrate

The title compound was prepared by the following routes:

Route A

The anhydrate of Example 1 (1.0g) was dissolved in a mixture of water and acetone (17ml, 10:7 v/v). The solvent was slowly evaporated in darkness leaving the title compound as a solid (0.8g).

Route B

The anhydrate of Example 1 (5.0g) was added to water (10ml) and the mixture was heated to 45°C to aid dissolution. Ethanol (20ml) was added and the resulting solution stirred then allowed to stand. The resulting solid was filtered and dried under a flow of nitrogen to

give the title compound (2.6g).

Example 4: Synthesis of the hydrate from 7-(3-aminomethyl-4-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate solvate using a humidified nitrogen gas

A sonicator filled with water was adjusted to 40°C and was sealed with a lid. Then, a nitrogen inlet and outlet were connected to the vessel. When the pressure of the dried nitrogen introduced through the nitrogen inlet was adjusted to about 20psi, the relative humidity of the humidified nitrogen gas exiting through the outlet was more than 93%. The solvate (1g, ethanol 0.11%) of the anhydrate of Example 1 was introduced into a fritted filter and the humidified nitrogen gas prepared as described above was passed through the filter. Samples were taken after 40 minutes, 3.5 and 6 hours, respectively. The change in the amount of residual organic solvent and X-ray diffraction pattern with the lapse of time were examined. After 3.5 hours, it was identified that the product contained the organic solvent in an amount of less than 50ppm and that the peaks based on the solvate disappeared, whilst the peaks based on the mixture of n=3 hydrate and n=1.5 hydrate appeared.

Example 5: Synthesis of the hydrate from 7-(3-aminomethyl-4-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate solvate using a high relative humidity

Saturated aqueous potassium nitrate solution was placed in a desiccator, and accordingly the relative humidity inside the desiccator was

1. La sociedad solicitante ha **TRASPASADO** la solicitud de patente aquí contenida a favor de la sociedad LG Life Sciences Limited.
2. En consecuencia, en la misma fecha de este escrito estoy radicando el Formulario de Modificación correspondiente junto con el comprobante de pago de la tasa respectiva.
3. Atentamente le solicito se sirva tener en cuenta esta modificación para el trámite de la solicitud.

Atentamente,

GERMAN CASTILLO ORAU

T.P. No. 2978 del C.S.J.