Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCION

21 **EXPEDIENTE No.** 04-99283

54 **TITULO** PROCESO PARA PREPARAR SALES ÁCIDAS DE GEMIFLOXACINA

51 **CLASIFICACION INTERNACIONAL**

71 **SOLICITANTE** LG LIFE SCIENCES LTD.

DOMICILIO Seul, República de Corea.

74 **APODERADO** EMILIO FERRERO

C.C. 438.019 de Usaquén.

22 **BOGOTA, D.C.,**

(FORMA P 10)

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINTENDENCIA Y COMERCIO
Radicacion : 04099283 00000000 Folios: 02
Fecha (MM/DD): 2004-10-05 17:07:39 sión
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.
☐ Capítulo I. ☒ Capítulo II.

2 SOLICITANTE (71)

Nombre: **LG LIFE SCIENCES LTD.** sociedad constituida y existente bajo las leyes de la República de Corea.

Dirección: LG Twin Tower, East Tower 20, Yoldo-dong, Youngdungpo-ku, Seul 150-010, República de Corea.
Domicilio: Seul, República de Corea.

IDENTIFICACIÓN
C.C. ☐ NIT ☐
C.E. ☐ Otro ☐
Cual ____
Número ____

3 REPRESENTANTE APODERADO

Nombre: EMILIO FERRERO
Dirección: Carrera 4ª. No. 72-35
Teléfono: 347 36 11
Fax: 217 92 11
E-mail: clientes@camyp.com.
Domicilio: Bogotá, Colombia.

IDENTIFICACIÓN
C.C. ☒ NIT ☐
C.E. ☐ Otro ☐
Cual ____
Número 438.019 T.P 31.929

4 INVENTOR (ES) (72)

1. **Hoon CHOI**
R & D Park, LG Life Sciences Ltd.
104-1, Moongi-dong, Yuseong-gu,
Taejeon 305-380
República de Corea.
2. **Sang-Chul CHOI**
R & D Park, LG Life Sciences Ltd.
104-1, Moongi-dong, Yuseong-gu,
Taejeon 305-380
República de Corea
3. **Do-Hyun NAM**
R & D Park, LG Life Sciences Ltd.
104-1, Moongi-dong, Yuseong-gu,
Taejeon 305-380
República de Corea.
4. **Bo-Seung CHOI**
R & D Park, LG Life Sciences Ltd.
104-1, Moongi-dong, Yuseong-gu,
Taejeon 305-380
República de Corea.

5 PCT (86)

Solicitud Internacional No. PCT/KR03/00683 Fecha: 4 de abril de 2003
Publicación Internacional No. WO 03/087100 A1 Fecha: 23 de octubre de 2003

6 Título (54)

PROCESO PARA PREPARAR SALES ÁCIDAS DE GEMIFLOXACINA

7 Clasificación Internacional (51) C07D 471/04

8 Prioridad	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
SI☒ NO☐	KR.	8 de abril de 2002	10-2002-0018847

9 Comprobante de pago No.: 04 - 76.090 **Fecha:** 27 de sepbre de 2004

10

Anex s:

- [x] Comprobante de pago de la tasa de presentación de la solicitud por $ 422.000.oo.
- [ ] Comprobante de pago por reivindicación de prioridad.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Copia del examen preliminar efectuado por la IPEA.
- [ ] Traducción del examen preliminar efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12x12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] Otros

11

FIGURA CARACTERÍSTICA

12

Solicito la concesión de la patente,

NOMBRE: EMILIO FERRERO

FIRMA : _____

C.C. 438.019 de Usaquén T.P. 31.929

×4 3

CONSULADO DE COLOMBIA

No. 387 .

10 JUL 2003

El suscrito Cónsul de Colombia en Seúl, Corea, vistos los documentos presentados por lo interesados, CERTIFICA:
Que el señor Paik Seung Hun quien como Notario Público de Seúl, Corea autenticó la firma del signatorio del poder precedente, ejercía a la fecha las funciones indicadas y su firma corresponde a la registrada en este Consulado; Que la compañía LG LIFE SCIENCES LTD, es una Sociedad constituida de acuerdo con las leyes de República de Corea y cumple su objeto conforme a las mismas: que el Señor Heung Joon Yang, quien en su caracter de Presidente de la citada compañía confiere el poder precedente y cuya firma fue autenticada ante el notario arriba citado, es su representante legal en este pais.

El Cónsul no asume responsabilidad por el contenido del documento.

ALVARO ENRIQUE AYALA MELENDEZ
Cónsul de Colombia

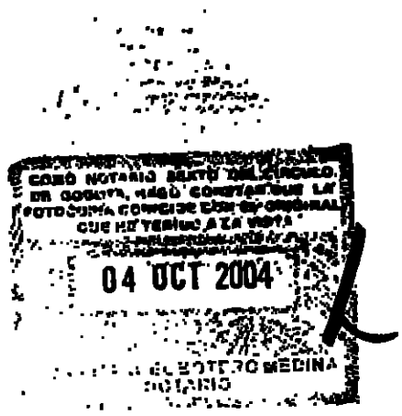
Esta certificación es válida para un documento de (4) páginas.

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA COPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
04 OCT 2004
JUAN MANUEL BOTERO MEDINA
NOTARIO

PAGADOS IMPUESTOS DE TIMBRE Y DERECHOS CONSULARES.
Valor: 23.oodólares americanos

Alvaro Ayala
DESEMPEÑA LAS FUNCIONES INDICADAS

NO SE ASUME ...LIDAD DEL ...


04 OCT 2004

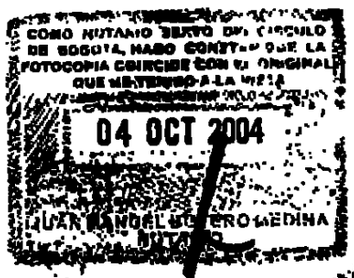
서울 강남구 역삼동 825-33
타헤란빌딩 8층

공증인가 법무법인 한 결

(02)3487-3500

Registered No.2003-1980

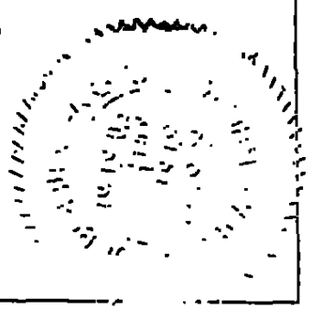
NOTARIAL CERTIFICATE



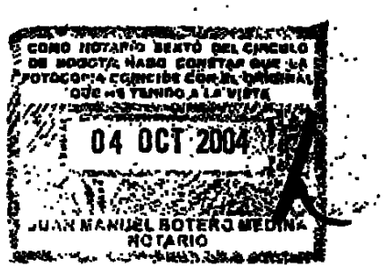
HANKYUL LAW FIRM & NOTARY OFFICE

#825-33, YOKSAM-DONG, KANGNAM-GU,

SEOUL, KOREA



제 41호 서식


COMO NOTARIO SEXTO DEL CIRCULO
DE BOGOTA HAGO CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA
04 OCT 2004
JUAN MANUEL BOTERO MEDINA
NOTARIO

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4a N° 72-35
BOGOTA, 8 - COLOMBIA

Representación y Poder con autenticación notarial y Apostille para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales, enseñas, nombres de dominio, lemas comerciales, licencias.

Representation and Power-of- Attorney with notarial authentication and Apostille for patents, utility models, industrial designs, trademarks, commercial names, trade emblems, domain names, slogans, licenses.

REPRESENTACION Y PODER

REPRESENTATION AND POWER- OF- ATTORNEY

Yo (nosotros), abajo firmado (s)/I (we), the undersigned
LG LIFE SCIENCES LTD.

domiciliado (s) en/of 20, Yoido-dong, Yongdungpo-ku,
150-010 Seoul, KOREA

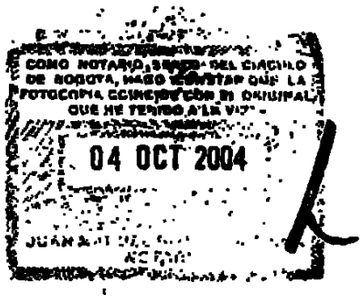
por el presente nombramos a EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y GERMAN CAVELIER, tpa. 832, domiciliados en la Carrera 4ª Nº 72 35, Bogotá, Colombia, en obedecimiento a lo dispuesto en el parágrafo 1o del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primero o segundo suplentes, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, nombres de dominio, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protección del consumidor, oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la protección de secretos industriales, y en general los juicios civiles, penales, administrativos o contencioso administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos

in due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 and GERMAN CAVELIER, tpa. 832, domiciled at Carrera 4ª Nº 72 35, Bogotá, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second alternate depending on cases and the mere fact or its exercise will suffice to the cessation of the representation by the first, second or third alternate acting until such time.

In addition, we grant [illegible] Power of Attorney in favor of the above named attorneys at law [illegible] may obtain the protection of my (our) industrial property [illegible] against unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models and industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, domain names, vegetal varieties and denominations of origin; its renewal, assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b) Actions of unfair competition, protection to the consumer, oppositions or observations, administrative or Court cancellation, nullity, infringement, granting of licenses, the action for writ mandamus, the protection of trade secrets, and in general the civil, penal, and administrative suits relating to those rights; actions and suits instituted by me (us) or against me (us). And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate,

04 OCT 2004


04 OCT 2004

promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

Dado y firmado hoy/Given and signed this July 15, 2003

en/in Seoul, Korea

por/by

Firma LG LIFE SCIENCES LTD. Signature

President : Heung Joon YANG

CORO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

04 OCT. 2004

JUAN MANUEL [illegible] MOLINA
NOTARIO

[redacted]

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE TUVE A LA VISTA

04 OCT 2004

JUAN MANUEL COTERO MEGIA
NOTARIO

서울 강남구 역삼동 825-33
한결빌딩 8층
공증인가 법무법인 한 결
(02)3487-3500

등부 2003 년 제 1980 호

Registered No. 2003-1980

인 증

NOTARIAL CERTIFICATE

위 위 임 장- - - - - - - - - - - - -
- - - - - - - - - - - - - - - - - -
에 기재된 주식회사 엘지생명과학
대표이사 양 홍 준 - - - - - - - - -
의 대리인 - - - - - - 이 규 형은(는)
본직의 면전에서 위 본인이 서명날인
한 것임을 자인하였다.

Kyu Hyung LEE
attorney-in-fact of
LG LIFE SCIENCES LTD.
PRESIDENT Heung Joon YANG
appeared before me and
admitted said principal's
subscription to the
attached POWER OF ATTORNEY.

2003 년 7 월 29 일
이 사무소에서 위 인증한다.

This is hereby attested
on this 29th day of Jul., 2003
at this office.

공증인가 법무법인 한 결
서울 강남구 역삼동 825-33

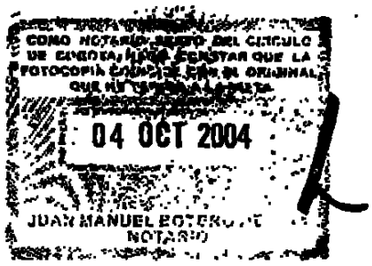
HANKYUL LAW FIRM & NOTARY OFFICE
825-33 YOKSAM-DONG, KANGNAM-GU,
SEOUL, KOREA

공증 담당변호사

Attorney at Law acting as Notary Public

This office has been authorized by the Minister of Justice, Republic of Korea, to act as Notary Public since 2000. 09. 30 under Law No. 3790.

제 43호 서식


04 OCT 2004
JUAN MANUEL

CERTIFICATE OF BUSINESS REGISTRATION

(Juridical person)

Registration Number: 107-86-21066

1. Name of Business: LG LIFE SCIENCES LTD.

2. Name of Representative: Heung Joon YANG

3. Starting Date of Biz.: August 1, 2002

4. I. D. Number: 110111-2581183

5. Place of Business: 20, Youido-Dong, Youngdungpo-Gu, Seoul, Korea

6. Place of Head Office: 20, Youido-Dong, Youngdungpo-Gu, Seoul, Korea

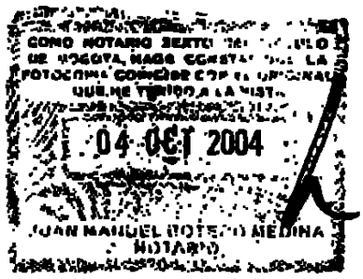
7. Kind of Business: Business: Manufacturing
Kind: Medicines, Farming drugs

8. Issuing Purpose: New Juridical person

Dated July 26, 2002

/S/ Official Seal Affixed

Head Officer
Youngdungpo Tax Office


04 OCT 2004
JUAN MANUEL ROTE
NOTARIO

9

사 업 자 등 록 증

(법인사업자)

등록번호 : 107-86-21066

법인명(단체명) : (주) 엘지생명과학

대 표 자 : 양홍준

개 업 년 월 일 : 2002 년 08 월 01 일 법인등록번호 :

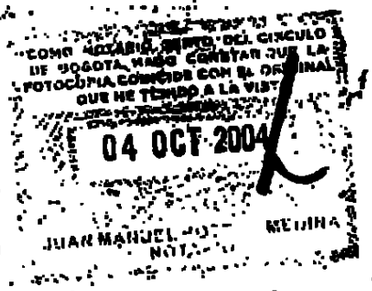
사업장 소재지 : 서울특별시 영등포구 여의도동 20

본 점 소 재 지 : 서울특별시 영등포구 여의도동 20

사 업 의 종 류 : 업태 제조 종목 의약품

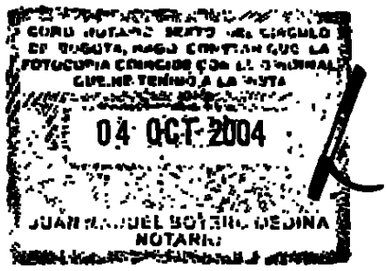
공과

교 부 사 유 : 신규법인



2002 년 07 월 26 일

영등포세무서장


04 OCT 2004
NOTARIA

10

TRADUCCIÓN OFICIAL 047/2004 DE UN DOCUMENTO ESCRITO EN INGLÉS Y EN ESPAÑOL, REALIZADA POR EDUARDO CALADO NOGUERA, TRADUCTOR OFICIAL APROBADO POR RESOLUCIÓN 541 DEL 27 DE FEBRERO DE 1976 POR EL MINISTERIO DE JUSTICIA Y DEBIDAMENTE REGISTRADO ANTE EL MINISTERIO DE RELACIONES EXTERIORES DE LA REPÚBLICA DE COLOMBIA Y MEDIANTE EL CUAL **LG LIFE SCIENCES LTD.**, EMPRESA DOMICILIADA EN 20, YOIDO-DONG, YONGDUNGPO-KU, 150-010, SEÚL, COREA OTORGA PODER A EMILIO FERRERO, TPA 31929, GONZALO PERDOMO, TPA 831; LUZ CLEMENCIA DE PAEZ TPA 23555 Y A GERMÁN CAVELIER, TPA 832. EXPEDIDO Y FIRMADO EN SEÚL, COREA EL 15 DE JULIO DE 2003. FIRMADO: LG LIFE SCIENCES LTD PRESIDENTE: HEUNG JOON YANG

NÚMERO DE REGISTRO 2003-1980

CERTIFICACIÓN NOTARIAL

KYU HYUNG LEE, apoderado de LG LIFE SCIENCES LTD.,PRESIDENTE HEUNG JOON YANG, compareció ante mi y admitió haber firmado como principal el poder adjunto.

Se atestigua hoy 29 de julio de 2003 en [illegible] OFICINA JURÍDICA Y NOTARIAL HANKYUL [illegible] YOKSAM-DONG, KANGNAM-GU, SEÚL, COREA.

FIRMADO: APODERADO QUE ACTÚA COMO NOTARIO PÚBLICO

Esta oficina ha sido autorizada por el Ministerio de Justicia de la República de Corea, para actuar como notaría pública desde el 30 de septiembre de 2000, de acuerdo con la Ley 3790.

CERTIFICACIÓN DE REGISTRO COMERCIAL

(PERSONA JURÍDICA)

NÚMERO DE REGISTRO: 107-86-21066

1. NOMBRE DE LA EMPRESA: LG LIFE SCIENCES LTD
2. NOMBRE DEL REPRESENTANTE: Heung Joon YANG

3. FECHA DE INICIACIÓN DE NEGOCIOS: 1 de agosto de 2002

4. NÚMERO DE IDENTIFICACIÓN: 110111-2581183

5. LUGAR DE NEGOCIOS: 20, YOUIDO-DONG, YOUNGDUNGPO-GU, SEÚL, COREA

6. LUGAR DE OFICINA PRINCIPAL: 20, YOUIDO-DONG, YOUNGDUNGPO-GU, SEÚL, COREA

7. TIPO DE NEGOCIOS: MANUFACTURA DE MEDICINAS Y DROGAS AGROPECUARIAS

8. OBJETIVO DE LA EXPEDICIÓN: NUEVA PERSONA JURÍDICA

FECHADO EL 26 DE JULIO DE 2002

SELLO OFICIAL FIJADO: FIRMA

FUNCIONARIO PRINCIPAL

OFICINA TRIBUTARIA DE YOUNGDUNGPO

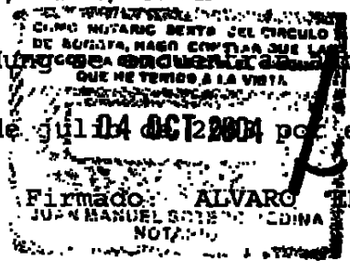
NÚMERO DE REGISTRO 2003-1980

CERTIFICADO NOTARIAL

OFICINA NOTARIAL Y DE FIRMA JURÍDICA HANKYUL

#825-33, YOKSAM-DONG, KANGNAM-GU, SEÚL, COREA

La firma y cargo de Paik Seung Hung fueron autenticados mediante diligencia 387 del 30 de julio de 2003 por el Consulado de Colombia en Seúl, Corea. Firmado: ALVARO ENRIQUE AYALA MELENDEZ, cónsul de Colombia.



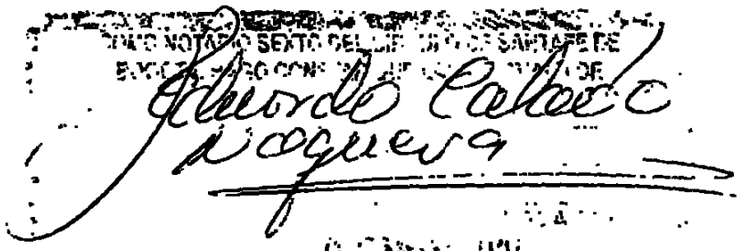
Sello fijado por el Ministerio de Relaciones Exteriores, diligencia 208440 del 26 de febrero de 2004 para autenticar la firma de Alvaro Ayala. Firma ilegible, jefe de legalizaciones, Bogotá, D.C.

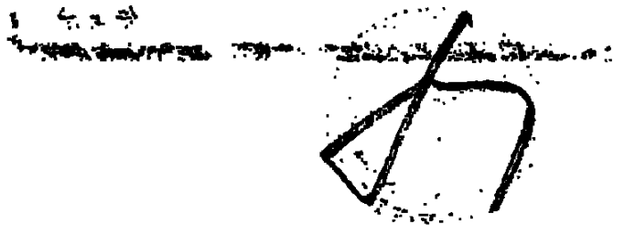
COLO-9281-706-003-1

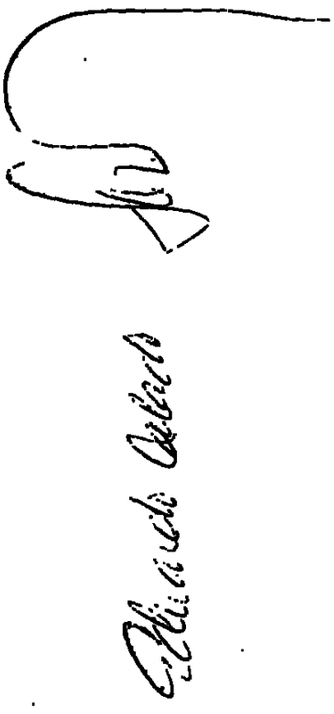
WPCL002G ID 3568

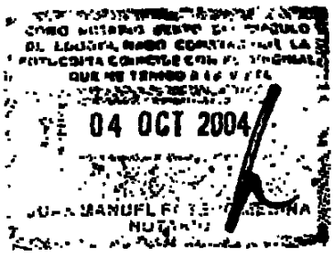
Bogotá, 27 de febrero de 2004.

Eduardo Calvo





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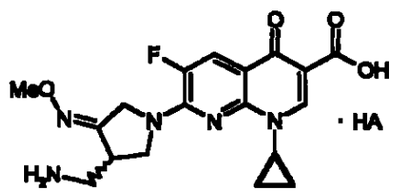
(54) Title: PROCESS FOR PREPARING ACID SALTS OF GEMIFLOXACIN

(57) Abstract: The present invention relates to a process for preparing acid salts of Gemifloxacin, a quinolone type antibiotic agent having potent antimicrobial activity. The process according to the present invention can provide advantages such as simplicity of process, improvement of productivity and improvement of yield, and the like by reducing conventional three-step process to two-step process.

Process for preparing acid salts of Gemifloxacin

TECHNICAL FIELD

This invention relates to a novel process for preparing acid salts of quinolone carboxylic acid, that is, 7-(3-aminomethyl-4-methoxyiminopyrrolidin-1-yl)- 1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (hereinafter referred to Gemifloxacin), having a potent antimicrobial activity and represented by the following formula 1:



1

wherein,

Me represents methyl,

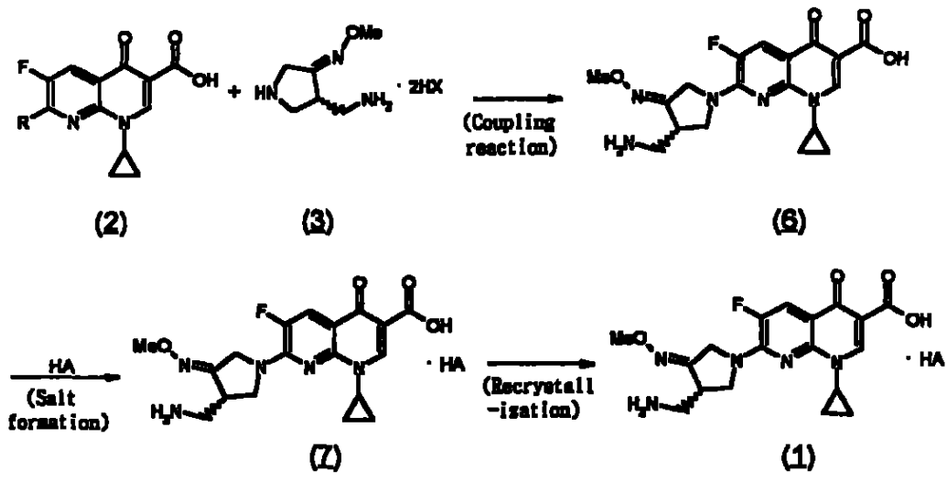
HA is an organic acid or an inorganic acid.

BACKGROUND ART

Said Gemifloxacin and its salts are compounds disclosed in Korean Patent No. 131999 to the present inventors (Korean Patent Application No. 94-13604, foreign patents corresponding to this patent: EP 688722 A1, JP Patent No. 41050/1996, Russian Patent No. 2120940, Canadian Patent No. 2151890, Chinese Patent No. 1114959, and US Patent Nos. 5962468, 5869670, 5840916, 5776944, 5698570 and 5633262). These compounds have a potent antimicrobial activity, and moreover can be effectively used as agents for treating human being or animals infected by bacteria.

The present inventors had prepared said acid salts of Gemifloxacin by a three-step reaction process, that is, a synthesis process through a coupling reaction, a salt formation, and a recrystallization, as represented by the following reaction scheme 1:

(Reaction scheme 1)



wherein,

Me represents methyl,

R represents Cl, F, Br, I, methanesulfonyl, or paratoluenesulfonyl,

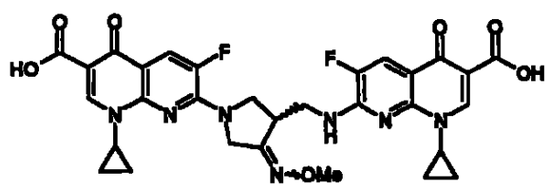
HX represents hydrochloric acid, hydrobromic acid, hydroiodic acid, trifluoroacetic acid, methanesulfonic acid, paratolunesulfonic acid, or sulfuric acid,

HA is an organic acid or an inorganic acid.

As shown in the above reaction scheme 1, the compound (1) is prepared through three-step reaction process, that is, a coupling reaction, a salt formation and a recrystallization. The reason why the three-step reaction process is carried out is because the compound (8) as impurity is formed in an amount of approximately 6-12% by a side-reaction under the coupling reaction and the compound (8) is remained in the compound (6) in an amount of approximately 0.3 to 1.0%. To remove the resulting impurity through the coupling reaction at 0.1% or less, the second step, that is a salt formation process, had to be carried out. Finally, the organic solvent used in the salt formation process had to be removed

from the step of recrystallization.

Through the three step process, an acid salt of Gemifloxacin (1) as a raw medicine having high purity was prepared in about 65% of total yield. Since the resulting impurity (8) from the coupling reaction of the above process was difficult to be removed, the salt formation and recrystallization steps for removing the impurity had to be carried out.



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DISCLOSURE OF INVENTION

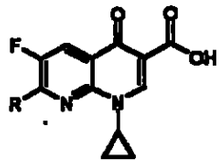
The present inventors have conducted intensive studies in view of reducing the above three-step reaction process to a two-step process. As a result, they have found that the preparing process comprising two steps below have several advantages, such as simplicity of the preparation process, improvement of productivity and increase of yield. Therefore, they have completed the present invention.

The present invention provides a process for preparing acid salts of Gemifloxacin represented by formula 1, which comprises the steps of

a) adding a compound of fomula 5 to naphthyridine carboxylic acid of formula 2 and 3-aminomethyl-4-methoxyiminopyrrolidine salt of formula 3 in water, an organic solvent or a mixed solvent thereof in the presence of an organic base to carry out a coupling reaction, and

b) adding an acid of formula HA to the resulting compound of formula 4 in water, an organic solvent or a mixed solvent thereof to carry out deprotection and salt formation

reactions at the same time:



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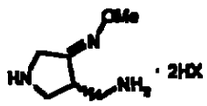

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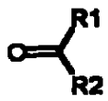

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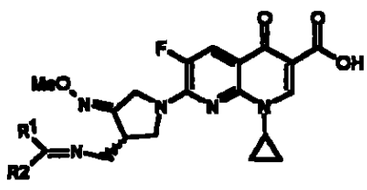

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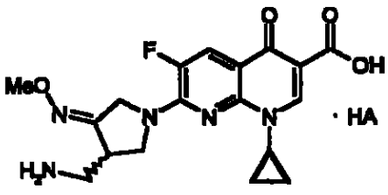


1

wherein,

R represents Cl, F, Br, I, methanesulfonyl or paratoluenesulfonyl,

Me represents methyl,

HX represents hydrochloric acid, hydrobromic acid, hydroiodic acid, trifluoroacetic acid, methanesulfonic acid, paratoluenesulfonic acid, or sulfuric acid,

R1 and R2 independently of each other represent hydrogen, a straight or branched, saturated or unsaturated $C_1 \sim C_6$ alkyl group, a saturated or unsaturated $C_3 \sim C_6$ cycloalkyl group, or an aromatic group which is unsubstituted or substituted by $C_1 \sim C_6$ alkyl, $C_1 \sim C_6$ alkoxy, hydroxy, cyano or halogen, or

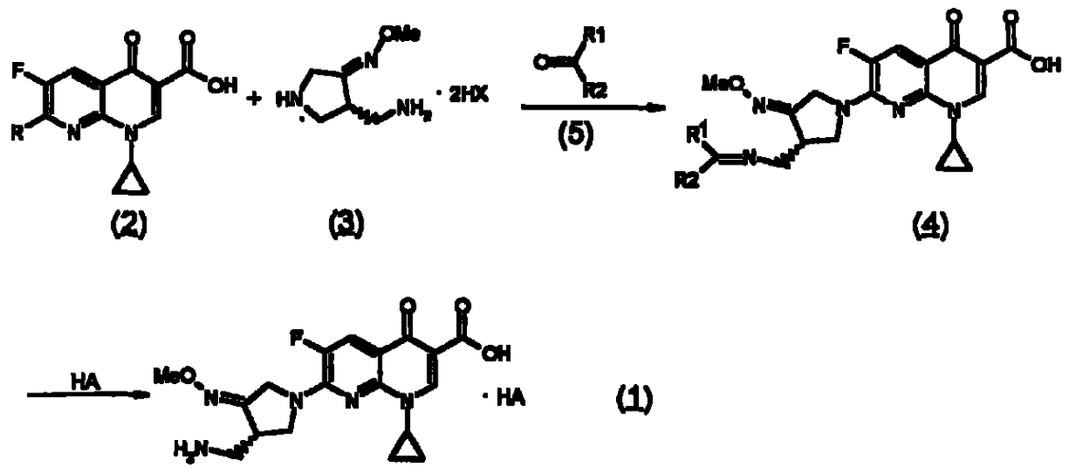
R1 and R2 together with a carbonyl group to which they are bonded form a ring, and

HA is an organic acid or an inorganic acid.

BEST MODE FOR CARRYING OUT THE INVENTION

The preparation process according to the present invention is described in detail as the following reaction scheme 2:

(Reaction scheme 2)



wherein,

Me, R, R1, R2, HX and HA are as defined above.

As shown in the above reaction scheme 2, to reduce the steps of a salt formation and a

recrystallization to one step by preventing production of impurity (8), the compound (5) having a carbonyl group may be added to the compound (3) under a coupling reaction to protect a primary amino group in the compound (3) with the compound (5). Due to this protection, production of by-product (8) may be remarkably prevented in an amount of 0.1% or less. The resultant compound (4), which is prepared from the above process in a yield of about 90% or more, is treated with an acid of formula HA to carry out deprotection and salt formation reactions by one step. By means of the above procedure omitting the step of the recrystallization reaction, an acid salt of Gemifloxacin of the compound (1) is produced in a yield of 90% or more, and the steps of the preparation process are simplified. In accordance with such a simplification of the preparation process, the following several effects can be obtained: reducing production time, improving productivity and increasing yield.

The process according to the present invention is explained as an example in detail as below:

First, the synthesis process of the compound (4) (step a) comprises dissolving the compound (3), the compound (5) and an organic base, for example triethylamine in a reaction solvent, for example a mixed solvent of acetonitrile with water, and adding the compound (2) thereto, and then reacting the resulting mixture. The reaction conditions of this reaction are as follows:

1) As a reaction solvent, water, an organic solvent, such as acetonitrile, tetrahydrofuran (THF), methanol, and ethanol, or a mixed solvent of an organic solvent with water may be used. Preferably, a mixed solvent of acetonitrile with water is advantageous in view of purity and yield.

2) As a compound (5), ketone or aldehyde compound, such as formaldehyde, acetone, benzaldehyde, 1-butylaldehyde, and the like, may be used. Preferably, benzaldehyde derivative, such as benzaldehyde, 2-hydroxybenzaldehyde, 2-chlorobenzaldehyde and

the like is advantageous in view of purity and yield. Particularly, benzaldehyde is the most advantageous in view of cost and stability. It is preferred that benzaldehye is used in an amount of the molar amount equal to or more than the molar amount of the compound (2).

3) A reaction temperature may be applied thereto in the wide range of 0℃ to 80℃. However, the most preferred temperature is in the range of 20~30℃ in view of reaction rate, yield and purity.

4) As an organic base, triethylamine, trimethylamine, diisopropylethylamine, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), DBN (1,5-diazabicyclo[4.3.0]non-5-one), as well as a number of the other bases may be used. The most suitable base is triethylamine in view of cost and yield. The amount thereof is used in 3 or more molar amount relative to the compound (2).

By carrying out the above reaction process, the compound (4) having high purity may be produced in high yield (more than 90%).

Second, the process (step b) for preparing the compound (1) from the compound (4) comprises dissolving the compound (4) in a reaction solvent, for example, a mixed solvent of isopropanol with water, heating the resultant mixture, adding an acid of formula HA, for example, methansulfonic acid, thereto to carry out deprotection and salt formation reactions at the same time, and then cooling the reaction material to prepare the compound (1) without the recrystallization step. The reaction conditions of this reaction are as follows:

1) As a reaction solvent, water, alcohol, such as isopropanol, THF, methanol, ethanol, butanol and the like, or a mixed solvent of alcohol with water may be used. Preferably, a mixed solvent of isopropanol with water is advantageous in view of purity and yield.

2) As an acid, a number of acids representing HA, such as hydrochloric acid, methanesulfonic acid, sulfuric acid, phosphoric acid, acetic acid, citric acid, tartaric acid, perhydrochloric acid, picric acid, (+)-camphor sulfonic acid and the like may be used. Particularly, methansulfonic acid is the most suitable. It is preferred that the molar amount equal to that of the compound (4) to about 20% or so of the equal molar amount is used in view of purity and yield.

3) A reaction temperature may be applied thereto in the wide range of 0℃ to 100℃. However, the reaction temperature of 40~50℃ on adding an acid and the reaction temperature of 0~20℃ after adding the acid are preferred, in view of reaction rate of the final compound (1), yield and purity.

By carrying out the above reaction process, the compound (4) having high purity may be produced in high yield (more than 90%).

As described hereinbefore, if a novel synthesis process of two steps is used, the improved effect such as simplicity of the preparation process, increase of yield (from about 65% to at least 80%), improvement of productivity, decrease of manufacturing costs and the like can be achieved by reducing three steps of conventional synthesis process to two steps. Specifically, it has an advantage that this process may be applied to quinolone type antibiotics having a similar structure to that of Gemifloxacin.

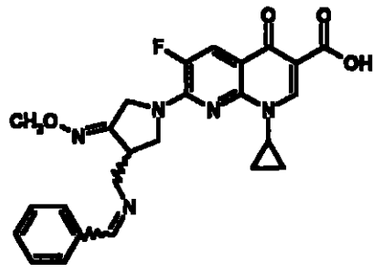
Therefore, the present invention provides an outstandingly improved technique over the prior art.

The present invention is explained in detail by means of the following examples, which are not intended to limit the scope of the invention.

EXAMPLES

Example 1.

Preparation of 7-(3-benzylidineaminomethyl-4-methoxyimino-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid



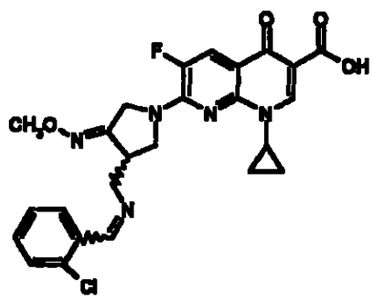
Acetonitrile (1900ml), 3-aminomethyl-4-methoxyiminopyrrolidine dimethanesulfonate (248.0g) and water(100ml) were in turn introduced into a reaction vessel and cooled to 0~5℃. Benzaldehyde (97.6g) and triethylamine (229.1g) were in turn added to the reaction mixture. After stirring the mixture for 0.5h, 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine- 3-carboxylic acid (200.0g) was introduced thereto. The resultant reaction mixture was slowly heated to room temperature, while stirring it. Then, the reaction was carried out by stirring the reaction mixture for about 3h at room temperature. The reaction material, which was formed in the form of a dispersion solution upon producing the title compound, was filtered, washed with water and acetonitrile, and then dried to prepare 320.3 g of the title compound (Yield: 94.8%).

^{1}H NMR (δ , $CDCl_3$): 8.66 (s, 1H), 8.32 (s, 1H), 7.98 (d, J=12.4Hz, 1H), 7.60 (d, J=7.0Hz, 2H), 7.37 (t, J=7.4Hz, 1H), 7.31 (t, J=7.4Hz, 2H), 4.58 (s, 2H), 4.21~4.15 (m, 2H), 4.00 (m, 1H), 3.93 (s, 3H), 3.83 (m, 1H), 3.56 (m, 1H), 3.40 (m, 1H), 1.21 (m, 2H), 1.00 (m, 2H)

Mass (FAB): 478 (M+H)

Exampe 2.

Preparation of 7-[3-(2-chlorobenzylidine)aminomethyl-4-methoxyimino-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphtyridine-3-carboxylic acid



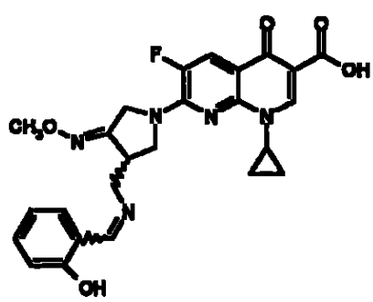
Acetonitrile (100ml), 3-aminomethyl-4-methoxyiminopyrrolidine dimethanesulfonate (12.5g), 2-chlorobenzaldehyde (10.0g) and triethylamine (12.2g) were in turn introduced into a reaction vessel at room temperature. After stirring the mixture for about 0.5h, 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8- naphthyridine-3-carboxylic acid (10.0g) was introduced thereto. The resultant reaction mixture was stirred for about 15h at room temperature, cooled to 0~5℃, and stirred for about 3h. The title compound in the form of solid was filtered, washed with acetonitrile, and dried to prepare 16.3g of the title compound (Yield: 90.0%).

^{1}H NMR (δ , $CDCl_3$): 8.74 (s, 1H), 8.66 (s, 1H), 7.96 (d, J=12.4Hz, 1H), 7.84 (d, J=7.3Hz, 1H), 7.29 (m, 2H), 7.16 (m, 1H), 4.59 (bs, 2H), 4.18 (m, 2H), 4.02 (m, 1H), 3.94 (s, 3H), 3.93 (m, 1H), 3.59 (m, 1H), 3.42 (m, 1H), 1.22 (m, 2H), 1.01 (m, 2H)

Mass (FAB): 512 (M+H)

Example 3.

Preparation of 7-[3-(2-hydroxybenzylidine)aminomethyl-4-methoxyimino-1- pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid



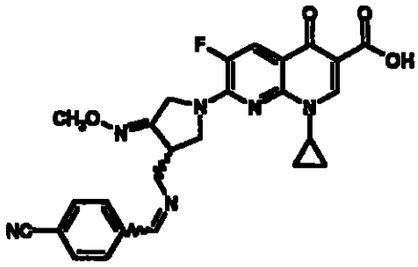
Acetonitrile (100ml), 3-aminomethyl-4-methoxyiminopyrrolidine dimethanesulfonate (12.5g), 2-hydroxybenzaldehyde (8.6g) and triethylamine (12.2g) were in turn introduced into a reaction vessel at room temperature. After stirring the mixture for about 0.5h, 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8- naphthyridine-3-carboxylic acid (10.0g) was introduced thereto. The resultant reaction mixture was stirred for about 15h at room temperature, cooled to 0~5℃, and stirred for about 3h. The title compound in the form of solid was filtered, washed with acetonitrile, and dried to prepare 16.0 g of the title compound (Yield: 91.8%).

^{1}H NMR (δ , $CDCl_3$): 8.68 (s, 1H), 8.42 (s, 1H), 8.01 (d, J=12.4Hz, 1H), 7.30~7.20 (m, 3H), 6.90~6.82 (m, 2H), 4.68~4.53 (m, 2H), 4.32~4.24 (m, 1H), 4.06 (dd, J1=11.9Hz, J2=5.5Hz, 1H), 4.02~3.85 (m, 3H), 3.95 (s, 3H), 3.60 (m, 1H), 3.40 (m, 1H), 1.29~1.21 (m, 2H), 1.07~1.00 (m, 2H)

Mass (FAB): 494 (M+H)

Example 4.

Preparation of 7-[3-(4-cyanobenzylidine)aminomethyl-4-methoxyimino-1- pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid



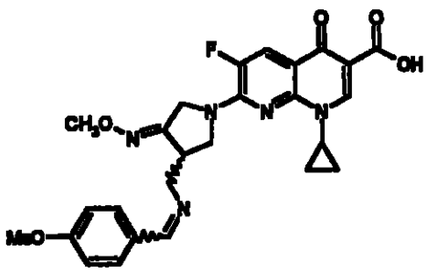
In accordance with the procedure and scale as described in Examples 2 and 3, 14.6 g of the title compound was prepared by using 4-cyanobenzalehyde (9.3 g) (Yield: 82.2%).

^{1}H NMR (δ , $CDCl_3$): 8.66 (s, 1H), 8.40 (s, 1H), 7.99 (d, J=12.4Hz, 1H), 7.80 (d, J=8.3Hz, 2H), 7.67 (d, J=8.3Hz, 2H), 4.59 (m, 2H), 4.30 (m, 1H), 4.08 (m, 2H), 3.92 (s, 3H), 3.90

(m, 1H), 3.61 (m, 1H), 3.45 (m, 1H), 1.24 (m, 2H), 1.05 (m. 2H)
Mass (FAB): 503 (M+H)

Example 5.

Preparation of 7-[3-(4-methoxybenzylidine)aminomethyl-4-methoxylimino-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid

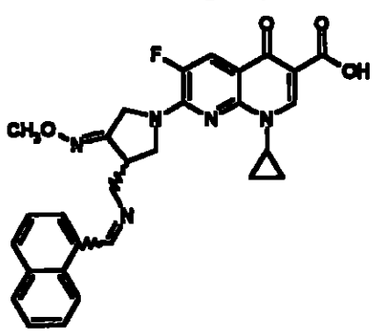


In accordance with the procedure and scale as described in Examples 2 and 3, 14.4 g of the title compound was prepared by using 4-methoxybenzaldehyde (9.6g) (Yield: 80.2%).

^{1}H NMR (δ , $CDCl_3$): 8.66 (s, 1H), 8.22 (s, 1H), 7.96 (d, J=12.4Hz , 1H), 7.52 (d, J=8.7Hz, 2H), 6.79 (d, J=8.3Hz, 2H), 4.59 (m, 2H), 4.16 (bs, 2H), 3.93 (s, 3H), 3.92 (m, 1H), 3.83 (m, 1H), 3.79 (s, 3H), 3.56 (m, 1H), 3.38 (m, 1H), 1.22 (m, 2H), 1.00 (m, 2H)
Mass (FAB): 508 (M+H)

Example 6.

Preparation of 7-[3-(1-naphthylidine)aminomethyl-4-methoxyimino-1- pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid



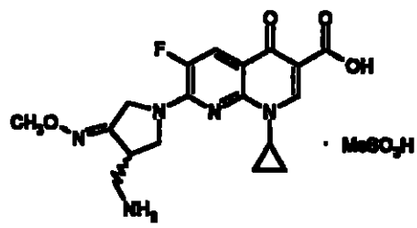
Acetonitrile (100ml), 3-aminomethyl-4-methoxyiminopyrrolydine dimethanesulfonate (12.5g) and 1-naphthaldehyde (11.1g) were in turn introduced into a reaction vessel at room temperature and cooled to 0~5℃. Triethylamine (12.2g) was dropwise added to the reaction mixture. After stirring the mixture for about 0.5h, the reaction mixture was diluted by adding ethanol (30ml). 7-Chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (10.0g) was introduced to the reaction mixture. After raising slowly the reaction temperature to room temperature, the reaction mixture was stirred for about 15h. The title compound in the form of solid was filtered, washed with water and ethanol, and dried to prepare 15.7 g of the title compound (Yield: 84.4%).

^{1}H NMR (δ , $CDCl_3$): 8.86 (m, 2H), 8.55 (s, 1H), 7.82 (m, 3H), 7.73 (m, 1H), 7.40 (m, 3H), 4.60 (m, 2H), 4.24 (m, 2H), 4.08 (m, 1H), 3.99 (m, 1H), 3.95 (s, 3H), 3.45 (m, 2H), 1.13 (m, 2H), 0.89 (m, 2H)

Mass (FAB): 528 (M+H)

Example 7.

Preparation of methanesulfonic acid salt of 7-(aminomethyl-4- methoxyimino-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid



Water (60ml), the compound (30.0g) synthesized in Example 1 and isopropanol (210ml) were in turn introduced into a reaction vessel, and heated to 40~45℃. Methanesulfonic acid (6.22g) was dropwise added to the reaction mixture. After stirring the reaction mixture for about 0.5h at a temperature of 40~45℃, it was cooled to 27~35℃. The

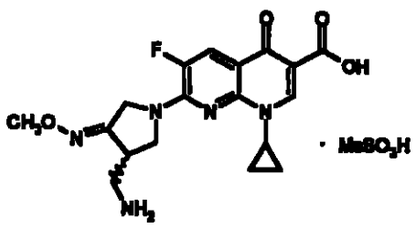
compound (1)(0.03g) was added to the reaction mixture. The reaction mixture was slowly cooled to room temperature and stirred for about 17h to precipitate the title compound in the form of solid. The reaction mixture in the form of dispersion solution was cooled to -1~1℃, stirred for about 3h, filtered, washed with isopropanol, dried and absorbed to prepare 29.0 g of the title compound (Yield: 95.1%).

^{1}H NMR (δ , DMSO-d_6): 8.59 (s, 1H), 8.06 (d, J=12.4Hz, 1H), 4.58 (bs, 2H), 4.37 (m, 1H), 3.90 (s, 3H), 3.83 (bs, 1H), 3.71 (m, 1H), 3.40 (m, 1H), 3.24~3.10 (m, 2H), 2.32 (s, 3H), 1.20~1.05 (m, 2H), 1.03~1.02 (m, 2H)

Mass (FAB): 486 (M+H)

Example 8.

Preparation of methanesulfonic acid salt of 7-(aminomethyl-4-methoxyimino- 1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid



The title compound was prepared in yield of 91.7% in accordance with the procedure as described in Example 7, except that THF (240ml) was used instead of isopropanol(210ml), and methansulfonic acid was used in the amount of 6.04g instead of 6.22g.

INDUSTRIAL AVAILABILITY

If the novel synthesis process of two steps according to the present invention is used, the improved effect such as simplicity of the preparation process, increase of yield, improvement of productivity, decrease of manufacturing costs and the like can be achieved

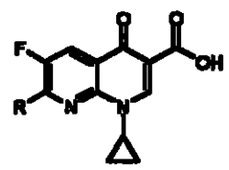
by reducing conventional three-step synthesis process to two-step process.

Claims

1. A process for preparing acid salts of Gemifloxacin represented by formula 1, which comprises the steps of

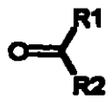
a) adding a compound of formula 5 to naphthyridine carboxylic acid of formula 2 and 3-aminomethyl-4-methoxyiminopyrrolidine salt of formula 3 in water, an organic solvent or a mixed solvent thereof in the presence of an organic base to carry out a coupling reaction, and

b) adding an acid of formula HA to the resulting compound of formula 4 in water, an organic solvent or a mixed solvent thereof to carry out deprotection and salt formation reactions at the same time:

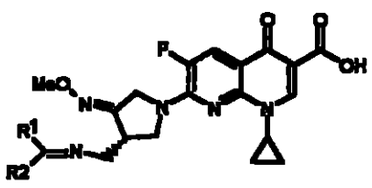


2

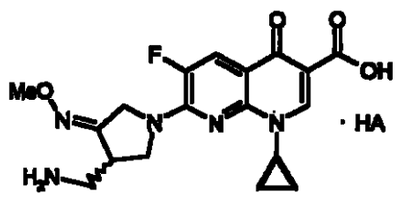
3



5



4



1

wherein,

R represents Cl, F, Br, I, methanesulfonyl or paratoluenesulfonyl,

Me represents methyl,

HX represents hydrochloric acid, hydrobromic acid, hydroiodic acid, trifluoroacetic acid, methanesulfonic acid, paratolunesulfonic acid, or sulfuric acid,

R1 and R2 independently of each other represent hydrogen, a straight or branched, saturated or unsaturated $C_1 \sim C_6$ alkyl group, a saturated or unsaturated $C_3 \sim C_6$ cycloalkyl group, or an aromatic group which is unsubstituted or substituted by $C_1 \sim C_6$ alkyl, $C_1 \sim C_6$ alkoxy, hydroxy, cyano or halogen, or

R1 and R2 together with a carbonyl group to which they are bonded form a ring, and

HA is an organic acid or an inorganic acid.

2. The process of claim 1, wherein step a), step b) or both steps a) and b) are carried out in a mixed solvent of an organic solvent with water.

3. The process of claim 1, wherein the compound of formula 5 is selected from the group consisting of benzaldehyde, 2-chlorobenzaldehyde, 2-hydroxybenzaldehyde, 4-methoxybenzaldehyde and 2-methylbenzaldehyde.

4. The process of claim 2, wherein the organic solvent of step a) is acetonitrile, and that of step b) is isopropanol or tetrahydrofuran (THF).

5. The process of claim 1, wherein the organic base is selected from the goup consisting of triethylamine, trimethylamine, diisopropylethylamine, 1,8-diazabicyclo

[5.4.0]undec-7-ene, and 1,5-diazabicyclo[4.3.0]non-5-one.

6. The process of claim 1, wherein the compound of formula 5 is used in an amount of 1 to 3 times to that of the compound of formula 2.

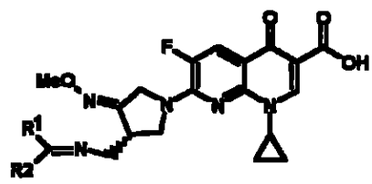
7. The process of claim 1, wherein the organic base of step a) is used in an amount of 3 to 4 times to that of the compound of formula 2, and the reaction is carried out at a reaction temperature of 0 to 30℃.

8. The process of claim 7, wherein the organic base is triethylamine.

9. The process of claim 1, wherein the acid of formula HA is used in an amount of 80mol% to 120mol% relative to the compound of formula 4, the temperature on adding the acid is in the range of 40~50℃, and the temperature after adding the acid is in the range of 0~20℃.

10. The process of any one of claims 1-9, wherein the acid of formula HA is methanesulfonic acid.

11. An intermediate, represented by the following formula 4, for preparing acid salts of Gemifloxacin according to claim 1:



4

wherein,

Me, R1 and R2 are as defined in claim 1.

INTERNATI NAL SEARCH REPORT

International application No.
PCT/KR03/00683

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07D 471/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC7 C07D 471/04, A61K 31/47, C07D 207/22

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
stn on line. pubmed on line

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5869670 A (LG Chemicls Ltd.) 9 Feb. 1999 see the whole document	1
A	WO 98/42705 A1 (LG Chemicls Ltd.) 01 Oct. 1998 see the whole document	1
A	WO 2001/018002 A1 (Sb Pharmco Puerto Rico Inc. et al.) 15 Mar. 2001 see pages 1-2	1
A	WO 99/44991 A1 (LG Chemicls Ltd.) 10 Sep.1999 see pages 10-14	1
A	Grau, A et al. 'Fluoronaphthyridinecarboxylic acid antibacterial'; In Drugs of the Future (1998), 23(11), 1199-1204	1

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 AUGUST 2003 (22.08.2003)	25 AUGUST 2003 (25.08.2003)
Name and mailing address of the ISA/KR Korean Intellectual Property Office 920 Dunsan-dong, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140	Authorized officer CHO, Hae Won Telephone No. 82-42-481-5607

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATI NAL SEARCH REPORT

International application No.
PCT/KR03/00683

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 2001/018002 A1	15/03/2001	BR 2000013751	A	07/05/2002
		EP 1214321	A1	19/06/2002
		JP 2003/508532	T2	04/03/2003
		GB 1999/20917	A	03/09/1999
WO 99/44991 A1	10/09/1999	ZA 9901663	A	06/09/1999
		TW 453993	B	11/09/2001
		CA 2322540	AA	10/09/1999
		AU 9926433	A1	20/09/1999
		AU 742497	B2	03/01/2002
		EP 1068182	A1	17/01/2001
		JP 3374155	B2	04/02/2003
		NZ 506312	A	26/04/2002
		NO 2000004288	A	25/10/2000
		US 6307059	B1	23/10/2001
US 5869670 A	09/02/1999	KR 131999	B1	17/04/1998
		CN 1114959	A	17/01/1996
		CN 1058010	B	01/11/2000
		US 5633262	A	27/05/1997
		RU 2120940	C1	27/10/1998
		US 5776944	A	07/07/1998
		US 5962468	A	05/10/1999
WO 98/42705 A1	01/10/1998	ZA 9802335	A	23/11/1999
		AU 9866366	A1	20/10/1998
		AU 726634	B2	16/11/2000
		EP 981527	A1	01/03/2000
		EP 981527	B1	07/05/2003
		NZ 337748	A	30/03/2001
		CZ 288673	B6	15/08/2001
		EP 1179533	A2	13/02/2002

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PC03003-LG	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/KR2003/000683	International filing date *(day/month/year)* 04 APRIL 2003 (04.04.2003)	Priority date *(day/month/year)* 08 APRIL 2002 (08.04.2002)

International Patent Classification (IPC) or national classification and IPC

IPC7 C07D 471/04

Applicant

LG LIFE SCIENCES LTD. et al

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14 OCTOBER 2003 (14.10.2003)	22 JUNE 2004 (22.06.2004)
Name and mailing address of the IPEA/KR Korean Intellectual Property Office 920 Dunsan-dong, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140	Authorized officer KIM, KYOUNG MI Telephone No. 82-42-481-8161

Form PCT/IPEA/409 (cover sheet) (July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International aplication No.
PCT/KR2003/000683

I. Basis of the report

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

- [X] the international application as originally filed
- [ ] the description:
  - pages _____, as originally filed
  - pages _____, filed with the demand
  - pages _____, filed with the letter of _____
- [ ] the claims:
  - pages _____, as originally filed
  - pages _____, as amended (together with any statment) under Article 19
  - pages _____, filed with the demand
  - pages _____, filed with the letter of _____
- [ ] the drawings:
  - pages _____, as originally filed
  - pages _____, filed with the demand
  - pages _____, filed with the letter of _____
- [ ] the sequence listing part of the description:
  - pages _____, as originally filed
  - pages _____, filed with the demand
  - pages _____, filed with the letter of _____

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

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

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

- [ ] contained inthe international application in written form.
- [ ] filed together with the international application in computer readable form.
- [ ] furnished subsequently to this Authority in written form.
- [ ] furnished subsequently to this Authority in computer readable form
- [ ] The statement that the subsequently furnished written sequence listing does not go beyond the disc losure in the international applicationas as filed has been furinshed.
- [ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. [ ] The amendments have resulted in the cancellation of:
   - [ ] the description, pages _____
   - [ ] the claims, Nos. _____
   - [ ] the drawings, sheet _____

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

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

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

INTERNATIONAL PRELIMINARY EXAMINATION

International aplication No.
PCT/KR2003/000683

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

1. Statement

Novelty (N)	Claims	1-11	YES
	Claims		NO
Inventive step (IS)	Claims	1-11	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-11	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The following documents are referred to in this report: the numbering will be adhered to in the rest of the procedure:

D1: US 5869670 A (Feb. 8, 1999)
D2: WO 0118002 A1 (March 15, 2001)
D3: WO 9944991 A1 (Sep. 10, 1999)

1. Novelty

The present invention relates to a method for producing acid salt of gemifloxacin and an intermediate thereof.

The preparation process of Claims 1-10 is novel over D1-D3 since none of the prior art discloses the preparation method for acid salt of gemifloxacin via an intermediate of Formula 4.

Although the compound of Formula 4 has structural similarity to Formula (I) in D1, it differs in an amino-protecting group from Formula (I) in D1. Therefore, the novelty can be acknowledged for the subject matter of Claim 11 [PCT Article 33(2)].

2. Inventive step

D1 and D2 disclose a process of conjugating a naphthyridine carboxylic acid and 3-amiomethyl-4-methoxyiminopyrrolidine (Formula 2 and 3, respectively in the present invention).

In the present invention, the coupling reaction of Formula 2 with Formula 3 and the protection of amino-group are simultaneously preformed, which prevents the production of a by-product. The invention is not considered to be obvious to a person skilled in the art. Furthermore, the present process has advantages of high yield, short reaction time and being purified without recrystallization. Therefore, the subject-matter of Claims 1-10 is considered to involve an inventive step.

(Continued on Supplemental Box)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International aplication No.
PCT/KR2003/000683

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

Continuation of:

Box V.

The subject matter of Claim 11 is also inventive since the compound of Formula 4 is an intermediate compound for the preparation method of Claims 1-10, which is inventive [PCT Article 33(3)].

3. Industrial applicability
The subject-matter of Claims 1-11 appears to be industrially applicable [PCT Article 33(4)].

37

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

IPEA/ KR

PCT

CHAPTER II

DEMAND

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

For International Preliminary Examining Authority use only	
Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference
		PC03003-LG
International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/KR03/00683	4 APRIL 2003(04.04.2003)	8 APRIL 2002(08.04.2002)

Title of invention

PROCESS FOR PREPARING ACID SALTS OF GEMIFLOXACIN

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*	Telephone No.
LG LIFE SCIENCES LTD. LG Twin Tower, East Tower 20, Yoido-dong, Youngdungpo-ku, 150-010 Seoul Republic of Korea	82-42-866-2075
	Facsimile No. 82-42-862-0332
	Teleprinter No.
	Applicant's registration No. with the Office

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
KR	KR

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

CHOI, Hoon
R&D Park, LG Life Sciences Ltd., 104-1
Moongi-dong, Yuseong-gu, 305-380 Taejeon

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
KR	KR

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

CHOI, Sang-Chul
R&D Park, LG Life Sciences Ltd., 104-1
Moongi-dong, Yuseong-gu, 305-380 Taejeon
Republic of Korea

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
KR	KR

[X] Further applicants are indicated on a continuation sheet.

Sheet No. 2

International application No.
PCT/KR03/00683

Continuation of Box No. II APPLICANT(S)

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

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

NAM, Do-Hyun
R&D Park, LG Life Sciences Ltd.,104-1
Moongi-dong, Yuseong-gu, 305-380 Taejeon
Republic of Korea

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
KR	KR

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

CHOI, Bo-Seung
R&D Park, LG Life Sciences Ltd.,104-1
Moongi-dong, Yuseong-gu, 305-380 Taejeon
Republic of Korea

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
KR	KR

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

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

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

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

☐ Further applicants are indicated on another continuation sheet.

Sheet No. 3

International application No.
PCT/KR03/00683

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

The following person is [X] agent [ ] common representative

and [X] has been appointed earlier and represents the applicant(s) also for international preliminary examination.

[ ] is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

[ ] is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

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

CHOI, Kyu-Pal
Halla Classic Building 4F.,
824-11, Yeoksam-dong, Kangnam-ku,
135-080 Seoul, Republic of Korea

Telephone No.
82-2-555-6888

Facsimile No.
82-2-555-9888

Teleprinter No.

Agent's registration No. with the Office

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

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

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

[X] the international application as originally filed

the description [ ] as originally filed
[ ] as amended under Article 34

the claims [ ] as originally filed
[ ] as amended under Article 19 (together with any accompanying statement)
[ ] as amended under Article 34

the drawings [ ] as originally filed
[ ] as amended under Article 34

2. [ ] The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. [ ] The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

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

Language for the purposes of international preliminary examination: English

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

Box No. V ELECTION OF STATES

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

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

International application No.
PCT/KR03/00683

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:			For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:	sheets	☐	☐
2. amendments under Article 34	:	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5. letter	:	sheets	☐	☐
6. other *(specify)*	:	sheets	☐	☐

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

1. [X] fee calculation sheet
2. ☐ original separate power of attorney
3. ☐ original general power of attorney
4. ☐ copy of general power of attorney; reference number, if any:
5. ☐ statement explaining lack of signature
6. ☐ sequence listings in computer readable form
7. ☐ tables in computer readable form related to sequence listings
8. ☐ other *(specify)*:

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

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

CHOI. Kyu-Pal

For International Preliminary Examining Authority use only

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

For International Bureau use only

Demand received from IPEA on:

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
PC03003-LG		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/KR03/00683	04 APRIL 2003 (04.04.2003)	08 APRIL 2002 (08.04.2002)

Applicant

LG LIFE SCIENCES LTD. et al

This International search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

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

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequenlty furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (See Box II).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawing to be published with the abstract is Figure No. none

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR03/00683

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07D 471/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC7 C07D 471/04, A61K 31/47, C07D 207/22

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
stn on line. pubmed on line

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5869670 A (LG Chemicla Ltd.) 9 Feb. 1999 see the whole document	1
A	WO 98/42705 A1 (LG Chemicla Ltd.) 01 Oct. 1998 see the whole document	1
A	WO 2001/018002 A1 (Sb Pharmco Puerto Rico Inc. et al.) 15 Mar. 2001 see pages 1-2	1
A	WO 99/44991 A1 (LG Chemicla Ltd.) 10 Sep.1999 see pages 10-14	1
A	Graul, A et al. 'Fluoronaphthyridinecarboxylic acid antibacterial'; In Drugs of the Future (1998), 23(11), 1199-1204	1

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 AUGUST 2003 (22.08.2003)	25 AUGUST 2003 (25.08.2003)

Name and mailing address of the ISA/KR
Korean Intellectual Property Office
920 Dunsan-dong, Seo-gu, Daejeon 302-701,
Republic of Korea
Facsimile No. 82-42-472-7140

Authorized officer
CHO, Hee Won
Telephone No. 82-42-481-5607

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR03/00683

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 2001/018002 A1	15/03/2001	BR 2000013751	A	07/05/2002
		EP 1214321	A1	19/06/2002
		JP 2003/508532	T2	04/03/2003
		GB 1999/20917	A	03/09/1999
WO 99/44991 A1	10/09/1999	ZA 9901663	A	06/09/1999
		TW 453993	B	11/09/2001
		CA 2322540	AA	10/09/1999
		AU 9926433	A1	20/09/1999
		AU 742497	B2	03/01/2002
		EP 1068182	A1	17/01/2001
		JP 3374155	B2	04/02/2003
		NZ 506312	A	26/04/2002
		NO 2000004288	A	25/10/2000
		US 6307059	B1	23/10/2001
US 5869670 A	09/02/1999	KR 131999	B1	17/04/1998
		CN 1114959	A	17/01/1996
		CN 1058010	B	01/11/2000
		US 5633262	A	27/05/1997
		RU 2120940	C1	27/10/1998
		US 5776944	A	07/07/1998
		US 5962468	A	05/10/1999
WO 98/42705 A1	01/10/1998	ZA 9802335	A	23/11/1999
		AU 9866366	A1	20/10/1998
		AU 726634	B2	16/11/2000
		EP 981527	A1	01/03/2000
		EP 981527	B1	07/05/2003
		NZ 337748	A	30/03/2001
		CZ 288673	B6	15/08/2001
		EP 1179533	A2	13/02/2002

PCT REQUEST

PC03003-LG

Original (for SUBMISSION) - printed on 04.04.2003 02:45:59 PM

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.01.2003)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	Korean Intellectual Property Office (RO/KR)
0-7	Applicant's or agent's file reference	PC03003-LG
I	Title of invention	PROCESS FOR PREPARING ACID SALTS OF GEMIFLOXACIN
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	LG LIFE SCIENCES LTD.
II-5	Address:	LG Twin Tower, East Tower 20, Yoido-dong, Youngdungpo-ku 150-010 Seoul Republic of Korea
II-6	State of nationality	KR
II-7	State of residence	KR
II-8	Telephone No.	82-42-866-2075
II-9	Facsimile No.	82-42-862-0332
II-10	e-mail	june_lee@lgls.co.kr
III-1	Applicant and/or inventor	
III-1-1	This person is:	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	CHOI, Hoon
III-1-5	Address:	R&D Park, LG Life Sciences Ltd. 104-1, Moongi-dong, Yuseong-gu 305-380 Taejeon Republic of Korea
III-1-6	State of nationality	KR
III-1-7	State of residence	KR

PCT REQUEST PC03003-LG

Original (for SUBMISSION) - printed on 04.04.2003 02:45:59 PM

III-2	Applicant and/or inventor	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	CHOI, Sang-Chul
III-2-5	Address:	R&D Park, LG Life Sciences Ltd. 104-1, Moongi-dong, Yuseong-gu 305-380 Taejeon Republic of Korea
III-2-6	State of nationality	KR
III-2-7	State of residence	KR
III-3	Applicant and/or inventor	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	NAM, Do-Hyun
III-3-5	Address:	R&D Park, LG Life Sciences Ltd. 104-1, Moongi-dong, Yuseong-gu 305-380 Taejeon Republic of Korea
III-3-6	State of nationality	KR
III-3-7	State of residence	KR
III-4	Applicant and/or inventor	
III-4-1	This person is:	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	CHOI, Bo-Seung
III-4-5	Address:	R&D Park, LG Life Sciences Ltd. 104-1, Moongi-dong, Yuseong-gu 305-380 Taejeon Republic of Korea
III-4-6	State of nationality	KR
III-4-7	State of residence	KR
IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	CHOI, Kyu-Pal
IV-1-2	Address:	Halla Classic Building 4F., 824-11, Yeoksam-dong, Kangnam-ku 135-080 Seoul Republic of Korea
IV-1-3	Telephone No.	82-2-555-6888
IV-1-4	Facsimile No.	82-2-555-9888
IV-1-5	e-mail	hansung@hsip.co.kr

PCT REQUEST PC03003-LG

Original (for SUBMISSION) - printed on 04.04.2003 02:45:59 PM

V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT SE SI SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
V-5	Precautionary Designation Statement In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-6	Exclusion(s) from precautionary designations	NONE
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	08 April 2002 (08.04.2002)
VI-1-2	Number	2002-18847
VI-1-3	Country	KR

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PCT REQUEST PC03003-LG

Original (for SUBMISSION) - printed on 04.04.2003 02:45:59 PM

VII-1	International Searching Authority Chosen	Korean Intellectual Property Office (KIPO) (ISA/KR)	
VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	5	-
IX-2	Description	15	-
IX-3	Claims	3	-
IX-4	Abstract	1	E2ABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	24	
	Accompanying Items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-9	Original separate power of attorney	✓	-
IX-11	Copy of general power of attorney	✓	-
IX-13	Priority document(s)	Item(s) VI-1	-
IX-17	PCT-EASY diskette	-	Diskette
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Name (LAST, First)	CHOI, Kyu-Pal	

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	

PCT REQUEST PC03003-LG

Original (for SUBMISSION) - printed on 04.04.2003 02:45:59 PM

10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/KR
10-6	Transmittal of search copy delayed until search fee is paid	

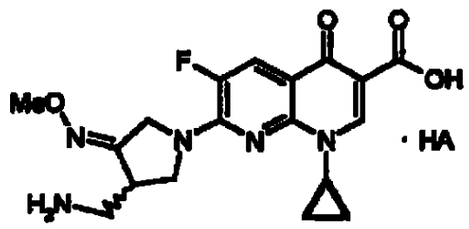
FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	

PROCESO PARA PREPARAR SALES ÁCIDAS DE GEMIFLOXACINA

CAMPO TÉCNICO

Esta invención se relaciona con un proceso novedoso para preparar salles ácidas de ácido quinolona carboxílico, este es, ácido 7-(3-aminometil-4-metoxiiminopirrolidin-1-il)-1-ciclopropil-6-fluoro-4-oxo-1,4-dihidro-1,8-naftiridina-3-carboxílico (en lo sucesivo denominado Gemifloxacina, que tiene una actividad antimicrobiana potente y esta representada por la siguiente fórmula 1:



1

En donde,

Me representa metil,

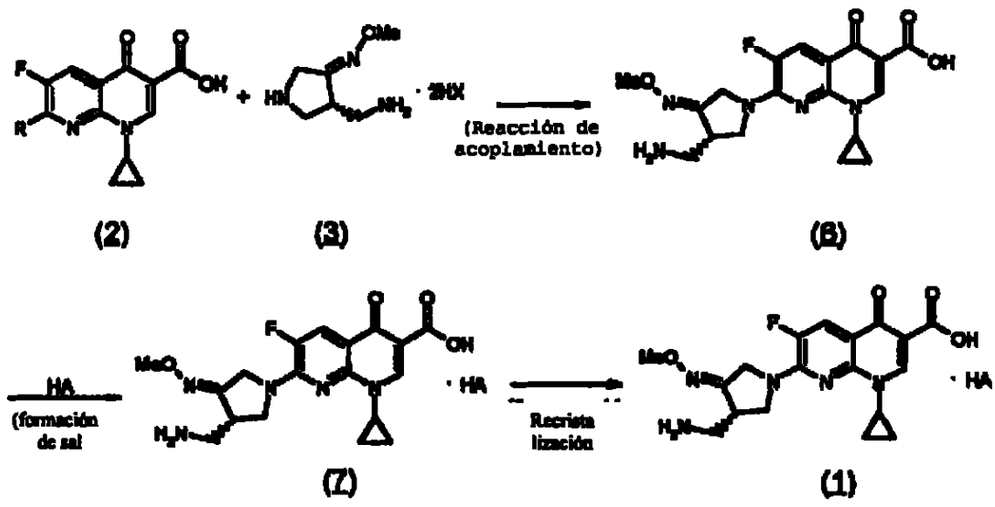
HA es un ácido orgánico o un ácido inorgánico

TÉCNICA ANTERIOR

Dicha Gemifloxacina y sus sales son compuestos descritos en la Patente Coreana No. 131999 de los presentes inventores (solicitud de Patente Coreana No. 94-13604, Patentes extranjeras que corresponden a esta Patente: EP 688722 A1, Patente JP No. 41050/1996, Patente Rusa No. 2120940, Patente Canadiense No. 2151890, Patente China No. 1114959, y Patente Estadounidense No. 5962468, 5869670, 5840916, 5776944, 5698570 y 5633262). Estos compuestos tienen potente actividad antimicrobiana y más aún pueden ser efectivamente utilizados como agentes para tratar seres humanos o animales infectados por bacterias.

Los presentes inventores habían preparado dichas sales ácidas de Gemifloxacina mediante un proceso de reacción de tres etapas, esto es, un proceso de síntesis a través de una reacción de acoplamiento, una formación de sal, y una recristalización, representada mediante el siguiente esquema de reacción 1:

(Esquema de reacción 1)



En donde,

Me representa metilo

R representa CL, F, Br, y metanosulfonilo, o paratoluenosulfonilo,

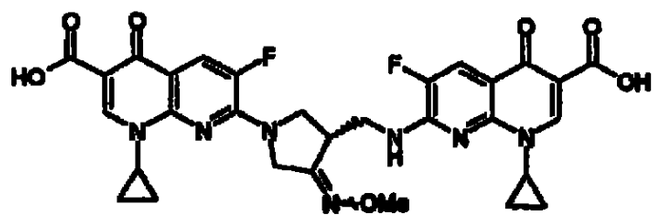
HX representa ácido clorhídrico, ácido bromhídrico, ácido yodídrico, ácido trifluoroacético, ácido metanosulfónico, ácido paratoluenosulfónico, o ácido sulfúrico,

HA es un ácido orgánico o un ácido inorgánico.

Como se muestra en el esquema de reacción anterior 1, el compuesto (1) se prepara a través de un proceso de reacción de tres etapas, esto es, una reacción de acoplamiento, una formación de sal y una recristalización. La razón de porqué este proceso de

reacción de tres etapas es llevado a cabo es porque el compuesto (8) como impureza se forma en una cantidad de aproximadamente 6-12% mediante una reacción lateral bajo la reacción de acoplamiento y el compuesto (8) permanece en el compuesto (&) en una cantidad de aproximadamente 0,3 a 1,0%. Para remover la impureza resultante a través de la reacción de acoplamiento en 0,1% o menos la segunda etapa, esto es el proceso de formación de sal, ha sido llevada a cabo. Finalmente, el solvente orgánico utilizado en el proceso de formación de sal tenía que ser removido de la etapa de recristalización.

A través del proceso de tres etapas, una sal ácida de Gemifloxacina (1) como medicina materia prima que tiene una alta pureza era preparada con aproximadamente el 65% de rendimiento total. En razón a que la impureza resultante (8) de la reacción de acoplamiento del proceso anterior era difícil de ser removida, la formación de sal y las etapas de recristalización para remover la impureza tenían que ser llevadas a cabo.



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DESCRIPCIÓN DE LA INVENCIÓN

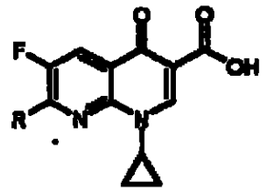
Los presentes inventores han conducido estudios intensivos con el fin de reducir el proceso de reacción de tres etapas anterior a un proceso de dos etapas. Como resultado, ellos han encontrado que el proceso de preparación que comprende las dos etapas anteriores tiene varias ventajas, tales como simplicidad del proceso de preparación, mejora de la productividad e incremento del rendimiento. Por lo tanto, ellos han completado la presente invención.

La presente invención suministra un proceso para preparar sales ácidas de Gemifloxacina representadas por la fórmula 1, que comprende las etapas de

57

a) agregar un compuesto de fórmula 5 al ácido naftiridino carboxílico de fórmula 2 y sal 3-aminometil-4-metoxiiminopirrolidona de fórmula 3 en agua, un solvente orgánico o un solvente mezclado de este en la presencia de una base orgánica para llevar a cabo una reacción de acoplamiento, y

b) agregar un ácido de fórmula HA al compuesto resultante de fórmula 4 en agua, un solvente orgánico o un solvente mezclado de este para llevar a cabo la desprotección y las reacciones de formación de sal al mismo tiempo:



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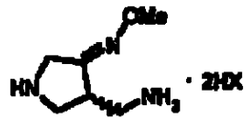
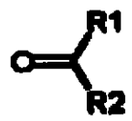


3

55



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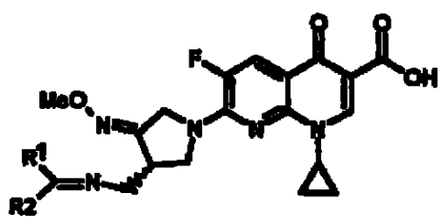
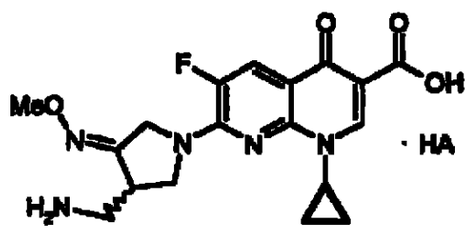


4



1

En donde,

R representa Cl, F, Br, I, metanosulfonilo o paratoluenosulfonilo,

Me representa metilo,

HX representa ácido clorhídrico, ácido bromhídrico, ácido yodídrico, ácido trifluoroacético, ácido metanosulfónico, ácido paratoluenosulfónico, o ácido sulfúrico,

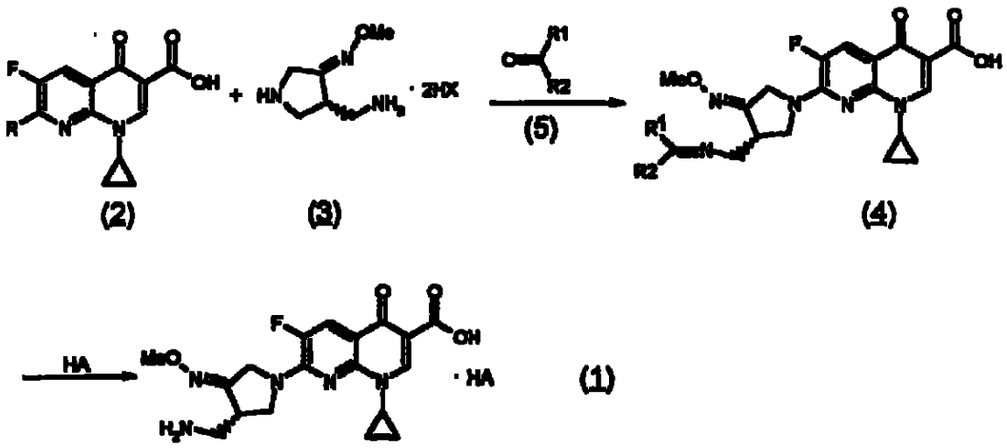
R1 y R2 independientemente uno del otro representan hidrógeno, un grupo alquilo C_1-C_6 recto o ramificado, saturado o insaturado, un grupo cicloalquilo C_3-C_6 saturado o insaturado, o un grupo aromático que es no sustituido o sustituido por alquilo C_1-C_6, alcoxi C_1-C_6, hidroxi ciano o halógeno, o

R1 y R2 juntos con un grupo carbonilo al cual ellos están unidos forman un anillo, y HA es un ácido orgánico o un ácido inorgánico.

MEJOR MODO DE LLEVAR A CABO LA INVENCIÓN

El proceso de preparación de acuerdo con la presente invención se describe en detalle como el siguiente esquema de reacción 2:

(Esquema de reacción 2)



En donde,

Me, R, R1, R2, HX, y HA son como se definió anteriormente.

Como se muestra en el esquema de reacción anterior 2, para reducir las etapas de una formación de sal y una recristalización a una etapa al evitar la producción de impurezas (8), el compuesto (5) que tiene el grupo carbonilo se puede agregar al compuesto (3) bajo una reacción de acoplamiento para proteger un grupo amino primario en el compuesto (3) con el compuesto (5). Debido a esta protección, la producción de subproducto (8) puede

ser notoriamente prevenida en una cantidad de 0,1% o menos. El compuesto resultante (4), que es preparado del proceso anterior con un rendimiento de aproximadamente el 90% o más, es tratado con un ácido de fórmula HA para llevar a cabo la desprotección y las reacciones de formación de sal en una etapa. Por medio del procedimiento anterior que omite la etapa de reacción de recristalización, se produce una sal de Gemifloxacina del compuesto (1) con un rendimiento del 90% o más, y las etapas del proceso de preparación se simplifican. De acuerdo con tal simplificación del proceso de preparación, se pueden obtener los siguientes varios efectos: reducir el tiempo de producción, mejorar la productividad e incrementar el rendimiento.

El proceso de acuerdo con la presente invención se explica como un ejemplo en detalle como sigue:

Primero, el proceso de síntesis del compuesto (4) (etapa ácida) comprende disolver el compuesto (3), el compuesto (5), y una base orgánica, por ejemplo trietilamina en un solvente de reacción, por ejemplo un solvente mezclado de acetonitrilo con agua, y agregar el compuesto (2) a este,

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y luego hacer reaccionar la mezcla resultante. Las condiciones de esta reacción son como sigue:

1) Como un solvente de reacción, agua, un solvente orgánico, tal como acetonitrilo, tetrahidrofurano, (THF) metanol, y etanol, o un solvente mezclado de un solvente orgánico con agua pueden ser utilizados. Preferiblemente, un solvente mezclado de acetonitrilo con agua es ventajoso en vista de la pureza y rendimiento.

2) Como un co compuesto (5), puede ser utilizada cetona o un compuesto aldehído, tal como formaldehído, acetona, benzaldehído, 1-butaldehído, y similares. Preferiblemente, derivado de benzaldehído tal como benzaldehído, 2-hidroxibenzaldehído, 2-clorobenzaldehído y similares son ventajosos en vista de la pureza y rendimiento. Particularmente, el benzaldehído es el más ventajoso en vista del costo y estabilidad. Se prefiere que el benzaldehído se utilice en una cantidad de la cantidad molar igual o más que la cantidad molar del compuesto (2).

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3) Una temperatura de reacción se puede aplicar a este en un rango amplio de 0° C a 80° C. Sin embargo, la temperatura más preferida está en el rango de 20-30° C en vista de la proporción de reacción, rendimiento y pureza.

4) Como una base orgánica se puede utilizar trietilamina, trimetilamina, diisopropiletilamina, DBU (1,8-diazabiciclo[5.4.0] undec-7-eno), DBN (1,5-diazabiciclo [4.3.0]non-5-ona), así como también un número de otras bases. La base más adecuada es trietilamina en vista del costo y rendimiento. La cantidad de esta se utiliza en 3 o más cantidades molares con relación al compuesto (2).

Al llevar a cabo el proceso de reacción anterior, el compuesto (4) que tiene alta pureza se puede producir en alto rendimiento (más del 90%).

Segundo, el proceso (etapa b) para preparar el compuesto (1) del componente (4) comprende disolver el compuesto (4) en un solvente de reacción, por ejemplo, un solvente mezclado de isopropanol con agua, calentar la mezcla resultante, agregar un ácido de fórmula HA, por ejemplo,

ácido metanosulfónico, a este para llevar a cabo la desprotección y las reacciones de formación de sal al mismo tiempo, y luego enfriar el material de reacción para preparar el compuesto (1) sin la etapa de recristalización. Las condiciones de reacción de esta reacción son como sigue:

1) Como solvente de reacción, agua, alcohol, tal como isopropanol, THF, metanol, etanol, butanol y similares, o un solvente mezclado de alcohol con agua pueden ser utilizados. Preferiblemente, un solvente mezclado de isopropanol con agua es ventajoso en vista de la pureza y rendimiento.

2) Como un ácido, pueden ser utilizados un número de ácidos que representan HA, tal como ácido clorhídrico, ácido metanosulfónico, ácido sulfúrico, ácido fosfórico, ácido acético, ácido cítrico, ácido tartárico, ácido perhidroclórico, ácido pícrico, ácido (+)-camfor sulfónico y similares. Particularmente, el ácido metansulfónico es más adecuado. Se prefiere que la cantidad molar igual a aquella del compuesto (4) de aproximadamente 20% más

o menos de igual cantidad molar se utilice en vista de la pureza y rendimiento.

3) Se puede aplicar una temperatura de reacción a esta en un rango amplio de 0° C a 100° C. Sin embargo, la temperatura de reacción de 40-50° C para agregar un ácido y la temperatura de reacción de 0-20° C después de agregar el ácido son preferidas, en vista de la proporción de reacción del compuesto final (1), rendimiento y pureza.

Al llevar a cabo el proceso de reacción anterior, el compuesto (4) que tiene alta pureza se puede producir con alto rendimiento (más del 90%).

Como se describió anteriormente, si se utiliza un proceso de síntesis novedoso de dos etapas, el efecto mejorado tal como simplicidad del proceso de preparación, incrementa el rendimiento (de aproximadamente el 65% a al menos el 80%), mejoramiento de la productividad, disminución de los costos de elaboración y similares se pueden lograr al reducir el proceso de síntesis convencional de tres etapas a dos etapas. Específicamente, es una ventaja que este proceso se pueda

aplicar a antibióticos tipo quinolona que tengan una estructura similar a aquella de la Gemifloxacina.

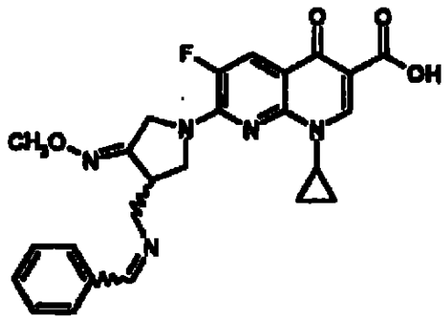
Por lo tanto, la presente invención suministra una técnica sorprendentemente mejorada sobre la técnica anterior.

La presente invención se explica en detalle por medio de los siguientes ejemplos, que no pretenden limitar el alcance de la invención.

EJEMPLOS

Ejemplo 1

Preparación de ácido 7-(3-benzilidinoaminometil-4-metoxiimino-1-pirrolidinil)-1-ciclopropil-6-fliuoro-1,4-dihidro-4-oxo-1,8-naftiridino-3-carboxílico.



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Acetonitrilo (1900 ml), 3-aminometil-4-metoxiiminopirrolidino dimetanosulfonato (248,0 g) y agua (10 ml) fueron introducidos en turnos en un recipiente de reacción y enfriados a 0-5° C. Benzaldehído (97,6 g) y trietilamina (229,1 g) fueron agregados en turnos a la mezcla de reacción. Después de agitar la mezcla durante 0,5 h, se introdujo a este 7-cloro-1-ciclopropil-6-fluoro-1,4-dihidro-4-oxo-1,8-naftiridino-3-carboxílico (200,0 g). La mezcla de reacción resultante se calentó lentamente a temperatura ambiente de cuarto, aunque agitándolo. Luego, la reacción se llevó a cabo al agitar la mezcla de reacción durante aproximadamente 3 horas a temperatura ambiente de cuarto. El material de reacción, que se formó en forma de una solución de dispersión luego de producir el compuesto del título, se filtró, se lavó con agua y acetonitrilo, y luego se secó para preparar 320,3 g del compuesto del título (rendimiento:94,8%).

^{1}H NMR (δ, $CDCl_3$): 8.66 (s, 1H), 8. 32 (s, 1H), 7. 98 (d, J=12. 4Hz, 1H), 7.60 (d, J=7. 0HZ, 2H), 7. 37 (t, J=7. 4Hz, 1H), 7.31 (t, J=7.4Hz, 2H), 4. 58 (s, 2H), 4. 21~4. 15 (m, 2H), 4.00 (m, 1H), 3.93 (s, 3H), 3.83 (m, 1H),

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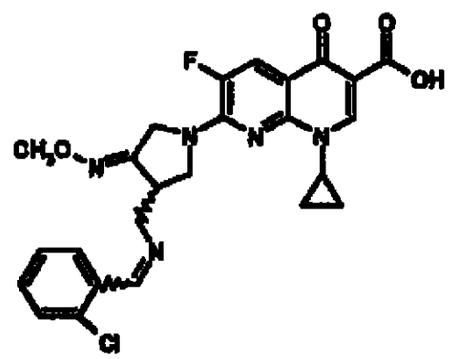
3.56 (m, 1H), 3.40 (m, 1H), 1.21 (m, 2H), 1.00 (m, 2H)
Mas (FAB): 478 (M+H)

Ejemplo 2

Preparación de ácido 7-[3-(2-clorobenzilideno)aminometil-4-metoxiimino-1-pirrolidinil]-1-ciclopropil-6-fluoro-1,4-dihidro-4-oxo-1,8-naftiridino-3-carboxílico.



Acetonitrilo (100 ml), 3-aminometil-4-metoxiiminopirrolidona dimetanosulfonato (12,5 g), 2-clorobenzaldehído (10,0 g) y trietilamina (12,2 g) fueron introducidos en turnos en un recipiente de reacción a temperatura ambiente de cuarto. Después de agitar la mezcla durante aproximadamente 0,5 h, se introdujo a este ácido 7-cloro-1-ciclopropil-6-fluoro-1,4-dihidro-4-oxo-

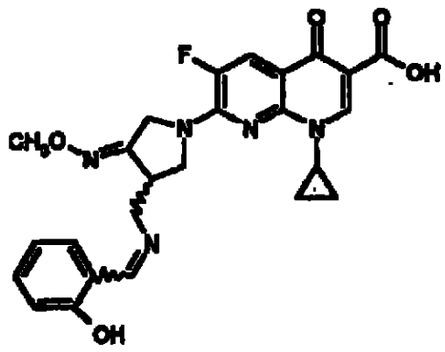
1,8-naftiridino -3-carboxílico (10,0 g). La mezcla de reacción resultante se agitó durante aproximadamente 15 h a temperatura ambiente, se enfrío a 0-5° C, y se agitó durante aproximadamente 3h. El compuesto del título en la forma de sólido se filtró, se lavó con acetonitrilo, y se secó para preparar 16, 3 g del compuesto del título (rendimiento: 90%).

^{1}H NMR (δ, $CDCl_3$) : 8.74 (s, 1H), 8.66 (s, 1H), 7.96 (d, J=12. 4Hz, 1H), 7.84 (d, J=7. 3Hz, 1H), 7.29 (m, 2H), 7.16 (m, 1H), 4.59 (bs, 2H), 4.18 (m, 2H), 4.02 (m, 1H), 3.94 (s, 3H), 3.93 (m, 1H), 3.59 (m, 1H), 3.42 (m, 1H), 1.22 (m, 2H), 1.01 (m, 2H)

Mas (FAB): 512 (M+H)

Ejemplo 3

Preparación de ácido 7-[3-(2-hidroxibenzilidino)aminometil-4-metoxiimino-1-pirrolidinil]-1-ciclopropil-6-fluoro-1,4-dihidro-4-oxo-1,8-naftiridino-3-carboxílico.



Acetonitrilo (100 ml), 3-aminometil-4-metoxiiminopirrolidina dimetanosulfonato (12,5 g), 2-hidroxibenzaldehído (8,6 g) y trietilamina (12,2 g) fueron introducidas en turnos en un recipiente de reacción a temperatura ambiente de cuarto. Después de agitar la mezcla durante aproximadamente 0,5 h, se introdujo a este ácido 7-cloro-1-ciclopropil-6-fluoro-1,4-dihídro-4-oxo-1,8-naftiridino -3-carboxílico (10,0 g). La mezcla de reacción resultante se agitó durante aproximadamente 15 h a temperatura ambiente de cuarto, se enfrío a 0-5° C, y se agitó durante aproximadamente 3h. El compuesto del título en la forma de sólido se filtró, se lavó con acetonitrilo, y se secó para preparar 16, 0 g del compuesto del título (rendimiento: 91,8%).

^{1}H NMR (δ, $CDCl_3$): 8. 68 (s, 1H), 8.42 (s, 1H), 8.01 (d, J=12.4Hz, 1H), 7. 30~7. 20 (m, 3H), 6. 90~6. 82 (m, 2H), 4.

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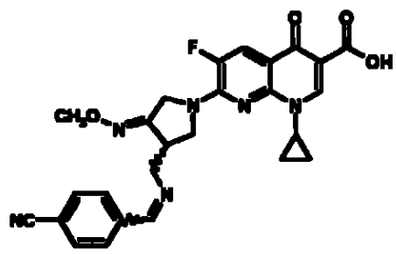
68~4. 53 (m, 2H), 4. 32~4. 24 (m, 1H), 4.06 (dd, J1=11. 9 Hz, J2=5.5 HZ, 1H), 4.02~3.85 (m, 3H), 3.95 (s, 3H), 3.60 (m, 1H), 3.40 (m, 1H), 1.29~1. 21 (m, 2H), 1.07~1.00 (m, 2H)

Mas (FAB): 494 (M+H)

Ejemplo 4

Preparación de ácido 7-[3-(4-cianobenzilidino) aminometil-4-metoxiimino-1-pirrolidinil]-1-ciclopropil-6-fluoro-1,4-dihidro-4-oxo-1,8-naftiridino-3-carboxílico.



De acuerdo con el procedimiento y escala como se describieron en el ejemplo 2 y 3, 14, 6 g del compuesto del título se prepararon al utilizar 4-cianobenzaldehído (9,3 g) (rendimiento: 82,2%).

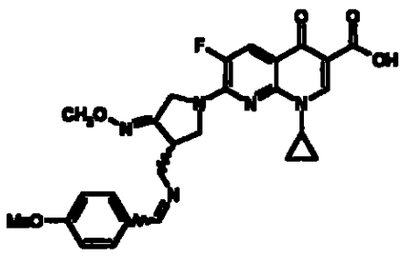
^{1}H NMR (δ, $CDCl_3$): 8.66 (s, 1H), 8.40 (s, 1H), 7.99 (d, J=12.4Hz, 1H), 7.80 (d, J=8.3Hz, 2H), 7.67 (d, J=8.3Hz, 2H), 4.59 (m, 2H), 4.30 (m, 1H), 4.08 (m, 2H), 3.92 (s,

3H), 3.90 (m, 1H), 3.61 (m, 1H), 3.45 (m, 1H), 1.24 (m, 2H), 1. 05 (m. 2H)

Mass (FAB): 503 (M+H)

Ejemplo 5

Preparación de ácido 7-[3-(4-metoxibenzilidino) aminometil-4-metoxiimino-1-pirrolidinil]-1-ciclopropil-6-fluoro-1,4-dihidro-4-oxo-1,8-naftiridino-3-carboxílico.



De acuerdo con el procedimiento y escala como se describieron en los ejemplo 2 y 3, 14, 4 g del compuesto del título se prepararon al utilizar 4-metoxibnezaldehído (9,6 g) (rendimiento: 80,2%).

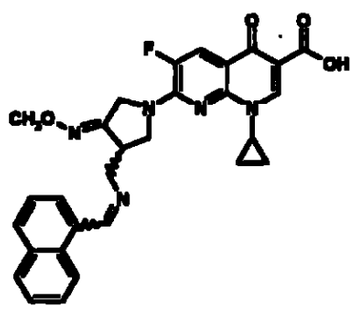
^{1}H NMR (δ, $CDCl_3$) : 8.66 (s, 1H), 8.22 (s, 1H), 7.96 (d, J=12.4Hz, 1H), 7.52 (d, J=8.7Hz, 2H), 6.79 (d, J=8. 3Hz, 2H), 4.59 (m, 2H), 4.16 (bs, 2H), 3.93 (s, 3H), 3.92 (m,

1H), 3.83 (m, 1H), 3.79 (s, 3H), 3.56 (m, 1H), 3.38 (m, 1H), 1.22 (m, 2H), 1.00 (m, 2H)

Mass (FAB): 508 (M+H)

Ejemplo 6

Preparación de ácido 7-[3-(1-naftilidino) aminometil-4-metoxiimino-1-pirrolidinil]-1-ciclopropil-6-fluoro-1,4-dihidro-4-oxo-1,8-naftiridino-3-carboxílico.



Acetonitrilo (100 ml), 3-aminometil-4-metoxiiminopirrolidino dimetanosulfonato (12,5 g), y 1-naftaldehído (11,1 g) fueron introducidas en turnos en un recipiente de reacción a temperatura ambiente de cuarto y enfriados a 0-5° C. Se agregó gota a gota trietilamina (12, 2 g) a la mezcla de reacción. Después de agitar la

mezcla durante aproximadamente 0,5 h, la mezcla de reacción se diluyó al agregar etanol (30 ml). Se introdujo ácido 7-cloro-1-ciclopropil-6-fluoro-1,4-dihídro-4-oxo-1,8-naftiridino -3-carboxílico (10,0 g) a la mezcla de reacción. Después de elevar lentamente la temperatura de reacción a su temperatura ambiente de cuarto, la mezcla de reacción se agitó durante aproximadamente 15 h. El compuesto del título en la forma de sólido se filtró, se lavó con agua y etanol, se secó para preparar 15,7 g del compuesto del título (rendimiento: 84,4%).

^{1}H NMR (O, $CDCl_3$): 8.86 (m, 2H), 8.55 (s, 1H), 7. 82 (m, 3H), 7.73 (m, 1H), 7.40 (m, 3H), 4.60 (m, 2H), 4.24 (m, 2H), 4.08 (m, 1H), 3.99 (m, 1H), 3.95 (s, 3H), 3.45 (m, 2H), 1.13 (m, 2H), 0. 89 (m, 2H)

Mass (FAB): 528 (M+H)

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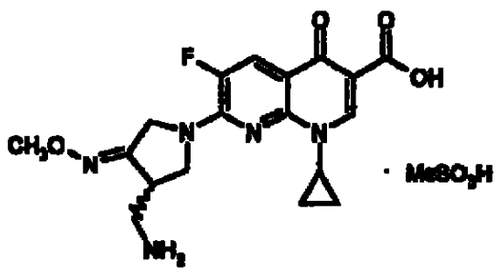
Ejemplo 7

Preparación de sal de ácido metansulfónico de ácido 7-(aminometil -4-metoxiimino-1-pirrolidinil)-1-ciclopropil-6-fluoro-1,4-dihidro-4-oxo-1,8-naftiridino-3-carboxílico.



Agua (60 ml), el compuesto (30,0 g) sintetizado en el ejemplo 1 e isopropanol (210 ml) fueron introducidos en turnos en un recipiente de reacción, y calentados a 40-45° C. Se agregó gota a gota ácido metanosulfónico (6,22 g) a la mezcla de reacción. Después de agitar la mezcla de reacción durante aproximadamente 0,5 h a una temperatura de 40-45° C, esta se enfrió a 27-35° C. El compuesto (1) (0,03 g) se agregó a la mezcla de reacción. La mezcla de reacción se enfrío lentamente a temperatura ambiente de cuarto y se agitó durante aproximadamente 17

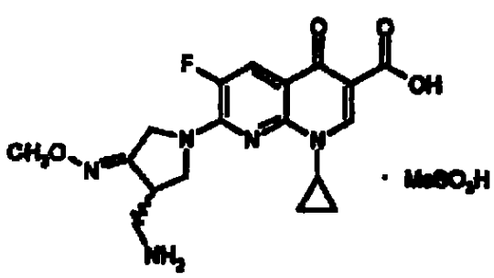
h para precipitar el compuesto del título en la forma de sólido. La mezcla de reacción en la forma de solución de dispersión se enfrío a -1~° C se agitó durante aproximadamente 3 h, se filtró, se lavó con isopropanol, se secó y se absorbió para preparar 29,0 g del compuesto del título (rendimiento 95,1&).

^{1}H NMR (δ, DMSO-d_6): 8.59 (s, 1H), 8.06 (d, J=12.4Hz, 1H), 4. 58 (bs, 2H), 4.37 (m, 1H), 3.90 (s, 3H), 3.83 (bs, 1H), 3.71 (m, 1H), 3.40 (m, 1H), 3. 24~3. 10 (m, 2H), 2.32 (s, 3H), 1.20~1.05 (m, 2H), 1.03~1.02 (m, 2H)

Masa (FAB): 486 (M+H)

Ejemplo 8

Preparación de sal de ácido metanosulfónico de ácido 7-(aminometil -4-metoxiimino-1-pirrolidinil)-1-ciclopropil-6-fluoro-1,4-dihidro-4-oxo-1,8-naftiridino-3-carboxílico.



El compuesto del título se preparó con rendimiento del 91,7% de acuerdo con el procedimiento como se describió en el ejemplo 7, excepto que se utilizó THF (240 ml) en lugar de isopropanol (210 ml), y se utilizó ácido metansulfónico en cantidad de 6,04 g en lugar de 6,22 g.

DISPONIBILIDAD INDUSTRIAL

Sí el proceso de síntesis novedoso de os etapas de acuerdo con la presente invención se utiliza, el efecto mejorado tal como la simplicidad de el proceso de preparación, incremento del rendimiento, mejora de la productividad, disminución de los costos de elaboración y similares se pueden lograr al reducir el proceso de síntesis convencional de tres etapas a un proceso de dos etapas.

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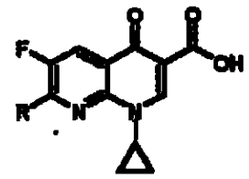
REIVINDICACIONES

1. Un proceso para preparar sales ácidas de Gemifloxacina representadas por la fórmula 1, que comprende las etapas de

a) agregar un compuesto de fórmula 5 al ácido naftiridino carboxílico de fórmula 2 y sal 3-aminometil-4-metoxiiminopirrolidona de fórmula 3 en agua, un solvente orgánico o un solvente mezclado de este en la presencia de una base orgánica para llevar a cabo una reacción de acoplamiento, y

b) agregar un ácido de fórmula HA al compuesto resultante de fórmula 4 en agua, un solvente orgánico o un solvente mezclado de este para llevar a cabo la desprotección y las reacciones de formación de sal al mismo tiempo:



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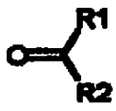

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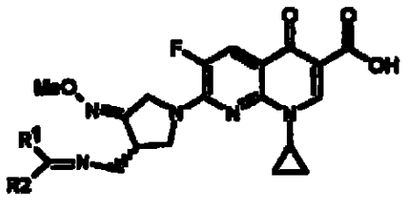

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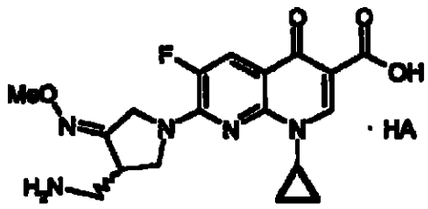

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En donde,

R representa Cl, F, Br, I, metanosulfonilo o paratoluenosulfonilo,

Me representa metilo,

HX representa ácido clorhídrico, ácido bromhídrico, ácido yodídrico, ácido trifluoroacético, ácido metanosulfónico, ácido paratoluenosulfónico, o ácido sulfúrico,

R1 y R2 independientemente uno del otro representan hidrógeno, un grupo alquilo C_1-C_6 recto o ramificado, saturado o insaturado, un grupo cicloalquilo C_3-C_6 saturado o insaturado, o un grupo aromático que es no sustituido o sustituido por alquilo C_1-C_6, alcoxi C_1-C_6, hidroxi, ciano o halógeno, o

R1 y R2 junto con un grupo carbonilo al cual ellos están unidos forman un anillo, y

HA es un ácido orgánico o un ácido inorgánico.

2. El proceso de la reivindicación 1, en donde la etapa a), la etapa b) o ambas etapas a) y b) son llevadas a cabo en un solvente mezclado de un solvente orgánico con agua.

3. El proceso de la reivindicación 1, en donde el compuesto de fórmula 5 se selecciona del grupo que consiste de benzaldehído, 2-clorobenzaldehído, 2-hidroxibenzaldehído, 4-metoxibenzaldehído y 2-metilbenzaldehído.

4. El proceso de la reivindicación 2, en donde el solvente orgánico de la etapa a) es acetonitrilo, y aquel de la etapa b) es isopropanol o tetrahidrofurano (THF).

5. El proceso de la reivindicación 1, en donde la base orgánica se selecciona del grupo que consiste de trietilamina, trimetilamina, diisopropiletilamina, 1,8-diazabiciclo [5.4.0]

undec-7-eno, y 1,5-diazabiciclo[4.3.0] non-5-ona.

6. El proceso de la reivindicación 1, en donde el compuesto de fórmula 5 se utiliza en una cantidad de 1 a 3 veces aquella del compuesto de fórmula 2.

7. El proceso de la reivindicación 1, en donde la base orgánica de la etapa a) se utiliza en una cantidad de 3 a 4 veces aquella del compuesto de fórmula 2, y la reacción es llevada a cabo a una temperatura de reacción de 0 a 30° C.

8. El proceso e la reivindicación 7, en donde la base orgánica es trietilamina.

9. El proceso de la reivindicación 1, en donde el ácido de fórmula HA se utiliza en una cantidad

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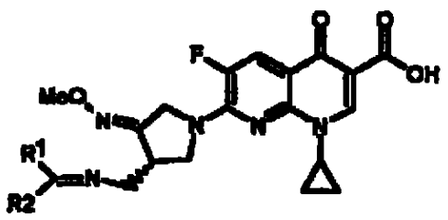
de 80 mol% a 120 mol% con relación al compuesto de fórmula 4, la temperatura al agregar el ácido está en el rango de 40-50° C, y la temperatura después de agregar el ácido está en el rango de 0-20° C.

10. El proceso de una cualquiera de las reivindicaciones 1-9, en donde el ácido de fórmula HA es ácido metanosulfónico.

11. Un intermedio, representado por la siguiente fórmula 4, para preparar sales ácidas de Gemifloxacina, de acuerdo a la reivindicación 1:



4

En donde

Me, R1 y R2 son como se definió en la reivindicación 1.

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RESUMEN

La presente invención se relaciona con un proceso para preparar sales de ácido de Gemofloxacin, un agente antibiótico del tipo quinolona que tiene una actividad antimicrobial potente. El proceso de acuerdo con la presente invención puede suministrar ventajas tales como simplicidad del proceso, mejoramiento de la productividad y mejoramiento de la producción, y similares mediante la reducción del proceso de tres etapas convencional al proceso de dos etapas.

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SUPERINDUSTRIA Y COMERCIO
Radicacion : 04099283 00000000 Folios: 82
Fecha (AMD): 2004-10-05 17:07:39
Tramite : 911 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 04 - 76,090
FECHA : SEPTIEMBRE 27 DE 2004

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	32758684	27/09/2004	39,426,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	422,000.00
		TOTAL : $	422,000.00

SON: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Colo 13548-841-002-2

83

SUPERINTENDENCIA Y COMERCIO
Radicacion : 04099283 00000000 Folios: 02
Fecha (MM): 2004-10-05 17:07:39
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN MODELO DE UTILIDAD	( )	( )
- Indicación de que se solicita la concesión de una patente.	( )	( )
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
- Descripción de la invención.	( )	( )
- Dibujos de ser estos pertinentes.	( )	( )
- Comprobante de Pago de las tasas establecidas.		
COMPLETA ( )	INCOMPLETA ( )	( )
DISEÑO INDUSTRIAL ( )		
- Indicación de qué se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta	( )	( )
- la solicitud.		
- Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( )	INCOMPLETA ( )	( )
ESQUEMA DE TRAZADO ( )		
- Indicación de que solicita el registro de un Esquema de trazado.	( )	( )
- Datos de identificación del solcitante o de la persona que presenta La solicitud.	( )	( )
Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( )	INCOMPLETA ( )	( )

Firma Responsable:

Fecha:

Industria y Comercio
SUPERINTENDENCIA

84

2020

Bogotá D C

Oficio N° 10057

Doctor(a)
EMILIO FERRERO
Apoderado
NOLG LIFESCIENCE LTD.

ASUNTO:

Radicación N°	**04-99283**
Solicitud internacional	**PCT/KR03/00683**
Fecha inicio fase nacional	**2004-11-08**
Trámite	011
Evento	379
Actuación	430
Folios	001

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

- La solicitud no contiene copia del documento en que consta la cesión del derecho de patente del inventor al solicitante o a su causante (Art. 26-k) Decisión 486).
- El solicitante debe aclarar si la solicitud corresponde al Capítulo I ó II del PCT, porque la indicación en el petitorio no corresponde a los documentos del expediente, en caso necesario adjuntar los documentos que corresponden.

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

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

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

El anterior requerimiento fue notificado por fijación en lista de fecha, 29 OCT. 2004

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