

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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División de Nuevas Creaciones

PCT
SOLICITUD

PATENTE DE INVENCION

ENTRADA EN FASE NACIONAL

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03-112619

54. TITULO

NUEVOS DERIVADOS DE OXAZOLIDINONAS COMO ANTIBACTERIANOS

51. CLASIFICACION INTERNACIONAL

A61M3/422, A61P31/04

71. SOLICITANTE

LABORATORIOS VITA. S.A.

DOMICILIO

SANT JOAN DESPI. BARCELONA. ESPAÑA

74. APODERADO

RAMIRO CASTRO DUQUE

22. SANTAFE DE BOGOTA, D.C.

26-12-03

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Oficina de Comunicaciones

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FORMULARIO ÚNICO 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

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Lugar de Constitución: España

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IDENTIFICACION

C.C. ☐NIT ☐C.E. ☐Otro ☐

Cual _____

Número _____

3

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O APODERADO

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Número 170.322 TP 1003

4

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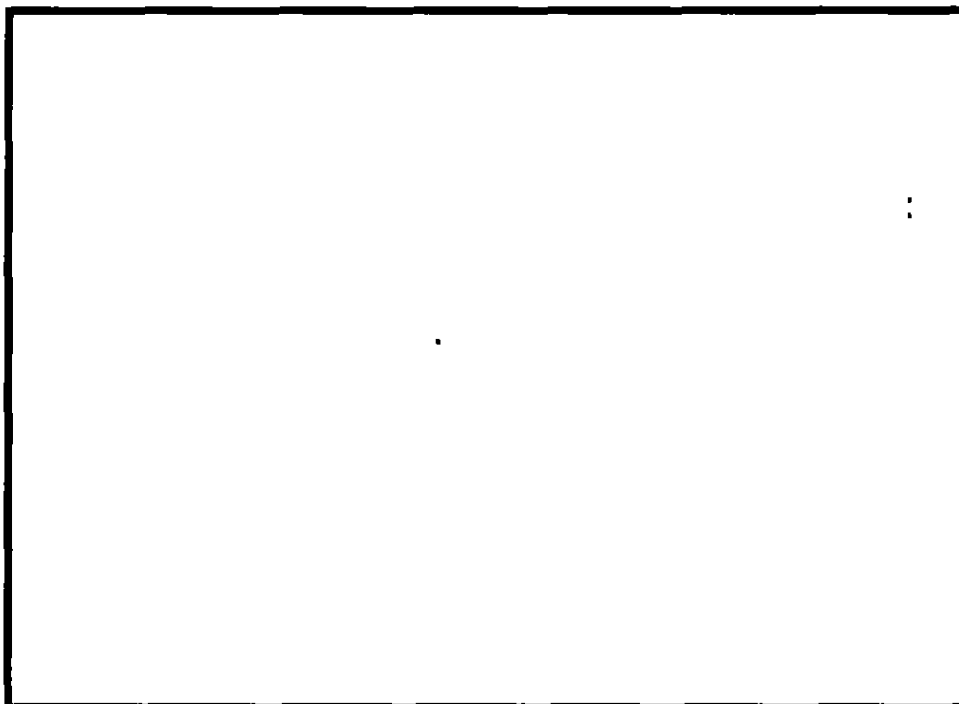
Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$400.000
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. Fotocopia Autenticada
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ 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.
- ☐ Arie 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 Tarjeta de Propietarios

11 FIGURA CARACTERÍSTICA:



12 Solicito la concesión de la patente.

NOMBRE: RAMIRO CASTRO DUQUE

FIRMA:

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

Instrucciones para la presentación de los anexos, ver reverso de esta página.

3
SOLICITUD DE PATENTE
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FECHA : NOVIEMBRE 28 DE 2003

***** CONSIGNACION *****

DEPOSITANTE	TIPO PASO	BANCO	CUENTA	No. PASO	FECHA PASO	Vr. PASO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	12686136	28/11/2003	23,080,000.00

***** CONCEPTO *****

CANT. HISTORICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	400,000.00
	TOTAL :	\$ 400,000.00

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(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, 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, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
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(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),

Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,
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Declarations under Rule 4.17:

— as to the identity of the inventor (Rule 4.17(i)) for the fol-
lowing designations AE, AG, AL, AM, AT, AU, AZ, BA, BB,
BG, BR, BY, BZ, CA, CH, 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, KR, KZ, LC, LK, LA, LS, LT,
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OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
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patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG,
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FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI
patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
MR, NR, SN, TD, TG)

— as to applicant's entitlement to apply for and be granted
a patent (Rule 4.17(ii)) for the following designations AE,
AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA,
CH, 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,
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UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS,
MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent
(AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent
(AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU,
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Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: NEW DERIVATIVES OF OXAZOLIDINONES AS ANTIBACTERIAL AGENTS

(57) Abstract: This invention discloses new fluoroquinolonic derivatives of oxazolidinones of general formula (I) and processes for
obtaining them, the corresponding pharmaceutical compositions and use thereof for manufacturing a medicament for the treatment of
microbial infections. These new compounds are useful as antibacterial agents. Formula (I). Furthermore phenalen-type compounds
according to general formula (II) are disclosed. Formula (II).

WO 03/002560 A1

NEW DERIVATIVES OF OXAZOLIDINONES AS ANTIBACTERIAL AGENTS

Field of the invention

This invention relates to fluorquinolonic 5 derivatives of oxazolidinones. The compounds are useful as antibacterial agents.

Background of the invention

For some years now the pharmaceutical industry has 10 not been pursuing the development of new antibacterial agents specifically directed at gram-positive bacteria such as Staphylococci, Enterococci, Streptococci and mycobacteria. The gram-positive bacteria have nevertheless taken on particular importance due to the fact that they 15 have developed resistance at an alarming rate to the conventionally used antibiotics, thus becoming organisms difficult both to treat and to eradicate from hospital environments. Examples of such strains are the *Staphylococcus* resistant to meticillin (MRSA), 20 *Enterococcus* resistant to vancomycin (VRE), *Staphylococcus epidermidis* resistant to meticillin (MRSE), *Staphylococcus pneumoniae* resistant to penicillin (PRSP), etc.

The oxazolidinonic antibacterial agents are the 25 most recent class of synthetic drugs which show high activity against gram-positive organisms. Owing to their new action mechanism, these compounds are effective against both sensitive and resistant pathogens, including MRSA, MRSE and VRE.

30

Various antibacterial oxazolidinones have been described in the patent literature, for example, to cite some of them, in WO 9507271, WO 9323384, WO 9854161, WO 9514684, WO 9721708, WO 9514684, WO 9730981, WO 9737980.

WO 9801447, WO 9912914, WO 9613502.

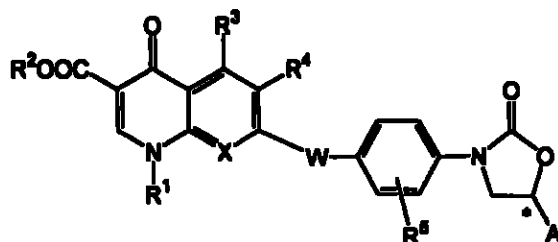
All these patents describe the oxazolidinones as compounds active against resistant gram-positive 5 organisms.

Owing to the constant appearance of new resistances, even to recently used antibiotics, it is desirable to develop powerful new antibiotics active 10 against the resistant strains, preferably with a broad antimicrobial spectrum.

This invention provides new derivatives of oxazolidinones, with a broad antimicrobial spectrum due to 15 their being active against gram-negative organisms while having improved activity against gram-positive organisms.

Description of the invention

20 The object of this invention are new fluorquinolonic derivatives of oxazolidinones of general formula (I):



25

(I)

in which:

X: CR⁶ or N;

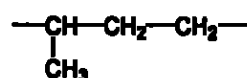
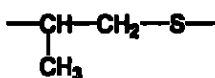
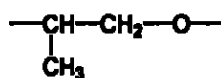
R¹: alkyl C₁-C₄, cycloalkyl C₃-C₆, alkenyl C₂-C₄, 2-
5 hydroxyethyl, 2-fluoroethyl, or phenyl optionally
substituted by 1 or 2 atoms of fluorine;

R²: H, alkyl C₁-C₄ or phenyl;

10 R³: H, halogen, alkyl C₁-C₄, or alkoxy C₁-C₄, amino;

R⁴: H or halogen;

R⁶: H, halogen, alkyl C₁-C₄, haloalkoxy C₁-C₄, or
15 else R¹ and R⁶ together form a bridge of structure



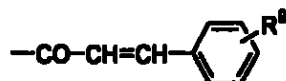
20 R⁵: H, halogen, OCH₃, alkoxy C₁-C₄, alkyl C₁-C₄, or
haloalkyl C₁-C₄;

A: -CH₂-NH-R⁷, -CHOH-C≡CH;

25

in which

R⁷: isoxazol, -CO-R⁸, -CS-R⁸, -CS-OR⁸, -COOR⁸, -
CONHR⁸, -CSNHR⁸, -SO₂-R⁸ or



30

in which

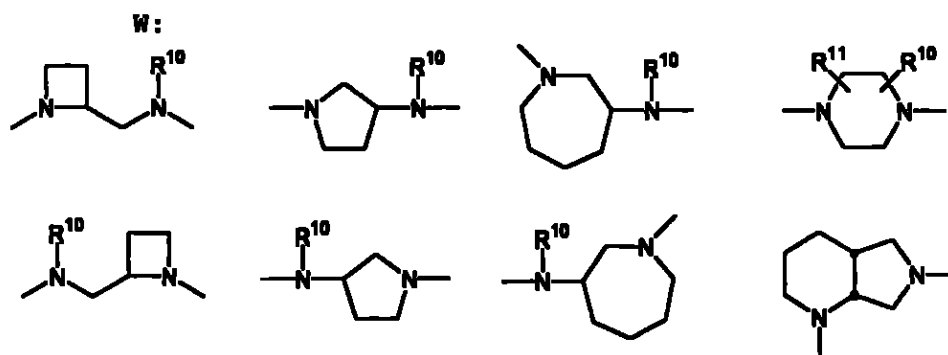
R^8 : alkyl C_1-C_4 , haloalkyl C_1-C_4 , alkenyl C_2-C_4 , aryl, alkyl C_1-C_4 substituted by an alkoxy group C_1-C_4 , carboxyalkyl C_1-C_4 , cyano, or amino, ...

5

R^9 : H, alkyl C_1-C_4 , alkenyl C_2-C_4 , OH, alkoxy C_1-C_4 , $NR^{12}R^{13}$, NO_2 , halogen, or $CO-R^{12}$;

R^{12} and R^{13} : independently, H or alkyl C_1-C_4 ;

10



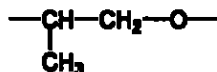
in which

R^{10} and R^{11} are independently H, or alkyl C_1-C_4 ;

15

a pharmaceutically acceptable salt or solvate, or any geometric isomer, optical isomer or mixture of isomers thereof in any proportion or polymorph thereof.

20 Preferably, R^1 is cyclopropyl, ethyl, 2-fluoroethyl, phenyl or difluorophenyl, or else R^1 and R^6 together form a bridge of structure:

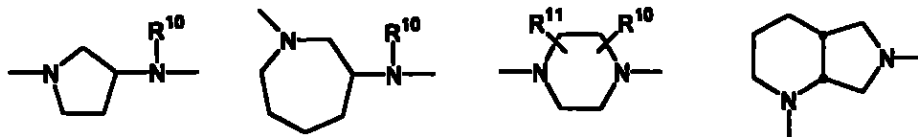


Preferably, R^6 is H, CH_3 , OCH_3 , $OCHF_2$, F or Cl.
More preferably, R^6 is H or F.

Preferably, R^4 is F or Cl and R^3 is H.

5

Preferably, W is



in which R^{10} and R^{11} are as defined previously.

10

The compounds of the invention have a chiral centre in position C5 of the oxazolidinone ring. The preferred configuration of the C5 of the oxazolidinone ring is (S) for the compounds of formula (I) in which $A = -CH_2-NH-R^7$ and (R) for the compounds of formula (I) in which $A = -CHOH-C\equiv CH$, in accordance with the Cahn-Ingold-Prelog nomenclature system.

Moreover, the compounds of formula (I) can contain other chiral centres. It is understood that the invention includes such optical isomers and diastereoisomers and mixtures thereof that possess antibacterial activity in any proportion.

The preferable compounds are selected from one of the following:

- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

- 7-[3-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-azepan-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 5 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6,8-difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 10 - 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid
- 9-[3-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-pyrrolidin-1-yl]-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid
- 15 - 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid
- 20 - 1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-methyl-thioureido)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 25 - 1-cyclopropyl-7-[4-(4-{5-(S)-[(3-ethyl-ureido)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 1-cyclopropyl-7-(4-{4-[5-(S)-(ethoxycarbonylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 30 - 1-cyclopropyl-6-fluoro-7-(4-[2-fluoro-4-(5-(S)-{[3-(4-fluoro-phenyl)-acryloylamino]-methyl}-2-oxo-oxazolidin-

- 3-yl)-phenyl]-piperazin-1-yl}-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 1-cyclopropyl-7-[4-(4-{5-(S)-[(3-ethyl-thioureido)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 5 - 1-(2,4-difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-5-[5-(R)-(1-(R,S)-hydroxy-prop-2-ynyl)-2-oxo-oxazolidin-3-yl]-phenyl}piperazin-1-yl)-4-oxo-1,4-dihydro-
- 10 [1,8]naphthyridine-3-carboxylic acid ethyl ester
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-(2,4-difluoro-phenyl)-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-carboxylic acid ethyl ester
- 15 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-carboxylic acid ethyl ester
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6,8-difluoro-1-(2-fluoro-ethyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
- 20 - 1-(2,4-Difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-4-[5-(S)-(isoxazol-3-ylaminomethyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-
- 25 [1,8]naphthyridine-3-carboxylic acid ethyl ester
- 1-(2,4-difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-4-[5-(R)-(1-hydroxy-prop-2-ynyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]
- 30 naphthyridine-3-carboxylic acid
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-(2,4-difluoro-phenyl)-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-carboxylic acid

13

12

- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-carboxylic acid
- 5 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6,8-difluoro-1-(2-fluoro-ethyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 1-(2,4-Difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-4-[5-(S)-(isoxazol-3-ylaminomethyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid
- 10 - 1-ethyl-6,8-difluoro-7-[4-(2-fluoro-4-{5-[(3-methyl-thioureido)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 15 - 1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{2-oxo-5-(S)-[(3-propyl-thioureido)-methyl]-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 20 - 1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-[5-(S)-(methanesulfonylamino-methyl)-2-oxo oxazolidin-3-yl]-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 25 - 7-(4-{4-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-1-ethyl-6,8-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
- 1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{2-oxo-5-(S)-[(2,2,2-trifluoro-acetylamino)-methyl]-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 30 - 7-(4-{4-[5-(S)-(benzoylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro 4-oxo-1,4-dihydro-quinoline-3-carboxylic acid.

- 14 13
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid methyl ester
 - 5 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6,8-difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid methyl ester
 - 10 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6,8-difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
 - 15 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6,8-difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
 - 20 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid methyl ester
 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
 - 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid methyl ester
 - 25 - 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid ethyl ester
 - 30 - 9-[3-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-pyrrolidin-1-yl]-8-

- fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid methyl ester
- 9-[3-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-pyrrolidin-1-yl]-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid ethyl ester
- 5 - 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid methyl ester
- 10 - 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid ethyl ester
- 15 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid methyl ester
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
- 20 - 1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-methyl-thioureido)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid methyl ester
- 25 - 1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-methyl-thioureido)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
- 30 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-carboxylic acid methyl ester

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- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6,8-difluoro-1-(2-fluoro-ethyl)-4-oxo-1,4-dihydro-quinoline-3- carboxylic acid methyl ester
- 5 - 1-Ethyl-6,8-difluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-methyl-thioureido)-methyl]-2-oxo-oxazolidin-3-yl)-phenyl]-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester

10 In this invention the term "a pharmaceutically acceptable solvate" is taken to mean a hydrate or solvate of an alcohol C₁-C₄.

 In this invention, the term "pharmacologically
15 acceptable salts" includes salts of alkaline metals such as sodium or potassium and salts of alkaline earth metals such as calcium or magnesium, as well as acid-addition salts formed with inorganic and organic acids such hydrochlorides, hydrobromides, sulphates, nitrates,
20 phosphates, formiates, mesylates, citrates, benzoates, fumarates, maleates, lactates and succinates, among others.

 The pharmacologically acceptable salts are
25 prepared by reaction of a compound of formula (I) with a suitable quantity of a base such as sodium, potassium, calcium or magnesium hydroxyde, or sodium methoxide, sodium hydride, potassium tert-butoxyde and the like in solvents such as ether, THF, methanol, ethanol, tert-
30 butanol, isopropanol, dioxane, etc., or else in a mixture of solvents. The addition salts, where applicable, can be prepared by treatment with acids, such as hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, formic, methanesulphonic, citric, benzoic, fumaric, maleic, lactic

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and succinic, in solvents such as ether, alcohols, acetone, THF, ethyl acetate, or mixtures of solvents.

The stereoisomers of this invention can be prepared by using reagents in a single enantiomeric form in processes where this is possible or by carrying out the reaction in the presence of reagents or catalysts in their single enantiomeric form or by resolution of mixtures of stereoisomers by conventional methods. Some of the preferred methods include resolution of diastereoisomeric salts formed with chiral acids such as mandelic, camphorsulphonic, tartaric acid and the like. Methods commonly used are included in Jaques et al. in "Enantiomers, Racemates and Resolution" (Wiley Interscience, 1981).

In the definitions of this invention, an alkyl group C_1-C_4 , as a group or as part of a group, is taken to mean a lineal or branching alkyl group which contains up to 4 atoms of carbon. Thus it includes, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl.

Likewise, an alkoxy group C_1-C_4 includes, for example, a methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy and tert-butoxy group.

An alkenyl group C_2-C_4 includes, for example, a vinyl, allyl, propenyl and 1-butenyl, 2-butenyl and 3-butenyl group.

A haloalkyl group C_1-C_4 means an alkyl group C_1-C_4 substituted by one or more atoms of halogen, the same or different. It thus includes, for example, chloromethyl,

fluoromethyl, trifluoromethyl, chloroethyl, fluoroethyl, difluoroethyl, trifluoroethyl, fluoropropyl, chloropropyl, etc.

5 A haloalkoxy group C₁-C₄ means an alkoxy group C₁-C₄ substituted by one or more atoms of halogen, the same or different. Thus it includes, for example, chloromethoxy, fluoromethoxy, trifluoromethoxy, chloroethoxy, fluoroethoxy, difluoroethoxy, 10 trifluoroethoxy, fluoropropoxy, chloropropoxy, etc.

A cycloalkyl group C₃-C₆ represents a cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl group.

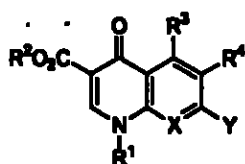
15 The term halogen, in this invention, refers to F, Cl, Br, I, preferably F and Cl.

The term aryl, in this invention, includes phenyl and naphthyl optionally substituted by up to five 20 substituents, the same or different, preferably up to two, in any position of the ring. Suitable substituents include halogen, amino, hydroxy, alkyl C₁-C₄, alkoxy C₁-C₄, phenyl.

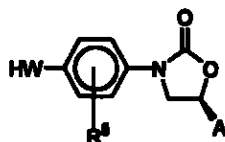
The compounds of this invention can be prepared in 25 various ways. They can be prepared by using the methods described below, together with methods known in the field of organic chemical synthesis, or by the variations that might be made thereto by an expert in the subject. Preferred methods include, but are not limited to, those 30 described below. The reactions are carried out in the solvents appropriate for the reagents and materials used and suited for the transformations carried out. An expert in organic synthesis will understand that the functional groups present in the molecule must be consistent with the

proposed transformations. This may in some cases require modifying the order of the synthesis steps or selecting one particular method rather than another, in order to obtain the desired compound of the invention. Moreover, in 5 some of the procedures described below it may be desirable or necessary to protect the reagent functional groups present in the compounds or intermediates of this invention with conventional protecting groups. Various protecting groups and procedures for introducing them and 10 removing them are described in Greene and Wuts (*Protective Groups in Organic Synthesis*, Wiley and Sons, 1999). All the references cited herein are incorporated integrally by reference.

15 The compounds of formula (I) can be obtained by reaction of a compound of formula (II), with a compound of formula (III):



(II)



(III)

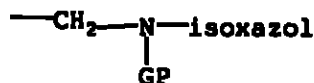
20 in which

A' is:

a) $-\text{CH}_2-\text{NH}-\text{R}^7$

b) $-\text{CHOH}-\text{C}\equiv\text{CH}$

c)



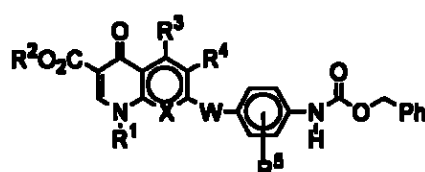
25

Y is an leaving group, such as an atom of halogen (F, Cl, Br, I), a tosylate or mesylate group and the like; R^1 , R^2 , R^3 , R^4 , R^5 , X and W have the meaning defined

above;

GP is an amine protecting group.

Alternatively, the compounds of formula (I) in 5 which A = -CHOH-C≡CH can also be obtained by reaction of a compound of formula (IV) with 2,3-hydroxy-pent-4-ynyl p-toluenesulphonate:

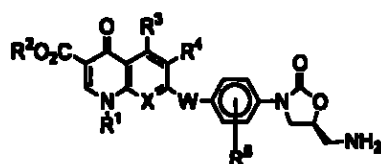


10

(IV)

in which R¹, R², R³, R⁴, R⁵, X and W have the meaning defined above.

The compounds of formula (I) in which A = -CH₂-NH-R⁷ 15 and R⁷ is different from isoxazol, can also be obtained by reaction of a compound of formula (V):



(V)

20

in which R¹, R², R³, R⁴, R⁵, X and W have the meaning defined above, with a compound of formula (VI) or with a compound of formula (VII)

25

R⁷-L
(VI)

R⁸-N=C=Z
(VII)

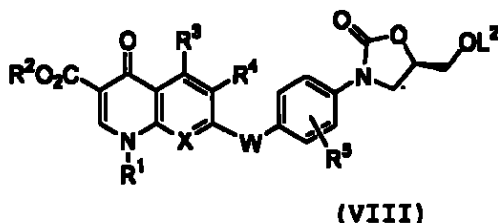
in which

L is a good leaving group, such as an atom of halogen (F, Cl, Br, I), a tosylate or mesylate group and the like;

Z is Oxygen or Sulphur, and

R⁷ and R⁸ have the meaning defined above, with R⁷ being different from isoxazol.

- 10 The compounds of formula (I) in which A= -CH₂-NH-R⁷ and R⁷ is isoxazol can also be obtained by reaction of a compound of formula (VIII)



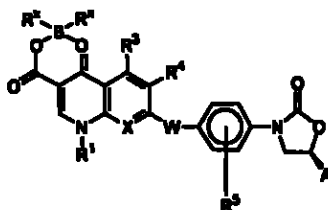
- 15 in which

- OL² represents a good leaving group, such as a residue of aryl or methyl sulphonic acid, whether substituted or not substituted, preferably by a tosylate or mesylate group;

- 20 - R¹, R², R³, R⁴, R⁵, X and W have the meaning defined above;

with isoxazolil-3-amine, with the amino group suitably protected with an amine protecting group, for example with Troc (2,2,2-trichloroethoxycarbonyl).

The compounds of formula (I), in which R²= H can also be obtained by hydrolysis of a boron chelate of formula (IX):



(IX)

in which

- 5 R² can be F or CH₃COO-;
 A, R¹, R³, R⁴, R⁵, X and W have the meaning defined
 above.

And if required, after any of the methods
 10 described herein, one or more of the following optional
 steps can be carried out:

- Converting a compound of general formula (I)
 into another compound of general formula (I);
- Eliminating any protecting group;
- 15 - Preparing a pharmacologically acceptable salt of
 a compound of formula (I) and/or pharmacologically
 acceptable solvate thereof.

The reaction of the compounds of formula (II) with
 20 compounds of formula (III) is carried out in an organic
 solvent in the presence of an organic base. Preferably the
 reaction is carried out in solvents such as pyridine,
 acetonitrile, dimethylformamide, N-methylpyrrolidone, etc.
 in the presence of bases such as triethylamine, DBU,
 25 diisopropylethylamine, etc.

The reaction of compounds of formula (IV) with
 2,3-hydroxy-pent-4-ynyl p-toluenesulphonate is carried out
 in an aprotic solvent such as N,N-dimethylformamide, THF,

preferably THF, at low temperature, preferably at -68°C, and in the presence of a base such as n-butyllithium, lithium tert-butoxide, LDA, preferably in n-butyllithium.

5 The reaction of compounds of formula (V) with a compound of formula (VI) is carried out in an organic aprotic solvent such as acetonitrile, dichloromethane or pyridine or in a mixture of an organic solvent and water in the presence of a base. Preferably L is Cl, EtO, etc,
10 so that R⁷-L can be an acid, an acid chloride, an anhydride, an ester, a dithioester, an alkyl or aryl chloroformate, etc. The reaction of compounds of formula (V) with a compound of formula (VII) is preferably carried out in pyridine.

15

 The reaction of the compounds of formula (VIII) with isoxazolil-3-amine, with the amino group suitably protected, is carried out in an aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, preferably
20 in N,N-dimethylformamide, at a temperature between 0 and 70°C, and in the presence of a strong base such as sodium hydride, lithium tert-butoxide, sodium tert-butoxide, potassium tert-butoxide or sodium amide, preferably sodium hydride.

25

 Hydrolysis of the compounds of formula (IX) can be carried out according to the methods previously described in the literature (Masuhiro Fujita Chem. Pharm. Bull. (1988), 46(5), 787-796, Joseph P. Sánchez J. Med.
30 Chem. (1995), 38, 4478-4487)

 For R^x = F, the hydrolysis is carried out preferably in a mixture of alcohol-water in the presence of a base. As water-alcohol mixture it is preferable to

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use ethanol-water or methanol-water and as base it is preferable to use an organic base such as triethylamine or another secondary or tertiary amine such as tributylamine, diisopropylethylamine, DBU, etc. The reaction is carried out at a temperature that can range between room temperature and the reflux temperature of the water-alcohol mixture. The reaction is carried out preferably at the reflux temperature of the water-alcohol mixture.

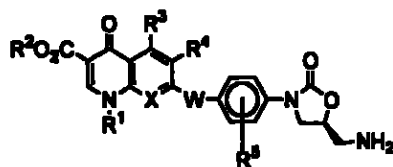
10 When $R^x = CH_3COO$ the hydrolysis is carried out preferably in a mixture of an organic aprotic solvent and another protic solvent in the presence of a base. As aprotic solvent it is preferable to use acetonitrile and as protic solvent it is preferable to use water. As base
15 it is preferable to use an inorganic base such as sodium, lithium or potassium hydroxide or sodium, lithium or potassium carbonate, etc.

A reaction of interconversion of a compound of
20 formula (I) into another compound of formula (I) consists, for example, in hydrolysing a compound of formula (I) in which R^2 is an alkyl C_1-C_4 or phenyl radical to convert it into a compound of formula I in which R^2 is hydrogen. The hydrolysis is carried out preferably in a water-alcohol
25 medium preferably using as base an inorganic base. Still more preferably, the hydrolysis is carried out in ethanol-water or methanol-water, while sodium, lithium or potassium hydroxide is used as a base.

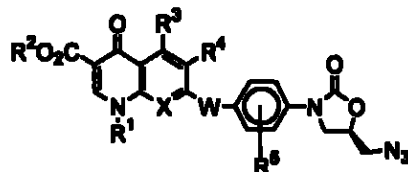
Another example of reaction of interconversion of
30 a compound of formula (I) in another compound of formula (I) consists in the esterification of a compound of formula (I) in which R^2 is hydrogen, to yield another compound of formula (I) in which R^2 is an alkyl C_1-C_4 or phenyl radical, by the conventional methods of

esterification described in the literature. For example, by reaction of a compound of formula R^2-OH with the compound of formula (I) in which R^2 is hydrogen, having previously activated the carboxylic acid with carbonyl 5 diimidazole, or else having previously converted the carboxylic acid into an acid chloride by reaction with thionyl chloride, or else having converted it into mixed anhydride by reaction with alkyl chloroformate.

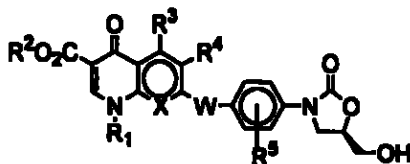
Also object of invention are the compounds of 10 formula (V), (X) and (XI):



(V)



(X)



(XI)

in which R^1 , R^2 , R^3 , R^4 , R^5 , X and W have the meaning defined above. These compounds are useful as 20 intermediates for making the compounds of formula (I) of

this invention.

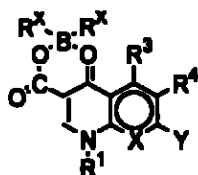
Described below are some of the procedures for making the intermediates used for preparing the compounds 5 of formula (I).

The compounds of formula (V), (X) and (XI) can be obtained in accordance with schemes 1A and 1B.

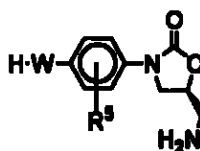
10 Thus, the compounds of formula (V) can be obtained:

a. by reaction of a compound of formula (II) or of formula (XII) with a compound of formula (XIII):

15



(XII)



(XIII)

20

The reaction can be carried out under the conditions described above for the reaction of a compound of formula (II) with a compound of formula (III);

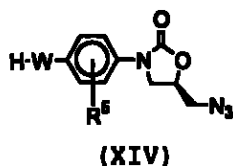
b. by catalytic reduction of a product of formula 25 (X) or by reduction of the azide group chemically with triphenylphosphine, etc.

The compounds of formula (X) can in their turn be obtained:

30 a. by reaction of a compound of formula (XII) or of formula (II) with a compound of formula (XIV):

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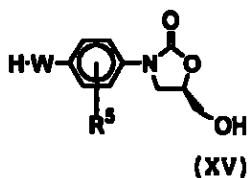


The reaction can be carried out under the 5 conditions described above for the reaction of a compound of formula (II) with a compound of formula (III);

b. from a compound of formula (XI) by conversion of the hydroxyl group into a good leaving group, such as mesylate, tosylate or halogen and subsequent reaction with 10 sodium azide.

The compounds of formula (XI) can in their turn be obtained:

a.- by reaction of a compound of formula (XII) or 15 of formula (II) with a compound of formula (XV):



The reaction can be carried out under the conditions described above for the reaction of a compound 20 of formula (II) with a compound of formula (III);

b.- by reaction of a compound of formula (IV) with (R)-glycidyl butirate. The reaction is carried out in an aprotic solvent such as N,N-dimethylformamide, THF, preferably THF, at low temperature, preferably at -68°C, 25 and in the presence of a base such as n-butyllithium, lithium tert-butoxide, LDA, preferably in n-butyllithium.

Utilisation of the compounds of formula (XII) to obtain the three foregoing intermediates requires an additional step of hydrolysis of the boron chelate, as indicated in schemes 1A and 1B, which step is carried out 5 under the conditions described above for hydrolysis of the compound of formula (IX).

The compounds of formula (VIII) can be obtained by reaction of a compound of formula (XI) with aryl or methyl 10 sulphonyl chloride, substituted or not substituted, preferably with mesyl chloride or p-toluenesulphonyl chloride, in an aprotic solvent, such as methylene chloride, and in the presence of an organic base, such as triethylamine.

15

The compounds of formula (IX) can be obtained by reaction of a compound of formula (XII) with a compound of formula (III). The reaction can be carried out under the conditions described above for the reaction of a compound 20 of formula (II) with a compound of formula (III).

The products of formula (II) and of formula (XII) are obtained according to the methods described in the literature. This products have been used as intermediates 25 in the synthesis of quinolones and similar with antibacterial activity such as cyprofloxacin, ofloxacin, moxyfloxacin, norfloxacin, tosufloxacin, etc. (See patents WO 8807993, WO 8807998, WO 9006922, JP 59122470. JP 58029789, EP 0351889).

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The compounds of formula (III), (XIII), (XIV) and (XV) can be obtained in accordance with scheme 2.

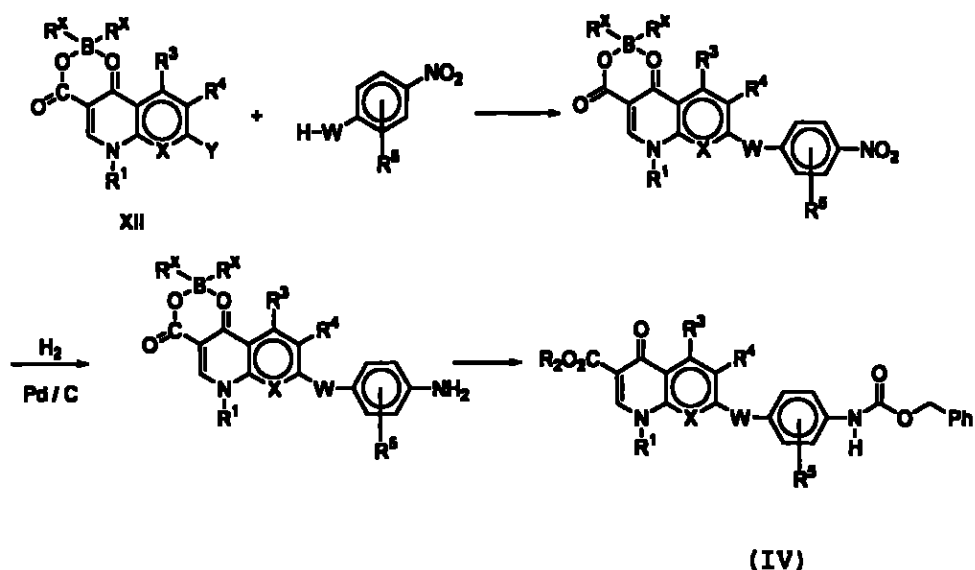
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Thus, the compounds of formula (IIIa), (XIII) and (XIV) can be obtained from a compound of formula (XVI) by conversion of the hydroxyl group into an NH_2 , N_3 or NHR^7 group, in accordance with reactions well-known to an expert in organic chemistry.

The compounds of formula (IIb) can be obtained by reaction of a compound of formula (XVII) with 2,3-hydroxypent-4-ynyl p-toluenesulphonate, under conditions analogous to those described for the reaction of a compound of formula (IV) with said reagent.

The compounds of formula (IIc) can be obtained by reaction of a compound of formula (XVI) with isoxazolil-3-amine, with the amino group suitably protected, for example with Troc, and prior conversion of the hydroxyl group into a good leaving group, for example, mesylate, tosylate, halogen, etc.

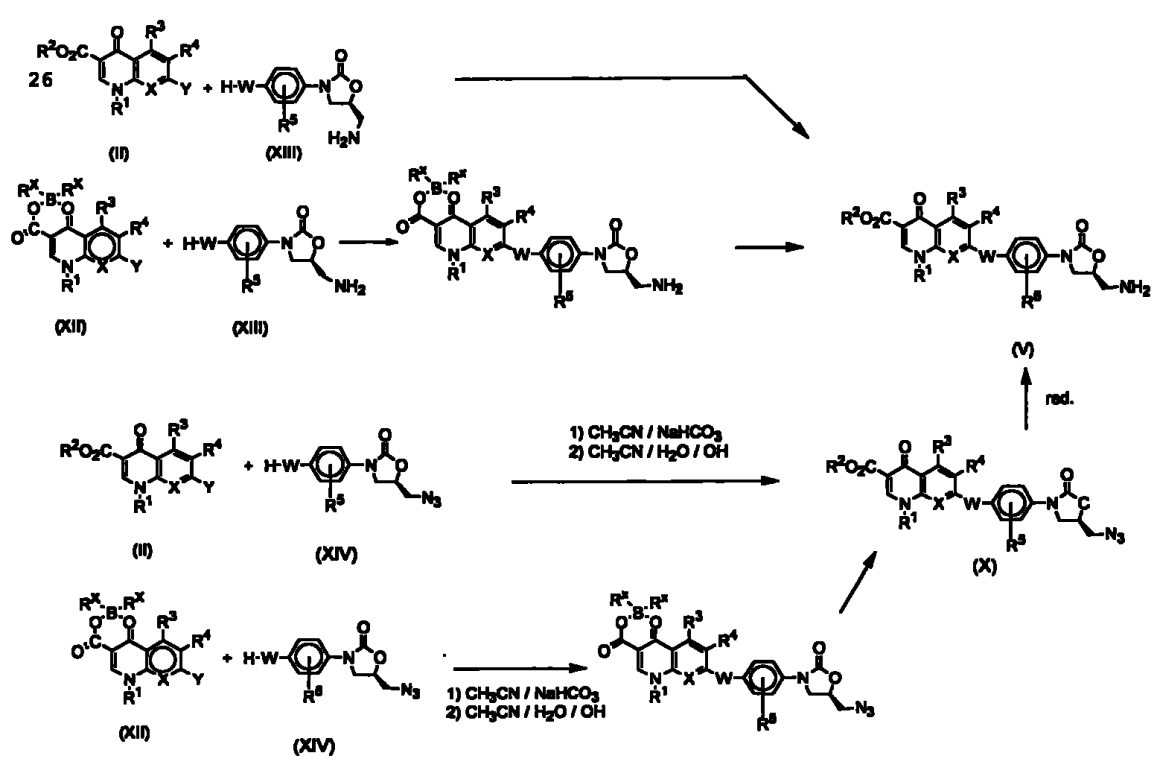
The compounds of formula (IV) can be obtained according to the following scheme:

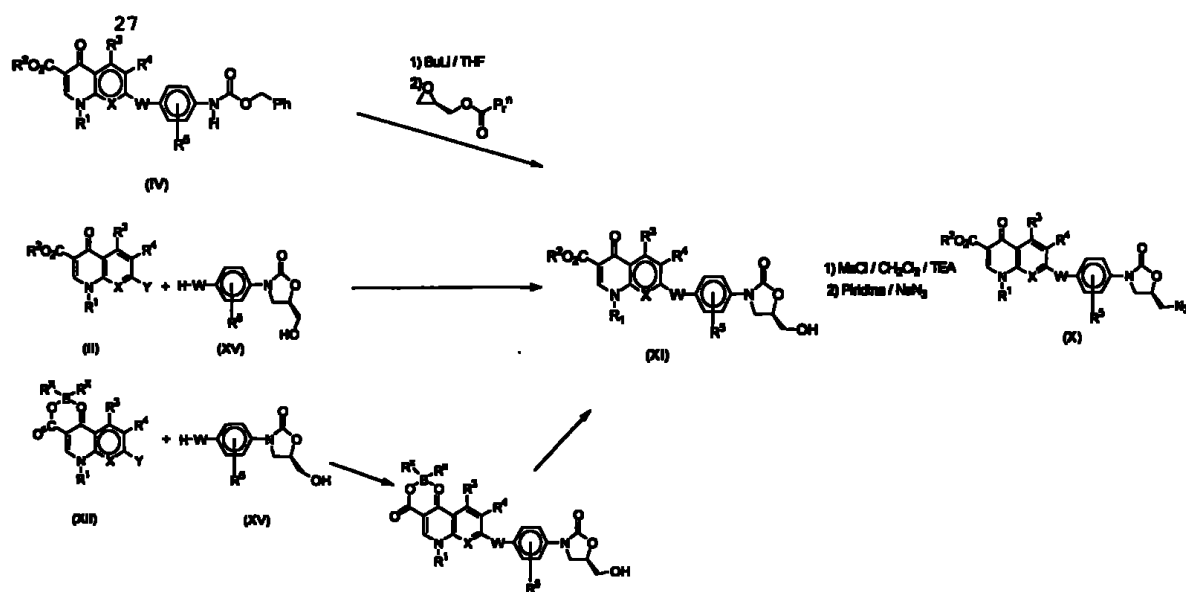


The reactions are carried out in suitable solvents, 5 and under conventional conditions. The schemes indicate the preferred reaction conditions.

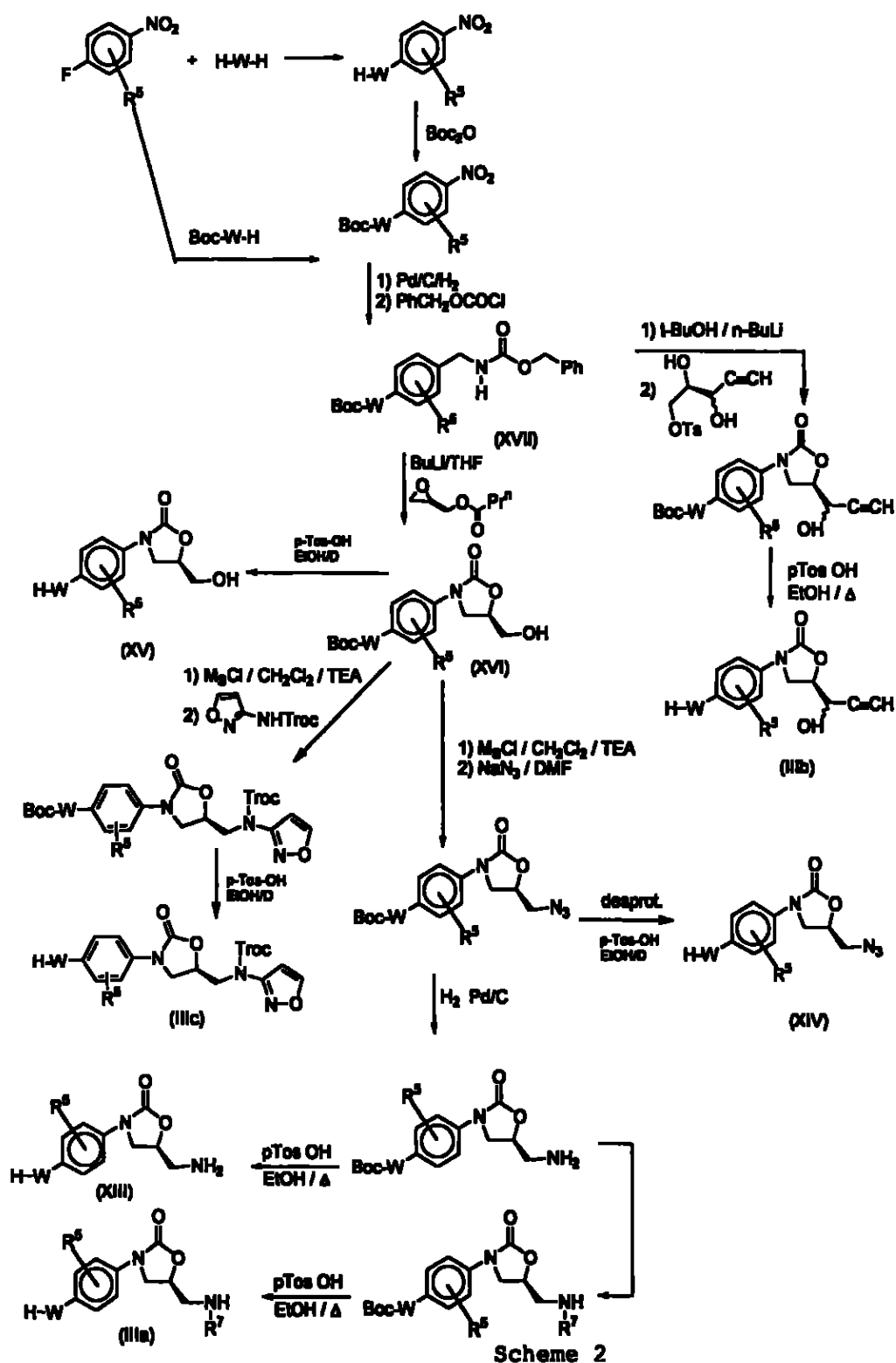
The 2,3-hydroxy-pent-4-ynyl p-toluenesulphonate is obtained according to the procedure described in EP 10 1029854A1.

The compounds of formula (VI) and of formula (VII) are commercial, are extensively described in the literature or can be prepared by methods analogous to 15 those known in the state of the art from products commercially available.





Scheme 1B



Also object of this invention are compositions which include a compound of general formula (I), a pharmaceutically acceptable salt or solvate, or any geometric isomer, optical isomer or mixture of isomers 5 thereof in any proportion or polymorph thereof, in a therapeutically active quantity and a suitable quantity of at least one pharmacologically acceptable excipient.

The compositions of the invention can be 10 formulated in solid or liquid form following the conventional pharmaceutical techniques. The solid formulations include tablets, capsules, sachets, powders, suppositories, etc. The excipients can include diluents, disintegrators, wetting agents, lubricants, colourants, 15 flavourings or other conventional adjuvants. The typical solid excipients include, for example, microcrystalline cellulose, starch, polyvinylpyrrolidone, magnesium stearate or sodium lauryl sulphate. The liquid compositions include solutions, suspensions or emulsions. 20 They can consist in solutions in water or in water-propyleneglycol or water-polyethyleneglycol systems, also optionally containing flavourings, colourants, stabilisers and thickeners.

25 The compositions can be administered orally, parenterally or topically.

The compounds of formula (I) show activity as antibacterial agents. Advantageously they possess a broad 30 spectrum of activity against gram-positive bacteria such as Staphylococcus, Streptococcus, Enterococcus and the like, as well as against gram-negative bacteria such as *E. Coli*, *H. Influenzae*, *M. catarrhalis*, etc., and even against strains resistant to known antibiotics such as

met icillin, vancomicine, penicillin, etc. They are also active against anaerobic microorganisms such as *Bacteroides fragilis*. Also object of this invention, therefore, is the use of a compound of formula (I) for making a pharmaceutical composition for the treatment of microbial infections, in humans or warm-blooded animals.

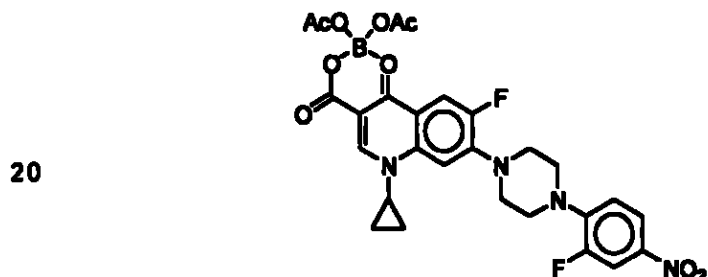
Below, and by way of non-restrictive explanation of the invention, the following examples are set out.

10 EXAMPLES OF SYNTHESIS

PREPARATION OF INTERMEDIATES

Reference Example No.1:

1-Cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-nitro-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-
15 carboxylic acid diacethoxyboron chelate



To 10 g (0.024 mol) of 1-cyclopropyl-7-chloro-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid diacethoxyboron chelate (obtained according to WO 8807998) in 150 ml of acetonitrile are added 5.4 g (0.024 mol) of 1-(2-fluoro-4-nitro-phenyl)piperazine (obtained according to the method described by S.J. Brickner and col. J. Med. Chem. 1996, 39, 673-679) and 2 g (0.024 moles) of sodium bicarbonate.

The reaction is heated to reflux for 48 h. It is concentrated to dryness and the residue is treated with 100 ml of water and extracted with 3 x 100 ml of

dichloromethane. The organic phase is dried and concentrated and the residue is chromatographed on silica gel.

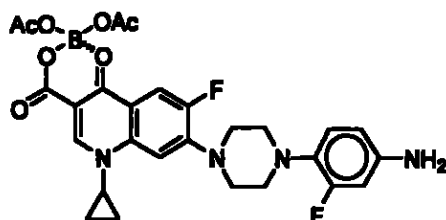
Elution with dichloromethane/ethanol 98/2 yields 6.7 g of 5 the product of the title.

¹H-RMN: (CDCl₃, 200 MHz, δppm): 9,08 (s, 1H); 8,14 (d, 1H); 8,10-7,94 (s.c., 2H); 7,56 (d, 1H); 7,01 (t, 1H); 3,82-3,75 (m, 1H); 3,75-3,50 (s.c., 8H); 2,04 (s, 6H); 1,64-1,30 10 (s.c., 4H).

Reference Example No.2:

7-[4-(4-amino-2-fluoro-phenyl)piperazin-1-yl]-1-cyclopropyl-6-fluoro-4-exo-1,4-dihydro-quinoline-3-carboxylic acid diacethoxyboron chelate.

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To 6.7 g (0.011 mol) of the product obtained in the 25 previous example, in 50 ml of dimethylformamide, are added 0.7 g of 10% Pd/C paste and it is placed under hydrogen atmosphere at 40°C and atmospheric pressure. When the reaction has finished it is filtered over decalite and the decalite washed with 20 ml of DMF.

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The filtrate liquids are poured onto 700 ml of water and extracted with 3 x 200 ml of dichloromethane. The organic phase is concentrated to dryness and the residues chromatographed on silica gel.

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Elution with dichloromethane-ethanol 95/5 yields 2.6 g of the product of the title as yellow solid.

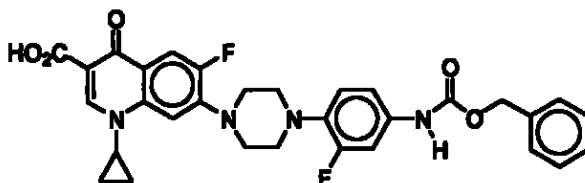
5 ¹H-RMN (CDCl₃, 200 MHz, δ(ppm)): 9,04 (s, 1H); 8,10 (d, 1H); 7,45 (d, 1H); 6,84 (dd, 1H); 6,44-6,36 (s.c., 2H); 3,79-3,64 (m, 1H); 3,62-3,56 (s.c., 4H); 3,24-3,16 (s.c., 4H); 2,05 (s, 6H); 1,80-1,20 (s.a., 2H, NH₂); 1,58-1,24 (s.c., 4H).

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Reference Example No.3:

7-[4-(4-benzylloxycarbonylamino-2-fluoro-phenyl)-piperazin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid.

15



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To 2.62 g (4.58 mmol) of the product obtained in the previous reference example in 30 ml of THF and 10 ml of water is added 0.4 g (5 mmol) of sodium bicarbonate.

Onto the previous solution is added dropwise 0.8 g (5 mmol) of benzyl chloroformate and is maintained with stirring for 48 h. It is concentrated to dryness, 50 ml of water are added and it is extracted with 3 x 75 ml of dichloromethane.

30 The organic phase is dried and concentrated. The residue is stirred with 10 ml of dichloromethane for 10 minutes and the precipitate obtained is filtered.

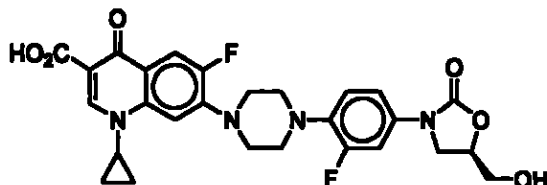
2 g of the product of the title are obtained thereby.

¹H-RMN (DMSO, 200 MHz, δ (ppm)): 9,84 (s.a., 1H); 8,64 (s, 1H); 7,92 (d, 1H); 7,61 (d, 1H); 7,50-7,30 (s.c., 6H); 7,22-7,01 (s.c., 2H); 5,18 (s, 2H); 3,92-3,78 (s.a., 5 1H); 3,70-3,10 (s.c., 8H); 1.42-1.10 (s.c., 4H).

Reference Example No.4:

1-cyclopropyl-6-fluoro-7-{4-[2-fluoro-4-5-(R)-hydroxymethyl-2-oxo-oxazolidin-3-yl]-phenyl]-piperazin-1-yl}-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid.

15



20 To 2.2 g (3.7 mmol) of the product obtained in the previous preparation in 60 ml of THF cooled to -78°C is added dropwise 3 ml (7.14 mmol) of n-butyllithium 2.5 M in hexane.

25 The reaction is maintained at -78°C for 1 h and then 0.51 g (3.57 mmol) of (R)-glycidil butirate dissolved in 10 ml of THF are added.

It is allowed to reach room temperature and stirred thus
30 for 16 h.

20 ml of saturated solution of ammonium chloride is added and it is concentrated until the THF is removed. 50 ml of

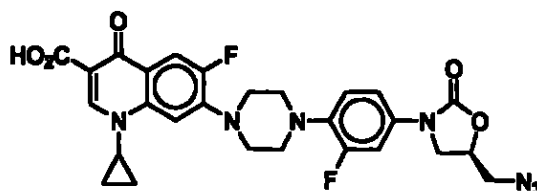
water are added and this is extracted with 3 x 100 ml of dichloromethane-ethanol (90/10).

The organic phase is dried and concentrated. The residue 5 is chromatographed on silica gel. Elution with dichloromethane-ethanol (90/10) yields 0.5 g of the product of the title.

¹H-RMN (DMSO-d₆, 200 MHz, δ (ppm)): 8,70 (s, 1H); 10 7,96 (d, 1H); 7,70-7,36 (s.c., 3H); 7,30-7,10 (s.c., 2H); 5,20-5,10 (s.a., 1H); 4,8-4,64 (m, 1H); 4,20-4,04 (m, 1H); 3,92-3,14 (s.c., 11H); 1,43-1,16 (s.c., 4H).

Reference Example No.5:

15 7-(4-[4-(5-(R)-azidomethyl-2-oxo-oxazolidin-3-yl)-2-fluoro-phenyl]-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



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Method 1:

To 0.5 g (0.92 mmol) of the product obtained in the previous preparation in 10 ml of dry dichloromethane is 25 added 2.6 ml of triethylamine and it is then cooled to 0°C. 1.4 ml of methanesulphonyl chloride is added and this is then stirred at 0°C for 1 h.

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It is poured onto water-ice(30 ml/20 g) saturated with sodium bicarbonate and the organic phase is decanted. It is dried on sodium sulphate, filtered and concentrated.

5 To the residue is added 10 ml of dimethylformamide and 1.17 g of sodium azide. This is heated to 75°C and stirred at this temperature for 16 h.

It is poured onto 100 ml of water and extracted with 3 x 10 100 ml of ethyl acetate. The organic phase is dried and concentrated and the residue is chromatographed on silica gel. Elution with dichloromethane-ethanol (90/10) yields 40 mg of the product of the title.

15 Method 2:

To 1.5 g (4.7 mmol) of 5-(R)-azidomethyl-3-(3-fluoro-4-piperazin-1-yl-phenyl)-oxazolidin-2-one (Reference Example No.19) and 1.9 g (4.7 mmol) of acid 1-cyclopropyl-7-20 chloro-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid diacethoxyboron chelate (obtained according to WO 8807998) in 60 ml of acetonitrile is added 0.4 g (4.7 mmol) of sodium bicarbonate and this is heated to reflux for 48 h.

25

It is concentrated to dryness and the residue is treated with 100 ml of water and extracted with 3 x 100 ml of CH₂Cl₂. The organic phase is dried and concentrated and the residue is chromatographed on silica gel.

30

Elution with CH₂Cl₂/EtOH 95/5 yields 1.1 g of the product of the title as diacetoxiboron chelate.

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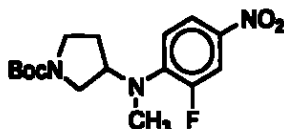
The 1.1 g thus obtained is dissolved in a mixture of 28 ml of water, 28 ml of acetonitrile and 8 ml of sodium hydroxide 1N. This is stirred at room temperature for 3 h, the acetonitrile is concentrated and 8 ml of hydrochloric 5 acid 1N is added.

The precipitated solid is filtered, yielding 0.6 g of product identical to that obtained by method 1.

¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 8,79 (s, 1H); 10 8,01 (d, 1H); 7,54-7,24 (s.c., 2H); 7,16-6,90 (s.c., 2H); 4,83-4,70 (m, 1H); 4,42-4,34 (m, 1H); 4,10-3,20 (s.c., 12H); 1.44-1.12 (s.c., 4H)

Reference Example No.6:

15 3(R,S)-[(2-fluoro-4-nitro-phenyl)-methylamino]-pyrrolidine-1-carboxylic acid tert-butyl ester



To 7 g (0.0375 mol) of 3(R,S)-methylamino-pyrrolidine-1-carboxylic acid tert-butyl ester and 4.11 ml (0.0375 mol) of 3,4-difluoronitrobenzene in 80 ml of DMF is added 3.15 g of sodium bicarbonate and this is heated at 45°C for 16 25 h.

It is poured onto 800 ml of water and extracted with 3 x 300 ml of AcOEt. The organic phase is dried and concentrated and the residue is chromatographed on silica 30 gel.

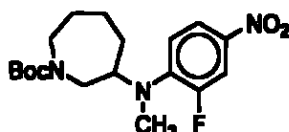
Elution with dichloromethane-ethanol 95/5 yields 7.9 g of the product of the title.

¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 8,00-7,88 (s.c, 2H); 6,88 (dd, 1H); 4,45-4,30 (m, 1H); 3,75-3,50 (s.a., 4H); 3,45-3,25 (s.c, 4H); 2,95 (s, 3H); 2,18-2,07 (m, 5 2H); 1.49 (s, 9H).

Reference Example No.7:

3(R, S)-[(2-fluoro-4-nitro-phenyl)-methyl-amino]-azepan-1- carboxylic acid tert-butyl ester.

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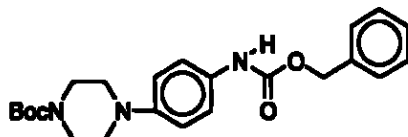
Following the previous procedure and using 3(R,S)-15 methylamino-azepan-1-carboxylic acid tert-butyl ester, the product of the title is obtained.

¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 8,10-7,80 (m, 2H); 6,90 (dt, 1H); 4,05-3,10 (m, 5H); 2,94 (m, 3H); 1.50 20 and 1.41 (s, 9H); 1.20-2,10 (m, 6H).

Reference Example No.8:

4-(4-Benzylloxycarbonylamino-phenyl)-piperazin-1- carboxylic acid tert-butyl ester.

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To 72.7 g (0.236 mol) of 4-(4-nitro-phenyl)-piperazin-1- carboxylic acid tert-butyl ester (WO 9725323), in 600 ml of THF and 125 ml of water is added 7.27 g of 10% Pd/C

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paste and it is placed under atmosphere of hydrogen at atmospheric pressure and room temperature.

When reduction of the nitro group has been completed (thin-layer chromatography eluted with heptane/AcOEt 1/1), 5.21 g (0.25 mol) of sodium bicarbonate and 40.2 g (0.236 mol) of benzyl chloroformate are added at 0°C.

It is shaken for 30 min at 0°C and filtered over decalite. The decalite is washed with 300 ml of THF and the filtrate 10 liquids are concentrated until the THF has been removed.

200 ml of water is added and 3 x 200 ml of dichloromethane is extracted. The organic phase is dried and concentrated and the residue is chromatographed on silica gel.

15

Elution with heptane/AcOEt yields 69.8 g (72%) of the product of the title.

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¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 7.42-7.24 (s.c., 7H); 6.86 (d.2H); 6.64 (s.a., 1H); 5.18 (s, 2H); 4.60-4.50 (s.c., 4H); 3.10-3.00 (s.c., 4H); 1.46 (s, 9H).

Using the procedure described above the following products 25 are obtained:

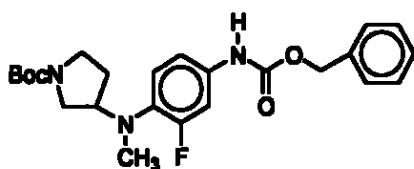
Reference Example No.9:

3(R, S) - [(4-benzoyloxycarbonylamino-2-fluoro-phenyl)-methyl-amino]-pyrrolidine-1-carboxylic acid tert-butyl ester.

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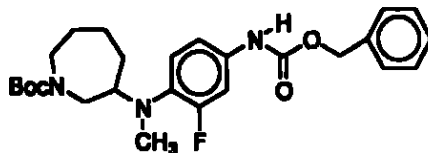
¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 7,42-7,26 (s.c. 6H); 7,01-6,92 (s.c., 3H, 2H aromatic + NH); 5,19 (s, 2H); 3,86-3,65 (m, 1H); 3,60-3,36 (s.c., 3H); 3,36-3,12 (s.c., 2H); 2,71 (s, 3H); 2,10-1,75 (s.c., 2H); 1,42 (s, 9H).

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Reference Example No.10:

3(R, S) - [(4-benzylloxycarbonylamino-2-fluoro-phenyl) - methyl-amino] - azepan-1-carboxylic acid tert-butyl ester.

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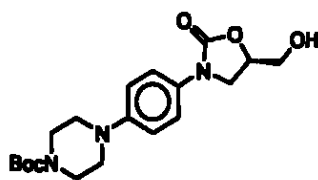
¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 7,60-7,20 (m, 5H); 7,20-6,80 (m, 3H); 3,95-2,90 (m, 5H); 2,71 (s, 3H); 1,45 and 1,37 (s, 9H); 1,05-2,00 (m, 6H).

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Reference Example No.11:

4- [4- (5- (R) -hydroxymethyl-2-oxo-oxasolidin-3-yl)phenyl] - piperazin-1-carboxylic acid tert-butyl ester.

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Following a procedure analogous to that of Reference Example No.4 and using 69.2 g (0.169 mol) of the product obtained in Reference Example No.8, 44.4 g (70%) of the product of the title is obtained.

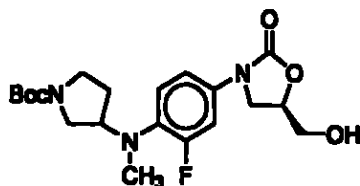
5 ^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 7.42 (d, 2H); 6.92 (d, 2H); 4.80-4.64 (s.c., 1H); 4.02-3.90 (s.c., 3H); 3.80-3.64 (m, 1H); 3.62-3.72 (s.c., 4H); 3.14-3.04 (s.c., 4H); 2.77 (t, 1H, OH); 1.45 (s, 9H).

10 As in the previous preparation, and following the procedure described in Reference Example No.4, the following products are obtained:

Reference Example No.12:

15 3-(R, S)-{[2-fluoro-4-(5-(R)-hydroxymethyl-2-oxo-oxazolidin-3-yl)-phenyl]-methyl-amino}-pyrrolidine-1-carboxylic acid tert-butyl ester.

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^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 7.41 (dd, 1H); 7.14-7.00 (s.c., 2H); 4.80-4.64 (m, 1H); 4.02-3.64 (s.c., 5H); 3.62-3.40 (s.c., 2H); 3.38-3.18 (s.c., 2H); 2.78 30 (s.a., 1H, OH); 2.70 (s, 3H); 2.06-1.80 (s.c., 2H); 1.42 (s, 9H).

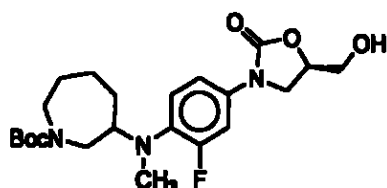
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Reference Example No.13:

3-(R, S)-{[2-fluoro-4-(5-(R)-hydroxymethyl-2-oxo-oxazolidin-3-yl)-phenyl]-methyl-amino}-azepan-1-carboxylic acid tert-butyl ester.

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¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 7,95 (m, 1H); 7,40 (dd, 1H); 7,10 (m, 1H); 4,75 (m, 1H); 4,10-3,00 (m, 9H); 2,73 and 2,76 (s, 3H); 1.39 and 1.46 (s, 9H); 1.20-2,00 (m, 6H).

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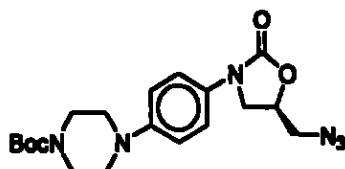
Following the procedure described in method 1 of Reference Example No.5 and using respectively the products obtained in reference examples 11 to 13, the following products are obtained:

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Reference Example No.14:

4-[4-(5-(R)-azidomethyl-2-oxo-oxazolidin-3-yl)-phenyl]-piperazin-1-carboxylic acid tert-butyl ester.

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¹H-RMN (DMSO-d₆, 200 MHz, δ (ppm)): 7,44 (d, 2H); 7.02 (d, 2H); 4,96-4,84 (m, 1H); 4,17 (t, 1H); 3,84-3,62 (s.c., 2H); 3,56-3,30 (s.c., 5H); 3,17-3,04 (s.c., 4H); 1.42 (s, 9H).

4X

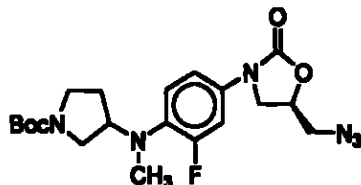
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Reference Example No.15:

3-(R, S)-{[4-(5(R)-azidomethyl-2-oxo-oxazolidin-3-yl)-2-fluoro-phenyl]-methyl-amino}-pyrrolidine-1-carboxylic acid tert-butyl ester.

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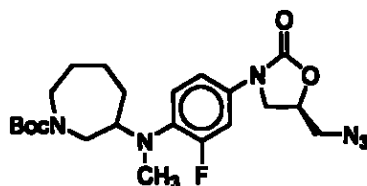


¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 7,41 (dd, 1H); 7,16-7,01 (s.c., 2H); 4,86-4,72 (m, 1H); 4,06 (t, 1H); 15 3,95-3,40 (s.c., 6H); 3,38-3,17 (s.c., 2H); 2,73 (s, 3H); 2,10-1,73 (s.c., 2H); 1,45 (s, 9H).

Reference Example No.16:

3-(R, S)-{[4-(5(R)-azidomethyl-2-oxo-oxazolidin-3-yl)-2-fluoro-phenyl]-methyl-amino}-azepan-1-carboxylic acid tert-butyl ester.

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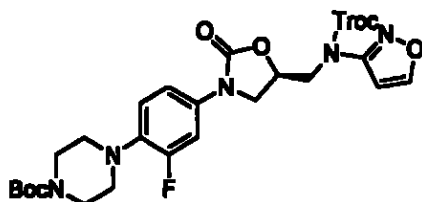
¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 7,35 (m, 1H); 30 7,20-6,80 (m, 2H); 4,75 (m, 1H); 4,05 (t, 1H); 3,95-3,00 (m, 8H); 2,74 (m, 3H); 2,00-1,00 (m, 6H); 1,46 and 1,39 (s, 9H).

Reference Example No.17:

4-[2-Fluoro-4-(5-(R)-{[isoxazol-3-yl-(2,2,2-trichloroethoxycarbonyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-phenyl]-piperazin-1-carboxylic acid tert-butyl ester.

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3.4 g (13 mmol) of 3-(2,2,2-trichloroethoxycarbonylamino)-isoxazol (prepared according to WO 0021960) is dissolved in 100 ml of DMF, and 536 mg (14.3 mmol) of sodium hydride (60% paste) is added in portions and stirred for 30 minutes. 6 g (12.7 mmol) of 4-(2-Fluoro-4-[2-oxo-5-(R)-(toluene-4-sulphonyloxymethyl)-oxazolidin-3-yl]-phenyl)-piperazine-1-carboxylic acid tert-butyl ester (obtained according to US 5547950) is then added dissolved in 30 ml of DMF.

The reaction is heated to 90°C for 20 h. It is allowed to cool and is poured onto 500 ml of water. It is extracted with 3x250 ml of a 4/1 mixture of toluene/ethyl acetate. The organic phase is dried and concentrated and the residue is chromatographed on silica gel.

Elution with Heptane/Ethyl acetate 7/3 yields 2.5 g of the product of the title.

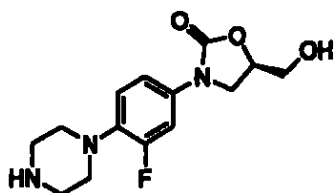
¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 8,34 (d, 1H); 7,45 (dd, 1H); 7,12 (m, 1H); 6,95 (m, 2H); 5,15 (m, 1H);

4,90 (m, 2H); 4,50 (dd, 1H); 4,25 (dd, 1H); 4,13 (t, 1H);
3,85 (dd, 1H); 3,60 (m, 4H); 3,00 (m, 4H); 1.49 (s, 9H).

Reference Example No.18:

5 3-(3-Fluoro-4-piperazin-1-yl-phenyl)-5-(R)-
hydroxymethyl-oxazolidin-2-one

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To 5 g (0.0126 mol) of 4-[2-fluoro-4-(5-(R)-
15 hydroxymethyl-2-oxo-oxazolidin-3-yl)-phenyl]-piperazin-1-
carboxylic acid tert-butyl ester (obtained according to US
5547950) in 100 ml of ethanol is added 2.6 g (0.0139 mol)
of para-toluenesulphonic acid and this is heated to reflux
for 16 h. It is concentrated to dryness and the residue is
20 chromatographed on silica gel (80 g) to the upper part of
which alumina (20 g) is added.

Elution with dichloromethane/ethanol/ammonium
hydroxide (90/10/1%) yields 1.6 g of the product of the
25 title.

¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 7,50 (d.d., 1H);
7,24-7,00 (s.c, 2H); 4,70 (m, 1H); 4,04 (t, 1H); 3,82-3,42
(s.c, 3H); 2,86 (s.a, 8H).

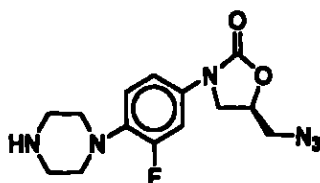
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Reference Example No.19:

5-(R)-azidomethyl-3-(3-fluoro-4-piperazin-1-yl-phenyl)-oxazolidin-2-one.

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To 5 g (0.011 mol) of 4-[4-(5-(R)-azidomethyl-2-oxo-oxazolidin-3-yl)-phenyl]-piperazin-1-carboxylic acid tert-butyl ester (obtained according to US 5547950) in 100 ml of ethanol is added 2.4 g (0.013 mol) of p-toluenesulphonic acid.

It is heated to reflux for 16 h. Once the reaction has ended it is concentrated to dryness and the residues pass through a column of silica gel (100 g) containing 25 g of alumina in the upper part.

Elution with dichloromethane/ethanol/ammonium hydroxide (80/20/1%) yields 3.5 g of the product of the title.

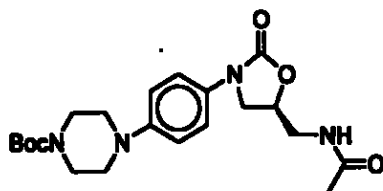
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¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 7,42 (dd, 1H); 7,10 (dd, 1H); 6,94 (t, 1H); 4,84-4,76 (m, 1H); 4,05 (t, 1H); 3,83-3,50 (s.c, 3H); 3,03 (s, 3H).

Reference Example No.20:

4-(4-5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl)-phenyl}-piperazin-1-carboxylic acid tert-butyl ester.

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To 40 g (0.0668 mol) of the product of Reference Example No.14 in 1,000 ml of ethyl acetate is added 4 g of 10% Pd/C paste and it is placed under atmosphere of hydrogen at atmospheric pressure and room temperature. When reduction of the azide group has finished (thin-layer chromatography), it is cooled to 0°C and 8.4 ml (0.103 mol) of pyridine and 13.4 ml (0.103 mol) of acetic anhydride are added.

20

It is stirred at 0°C for 30 min and then for 16 h at room temperature. It is filtered over decalite and the filtration liquids are concentrated to dryness.

25 The residue is chromatographed on silica gel. Elution with dichloromethane/ethanol 95/5 yields 27 g (97%) of the product of the title.

¹H-RMN (DMSO, 200 MHz, δ (ppm)): 8,30 (t, 1H, NH); 7,41 (d, 2H); 7,00 (d, 2H); 4,80-4,60 (m, 1H); 4,10 (t, 1H); 3,72 (t, 1H); 3,55-3,38 (s.c., 6H); 3,15-3,03 (s.c., 4H); 1.83 (s, 3H); 1.42 (s, 9H).

52

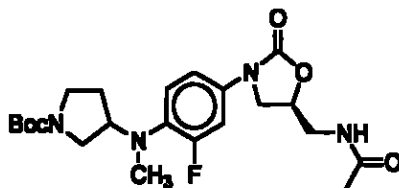
S1

Following the procedure described above and using the products of reference examples No. 15 and No. 16, the following products are obtained:

5 **Reference Example No.21.**

3-(R, S)-({4-5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-methyl-amino)-pyrrolidine-1-carboxylic acid tert-butyl ester.

10



15

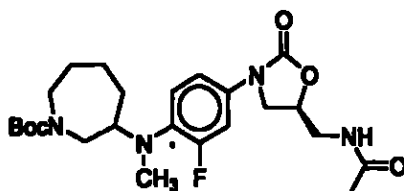
^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 7,41 (dd, 1H); 7,10-7,00 (s.c., 2H); 6,61 (t, 1H, NH); 4,82-4,70 (m, 1H); 4,02 (t, 1H); 3,97-3,40 (s.c., 6H); 3,40-3,18 (s.c., 2H); 2,75 (s, 3H); 2,10-1,80 (s.c., 2H); 1,42 (s, 9H).

20

Reference Example No.22.

3-(R, S)-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-azepan-1-carboxylic acid tert-butyl ester.

25



30

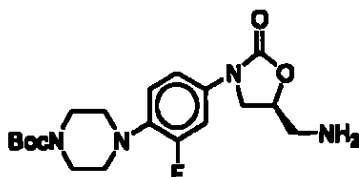
^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 7,35 (dd, 1H); 7,15-6,85 (m, 2H); 6,45 (m, 1H); 4,75 (m, 1H); 4,01 (t,

1H); 3,90-3,00 (m, 8H); 2,76 and 2,23 (s, 3H); 2,03 (s, 3H); 1,46 and 1,39 (s, 9H); 2,00-1,10 (m, 6H).

Reference Example No.23.

5 4-[4-(5-(S)-aminomethyl-2-oxo-oxazolidin-3-yl)-2-fluoro-phenyl]-piperazin-1-carboxylic tert-butyl ester.

10



To 30 g (0.071 mol) of 4-[4-(5-(R)-azidomethyl-2-oxo-oxazolidin-3-yl)-phenyl]-piperazin-1-carboxylic acid tert-butyl ester (obtained according to US 5547950) in 300 ml of ethanol is added 3 g of 10% Pd/C paste and it is placed under atmosphere of hydrogen at atmospheric pressure and room temperature. When the reaction has finished (thin-layer chromatography eluted with dichloromethane-ethanol 95/5) it is filtered over decalite and the decalite washed with 50 ml of ethanol.

The filtering liquids are concentrated to dryness and the residue is chromatographed on silica gel.

Elution with dichloromethane/ethanol/ammonium hydroxide 90/10/1% yields 14 g (50%) of the product of the title.

30

¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 7,47 (dd, 1H); 7,13 (dd, 1H); 6,94 (t, 1H); 4,75-4,60 (m, 1H); 4,01 (t, 1H); 3,82 (dd, 1H); 3,62-3,51 (s.c., 4H); 3,20-2,90 (s.c., 6H); 1,50 (s, 9H); 1,40 (s.a., 2H, NH₂).

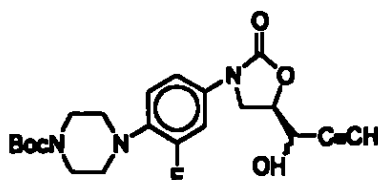
74

S3

Reference Example No.24.

4-{2-fluoro-4-[5-(R)-(1-(R,S)-hydroxy-prop-2-ynyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-carboxylic acid tert-butyl ester.

5



10

To 2.4 g (32.2 mmol) of tert-butanol in 30 ml of dry tetrahydrofuran, cooled to -10°C, is added 9.2 ml (23 mmol) of n-BuLi (2.5 M in hexane).

15 It is stirred for 30 min and allowed to reach a temperature of 0°C. 4.49 g (10 mmol) of 4-(4-benzyloxycarbonylamino-2-fluoro-phenyl)-piperazin-1-carboxylic acid tert-butyl ester (obtained according to US 5547950) is then added, dissolved in 10 ml of dry
20 dimethylformamide.

After stirring for 10 min at 0°C, 3.4 g (12.5 mmol) of 2,3-hydroxy-pent-4-ynyl p-toluenesulphonate (obtained according to EP 1029854 A1) dissolved in 5 ml of DMF is
25 then added dropwise.

It is allowed to reach room temperature and stirred for 16 h. It is poured onto 200 ml of saturated solution of sodium bicarbonate and extracted with 3 x 150 ml of ethyl
30 acetate. The organic extracts are washed with 150 ml of water. The organic phase is dried and concentrated and the residue is chromatographed on silica gel.

¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 7,45 (dd, 1H); 5 7,15 (m, 1H); 6,95 (t, 1H); 4,75 (m, 2H); 4,30-2,90 (m, 3H); 3,60 (m, 4H); 3,00 (m, 4H); 2,53 (d, 1H); 1.48 (s, 9H).

Reference Example No.25.

20

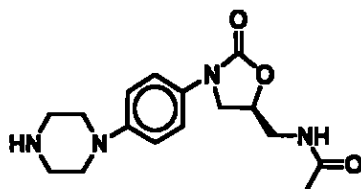


¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 8,34 (d, 1H); 7,42 (dd, 1H); 7,10 (dd, 1H); 6,95 (m, 2H); 5,15 (m, 1H); 4,95 (m, 2H); 4,52 (dd, 1H); 4,25 (dd, 1H); 4,12 (t, 1H); 3,80 (dd, 1H); 3,12 (m, 8H).

Reference Example No.26.

N-[2-oxo-3-(4-piperazin-1-yl-phenyl)-oxazolidin-5-(S)-ylmethyl]acetamide.

5



10

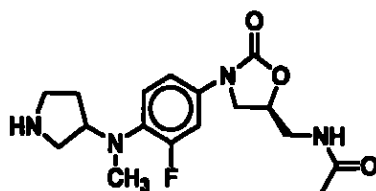
¹H-RMN (DMSO-d₆, 200 MHz, δ (ppm)): 8,30 (t, 1H, NH); 7,41 (dd, 2H); 7,00 (dd, 2H); 4,80-4,60 (m, 1H); 4,06 (t, 1H); 3,71 (dd, 1H); 3,42 (t, 2H); 3,30-3,10 (s.c., 8H); 1.82 (s, 3H).

15

Reference Example No.27.

N-{3(R,S)-[3-fluoro-4-(methyl-pyrrolidine-3-yl-amino)-phenyl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide.

20



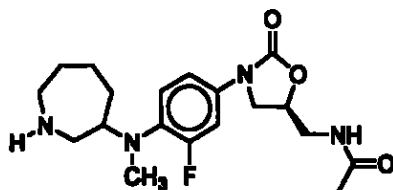
25

¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 7,39 (dd, 1H); 7,10-6,97 (s.c., 2H); 6,49 (t, 1H, NH); 4,83-4,70 (m, 1H); 4,02 (t, 1H); 3,90-3,60 (s.c., 4H); 3,13-2,80 (s.c., 30 4H); 2,72 (s, 3H); 2,02 (s, 3H); 2,00-1.65 (s.c., 2H).

Reference Example No.28.

N-{3(R,S)-[4-(azepan-3-yl-methyl-amino)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide.

5



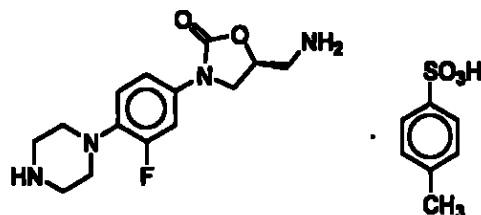
10

¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 7,35 (dd, 1H); 7,05 (m, 1H); 6,90 (t, 1H); 6,75 (t, 1H, NH); 4,75 (m, 1H); 4,00 (t, 1H); 3,90-3,30 (m, 4H); 3,20-2,60 (m, 4H); 2,72 (s, 3H); 2,30 (s.a., 1H); 2,02 (s, 3H); 1.90-1.00 (m, 15 6H).

Reference Example No.29.

p-toluenesulphate of 5-(S)-aminomethyl-3-(3-fluoro-4-piperazin-1-yl-phenyl)-oxazolidin-2-one.

20



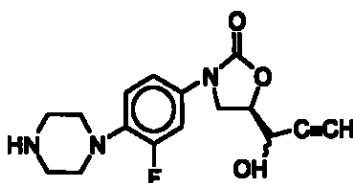
25

¹H-RMN (DMSO-d₆, 200 MHz, δ (ppm)): 7,56 (dd, 1H); 7,50 (d, 2H); 7,22-7,06 (s.c., 4H); 4,90-4,74 (m, 1H); 4,14 (t, 1H); 3,84-3,76 (m, 1H); 3,25-3,05 (s.c., 10H); 30 2,26 (s, 3H).

Reference Example No.30.

3-(3-fluoro-4-piperazin-1-yl-phenyl)-5-(R)-(1-(R,S)-hydroxy-prop-2-ynyl)-oxazolidin-2-one.

5



10

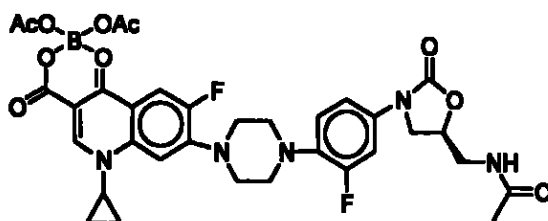
¹H-RMN (DMSO-d₆, 200 MHz, δ (ppm)): 7,50 (m, 1H); 7,20 (m, 1H); 7,03 (m, 1H); 6,15 (s.a., 1H); 4,70 (m, 1H); 4,52 (m, 1H); 4,10 (t, 1H); 3,85 (m, 1H); 3,25 (m, 1H); 3,23 (s.a., 1H).

15

Reference Example No.31:

7-(4-(-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl)-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid diacethoxyboron
20 chelate.

25



30

To 1 g (3 mmol) of N-[3-(3-Fluoro-4-piperazin-1-yl-phenyl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide (obtained according to US 5547950) in 30 ml of acetonitrile are added 1.22 g of 7-chloro-1-cyclopropyl-6-

fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
diacethoxyboron chelate (obtained according to WO 8807998)
and 0.43 ml (3 mmol) of triethylamine.

5 The reaction is heated to reflux for 16 h. It is
concentrated to dryness and the residue is chromatographed
on silica gel.

Elution with dichloromethane/ethanol 90/10 yields 0.8 g of
10 the product of the title.

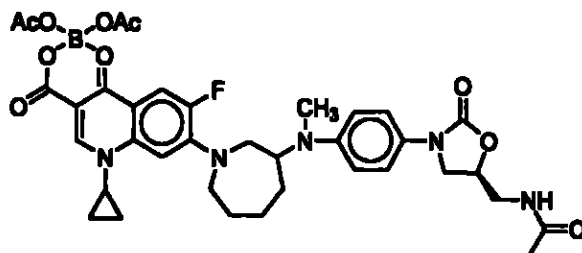
¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 9,04 (s, 1H);
8,10 (d, 1H); 7,56-7,44 (s.c., 2H); 7,08 (dd, 1H); 6,97
(t, 1H); 6,38 (t, 1H, NH); 4,82-4,68 (m, 1H); 4,01 (t,
15 1H); 3,90-3,56 (s.c., 8H); 3,30-3,20 (s.a., 4H); 2,04 (s,
6H); 2,02 (s, 3H); 1.90-1.20 (s.c., 2H).

Reference Example No.32.

7- [3- (R,S) - ({4- [5- (S) - (acetylamino-methyl) -2-oxo-
20 oxazolidin-3-yl] -2-fluoro-phenyl} -methylemino) -azepan-1-
yl] -1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-
carboxylic acid diacethoxyboron chelate.

25

30



Following the procedure of the previous example and using
the product obtained in Reference Example No. 28, the
product of the title is obtained.

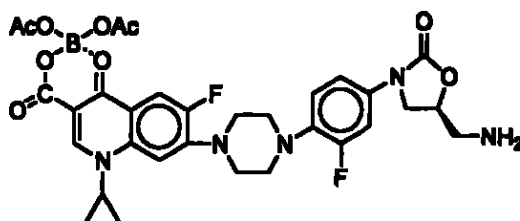
¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 8,94 (s, 1H); 8,30 (t, 1H); 7,90 (d, 1H); 7,60-7,40 (m, 2H); 7,30-7,10 (m, 2H); 4,75 (m, 1H); 4,30-3,40 (m, 10H); 2,80 (s, 3H); 2,10-1.05 (m, 10H); 1.93 (s, 6H); 1.88 (s, 3H).

5

Reference Example No.33.

7-(4-[4-(5-(S)-aminomethyl-2-oxo-oxasolidin-3-yl)-2-fluoro-phenyl]-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
10 diacethoxyboron chelate.

15



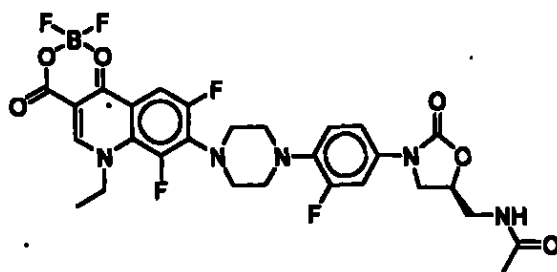
20 Following the procedure described in Reference Example No. 31 and using the product obtained in Reference Example No. 29 and using 2 equivalents of triethylamine instead of only one equivalent, the product of the title is obtained.

25 ¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 9,03 (s, 1H); 8,04 (d, 1H); 7,82 (d, 1H); 7,59 (dd, 1H); 7,24 (dd, 1H); 7,17 (t, 1H); 4,70-4,56 (m, 1H); 4,14 (s.a., 1H); 4,08 (t, 1H); 3,84 (dd, 1H); 3,64 (s.a., 4H); 3,23 (s.a., 4H); 2,90-2,70 (s.c., 2H); 2,20 (s.a., 2H, NH₂); 1.90 (s, 6H);
30 1.50-1.20 (s.c., 4H).

Reference Example No.34.

7-(4-{5-[5-(8)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6,8-difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid boron
5 difluoride chelate.

10



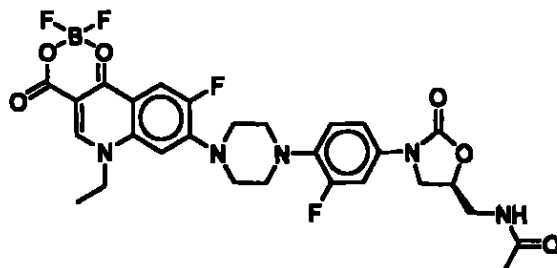
Following a procedure analogous to that described in
 15 Reference Example No. 31 and using 1-ethyl-6,7,8-
 trifluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
 boron difluoride chelate (obtained according to WO
 8807998) the product of the title is obtained.

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 9,44 (s, 1H);
 20 8,27 (t, 1H, NH); 8,09 (d, 1H); 7,54 (dd, 1H); 7,30-7,06
 (s.c., 2H); 5,00-4,60 (s.c., 3H); 4,10 (t, 1H); 3,80-2,95
 (s.c., 11H); 1.85 (s, 3H); 1.55 (t, 3H).

Reference Example No.35.

25 7-(4-{4-[5-(8)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid boron
difluoride chelate.

30

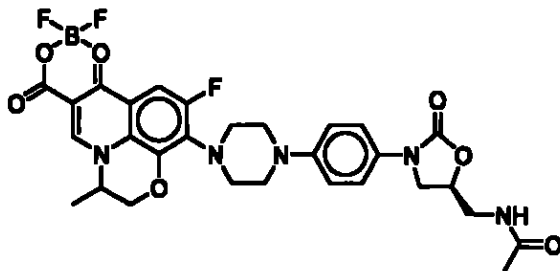


Following a procedure analogous to that described in Reference Example No. 31 and using 7-chloro-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid boron difluoride chelate (obtained according to JP 59122470) the product of the title is obtained.

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 9,42 (s, 1H); 8,30 (t, 1H, NH); 8,17 (d, 1H); 7,60-7,40 (s.c., 2H); 7,25-7,05 (s.c., 2H); 4,90 (c, 2H); 4,80-4,60 (m, 1H); 4,14 (t, 1H); 3,80-2,90 (s.c., 11H); 1.84 (s, 3H); 1.52 (t, 3H).

Reference Example No.36.

9-(4-{4-[5-(8)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3-aza-phenalen-5-carboxylic acid boron difluoride chelate.



Using 8,9-difluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid boron difluoride chelate (obtained according to JP 58029789) and following a procedure analogous to that described in Reference Example No.31 the product of the title is obtained.

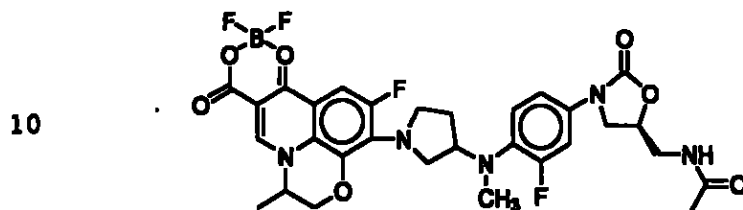
¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 9,44 (s, 1H); 8,30 (t, 1H, NH); 7,84 (d, 1H); 7,43 (d, 2H); 7,05 (d, 2H); 5,30-5,10 (m, 1H); 4,80-4,30 (s.c., 3H); 4,10 (t, 1H); 3,80-3,15 (s.c., 11H); 1.84 (s, 3H); 1.58 (d, 3H).

63

62

Reference Example No.37.

9-[3-({4-[5-(8)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluorophenyl}-methyl-amino)-pyrrolidone-1-yl]-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-
5 phenalen-5-carboxylic acid boron difluoride chelate.



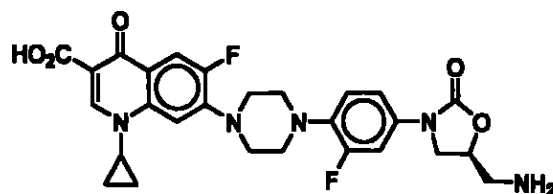
In a manner analogous to the previous example and using
15 the compound obtained in Reference Example No.27 the
product of the title is obtained.

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 9,36 (s, 1H);
8,25 (t, 1H, NH); 7,74 (d, 1H); 7,50 (dd, 1H); 7,30-7,10
20 (s.c., 2H); 5,20-3,00 (s.c., 13H); 2,78 (s, 3H); 1.82 (s,
3H); 2,20-1.80 (s.c., 2H); 1.50 (d, 3H).

Reference Example No.38.

4-{4-[4(5-(8)-aminomethyl-2-oxo-oxazolidin-3-yl)-2-fluoro-
25 phenyl]-piperazin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-
dihydro-quinoline-3-carboxylic acid.

30



G3

Method 1:

To 13.3 g (0.02 mol) of the product obtained in Reference Example No.33 in 300 ml of acetonitrile and 300 ml of water is added 96 ml (0.096 mol) of sodium hydroxide 1N.

It is stirred at room temperature for 2 h. The acetonitrile is concentrated in a rotovapor and to the resulting aqueous solution is added 96 ml of hydrochloric acid 1 N.

The precipitate formed is filtered to yield 2.8 g. The filtering liquids are extracted with 4 x 200 ml of dichloromethane/ethanol 90/10. The extracts are dried and concentrated, thus yielding a further 6.8 g of the product of the title.

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 8,70 (s, 1H); 7,95 (d, 1H); 7,63 (d, 1H); 7,58 (dd, 1H); 7,26-7,10 (s.c., 2H); 4,80-4,60 (m, 1H); 4,08 (t, 1H); 3,96-3,80 (s.c., 2H); 3,50 (s.a., 4H + NH₂); 3,23 (s.a., 4H); 3,00-2,80 (s.c., 2H); 1.42-1.15 (s.c., 4H).

Method 2:

To 40 mg of the product obtained by method 1 of Reference Example No.5, dissolved in 10 ml of ethanol, is added 0.10 mg of 10% Pd/C paste, and it is placed under atmosphere of hydrogen at atmospheric pressure and room temperature. When the reaction finishes it is filtered over decalite, which is washed with 2 x 10 ml of ethanol.

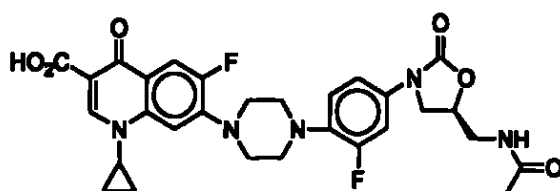
The filtering liquids are concentrated to dryness and thus yield 20 mg of a product identical to that obtained by method 1.

5 COMPOUNDS OF GENERAL FORMULA (I)

Example 1:

7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-
10 fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

15



To 0.8 g (1.13 mol) of the product of Reference Example No.31 in 20 ml of water and 20 ml of acetonitrile is added 5.6 ml of sodium hydroxyde 1N, and it is stirred at room
20 temperature for 1 h.

The acetonitrile is concentrated and the aqueous phase is acidified with 5.6 ml of hydrochloric acid 1N.

It is extracted with 3 x 50 ml of dichloromethane/ethanol 9/1.

25

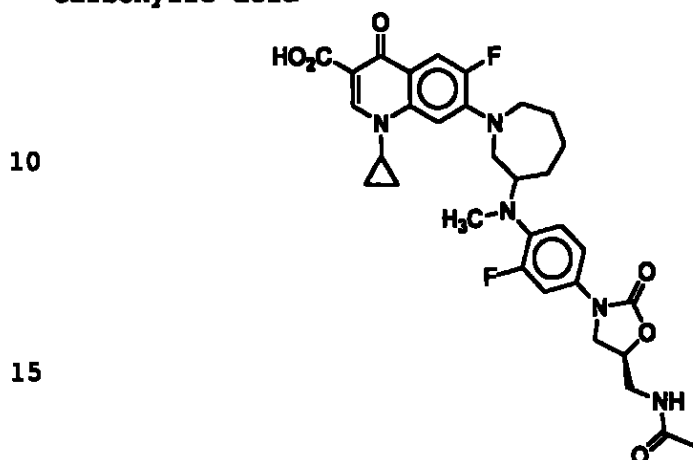
The organic phase is dried and concentrated. The residue is stirred for 10 min with 2-propanol and the precipitated solid is filtered. Thus are obtained 290 mg of the product of the title.

30

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 8,72 (s, 1H); 8,33 (t, 1H, NH); 7,99 (d, 1H); 7,64 (d, 1H); 7,58 (dd, 1H); 7,30-7,10 (s.c., 2H); 4,84-4,64 (m, 1H); 4,16 (t, 1H); 3,90-2,90 (s.c., 12H); 1,90 (s, 3H); 1,44-1,16 (s.c., 4H).

Example 2:

7-[3-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-azepan-1-yl]-1-
5 cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-
carboxylic acid



It is obtained by following the procedure of Example 1 and
using the product obtained in Reference Example No.32.

20

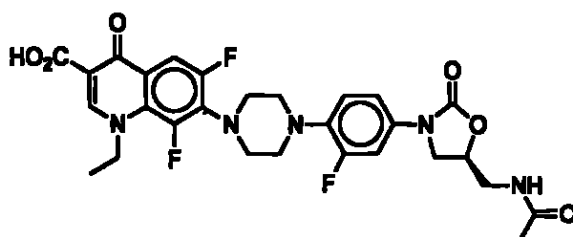
¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 8,59 (s, 1H);
8,30 (t, 1H, NH); 7,80 (d, 1H); 7,50 (dd, 1H); 7,30 (d,
1H); 7,25-7,05 (s.c., 2H); 4,75 (m, 1H); 4,20-3,20 (m,
10H); 2,76 (s, 3H); 2,20-1.00 (m, 10H); 1.86 (s, 3H).

25

Example 3:

7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-
yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6,8-difluoro-
4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

30



To 1.9 g (3mmol) of the product obtained in Reference Example No.34 in 100 ml of ethanol and 2.5 ml of water is added 10 ml of triethylamine, and it is heated to reflux 5 for 16 h.

The precipitated salts are filtered. The filtering liquids are concentrated to dryness and the residue is treated with 50 ml of water and the pH adjusted to 5 by addition 10 of hydrochloric acid 1N.

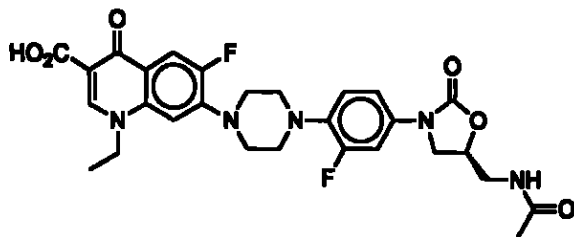
It is extracted with 3 x 75 ml of dichloromethane/ethanol 9/1. The organic phase is dried and concentrated. Thus are obtained 1.2 g of a white solid.

15 ¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 8,94 (s, 1H); 8,30 (t, 1H, NH); 7,87 (d, 1H); 7,50 (dd, 1H); 7,25-7,02 (s.c., 2H); 4,80-4,30 (s.c., 3H); 4,10 (t, 1H); 3,80-3,20 (s.c., 7H); 3,10 (s.a., 4H); 1,82 (s, 3H); 1,42 (t, 3H).

20 **Example 4:**

7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

25



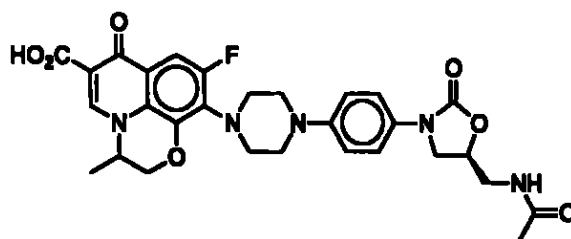
30

Following the procedure of the previous example and using the product obtained in Reference Example No.35 the product of the title is achieved.

5 ¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 8,99 (s, 1H); 8,30 (t, 1H, NH); 7,96 (d, 1H); 7,54 (d, 1H); 7,20-7,05 (s.c., 3H); 5,00-4,56 (s.c., 3H); 4,14 (t, 1H); 3,90-3,10 (s.c., 11H); 1,82 (s, 3H); 1,60-1,35 (s.a., 3H).

10 **Example 5:**

9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid



15

Following the procedure described in Example 3 and using the product obtained in Reference Example No.36 the product of the title is achieved.

20 ¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 9,00 (s, 1H); 8,26 (t, 1H, NH); 7,62 (d, 1H); 7,41 (d, 2H); 7,02 (d, 2H); 5,05-4,90 (m, 1H); 4,80-4,75 (s.c., 2H); 4,41 (d, 1H); 4,10 (t, 1H); 3,80-3,00 (s.c., 11H); 1,84 (s, 3H); 1,46 (d, 3H).

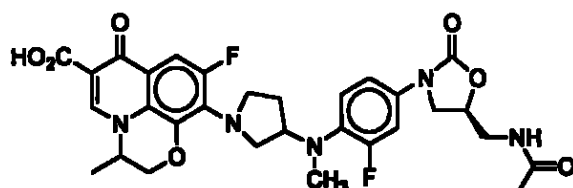
25

Example 6:

9-[3-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-pyrrolidin-1-yl]-8-

fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid

5



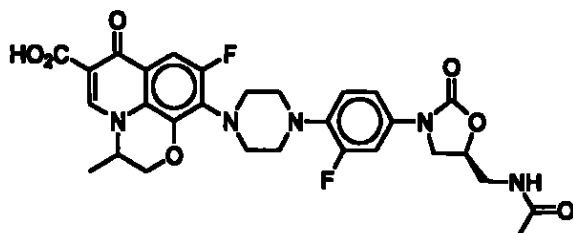
10 Following the procedure of Example No.3 and using the product of Reference Example No.37 the product of the title is obtained.

^1H -RMN (DSMO- d_6 , 200 MHz, δ (ppm)): 8,92 (s, 1H); 8,30 (t, 1H, NH); 7,60-7,40 (s.c., 2H); 7,30-7,10 (s.c., 2H); 4,95-4,80 (m, 1H); 4,80-4,45 (s.c., 3H); 4,40-4,20 (s.c., 1H); 4,10 (t, 1H), 4,02-3,20 (s.c., 7H); 2,70 (s, 3H); 2,20-1,90 (s.c., 2H); 1,84 (s, 3H); 1,45 (s.a., 3H).

20 Example 7:

9-(4-{4-[5-(8)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid

25



30

To 1.6 g (5mmol) of 8,9-difluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid boron difluoride chelate and 1.7 g (5mmol) of N-[3-(3-Fluoro-4-piperazin-1-yl-phenyl)-2-oxo-oxazolidin-5-(8)-ylmethyl]-

acetamide (obtained according to US 5547950) in 50 ml of N-methyl-pyrrolidin-2-one is added 0.7 ml (5mmol) of triethylamine and it is heated at 110°C for 16 h.

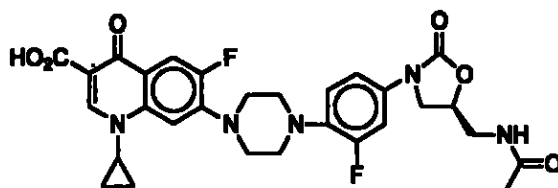
5 The solvent is distilled under vacuum and the residue is stirred for 30 min with dichloromethane/ethanol, precipitating a solid which is filtered and yields 1.2 g (40%) of pure product.

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 9,00 (s, 1H); 10 8,25 (t, 1H, NH); 7,62 (d, 1H); 7,52 (dd, 1H); 7,30-7,10 (s.c., 2H); 4,99 (m, 1H); 4,80-4,60 (m, 1H); 4,62 (d, 1H); 4,40 (d, 1H); 4,10 (t, 1H); 3,80-3,60 (m, 1H); 3,60-2,80 (s.c., 10H); 1,84 (s, 3H); 1,50 (d, 3H).

15 **Example 8:**

7-(4-{4-[5-(8)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

20



25 To 6 g (0.011 mol) of the product of Reference Example No.38 in 100 ml of pyridine is added 2.8 ml (0.022 mol) of acetic anhydride. It is heated at 50°C for 2 h. The pyridine is concentrated to dryness and to the residue is added 200 ml of water and it is stirred for 5 min. The
30 precipitated solid is filtered and dissolved in dichloromethane and chromatographed on silica gel. Elution with dichloromethane-ethanol 90/10 yields 4 g (63%) of pure product identical to that obtained in Example 1.

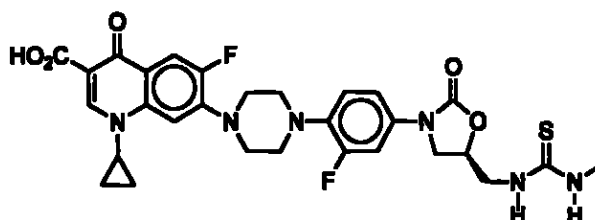
7/

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Example 9:

1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-methylthioureido)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

10



To 0.81 g (1.5 mmol) of the product of Reference Example No.38 in 10 ml of pyridine is added 0.22 g (3 mmol) of methylisothiocyanate. It is heated at 60°C for 10 minutes. It is concentrated to dryness and the residue is stirred for 20 min with 30 ml of water. The precipitated solid is filtered and 0.5 g of pure product is obtained.

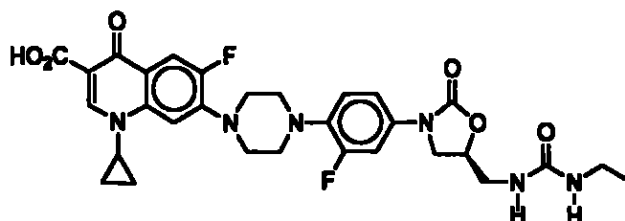
¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 8,70 (s, 1H); 7,98 (d, 1H); 7,82 (t, 1H, NH); 7,80-7,50 (s.a., 1H, NH); 7,64 (d, 1H); 7,56 (dd, 1H); 7,30-7,10 (s.c., 2H); 4,95-4,80 (m, 1H); 4,16 (t, 1H); 4,00-3,70 (s.a., 4H); 3,60-3,40 (s.a., 4H); 3,30-3,10 (s.a., 4H); 2,82 (s.a., 3H); 1.44 -1.16 (s.c., 4H).

25

Example 10:

1-cyclopropyl-7-[4-(4-{5-(S)-[(3-ethyl-ureido)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

30



In a similar way to the previous Example and replacing the methylisothiocyanate by ethylisocyanate the product of the title is obtained.

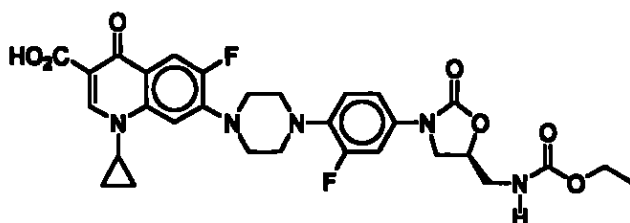
5

¹H-RMN (DSMO-d₆, 200 MHz, 8 (ppm)): 8,70 (s, 1H); 7,96 (d, 1H); 7,66 (d, 1H); 7,58 (dd, 1H); 7,30-7,10 (s.c., 1H); 6,22 (t, 1H, NH); 5,99 (t, 1H, NH); 4,80-4,64 (s.c., 1H); 4,10 (t, 1H); 3,90-3,78 (m, 1H); 3,72 (dd, 10 1H); 3,60-3,20 (s.c., 10H); 3,10-2,90 (s.c., 2H); 1.44-1.10 (s.c., 4H); 0.98 (t, 3H).

Example 11:

1-cyclopropyl-7-(4-{4-[5-(S)-(ethoxycarbonylamino-methyl)-
15 2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

20



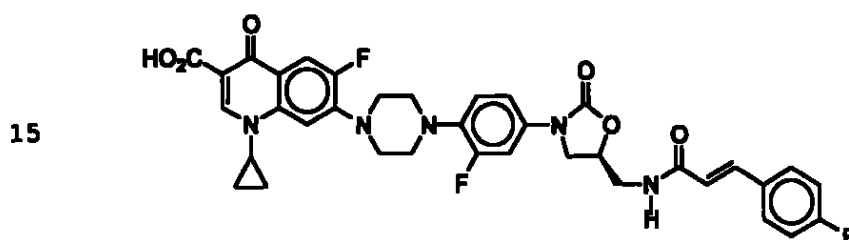
To 0.81 g of the product of Reference Example
25 No.38 in 20 ml of tetrahydrofuran are added 0.25 g of sodium bicarbonate and 0.3 g of ethyl chloroformate.

It is heated to reflux for 16 h. It is concentrated to dryness and the residue is treated with 30 ml of water and extracted with 3 x 50 ml of dichloromethane-ethanol 90/10. The organic phase is dried and concentrated to a volume of 20 ml. The precipitated solid is filtered and 0.3 g of pure product is obtained.

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 8,70 (s, 1H); 7,98 (d, 1H); 7,64 (d, 1H); 7,56 (dd, 1H); 7,50 (t, 1H, NH); 7,30-7,10 (s.c., 2H); 4,80-4,64 (m, 1H); 4,14 (t, 1H); 4,02 (c, 2H); 3,96-3,70 (s.c., 2H); 3,60-3,10 (s.c., 5 10H); 1.42-1.10 (s.c., 4H); 1.17 (t, 3H).

Example 12:

1-cyclopropyl-6-fluoro-7-{4-[2-fluoro-4-(5-(S)-{[3-(4-fluoro-phenyl)-acryloylamino]-methyl}-2-oxo-oxazolidin-3-10 yl)-phenyl]-piperazin-1-yl}-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



To 0.6 g (1.1 mmol) of the product of Reference 20 Example No.38 in 20 ml of dry dichloromethane are added 0.17 ml (1.22 mmol) of triethylamine and 0.3 g (1.33 mmol) of 4-fluorocinnamoyl chloride.

The reaction is maintained at room temperature for 25 16 h, then concentrated to dryness and the residue is chromatographed on silica gel.

Elution with dichloromethane-ethanol 95/5 yields 0.3 g of pure product.

30

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 8,70 (s, 1H); 8,58 (t, 1H, NH); 7,96 (d, 1H); 7,70-7,58 (s.c., 4H); 7,44 (d, 1H); 7,30-7,10 (s.c., 4H); 6,64 (d, 1H); 4,90-4,76 (m,

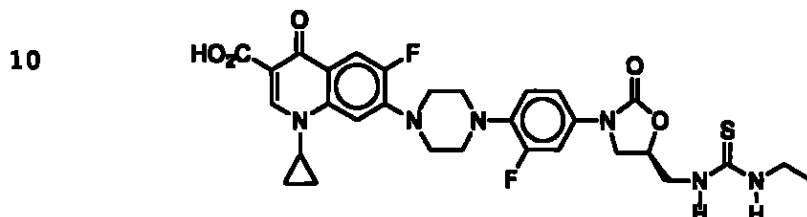
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1H); 4,16 (t, 1H); 3,92-3,70 (s.c., 2H); 3,64-3,10 (s.c., 10H); 1.42-1.10 (s.c., 4H).

Example 13:

5 1-cyclopropyl-7-[4-(4-{5-(S)-[(3-ethylthioureido)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluorophenyl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

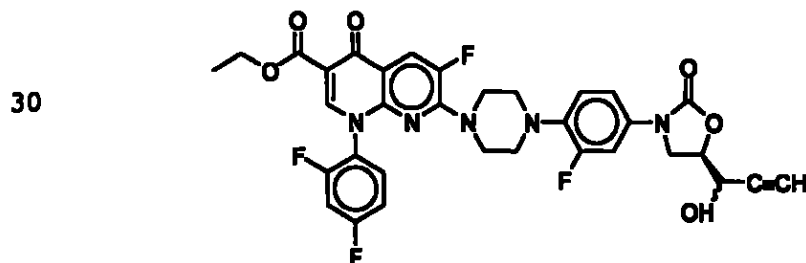


15 Following the procedure described in Example No. 9, replacing the methylisothiocyanate by ethylisothiocyanate, the product of the title is obtained.

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 15,06 (s.a., 1H); 8,70 (s, 1H); 7,98-7,50 (m, 4H); 7,30-7,10 (s.c., 2H); 4,95-4,80 (m, 1H); 4,16 (t, 1H); 4,00-3,70 (s.a., 4H); 3,60-3,10 (m., 10H); 1.44 -1.16 (s.c., 4H); 1.02 (t., 3H).

Example 14

1-(2,4-difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-5-[5-(R)-
25 (1-(R,S)-hydroxy-prop-2-ynyl)-2-oxo-oxazolidin-3-yl]-phenyl}piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid ethyl ester



To 0.32 g (1 mmol) of the product of Reference Example No.30 in 10 ml of pyridine are added 0.42 g (1mmol) of 7-chloro-1-(2,4-difluorophenyl)-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid ethyl ester (ACROS) and 0.28 ml of triethylamine. The reaction is maintained at room temperature for 48 h. It is concentrated to dryness and the residue is chromatographed on silica gel.

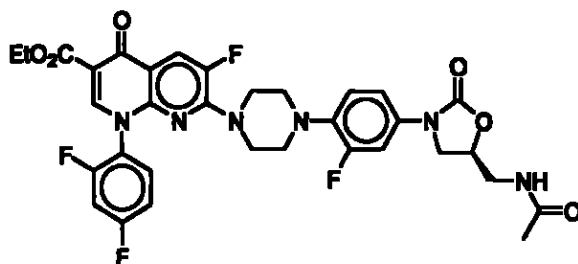
10 Elution with dichloromethane/ethanol/ammonium hydroxide 95/5/1% yields 0.436 g (66%) of the product of the title.

¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 8,42 (s, 1H);
15 8,15 (d, 1H); 7,40 (m, 2H); 7,10 (m, 3H); 6,90 (t, 1H);
4,75 (m, 1H); 4,70 (m, 1H); 4,38 (c, 2H); 4,10 (m, 2H);
3,70 (m, 4H); 3,04 (m, 4H); 2,50 (m, 1H); 1.40 (t, 3H).

Example 15

20 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-(2,4-difluoro-phenyl)-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-carboxylic acid ethyl ester.

25



30

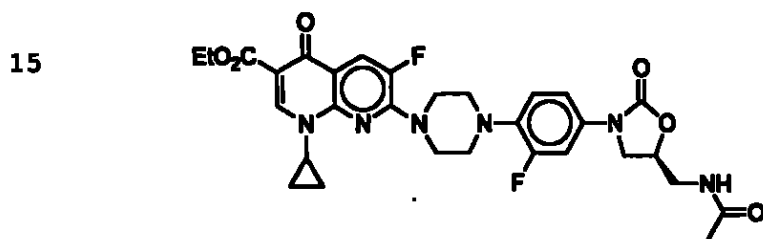
Following the procedure of the previous example and using N-[3-(3-Fluoro-4-piperazin-1-yl-phenyl)-2-oxo-

oxazolidin-5-(S)-ylmethyl]-acetamide (obtained according to US 5547950) the product of the title is obtained.

¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 8,41 (s, 1H); 8,15 (d, 1H); 7,42 (dd, 1H); 7,16-6,80 (s.c., 5H); 6,41 5 (t, 1H, NH); 4,84-4,70 (m, 1H); 4,39 (c, 2H); 4,02 (t, 1H); 4,80-4,60 (s.c., 7H); 3,10-2,95 (s.a., 4H); 2,02 (s, 3H); 1.40 (t, 3H).

Example 16

10 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-carboxylic acid ethyl ester



20 Following the procedure described in example 14 and using N-[3-(3-Fluoro-4-piperazin-1-yl-phenyl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide (obtained according to US 5547950) and 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-carboxylic acid ethyl ester (EP 0187376B1) the product of the title is obtained.

¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 8,52 (s, 1H); 8,11 (d, 1H); 7,48 (dd, 1H); 7,08 (m, 1H); 6,94 (t, 1H); 6,74 (t, 1H, NH); 4,79 (m, 1H); 4,37 (c, 2H); 4,01 (m, 30 5H); 3,76 (m, 1H); 3,66 (m, 2H); 3,53 (m, 1H); 3,20 (m, 4H); 2,04 (s, 3H); 1.40 (t, 3H); 1.23 (m, 2H); 1.05 (m, 2H).

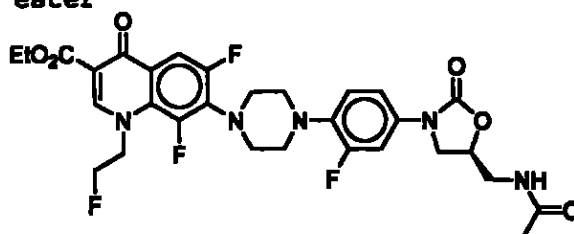
27

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Example 17

7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6,8-difluoro-1-(2-fluoro-ethyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester

10

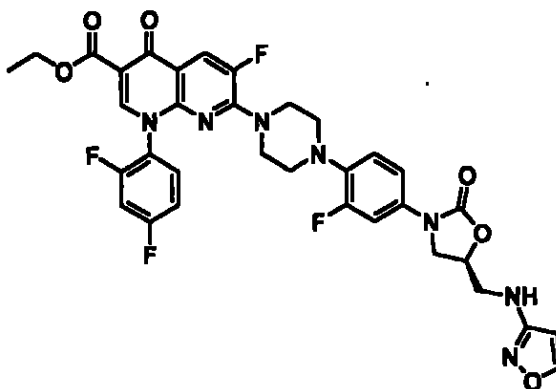


Following a procedure analogous to the previous ones and replacing the derivative of naphthyridine by 6,7,8-trifluoro-1-(2-fluoro-ethyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester, the product of the title is obtained.

¹H-RMN (DMSO-d₆, 200 MHz, δ (ppm)): 8,59 (s, 1H); 8,30 (t, 1H, NH); 7,79 (d, 1H); 7,50 (d, 1H); 7,30-7,00 (s.c., 2H); 5,05-4,60 (s.c., 5H); 4,21 (c, 2H); 4,15 (t, 1H); 3,80-3,00 (s.c., 11H); 1.82 (s, 3H); 1.27 (t, 3H).

Example 18

1-(2,4-Difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-4-[5-(S)-(isoxazol-3-ylaminomethyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid ethyl ester.



Following the procedure of example 14 and replacing the product of Reference Example No.30 by the product of Reference Example No.25 1-(2,4-difluoro-5-phenyl)-6-fluoro-7-(4-[2-fluoro-4-(5-(R)-([isoxazol-3-yl-(2,2,2-trichloro-ethoxycarbonyl)-amino]-methyl)-2-oxo-oxazolidin-3-yl)-phenyl]-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid ethyl ester is obtained. To 500 mg thereof, dissolved in 10 ml of 10 tetrahydrofuran is added 5 ml of water, 5 ml of glacial acetic acid and 700 mg of powdered zinc. After stirring for 3 h at room temperature it is filtered over decalite and the filtering liquids concentrated and chromatographed on silica gel. Elution with 15 dichloromethane/ethanol/ammonium hydroxide 98/2/02% yields 247 mg of the product of the title.

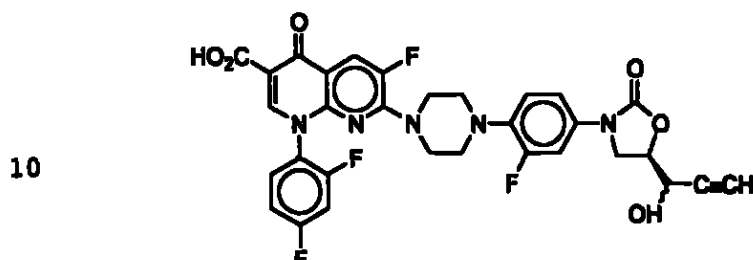
¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 8,41 (s, 1H); 8,15 (d, 1H); 8,07 (d, 1H); 7,45 (m, 2H); 7,05 (m, 3H); 20 6,85 (t, 1H); 5,85 (s, 1H); 4,95 (m, 1H); 4,50 (m, 1H); 4,38 (c, 2H); 4,05 (t, 1H); 3,80 (m, 2H); 3,68 (m, 4H); 3,03 (m, 4H); 1.39 (t, 3H).

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Example 19

1-(2,4-difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-4-[5-(R)-(1-hydroxy-prop-2-ynyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-5 carboxylic acid



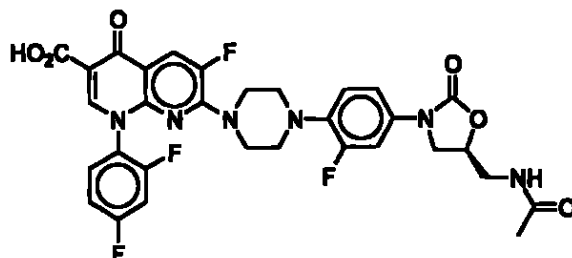
To 0.436 g (0.6 mmol) of the product of example 14 in 5 ml of ethanol and 5 ml of water is added 1.32 ml of sodium hydroxyde 1N. It is heated at 50°C for 3 h. 1.32 ml of HCl 1N is added and it is concentrated to dryness. The residue is chromatographed on silica gel. Elution with dichloromethane/ethanol/acetic acid 95/5/0.5% yields 0.287 g (75%) of the product of the title.

¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 8,68 (s, 1H); 8,15 (d, 1H); 7,60-7,27 (m, 2H); 7,20-7,00 (m, 3H); 6,90 (t, 1H); 4,75 (m, 1H); 4,30-4,00 (m, 2H); 3,80 (m, 4H); 25 3,28 (dd, 1H); 3,20 (m, 1H); 2,50 (d, 1H).

Example 20

7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-(2,4-difluoro-phenyl)-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-carboxylic acid

5



10 Following the procedure described in the previous example and using the product described in Example No.15 the product of the title is obtained.

^1H -RMN (DMSO- d_6 , 200 MHz, δ (ppm)): 8,90 (s, 1H),
 15 8,27 (t, 1H); 8,22 (d, 1H); 7,95-7,80 (m, 1H); 7,80-7,60 (m, 1H); 7,50 (d, 1H); 7,45-7,30 (m, 1H); 7,25-7,00 (s.c., 2H); 4,80-4,62 (m, 1H); 4,12 (t, 1H); 3,80-2,95 (s.c., 11H); 1.84 (s, 3H).

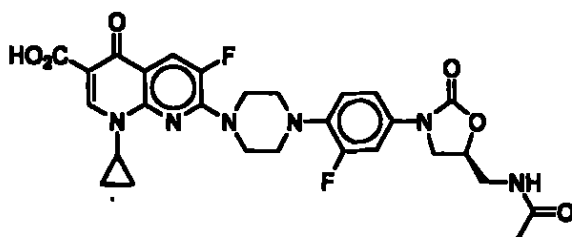
20

Example 21

7-(4-{4-[5-(8)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-carboxylic acid

25

30

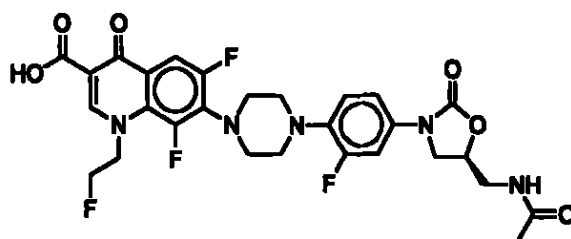


From the product of Example No.16 and following the procedure described above the product of the title is obtained.

¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 8,74 (s, 1H); 8,12 (m, 1H); 8,10 (d, 1H); 7,50 (m, 1H); 7,12 (m, 1H); 6,95 (t, 1H); 4,79 (m, 1H); 4,10 (m, 4H); 4,05 (m, 1H); 3,89 (m, 1H); 3,67 (m, 1H); 3,58 (m, 2H); 3,24 (m, 4H); 2,00 (s, 3H); 1,30 (m, 2H); 1,15 (m, 2H).

Example 22

7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6,8-difluoro-1-(2-fluoro-ethyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

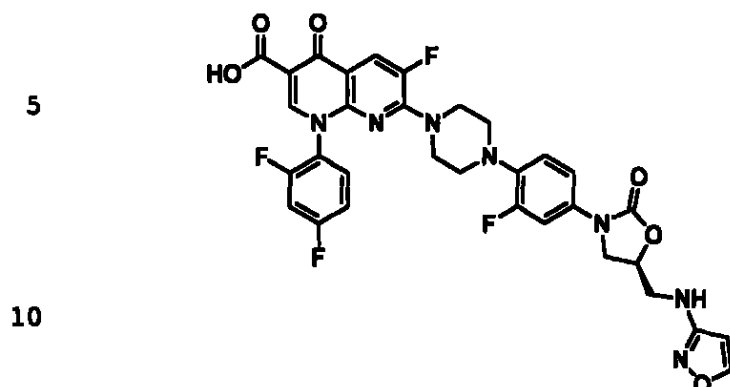


From the product of Example No.17 and following the procedure described in Example No.19, the product of the title is obtained.

¹H-RMN (DMSO-d₆, 200 MHz, δ (ppm)): 8,84 (s, 1H); 8,26 (t, 1H, NH); 7,92 (d, 1H); 7,56 (d, 1H); 7,35 -7,05 (s.c., 2H); 5,16-4,64 (s.c., 5H); 4,12 (t, 1H); 3,80-3,00 (s.c., 11H); 1,82 (s, 3H).

Example 23

1-(2,4-Difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-4-[5-(S)-(isoxazol-3-ylaminomethyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid

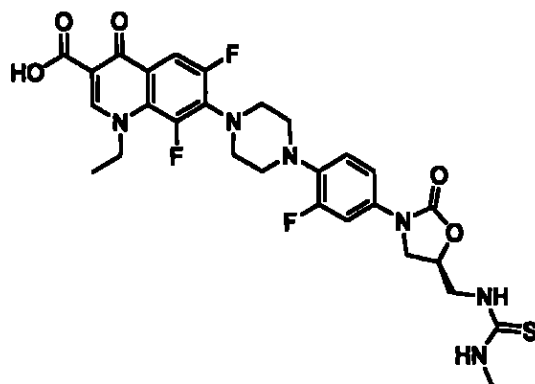


From the product of Example No.18 and following procedure described in Example No.19, the product of the title is 15 obtained.

¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 8,69 (s, 1H); 8,15 (d, 1H); 8,06 (d, 1H); 7,45 (m, 2H); 7,10 (m, 3H); 6,90 (t, 1H); 5,90 (s, 1H); 4,95 (m, 1H); 4,50 (m, 1H); 20 4,06 (t, 1H); 4,00-3,50 (m, 6H); 3,05 (m, 4H).

Example 24

1-ethyl-6,8-difluoro-7-[4-(2-fluoro-4-{5-[(3-methylthioureido)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



To 2 g (6,7 mmol) of 1-ethyl-6,7,8-trifluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester in 50 ml of N-methyl-2-pyrrolidone are added 3.1 g (6.7 mmol) of the product of Reference Example No.33 and 1.85 ml of triethylamine. The reaction is heated at 100°C for 48 h.

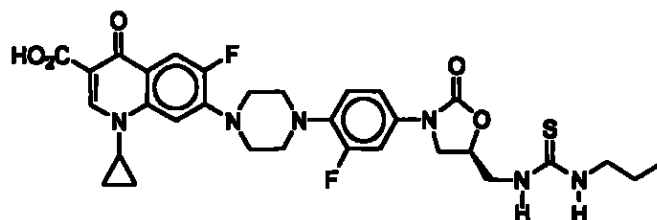
The solvent is distilled under vacuum and the residue is chromatographed on silica gel. Elution with dichloromethane/ethanol 90/10 yields 7-(4-[4-(5-(S)-aminomethyl-2-oxo-oxazolidin-3-yl)-2-fluoro-phenyl]-piperazin-1-yl)-1-ethyl-6,8-difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester. From said product 15 and by following procedure described in Example No.19, the product of the title is obtained.

IR: 3380 cm^{-1} , 1750 cm^{-1} , 1620 cm^{-1} , 1510 cm^{-1}

20 Example 25

1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{2-oxo-5-(S)-[(3-propyl-thioureido)-methyl]-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid 25

5



10 Following the procedure described in Example No. 9,
replacing the methylisothiocyanate by
propylisothiocyanate, the product of the title is
obtained.

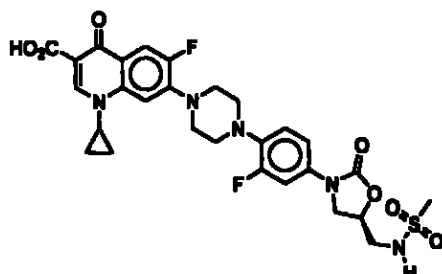
¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 8,70 (s, 1H);
15 7,92 (d., 1H), 7,90-7,70 (m, 2H, NH); 7,70-7,50 (m., 2H);
7,30-7,10 (m., 2H); 4,95-4,80 (m, 1H); 4,16 (t, 1H); 4,00-
3,70 (s.a., 4H); 3,60-3,10 (m., 10H); 1.60 -1.16 (s.c.,
6H).; 0.84 (t., 3H).

20

Example 26

1-cyclopropyl-6-fluoro-7-[4-{2-fluoro-4-[5-(S)-
(methanesulfonylamino-methyl)-2-oxo oxazolidin-3-yl]-
phenyl}-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-
25 carboxylic acid

5



10 Following the procedure described in Example No. 9, replacing the methylisothiocyanate by methanesulphonylchloride, the product of the title is obtained.

15 ^1H -RMN (DSMO- d_6 , 200 MHz, δ (ppm)): 15,00 (s.a., 1H); 8,70 (s, 1H); 7,96 (d., 1H), 7,76-7,42 (m, 3H); 7,30-7,10 (m., 2H); 4,90-4,76 (m, 1H); 4,18 (t, 1H); 4,00-3,20 (m., 12H); 2,98 (s, 3H); 1.44 -1.16 (m., 4H).

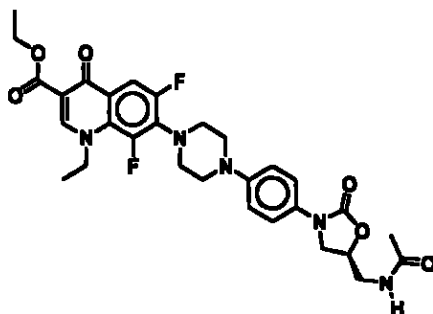
20

Example 27

7-(4-{4-(5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl)-phenyl}-piperazin-1-yl)-1-ethyl-6,8-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester

25

30



86

Following the procedure described in Example No. 14, using the product obtained in Reference Example No. 26 and 1-ethyl-6,7,8-trifluoro-4-oxo-1,4-dihydro-quinoline-3-5 carboxylic acid ethyl ester (obtained by esterification of the corresponding acid, described in GB 2057440).

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 8,62 (s, 1H); 8,30 (t, 1H, NH); 7,80 (d., 1H), 7,42 (d, 2H); 7,04 (d., 10 2H); 4,84-4,64 (m, 1H); 4,60-4,40 (s.a., 2H); 4,26 (c, 2H); 4,16 (t, 1H); 3,78 (t, 1H); 3,60-3,20 (m., 10H); 1.90 (s, 3H); 1.44 (t, 3H); 1.30 (t., 3H).

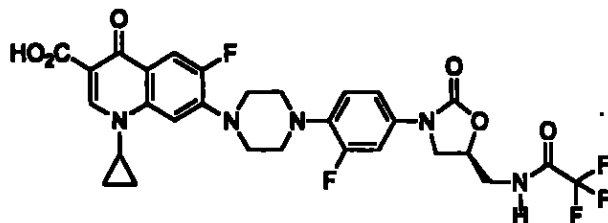
Example 28

15

1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{2-oxo-5-(S)-[(2,2,2-trifluoro-acetyl-amino)-methyl]-oxazolidin-3-yl)-phenyl]-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid.

20

25

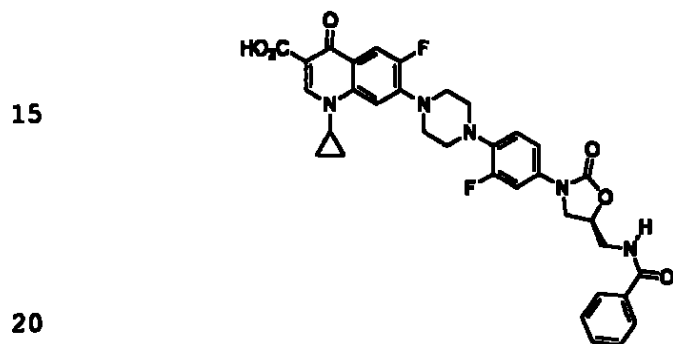


30 Following the procedure described in Example No. 9, replacing the methylisothiocyanate by trifluoroacetic anhydride, the product of the title is obtained.

¹H-RMN (DMSO-d₆, 200 MHz, δ (ppm)): 15,06 (s.a., 1H); 9,92 (s.a., 1H, NH); 8,70 (s, 1H); 7,95 (d, 1H,); 7,70-7,50 (m, 2H); 7,30-7,10 (s.c., 2H); 4,95-4,80 (m, 1H); 4,20 (t, 1H); 4,00-3,80 (s.a., 2H); 3,60-3,20 (m., 5 10H); 1.44 -1.16 (m., 4H).

Example 29

7-(4-{4-[5-(S)-(benzoylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro 4-oxo-1,4-dihydro-quinoline-3-carboxylic acid.



Following the procedure described in Example No. 9, replacing the methylisothiocyanate by benzoyl chloride, the product of the title is obtained.

25

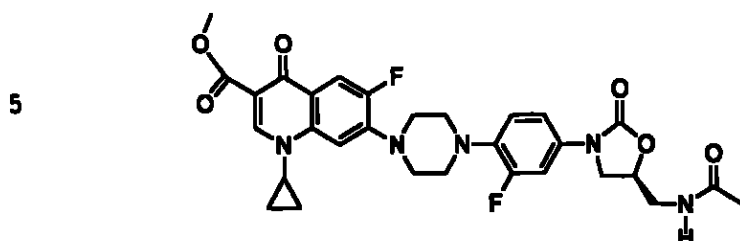
¹H-RMN (DMSO-d₆, 200 MHz, δ (ppm)): 15,20 (s.a., 1H); 8,90 (t, 1H, NH); 8,70 (s, 1H); 8,00-7,85 (m., 3H), 7,76-7,42 (m, 5H); 7,30-7,10 (m., 2H); 4,96-4,80 (m, 1H); 4,20 (t, 1H); 4,00-3,20 (m., 12H); 1.44 -1.16 (m., 4H).

30

Example 30

7-(4-{4-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-

fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
methyl ester.



To 1 g (1.7 mmol) of the product of Example 1 in 30 ml of
10 methanol cooled to 0°C is added dropwise 0.37 ml (5.2
mmol) of thionyl chloride. When the addition is finished
it is heated to reflux for 48 hours. It is concentrated to
dryness and the residue is chromatographed on silica gel.
Elution with dichloromethane/methanol/acetic acid 90/10/1
15 yields the product of the title as hydrochloride.

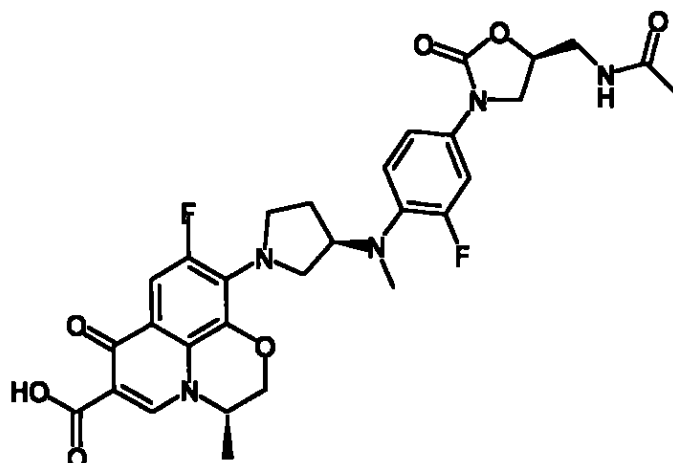
The product thus obtained is dissolved in
dichloromethane/methanol 90/10 and washed with saturated
solution of sodium bicarbonate. The organic phase is dried
20 and concentrated to yield the product of the title in the
form of free base.

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 8,50 (s, 1H);
8,25 (s.a., 1H, NH); 7,92 (d., 1H), 7,64-7,50 (m, 2H);
25 7,30-7,10 (m., 2H); 4,90-4,70 (m, 1H); 4,16 (t, 1H); 3,90-
3,60 (m., 5H); 3,60-3,20 (m., 10H); 1,86 (s., 1H); 1,45 -
1,10 (m., 4H).

EXAMPLE 31

30

9-[3-(S)-((4-[5-(S)-(Acetylamino-methyl)-2-oxo-
oxazolidin-3-yl]-2-fluoro-phenyl)-methyl-amino)-
pyrrolidin-1-yl]-8-fluoro-3-(S)-methyl-6-oxo-2,3-dihydro-
6H-1-oxa-3a-aza-phenalene-5-carboxylic acid.



Following the procedure described in Example 3 and starting 5 with the corresponding chelate obtained by reaction of N-{3-(S)-[3-Fluoro-4-(methyl-pyrrolidin-3-yl-amino)-phenyl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide (obtained following the procedure for the obtention of Reference Example No.27, but replacing 3(R,S)-aminopyrrolidine by 3-10 (S)-aminopyrrolidine) and 8,9-Difluoro-3-(S)-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid boron difluoride chelate the product of the title is obtained.

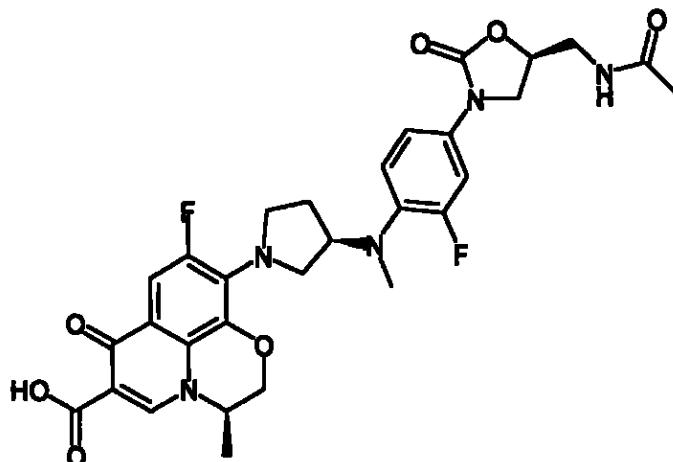
15 $^1\text{H-RMN}$ (DSMO-d_6 , 200 MHz, δ (ppm)): 8.92 (s, 1H); 8.24 (t, 1H, NH); 7.60-7.40 (m, 2H); 7.30-7.10 (m, 2H); 4.95-4.80 (m, 1H); 4.80-4.60 (m, 1H); 4.52 (d, 1H); 4.30 (d, 1H); 4.10 (t, 1H), 4.00-3.30 (m, 8H); 2.74 (s, 3H); 2.20-1.80 (m, 2H); 1.84 (s, 3H); 1.42 (d, 3H).

20

$[\alpha]_D^{25} = -34^\circ$ (c 0.5, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9/1)

EXAMPLE 32

9-[3-(S)-({4-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-pyrrolidin-1-yl]-8-5 fluoro-3-(R)-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid



Following the procedure described in Example 3 and starting
 10 with the corresponding chelate obtained by reaction of N-{3-(S)-[3-Fluoro-4-(methyl-pyrrolidin-3-yl-amino)-phenyl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide (obtained following the procedure for the obtention of Reference
 Example No.27, but replacing 3(R,S)-aminopyrrolidine by 3-
 15 (S)-aminopyrrolidine) and 8,9-Difluoro-3-(R)-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid boron difluoride chelate (obtained according to Shohgo Atarashi et al., *Chem. Pharm. Bull.* (1987), 35 (5), 1896-1902) the product of the title is obtained.

20

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 8.90 (s, 1H); 8.24 (t, 1H, NH); 7.60-7.40 (m, 2H); 7.36-7.10 (m, 2H); 4.95-4.80 (m, 1H); 4.80-4.60 (m, 1H); 4.54 (d, 1H); 4.24

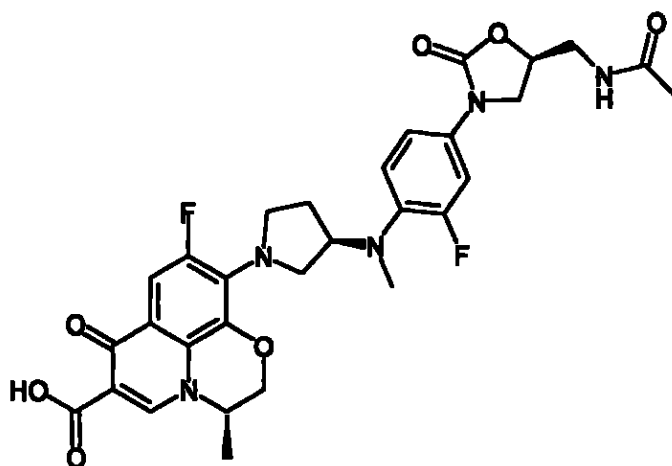
(d, 1H); 4.10 (t, 1H), 4.00-3.30 (m, 8H); 2.74 (s, 3H);
2.20-1.80 (m, 2H); 1.84 (s, 3H); 1.42 (d, 3H).

$[\alpha]^{25}_D = +66.4^\circ$ (c 0.5, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9/1)

5

EXAMPLE 33

9-[3-(R)-({4-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-
10 3-yl]-2-fluoro-phenyl}-methyl-amino)-pyrrolidin-1-yl]-8-
fluoro-3-(S)-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-
phenalene-5-carboxylic acid



15

Following the procedure described in Example 3 and starting
with the corresponding chelate obtained by reaction of N-
{3-(R)-[3-Fluoro-4-(methyl-pyrrolidin-3-yl-amino)-phenyl]-
20 2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide (obtained
following the procedure for the obtention of Reference
Example No.27, but replacing 3(R,S)-aminopyrrolidine by 3-
(R)-aminopyrrolidine) and 8,9-Difluoro-3-(S)-methyl-6-oxo-

92

91

2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid boron difluoride chelate the product of the title is obtained.

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 8.92 (s, 1H); 8.24 (t, 1H, NH); 7.60-7.40 (m, 2H); 7.36-7.10 (m, 2H); 4.95-4.80 (m, 1H); 4.80-4.60 (m, 1H); 4.56 (d, 1H); 4.26 (d, 1H); 4.10 (t, 1H), 4.02-3.30 (m, 8H); 2.76 (s, 3H); 2.20-1.80 (m, 2H); 1.82 (s, 3H); 1.40 (d, 3H).

10

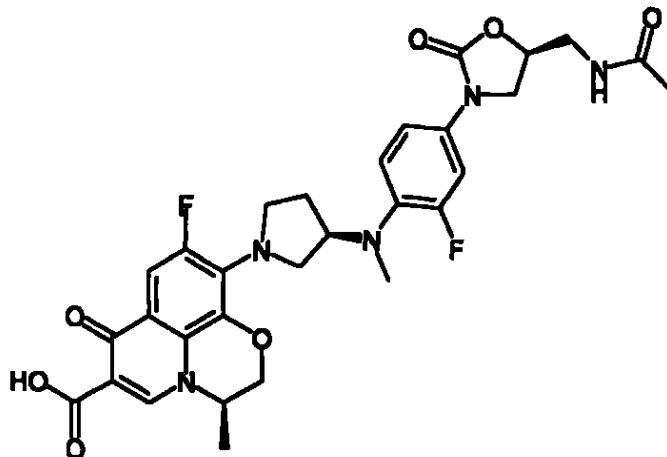
[α]_D²⁵ = -80.6° (c 0.5, CH₂Cl₂/MeOH 9/1)

EXAMPLE 34

15

9-[3-(R)-({4-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-pyrrolidin-1-yl]-8-fluoro-3-(R)-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid

20



93 92

Following the procedure described in Example 3 and starting with the corresponding chelate obtained by reaction of N-(3-(R)-[3-Fluoro-4-(methyl-pyrrolidin-3-yl-amino)-phenyl]-2-oxo-oxazolidin-5-(S)-ylmethyl)-acetamide (obtained 5 following the procedure for the obtention of Reference Example No.27, but replacing 3(R,S)-aminopyrrolidine by 3-(R)-aminopyrrolidine) and 8,9-Difluoro-3-(R)-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid boron difluoride chelate (obtained according to Shohgo 10 Atarashi et al., *Chem. Pharm. Bull.* (1987), 35 (5), 1896-1902) the product of the title is obtained.

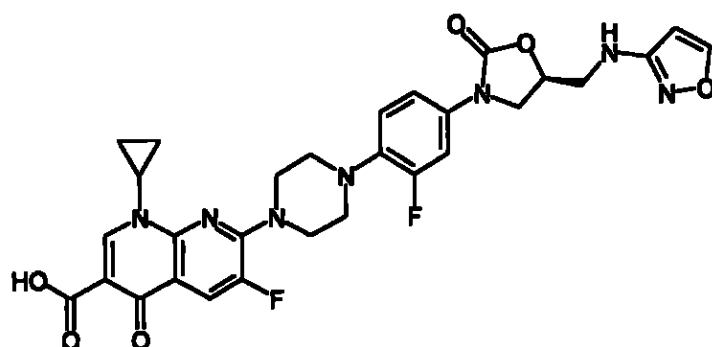
^1H -RMN (DSMO- d_6 , 200 MHz, δ (ppm)): 8.90 (s, 1H); 8.24 (t, 1H, NH); 7.60-7.40 (m, 2H); 7.36-7.10 (m, 2H); 15 4.95-4.80 (m, 1H); 4.80-4.60 (m, 1H); 4.54 (d, 1H); 4.30 (d, 1H); 4.10 (t, 1H), 4.00-3.30 (m, 8H); 2.72 (s, 3H); 2.20-1.80 (m, 2H); 1.84 (s, 3H); 1.42 (d, 3H).

$[\alpha]^{25}_D = +18^\circ$ (c 0.5, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9/1)

20

EXAMPLE 35

1-Cyclopropyl-6-fluoro-7-(4-{2-fluoro-4-[5-(S)-(isoxazol- 25 3-ylaminomethyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid



Following the procedure described in Example 14 and starting with the corresponding product obtained by 5 reaction of the compound in reference Example 25 N-deprotected and 7-Chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid the product of the title is obtained.

10 ^1H -RMN (DSMO- d_6 , 200 MHz, δ (ppm)): 13.2 (s, 1H); 8.61 (s, 1H); 8.40 (s, 1H); 8.10 (d, 1H); 7.50 (d, 1H); 7.10 (m, 2H); 6.55 (t, 1H); 5.98 (s, 1H); 4.85 (m, 1H); 4.04 (m, 5H); 3.75 (m, 2H); 3.40 (m, 2H); 3.17 (m, 4H); 1.2 (m, 4H).

15

EXAMPLES OF PHARMACOLOGICAL RESULTS

Description of the methods used for evaluation of the pharmacological properties

20

The antibacterial activity of the new synthesised compounds on the various strains of the bacterial species was implemented using the technique of microdilution in culture broth according to the regulations of the National 25 Committee for Clinical Laboratory Standards (NCCLS),

(NCCLS. 1993. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Approved standard M7-A3. NCCLS, Vilanova. PA., and NCCLS. 1993. Methods for dilution antimicrobial susceptibility tests for anaerobic bacteria that grow aerobically. Approved standard M1-A3. NCCLS, Vilanova. PA).

The inoculum used was 5×10^5 UFC/ml following dilution of the cultures overnight in the exponential phase of bacterial growth.

The MIC expressed in mg/l was defined as the minimum concentration of antibiotic which inhibited any visible growth.

15

Linezolid was included as comparative compound.

The compounds were tested on the strains of G(+) and G(-) bacteria set out in Table 1, in which:

20

- | | |
|----|--|
| A: | <i>S. aureus</i> resistant to meticillin |
| B: | <i>E. faecalis</i> resistant to vancomycin |
| C: | <i>S. pneumoniae</i> resistant to penicillin |
| D: | <i>S. agalactiae</i> |
| 25 | E: <i>S. epidermidis</i> |
| | F: <i>S. pyogenes</i> |
| | G: <i>B. fragilis</i> |
| | H: <i>E. coli</i> |
| | I: <i>H. influenzae</i> |
| 30 | J: <i>M. Catarrhalis</i> . |

95

Table 1 – Antibacterial activity on hospital strains (resistant) of Gram (+) and Gram (-) bacteria

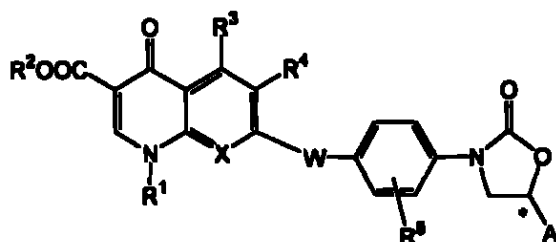
5	PRO- DUCT	G (+) strains						Anae- robic	G (-) strains		
		A	B	C	D	E	F	G	H	I	J
	Linezo- lid	2	2	1	2	1	1	2	>64	16	16
	EXAMP. 1 + 8	0,25	0,125	<0,125	0,125	0,125	<0,125	0,25	8	0,25	0,25
	EXAMP. 3	<0,125	<0,125	<0,125	<0,125	<0,125	<0,125	0,5	64	4	0,5
	EXAMP. 4	0,25	0,25	<0,125	<0,125	<0,125	<0,125	0,5	16	2	1
	EXAMP. 5	0,5	0,5	0,5	0,5	0,25	0,5	2	4	1	1
	EXAMP. 6	2	1	1	0,5	0,5	1	16	2	<0,125	0,25
	EXAMP. 7	0,25	0,5	0,25	0,5	0,25	0,25	2	8	4	1
	EXAMP. 9	<0,125	<0,125	<0,125	<0,125	<0,125	<0,125	0,5	>64	1	0,25
	EXAMP. 10	1	2	1	1	0,25	1	4	64	4	2
	EXAMP. 11	0,5	0,5	0,5	1	0,125	0,5	1	32	4	1
	EXAMP. 16	4	2	1	1	2	1	8	>64	>64	8
	EXAMP. 17	2	2	0,5	0,5	1	1	4	>64	64	4
	EXAMP. 19	4	8	4	8	4	8	>64	32	1	2
	EXAMP. 20	1	2	1	1	0,50	1	>64	>64	2	4
	EXAMP. 21	0,25	<0,125	<0,125	<0,125	<0,125	<0,125	0,25	64	2	0,5
	EXAMP. 22	<0,125	<0,125	0,25	<0,125	<0,125	<0,125	0,5	64	2	0,5

97 96

CLAIMS

1. Compound of general formula (I):

5



(I)

10 wherein:

X: CR⁶ or N;

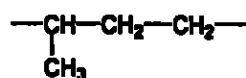
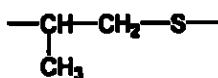
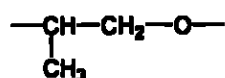
R¹: alkyl C₁-C₄, cycloalkyl C₃-C₆, alkenyl C₂-C₄, 2-15 hydroxyethyl, 2-fluoroethyl, or phenyl optionally substituted by 1 or 2 atoms of fluorine;

R²: H, alkyl C₁-C₄ or phenyl;

20 R³: H, halogen, alkyl C₁-C₄, or alkoxy C₁-C₄, amino;

R⁴: H or halogen;

R⁶: H, halogen, alkyl C₁-C₄, haloalkoxy C₁-C₄, or
25 else R¹ and R⁶ together form a bridge of structure



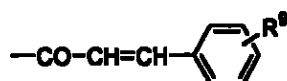
R^5 : H, halogen, OCH_3 , alkoxy $\text{C}_1\text{--C}_4$, alkyl $\text{C}_1\text{--C}_4$, or haloalkyl $\text{C}_1\text{--C}_4$;

5

A: $-\text{CH}_2\text{--NH--R}^7$, $-\text{CHOH--C}\equiv\text{CH}$;

wherein

10 R^7 : isoxazol, $-\text{CO--R}^8$, $-\text{CS--R}^8$, $-\text{CS--OR}^8$, $-\text{COOR}^8$, $-\text{CONHR}^8$, $-\text{CSNHR}^8$, $-\text{SO}_2\text{--R}^8$ or



15 wherein

R^8 : alkyl $\text{C}_1\text{--C}_4$, haloalkyl $\text{C}_1\text{--C}_4$, alkenyl $\text{C}_2\text{--C}_4$, aryl, alkyl $\text{C}_1\text{--C}_4$ substituted by an alkoxy group $\text{C}_1\text{--C}_4$, carboxyalkyl $\text{C}_1\text{--C}_4$, cyano, or amino;

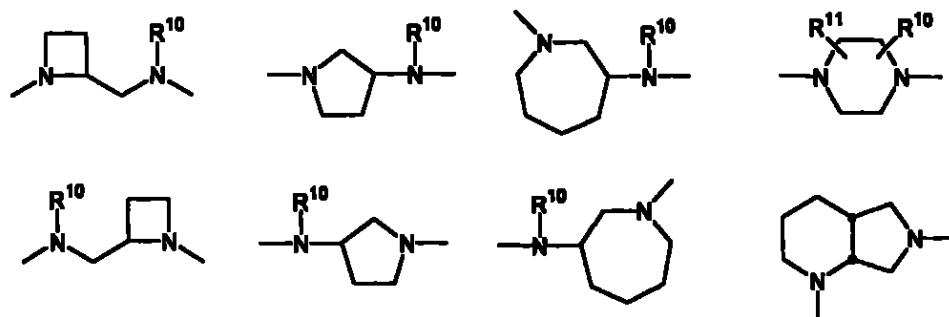
20

R^9 : H, alkyl $\text{C}_1\text{--C}_4$, alkenyl $\text{C}_2\text{--C}_4$, OH, alkoxy $\text{C}_1\text{--C}_4$, $\text{NR}^{12}\text{R}^{13}$, NO_2 , halogen, or CO--R^{12} ;

R^{12} and R^{13} : independently, H or alkyl $\text{C}_1\text{--C}_4$;

25

W:



wherein

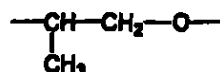
R^{10} and R^{11} are independently H, or alkyl C_1-C_4 ;

5

a pharmaceutically acceptable salt or solvate, or any geometric isomer, optical isomer or mixture of isomers thereof in any proportion or polymorph thereof.

- 10 2. Compound according to Claim 1, characterised in that R^1 is cyclopropyl, ethyl, 2-fluoroethyl, phenyl or difluorophenyl, or else R^1 and R^6 together form a bridge of structure:

15

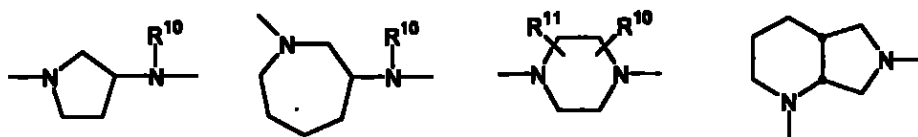


3. Compound according to Claim 1, characterised in that R^6 is H, CH_3 , OCH_3 , $OCHF_2$, F or Cl.

4. Compound according to Claim 3, characterised in
20 that R^6 is H or F.

5. Compound according to Claim 1, characterised in that R^4 is F or Cl and R^3 is H.

6. Compound according to Claim 1, characterised in that W is



5 wherein R^{10} and R^{11} are as defined in Claim 1.

7. Compound according to Claim 1, characterised in that the C5 of oxazolidinone ring has an (S) configuration when $A = -CH_2-NH-R^7$ and (R) when $A = -CHOH-C\equiv CH$.

10

8. Compound according to claims 1 to 6, characterised in that it is selected from one of the following:

- 15 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 7-[3-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-azepan-1-yl]-1-
- 20 cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6,8-difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 25 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-
- 30 dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid

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- 9-({3-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-pyrrolidin-1-yl}-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid
 - 5 - 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic
 - 1-cyclopropyl-6-fluoro-7-{4-(2-fluoro-4-{5-(S)-({3-methyl-thioureido)-methyl}-2-oxo-oxazolidin-3-yl)-phenyl)-piperazin-1-yl}-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
 - 10
 - 1-cyclopropyl-7-{4-(4-{5-(S)-({3-ethyl-ureido)-methyl}-2-oxo-oxazolidin-3-yl)-2-fluoro-phenyl)-piperazin-1-yl}-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
 - 15 - 1-cyclopropyl-7-(4-{4-[5-(S)-(ethoxycarbonylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
 - 1-cyclopropyl-6-fluoro-7-{4-[2-fluoro-4-(5-(S)-({3-(4-fluoro-phenyl)-acryloylamino)-methyl}-2-oxo-oxazolidin-3-yl)-phenyl]-piperazin-1-yl}-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
 - 20
 - 1-cyclopropyl-7-{4-(4-{5-(S)-({3-ethyl-thioureido)-methyl}-2-oxo-oxazolidin-3-yl)-2-fluoro-phenyl)-piperazin-1-yl}-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
 - 25
 - 1-(2,4-difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-5-[5-(R)-(1-(R,S)-hydroxy-prop-2-ynyl)-2-oxo-oxazolidin-3-yl]-phenyl}piperazin-1-yl)-4-oxo-1,4-dihydro-
 - 30 [1,8]naphthyridine-3-carboxylic acid ethyl ester
 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-(2,4-difluoro-phenyl)-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-carboxylic acid ethyl ester

- 102 101
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid ethyl ester
 - 5 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6,8-difluoro-1-(2-fluoro-ethyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
 - 1-(2,4-Difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-4-[5-
 - 10 (S)-(isoxazol-3-ylaminomethyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid ethyl ester
 - 1-(2,4-difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-4-[5-
 - 15 (R)-(1-hydroxy-prop-2-ynyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid
 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-(2,4-difluoro-
 - 20 phenyl)-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid
 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid
 - 25 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6,8-difluoro-1-(2-fluoro-ethyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
 - 1-(2,4-Difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-4-[5-
 - 30 (S)-(isoxazol-3-ylaminomethyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid
 - 1-ethyl-6,8-difluoro-7-[4-(2-fluoro-4-(5-[(3-methylthioureido)-methyl]-2-oxo-oxazolidin-3-yl)-phenyl)-

- 103
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- piperazin-1-yl}-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{2-oxo-5-(S)-[(3-propyl-thioureido)-methyl]-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 5 - 1-cyclopropyl-6-fluoro-7-[4-{2-fluoro-4-[5-(S)-(methanesulfonylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 10 - 7-(4-{4-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-1-ethyl-6,8-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
- 1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{2-oxo-5-(S)-[(2,2,2-trifluoro-acetylamino)-methyl]-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 15 - 7-(4-{4-[5-(S)-(benzoylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro 4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 20 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid methyl ester
- 25 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6,8-difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid methyl ester
- 30 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6,8-

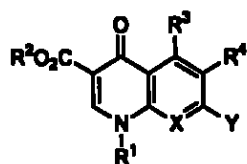
- ~~set~~ 103
- difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid methyl ester
- 5 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
- 10 - 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid methyl ester
- 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid ethyl ester
- 15 - 9-[3-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-pyrrolidin-1-yl]-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid methyl ester
- 20 - 9-[3-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-pyrrolidin-1-yl]-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid ethyl ester
- 25 - 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid methyl ester
- 30 - 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid ethyl ester

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- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid methyl ester
 - 5 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
 - 1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-methyl-thioureido)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid methyl ester
 - 10 - 1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-methyl-thioureido)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
 - 15 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid methyl ester
 - 20 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6,8-difluoro-1-(2-fluoro-ethyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid methyl ester
 - 25 - 1-Ethyl-6,8-difluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-methyl-thioureido)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester

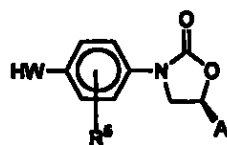
30 9. Process for obtaining a compound of general formula (I), according to Claim 1, characterised in that it comprises the reaction of a compound of general formula (II) with a compound of general formula (III):

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(II)

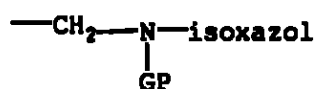


(III)

wherein:

A' is:

- 5 a) $-\text{CH}_2-\text{NH}-\text{R}^7$
 b) $-\text{CHOH}-\text{C}\equiv\text{CH}$
 c)

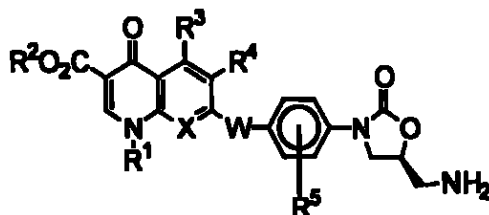


- 10 Y is an leaving group, such as an atom of halogen (F, Cl, Br, I), a tosylate or mesylate group, and the like;

 R¹, R², R³, R⁴, R⁵, X and W have the meaning defined in Claim 1;

- 15 GP is a protecting group of amines.

10. Process for obtaining a compound of general formula (I), according to Claim 1, in which A is $-\text{CH}_2-\text{NH}-\text{R}^7$ and R⁷ is different from isoxazole, characterised in that it
 20 comprises the reaction of a compound of formula (V)



(V)

wherein R¹, R², R³, R⁴, R⁵, X and W have the meaning

defined in Claim 1.

with a compound of formula (VI) or with a compound of formula (VII)



(VI)



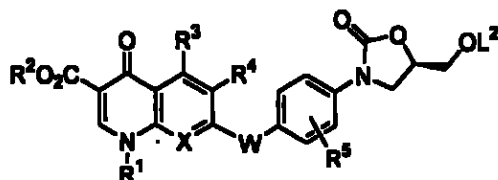
(VII)

wherein L is a good leaving group, such as an atom of halogen (F, Cl, Br, I), a tosylate or mesylate group, and the like;

Z is Oxygen or Sulphur, and

R^7 and R^8 have the meaning defined in Claim 1, with R^7 being different from isoxazol.

11. Process for obtaining a compound of general formula (I), according to Claim 1, in which A is $-CH_2-NH-R^7$ and R^7 is isoxazol, characterised in that it comprises the reaction of a compound of general formula (VIII):



(VIII)

20

wherein

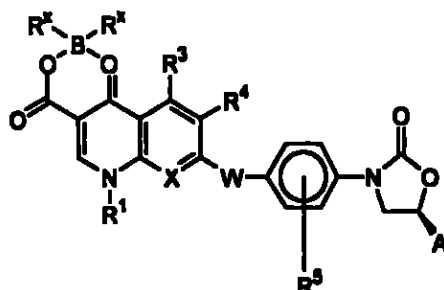
- OL^2 represents a good leaving group, such as a residue of aryl or methyl sulphonic acid, substituted or not substituted, preferably by a tosylate or mesylate group;

- R^1 , R^2 , R^3 , R^4 , R^5 , X and W have the meaning defined in Claim 1;

with isoxazolil-3-amine, the amine group being protected with a protecting group of amines.

30

12. Process for obtaining a compound of general formula (I), according to Claim 1, in which R^2 is hydrogen, characterised in that it comprises the hydrolysis of a boron chelate of formula (IX)



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(IX)

wherein

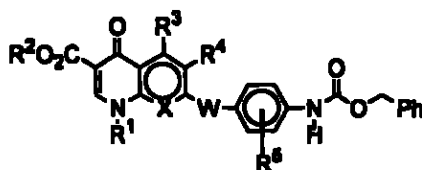
 R^x can be F or $\text{CH}_3\text{COO}-$;

10 A, R^1 , R^3 , R^4 , R^5 , X and W have the meaning defined in Claim 1.

13. Process for obtaining a compound of general formula (I), according to Claim 1, in which A is

15 $-\text{CHOH}-\text{C}\equiv\text{CH}$

characterised in that it comprises the reaction of a compound of formula (IV)



(IV)

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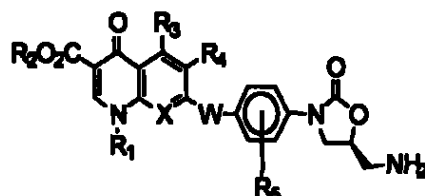
wherein R^1 , R^2 , R^3 , R^4 , R^5 , X and W have the meaning defined in Claim 1,

with 2,3-hydroxy-pent-4-ynyl p-toluenesulphonate.

14. Process as claimed in any of claims 11 to 13, characterised in that it comprises subjecting the product 5 obtained, optionally, to one or more of the following final steps:

- a) Conversion of a compound of general formula (I) into another compound of general formula (I);
- b) Elimination of the protecting group;
- 10 c) Preparation of a pharmacologically acceptable salt of a compound of formula (I) and/or a pharmacologically acceptable solvate thereof.

15. Compound of formula (V)

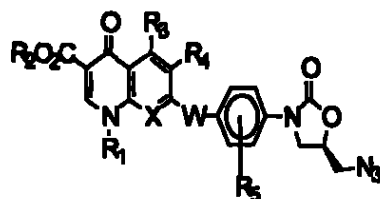


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(V)

wherein R^1 , R^2 , R^3 , R^4 , R^5 , X and W have the meaning defined in Claim 1.

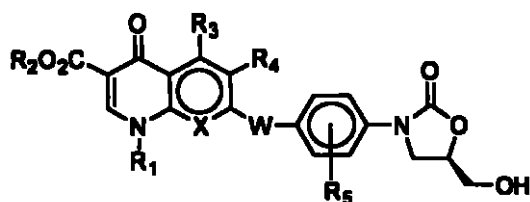
20 16. Compound of formula (X)



(X)

wherein R^1 , R^2 , R^3 , R^4 , R^5 , X and W have the meaning defined in Claim 1.

17. Compound of formula (XI)



5

(XI)

wherein R^1 , R^2 , R^3 , R^4 , R^5 , X and W have the meaning defined in Claim 1.

10 18. Pharmaceutical composition which comprises a compound of general formula (I) according to any of claims 1 to 8, for use as a medicament.

15 19. Use of a compound of general formula (I), according to any of claims 1 to 8, for the preparation of a pharmaceutical composition for treating microbial infections in humans or warm-blooded animals.

20 20. Pharmaceutical composition which comprises a compound of general formula (I) according to any of claims 1 to 8 in a therapeutically active quantity and with a suitable quantity of at least one excipient.

25

Nuevos derivados de oxazolidinonas como antibacterianos

Campo de la invención

La presente invención se refiere a derivados 5 fluorquinolónicos de oxazolidinonas. Los compuestos son útiles como antibacterianos.

Antecedentes de la invención

Durante años la industria farmacéutica no ha
10 perseguido el desarrollo de nuevos agentes antimicrobianos
específicamente dirigidos a bacterias Gram-positivas,
tales como *Staphylococos*, *Enterococos*, *Streptococos* y
micobacterias. Sin embargo, las bacterias Gram-positivas
han cobrado especial importancia debido a que han
15 desarrollado resistencias a los antibióticos de uso
convencional a una velocidad alarmante, convirtiéndose en
organismos difíciles tanto de tratar como de erradicar de
los ambientes hospitalarios. Ejemplos de tales cepas son
el *Staphylococcus* resistente a la meticilina (MRSA),
20 *Enterococcus* resistente a la vancomicina (VRE),
Staphylococcus epidermidis resistente a la meticilina
(MRSE), *Staphylococcus pneumoniae* resistente a la
penicilina (PRSP), etc.

25 Los agentes antibacterianos oxazolidinónicos son
la clase más reciente de fármacos sintéticos que muestran
una elevada actividad contra organismos Gram-positivos.
Debido a su nuevo mecanismo de acción, estos compuestos
son efectivos tanto contra patógenos sensibles como
30 resistentes, incluyendo el MRSA, MRSE y VRE.

Distintas oxazolidinonas antibacterianas han sido
descritas en la literatura de patentes, por citar algunas
de ellas, en WO 9507271, WO 9323384, WO 9854161, WO

9514684, WO 9721708, WO 9514684, WO 9730981, WO 9737980,
WO 9801447, WO 9912914, WO 9613502.

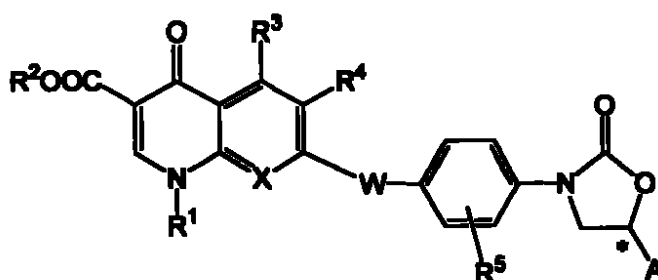
Todas estas patentes describen las oxazolidinonas
5 como compuestos activos frente a organismos Gram-positivos
resistentes.

Debido a que constantemente están apareciendo
nuevas resistencias incluso a antibióticos de uso
10 reciente, es deseable el desarrollo de nuevos antibióticos
potentes y activos frente a cepas resistentes,
preferiblemente con un amplio espectro antimicrobiano.

La presente invención proporciona nuevos derivados
15 de oxazolidinonas, con un amplio espectro antimicrobiano
al ser activos frente a organismos Gram-negativos y
mejorando su actividad frente a organismos Gram-positivos.

Descripción de la invención

20 Son objeto de la presente invención nuevos
derivados fluorquinolónicos de oxazolidinonas de fórmula
general (I):



(I)

donde:

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X: CR⁶ ó N;

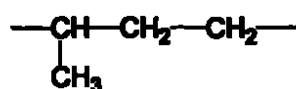
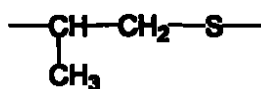
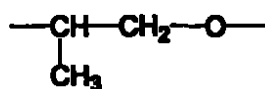
R¹: alquilo C₁-C₄, cicloalquilo C₃-C₆, alquenilo C₂-C₅, 2-hidroxietilo, 2-fluoroetilo, ó fenilo opcionalmente sustituido por 1 ó 2 átomos de flúor;

R²: H, alquilo C₁-C₄ o fenilo;

10 R³: H, halógeno, alquilo C₁-C₄, ó alcoxí C₁-C₄, amino;

R⁴: H ó halógeno;

15 R⁶: H, halógeno, alquilo C₁-C₄, haloalcoxí C₁-C₄, o bien R¹ y R⁶ juntos forman un puente de estructura



20

R⁵: H, halógeno, OCH₃, alcoxí C₁-C₄, alquilo C₁-C₄, o haloalquilo C₁-C₄;

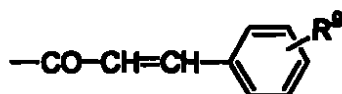
A: -CH₂-NH-R⁷, -CHOH-C≡CH;

25

donde

R⁷: isoxazol, -CO-R⁸, -CS-R⁸, -CS-OR⁸, -COOR⁸, -CONHR⁸, -CSNHR⁸, -SO₂-R⁸ o

30



114

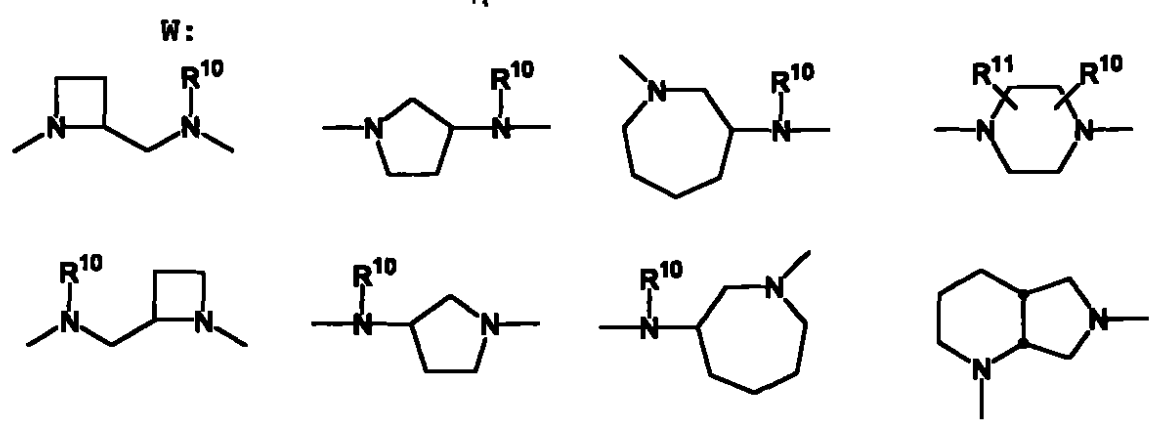
113

donde

R^8 : alquilo C_1-C_4 , haloalquilo C_1-C_4 , alquenilo C_2-C_4 , arilo, alquilo C_1-C_4 sustituido por un grupo alcoxi $C_1-5 C_4$, carboxialquilo C_1-C_4 , ciano, o amino, ...

R^9 : H, alquilo C_1-C_4 , alquenilo C_2-C_4 , OH, alcoxi C_1-C_4 , $NR^{12}R^{13}$, NO_2 , halógeno, ó $CO-R^{12}$;

10 R^{12} y R^{13} : independientemente, H o alquilo C_1-C_4 ;



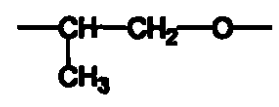
donde

15 R^{10} y R^{11} son independientemente H, o alquilo C_1-C_4 ;

una sal o un solvato farmacéuticamente aceptable, o cualquier isómero geométrico, isómero óptico o mezcla de isómeros del mismo en cualquier proporción o polimorfo del 20 mismo.

Preferentemente, R^1 es ciclopropilo, etilo, 2-fluoroetilo, fenilo o difluorofenilo, o bien R^1 y R^6 juntos forman un puente de estructura:

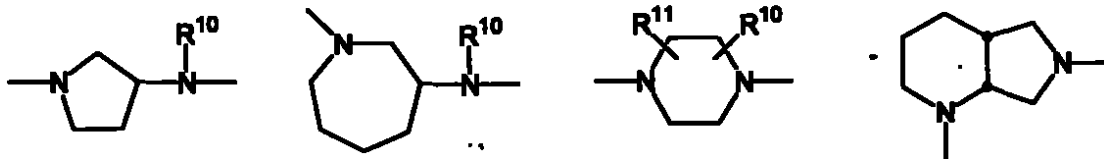
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Preferentemente, R^6 es H, CH_3 , OCH_3 , $OCHF_2$, F o Cl.
 Más preferentemente, R^6 es H o F.

5 Preferentemente, R^4 es F o Cl y R^3 es H.

Preferentemente, W es



10 donde R^{10} y R^{11} son tal como se han definido anteriormente.

Los compuestos de la presente invención tienen un centro quiral en la posición C5 del anillo de oxazolidinona. La configuración preferida del C5 del anillo de oxazolidinona es la (S) para los compuestos de fórmula (I) en los que $A = -CH_2-NH-R^7$ y (R) para los compuestos de fórmula (I) en los que $A = -CHOH-C=CH$, de acuerdo con el sistema de nomenclatura Cahn-Ingold-Prelog.

20

Además los compuestos de fórmula (I) pueden contener otros centros quirales. Se entiende que la invención comprende tales isómeros ópticos y diastereoisómeros y sus mezclas en cualquier proporción, 25 que posean actividad antibacteriana.

Los compuestos preferibles se seleccionan entre uno de los siguientes:

30 - Ácido 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-

- ciclopropil-6-fluoro-4-oxo-1,4-dihidro-quinolein-3-carboxílico
- Ácido 7-[3-({4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-metil-amino)-azepan-1-il]-1-ciclopropil-6-fluoro-4-oxo-1,4-dihidro-quinolein-3-carboxílico
 - Ácido 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-etil-6,8-difluoro-4-oxo-1,4-dihidro-quinolein-3-carboxílico
 - 10 - Ácido 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-etil-6-fluoro-4-oxo-1,4-dihidro-quinolin-3-carboxílico
 - Ácido 9-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-fenil}-piperazin-1-il)-8-fluoro-3-
 - 15 metil-6-oxo-2,3-dihidro-6H-1-oxa-3a-aza-fenalen-5-carboxílico
 - Ácido 9-[3-({4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-metil-amino)-pirrolidin-1-il]-8-fluoro-3-metil-6-oxo-2,3-dihidro-6H-
 - 20 1-oxa-3a-aza-fenalen-5-carboxílico
 - Ácido 9-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-8-fluoro-3-metil-6-oxo-2,3-dihidro-6H-1-oxa-3a-aza-fenalen-5-carboxílico
 - 25 - Ácido 1-ciclopropil-6-fluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-metil-tioureido)-metil]-2-oxo-oxazolidin-3-il}-fenil)-piperazin-1-il]-4-oxo-1,4-dihidro-quinolein-3-carboxílico
 - Ácido 1-ciclopropil-7-[4-(4-{5-(S)-[(3-etil-ureido)-metil]-2-oxo-oxazolidin-3-il}-2-fluoro-fenil)-piperazin-
 - 30 1-il]-6-fluoro-4-oxo-1,4-dihidro-quinolein-3-carboxílico
 - Ácido 1-ciclopropil-7-(4-{4-[5-(S)-(etoxicarbonilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-

- 1-il)-6-fluoro-4-oxo-1,4-dihidro-quinolein-3-carboxílico
- Ácido 1-ciclopropil-6-fluoro-7-{4-[2-fluoro-4-(5-(S)-{[3-(4-fluoro-fenil)-acriloilamino]-metil}-2-oxo-oxazolidin-3-il)-fenil]-piperazin-1-il}-4-oxo-1,4-dihidro-quinolein-3-carboxílico
 - Ácido 1-ciclopropil-7-{4-(4-{5-(S)-[(3-etil-tioureido)-metil]-2-oxo-oxazolidin-3-il}-2-fluoro-fenil)-piperazin-1-il}-6-fluoro-4-oxo-1,4-dihidro-quinolein-3-carboxílico
 - 1-(2,4-difluoro-fenil)-6-fluoro-7-(4-{2-fluoro-5-[5-(R)-(1-(R,S)-hidroxi-prop-2-inil)-2-oxo-oxazolidin-3-il]-fenil}piperazin-1-il)-4-oxo-1,4-dihidro-[1,8]naftiridin-3-carboxilato de etilo
 - 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-(2,4-difluoro-fenil)-6-fluoro-4-oxo-1,4-dihidro-[1,8] naftiridin-3-carboxilato de etilo
 - 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-ciclopropil-6-fluoro-4-oxo-1,4-dihidro-[1,8] naftiridin-3-carboxilato de etilo
 - 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-6,8-difluoro-1-(2-fluoro-etil)-4-oxo-1,4-dihidro-quinoleine-3-carboxilato de etilo
 - 1-(2,4-Difluoro-fenil)-6-fluoro-7-(4-{2-fluoro-4-[5-(S)-(isoxazol-3-ilaminometil)-2-oxo-oxazolidin-3-il]-fenil}-piperazin-1-il)-4-oxo-1,4-dihidro-[1,8]naftiridine-3-carboxilato de etilo
 - Ácido 1-(2,4-difluoro-fenil)-6-fluoro-7-(4-{2-fluoro-4-[5-(R)-(1-hidroxi-prop-2-inil)-2-oxo-oxazolidin-3-il]-fenil}-piperazin-1-il)-4-oxo-1,4-dihidro-[1,8]naftiridin-3-carboxílico

- 117
- Ácido 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-(2,4-difluoro-fenil)-6-fluoro-4-oxo-1,4-dihidro-[1,8]naftiridin-3-carboxílico
 - 5 - Ácido 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-ciclopropil-6-fluoro-4-oxo-1,4-dihidro-[1,8]naftiridin-3-carboxílico
 - Ácido 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-6,8-difluoro-1-(2-fluoro-etil)-4-oxo-1,4-dihidro-quinolin-3-carboxílico
 - 10 - Ácido 1-(2,4-Difluoro-fenil)-6-fluoro-7-(4-{2-fluoro-4-[5-(S)-(isoxazol-3-ilaminometil)-2-oxo-oxazolidin-3-il]-fenil}-piperazin-1-il)-4-oxo-1,4-dihidro-[1,8]naftiridin-3-carboxílico
 - Ácido 1-etil-6,8-difluoro-7-[4-(2-fluoro-4-{5-[(3-metil-tioureido)-metil]-2-oxo-oxazolidin-3-il}-fenil)-piperazin-1-il]-4-oxo-1,4-dihidro-quinolein-3-carboxílico
 - 20 - Ácido 1-ciclopropil-6-fluoro-7-[4-(2-fluoro-4-{2-oxo-5-(S)-[(3-propil-tioureido)-metil]-oxazolidin-3-il}-fenil)-piperazin-1-il]-4-oxo-1,4-dihidro-quinolein-3-carboxílico
 - 25 - Ácido 1-ciclopropil-6-fluoro-7-[4-{2-fluoro-4-[5-(S)-(metanosulfonilamino-metil)-2-oxo oxazolidin-3-il]-fenil}-piperazin-1-il)-4-oxo-1,4-dihidro-quinolein-3-carboxílico.
 - 7-(4-{4-[5-(S)-(Acetilamino-metil)-2-oxo-oxazolidin-3-il]-fenil}-piperazin-1-il)-1-etil-6,8-fluoro-4-oxo-1,4-dihidro-quinolein-3-carboxilato de etilo
 - 30 - Ácido 1-ciclopropil-6-fluoro-7-[4-(2-fluoro-4-{2-oxo-5-(S)-[(2,2,2-trifluoro-acetilamino)-metil]-oxazolidin-3-

- il}-fenil)-piperazin-1-il]-4-oxo-1,4-dihidro-quinolein-3-carboxílico
- Ácido 7-(4-{4-[5-(S)-(benzoilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-
 - 5 ciclopropil-6-fluoro 4-oxo-1,4-dihidro-quinolein-3-carboxílico.
 - 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-ciclopropil-6-fluoro-4-oxo-1,4-dihidro-quinolein-3-carboxilato de
 - 10 metilo
 - 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-ciclopropil-6-fluoro-4-oxo-1,4-dihidro-quinolein-3-carboxilato de etilo
 - 15 - 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-etil-6,8-difluoro-4-oxo-1,4-dihidro-quinolein-3-carboxilato de metilo
 - 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-etil-6,8-difluoro-
 - 20 4-oxo-1,4-dihidro-quinolein-3-carboxilato de etilo
 - 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-etil-6-fluoro-4-oxo-1,4-dihidro-quinolin-3-carboxilato de metilo
 - 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-etil-6-fluoro-4-
 - 25 oxo-1,4-dihidro-quinolin-3-carboxilato de etilo
 - 9-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-fenil}-piperazin-1-il)-8-fluoro-3-metil-6-oxo-2,3-dihidro-6H-1-oxa-3a-aza-fenalen-5-carboxilato de
 - 30 metilo
 - 9-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-fenil}-piperazin-1-il)-8-fluoro-3-metil-6-oxo-2,3-dihidro-6H-1-oxa-3a-aza-fenalen-5-carboxilato de etilo

- 9-[3-({4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-metil-amino)-pirrolidin-1-il]-8-fluoro-3-metil-6-oxo-2,3-dihidro-6H-1-oxa-3a-aza-fenalen-5- carboxilato de metilo
- 5 - 9-[3-({4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-metil-amino)-pirrolidin-1-il]-8-fluoro-3-metil-6-oxo-2,3-dihidro-6H-1-oxa-3a-aza-fenalen-5-carboxilato de etilo
- 9-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-8-fluoro-3-metil-6-oxo-2,3-dihidro-6H-1-oxa-3a-aza-fenalen-5- carboxilato de metilo
- 10
- 9-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-8-fluoro-3-metil-6-oxo-2,3-dihidro-6H-1-oxa-3a-aza-fenalen-5-carboxilato de etilo
- 15
- 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-ciclopropil-6-fluoro-4-oxo-1,4-dihidro-quinolein-3- carboxilato de metilo
- 20
- 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-ciclopropil-6-fluoro-4-oxo-1,4-dihidro-quinolein-3-carboxilato de etilo
- 25 - 1-ciclopropil-6-fluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-metil-tioureido)-metil]-2-oxo-oxazolidin-3-il}-fenil)-piperazin-1-il]-4-oxo-1,4-dihidro-quinolein-3-carboxilato de metilo
- 1-ciclopropil-6-fluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-metil-tioureido)-metil]-2-oxo-oxazolidin-3-il}-fenil)-piperazin-1-il]-4-oxo-1,4-dihidro-quinolein-3-carboxilato de etilo
- 30
- 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-ciclopropil-6-

- fluoro-4-oxo-1,4-dihidro-[1,8] naftiridin-3-
 carboxilato de metilo
- 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-
 il]-2-fluoro-fenil}-piperazin-1-il)-6,8-difluoro-1-(2-
 5 fluoro-etil)-4-oxo-1,4-dihidro-quinolin-3- carboxilato
 de metilo
- 1-Etil-6,8-difluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-metil-
 tioureido)-metil]-2-oxo-oxazolidin-3-il}-fenil)-
 piperazin-1-il]-4-oxo-1,4-dihidro-quinolein-3-
 10 carboxilato de etilo

En la presente invención por el término "un
 solvato farmacéuticamente aceptable" se entiende un
 hidrato o solvato de un alcohol C₁-C₄.

15

En la presente invención, el término "sales
 farmacológicamente aceptables" incluye sales de metales
 alcalinos tales como sodio o potasio y sales de metales
 alcalinotérreos como calcio o magnesio, así como sales de
 20 adición de ácido formados con ácidos inorgánicos y
 orgánicos, por ejemplo, clorhidratos, bromhidratos,
 sulfatos, nitratos, fosfatos, formiatos, mesilatos,
 citratos, benzoatos, fumaratos, maleatos, lactatos y
 succinatos entre otros.

25

Las sales farmacológicamente aceptables se
 preparan por reacción de un compuesto de fórmula (I) con
 la cantidad adecuada de una base tal como hidróxido
 sódico, potásico, cálcico o magnésico, o metóxido sódico,
 30 hidruro sódico, tert-butóxido potásico, y similares en
 disolventes tales como éter, THF, metanol, etanol, tert-
 butanol, isopropanol, dioxano, etc o bien en una mezcla de
 disolventes. Las sales de adición, cuando sea aplicable,
 pueden prepararse por tratamiento con ácidos, tales como

clorhídrico, bromhídrico, sulfúrico, nítrico, fosfórico, fórmico, metanosulfónico, cítrico, benzoico, fumárico, maleico, láctico y succínico, en disolventes como éter, alcoholes, acetona, THF, acetato de etilo, o mezclas de 5 disolventes.

Los estereoisómeros de la presente invención pueden prepararse utilizando reactivos en una única forma enantiomérica en los procesos en los que sea posible o 10 llevando a cabo la reacción en presencia de reactivos o catalizadores en su única forma enantiomérica o por resolución de mezclas de estereoisómeros por métodos convencionales. Algunos de los métodos preferidos incluyen resolución de sales diastereoisoméricas formadas con 15 ácidos quirales, tales como ácido mandélico, camforsulfónico, tartárico, y similares. Métodos comúnmente utilizados están recogidos en Jaques et al. en "Enantiomers, Racemates and Resolution" (Wiley Interscience, 1981).

20

En las definiciones de la presente invención, por un grupo alquilo C₁-C₄, como grupo o como parte de un grupo, se entiende un grupo alquilo lineal o ramificado que contiene hasta 4 átomos de carbono. Así, incluye, por 25 ejemplo, metilo, etilo, propilo, isopropilo, butilo, isobutilo, sec-butilo y tert-butilo.

Del mismo modo, un grupo alcoxi C₁-C₄ incluye, por ejemplo, un grupo metoxi, etoxi, propoxi, isopropoxi, 30 butoxi, isobutoxi, sec-butoxi y tert-butoxi.

Un grupo alquenilo C₂-C₄ incluye, por ejemplo, un grupo vinilo, alilo, propenilo y 1-butenilo, 2-butenilo y 3-butenilo.

Un grupo haloalquilo C₁-C₄ significa un grupo alquilo C₁-C₄ sustituido por uno o más átomos de halógeno, iguales o distintos. Así, incluye, por ejemplo, 5 clorometilo, fluorometilo, trifluorometilo, cloroetilo, fluoroetilo, difluoroetilo, trifluoroetilo, fluoropropilo, cloropropilo, etc.

Un grupo haloalcoxi C₁-C₄ significa un grupo alcoxi C₁-C₄ sustituido por uno o más átomos de halógeno, iguales o distintos. Así, incluye, por ejemplo, clorometoxi, fluorometoxi, trifluorometoxi, cloroetoxi, fluoroetoxi, difluoroetoxi, trifluoroetoxi, fluoropropoxi, cloropropoxi, etc.

15

Un grupo cicloalquilo C₃-C₆ representa ciclopropilo, ciclobutilo, ciclopentilo y ciclohexilo.

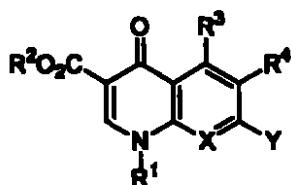
El término halógeno, en la presente invención, se 20 refiere a F, Cl, Br, I, preferentemente F y Cl.

El término arilo, en la presente invención, incluye fenilo y naftilo opcionalmente sustituidos por hasta cinco sustituyentes, iguales o distintos, 25 preferentemente hasta dos, en cualquier posición del anillo. Sustituyentes adecuados incluyen halógeno, amino, hidroxilo, alquilo C₁-C₄, alcoxi C₁-C₄, fenilo.

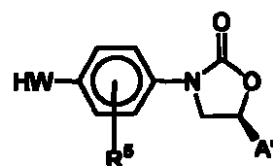
Los compuestos de la presente invención pueden ser 30 preparados de diversos modos. Pueden prepararse utilizando los métodos descritos a continuación, junto con métodos conocidos en el campo de la síntesis de química orgánica, o por las variaciones que sobre ellos pudiera realizar un experto en la materia. Métodos preferidos incluyen, pero

no se limitan a, los que se describen a continuación. Las reacciones se llevan a cabo en los disolventes apropiados para los reactivos y materiales utilizados adecuados a las transformaciones que se efectúan. Un experto en síntesis orgánica entenderá que los grupos funcionales presentes en la molécula deberían ser consistentes con las transformaciones propuestas. Esto puede en algunos casos requerir modificar el orden de los pasos de síntesis o seleccionar un método determinado respecto a otro, para obtener el compuesto deseado de la invención. Además, en alguno de los procedimientos descritos a continuación puede ser deseable o necesario proteger los grupos funcionales reactivos presentes en los compuestos o intermedios de la presente invención con grupos protectores convencionales. Distintos grupos protectores y procedimientos para su introducción y eliminación están descritos en Greene y Wuts (*Protective Groups in Organic Synthesis*, Wiley and Sons, 1999). Todas las referencias aquí citadas están incorporadas íntegramente por referencia.

Los compuestos de fórmula (I) pueden obtenerse por reacción de un compuesto de fórmula (II), con un compuesto de fórmula (III):



(II)



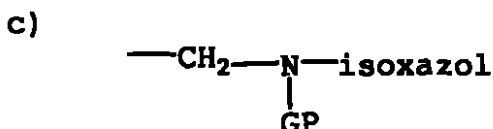
(III)

donde

A' es:

a) $-\text{CH}_2-\text{NH}-\text{R}^7$

b) $-\text{CHOH}-\text{C}\equiv\text{CH}$

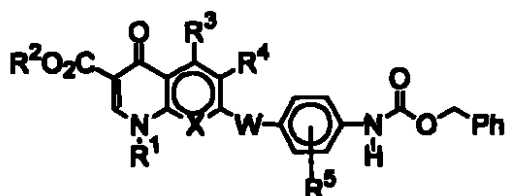


Y es un grupo saliente, tal como un átomo de halógeno (F, Cl, Br, I), un grupo tosilato ó mesilato, y 5 similares;

R¹, R², R³, R⁴, R⁵, X y W tienen el significado definido anteriormente;

GP es un grupo protector de aminas.

10 Alternativamente, los compuestos de fórmula (I) en los que A= -CHOH-C≡CH pueden obtenerse también por reacción de un compuesto de fórmula (IV) con p-toluensulfonato de 2,3-hidroxi-pent-4-inil:

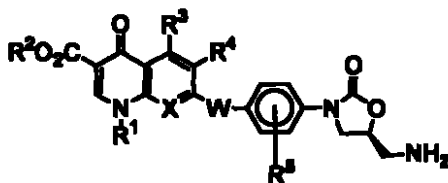


15

(IV)

donde R¹, R², R³, R⁴, R⁵, X y W tienen el significado definido anteriormente.

Los compuestos de fórmula (I) en los que A= -CH₂-NH-R⁷ y R⁷ es distinto de isoxazol, pueden obtenerse también por reacción de un compuesto de fórmula (V):



(V)

donde R^1 , R^2 , R^3 , R^4 , R^5 , X y W tienen el significado definido anteriormente, con un compuesto de fórmula (VI) o con un compuesto de fórmula (VII)



donde

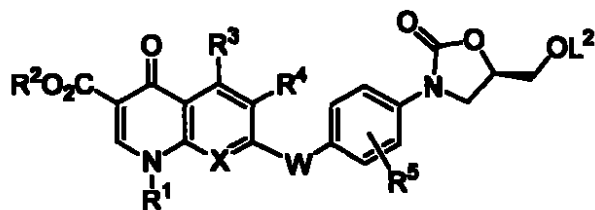
L es un buen grupo saliente, tal como un átomo de halógeno (F, Cl, Br, I), un grupo tosilato ó mesilato, y similares;

Z es Oxígeno ó Azufre, y

R^7 y R^8 tiene el significado definido anteriormente, siendo R^7 distinto de isoxazol.

15

Los compuestos de fórmula (I) en los que $A = -CH_2-NH-R^7$ y R^7 es isoxazol pueden obtenerse también por reacción de un compuesto de fórmula (VIII)



20 (VIII)

donde

- OL^2 representa un buen grupo saliente, tal como un residuo del ácido aril o metil sulfónico, sustituido o no sustituido, preferentemente un grupo tosilato ó mesilato;

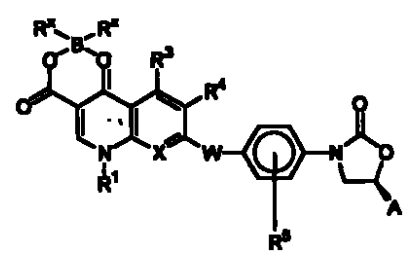
- R^1 , R^2 , R^3 , R^4 , R^5 , X y W tienen el significado definido anteriormente;

con isoxazolil-3-amina, con el grupo amino convenientemente protegido con un grupo protector de

127 126

aminas, por ejemplo con Troc (2,2,2-tricloroetoxicarbonil).

Los compuestos de fórmula (I), en los que $R^2 = H$ 5 pueden obtenerse también por hidrólisis de un quelato de boro de fórmula (IX):



(IX)

10

donde

R^x puede ser F o CH_3COO^- ;

A, R^1 , R^3 , R^4 , R^5 , X y W tienen el significado 15
definido anteriormente.

15

Y si se requiere, después de cualquiera de los métodos aquí descritos, puede efectuarse uno o más de los siguientes pasos opcionales:

20 - Convertir un compuesto de fórmula general (I) en otro compuesto de fórmula general (I);

- Eliminar cualquier grupo protector;

- Preparar una sal farmacológicamente aceptable de un compuesto de fórmula (I) y/o un solvato farmacológicamente aceptable del mismo.

25

La reacción de los compuestos de fórmula (II) con compuestos de fórmula (III) se lleva a cabo en un disolvente orgánico en presencia de una base orgánica. Preferentemente la reacción se lleva a cabo en disolventes

tales como piridina, acetonitrilo, dimetilformamida, N-metilpirrolidona, etc. en presencia de bases tales como trietilamina, DBU, diisopropiletilamina, etc.

5 La reacción de compuestos de fórmula (IV) con p-toluensulfonato de 2,3-hidroxi-pent-4-inil se lleva a cabo en un disolvente aprótico tal como N,N-dimetilformamida, THF, preferentemente THF, a baja temperatura, preferentemente a -68°C , y en presencia de una base tal
10 como n-butil-litio, tert-butóxido de litio, LDA, preferentemente en n-butil-litio.

La reacción de compuestos de fórmula (V) con un compuesto de fórmula (VI) se lleva a cabo en un disolvente
15 orgánico aprótico tal como acetonitrilo, diclorometano ó piridina o en mezcla de un disolvente orgánico y agua en presencia de una base. Preferentemente L es Cl, EtO, etc, de modo que $\text{R}^7\text{-L}$ puede ser un ácido, un cloruro de ácido, un anhídrido, un éster, un ditioéster, un cloroformiato de
20 alquilo o arilo, etc. La reacción de compuestos de fórmula (V) con un compuesto de fórmula (VII) se lleva a cabo preferentemente en piridina.

La reacción de los compuestos de fórmula (VIII)
25 con isoxazolil-3-amina, con el grupo amino convenientemente protegido se lleva a cabo en un disolvente aprótico tal como N,N-dimetilformamida, N,N-dimetilacetamida, preferentemente en N,N-dimetilformamida, a una temperatura comprendida entre 0 y 70°C , y en
30 presencia de una base fuerte tal como hidruro sódico, tert-butóxido de litio, tert-butóxido de sodio, tert-butóxido de potasio o amiduro sódico, preferentemente hidruro sódico.

La hidrólisis de los compuestos de fórmula (IX) se puede llevar a cabo según los métodos previamente descritos en la literatura (Masuhiro Fujita Chem. Pharm. Bull. (1988), 46(5), 787-796, Joseph P. Sánchez J. 5 Med. Chem. (1995), 38, 4478-4487)

Para $R^x = F$, la hidrólisis se realiza preferentemente en una mezcla de alcohol-agua en presencia de una base. Como mezcla hidroalcohólica se utiliza 10 preferentemente etanol-agua o metanol-agua y como base se utiliza preferentemente una base orgánica tal como trietilamina u otra amina secundaria o terciaria tales como tributilamina, diisopropiletilamina, DBU, etc. La 15 reacción se lleva a cabo a una temperatura que puede oscilar entre la temperatura ambiente y la temperatura de reflujo de la mezcla hidroalcohólica. La reacción se realiza preferentemente a la temperatura de reflujo de la mezcla hidroalcohólica.

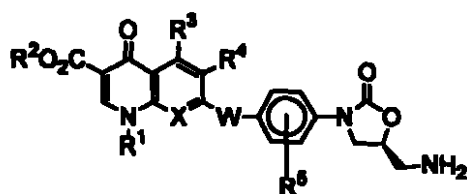
20 Para $R^x = CH_3COO$ la hidrólisis se realiza preferentemente en una mezcla de un disolvente orgánico aprótico y otro disolvente prótico en presencia de una base. Como disolvente aprótico se utiliza preferentemente acetonitrilo y como disolvente prótico se utiliza 25 preferentemente agua. Como base se utiliza preferentemente una base inorgánica tal como hidróxido de sodio, de litio o de potasio, o un carbonato de sodio, litio o potasio, etc.

30 Una reacción de interconversión de un compuesto de fórmula (I) en otro compuesto de fórmula (I) consiste, por ejemplo, en hidrolizar un compuesto de fórmula (I) en el que R^2 es un radical alquilo C_1-C_4 o fenilo para transformarlo en un compuesto de fórmula I en el que R^2 es

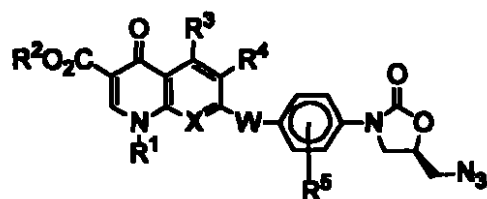
hidrógeno. La hidrólisis se realiza preferentemente en un medio hidroalcohólico utilizando como base preferentemente una base inorgánica. Más preferentemente la hidrólisis se realiza en etanol-agua o metanol-agua y como base se usa 5 hidróxido de sodio, litio o de potasio.

Otro ejemplo de reacción de interconversión de un compuesto de fórmula (I) en otro compuesto de fórmula (I) consiste en la esterificación de un compuesto de fórmula (I) en el que R^2 es hidrógeno, para rendir otro compuesto 10 de fórmula (I) en el que R^2 es un radical alquilo C_1-C_4 o fenilo, por los métodos convencionales de esterificación descritos en la literatura. Por ejemplo, por reacción de un compuesto de fórmula R^2-OH con el compuesto de fórmula (I) en el que R^2 es hidrógeno, habiendo previamente 15 activado el ácido carboxílico con carbonil diimidazol, o bien habiendo transformado previamente el ácido carboxílico en un cloruro de ácido por reacción con cloruro de tionilo, o bien habiéndolo transformado en anhídrido mixto por reacción con cloroformiato de alquilo.

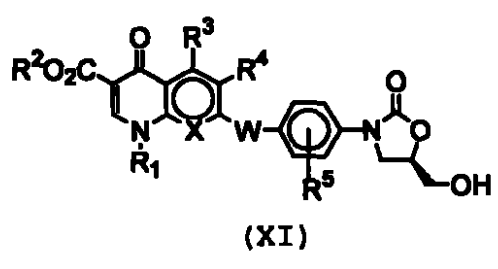
20 También son objeto de la presente invención los compuestos de fórmula (V), (X) y (XI):



(V)



(X)



donde R¹, R², R³, R⁴, R⁵, X y W tienen el
5 significado definido anteriormente. Estos compuestos son
útiles como intermedios para la obtención de los
compuestos de fórmula (I) de la presente invención.

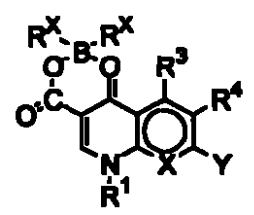
A continuación se describen procedimientos de
10 obtención de los intermedios utilizados en la preparación
de los compuestos de fórmula (I).

Los compuestos de fórmula (V), (X) y (XI) pueden
obtenerse de acuerdo con el esquema 1A y 1B.
15

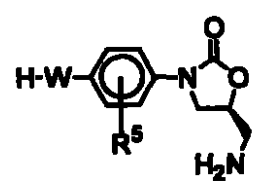
Así, los compuestos de fórmula (V) pueden
obtenerse:

a.- por reacción de un compuesto de fórmula (II) o
de fórmula (XII) con un compuesto de fórmula (XIII):

20



25



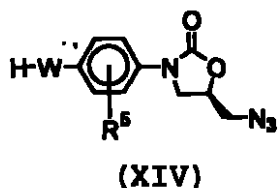
La reacción puede llevarse a cabo en las
condiciones anteriormente descritas para la reacción de un
compuesto de fórmula (II) con un compuesto de fórmula
30 (III);

b.- por reducción catalítica de un producto de fórmula (X) o por reducción del grupo azido por vía química con trifenilfosfina, etc.

5 Los compuestos de fórmula (X) pueden obtenerse a su vez:

a.- por reacción de un compuesto de fórmula (XII) o de fórmula (II) con un compuesto de fórmula (XIV):

10

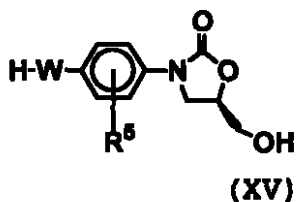


La reacción puede llevarse a cabo en las condiciones anteriormente descritas para la reacción de un
15 compuesto de fórmula (II) con un compuesto de fórmula (III);

b.- a partir de un compuesto de fórmula (XI) por transformación del grupo hidróxilo en un buen grupo saliente, tal como mesilato, tosilato o halógeno y
20 posterior reacción con azida sódica.

Los compuestos de fórmula (XI) pueden obtenerse a su vez:

a.- por reacción de un compuesto de fórmula (XII)
25 o de fórmula (II) con un compuesto de fórmula (XV):



La reacción puede llevarse a cabo en las condiciones anteriormente descritas para la reacción de un compuesto de fórmula (II) con un compuesto de fórmula (III);

- 5 b.- por reacción de un compuesto de fórmula (IV) con (R)-glicidil butirato. La reacción se lleva a cabo en un disolvente aprótico tal como N,N-dimetilformamida, THF, preferentemente THF, a baja temperatura, preferentemente a -68°C, y en presencia de una base tal como n-butil-litio, 10 tert-butóxido de litio, LDA, preferentemente en n-butil-litio.

La utilización de los compuestos de fórmula (XII) para la obtención de los tres intermedios anteriores 15 requiere un paso adicional de hidrólisis del quelato de boro, tal como se indica en el esquema 1A y 1B, el cual se lleva a cabo en las condiciones anteriormente descritas para la hidrólisis del compuesto de fórmula (IX).

- 20 Los compuestos de fórmula (VIII) pueden obtenerse por reacción de un compuesto de fórmula (XI) con cloruro de aril o metil sulfonilo, sustituido o no sustituido, preferentemente con cloruro de mesilo o cloruro de p-toluensulfonilo, en un disolvente aprótico, tal como 25 cloruro de metileno, y en presencia de una base orgánica, tal como trietilamina.

Los compuestos de fórmula (IX) pueden obtenerse por reacción de un compuesto de fórmula (XII) con un 30 compuesto de fórmula (III). La reacción puede llevarse a cabo en las condiciones anteriormente descritas para la reacción de un compuesto de fórmula (II) con un compuesto de fórmula (III).

Los productos de fórmula (II) y de fórmula (XII) se obtienen según los métodos descritos en la literatura. Estos productos han sido utilizados como intermedios de la síntesis de quinolonas y análogos con actividad 5 antibacteriana tales como ciprofloxacina, ofloxacina, moxifloxacina, norfloxacina, tosufloxacina, etc. (Ver patentes WO 8807993, WO 8807998, WO 9006922, JP 59122470, JP 58029789, EP 0351889).

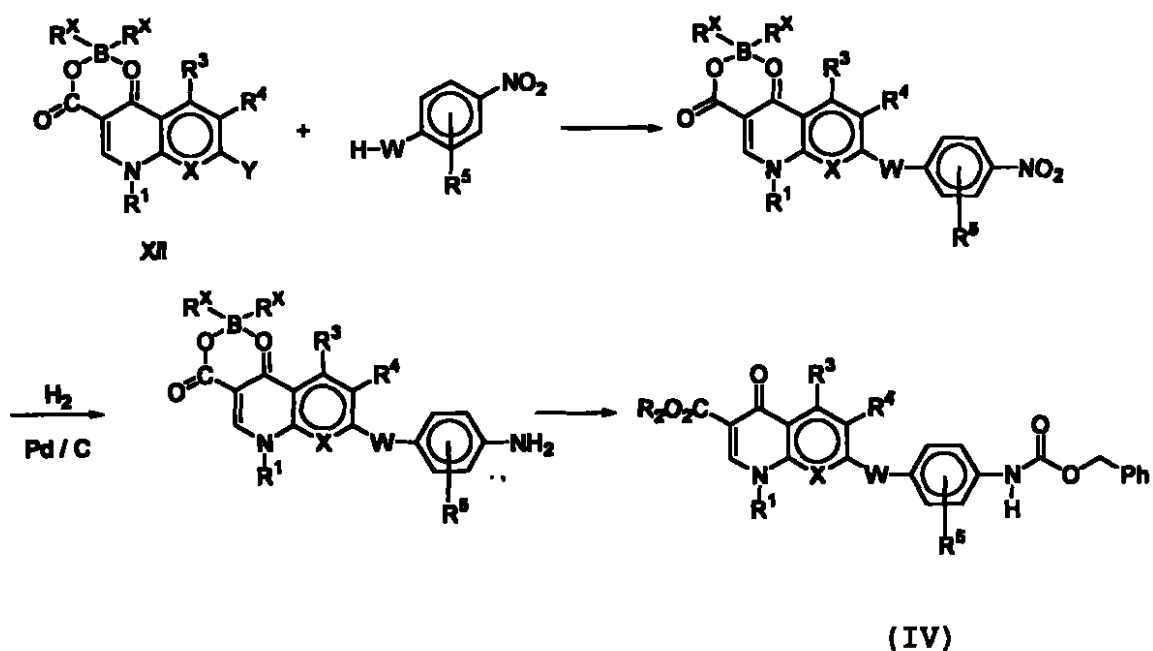
10 Los compuestos de fórmula (III), (XIII), (XIV) y (XV) pueden obtenerse de acuerdo con el esquema 2.

Así, los compuestos de fórmula (IIIa), (XIII) y (XIV) pueden obtenerse a partir de un compuesto de fórmula 15 (XVI) por transformación del grupo hidroxilo en un grupo NH_2 , N_3 o NHR^7 , de acuerdo con reacciones bien conocidas para un experto en química orgánica.

Los compuestos de fórmula (IIIb) pueden obtenerse 20 por reacción de un compuesto de fórmula (XVII) con p-toluensulfonato de 2,3-hidroxi-pent-4-ínil, en condiciones análogas a las descritas para la reacción de un compuesto de fórmula (IV) con dicho reactivo.

25 Los compuestos de fórmula (IIIc) pueden obtenerse por reacción de un compuesto de fórmula (XVI) con isoxazolil-3-amina, con el grupo amino convenientemente protegido, por ejemplo con Troc, y previa transformación del grupo hidroxilo en un buen grupo saliente, por 30 ejemplo, mesilato, tosilato, halógeno, etc.

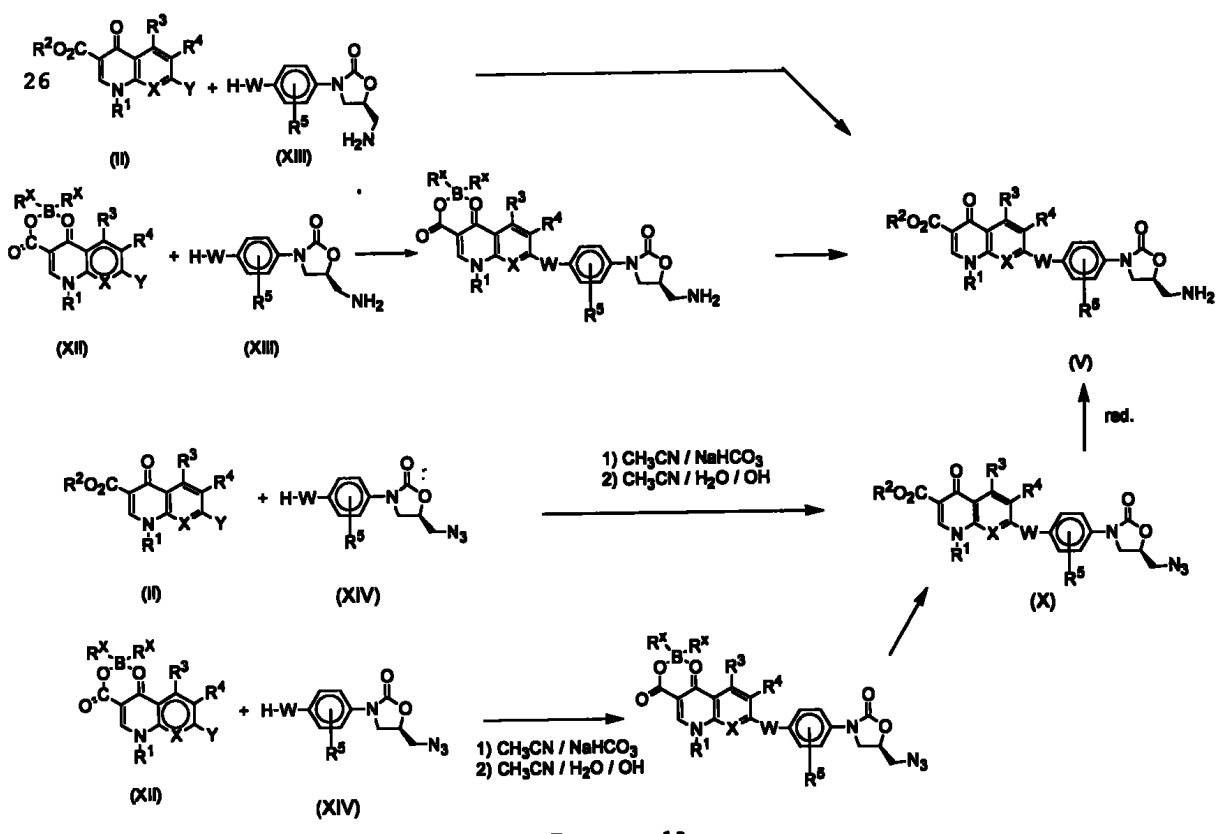
Los compuestos de fórmula (IV) pueden obtenerse según el siguiente esquema:



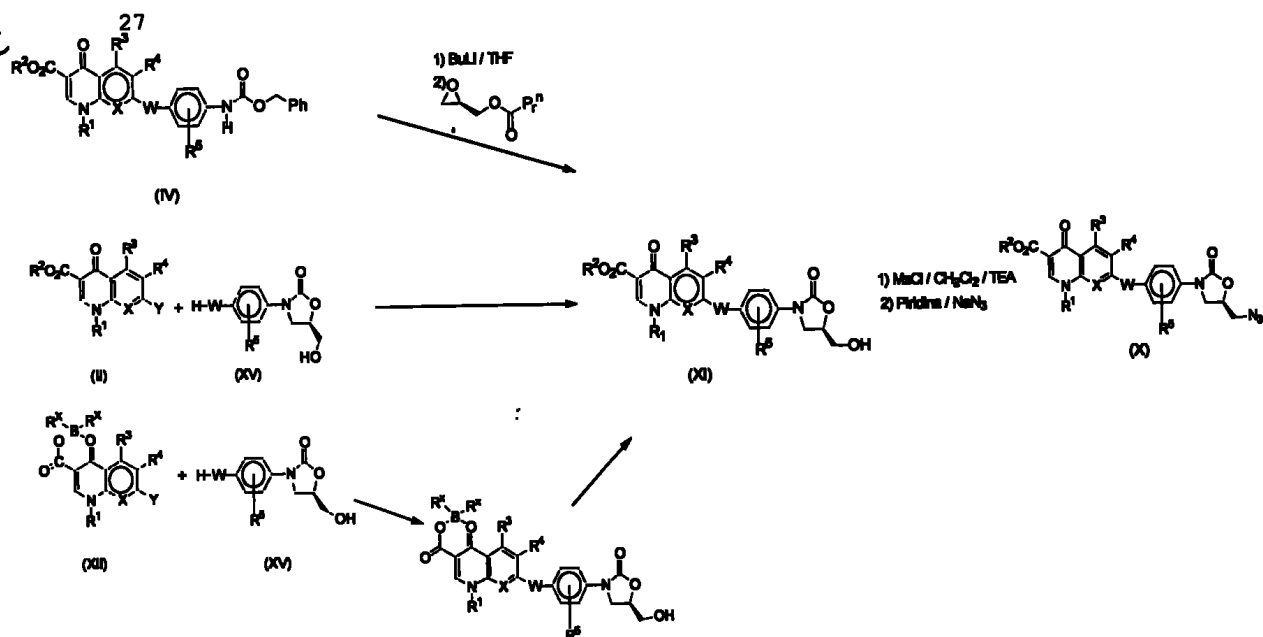
5 Las reacciones se llevan a cabo en los disolventes apropiados, y en condiciones convencionales. En los esquemas se indican las condiciones preferidas de reacción.

10 El p-toluensulfonato de 2,3-hidroxipent-4-enil se obtiene según el procedimiento descrito en EP 1029854A1.

Los compuestos de fórmula (VI) y de fórmula (VII) son comerciales, están ampliamente descritos en la literatura o se pueden preparar por métodos análogos a los conocidos en el estado de la técnica a partir de productos asequibles comercialmente.



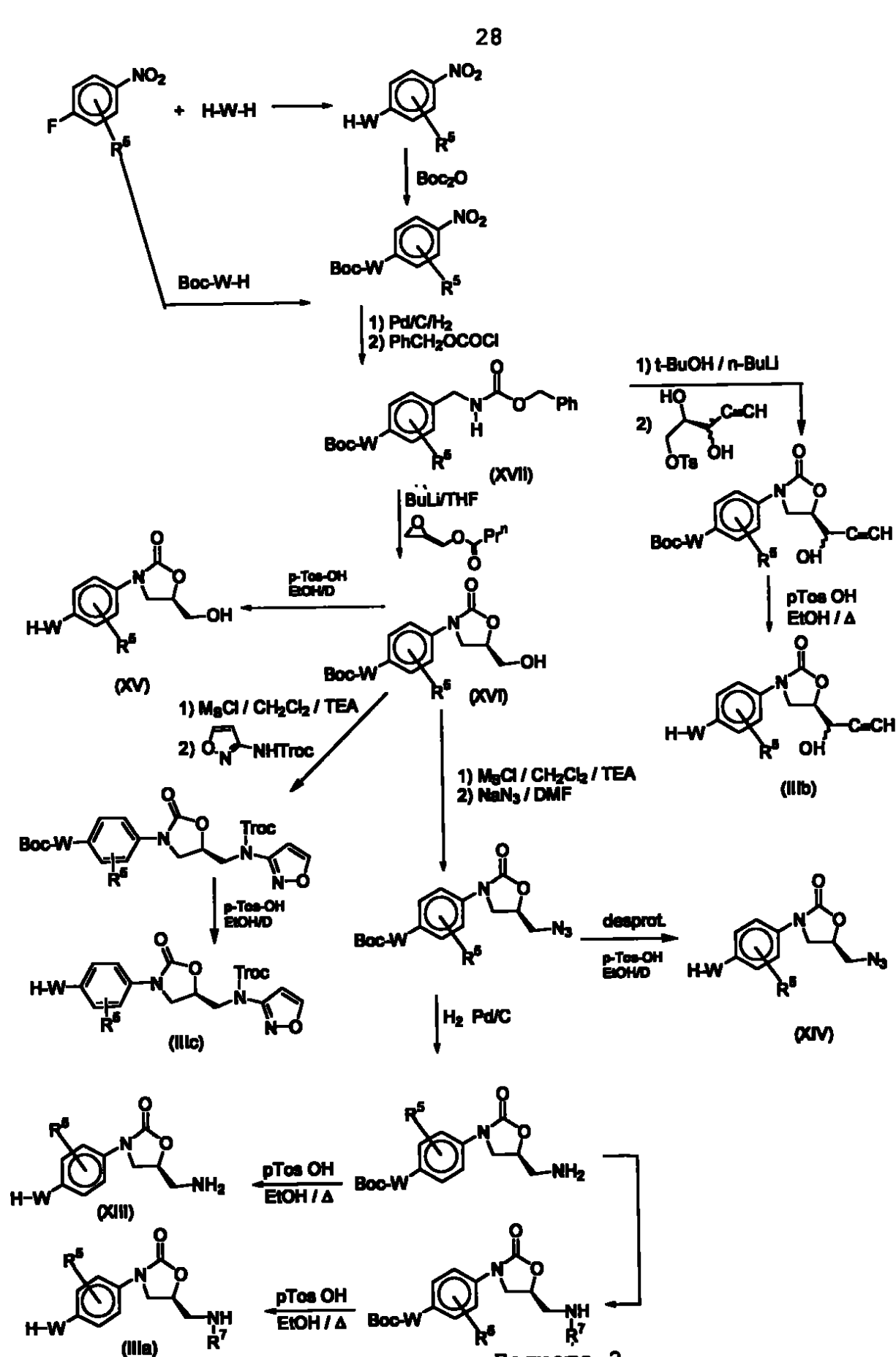
Esquema 1A



Esquema 1B

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Esquema 2

Son también objeto de la presente invención las composiciones que comprendan un compuesto de fórmula general (I), una sal o un solvato farmacéuticamente aceptable, o cualquier isómero geométrico, isómero óptico o mezcla de isómeros del mismo en cualquier proporción o polimorfo del mismo, en una cantidad terapéuticamente activa y una cantidad adecuada de, al menos, un excipiente farmacológicamente aceptable.

10 Las composiciones de la invención pueden formularse en forma sólida o líquida siguiendo las técnicas farmacéuticas convencionales. Las formulaciones sólidas incluyen comprimidos, cápsulas, sobres, polvos, supositorios, etc. Los excipientes pueden comprender
15 diluyentes, desintegrantes, agentes humectantes, lubricantes, colorantes, aromas u otros adyuvantes convencionales. Los excipientes sólidos típicos comprenden, por ejemplo, celulosa microcristalina, almidón, polivinilpirrolidona, estearato magnésico o
20 lauril sulfato sódico. Las composiciones líquidas incluyen soluciones, suspensiones o emulsiones. Pueden consistir en disoluciones en agua o en sistemas de agua-propilenglicol o agua-polietilenglicol, conteniendo además opcionalmente aromas, colorantes, estabilizantes y espesantes.

25

Las composiciones pueden administrarse por vía oral, parenteral o tópica.

Los compuestos de fórmula (I) muestran actividad
30 como antibacterianos. Ventajosamente poseen un amplio espectro de actividad frente a bacterias Gram-positivas tales como *Staphylococcus*, *Streptococcus*, *Enterococcus* y similares, así como frente a Gram-negativas tales como *E. Coli*, *H. Influenzae*, *M. catarrhalis*, etc, incluso frente

a cepas resistentes a antibióticos conocidos tales como la meticilina, la vancomicina, penicilina etc. Asimismo, son también activos frente a microorganismos anaerobios, tales como *Bacteroides fragilis*. Así pues, es objeto también de la presente invención el uso de un compuesto de fórmula (I) para la preparación de una composición farmacéutica destinada al tratamiento de infecciones microbianas, en humanos o animales de sangre caliente

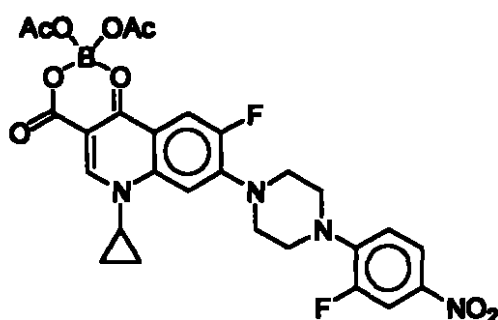
A continuación y a título explicativo aunque no limitativo de la invención se exponen los siguientes ejemplos.

EJEMPLOS DE SÍNTESIS

PREPARACIÓN DE INTERMEDIOS

Ejemplo de referencia N°1:

1-Ciclopropil-6-fluoro-7-[4-(2-fluoro-4-nitro-fenil)-piperazin-1-il]-4-oxo-1,4-dihidro-quinolein-3-carboxílico borodiacetoxi quelato



A 10 g (0,024 mol) de 1-ciclopropil-7-cloro-6-fluoro-4-oxo-1,4-dihidro-quinolein-3-carboxílico borodiacetoxi quelato (obtenido según WO 8807998) en 150 ml de acetonitrilo se adicionan 5,4 g (0,024 mol) de 1-(2-fluoro-4-nitro-fenil)piperazina (Obtenido según el método descrito por S.J. Brickner y col. J. Med. Chem. 1996, 39, 673-679) y 2 g (0,024 moles) de bicarbonato sódico.

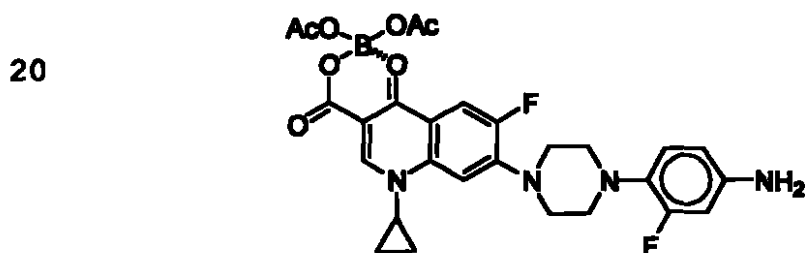
La reacción se calienta a reflujo durante 48 h. Se concentra a sequedad y el residuo se trata con 100 ml de agua y se extrae con 3 x 100 ml de diclorometano. La fase orgánica se seca y concentra y el residuo se cromatografía 5 sobre gel de sílice.

Eluyendo con diclorometano/etanol 98/2 se obtienen 6,7 g del producto del título.

^1H -RMN: (CDCl_3 , 200 MHz, δ ppm): 9,08 (s, 1H); 8,14 (d, 1H); 8,10-7,94 (s.c., 2H); 7,56 (d, 1H); 7,01 (t, 1H); 3,82-3,75 (m, 1H); 3,75-3,50 (s.c., 8H); 2,04 (s, 6H); 1,64-1,30 (s.c., 4H).

Ejemplo de referencia N°2:

15 7-[4-(4-amino-2-fluoro-fenil)piperazin-1-il]-1-ciclopropil-6-fluoro-4-oxo-1,4-dihidro-quinolein-3-carboxílico boro diacetoxi quelato.



25

A 6,7 g (0,011 mol) del producto obtenido en el ejemplo anterior, en 50 ml de dimetilformamida se adicionan 0,7 g de Pd/C del 10% pasta y se coloca bajo atmósfera de hidrógeno a 40°C y presión atmosférica. Finalizada la 30 reacción se filtra sobre decalite y se lava la decalite con 20 ml de DMF.

Los líquidos de filtrado se vierten sobre 700 ml de agua y se extrae con 3 x 200 ml de diclorometano. La

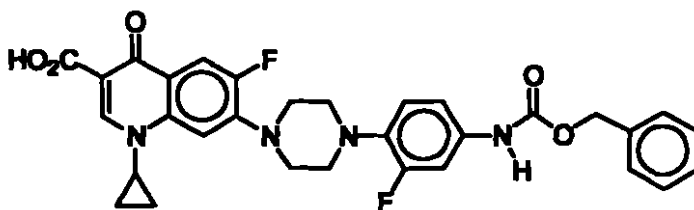
fase orgánica se concentra a sequedad y el residuo se cromatografía sobre gel de sílice.

Eluyendo con diclorometano-etanol 95/5 se obtienen 5 2,6 g del producto del título como sólido amarillo.

^1H -RMN (CDCl_3 , 200 MHz, $\delta(\text{ppm})$): 9,04 (s, 1H); 8,10 (d, 1H); 7,45 (d, 1H); 6,84 (dd, 1H); 6,44-6,36 (s.c., 2H); 3,79-3,64 (m, 1H); 3,62-3,56 (s.c., 4H); 3,24-3,16 (s.c., 4H); 2,05 (s, 6H); 1,80-1,20 (s.a., 2H, NH_2); 1,58-1,24 (s.c., 4H).

Ejemplo de referencia N°3:

Acido 7-[4-(4-benciloxycarbonilamino-2-fluoro-fenil)-piperazin-1-il]-1-ciclopropil-6-fluoro-4-oxo-1,4-dihidro-quinolein-3-carboxílico.



A 2,62 g (4,58 mmol) del producto obtenido en el ejemplo de referencia anterior en 30 ml de THF y 10 ml de agua se adicionan 0,4 g (5 mmol) de bicarbonato sódico.

Sobre la solución anterior se adicionan gota a gota 0,8 g (5 mmol) de cloroformiato de bencilo y se mantiene con agitación durante 48 h. Se concentra a sequedad, se adicionan 50 ml de agua y se extrae con 3 x 75 ml de diclorometano.

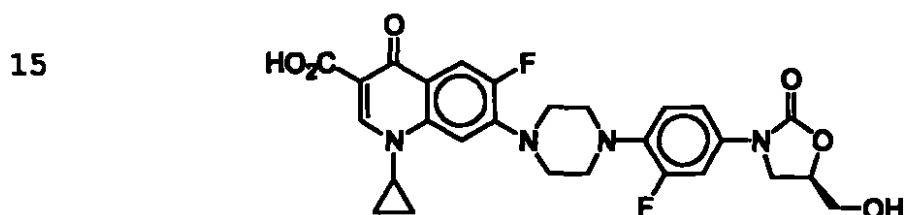
La fase orgánica se seca y concentra. El residuo se agita con 10 ml de diclorometano durante 10 minutos y se filtra el precipitado obtenido.

Se obtienen así 2 g del producto del título.

^1H -RMN (DMSO, 200 MHz, δ (ppm)): 9,84 (s.a., 1H); 8,64 (s, 1H); 7,92 (d, 1H); 7,61 (d, 1H); 7,50-7,30 (s.c., 5 6H); 7,22-7,01 (s.c., 2H); 5,18 (s, 2H); 3,92-3,78 (s.a., 1H); 3,70-3,10 (s.c., 8H); 1,42-1,10 (s.c., 4H).

Ejemplo de referencia N°4:

Ácido 1-ciclopropil-6-fluoro-7-{4-[2-fluoro-4-5-(R)-hidroximetil-2-oxo-oxazolidin-3-il]-fenil]-piperazin-1-il}-4-oxo-1,4-dihidro-quinolein-3-carboxílico.



20

A 2,2 g (3,57 mmol) del producto obtenido en la preparación anterior en 60 ml de THF enfriados a -78°C se adicionan gota a gota 3 ml (7,14 mmol) de n-butil-litio 2,5 M en hexano.

25

Se mantiene la reacción a -78°C durante 1 h y entonces se adicionan 0,51 g (3,57 mmol) de R-Glicidil butirato disuelto en 10 ml de THF.

30 Se deja alcanzar la temperatura ambiente y se agita así durante 16 h.

Se adicionan 20 ml de disolución saturada de cloruro amónico y se concentra hasta eliminar el THF. Se adicionan

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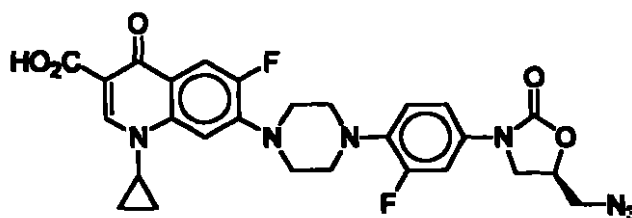
50 ml de agua y se extrae con 3 x 100 ml de diclorometano-etanol (90/10).

La fase orgánica se seca y concentra. El residuo se 5 cromatografía sobre gel de sílice. Eluyendo con diclorometano-etanol (90/10) se obtienen 0,5 g del producto del título.

^1H -RMN (DMSO- d_6 , 200 MHz, δ (ppm)): 8,70 (s, 1H);
10 7,96 (d, 1H); 7,70-7,36 (s.c., 3H); 7,30-7,10 (s.c., 2H);
5,20-5,10 (s.a., 1H); 4,8-4,64 (m, 1H); 4,20-4,04 (m, 1H);
3,92-3,14 (s.c., 11H); 1,43-1,16 (s.c., 4H).

Ejemplo de referencia N°5:

15 Ácido 7-{4-[4-(5-(R)-azidometil-2-oxo-oxazolidin-3-il)-2-fluoro-fenil]-piperazin-1-il}-1-ciclopropil-6-fluoro-4-oxo-1,4-dihidro-quinolein-3-carboxílico.



20

Método 1:

A 0,5 g (0,92 mmol) del producto obtenido en la preparación anterior en 10 ml de diclorometano seco se 25 adicionan 2,6 ml de trietilamina y se enfría a 0°C. Se adicionan 1,4 ml de metanosulfonilo cloruro y se agita a 0°C durante 1 h.

Se vierte sobre agua-hielo (30 ml/20 g) saturada de sodio bicarbonato y se decanta la fase orgánica. Se seca sobre sulfato sódico, se filtra y concentra.

5 Al residuo se le adicionan 10 ml de dimetilformamida y 1,17 g de azida sódica. Se calienta a 75°C y se agita a esta temperatura durante 16 h.

Se vierte sobre 100 ml de agua y se extrae con 3 x 100 ml de acetato de etilo. La fase orgánica se seca y concentra y el residuo se cromatografía sobre gel de sílice. Eluyendo con diclorometano-etanol (90/10) se obtienen 40 mg del producto del título.

15 Método 2:

A 1,5 g (4,7 mmol) de 5-(R)-azidometil-3-(3-fluoro-4-piperazina-1-il-fenil)-oxazolidin-2-ona (ejemplo de referencia N°19) y 1,9 g (4,7 mmol) de ácido 1-ciclopropil-7-cloro-6-fluoro-4-oxo-1,4-dihidroquinolina-3-carboxílico borodiacetoxi quelato (obtenido según WO 8807998) en 60 ml de acetonitrilo se adicionan 0.4 g (4.7 mmol) de bicarbonato sódico y se calienta a reflujo durante 48 h.

25

Se concentra a sequedad y el residuo se trata con 100 ml de agua y se extrae con 3 x 100 ml de CH₂Cl₂. La fase orgánica se seca y concentra y el residuo se cromatografía sobre gel de sílice.

30

Eluyendo con CH₂Cl₂/EtOH 95/5 se obtienen 1,1 g del producto del título como quelato de borodiacetato.

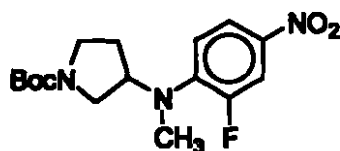
Los 1,1 g así obtenidos se disuelven en una mezcla de 28 ml de agua, 28 ml de acetonitrilo y 8 ml de hidróxido de sodio 1N. Se agita a temperatura ambiente 3 h, se concentra el acetonitrilo y se adicionan 8 ml de ácido 5 clorhídrico 1N.

Se filtra el sólido precipitado obteniéndose 0,6 g de producto idéntico al obtenido por el método 1.

^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 8,79 (s, 1H); 8,01 (d, 1H); 7,54-7,24 (s.c., 2H); 7,16-6,90 (s.c., 2H); 4,83-4,70 (m, 1H); 4,42-4,34 (m, 1H); 4,10-3,20 (s.c., 12H); 1,44-1,12 (s.c., 4H)

Ejemplo de referencia N°6:

15 3(R,S)-[(2-fluoro-4-nitro-fenil)-metilamino]-pirrolidin-1-carboxilato de tert-butilo.



20

A 7 g (0,0375 mol) de 3(R,S)-metilamino-pirrolidin-1-carboxilato de tert-butilo y 4,11 ml (0,0375 mol) de 3,4-difluoronitrobenceno en 80 ml de DMF se adicionan 3,15 g de bicarbonato sódico y se calienta a 45°C durante 16 h.

25

Se vierte sobre 800 ml de agua y se extrae con 3 x 300 ml de AcOEt. La fase orgánica se seca y concentra y el residuo se cromatografía sobre gel de sílice.

30 Eluyendo con diclorometano-etanol 95/5 se obtienen 7,9 g del producto del título.

147 146

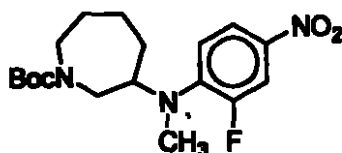
^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 8,00-7,88 (s.c, 2H); 6,88 (dd, 1H); 4,45-4,30 (m, 1H); 3,75-3,50 (s.a., 4H); 3,45-3,25 (s.c, 4H); 2,95 (s, 3H); 2,18-2,07 (m, 2H); 1,49 (s, 9H).

5

Ejemplo de referencia N°7:

3(R, S)-[(2-fluoro-4-nitro-fenil)-metil-amino]-azepan-1-carboxilato de tert-butilo.

10



Siguiendo el procedimiento anterior a partir de 3(R,S)-metilamino-azepan-1-carboxilato de tert-butilo se obtiene el producto del título.

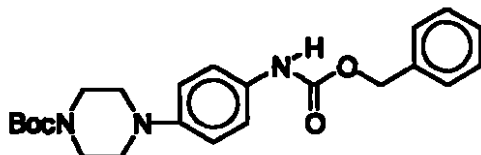
^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 8,10-7,80 (m, 2H); 6,90 (dt, 1H); 4,05-3,10 (m, 5H); 2,94 (m, 3H); 1,50 y 1,41 (s, 9H); 1,20-2,10 (m, 6H).

20

Ejemplo de referencia N°8:

4-(4-Benciloxycarbonilamino-fenil)-piperazin-1-carboxilato de tert-butilo.

25



30 A 72,7 g (0,236 mol) de 4-(4-nitro-fenil)-piperazin-1-carboxilato de tert-butilo (WO 9725323), en 600 ml de THF y 125 ml de agua se adicionan 7,27 g de Pd/C del 10% pasta y se coloca bajo atmósfera de hidrógeno a presión atmosférica y temperatura ambiente.

Finalizada la reducción del grupo nitro (cromatografía en capa fina eluida con heptano/AcOEt 1/1) se adicionan a 0°C 21 g (0,25 mol) de bicarbonato sódico y 40,2 g (0,236 mol) de cloroformiato de bencilo.

5

Se agita 30 min a 0°C y se filtra sobre decalite. Se lava la decalite con 300 ml de THF y los líquidos de filtrado se concentran hasta eliminar el THF.

10 Se adicionan 200 ml de agua y se extrae a 3 x 200 ml de diclorometano. La fase orgánica se seca y concentra y el residuo se cromatografía sobre gel de sílice.

Eluyendo con heptano/AcOEt se obtiene 69,8 g (72%) del 15 producto del título.

^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 7,42-7,24 (s.c., 7H); 6,86 (d.2H); 6,64 (s.a., 1H); 5,18 (s, 2H); 4,60-4,50 20 (s.c., 4H); 3,10-3,00 (s.c., 4H); 1,46 (s, 9H).

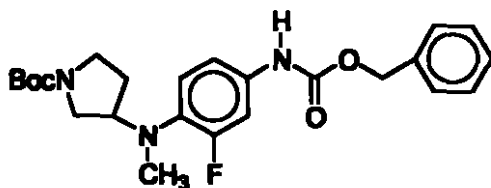
Siguiendo el procedimiento anteriormente descrito se obtienen los siguientes productos:

25

Ejemplo de referencia N°9:

3(R, S)-[(4-benciloxicarbonilamino-2-fluoro-fenil)-metil-amino]-pirrolidin-1-carboxilato de tert-butilo.

30

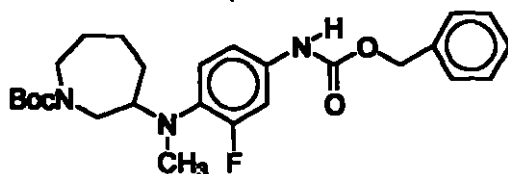


¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 7,42-7,26 (s.c. 6H); 7,01-6,92 (s.c., 3H, 2H aromático + NH); 5,19 (s, 2H); 3,86-3,65 (m, 1H); 3,60-3,36 (s.c., 3H); 3,36-3,12 (s.c., 2H); 2,71 (s, 3H); 2,10-1,75 (s.c., 2H); 1,42 (s, 5 9H).

Ejemplo de referencia N°10:

3(R, S)-[(4-benciloxycarbonilamino-2-fluoro-fenil)-metil-amino]-azepan-1-carboxilato de tert-butilo.

10



15

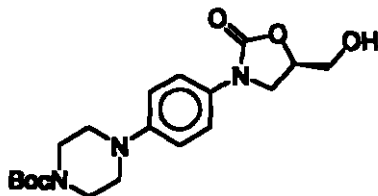
¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 7,60-7,20 (m, 5H); 7,20-6,80 (m, 3H); 3,95-2,90 (m, 5H); 2,71 (s, 3H); 1,45 y 1,37 (s, 9H); 1,05-2,00 (m, 6H).

20

Ejemplo de referencia N°11:

4-[4-(5-(R)-hidroximetil-2-oxo-oxazolidin-3-il)fenil]-piperazin-1-carboxilato de tert-butilo.

25



30

Siguiendo el procedimiento análogo al descrito en el ejemplo de referencia N°4 y partiendo de 69,2 g (0,169 mol) del producto obtenido en el ejemplo de referencia N°8 se obtienen 44,4 g (70%) del producto del título.

^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 7,42 (d, 2H); 6,92 (d, 2H); 4,80-4,64 (s.c., 1H); 4,02-3,90 (s.c., 3H); 3,80-3,64 (m, 1H); 3,62-3,72 (s.c., 4H); 3,14-3,04 (s.c., 4H); 2,77 (t, 1H, OH); 1,45 (s, 9H).

5

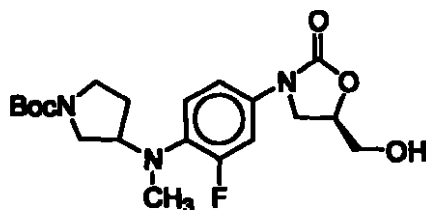
Al igual que en la preparación anterior, siguiendo el procedimiento descrito en el ejemplo de referencia N°4 se obtienen los siguientes productos:

10

Ejemplo de referencia N°12:

3-(R, S)-{ [2-fluoro-4-(5-(R)-hidroximetil-2-oxo-oxazolidin-3-il)-fenil]-metil-amino}-pirrolidin-1-carboxilato de tert-butilo.

15



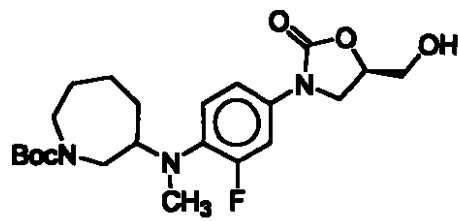
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^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 7,41 (dd, 1H); 7,14-7,00 (s.c., 2H); 4,80-4,64 (m, 1H); 4,02-3,64 (s.c., 25 5H); 3,62-3,40 (s.c., 2H); 3,38-3,18 (s.c., 2H); 2,78 (s.a., 1H, OH); 2,70 (s, 3H); 2,06-1,80 (s.c., 2H); 1,42 (s, 9H).

Ejemplo de referencia N°13:

30

3-(R, S)-{ [2-fluoro-4-(5-(R)-hidroximetil-2-oxo-oxazolidin-3-il)-fenil]-metil-amino}-azepan-1-carboxilato de tert-butilo.



5

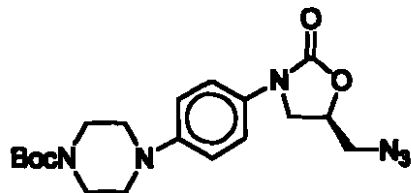
^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 7,95 (m, 1H); 7,40 (dd, 1H); 7,10 (m, 1H); 4,75 (m, 1H); 4,10-3,00 (m, 9H); 2,73 y 2,76 (s, 3H); 1,39 y 1,46 (s, 9H); 1,20-2,00 (m, 6H).

Si siguiendo el procedimiento descrito en el método 1 del ejemplo de referencia N°5 y partiendo respectivamente de los productos obtenidos en los ejemplos de referencia 15 11 a 13 se obtienen los siguientes productos:

Ejemplo de referencia N°14:

4-[4-(5-(R)-azidometil-2-oxo-oxazolidin-3-il)-fenil]-piperazin-1-carboxilato de tert-butilo.

20



25

^1H -RMN ($\text{DMSO}-d_6$, 200 MHz, δ (ppm)): 7,44 (d, 2H); 7,02 (d, 2H); 4,96-4,84 (m, 1H); 4,17 (t, 1H); 3,84-3,62 (s.c., 2H); 3,56-3,30 (s.c., 5H); 3,17-3,04 (s.c., 4H); 30 1,42 (s, 9H).

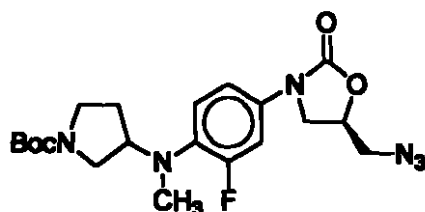
151

Ejemplo de referencia N°15:

3-(R, S)-{[4-(5-(R)-azidometil-2-oxo-oxazolidin-3-il)-2-fluoro-fenil]-metil-amino}-pirrolidin-1-carboxilato de tert-butilo.

5

10

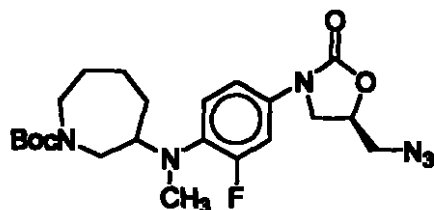


$^1\text{H-RMN}$ (CDCl_3 , 200 MHz, δ (ppm)): 7,41 (dd, 1H); 7,16-7,01 (s.c., 2H); 4,86-4,72 (m, 1H); 4,06 (t, 1H); 3,95-3,40 (s.c., 6H); 3,38-3,17 (s.c., 2H); 2,73 (s, 3H); 2,10-1,73 (s.c., 2H); 1,45 (s, 9H).

Ejemplo de referencia N°16:

3-(R, S)-{[4-(5(R)-azidometil-2-oxo-oxazolidin-3-il)-2-fluoro-fenil]-metil-amino}-azepan-1-carboxilato de tert-butilo.

25



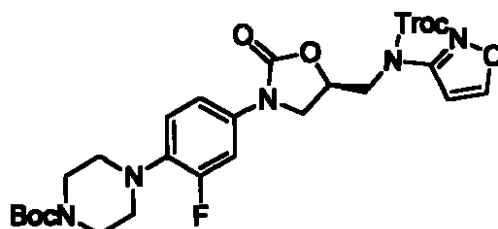
$^1\text{H-RMN}$ (CDCl_3 , 200 MHz, δ (ppm)): 7,35 (m, 1H); 7,20-6,80 (m, 2H); 4,75 (m, 1H); 4,05 (t, 1H); 3,95-3,00 (m, 8H); 2,74 (m, 3H); 2,00-1,00 (m, 6H); 1,46 y 1,39 (s, 9H).

Ejemplo de referencia N°17:

4-[2-Fluoro-4-(5-(R)-{[isoxazol-3-il-(2,2,2-tricloroetoxicarbonil)-amino]-metil}-2-oxo-oxazolidin-3-il)-fenil]-piperazin-1-carboxilato de tert-butilo.

5

10



Se disuelven 3,4 g (13 mmol) de 3-(2,2,2-tricloroetoxicarbonilamino)-isoxazol (preparado según WO 15 0021960) en 100 ml de DMF y se adicionan en porciones 536 mg (14,3 mmol) de hidruro de sodio (pasta al 60%) y se agita durante 30 minutos. A continuación se adicionan 6 g (12,7 mmol) de 4-{2-Fluoro-4-[2-oxo-5-(R)-(toluene-4-sulfoniloximetil)-oxazolidin-3-il]-fenil}-piperazine-1-
20 carboxilato de tert-butilo (obtenido según US 5547950) disuelto en 30 ml de DMF.

La reacción se calienta a 90°C durante 20 h. Se deja enfriar y se vierte sobre 500 ml de agua. Se extrae 25 con 3x250 ml de una mezcla 4/1 de tolueno/acetato de etilo. La fase orgánica se seca y concentra y el residuo se cromatografía sobre gel de sílice.

Eluyendo con Heptano/Acetato de etilo 7/3 se 30 obtienen 2,5 g del producto del título.

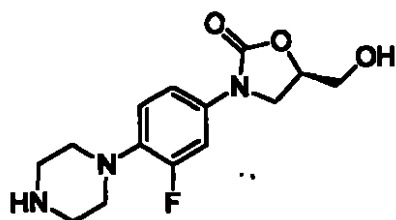
¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 8,34 (d, 1H); 7,45 (dd, 1H); 7,12 (m, 1H); 6,95 (m, 2H); 5,15 (m, 1H);

4,90 (m, 2H); 4,50 (dd, 1H); 4,25 (dd, 1H); 4,13 (t, 1H);
3,85 (dd, 1H); 3,60 (m, 4H); 3,00 (m, 4H); 1,49 (s, 9H).

Ejemplo de referencia N°18:

5 **3-(3-Fluoro-4-piperazin-1-il-fenil)-5-(R)-**
hidroximetil-oxazolidin-2-ona

10



A 5 g (0,0126 mol) de 4-[2-fluoro-4-(5-(R)-
15 hidroximetil-2-oxo-oxazolidin-3-il)-fenil]-piperazin-1-
carboxilato de tert-butilo (obtenido según US 5547950) en
100 ml de etanol se adicionan 2,6 g (0,0139 mol) de ácido
para-toluensulfónico y se calienta a reflujo durante 16 h.
Se concentra a sequedad y el residuo se cromatografía
20 sobre gel de sílice (80 g) a la que se adiciona en la
parte superior alúmina (20 g).

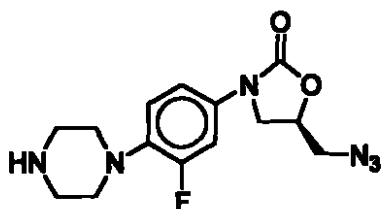
Eluyendo con diclorometano/etanol/hidróxido
amónico (90/10/1%) se obtienen 1,6 g del producto del
25 título.

¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 7,50 (d.d., 1H);
7,24-7,00 (s.c, 2H); 4,70 (m, 1H); 4,04 (t, 1H); 3,82-3,42
(s.c, 3H); 2,86 (s.a, 8H).

30

Ejemplo de referencia N°19:

5-(R)-azidometil-3-(3-fluoro-4-piperazina-1-il-
fenil)-oxazolidin-2-ona.



5

A 5 g (0,011 mol) de 4-[4-(5-(R)-azidometil-2-oxo-oxazolidin-3-il)-fenil]-piperazin-1-carboxilato de tert-butilo (obtenido según US 5547950) en 100 ml de etanol se 10 adicionan 2,4 g (0,013 mol) de ácido p-toluenisulfónico.

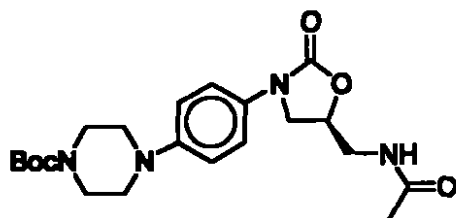
Se calienta a reflujo durante 16 h. Finalizada la reacción se concentra a sequedad y el residuo se pasa a través de una columna de gel de sílice (100 g) conteniendo en la 15 parte superior 25 g de alúmina.

Eluyendo con diclorometano/etanol/hidróxido amónico (80/20/1%) se obtienen 3,5 g del producto del título.

20 ^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 7,42 (dd, 1H); 7,10 (dd, 1H); 6,94 (t, 1H); 4,84-4,76 (m, 1H); 4,05 (t, 1H); 3,83-3,50 (s.c, 3H); 3,03 (s, 3H).

Ejemplo de referencia N°20:

25 4-[4-5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-fenil]-piperazin-1-carboxilato de tert-butilo.



30

A 40 g (0,0668 mol) del producto del ejemplo de referencia N°14 en 1.000 ml de acetato de etilo se adicionan 4 g de Pd/C pasta del 10% y se coloca bajo atmósfera de hidrógeno a presión atmosférica y temperatura ambiente. Finalizada la reducción del grupo azido (cromatografía en capa fina), se enfría a 0°C y se adicional 8,4 ml (0,103 mol) de piridina y 13,4 ml (0,103 mol) de anhídrido acético.

Se agita a 0°C durante 30 min y después 16 h a temperatura ambiente. Se filtra sobre decalite y los líquidos de filtrado se concentran a sequedad.

El residuo se cromatografía sobre gel de sílice. Eluyendo con diclorometano/etanol 95/5 se obtienen 27 g (97%) del producto del título.

¹H-RMN (DMSO, 200 MHz, δ (ppm)): 8,30 (t, 1H, NH); 7,41 (d, 2H); 7,00 (d, 2H); 4,80-4,60 (m, 1H); 4,10 (t, 1H); 3,72 (t, 1H); 3,55-3,38 (s.c., 6H); 3,15-3,03 (s.c., 20 4H); 1,83 (s, 3H); 1,42 (s, 9H).

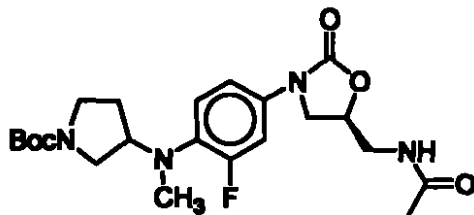
Siguiendo el procedimiento anteriormente descrito y partiendo de los productos de los ejemplos de referencia N°15 y N°16 se obtienen los siguientes productos:

25

Ejemplo de referencia N°21.

3-(R, S)-({4-5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il}-2-fluoro-fenil)-metil-amino)-pirrolidin-1-carboxilato de tert-butilo.

30



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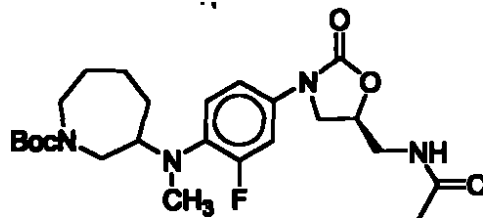
^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 7,41 (dd, 1H); 7,10-7,00 (s.c., 2H); 6,61 (t, 1H, NH); 4,82-4,70 (m, 1H); 4,02 (t, 1H); 3,97-3,40 (s.c., 6H); 3,40-3,18 (s.c., 2H); 2,75 (s, 3H); 2,10-1,80 (s.c., 2H); 1,42 (s, 9H).

5

Ejemplo de referencia N°22.

3-(R, S)-({4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-metil-amino)-azepan-1-carboxilato de tert-butilo.

10



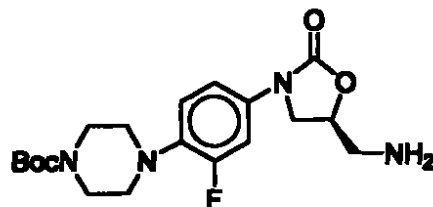
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^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 7,35 (dd, 1H); 7,15-6,85 (m, 2H); 6,45 (m, 1H); 4,75 (m, 1H); 4,01 (t, 1H); 3,90-3,00 (m, 8H); 2,76 y 2,23 (s, 3H); 2,03 (s, 3H); 20 1,46 y 1,39 (s, 9H); 2,00-1,10 (m, 6H).

Ejemplo de referencia N°23.

4-[4-(5-(S)-aminometil-2-oxo-oxazolidin-3-il)-2-fluoro-fenil]-piperazina-1-carboxílico tert-butil ester.

25



30

A 30 g (0,071 mol) de 4-[4-(5-(R)-azidometil-2-oxo-oxazolidin-3-il)-fenil]-piperazin-1-carboxilato de tert-butilo (obtenido según US 5547950) en 300 ml de

etanol se adicionan 3 g de Pd/C pasta del 10% y se coloca bajo atmósfera de hidrógeno a presión atmosférica y temperatura ambiente. Finalizada la reacción (cromatografía en capa fina eluida con diclorometano-
5 etanol 95/5) se filtra sobre decalite y se lava la decalite con 50 ml de etanol.

Los líquidos de filtrado se concentran a sequedad y el residuo se cromatografía sobre gel de sílice.

10

Eluyendo con diclorometano/etanol/hidróxido amónico 90/10/1% se obtienen 14 g (50%) del producto del título.

15

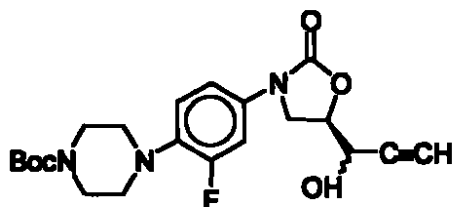
^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 7,47 (dd, 1H); 7,13 (dd, 1H); 6,94 (t, 1H); 4,75-4,60 (m, 1H); 4,01 (t, 1H); 3,82 (dd, 1H); 3,62-3,51 (s.c., 4H); 3,20-2,90 (s.c., 6H); 1,50 (s, 9H); 1,40 (s.a., 2H, NH_2).

20

Ejemplo de referencia N°24.

4-{2-fluoro-4-[5-(R)-(1-(R,S)-hidroxi-prop-2-inil)-2-oxo-oxazolidin-3-il]-fenil}-piperasina-1-carboxilato de tert-butilo.

25



30 A 2,4 g (32,2 mmol) de tert-butanol en 30 ml de tetrahidrofurano seco, enfriado a -10°C , se adicionan 9,2 ml (23 mmol) de n-Buli (2,5 M en hexano).

Se agita durante 30 min y se deja alcanzar la temperatura de 0°C. Se adicionan entonces 4,49 g (10 mmol) de 4-(4-benciloxicarbonilamino-2-fluoro-fenil)-piperazin-1-carboxilato de tert-butilo (obtenido según US 5547950) 5 disuelto en 10 ml de dimetilformamida seca.

Tras agitar 10 min a 0°C se adiciona gota a gota 3,4 g (12,5 mmol) de p-toluensulfonato de 2,3-hidroxi-pent-4-inil (obtenido según EP 1029854 A1) disuelto en 5 ml de 10 DMF.

Se deja alcanzar la temperatura ambiente y se agita durante 16 h. Se vierte sobre 200 ml de solución saturada de bicarbonato sódico y se extrae con 3 x 150 ml de 15 acetato de etilo. Los extractos orgánicos se lavan con 150 ml de agua. La fase orgánica se seca y concentra y el residuo se cromatografía sobre gel de sílice.

Eluyendo con acetato de etilo/heptano 1/1 se obtienen 2,6 20 g (62%) del producto del título.

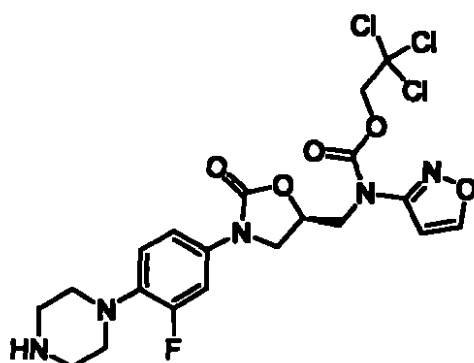
¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 7,45 (dd, 1H); 7,15 (m, 1H); 6,95 (t, 1H); 4,75 (m, 2H); 4,30-2,90 (m, 3H); 3,60 (m, 4H); 3,00 (m, 4H); 2,53 (d, 1H); 1,48 (s, 25 9H).

Siguiendo el procedimiento descrito en los ejemplos de referencia N°18 y N°19 y partiendo respectivamente de los compuestos obtenidos en los 30 ejemplos de referencia 17 y 20 a 24 se obtienen los siguientes productos:

Ejemplo de referencia N°25.

[3-(3-Fluoro-4-piperazin-1-il-fenil)-2-oxo-oxazolidin-5-ilmetil]-isoxazol-3-il-carbamato de 2,2,2-tricloro-etil

10



15

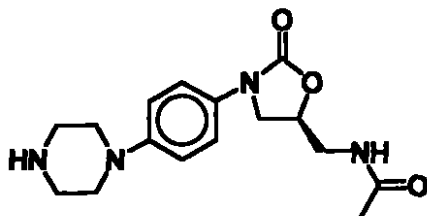
^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 8,34 (d, 1H); 7,42 (dd, 1H); 7,10 (dd, 1H); 6,95 (m, 2H); 5,15 (m, 1H); 4,95 (m, 2H); 4,52 (dd, 1H); 4,25 (dd, 1H); 4,12 (t, 1H); 3,80 (dd, 1H); 3,12 (m, 8H).

20

Ejemplo de referencia N°26.

N-[2-oxo-3-(4-piperazin-1-il-fenil)-oxazolidin-5-(S)-ilmetil]acetamida.

25

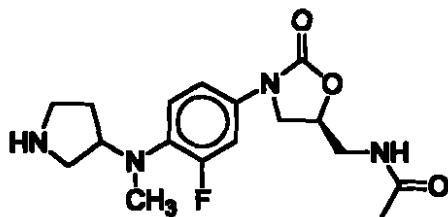


^1H -RMN ($\text{DMSO}-d_6$, 200 MHz, δ (ppm)): 8,30 (t, 1H, 30 NH); 7,41 (dd, 2H); 7,00 (dd, 2H); 4,80-4,60 (m, 1H); 4,06 (t, 1H); 3,71 (dd, 1H); 3,42 (t, 2H); 3,30-3,10 (s.c., 8H); 1,82 (s, 3H).

Ejemplo de referencia N°27.

N-{3(R,S)-[3-fluoro-4-(metil-pirrolidin-3-il-amino)-
5 fenil]-2-oxo-oxazolidin-5-(S)-ilmetil}-acetamida.

10

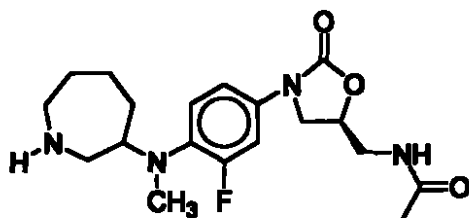


$^1\text{H-RMN}$ (CDCl_3 , 200 MHz, δ (ppm)): 7,39 (dd, 1H);
 15 7,10-6,97 (s.c., 2H); 6,49 (t, 1H, NH); 4,83-4,70 (m, 1H); 4,02 (t, 1H); 3,90-3,60 (s.c., 4H); 3,13-2,80 (s.c., 4H); 2,72 (s, 3H); 2,02 (s, 3H); 2,00-1,65 (s.c., 2H).

Ejemplo de referencia N°28.

N-{3(R,S)-[4-(azepan-3-il-metil-amino)-3-fluoro-fenil]-2-
oxo-oxazolidin-5-(S)-ilmetil}-acetamida.

25

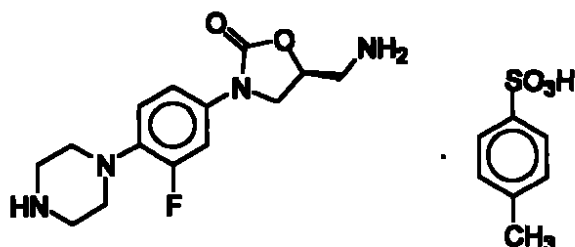


$^1\text{H-RMN}$ (CDCl_3 , 200 MHz, δ (ppm)): 7,35 (dd, 1H);
 30 7,05 (m, 1H); 6,90 (t, 1H); 6,75 (t, 1H, NH); 4,75 (m, 1H); 4,00 (t, 1H); 3,90-3,30 (m, 4H); 3,20-2,60 (m, 4H); 2,72 (s, 3H); 2,30 (s.a., 1H); 2,02 (s, 3H); 1,90-1,00 (m, 6H).

Ejemplo de referencia N°29.

p-toluenosulfato de 5-(S)-aminometil-3-(3-fluoro-4-piperazin-1-il-fenil)-oxazolidin-2-ona.

5



10

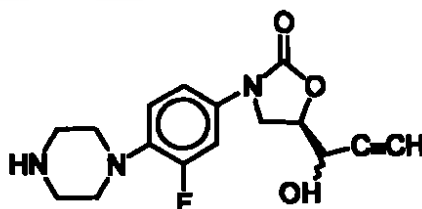
$^1\text{H-RMN}$ (DMSO- d_6 , 200 MHz, δ (ppm)): 7,56 (dd, 1H); 7,50 (d, 2H); 7,22-7,06 (s.c., 4H); 4,90-4,74 (m, 1H); 4,14 (t, 1H); 3,84-3,76 (m, 1H); 3,25-3,05 (s.c., 10H); 2,26 (s, 3H).

15

Ejemplo de referencia N°30.

3-(3-fluoro-4-piperazin-1-il-fenil)-5-(R)-(1-(R,S)-hidroxi-prop-2-inil)-oxazolidin-2-ona.

20



25

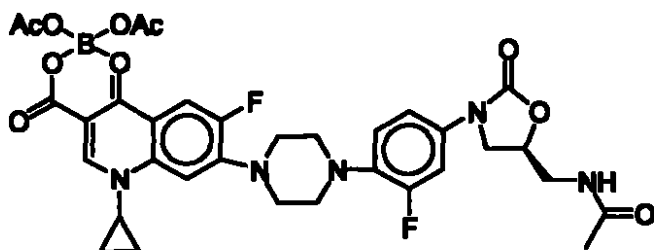
$^1\text{H-RMN}$ (DMSO- d_6 , 200 MHz, δ (ppm)): 7,50 (m, 1H); 7,20 (m, 1H); 7,03 (m, 1H); 6,15 (s.a., 1H); 4,70 (m, 1H); 4,52 (m, 1H); 4,10 (t, 1H); 3,85 (m, 1H); 3,25 (m, 1H); 3,23 (s.a., 1H).

30

Ejemplo de referencia N°31:

7-(4-{-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-ciclopropil-6-fluoro-4-oxo-1,4-dihidroquinolein-3-carboxílico boro diacetoxi quelato.

5



10 A 1 g (3 mmol) de N-[3-(3-Fluoro-4-piperazin-1-il-fenil)-
2-oxo-oxazolidin-5-(S)-ilmetil]-acetamida (obtenida según
US 5547950) en 30 ml de acetonitrilo se adicionan 1,22 g
de 7-cloro-1-ciclopropil-6-fluoro-4-oxo-1,4-dihidro-
quinolein-3-carboxílico boro diacetoxi quelato (obtenido
15 según WO 8807998) y 0,43 ml (3 mmol) de trietilamina.

La reacción se calienta a reflujo durante 16 h. Se
concentra a sequedad y el residuo se cromatografía sobre
gel de sílice.

20

Eluyendo con diclorometano/etanol 90/10 se obtienen 0,8 g
del producto del título.

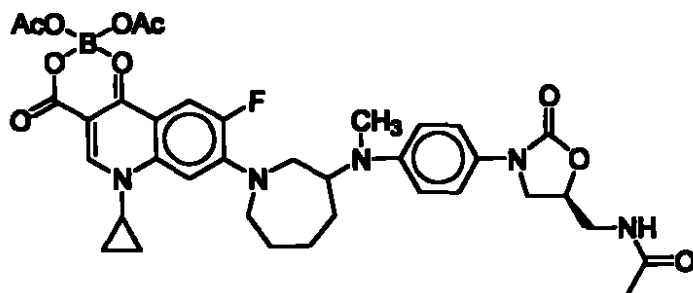
¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 9,04 (s, 1H);
25 8,10 (d, 1H); 7,56-7,44 (s.c., 2H); 7,08 (dd, 1H); 6,97
(t, 1H); 6,38 (t, 1H, NH); 4,82-4,68 (m, 1H); 4,01 (t,
1H); 3,90-3,56 (s.c., 8H); 3,30-3,20 (s.a., 4H); 2,04 (s,
6H); 2,02 (s, 3H); 1,90-1,20 (s.c., 2H).

30

Ejemplo de referencia N°32.

7-[3-(R,S)-({4-[5-(S)-(acetilamino-metil)-2-oxo-
oxazolidin-3-il]-2-fluoro-fenil}-metilamino)-azepan-1-il]-
1-ciclopropil-6-fluoro-4-oxo-1,4-dihidro-quinolein-3-
carboxílico boro diacetoxi quelato.

5



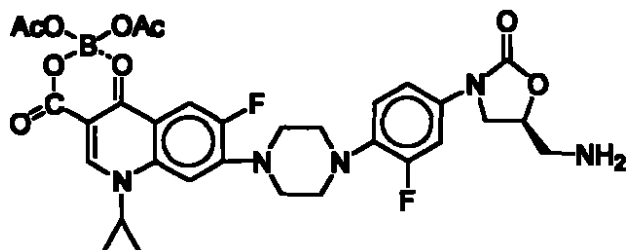
Siguiendo el procedimiento del ejemplo anterior y partiendo del producto obtenido en el ejemplo de 10 referencia N°28, se obtiene el producto del título.

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 8,94 (s, 1H); 8,30 (t, 1H); 7,90 (d, 1H); 7,60-7,40 (m, 2H); 7,30-7,10 (m, 2H); 4,75 (m, 1H); 4,30-3,40 (m, 10H); 2,80 (s, 3H); 15 2,10-1,05 (m, 10H); 1,93 (s, 6H); 1,88 (s, 3H).

Ejemplo de referencia N°33.

7-{4-[4-(5-(S)-aminometil-2-oxo-oxazolidin-3-il)-2-fluoro-
fenil]-piperazin-1-il}-1-ciclopropil-6-fluoro-4-oxo-1,4-
20 dihidro-quinolein-3-carboxílico borodiacetoxi quelato.

25



30 Siguiendo el procedimiento descrito en el ejemplo de referencia N°31 y partiendo del producto obtenido en el ejemplo de referencia N°29 y utilizando 2 equivalentes de trietilamina en lugar de un solo equivalente, se obtiene el producto del título.

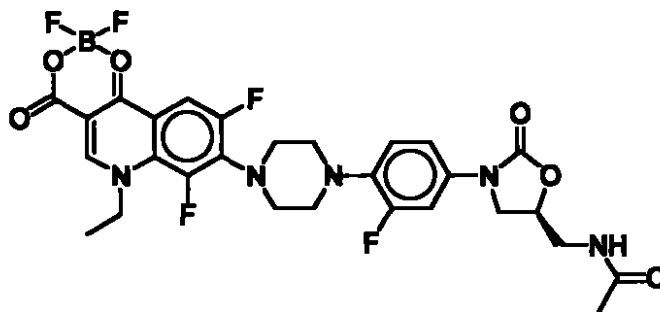
^1H -RMN (DSMO- d_6 , 200 MHz, δ (ppm)): 9,03 (s, 1H); 8,04 (d, 1H); 7,82 (d, 1H); 7,59 (dd, 1H); 7,24 (dd, 1H); 7,17 (t, 1H); 4,70-4,56 (m, 1H); 4,14 (s.a., 1H); 4,08 (t, 1H); 3,84 (dd, 1H); 3,64 (s.a., 4H); 3,23 (s.a., 4H); 2,90-2,70 (s.c., 2H); 2,20 (s.a., 2H, NH_2); 1,90 (s, 6H); 1,50-1,20 (s.c., 4H).

Ejemplo de referencia N°34.

7-(4-{5-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-etil-6,8-difluoro-4-oxo-1,4-dihidro-quinolein-3-carboxílico borodifluoruro quelato.

15

20



Siguiendo un procedimiento análogo al descrito en el ejemplo de referencia N°31 y partiendo de 1-etil-6,7,8-trifluoro-4-oxo-1,4-dihidro-quinolina-3-carboxílico borodifluoruro quelato (obtenido según WO 8807998) se obtiene el producto del título.

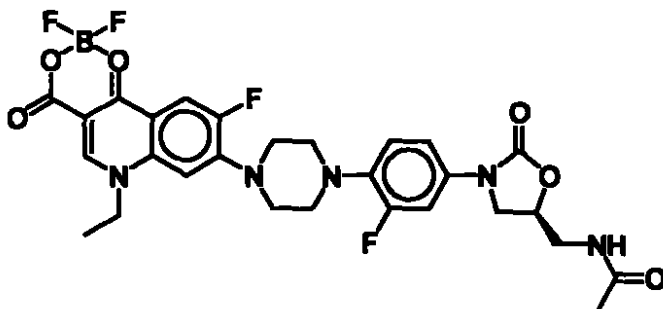
^1H -RMN (DSMO- d_6 , 200 MHz, δ (ppm)): 9,44 (s, 1H); 8,27 (t, 1H, NH); 8,09 (d, 1H); 7,54 (dd, 1H); 7,30-7,06 (s.c., 2H); 5,00-4,60 (s.c., 3H); 4,10 (t, 1H); 3,80-2,95 (s.c., 11H); 1,85 (s, 3H); 1,55 (t, 3H).

Ejemplo de referencia N°35.

7-(4-{4-[5-(8)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-etil-6-fluoro-4-oxo-1,4-dihidro-quinolein-3-carboxílico borodifluoruro quelato.

5

10



Siguiendo el procedimiento análogo al descrito en el
15 ejemplo de referencia N°31 y partiendo de 7-cloro-1-etil-6-fluoro-4-oxo-1,4-dihidro-quinolina-3-carboxílico borodifluoruroquelato (obtenido según JP 59122470) se obtiene el producto del título.

20 ^1H -RMN (DSMO- d_6 , 200 MHz, δ (ppm)): 9,42 (s, 1H); 8,30 (t, 1H, NH); 8,17 (d, 1H); 7,60-7,40 (s.c., 2H); 7,25-7,05 (s.c., 2H); 4,90 (c, 2H); 4,80-4,60 (m, 1H); 4,14 (t, 1H); 3,80-2,90 (s.c., 11H); 1,84 (s, 3H); 1,52 (t, 3H).

25

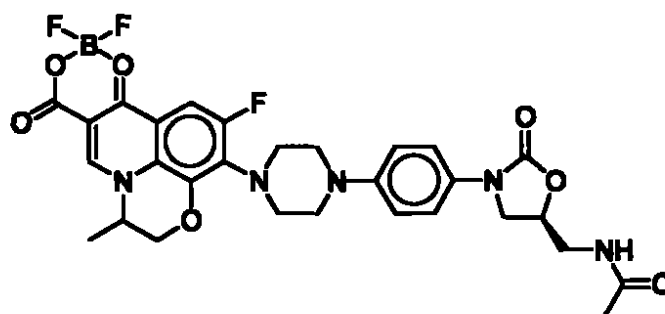
Ejemplo de referencia N°36.

9-(4-{4-[5-(8)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-fenil}-piperazin-1-il)-8-fluoro-3-metil-6-oxo-2,3-dihidro-6H-1-oxa-3-aza-fenalen-5-carboxílico borodifluoro quelato.

30

167 166

57



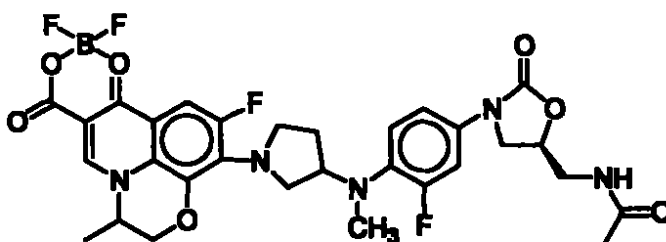
Partiendo de 8,9-difluoro-3-metil-6-oxo-2,3-dihidro-6H-1-oxa-3a-aza-fenalen-5-carboxílico borodifluoruro quelato (obtenido según JP 58029789) y siguiendo un procedimiento 5 análogo al descrito en el ejemplo de referencia N°31 se obtiene el producto del título.

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 9,44 (s, 1H); 8,30 (t, 1H, NH); 7,84 (d, 1H); 7,43 (d, 2H); 7,05 (d, 10 2H); 5,30-5,10 (m, 1H); 4,80-4,30 (s.c., 3H); 4,10 (t, 1H); 3,80-3,15 (s.c., 11H); 1,84 (s, 3H); 1,58 (d, 3H).

Ejemplo de referencia N°37.

9-[3-({4-[5-(8)-(acetilamino-metil)-2-oxo-oxazolidin-3-15 il]-2-fluorofenil}-metil-amino)-pirrolidona-1-il]-8-fluoro-3-metil-6-oxo-2,3-dihidro-6H-1-oxa-3a-aza-fenalen-5-carboxílico borodifluoruro quelato.

20



25

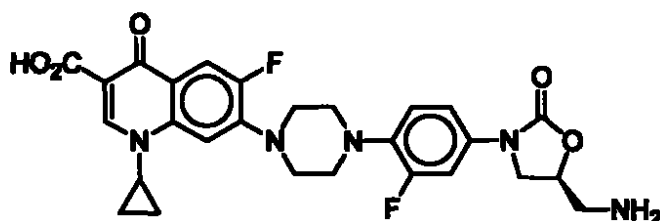
De manera análoga al ejemplo anterior y partiendo del compuesto obtenido en el ejemplo de referencia N°27 se obtiene el producto del título.

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 9,36 (s, 1H); 8,25 (t, 1H, NH); 7,74 (d, 1H); 7,50 (dd, 1H); 7,30-7,10 (s.c., 2H); 5,20-3,00 (s.c., 13H); 2,78 (s, 3H); 1,82 (s, 5 3H); 2,20-1,80 (s.c., 2H); 1,50 (d, 3H).

Ejemplo de referencia N°38.

Ácido 4-{4-[4(5-(8)-aminometil-2-oxo-oxazolidin-3-il)-2-fluoro-fenil]-piperazin-1-il}-1-ciclopropil-6-fluoro-4-oxo-1,4-dihidro-quinolein-3-carboxílico.

15



20 Método 1:

A 13,3 g (0,02 mol) del producto obtenido en el ejemplo de referencia N°33 en 300 ml de acetonitrilo y 300 ml de agua se adicionan 96 ml (0,096 mol) de hidróxido de sodio 1N.

25

Se agita a temperatura ambiente durante 2 h. Se concentra en el rotavapor el acetonitrilo y a la disolución acuosa resultante se adicionan 96 ml de ácido clorhídrico 1 N.

30 Se filtra el precipitado formado obteniéndose así 2,8 g. Los líquidos de filtrado se extraen con 4 x 200 ml de diclorometano/etanol 90/10. Los extractos se secan y concentran obteniéndose así otros 6,8 g del producto del título.

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 8,70 (s, 1H); 7,95 (d, 1H); 7,63 (d, 1H); 7,58 (dd, 1H); 7,26-7,10 (s.c., 2H); 4,80-4,60 (m, 1H); 4,08 (t, 1H); 3,96-3,80 (s.c., 2H); 3,50 (s.a., 4H + NH₂); 3,23 (s.a., 4H); 3,00-2,80 (s.c., 2H); 1,42-1,15 (s.c., 4H).

Método 2:

10 A 40 mg del producto obtenido por el método 1 del ejemplo de referencia N°5, disueltos en 10 ml de etanol se adicionan 0,10 mg de Pd/C pasta del 10% y se coloca bajo atmósfera de hidrógeno a presión atmosférica y temperatura ambiente. Finalizada la reacción se filtra sobre decalite, 15 la cual se lava 2 x 10 ml de etanol.

Los líquidos de filtrado se concentran a sequedad y se obtienen así 20 mg de un producto idéntico al obtenido por el método 1.

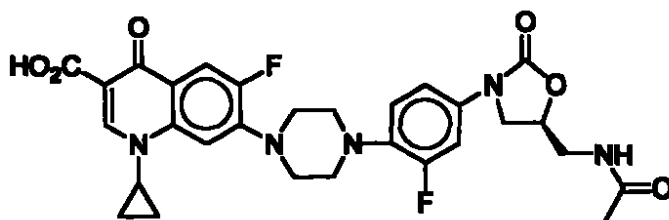
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COMPUESTOS DE FÓRMULA GENERAL (I)

Ejemplo 1:

Ácido 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-ciclopropil-6-25 fluoro-4-oxo-1,4-dihidro-quinolein-3-carboxílico

30



A 0,8 g (1,13 mol) del producto del ejemplo de referencia N°31 en 20 ml de agua y 20 ml de acetonitrilo se adicionan

5,6 ml de hidróxido sódico 1N y se agita a temperatura ambiente durante 1 h.

Se concentra el acetonitrilo y la fase acuosa se acidula 5 con 5,6 ml de ácido clorhídrico 1N.

Se extrae con 3 x 50 ml de diclorometano/etanol 9/1.

La fase orgánica se seca y concentra. El residuo se agita 10 10 min con 2-propanol y se filtra el sólido precipitado. Se obtienen así 290 mg del producto del título.

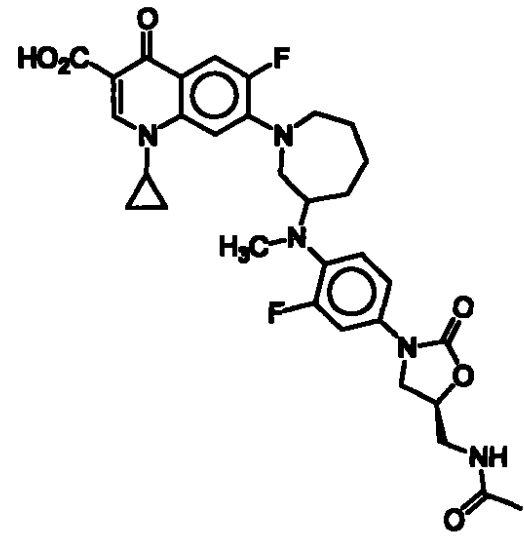
¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 8,72 (s, 1H); 8,33 (t, 1H, NH); 7,99 (d, 1H); 7,64 (d, 1H); 7,58 (dd, 1H); 7,30-7,10 (s.c., 2H); 4,84-4,64 (m, 1H); 4,16 (t, 1H); 3,90-2,90 (s.c., 12H); 1,90 (s, 3H); 1,44-1,16 (s.c., 4H).

Ejemplo 2:

Ácido 7-[3-({4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-metil-amino)-azepan-1-il]-1-ciclopropil-6-fluoro-4-oxo-1,4-dihidro-quinolein-3-carboxílico

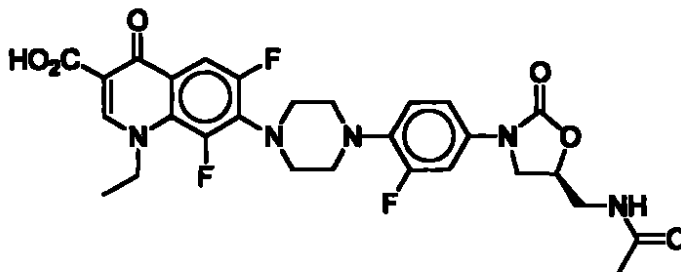
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5 ^1H -RMN (DSMO- d_6 , 200 MHz, δ (ppm)): 8,59 (s, 1H); 8,30 (t, 1H, NH); 7,80 (d, 1H); 7,50 (dd, 1H); 7,30 (d, 1H); 7,25-7,05 (s.c., 2H); 4,75 (m, 1H); 4,20-3,20 (m, 10H); 2,76 (s, 3H); 2,20-1,00 (m, 10H); 1,86 (s, 3H).

Ácido 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-etil-6,8-difluoro-4-oxo-1,4-dihidro-quinolein-3-carboxílico



A 1,9 g (3mmol) del producto obtenido en el ejemplo de referencia N°34 en 100 ml de etanol y 2,5 ml de agua se adicionan 10 ml de trietilamina y se calienta a reflujo 25 durante 16 h.

Se filtran las sales precipitadas. Los líquidos de filtrado se concentran a sequedad y el residuo se trata con 50 ml de agua y se ajusta el pH a 5 por adición de 30 ácido clorhídrico 1N.

Se extrae con 3 x 75 ml de diclorometano/etanol 9/1. La fase orgánica se seca y concentra. Se obtienen así 1,2 g de un sólido blanco.

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 8,94 (s, 1H); 8,30 (t, 1H, NH); 7,87 (d, 1H); 7,50 (dd, 1H); 7,25-7,02 (s.c., 2H); 4,80-4,30 (s.c., 3H); 4,10 (t, 1H); 3,80-3,20 (s.c., 7H); 3,10 (s.a., 4H); 1,82 (s, 3H); 1,42 (t, 3H).

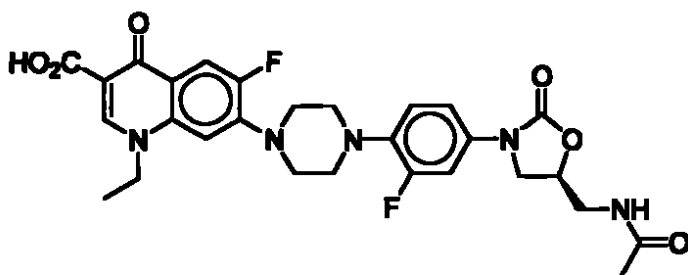
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Ejemplo 4:

Ácido 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-etil-6-fluoro-4-oxo-1,4-dihidro-quinolin-3-carboxílico

10

15

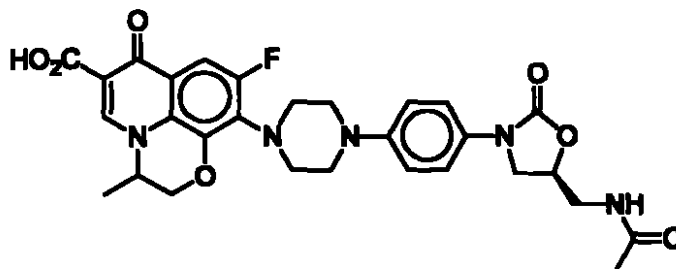


20 Siguiendo el procedimiento del ejemplo anterior y partiendo del producto obtenido en el ejemplo de referencia N°35 se llega al producto del título.

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 8,99 (s, 1H); 25 8,30 (t, 1H, NH); 7,96 (d, 1H); 7,54 (d, 1H); 7,20-7,05 (s.c., 3H); 5,00-4,56 (s.c., 3H); 4,14 (t, 1H); 3,90-3,10 (s.c., 11H); 1,82 (s, 3H); 1,60-1,35 (s.a., 3H).

Ejemplo 5:

30 Ácido 9-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-fenil}-piperazin-1-il)-8-fluoro-3-metil-6-oxo-2,3-dihidro-6H-1-oxa-3a-aza-fenalen-5-carboxílico



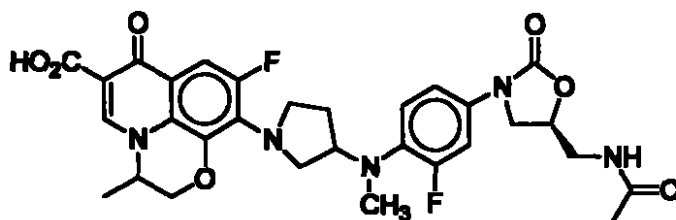
5 Siguiendo el procedimiento descrito en el ejemplo 3 y partiendo del producto obtenido en el ejemplo de referencia N°36 se llega al producto del título.

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 9,00 (s, 1H); 10 8,26 (t, 1H, NH); 7,62 (d, 1H); 7,41 (d, 2H); 7,02 (d, 2H); 5,05-4,90 (m, 1H); 4,80-4,75 (s.c., 2H); 4,41 (d, 1H); 4,10 (t, 1H); 3,80-3,00 (s.c., 11H); 1,84 (s, 3H); 1,46 (d, 3H).

15 Ejemplo 6:

Ácido 9-[3-({4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-metil-amino)-pirrolidin-1-il]-8-fluoro-3-metil-6-oxo-2,3-dihidro-6H-1-oxa-3a-aza-fenalen-5-carboxílico

20



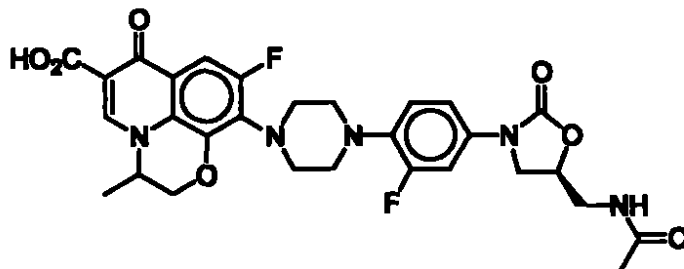
25

Siguiendo el procedimiento del ejemplo N°3 y partiendo del producto del ejemplo de referencia N°37 se obtiene el producto del título.

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 8,92 (s, 1H); 8,30 (t, 1H, NH); 7,60-7,40 (s.c., 2H); 7,30-7,10 (s.c., 2H); 4,95-4,80 (m, 1H); 4,80-4,45 (s.c., 3H); 4,40-4,20 (s.c., 1H); 4,10 (t, 1H), 4,02-3,20 (s.c., 7H); 2,70 (s, 3H); 2,20-1,90 (s.c., 2H); 1,84 (s, 3H); 1,45 (s.a., 3H).

Ejemplo 7:

Ácido 9-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-8-fluoro-3-metil-6-oxo-2,3-dihidro-6H-1-oxa-3a-aza-fenalen-5-carboxílico



A 1,6 g (5mmol) de 8,9-difluoro-3-metil-6-oxo-2,3-dihidro-6H-1-oxa-3a-aza-fenaleno-5-carboxílico borodifloruro quelato y 1.7 g (5mmol) de N-[3-(3-Fluoro-4-piperazin-1-il-fenil)-2-oxo-oxazolidin-5-(S)-ilmetil]-

acetamida (obtenida según US 5547950) en 50 ml de N-metil-pirrolidin-2-ona se adicionan 0.7 ml (5mmol) de trietilamina y se calienta a 110°C durante 16 h.

Se destila a vacío el disolvente y el residuo se agita 30 min con diclorometano/etanol precipitando un sólido que se filtra y rinde 1,2 g (40%) de producto puro.

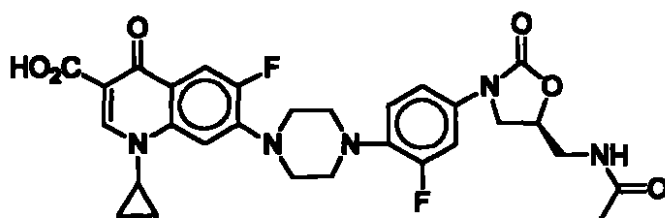
¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 9,00 (s, 1H); 8,25 (t, 1H, NH); 7,62 (d, 1H); 7,52 (dd, 1H); 7,30-7,10

(s.c., 2H); 4,99 (m, 1H); 4,80-4,60 (m, 1H); 4,62 (d, 1H); 4,40 (d, 1H); 4,10 (t, 1H); 3,80-3,60 (m, 1H); 3,60-2,80 (s.c., 10H); 1,84 (s, 3H); 1,50 (d, 3H).

5 Ejemplo 8:

Ácido 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-ciclopropil-6-fluoro-4-oxo-1,4-dihidro-quinolein-3-carboxílico

10

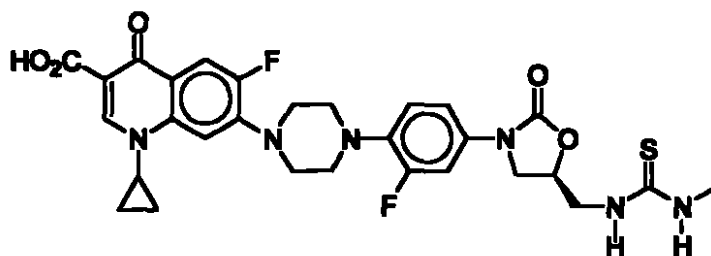


15 A 6 g (0,011 mol) del producto del ejemplo de referencia N°38 en 100 ml de piridina se adicionan 2,8 ml (0,022 mol) de anhídrido acético. Se calienta a 50°C durante 2 h. Se concentra a sequedad la piridina y al residuo se adicionan 200 ml de agua y se agita durante 5 min. Se filtra el
20 sólido precipitado el cual se disuelve en diclorometano y se cromatografía sobre gel de sílice. Eluyendo con diclorometano-etanol 90/10 se obtienen 4 g (63%) de producto puro que es idéntico al obtenido en el ejemplo 1.

25 Ejemplo 9:

Ácido 1-ciclopropil-6-fluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-metil-tioureido)-metil]-2-oxo-oxazolidin-3-il}-fenil)-piperazin-1-il]-4-oxo-1,4-dihidro-quinolein-3-carboxílico

30



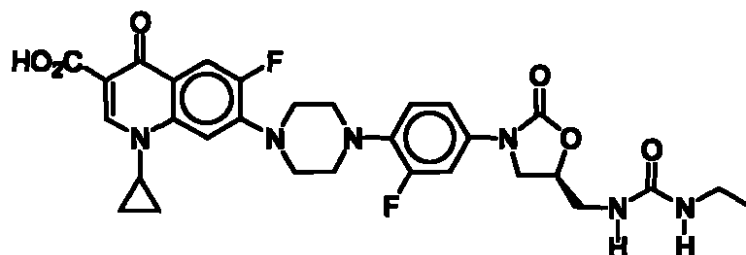
A 0,81 g (1,5 mmol) del producto del ejemplo de referencia N°38 en 10 ml de piridina se adicionan 0,22 g (3 mmol) de metilisotiocianato. Se calienta a 60°C durante 10 minutos. Se concentra a sequedad y el residuo se agita 20 min con 5 30 ml de agua. Se filtra el sólido precipitado y se obtienen 0,5 g de producto puro.

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 8,70 (s, 1H); 7,98 (d, 1H); 7,82 (t, 1H, NH); 7,80-7,50 (s.a., 1H, NH); 10 7,64 (d, 1H); 7,56 (dd, 1H); 7,30-7,10 (s.c., 2H); 4,95-4,80 (m, 1H); 4,16 (t, 1H); 4,00-3,70 (s.a., 4H); 3,60-3,40 (s.a., 4H); 3,30-3,10 (s.a., 4H); 2,82 (s.a., 3H); 1,44 -1,16 (s.c., 4H).

15 Ejemplo 10:

Ácido 1-ciclopropil-7-[4-(4-{5-(S)-[(3-etil-ureido)-metil]-2-oxo-oxazolidin-3-il}-2-fluoro-fenil)-piperazin-1-il]-6-fluoro-4-oxo-1,4-dihidro-quinolein-3-carboxílico

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25

De forma análoga al ejemplo anterior sustituyendo el metilisotiocianato por etilisocianato se obtiene el 30 producto del título.

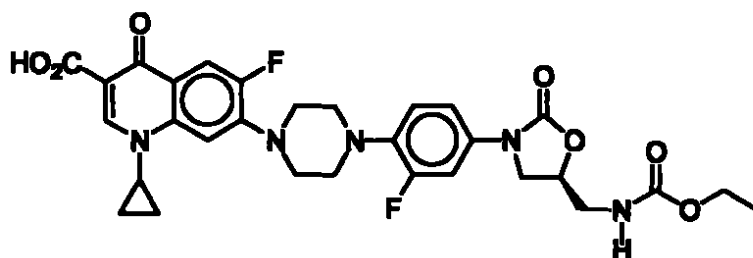
¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 8,70 (s, 1H); 7,96 (d, 1H); 7,66 (d, 1H); 7,58 (dd, 1H); 7,30-7,10 (s.c., 1H); 6,22 (t, 1H, NH); 5,99 (t, 1H, NH); 4,80-4,64

(s.c., 1H); 4,10 (t, 1H); 3,90-3,78 (m, 1H); 3,72 (dd, 1H); 3,60-3,20 (s.c., 10H); 3,10-2,90 (s.c., 2H); 1,44-1,10 (s.c., 4H); 0,98 (t, 3H).

5 Ejemplo 11:

Ácido 1-ciclopropil-7-(4-{4-[5-(S)-(etoxycarbonilamino-
metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-
il)-6-fluoro-4-oxo-1,4-dihidro-quinolein-3-carboxílico

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15

A 0,81 g del producto del ejemplo de referencia N°38 en 20 ml de tetrahidrofurano se adicionan 0,25 g de bicarbonato sódico y 0,3 g de cloroformiato de etilo.

20

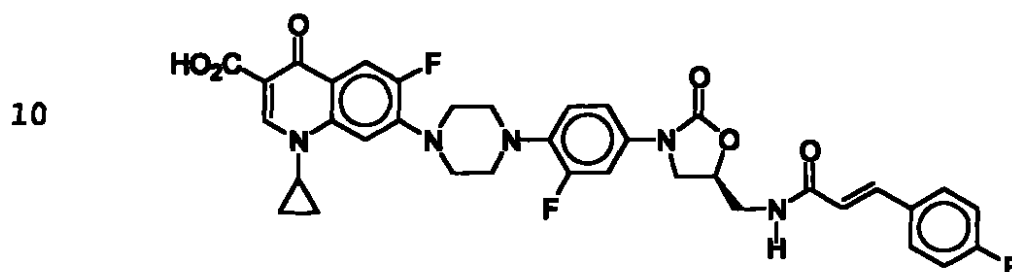
Se calienta a reflujo 16 h. Se concentra a sequedad y el residuo se trata con 30 ml de agua y se extrae con 3 x 50 ml de diclorometano-etanol 90/10. La fase orgánica se seca y concentra hasta un volumen de 20 ml. Se filtra el sólido precipitado y se obtienen 0,3 g de

25 producto puro.

^1H -RMN (DSMO- d_6 , 200 MHz, δ (ppm)): 8,70 (s, 1H); 7,98 (d, 1H); 7,64 (d, 1H); 7,56 (dd, 1H); 7,50 (t, 1H, NH); 7,30-7,10 (s.c., 2H); 4,80-4,64 (m, 1H); 4,14 (t, 30 1H); 4,02 (c, 2H); 3,96-3,70 (s.c., 2H); 3,60-3,10 (s.c., 10H); 1,42-1,10 (s.c., 4H); 1,17 (t, 3H).

Ejemplo 12:

Ácido 1-ciclopropil-6-fluoro-7-{4-[2-fluoro-4-(5-(S)-{[3-(4-fluoro-fenil)-acriloilamino]-metil}-2-oxo-oxazolidin-3-il)-fenil]-piperazin-1-il}-4-oxo-1,4-dihidro-quinolein-3-5 carboxílico



15 A 0,6 g (1,1 mmol) del producto del ejemplo de referencia N°38 en 20 ml de diclorometano seco se adiciona 0,17 ml (1,22 mmol) de trietilamina y 0,3 g (1,33 mmol) del cloruro de 4-fluorocinnamoilo.

20 La reacción se mantiene a temperatura ambiente durante 16 h, se concentra a sequedad y el residuo se cromatografía sobre gel de sílice.

Eluyendo con diclorometano-etanol 95/5 se obtienen 25 0,3 g de producto puro.

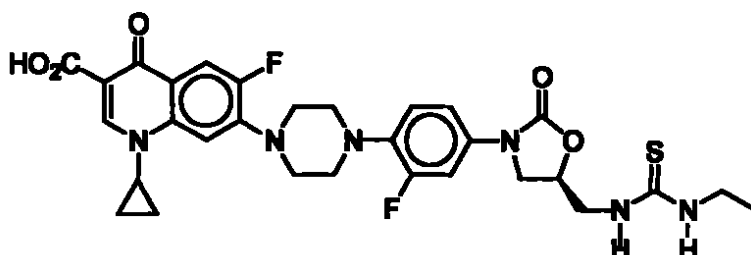
¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 8,70 (s, 1H); 8,58 (t, 1H, NH); 7,96 (d, 1H); 7,70-7,58 (s.c., 4H); 7,44 (d, 1H); 7,30-7,10 (s.c., 4H); 6,64 (d, 1H); 4,90-4,76 (m, 30 1H); 4,16 (t, 1H); 3,92-3,70 (s.c., 2H); 3,64-3,10 (s.c., 10H); 1,42-1,10 (s.c., 4H).

178

Ejemplo 13:

Ácido 1-ciclopropil-7-[4-(4-{5-(S)-[(3-etil-tioureido)-metil]-2-oxo-oxazolidin-3-il}-2-fluoro-fenil)-piperazin-1-il]-6-fluoro-4-oxo-1,4-dihidro-quinolein-3-5 carboxílico

10



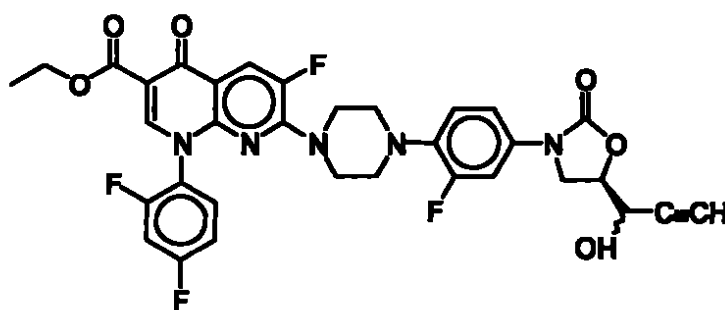
Siguiendo el procedimiento descrito en el ejemplo N° 9, sustituyendo el metilisotiocianato por etilisotiocianato, se obtiene el producto del título.

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 15,06 (s.a., 1H); 8,70 (s, 1H); 7,98-7,50 (m, 4H,); 7,30-7,10 (s.c., 2H); 4,95-4,80 (m, 1H); 4,16 (t, 1H); 4,00-3,70 (s.a., 4H); 3,60-3,10 (m., 10H); 1,44 -1,16 (s.c., 4H).; 1,02 (t., 3H).

Ejemplo 14

1-(2,4-difluoro-fenil)-6-fluoro-7-(4-{2-fluoro-5-[5-(R)-(1-(R,S)-hidroxi-prop-2-inil)-2-oxo-oxazolidin-3-il]-fenil}piperazin-1-il)-4-oxo-1,4-dihidro-[1,8]naftiridin-3-carboxilato de etilo

30



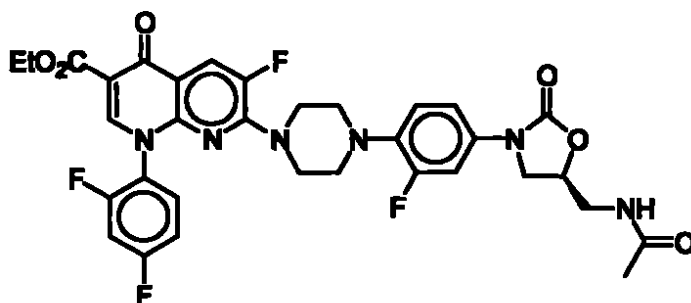
A 0,32 g (1 mmol) del producto del ejemplo de referencia N°30 en 10 ml de piridina se adicionan 0,42 g (1mmol) de 7-cloro-1-(2,4-difluorofenil)-6-fluoro-4-oxo-1,4-dihidro-[1,8]naftiridin-3-carboxilato de etilo (ACROS) y 0,28 ml de trietilmina. La reacción se mantiene a temperatura ambiente durante 48 h. Se concentra a sequedad y el residuo se cromatografía sobre gel de sílice.

Eluyendo con diclorometano/etanol/hidróxido amónico 95/5/1% se obtienen 0,436 g (66%) del producto del título.

¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 8,42 (s, 1H); 8,15 (d, 1H); 7,40 (m, 2H); 7,10 (m, 3H); 6,90 (t, 1H); 4,75 (m, 1H); 4,70 (m, 1H); 4,38 (c, 2H); 4,10 (m, 2H); 3,70 (m, 4H); 3,04 (m, 4H); 2,50 (m, 1H); 1,40 (t, 3H).

Ejemplo 15

7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-(2,4-difluoro-fenil)-6-fluoro-4-oxo-1,4-dihidro-[1,8] naftiridin-3-carboxilato de etilo.

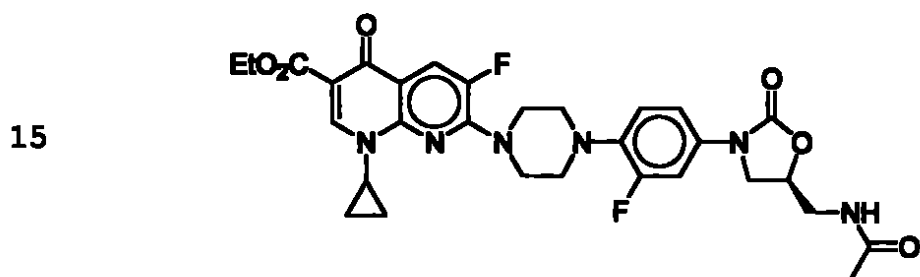


Siguiendo el procedimiento del ejemplo anterior y partiendo de N-[3-(3-Fluoro-4-piperazin-1-il-fenil)-2-oxo-oxazolidin-5-(S)-ilmetil]-acetamida (obtenido según US 5547950) se obtiene el producto del título.

¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 8,41 (s, 1H); 8,15 (d, 1H); 7,42 (dd, 1H); 7,16-6,80 (s.c., 5H); 6,41 (t, 1H, NH); 4,84-4,70 (m, 1H); 4,39 (c, 2H); 4,02 (t, 1H); 4,80-4,60 (s.c., 7H); 3,10-2,95 (s.a., 4H); 2,02 (s, 3H); 1,40 (t, 3H).

Ejemplo 16

7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-ciclopropil-6-fluoro-4-oxo-1,4-dihidro-[1,8] naftiridin-3-carboxilato de etilo



20 Siguiendo el procedimiento descrito en el ejemplo 14 y partiendo de N-[3-(3-Fluoro-4-piperazin-1-il-fenil)-2-oxo-oxazolidin-5-(S)-ilmetil]-acetamida (obtenido según US 5547950) y de la 7-cloro-1-ciclopropil-6-fluoro-4-oxo-1,4-dihidro-[1,8] naftiridin-3-carboxilato de etilo (EP 0187376B1) se obtiene el producto del título.

25

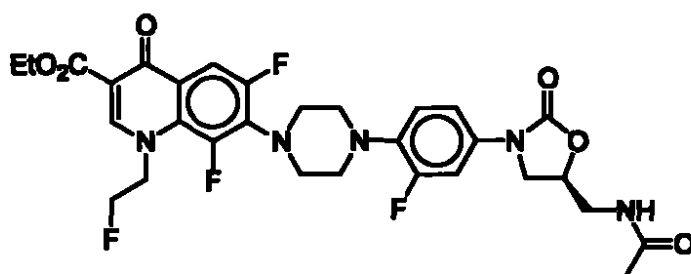
¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 8,52 (s, 1H); 8,11 (d, 1H); 7,48 (dd, 1H); 7,08 (m, 1H); 6,94 (t, 1H); 6,74 (t, 1H, NH); 4,79 (m, 1H); 4,37 (c, 2H); 4,01 (m, 5H); 3,76 (m, 1H); 3,66 (m, 2H); 3,53 (m, 1H); 3,20 (m, 4H); 2,04 (s, 3H); 1,40 (t, 3H); 1,23 (m, 2H); 1,05 (m, 2H).

Ejemplo 17

7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-6,8-difluoro-1-(2-fluoro-etil)-4-oxo-1,4-dihidro-quinolein-3-carboxilato de etilo

5

10



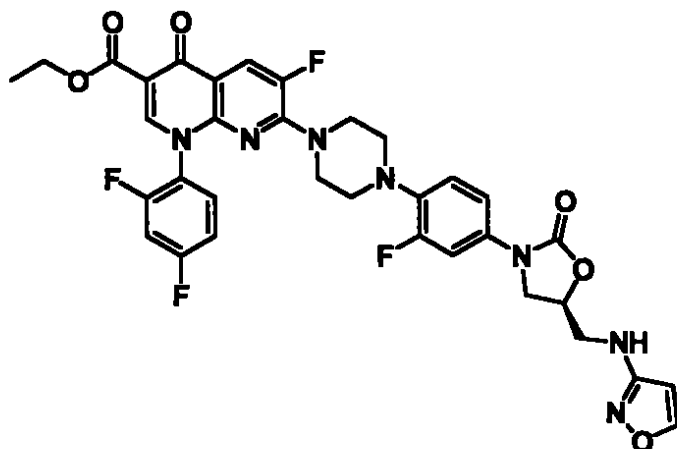
15 Siguiendo un procedimiento análogo a los anteriores y sustituyendo el derivado de naftiridina por el 6,7,8-trifluoro-1-(2-fluoro-etil)-4-oxo-1,4-dihidro-quinolin-3-carboxilato de etilo, se obtiene el producto del título.

$^1\text{H-RMN}$ (DMSO- d_6 , 200 MHz, δ (ppm)): 8,59 (s, 1H); 20 8,30 (t, 1H, NH); 7,79 (d, 1H); 7,50 (d, 1H); 7,30-7,00 (s.c., 2H); 5,05-4,60 (s.c., 5H); 4,21 (c, 2H); 4,15 (t, 1H); 3,80-3,00 (s.c., 11H); 1,82 (s, 3H); 1,27 (t, 3H).

Ejemplo 18

25 1-(2,4-Difluoro-fenil)-6-fluoro-7-(4-{2-fluoro-4-[5-(S)-(isoxazol-3-ilaminometil)-2-oxo-oxazolidin-3-il]-fenil}-piperazin-1-il)-4-oxo-1,4-dihidro-[1,8]naftiridin-3-carboxilato de etilo.

30



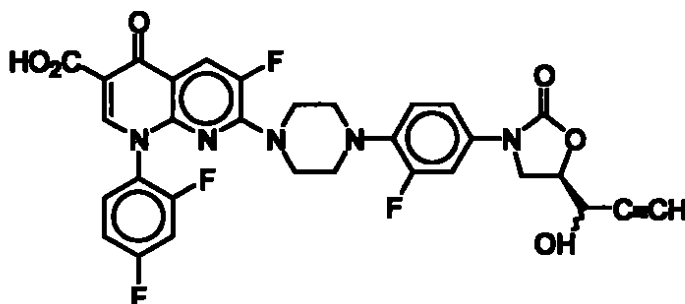
Siguiendo el procedimiento del ejemplo 14 y sustituyendo el producto del ejemplo de referencia N°30 por el producto del ejemplo de referencia N°25 se obtiene el 1-(2,4-difluoro-fenil)-6-fluoro-7-(4-[2-fluoro-4-(5-(R)-{[isoxazol-3-il-(2,2,2-tricloro-etoxicarbonil)-amino]-metil)-2-oxo-oxazolidin-3-il]-fenil]-piperazin-1-il)-4-oxo-1,4-dihidro-[1,8]naftiridin-3-carboxilato de etilo. A 500 mg del mismo, disueltos en 10 ml de tetrahidrofurano se le adicionan 5 ml de agua, 5 ml de ácido acético glacial y 700 mg de zinc en polvo. Después de agitar 3 h a temperatura ambiente se filtra a través de decalite y los líquidos de filtrado se concentran y se cromatografía sobre gel de sílice. Eluyendo con 15 diclorometano/etanol/hidróxido amónico 98/2/02% se obtienen 247 mg del producto del título.

^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 8,41 (s, 1H); 8,15 (d, 1H); 8,07 (d, 1H); 7,45 (m, 2H); 7,05 (m, 3H); 6,85 (t, 1H); 5,85 (s, 1H); 4,95 (m, 1H); 4,50 (m, 1H); 4,38 (c, 2H); 4,05 (t, 1H); 3,80 (m, 2H); 3,68 (m, 4H); 3,03 (m, 4H); 1,39 (t, 3H).

Ejemplo 19

Ácido 1-(2,4-difluoro-fenil)-6-fluoro-7-(4-{2-fluoro-4-[5-(R)-(1-hidroxi-prop-2-inil)-2-oxo-oxazolidin-3-il]-fenil}-piperazin-1-il)-4-oxo-1,4-dihidro-[1,8] naftiridin-3-5 carboxílico

10



A 0,436 g (0,6 mmol) del producto del ejemplo 14 en 5 ml de etanol y 5 ml de agua se adicionan 1,32 ml de hidróxido sódico 1N. Se calienta a 50°C durante 3 h. Se adicionan 1,32 ml de HCl 1N y se concentra a sequedad. El residuo se cromatografía sobre gel de sílice. Eluyendo con diclorometano/etanol/ácido acético 95/5/0,5% se obtienen 0,287 g (75%) del producto del título.

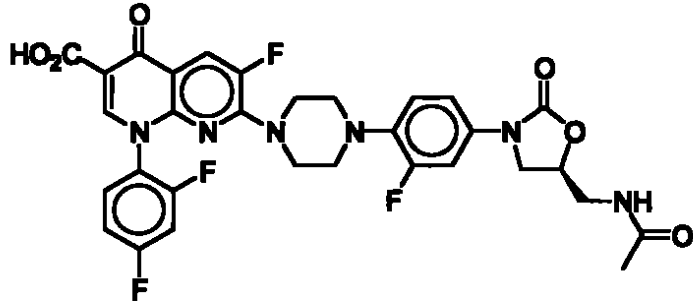
¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 8,68 (s, 1H); 8,15 (d, 1H); 7,60-7,27 (m, 2H); 7,20-7,00 (m, 3H); 6,90 (t, 1H); 4,75 (m, 1H); 4,30-4,00 (m, 2H); 3,80 (m, 4H); 3,28 (dd, 1H); 3,20 (m, 1H); 2,50 (d, 1H).

Ejemplo 20

Ácido 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-(2,4-difluoro-fenil)-6-fluoro-4-oxo-1,4-dihidro-[1,8] naftiridin-3-carboxílico

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Siguiendo el procedimiento descrito en el ejemplo anterior y a partir del producto descrito en el ejemplo N°15 se obtiene el producto del título.

15

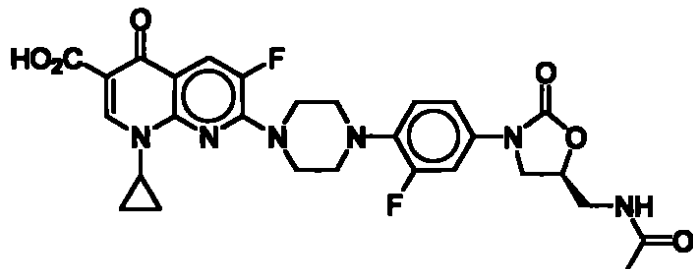
¹H-RMN (DMSO-d₆, 200 MHz, δ (ppm)): 8,90 (s, 1H), 8,27 (t, 1H); 8,22 (d, 1H); 7,95-7,80 (m, 1H); 7,80-7,60 (m, 1H); 7,50 (d, 1H); 7,45-7,30 (m, 1H); 7,25-7,00 (s.c., 2H); 4,80-4,62 (m, 1H); 4,12 (t, 1H); 3,80-2,95 (s.c., 11H); 1,84 (s, 3H).

20

Ejemplo 21

Ácido 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-ciclopropil-6-fluoro-4-oxo-1,4-dihidro-[1,8] naftiridin-3-carboxílico

25



30

Partiendo del producto del ejemplo N°16 y siguiendo el procedimiento anteriormente descrito se obtiene el producto del título.

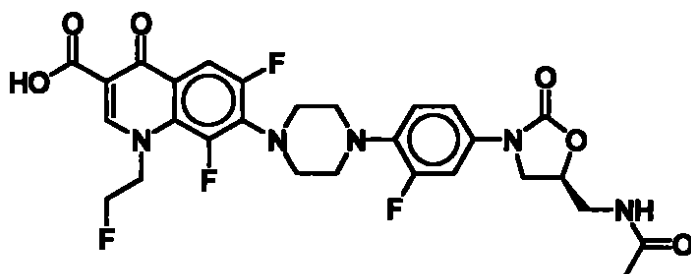
186 185

^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 8,74 (s, 1H); 8,12 (m, 1H); 8,10 (d, 1H); 7,50 (m, 1H); 7,12 (m, 1H); 6,95 (t, 1H); 4,79 (m, 1H); 4,10 (m, 4H); 4,05 (m, 1H); 3,89 (m, 1H); 3,67 (m, 1H); 3,58 (m, 2H); 3,24 (m, 4H); 2,00 (s, 3H); 1,30 (m, 2H); 1,15 (m, 2H).

Ejemplo 22

Ácido 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-6,8-difluoro-1-(2-fluoro-etil)-4-oxo-1,4-dihidro-quinolin-3-carboxílico

15

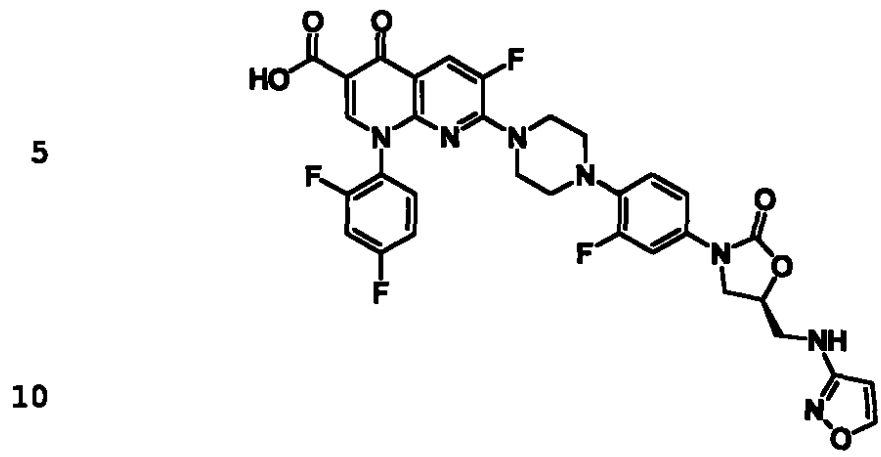


A partir del producto del ejemplo N°17 y siguiendo 20 el procedimiento descrito en el ejemplo N°19, se obtiene el producto del título.

^1H -RMN ($\text{DMSO}-d_6$, 200 MHz, δ (ppm)): 8,84 (s, 1H); 8,26 (t, 1H, NH); 7,92 (d, 1H); 7,56 (d, 1H); 7,35 -7,05 25 (s.c., 2H); 5,16-4,64 (s.c., 5H); 4,12 (t, 1H); 3,80-3,00 (s.c., 11H); 1,82 (s, 3H).

Ejemplo 23

Ácido 1-(2,4-Difluoro-fenil)-6-fluoro-7-(4-{2-fluoro-4-[5-30 (S)-(isoxazol-3-ilaminometil)-2-oxo-oxazolidin-3-il]-fenil}-piperazin-1-il)-4-oxo-1,4-dihidro-[1,8]naftiridin-3-carboxílico

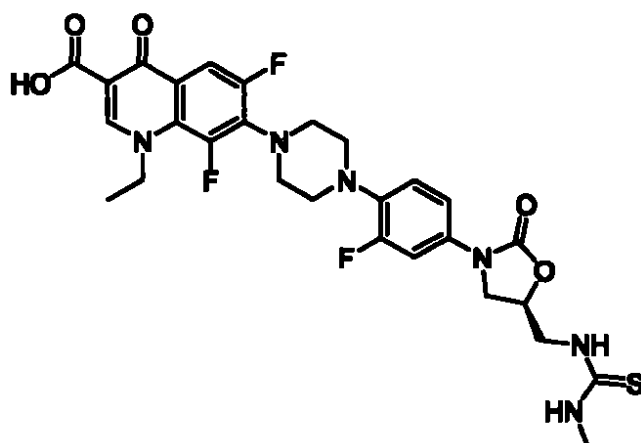


A partir del producto del ejemplo N°18 y siguiendo el 15 procedimiento descrito en el ejemplo N°19, se obtiene el producto del título.

¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 8,69 (s, 1H); 8,15 (d, 1H); 8,06 (d, 1H); 7,45 (m, 2H); 7,10 (m, 3H); 6,90 (t, 1H); 5,90 (s, 1H); 4,95 (m, 1H); 4,50 (m, 1H); 4,06 (t, 1H); 4,00-3,50 (m, 6H); 3,05 (m, 4H).

Ejemplo 24

Ácido 1-etil-6,8-difluoro-7-[4-(2-fluoro-4-{5-[(3-metil-25 tioureido)-metil]-2-oxo-oxazolidin-3-il}-fenil)-piperazin-1-il]-4-oxo-1,4-dihidro-quinolein-3-carboxílico



A 2 g (6,7 mmol) de 1-etil-6,7,8-trifluoro-4-oxo-1,4-dihidro-quinolein-3-carboxilato de etilo en 40 ml de 5 N-metil-2-pirrolidona se adicionan 3,1 g (6,7 mmol) del producto del ejemplo de referencia N°33 y 1,85 ml de trietilamina. La reacción se calienta a 100°C durante 48 h.

10 Se destila a vacío el disolvente y el residuo se cromatografía sobre gel de sílice. Eluyendo con diclorometano/etanol 90/10 se obtiene el 7-{4-[4-(5-(S)-aminometil-2-oxo-oxazolidin-3-il)-2-fluoro-fenil]-piperazin-1-il}-1-ethyl-6,8-difluoro-4-oxo-1,4-dihidro-
15 quinolein-3-carboxilato de etilo. A partir de dicho producto y siguiendo el procedimiento descrito en el ejemplo N°19, se obtiene el producto del título.

IR: 3380 cm^{-1} , 1750 cm^{-1} , 1620 cm^{-1} , 1510 cm^{-1}

20

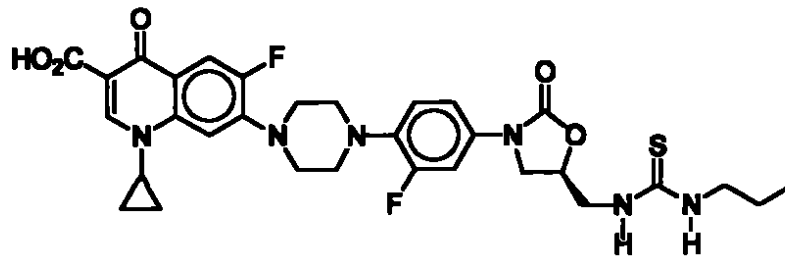
Ejemplo 25

Ácido 1-ciclopropil-6-fluoro-7-[4-(2-fluoro-4-{2-oxo-5-(S)-[(3-propil-tioureido)-metil]-oxazolidin-3-il}-fenil)-piperazin-1-il]-4-oxo-1,4-dihidro-quinolein-3-carboxílico
25

189

188

5



10 Siguiendo el procedimiento descrito en el ejemplo N° 9, sustituyendo el metilisotiocianato por propilisotiocianato, se obtiene el producto del título.

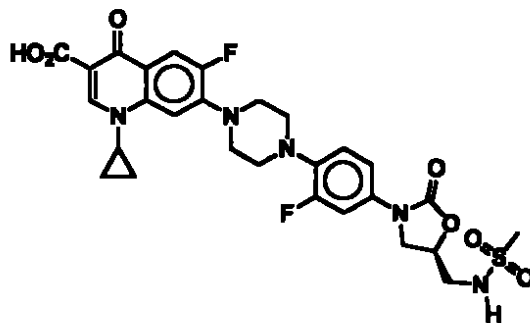
^1H -RMN (DSMO- d_6 , 200 MHz, δ (ppm)): 8,70 (s, 1H);
15 7,92 (d., 1H), 7,90-7,70 (m, 2H, NH); 7,70-7,50 (m., 2H);
7,30-7,10 (m., 2H); 4,95-4,80 (m, 1H); 4,16 (t, 1H); 4,00-
3,70 (s.a., 4H); 3,60-3,10 (m., 10H); 1,60 -1,16 (s.c.,
6H).; 0,84 (t., 3H).

20

Ejemplo 26

Ácido 1-ciclopropil-6-fluoro-7-[4-{2-fluoro-4-[5-(S)-(metanosulfonilamino-metil)-2-oxo oxazolidin-3-il]-fenil}-piperazin-1-il)-4-oxo-1,4-dihidro-quinoleín-3-carboxílico.

25



30

Siguiendo el procedimiento descrito en el ejemplo N° 9, sustituyendo el metilisotiocianato por metanosulfonilcloruro, se obtiene el producto del título.

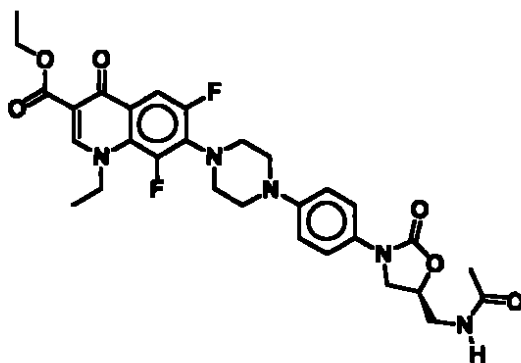
¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 15,00 (s.a., 1H); 8,70 (s, 1H); 7,96 (d., 1H), 7,76-7,42 (m, 3H); 7,30-7,10 (m., 2H); 4,90-4,76 (m, 1H); 4,18 (t, 1H); 4,00-3,20 (m., 12H); 2,98 (s, 3H); 1,44 -1,16 (m., 4H).

10 Ejemplo 27

7-(4-{4-[5-(S)-(Acetilamino-metil)-2-oxo-oxazolidin-3-il]-fenil}-piperazin-1-il)-1-etil-6,8-fluoro-4-oxo-1,4-dihidro-quinolein-3-carboxilato de etilo

15

20



25

Siguiendo el procedimiento descrito en el ejemplo N° 14, partiendo del producto obtenido en el ejemplo de referencia N° 26 y de 1-etil-6,7,8-trifluoro-4-oxo-1,4-dihidro-quinolein-3-carboxilato de etilo (obtenido por esterificación del ácido correspondiente, descrito en GB 2057440).

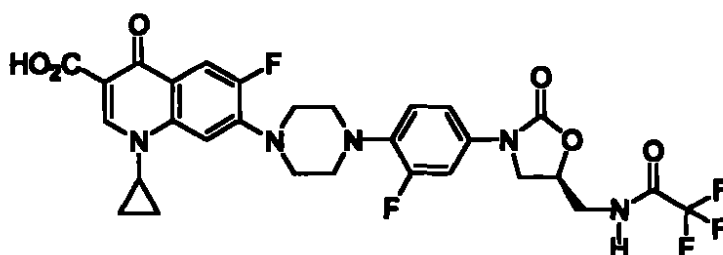
¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 8,62 (s, 1H); 8,30 (t, 1H, NH); 7,80 (d., 1H), 7,42 (d, 2H); 7,04 (d.,

2H); 4,84-4,64 (m, 1H); 4,60-4,40 (s.a., 2H); 4,26 (c, 2H); 4,16 (t, 1H); 3,78 (t, 1H); 3,60-3,20 (m., 10H); 1,90 (s, 3H); 1,44 (t, 3H); 1,30 (t., 3H).

5 Ejemplo 28

Ácido 1-ciclopropil-6-fluoro-7-[4-(2-fluoro-4-{2-oxo-5-(S)-[(2,2,2-trifluoro-acetilamino)-metil]-oxazolidin-3-il}-fenil)-piperazin-1-il]-4-oxo-1,4-dihidro-quinolein-3-10 carboxílico.

15



20

Siguiendo el procedimiento descrito en el ejemplo N° 9, sustituyendo el metilisotiocianato por anhídrido trifluoroacético, se obtiene el producto del título.

25 ^1H -RMN (DSMO- d_6 , 200 MHz, δ (ppm)): 15,06 (s.a., 1H); 9,92 (s.a., 1H, NH); 8,70 (s, 1H); 7,95 (d, 1H,); 7,70-7,50 (m, 2H); 7,30-7,10 (s.c., 2H); 4,95-4,80 (m, 1H); 4,20 (t, 1H); 4,00-3,80 (s.a., 2H); 3,60-3,20 (m., 10H); 1,44 -1,16 (m., 4H).

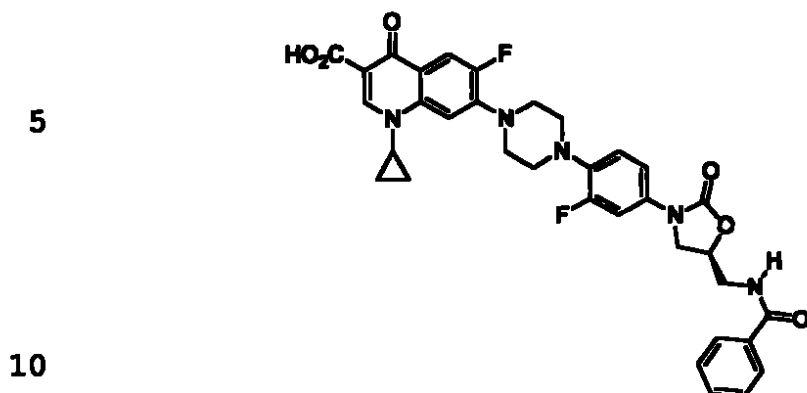
30

Ejemplo 29

Ácido 7-(4-{4-[5-(S)-(benzoilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-

ciclopropil-6-fluoro
carboxílico.

4-oxo-1,4-dihidro-quinolein-3-

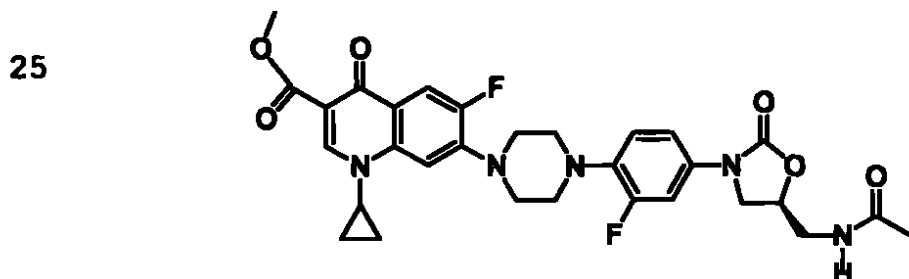


Siguiendo el procedimiento descrito en el ejemplo N° 9, sustituyendo el metilisotiocianato por cloruro de benzoilo, se obtiene el producto del título.

15 ^1H -RMN (DSMO- d_6 , 200 MHz, δ (ppm)): 15,20 (s.a., 1H); 8,90 (t, 1H, NH); 8,70 (s, 1H); 8,00-7,85 (m., 3H), 7,76-7,42 (m, 5H); 7,30-7,10 (m., 2H); 4,96-4,80 (m, 1H); 4,20 (t, 1H); 4,00-3,20 (m., 12H); 1,44 -1,16 (m., 4H).

20 **Ejemplo 30**

7-(4-{4-[5-(S)-(Acetilamino-metil)-2-oxo-oxazolidin-3-il]2-fluoro-fenil}-piperazin-1-il)-1-ciclopropil-6-fluoro-4-oxo-1,4-dihidro-quinolein-3-carboxilato de metilo.



30 A 1 gr (1,7 mmol) del producto del ejemplo 1 en 30 ml de metanol enfriado a 0°C se adicionan 0,37 ml (5,2 mmol) de cloruro de tionilo gota a gota. Finalizada la adición se calienta a reflujo durante 48 horas. Se concentra a sequedad y el residuo se cromatografía sobre gel de

sílice. Eluyendo con diclorometano/metanol/ácido acético 90/10/1 se obtiene el producto del título como clorhidrato.

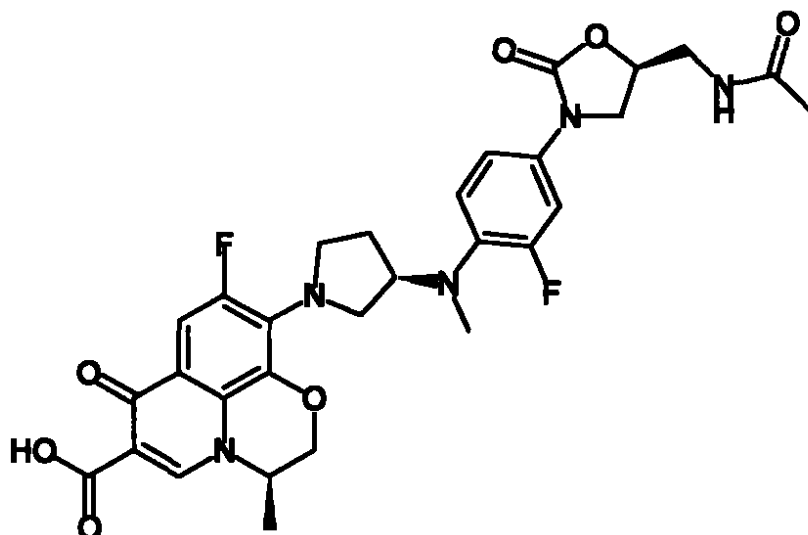
5 El producto así obtenido se disuelve en diclorometano/metanol 90/10 y se lava con solución saturada de bicarbonato sódico. La fase orgánica se seca y concentra para obtener el producto del título en forma de base libre.

10

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 8,50 (s, 1H); 8,25 (s.a., 1H, NH); 7,92 (d., 1H), 7,64-7,50 (m, 2H); 7,30-7,10 (m., 2H); 4,90-4,70 (m, 1H); 4,16 (t, 1H); 3,90-3,60 (m., 5H); 3,60-3,20 (m., 10H); 1,86 (s., 1H); 1,45 - 15 1,10 (m., 4H).

EJEMPLO 31

Acido 9-[3-(S)-({4-[5-(S)-(acetilamino-metil)-2-oxo-20 oxazolidin-3-il]-2-fluoro-fenil}-metil-amino)-pirrolidin-1-il]-8-fluoro-3-(S)-metil-6-oxo-2,3-dihidro-6H-1-oxa-3a-aza-fenalen-5-carboxílico.



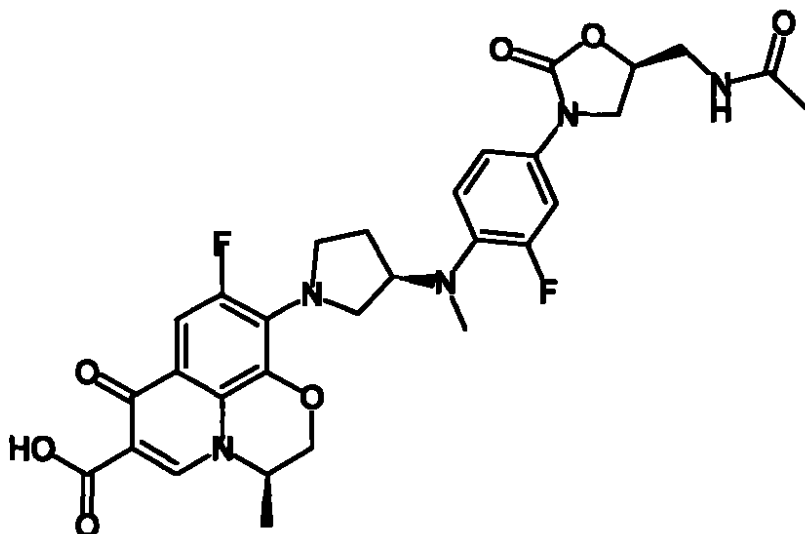
Siguiendo el procedimiento descrito en el Ejemplo 3 y partiendo del correspondiente quelato obtenido por reacción 5 de N-{3-(S)-[3-fluoro-4-(metil-pirrolidin-3-il-amino)-fenil]-2-oxo-oxazolidin-5-(S)-ilmetil}-acetamida (obtenida siguiendo el procedimiento para la obtención del Ejemplo de Referencia No.27, pero sustituyendo 3-(R,S)-aminopirrolidina por 3-(S)-aminopirrolidina), y 8,9-10 difluoro-3-(S)-metil-6-oxo-2,3-dihidro-6H-1-oxa-3a-aza-fenalen-5-carboxílico boro difluoruro quelato se obtiene el producto del título.

$^1\text{H-RMN}$ (DSMO- d_6 , 200 MHz, δ (ppm)): 8,92 (s, 1H); 15 8,24 (t, 1H, NH); 7,60-7,40 (m, 2H); 7,30-7,10 (m, 2H); 4,95-4,80 (m, 1H); 4,80-4,60 (m, 1H); 4,52 (d, 1H); 4,30 (d, 1H); 4,10 (t, 1H), 4,00-3,30 (m, 8H); 2,74 (s, 3H); 2,20-1,80 (m, 2H); 1,84 (s, 3H); 1,42 (d, 3H).

20 $[\alpha]^{25}_D = -34^\circ$ (c 0,5, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9/1)

EJEMPLO 32

Acido 9-[3-(S)-({4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-metil-amino)-pirrolidin-5-1-il]-8-fluoro-3-(R)-metil-6-oxo-2,3-dihidro-6H-1-oxa-3a-aza-fenalen-5-carboxílico



Siguiendo el procedimiento descrito en el Ejemplo 3 y 10 partiendo del correspondiente quelato obtenido por reacción de N-{3-(S)-[3-fluoro-4-(metil-pirrolidin-3-il-amino)-fenil]-2-oxo-oxazolidin-5-(S)-ilmetil}-acetamida (obtenida siguiendo el procedimiento para la obtención del Ejemplo de Referencia No.27, pero sustituyendo 3-(R,S)-15 aminopirrolidina por 3-(S)-aminopirrolidina), y 8,9-difluoro-3-(R)-metil-6-oxo-2,3-dihidro-6H-1-oxa-3a-aza-fenalen-5-carboxílico boro difluoruro quelato (obtenido según Shohgo Atarashi et al., *Chem. Pharm. Bull.* (1987), 35 (5), 1896-1902) se obtiene el producto del título.

20

^1H -RMN (DSMO- d_6 , 200 MHz, δ (ppm)): 8,90 (s, 1H); 8,24 (t, 1H, NH); 7,60-7,40 (m, 2H); 7,36-7,10 (m, 2H); 4,95-4,80 (m, 1H); 4,80-4,60 (m, 1H); 4,54 (d, 1H); 4,24

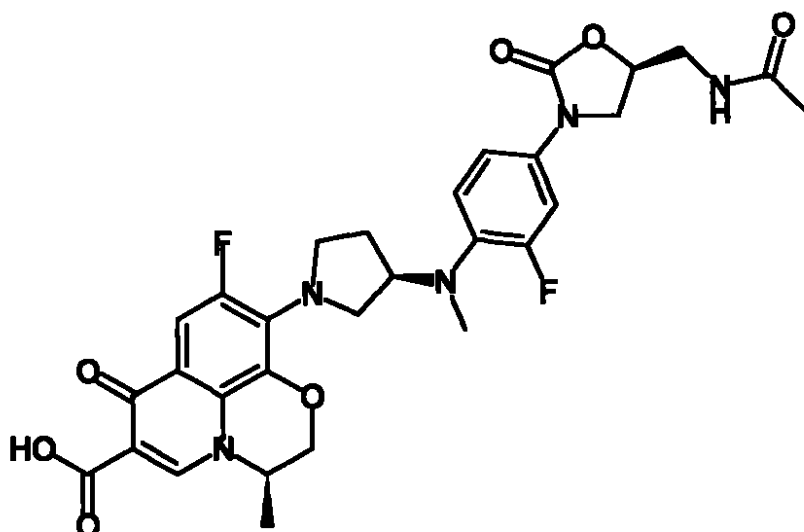
(d, 1H); 4,10 (t, 1H), 4,00-3,30 (m, 8H); 2,74 (s, 3H); 2,20-1,80 (m, 2H); 1,84 (s, 3H); 1,42 (d, 3H).

$[\alpha]^{25}_D = +66,4^\circ$ (c 0,5; CH₂Cl₂/MeOH 9/1)

5

EJEMPLO 33

Acido 9-[3-(R)-({4-[5-(S)-(acetilamino-metil)-2-oxo-
10 oxazolidin-3-il]-2-fluoro-fenil}-metil-amino)-pirrolidin-
1-il]-8-fluoro-3-(S)-metil-6-oxo-2,3-dihidro-6H-1-oxa-3a-
aza-fenalen-5-carboxílico



15

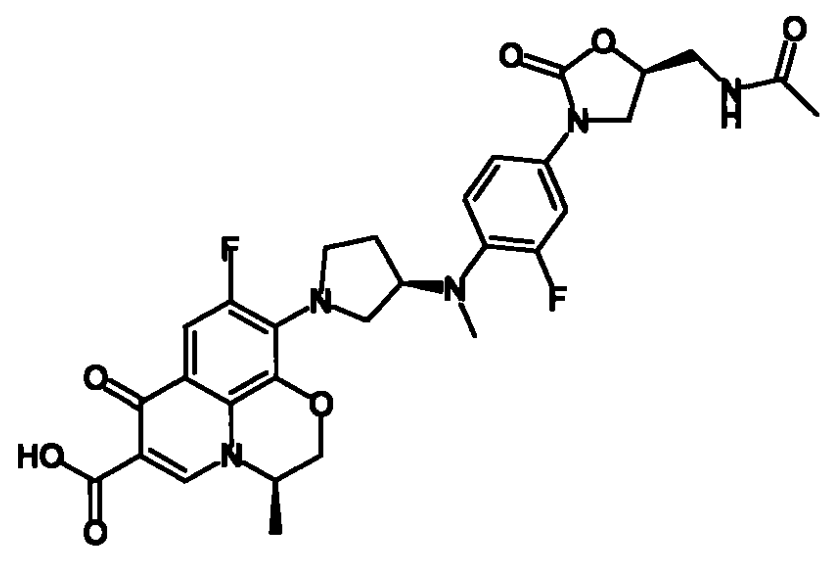
Siguiendo el procedimiento descrito en el Ejemplo 3 y partiendo del correspondiente quelato obtenido por reacción de N-{3-(R)-[3-fluoro-4-(metil-pirrolidin-3-il-amino)-
20 fenil]-2-oxo-oxazolidin-5-(S)-ilmetil}-acetamida (obtenida siguiendo el procedimiento para la obtención del Ejemplo de Referencia No.27, pero sustituyendo 3-(R,S)-aminopirrolidina por 3-(R)-aminopirrolidina), y 8,9-

difluoro-3-(S)-metil-6-oxo-2,3-dihidro-6H-1-oxa-3a-aza-fenalen-5-carboxílico boro difluoruro quelato se obtiene el producto del título.

- 5 $^1\text{H-RMN}$ (DSMO-d_6 , 200 MHz, δ (ppm)): 8,92 (s, 1H); 8,24 (t, 1H, NH); 7,60-7,40 (m, 2H); 7,36-7,10 (m, 2H); 4,95-4,80 (m, 1H); 4,80-4,60 (m, 1H); 4,56 (d, 1H); 4,26 (d, 1H); 4,10 (t, 1H), 4,02-3,30 (m, 8H); 2,76 (s, 3H); 2,20-1,80 (m, 2H); 1,82 (s, 3H); 1,40 (d, 3H).
- 10 $[\alpha]^{25}_D = -80,6^\circ$ (c 0,5; $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9/1)

EJEMPLO 34

- 15 Acido 9-[3-(R)-({4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-metil-amino)-pirrolidin-1-il]-8-fluoro-3-(R)-metil-6-oxo-2,3-dihidro-6H-1-oxa-3a-aza-fenalen-5-carboxílico
- 20



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Siguiendo el procedimiento descrito en el Ejemplo 3 y partiendo del correspondiente quelato obtenido por reacción de N-{3-(R)-[3-fluoro-4-(metil-pirrolidin-3-il-amino)-fenil]-2-oxo-oxazolidin-5-(S)-ilmetil}-acetamida (obtenida 5 siguiendo el procedimiento para la obtención del Ejemplo de Referencia No.27, pero sustituyendo 3-(R,S)-aminopirrolidina por 3-(R)-aminopirrolidina), y 8,9-difluoro-3-(R)-metil-6-oxo-2,3-dihidro-6H-1-oxa-3a-aza-fenalen-5-carboxílico boro difluoruro quelato (obtenido 10 según Shohgo Atarashi et al., *Chem. Pharm. Bull.* (1987), 35 (5), 1896-1902) se obtiene el producto del título.

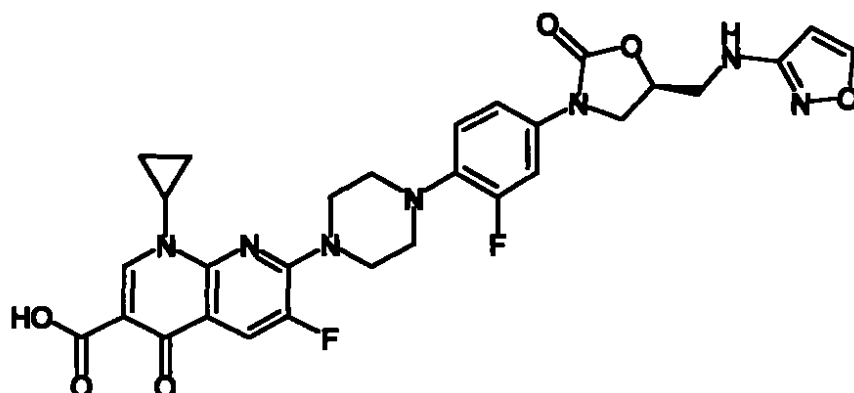
¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 8,90 (s, 1H); 8,24 (t, 1H, NH); 7,60-7,40 (m, 2H); 7,36-7,10 (m, 2H); 15 4,95-4,80 (m, 1H); 4,80-4,60 (m, 1H); 4,54 (d, 1H); 4,30 (d, 1H); 4,10 (t, 1H), 4,00-3,30 (m, 8H); 2,72 (s, 3H); 2,20-1,80 (m, 2H); 1,84 (s, 3H); 1,42 (d, 3H).

$[\alpha]_D^{25} = +18^\circ$ (c 0,5; CH₂Cl₂/MeOH 9/1)

20

EJEMPLO 35

Acido 1-ciclopropil-6-fluoro-7-(4-{2-fluoro-4-[5-(S)-25 (isoxazol-3-ilaminometil)-2-oxo-oxazolidin-3-il]-fenil}-piperazin-1-il)-4-oxo-1,4-dihidro-[1,8]naftiridin-3-carboxílico



Siguiendo el procedimiento descrito en el Ejemplo 14 y a partir del correspondiente producto obtenido por reacción 5 del compuesto del Ejemplo de Referencia 25 N-desprotegido y ácido 7-cloro-1-ciclopropil-6-fluoro-4-oxo-1,4-dihidro-[1,8]naftiridin-3-carboxílico se obtiene el producto del título.

10 ^1H -RMN (DSMO- d_6 , 200 MHz, δ (ppm)): 13,2 (s, 1H); 8,61 (s, 1H); 8,40 (s, 1H); 8,10 (d, 1H); 7,50 (d, 1H); 7,10 (m, 2H); 6,55 (t, 1H); 5,98 (s, 1H); 4,85 (m, 1H); 4,04 (m, 5H); 3,75 (m, 2H); 3,40 (m, 2H); 3,17 (m, 4H); 1,2 (m, 4H).

15

EJEMPLOS DE RESULTADOS FARMACOLÓGICOS

Descripción de los métodos utilizados para la valoración 20 de las propiedades farmacológicas

La actividad antibacteriana de los nuevos compuestos sintetizados ante las diferentes cepas de las especies bacterianas se realizó mediante la técnica de 25 microdilución en caldo según las normativas del National

Committee for Clinical Laboratory Standards (NCCLS), (NCCLS. 1993. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Approved standard M7-A3. NCCLS, Vilanova. PA., y NCCLS. 5 1993. Methods for dilution antimicrobial susceptibility tests for anaerobic bacteria that grow aerobically. Approved standard M1-A3. NCCLS, Vilanova. PA).

El inóculo utilizado fue de 5×10^5 UFC/ml 10 después de la dilución de los cultivos de toda la noche en la fase de crecimiento logarítmico bacteriano.

La CMI expresada en mg/l se definió como la concentración mínima de antibiótico que inhibe cualquier 15 crecimiento visible.

Como producto de comparación se ha incluido linezolid.

20 Los compuestos se ensayaron en las cepas de bacterias G(+) y G(-) que se describen en la tabla 1, donde:

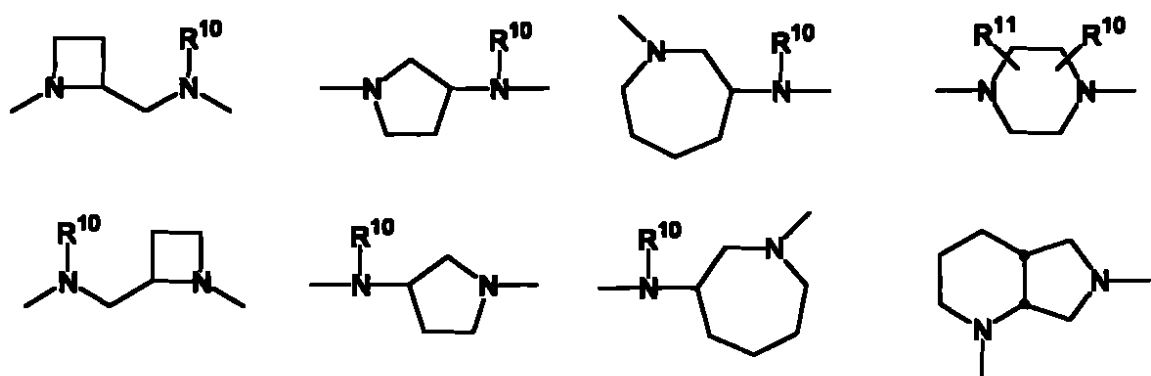
- A: *S. aureus* resistente a la meticilina
- 25 B: *E. faecalis* resistente a la vancomicina
- C: *S. pneumoniae* resistente a la penicilina
- D: *S. agalactiae*
- E: *S. epidermidis*
- F: *S. pyogenes*
- 30 G: *B. fragilis*
- H: *E. coli*
- I: *H. influenzae*
- J: *M. Catarrhalis*.

200 200

Tabla 1 – Actividad antibacteriana sobre cepas hospitalarias (resistentes) de bacterias Gram (+) y Gram (-)

5	PRO- DUCTO	Cepas G (+)						Anaer o- bios	Cepas G (-)		
		A	B	C	D	E	F	G	H	I	J
	Linezo- lid	2	2	1	2	1	1	2	>64	16	16
	EJEM- PLO 1 y 8	0,25	0,125	<0,125	0,125	0,125	<0,125	0,25	8	0,25	0,25
	EJEM- PLO 3	<0,125	<0,125	<0,125	<0,125	<0,125	<0,125	0,5	64	4	0,5
	EJEM- PLO 4	0,25	0,25	<0,125	<0,125	<0,125	<0,125	0,5	16	2	1
	EJEM- PLO 5	0,5	0,5	0,5	0,5	0,25	0,5	2	4	1	1
	EJEM- PLO 6	2	1	1	0,5	0,5	1	16	2	<0,125	0,25
	EJEM- PLO 7	0,25	0,5	0,25	0,5	0,25	0,25	2	8	4	1
	EJEM- PLO 9	<0,125	<0,125	<0,125	<0,125	<0,125	<0,125	0,5	>64	1	0,25
	EJEM- PLO 10	1	2	1	1	0,25	1	4	64	4	2
	EJEM- PLO 11	0,5	0,5	0,5	1	0,125	0,5	1	32	4	1
	EJEM- PLO 16	4	2	1	1	2	1	8	>64	>64	8
	EJEM- PLO 17	2	2	0,5	0,5	1	1	4	>64	64	4
	EJEM- PLO 19	4	8	4	8	4	8	>64	32	1	2
	EJEM- PLO 20	1	2	1	1	0,50	1	>64	>64	2	4
	EJEM- PLO 21	0,25	<0,125	<0,125	<0,125	<0,125	<0,125	0,25	64	2	0,5
	EJEM- PLO 22	<0,125	<0,125	0,25	<0,125	<0,125	<0,125	0,5	64	2	0,5

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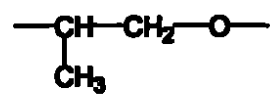


dónde

R¹⁰ y R¹¹ son independientemente H, o alquilo C₁-C₄;

5 una sal o un solvato farmacéuticamente aceptable, o cualquier isómero geométrico, isómero óptico o mezcla de isómeros del mismo en cualquier proporción o polimorfo del mismo.

10 2. Compuesto según la reivindicación 1, caracterizado por el hecho de que R¹ es ciclopropilo, etilo, 2-fluoroetilo, fenilo o difluorofenilo, o bien R¹ y R⁶ juntos forman un puente de estructura:

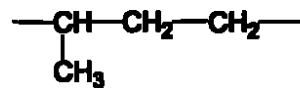
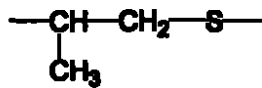
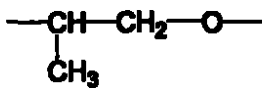


15 3. Compuesto según la reivindicación 1, caracterizado por el hecho de que R⁶ es H, CH₃, OCH₃, OCHF₂, F o Cl.

20 4. Compuesto según la reivindicación 3, caracterizado por el hecho de que R⁶ es H o F.

5. Compuesto según la reivindicación 1, caracterizado por el hecho de que R⁴ es F o Cl y R³ es H.

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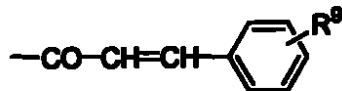
R^5 : H, halógeno, OCH_3 , alcoxi $\text{C}_1\text{--C}_4$, alquilo $\text{C}_1\text{--C}_4$, o haloalquilo $\text{C}_1\text{--C}_4$;

5

A: $-\text{CH}_2\text{--NH--R}^7$, $-\text{CHOH--C}\equiv\text{CH}$;

donde

10 R^7 : isoxazol, $-\text{CO--R}^8$, $-\text{CS--R}^8$, $-\text{CS--OR}^8$, $-\text{COOR}^8$, $-\text{CONHR}^8$, $-\text{CSNHR}^8$, $-\text{SO}_2\text{--R}^8$ o



15

donde

R^8 : alquilo $\text{C}_1\text{--C}_4$, haloalquilo $\text{C}_1\text{--C}_4$, alquenilo $\text{C}_2\text{--C}_4$, arilo, alquilo $\text{C}_1\text{--C}_4$ sustituido por un grupo alcoxi $\text{C}_1\text{--C}_4$, carboxialquilo $\text{C}_1\text{--C}_4$, ciano, o amino;

20

R^9 : H, alquilo $\text{C}_1\text{--C}_4$, alquenilo $\text{C}_2\text{--C}_4$, OH, alcoxi $\text{C}_1\text{--C}_4$, $\text{NR}^{12}\text{R}^{13}$, NO_2 , halógeno, ó CO--R^{12} ;

R^{12} y R^{13} : independientemente, H o alquilo $\text{C}_1\text{--C}_4$;

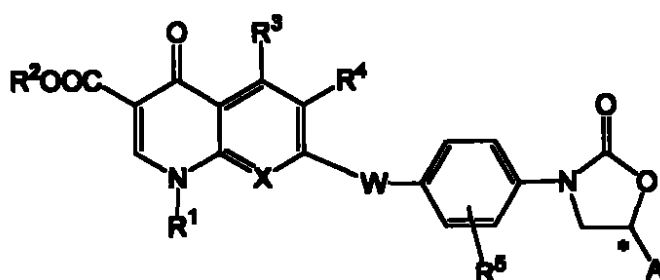
25

W:

REIVINDICACIONES

1. Compuesto de fórmula general (I):

5



(I)

10 donde:

X: CR⁶ ó N;

R¹: alquilo C₁-C₄, cicloalquilo C₃-C₆, alqueno C₂-C₄, 2-hidroxietilo, 2-fluoroetilo, ó fenilo opcionalmente sustituido por 1 ó 2 átomos de flúor;

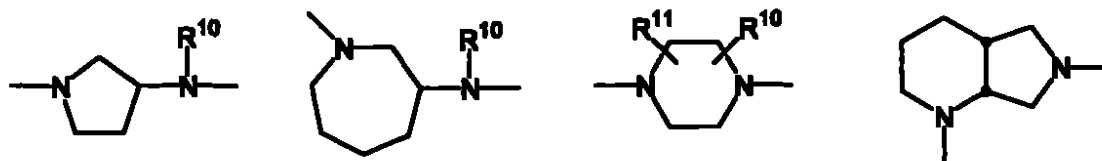
R²: H, alquilo C₁-C₄ o fenilo;

20 R³: H, halógeno, alquilo C₁-C₄, ó alcoxi C₁-C₄, amino;

R⁴: H ó halógeno;

25 R⁶: H, halógeno, alquilo C₁-C₄, haloalcoxi C₁-C₄, o bien R¹ y R⁶ juntos forman un puente de estructura

6. Compuesto según la reivindicación 1, caracterizado por el hecho de que W es



5 dónde R^{10} y R^{11} son tal como se definen en la reivindicación 1.

7. Compuesto según la reivindicación 1, caracterizado por el hecho de que el C5 del anillo de oxazolidinona tiene una configuración (S) cuando $A = -CH_2-NH-R^7$ y (R) cuando $A = -CHOH-C=CH$.

8. Compuesto según las reivindicaciones 1 a 6, caracterizado por el hecho de que se selecciona entre uno 15 de los siguientes:

- Ácido 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-ciclopropil-6-fluoro-4-oxo-1,4-dihidro-quinolein-3-carboxílico
- 20 - Ácido 7-[3-({4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-metil-amino)-azepan-1-il]-1-ciclopropil-6-fluoro-4-oxo-1,4-dihidro-quinolein-3-carboxílico
- 25 - Ácido 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-etil-6,8-difluoro-4-oxo-1,4-dihidro-quinolein-3-carboxílico
- Ácido 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-etil-
- 30 6-fluoro-4-oxo-1,4-dihidro-quinolin-3-carboxílico

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- Ácido 9-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-fenil}-piperazin-1-il)-8-fluoro-3-metil-6-oxo-2,3-dihidro-6H-1-oxa-3a-aza-fenalen-5-carboxílico
- 5 - Ácido 9-[3-({4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-metil-amino)-pirrolidin-1-il]-8-fluoro-3-metil-6-oxo-2,3-dihidro-6H-1-oxa-3a-aza-fenalen-5-carboxílico
- Ácido 9-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-8-fluoro-3-metil-6-oxo-2,3-dihidro-6H-1-oxa-3a-aza-fenalen-5-carboxílico
- 10 - Ácido 1-ciclopropil-6-fluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-metil-tioureido)-metil]-2-oxo-oxazolidin-3-il}-fenil)-piperazin-1-il]-4-oxo-1,4-dihidro-quinolein-3-carboxílico
- Ácido 1-ciclopropil-7-[4-(4-{5-(S)-[(3-etil-ureido)-metil]-2-oxo-oxazolidin-3-il}-2-fluoro-fenil)-piperazin-1-il]-6-fluoro-4-oxo-1,4-dihidro-quinolein-3-carboxílico
- 20 - Ácido 1-ciclopropil-7-(4-{4-[5-(S)-(etoxycarbonilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-6-fluoro-4-oxo-1,4-dihidro-quinolein-3-carboxílico
- 25 - Ácido 1-ciclopropil-6-fluoro-7-{4-[2-fluoro-4-(5-(S)-{[3-(4-fluoro-fenil)-acriloilamino]-metil}-2-oxo-oxazolidin-3-il)-fenil]-piperazin-1-il}-4-oxo-1,4-dihidro-quinolein-3-carboxílico
- Ácido 1-ciclopropil-7-[4-(4-{5-(S)-[(3-etil-tioureido)-metil]-2-oxo-oxazolidin-3-il}-2-fluoro-fenil)-piperazin-1-il]-6-fluoro-4-oxo-1,4-dihidro-quinolein-3-carboxílico
- 30 - 1-(2,4-difluoro-fenil)-6-fluoro-7-(4-{2-fluoro-5-[5-(R)-(1-(R,S)-hidroxi-prop-2-inil)-2-oxo-oxazolidin-3-

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- il]-fenil}piperazin-1-il)-4-oxo-1,4-dihidro-
[1,8]naftiridin-3-carboxilato de etilo
- 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-(2,4-difluoro-
5 fenil)-6-fluoro-4-oxo-1,4-dihidro-[1,8] naftiridin-3-carboxilato de etilo
- 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-ciclopropil-6-fluoro-4-oxo-1,4-dihidro-[1,8] naftiridin-3-carboxilato
10 de etilo
- 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-6,8-difluoro-1-(2-fluoro-etil)-4-oxo-1,4-dihidro-quinoleine-3-carboxilato de etilo
- 15 - 1-(2,4-Difluoro-fenil)-6-fluoro-7-(4-{2-fluoro-4-[5-(S)-(isoxazol-3-ilaminometil)-2-oxo-oxazolidin-3-il]-fenil}-piperazin-1-il)-4-oxo-1,4-dihidro-[1,8]naftiridine-3-carboxilato de etilo
- Ácido 1-(2,4-difluoro-fenil)-6-fluoro-7-(4-{2-fluoro-4-[5-(R)-(1-hidroxi-prop-2-inil)-2-oxo-oxazolidin-3-il]-fenil}-piperazin-1-il)-4-oxo-1,4-dihidro-[1,8]
20 naftiridin-3-carboxílico
- Ácido 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-(2,4-difluoro-fenil)-6-fluoro-4-oxo-1,4-dihidro-[1,8]
25 naftiridin-3-carboxílico
- Ácido 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-ciclopropil-6-fluoro-4-oxo-1,4-dihidro-[1,8]
30 naftiridin-3-carboxílico
- Ácido 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-6,8-difluoro-1-(2-fluoro-etil)-4-oxo-1,4-dihidro-quinolin-3-carboxílico

- 207
- Ácido 1-(2,4-Difluoro-fenil)-6-fluoro-7-[4-(2-fluoro-4-[5-(S)-(isoxazol-3-ilaminometil)-2-oxo-oxazolidin-3-il]-fenil)-piperazin-1-il]-4-oxo-1,4-dihidro-[1,8]naftiridin-3-carboxílico
 - 5 - Ácido 1-etil-6,8-difluoro-7-[4-(2-fluoro-4-[5-[(3-metil-tioureido)-metil]-2-oxo-oxazolidin-3-il]-fenil)-piperazin-1-il]-4-oxo-1,4-dihidro-quinolein-3-carboxílico
 - Ácido 1-ciclopropil-6-fluoro-7-[4-(2-fluoro-4-[2-oxo-5-
 - 10 (S)-[(3-propil-tioureido)-metil]-oxazolidin-3-il]-fenil)-piperazin-1-il]-4-oxo-1,4-dihidro-quinolein-3-carboxílico
 - Ácido 1-ciclopropil-6-fluoro-7-[4-(2-fluoro-4-[5-(S)-(metanosulfonilamino-metil)-2-oxo oxazolidin-3-il]-
 - 15 fenil)-piperazin-1-il]-4-oxo-1,4-dihidro-quinolein-3-carboxílico.
 - 7-(4-[4-[5-(S)-(Acetilamino-metil)-2-oxo-oxazolidin-3-il]-fenil)-piperazin-1-il]-1-etil-6,8-fluoro-4-oxo-1,4-dihidro-quinolein-3-carboxilato de etilo
 - 20 - Ácido 1-ciclopropil-6-fluoro-7-[4-(2-fluoro-4-[2-oxo-5-(S)-[(2,2,2-trifluoro-acetilamino)-metil]-oxazolidin-3-il]-fenil)-piperazin-1-il]-4-oxo-1,4-dihidro-quinolein-3-carboxílico
 - Ácido 7-(4-[4-[5-(S)-(benzoilamino-metil)-2-oxo-
 - 25 oxazolidin-3-il]-2-fluoro-fenil)-piperazin-1-il)-1-ciclopropil-6-fluoro 4-oxo-1,4-dihidro-quinolein-3-carboxílico.
 - 7-(4-[4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil)-piperazin-1-il)-1-ciclopropil-6-
 - 30 fluoro-4-oxo-1,4-dihidro-quinolein-3-carboxilato de metilo
 - 7-(4-[4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil)-piperazin-1-il)-1-ciclopropil-6-

- fluoro-4-oxo-1,4-dihidro-quinolein-3- carboxilato de etilo
- 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-etil-6,8-difluoro-
 - 5 4-oxo-1,4-dihidro-quinolein-3- carboxilato de metilo
 - 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-etil-6,8-difluoro-
 - 4-oxo-1,4-dihidro-quinolein-3-carboxilato de etilo
 - 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-
 - 10 il]-2-fluoro-fenil}-piperazin-1-il)-1-etil-6-fluoro-4-oxo-1,4-dihidro-quinolin-3- carboxilato de metilo
 - 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-etil-6-fluoro-4-oxo-1,4-dihidro-quinolin-3-carboxilato de etilo
 - 15 - 9-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-fenil}-piperazin-1-il)-8-fluoro-3-metil-6-oxo-2,3-dihidro-6H-1-oxa-3a-aza-fenalen-5- carboxilato de metilo
 - 9-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-
 - 20 il]-fenil}-piperazin-1-il)-8-fluoro-3-metil-6-oxo-2,3-dihidro-6H-1-oxa-3a-aza-fenalen-5-carboxilato de etilo
 - 9-[3-({4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-metil-amino)-pirrolidin-1-il]-8-fluoro-3-metil-6-oxo-2,3-dihidro-6H-1-oxa-3a-aza-
 - 25 fenalen-5- carboxilato de metilo
 - 9-[3-({4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-metil-amino)-pirrolidin-1-il]-8-fluoro-3-metil-6-oxo-2,3-dihidro-6H-1-oxa-3a-aza-fenalen-5-carboxilato de etilo
 - 30 - 9-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-8-fluoro-3-metil-6-oxo-2,3-dihidro-6H-1-oxa-3a-aza-fenalen-5- carboxilato de metilo

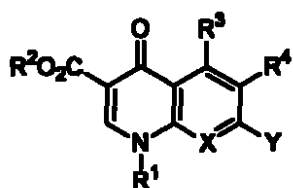
- 9-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-8-fluoro-3-metil-6-oxo-2,3-dihidro-6H-1-oxa-3a-aza-fenalen-5-carboxilato de etilo
- 5 - 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-ciclopropil-6-fluoro-4-oxo-1,4-dihidro-quinolein-3- carboxilato de metilo
- 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-ciclopropil-6-fluoro-4-oxo-1,4-dihidro-quinolein-3-carboxilato de etilo
- 10
- 1-ciclopropil-6-fluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-metil-tioureido)-metil]-2-oxo-oxazolidin-3-il}-fenil)-piperazin-1-il]-4-oxo-1,4-dihidro-quinolein-3-carboxilato de metilo
- 15
- 1-ciclopropil-6-fluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-metil-tioureido)-metil]-2-oxo-oxazolidin-3-il}-fenil)-piperazin-1-il]-4-oxo-1,4-dihidro-quinolein-3-carboxilato de etilo
- 20
- 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-1-ciclopropil-6-fluoro-4-oxo-1,4-dihidro-[1,8] naftiridin-3-carboxilato de metilo
- 25 - 7-(4-{4-[5-(S)-(acetilamino-metil)-2-oxo-oxazolidin-3-il]-2-fluoro-fenil}-piperazin-1-il)-6,8-difluoro-1-(2-fluoro-etil)-4-oxo-1,4-dihidro-quinolin-3- carboxilato de metilo
- 1-Etil-6,8-difluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-metil-tioureido)-metil]-2-oxo-oxazolidin-3-il}-fenil)-piperazin-1-il]-4-oxo-1,4-dihidro-quinolein-3-carboxilato de etilo
- 30

9. Procedimiento de obtención de un compuesto de

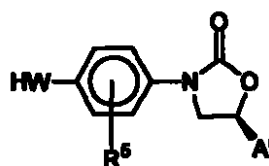
210

fórmula general (I), según la reivindicación 1, caracterizado por el hecho de que comprende la reacción de un compuesto de fórmula general (II) con un compuesto de fórmula general (III):

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(II)

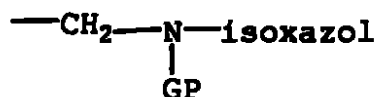


(III)

donde:

A' es:

- 5 a) $-\text{CH}_2-\text{NH}-\text{R}^7$
b) $-\text{CHOH}-\text{C}=\text{CH}$
c)

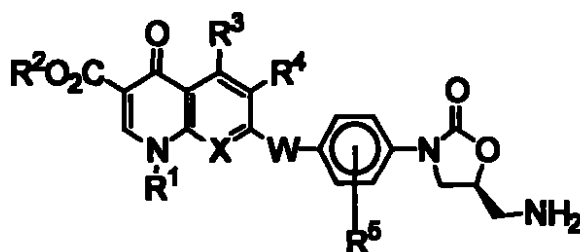


10 Y es un grupo saliente, tal como un átomo de halógeno (F, Cl, Br, I), un grupo tosilato ó mesilato, y similares;

R^1 , R^2 , R^3 , R^4 , R^5 , X y W tienen el significado definido en la reivindicación 1;

15 GP es un grupo protector de aminas.

10. Procedimiento de obtención de un compuesto de fórmula general (I), según la reivindicación 1, en el que A es $-\text{CH}_2-\text{NH}-\text{R}^7$ y R^7 es distinto de isoxazol, caracterizado por el
20 hecho de que comprende la reacción de un compuesto de fórmula (V)



(V)

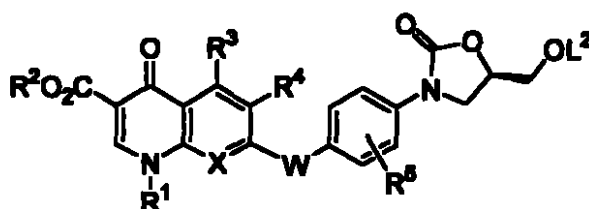
donde R^1 , R^2 , R^3 , R^4 , R^5 , X y W tienen el significado definido en la reivindicación 1, con un compuesto de fórmula (VI) o con un compuesto de fórmula (VII)



donde L es un buen grupo saliente, tal como un átomo de halógeno (F, Cl, Br, I), un grupo tosilato ó mesilato, y similares;

10 Z es Oxígeno ó Azufre, y R^7 y R^8 tienen el significado definido en la reivindicación 1, siendo R^7 distinto de isoxazol.

11. Procedimiento de obtención de un compuesto de fórmula general (I), según la reivindicación 1, en el que A es -CH₂-NH- R^7 y R^7 es isoxazol, caracterizado por el hecho de que comprende la reacción de un compuesto de fórmula general (VIII):



20 (VIII)

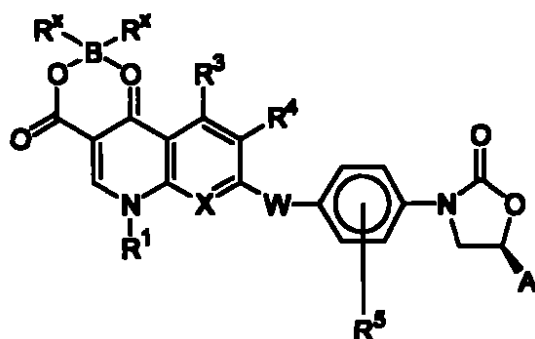
donde

25 - OL² representa un buen grupo saliente, tal como un residuo del ácido aril o metil sulfónico, sustituido o no sustituido, preferentemente un grupo tosilato ó mesilato;

- R^1 , R^2 , R^3 , R^4 , R^5 , X y W tienen el significado definido en la reivindicación 1;

con isaoxazolil-3-amina, con el grupo amino protegido a través de un grupo protector de aminos.

12. Procedimiento de obtención de un compuesto de fórmula 5 general (I), según la reivindicación 1, en el que R^2 es hidrógeno, caracterizado por el hecho de que comprende la hidrólisis de un quelato de boro de fórmula (IX)



(IX)

10 donde

R^x puede ser F o CH_3COO^- ;

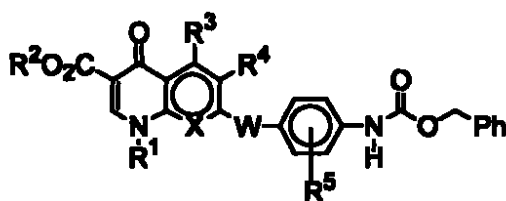
A, R^1 , R^3 , R^4 , R^5 , X y W tienen el significado definido en la reivindicación 1.

15 13. Procedimiento de obtención de un compuesto de fórmula general (I), según la reivindicación 1, en el que A es



caracterizado por el hecho de que comprende la reacción de un compuesto de fórmula (IV)

20



(IV)

donde R^1 , R^2 , R^3 , R^4 , R^5 , X y W tienen el significado

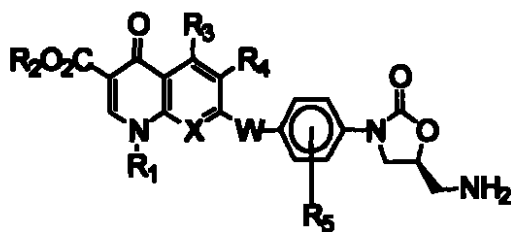
124
2

definido en la reivindicación 1,
con p-toluensulfonato de 2,3-hidroxi-pent-4-inil.

14. Procedimiento según cualquiera de las reivindicaciones 5 11 a 13, caracterizado por el hecho de que comprende someter, opcionalmente, el producto obtenido a una o más de las siguientes etapas finales:

- a) Conversión de un compuesto de fórmula general (I) en otro compuesto de fórmula general (I);
- 10 b) Eliminación del grupo protector;
- c) Preparación de una sal farmacológicamente aceptable de un compuesto de fórmula (I) y/o un solvato farmacológicamente aceptable del mismo.

15 15. Compuesto de fórmula (V)

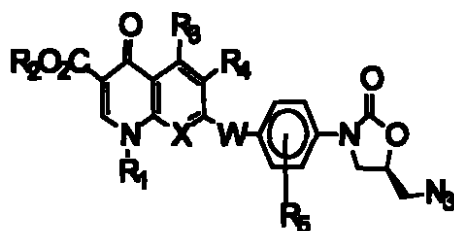


(V)

donde R^1 , R^2 , R^3 , R^4 , R^5 , X y W tienen el significado definido en la reivindicación 1.

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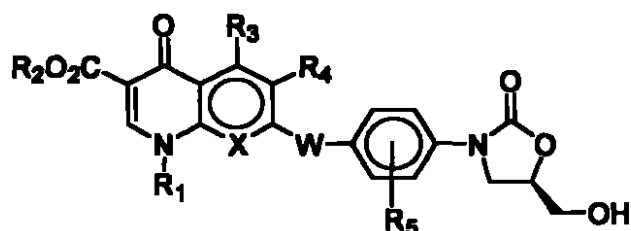
16. Compuesto de fórmula (X)



(X)

donde R^1 , R^2 , R^3 , R^4 , R^5 , X y W tienen el significado definido en la reivindicación 1.

17. Compuesto de fórmula (XI)



5 (XI)

donde R^1 , R^2 , R^3 , R^4 , R^5 , X y W tienen el significado definido en la reivindicación 1.

10 18. Composición farmacéutica que comprende un compuesto de fórmula general (I), según cualquiera de las reivindicaciones 1 a 8, para su utilización como medicamento.

15 19. Utilización de un compuesto de fórmula general (I) , según cualquiera de las reivindicaciones 1 a 8, para la preparación de una composición farmacéutica destinada al tratamiento de infecciones microbianas, en humanos o animales de sangre caliente.

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20. Composición farmacéutica que comprende un compuesto de fórmula general (I), según cualquiera de las reivindicaciones 1 a 8, en una cantidad terapéuticamente activa y una cantidad adecuada de al menos un excipiente.

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RESUMEN

La presente invención proporciona nuevos derivados
5 fluorquinolónicos de oxazolidinonas de fórmula general (I)
así como procedimientos para su obtención, las
correspondientes composiciones farmacéuticas y su
utilización para la fabricación de un medicamento
destinado al tratamiento de infecciones microbianas.
10 Estos nuevos compuestos son útiles como
antibacterianos.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Article 36 and Rule 70)

217
A

Applicant's or agent's file reference A-153813		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA418)	
International application No. PCT/B0202408	International filing date (day/month/year) 24.06.2002	Priority date (day/month/year) 27.06.2001	
International Patent Classification (IPC) or both national classification and IPC C07D413/14			
Applicant VITA-INVEST, S.A. 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 opinion 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 Rule 68.2(a)(II) 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 23.12.2002		Date of completion of this report 21.07.2003	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-60298 Munich Tel. +49 89 2369 - 0 Fax: +49 89 2369 - 4465		Authorized Officer Boston, E Telephone No. +1 617 237-8229 	

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/IB02/02408**

I. Basis of the report

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

Description, Pages

1-91 as originally filed

Claims, Numbers

1-20 as originally filed

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 the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 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 in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure 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.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

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 (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/IB02/02408

**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)	Yes: Claims	1-20
	No: Claims	
Inventive step (IS)	Yes: Claims	1-20
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-20
	No: Claims	

2. Citations and explanations
see separate sheet

1/2

INTERNATIONAL PRELIMINARY

International application No. PCT/IB02/02408

EXAMINATION REPORT - SEPARATE SHEET**To section V**

(1) The following documents were cited in the search report and were considered for the examination of the present application:

- D1: FR-A-2 403 339 (BELLON LABOR SA ROGER) 13 April 1979
D2: WO 97 37980 A (BARBACHYN MICHAEL R ;UPJOHN CO (US); FLECK THOMAS J (US); HOUSER D) 16 October 1997
D3: WO 98 01447 A (DARBYSHIRE CATHERINE JANE ;ZENECA LTD (GB); BETTS MICHAEL JOHN (GB) 15 January 1998
D4: WO 93 23384 A (UPJOHN CO ;HUTCHINSON DOUGLAS K (US); BRICKNER STEVEN JOSEPH (US);) 25 November 1993
D5: EP-A-0 878 194 (SANKYO CO ;UBE INDUSTRIES (JP)) 18 November 1998
D6: HAYAKAWA I ET AL: 'SYNTHESIS AND ANTIBACTERIAL ACTIVITIES OF SUBSTITUTED 7-OXO-2,3-DIHYDRO-7H-PYRIDOU1,2,3-DEU1,4BE NZOXAZINE-6-CARBOXYLIC ACIDS' CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 32, no. 12, 1 December 1984, pages 4907-4913.

(2) The present application relates to 4-quinollinones having a carboxylic acid moiety in position 3 and to phenalen-type compounds (R¹ and R² being connected via a bridging element) with also a carboxylic acid group present alpha to the C=O group. All these structures have in common an isoxazole-moiety, which is attached via a phenyl-ring to the rest of the molecule. These compounds are useful as antibacterial agents.

(3) None of the documents of the prior art either discloses or suggests the claimed structures. E.g. D2-D4 also relate to compounds having antibacterial activity with an isoxazole substituent being present, but the basic structure is in all cases very different. D3 and D4 describe piperazines that are attached via a benzene ring with an isoxazole heterocycle. D7 discloses benzoxazine-6-carboxylic acid derivatives that are similar to those phenalene compounds claimed, but do not have the isoxazole substitution. The application contains a sufficient number of examples and table 1 on page 91 gives results for various examples with respect to their antibacterial activity. The requirements of Art. 33(2) and 33(3) PCT are met.

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TRATADO DE COOPERACIÓN DE PATENTES
PCT
INFORME DEL EXAMEN INTERNACIONAL PRELIMINAR
(PCT Artículo 36 y Regla 70)

Número de expediente del solicitante o apoderado A-153913	PARA ACTIVIDAD ULTERIOR Vea Notificación de Traspaso del Informe del Examen Internacional Preliminar (Forma PCI/IPEA/416)	
Solicitud Internacional No. PCT/IB02/02408	Fecha internacional de presentación (día/mes/año) 24.00.2002	Fecha de Prioridad (día/mes/año) 27.06.2001
Clasificación Internacional de Patente (IPC) o tanto la clasificación nacional como la IPC CO7D413/14		
Solicitante VITA-INVEST S.A. et al.		
1. Este informe del examen internacional preliminar ha sido preparado por esta Autoridad de Calificación Preliminar Internacional y es traspasado al solicitante de acuerdo al Artículo 36. 2. Este informe consiste de un total de 4 hojas, incluyendo esta hoja de portada ☐ Este informe también está acompañado de ANEXOS, en otras palabras hojas de la descripción, las reivindicaciones y/o los dibujos que han sido enmendados y que son la base de este informe y/o hojas que contienen rectificaciones hechas ante esta autoridad (vea la Regla 70,16 y la Sección 807 de las Instrucciones Administrativas bajo el PCT) Estos anexos consisten de un total de hojas.		
3. Este informe contiene indicaciones relacionadas con los siguientes asuntos: I. ☒ Base del informe II. ☐ Prioridad III. ☐ Sin elaboración de un dictamen sobre novedad, nivel inventivo y aplicabilidad industrial IV. ☐ Uniformidad deficiente en la invención V. ☒ Declaración justificada bajo la regla 66.2 (a)(II) VI. ☐ Ciertos documentos enumerados VII. ☐ Ciertas deficiencias en la solicitud Internacional ☐ Ciertas observaciones en la solicitud Internacional		
Fecha de presentación de la solicitud 23.12.2002	Fecha de terminación de este informe 21.07.2003	
Nombre y dirección de correo de la Autoridad de Calificación Preliminar Internacional Oficina Europea de Patentes D-80298 Munich Teléfono +49 89 2399 – o Telex 523656 epmu d Fax +49 892399-4465	Empleado Autorizado Baston E Teléfono No. +49 892399-8229	

**INFORME DEL EXAMEN
PRELIMINAR INTERNACIONAL**

Solicitud Internacional No. PCT/IB02/02408

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I. Base del reporte

1. Con respecto a lo elementos de la solicitud internacional (Las hojas de reemplazo que han sido proporcionadas a la Oficina de recepción en respuesta a una invitación bajo el Artículo 14 están referenciadas en este Informe como "entregadas originalmente" y no se encuentran anexas a este informe debido a que no contienen enmendaduras (Reglas 70.16 y 70.17):

Descripción, Páginas

1-91 como se entregaron originalmente

Reivindicaciones, Números

1-20 como se entregaron originalmente

2. Con respecto al idioma, todos los elementos marcados arriba estaban disponibles o fueron proporcionados a esta Autoridad en el idioma en el cual se hizo la solicitud Internacional, excepto los que se indican bajo este asunto.

Estos elementos estaban disponibles o fueron proporcionados en el siguiente idioma: , el cual es:

- ☐ el idioma de una traducción proporcionada para propósito de la búsqueda internacional (Bajo la regla 23.1(b))
- ☐ el idioma de la publicación de la solicitud Internacional (bajo la Regla 48.3(b))
- ☐ el idioma de la traducción proporcionada para propósito del examen preliminar Internacional (bajo la regla 55.2 y/o 55.3)

3. Con respecto a cualquier nucleótido y/o secuencia de aminoácidos dada a conocer en la solicitud internacional, el examen preliminar internacional se llevó a cabo sobre la base del listado de secuencias:

- ☐ contenida en la solicitud Internacional de forma escrita
- ☐ entregada junto con la solicitud internacional en una forma a computador legible
- ☐ proporcionada de forma subsiguiente a esta Autoridad de forma escrita
- ☐ proporcionada de forma subsiguiente a esta Autoridad en una forma a computador legible
- ☐ se ha proporcionado la afirmación de que el listado escrito de la secuencia entregado de forma subsiguiente no va más allá de la divulgación en la solicitud internacional como fue presentada
- ☐ se ha proporcionado la afirmación de que la información registrada en la forma a computador legible es idéntica a la secuencia escrita.

4. Las enmendaduras han dado como resultado la cancelación de:

- ☐ la descripción páginas:
- ☐ las reivindicaciones números:
- ☐ los diagramas hojas:

5. ☐ Este informe ha sido admitido como si (alguna de) las enmendaduras no han sido hechas, ya que se considera que estas van más allá de la divulgación presentada.

(Cualquier hoja de reemplazo que contiene dichas enmendaduras debe estar referenciada bajo el asunto 1 y anexada a este informe)

6. Observaciones adicionales, si son necesarias:

V. **Afirmación concluyente bajo el Artículo 35(2) en relación con la novedad, el nivel inventivo y la aplicabilidad industrial; citas y explicaciones que soportan tal afirmación.**

1. **Afirmación**

Novedad (N)	Si: Reivindicaciones	1-20
	No: Reivindicaciones	
Nivel inventivo (NI)	Si: Reivindicaciones	1-20
	No: Reivindicaciones	
Aplicabilidad industrial (AI)	Si: Reivindicaciones	1-20
	No: Reivindicaciones	

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2. **Citas y explicaciones**

ver hoja separada

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A la sección V

(1) Los siguientes documentos fueron citados en la búsqueda del informe y fueron considerados para el examen de la presente solicitud:

- D1: FR-A-2 403 339 (BELLON LABOR SA ROGER) 13 de Abril de 1979
D2: WO 97 37980 A (BARBACHYN MICHAEL R; UPJOHN CO (US); FLECK THOMAS J (US); HOUSER D) 16 de octubre de 1997
D3: WO 98 01447A (DARBYSHIRE CATHERINE JANE; ZENECA LTD (GB); BETTS MICHEAL JOHN (GB) 15 de Enero de 1998
D4: WO93 23384 A (UPJOHN CO; HUTCHINSON DOUGLAS K (US); BRICKNER STEVEN JOSEPH (US) 25 de Noviembre de 1993
D5: EP-A-0 878 194 (SANYO CO; UBE INDUSTRIES (JP) 18 de Noviembre de 1998
D6: HAYAKAWA I ET AL: "SINTESIS Y ACTIVIDADES ANTIBACTERIALES DE LOS ACIDOS 7-OXO-3,2-DIHIDRO-7H-PYRIDOU1,2,3-DEU1,4BENZOXAZINA-6-CARBOXILO SUSTITUIDOS Y BOLETIN FARMACEUTICO, SOCIEDAD FARMACEUTICA DEL JAPON, TOKIO, JP, vol 32, no 12, 1 de Diciembre de 1984, páginas 4907-4913.

(2) La siguiente solicitud se relaciona con las 4-quinolinonas que tienen una unidad de ácido carboxílico en la posición 3 y con los compuestos del tipo fenaleno (donde R' y R⁶ se encuentran conectados por un elemento de puente) también con un grupo de ácido carboxílico presente con enlace alfa al grupo C=O. Todas estas estructuras tienen en común una unidad isoxasola, la cual está unida por medio de un anillo de fenilo al resto de la molécula. Estos compuestos son útiles como agentes antibacteriales.

(3) Ninguno de los documentos del arte previo divulgan o sugieren dichas estructuras. Por ejemplo D2-D4 también se relacionan con compuestos que tienen actividad antibacterial con la presencia de un sustituto de isoxasola, pero la estructura básica en todos los casos es muy diferente. D3 y D4 describen piperazinas que se encuentran unidas por un anillo de benceno con un heterociclo de isoxasola. D7 divulga derivados del ácido de benzoxazina-6- carboxilo que son similares a aquellos compuestos de fenaleno reivindicados, pero no tienen la sustitución de isoxasola. La solicitud contiene un número suficiente de ejemplos y la tabla 1 en la página 91da resultados para varios ejemplos en relación a su actividad antibacterial.
Se cumplen los requisitos de los Artículos 33(2) y 33(3) de la PCT.

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

PONTI SALES, Adelaida
Consell de Cent, 322
E-08007 Barcelona
Spain

Date of mailing (day/month/year) 25 April 2003 (25.04.03)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference A-163913	
International application No. PCT/IB02/02408	International filing date (day/month/year) 24 June 2002 (24.06.02)

1. The following indications appeared on record concerning: ☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative		
Name and Address VITA-INVEST, S.A. Fontanils, 12-14 E-08970 Sant Joan Despi Spain	State of Nationality ES	State of Residence ES
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	
2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning: ☒ the person ☒ the name ☒ the address ☐ the nationality ☐ the residence		
Name and Address LABORATORIOS VITA, S.A. Av. de Barcelona 69 E-08970 Sant Joan Despi Barcelona Spain	State of Nationality ES	State of Residence ES
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	
3. Further observations, if necessary:		
4. A copy of this notification has been sent to: ☒ the receiving Office ☐ the designated Offices concerned ☐ the International Searching Authority ☒ the elected Offices concerned ☒ the International Preliminary Examining Authority ☐ other:		

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 28, Switzerland Facsimile No. (41-22) 740.14.36	Authorized officer Gabriele BAEHR Telephone No. (41-22) 338 9829
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INTERNATIONAL SEARCH REPORT

Int. nat. Application No
PC1/1B 02/02408

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D413/14 A61K31/422 A61P31/04 C07D471/04		
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) IPC 7 C07D		
Documentation searched other than minimum documentation to the extent that each document is included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, PAJ		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Character of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FR 2 403 339 A (BELLON LABOR SA ROGER) 13 April 1979 (1979-04-13) claim 1	1-20
A	WO 97 37980 A (BARBACHYN MICHAEL R ;UPJOHN CO (US); FLECK THOMAS J (US); HOUSER D) 16 October 1997 (1997-10-16) claim 1	1-20
A	WO 98 01447 A (DARBYSHIRE CATHERINE JANE ;ZENECA LTD (GB); BETTS MICHAEL JOHN (GB) 15 January 1998 (1998-01-15) claim 1	1-20
A	WO 93 23384 A (UPJOHN CO ;HUTCHINSON DOUGLAS K (US); BRICKNER STEVEN JOSEPH (US);) 25 November 1993 (1993-11-25) claim 1	1-20
-/-		
☒ Further documents are listed in the continuation of box C. ☒ Patent family members are listed in 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 document 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 another citation or other special reason (as specified) "O" document relating to an oral disclosure, use, exhibition or other event "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 considered with one or more other such documents, such consideration being obvious to a person skilled in the art "B" document member of the same patent family		
Date of the actual completion of the international search 11 September 2002		Date of mailing of the international search report 25/09/2002
Name and mailing address of the ISA European Patent Office, P.O. Box 6018 Petershof 2 NL - 6800 PH Dordrecht Tel. (+31-70) 340-2040, Tel. 31 651 651 651 ext. Fax (+31-70) 340-2016		Authorized officer Baston, E

Form PCT/ISA/210 (second sheet) (July 1993)

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INTERNATIONAL SEARCH REPORT

Int. No.	of Application No.
PCT/IB 02/02408	

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 878 194 A (SANKYO CO ;UBE INDUSTRIES (JP)) 18 November 1998 (1998-11-18) claim 1	1-20
A	HAYAKAWA I ET AL: "SYNTHESIS AND ANTIBACTERIAL ACTIVITIES OF SUBSTITUTED 7-OXO-2,3-DIHYDRO-7H-PYRIDOU1,2,3-DEU1,4BE NZOXAZINE-6-CARBOXYLIC ACIDS" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 32, no. 12, 1 December 1984 (1984-12-01), pages 4907-4913, XP000654032 ISSN: 0009-2363 table 1	1-20

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INTERNATIONAL SEARCH REPORT

translation on patent family members

 Int. Application No.
 PCT/18 02/02408

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR 2403339 A	13-04-1979	GB 1598915 A	23-09-1981
		AU 3996278 A	27-03-1980
		CA 1175836 A1	09-10-1984
		DE 2840910 A1	05-04-1979
		ES 473486 A1	01-11-1979
		FR 2403339 A1	13-04-1979
		FR 2498931 A1	06-08-1982
		JP 1147604 C	26-05-1983
		JP 54066686 A	29-05-1979
		JP 57038581 B	16-08-1982
		NL 7809591 A ,B,	22-03-1979
		SE 444566 B	21-04-1986
		SE 7809411 A	21-03-1979
		US 4292317 A	29-09-1981
		AU 520458 B2	04-02-1982
		BE 870576 A1	19-03-1979
WO 9737980 A	16-10-1997	AT 209193 T	15-12-2001
		AU 706117 B2	10-06-1999
		AU 2318297 A	29-10-1997
		CA 2248143 A1	16-10-1997
		CN 1215393 A ,B	28-04-1999
		CZ 9802871 A3	17-02-1999
		DE 69709718 D1	21-02-2002
		DE 69709718 T2	20-06-2002
		DK 892792 T3	02-04-2002
		EP 1114819 A1	11-07-2001
		EP 0892792 A1	27-01-1999
		ES 2166073 T3	01-04-2002
		JP 2000508312 T	04-07-2000
		KR 2000005358 A	25-01-2000
		NO 984737 A	09-12-1998
		NO 20015253 A	09-12-1998
		NZ 332278 A	26-05-2000
		PL 329295 A1	15-03-1999
		PT 892792 T	31-05-2002
		RU 2176643 C2	10-12-2001
		SI 892792 T1	30-06-2002
		SK 133698 A3	11-06-1999
		TW 449593 B	11-08-2001
		US 2002095054 A1	18-07-2002
		WO 9737980 A1	16-10-1997
		US 5837870 A	17-11-1998
		ZA 9702983 A	08-10-1998
WO 9801447 A	15-01-1998	AU 3352197 A	02-02-1998
		EP 0918770 A1	02-06-1999
		WO 9801447 A1	15-01-1998
		JP 2000514084 T	24-10-2000
WO 9323384 A	25-11-1993	AT 219770 T	15-07-2002
		AU 668733 B2	16-05-1996
		AU 4287793 A	13-12-1993
		CA 2133079 A1	25-11-1993
		CN 1079964 A ,B	29-12-1993
		CZ 9402505 A3	16-08-1995
		DE 69332061 D1	01-08-2002
		EP 0640077 A1	01-03-1995

Form PCT/ISA/210 (patent family search) (July 1999)

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INTERNATIONAL SEARCH REPORT

relation on patent family members

Info I Application No
PCT/IB 02/02408

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9323384	A	FI 945246 A	08-11-1994
		HU 72296 A2	29-04-1996
		HU 9500659 A3	28-11-1995
		IL 105555 A	15-07-1998
		JP 3255920 B2	12-02-2002
		JP 7506829 T	27-07-1995
		MX 9302665 A1	01-11-1993
		NO 944237 A	04-01-1995
		PL 174909 B1	30-10-1998
		PL 174850 B1	30-09-1998
		RU 2105003 C1	20-02-1998
		SK 133794 A3	07-06-1995
		WO 9323384 A1	25-11-1993
		US 5547950 A	20-08-1996
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		ZA 9302855 A	24-10-1994
EP 0878194	A 18-11-1998	AU 713704 B2	09-12-1999
		AU 1556497 A	22-08-1997
		EP 0878194 A1	18-11-1998
		NO 983512 A	30-09-1998
		CA 2245179 A1	07-08-1997
		CN 1214632 A	21-04-1999
		CZ 9802386 A3	16-12-1998
		HU 9901642 A2	28-09-1999
		JP 9323932 A	16-12-1997
		WO 9727856 A1	07-08-1997

Form PCT/IB/210 (patent family search) (July 1999)

PCT

REQUEST

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

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT" International Application

Applicant's or agent's file reference
(if desired) (12 characters maximum) A-153913

Box No. I TITLE OF INVENTION

New derivatives of oxazolidinones as antibacterial agents

Box No. II APPLICANT

☐ This person is also inventor

Name and address: (Family name followed by given names; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

VITA-INVEST, S.A.
Fontsanta 12-14
08970 SANT JOAN DESPI
Spain

Telephone No.

Facsimile No.

Teleprinter No.

Applicant's registration No. with the Office

State (that is, country) of nationality:

Spain

State (that is, country) of residence:

Spain

This person is applicant
for the purposes of:☐ all designated
States☒ all designated States except
the United States of America☐ the United States
of America only☐ the States indicated in
the Supplemental Box

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

Name and address: (Family name followed by given names; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

MOURELLE MANCINI, Marisabel
Av. Xile 28
08028 Barcelona
Spain

This person is:

☐ applicant only☒ applicant and inventor☐ inventor only (if this check-box
is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

Spain

State (that is, country) of residence:

Spain

This person is applicant
for the purposes of:☐ all designated
States☐ all designated States except
the United States of America☒ the United States
of America only☐ the States indicated in
the Supplemental Box☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

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

The person identified below is hereby/has been appointed to act on behalf
of the applicant(s) before the competent International Authorities as:

☒ agent☐ common
representative

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

PONTI SALES, Adelaida
Consell de Cent 322
08007 Barcelona
Spain

Telephone No.

+34 93 488 33 30

Facsimile No.

+34 93 487 80 82

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.

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

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

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. The country of the address indicated in this box is the applicant's State (that is, country) of residence (if no State of residence is indicated below.)

HUGUET CLOTET, Juan
Riera Nofre 11-13
08970 SANT JOAN DESPI
Spain

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

Spain

State (that is, country) of residence:

Spain

This person is applicant for the purposes of:

☐ all designated States☐ all designated States except the United States of America☒ the United States of America only☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence (if no State of residence is indicated below.)

HIDALGO RODRIGUEZ, Jose
Calderon de la Barca 99 Bis 1° 2ª
08914 Badalona
Spain

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

Spain

State (that is, country) of residence:

Spain

This person is applicant for the purposes of:

☐ all designated States☐ all designated States except the United States of America☒ the United States of America only☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence (if no State of residence is indicated below.)

DEL CASTILLO, Juan Carlos
Castillejos 389 1° 1ª
08025 Barcelona
Spain

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

☐ all designated States☐ all designated States except the United States of America☒ the United States of America only☐ the States indicated in the Supplemental Box

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. The country of the address indicated in this box is the applicant's State (that is, country) of residence (if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

☐ all designated States☐ all designated States except the United States of America☐ the United States of America only☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. V DESIGNATION OF STATES

Mark the applicable check-boxes below; at least one must be marked.

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The following designations are hereby made under Rule 4.9(a):

Regional Patent

- ☒ AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT (if other kind of protection or treatment desired, specify on dotted line)
- ☒ EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP European Patent: AT Austria, BE Belgium, CH & LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | | |
|---|--|--|
| ☒ AE United Arab Emirates | ☒ GM Gambia | ☒ NZ New Zealand |
| ☒ AG Antigua and Barbuda | ☒ HR Croatia | ☒ OM Oman |
| ☒ AL Albania | ☒ HU Hungary | ☒ PH Philippines |
| ☒ AM Armenia | ☒ ID Indonesia | ☒ PL Poland |
| ☒ AT Austria | ☒ IL Israel | ☒ PT Portugal |
| ☒ AU Australia | ☒ IN India | ☒ RO Romania |
| ☒ AZ Azerbaijan | ☒ IS Iceland | ☒ RU Russian Federation |
| ☒ BA Bosnia and Herzegovina | ☒ JP Japan | |
| ☒ BB Barbados | ☒ KE Kenya | ☒ SD Sudan |
| ☒ BG Bulgaria | ☒ KG Kyrgyzstan | ☒ SE Sweden |
| ☒ BR Brazil | ☒ KP Democratic People's Republic of Korea | ☒ SG Singapore |
| ☒ BY Belarus | ☒ KR Republic of Korea | ☒ SI Slovenia |
| ☒ BZ Belize | ☒ KZ Kazakhstan | ☒ SK Slovakia |
| ☒ CA Canada | ☒ LC Saint Lucia | ☒ SL Sierra Leone |
| ☒ CH & LI Switzerland and Liechtenstein | ☒ LK Sri Lanka | ☒ TJ Tajikistan |
| ☒ CN China | ☒ LR Liberia | ☒ TM Turkmenistan |
| ☒ CO Colombia | ☒ LS Lesotho | ☒ TN Tunisia |
| ☒ CR Costa Rica | ☒ LT Lithuania | ☒ TR Turkey |
| ☒ CU Cuba | ☒ LU Luxembourg | ☒ TT Trinidad and Tobago |
| ☒ CZ Czech Republic | ☒ LV Latvia | |
| ☒ DE Germany | ☒ MA Morocco | ☒ TZ United Republic of Tanzania |
| ☒ DK Denmark | ☒ MD Republic of Moldova | ☒ UA Ukraine |
| ☒ DM Dominica | | ☒ UG Uganda |
| ☒ DZ Algeria | ☒ MG Madagascar | ☒ US United States of America |
| ☒ EC Ecuador | ☒ MK The former Yugoslav Republic of Macedonia | |
| ☒ EE Estonia | ☒ MN Mongolia | ☒ UZ Uzbekistan |
| ☒ ES Spain | ☒ MW Malawi | ☒ VN Viet Nam |
| ☒ FI Finland | ☒ MX Mexico | ☒ YU Yugoslavia |
| ☒ GB United Kingdom | ☒ MZ Mozambique | ☒ ZA South Africa |
| ☒ GD Grenada | ☒ NO Norway | ☒ ZM Zambia |
| ☒ GE Georgia | | ☒ ZW Zimbabwe |
| ☒ GH Ghana | | |

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

- | | | |
|--------------------------------|--------------------------------|--------------------------------|
| ☐ | ☐ | ☐ |
| ☐ | ☐ | ☐ |

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. 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. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

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Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

- i. *If, in any of the Boxes, except Boxes Nos. VIII(i) to (v) for which a special continuation box is provided, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No. ..." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient. In particular:*
 - (i) *If more than two persons are to be indicated as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence (if no State of residence is indicated below:*

"Continuation of Box n° IV"
TRIBO SEGALÉS, Luis
C. Consell de Cent 322
08007 Barcelona, Spain

Tel: +34 93 488 33 30
Telex: +34 93 487 80 82

PONTI SALES, Ignacio
C. Consell de Cent 322
08007 Barcelona, Spain

Tel: +34 93 488 33 30
Telex: +34 93 487 80 82
 - (ii) *if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be). Indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant:*
 - (iii) *if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be). Indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor:*
 - (iv) *If, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV:*
 - (v) *if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application:*
 - (vi) *if, in Box No. VI, there are more than five earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.*
- ii. *with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of this statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.*

Box No. VI PRIORITY CLAIM

234

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application: regional Office	international application: receiving Office
item (1) 27.08.2001 27 June 01	P-200101559	Spain		
item (2)				
item (3)				
item (4)				
item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office) identified above as:

☐ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box

* Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(II)):

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA / EP

Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year)

Number

Country (or regional Office)

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):

Number of
declarations

☒ Box No. VIII (i)	Declaration as to the identity of the inventor	:	1
☒ Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	:	1
☐ Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	:	
☒ Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)	:	1
☐ Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	:	

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Box No. VIII (i) DECLARATION: IDENTITY OF THE INVENTOR

The declaration must conform to the standardized wording provided for in Section 211; see Notes to Boxes Nos. VIII, VIII (i) to (v) (in general) and the specific Notes to Box No. VIII (i). If this Box is not used, this sheet should not be included in the request.

Declaration as to the identity of the inventor (Rules 4.17(i) and 51bis.1(a)(i)):

Concerning this international application:

i) MOURELLE MANCINI, Marisabel, of Av. Xile 28 08028 Barcelona Spain

HUGUET CLOTET, Juan, of Riera Nofre 11-13 08970 SANT JOAN DESPI Spain

HIDALGO RODRIGUEZ, Jose, of Calderon de la Barca 99 Bis 1º 2º 08914 Badalona Spain

DEL CASTILLO, Juan Carlos of Castillejos 389 1º 1º 08025 Barcelona Spain

are the inventors of the subject matter for which protection is sought by way of this international application.

ii) This declaration is made for the purposes of:

a) All the designations (except the designation of the United States of America)

☐ This declaration is continued on the following sheet, "Continuation of Box No. VIII (i)".

Box No. VIII (II) DECLARATION: ENTITLEMENT TO APPLY FOR AND BE GRANTED A PATENT

The declaration must conform to the standardized wording provided for in Section 212; see Notes to Boxes Nos. VII, VIII (I) to (V) (in general) and the specific Notes to Box No. VIII (II). If this Box is not used, this sheet should not be included in the request.

Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51Aix.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate:

Concerning this international application:

VITA-INVEST, S.A. is entitled to apply for and be granted a patent by virtue of the following:

i) VITA-INVEST, S.A. is entitled as employer of the inventors,

MOURELLE MANCINI, Marisabel

HIDALGO RODRIGUEZ, José

HUGUET CLOTET, Juan

DEL CASTILLO, Juan Carlos

ii) This declaration is made for the purposes of:

a) All designations (except the designation of the United States of America)

☐ This declaration is continued on the following sheet, "Continuation of Box No. VIII (ii)".

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Box No. IX CHECK LIST: LANGUAGE OF FILING

237

This international application contains:

(a) the following number of sheets in paper form:

request (including declaration sheets) : 8
 description (excluding sequence listing part) : 91
 claims : 13
 abstract : 1
 drawings : 1

Sub-total number of sheets : 113

sequence listing part of description (actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below) :

Total number of sheets : 113

(b) sequence listing part of description filed in computer readable form

(i) ☐ only (under Section 801(a)(i))(ii) ☐ in addition to being filed in paper form (under Section 801(a)(ii))

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained (additional copies to be indicated under item 9(ii), in right column):

This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item):

- | | | |
|---|---|---|
| 1. ☒ fee calculation sheet | : | 1 |
| 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. ☒ priority document(s) identified in Box No. VI as item(s): 1 | : | 1 |
| 7. ☐ translation of international application into (language): | : | |
| 8. ☐ separate indications concerning deposited microorganism or other biological material | : | |
| 9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other)) | : | |
| (i) ☐ copy submitted for the purposes of international search under Rule 13 _{ter} only (and not as part of the international application) | : | |
| (ii) ☐ (only where check-box (b)(i) or (b)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13 _{ter} | : | |
| (iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column | : | |
| 10. ☐ other (specify): | : | |

Figure of the drawings which should accompany the abstract: 1

Language of filing of the international application: English

Box No. X 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 request).


 PONTI SALES, Adelaide

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International Application No.

238

Applicant's or agent's
file reference

A-153913

Date stamp of the receiving Office

Applicant

VITA-INVEST, S.A. et al.

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE	CHF 100	T
2. SEARCH FEE	CHF 1460	S
International search to be carried out by <u>EP</u> (If two or more International Searching Authorities are competent to carry out the international search, indicate the name of the Authority which is chosen to carry out the international search.)		
3. INTERNATIONAL FEE		
Basic Fee		
Where item (b) of Box No. IX applies, enter Sub-total number of sheets	113	
Where item (b) of Box No. IX does not apply, enter Total number of sheets		
b1 first 30 sheets	CHF 650	b1
b2 <u>83</u> number of sheets in excess of 30 x <u>15</u> fee per sheet	CHF 1245	b2
b3 additional component (only if sequence listing part of description is filed in computer readable form under Section 801(a)(i), or both in that form and on paper, under Section 801(a)(ii): 400 x _____ fee per sheet		b3
Add amounts entered at b1, b2 and b3 and enter total at B	CHF 1895	B
Designation Fees		
The international application contains <u>93</u> designations.		
<u>5</u> number of designation fees payable (maximum 5) x <u>140</u> amount of designation fee	CHF 840	D
Add amounts entered at B and D and enter total at I	CHF 2735	I
(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)		P
4. FEE FOR PRIORITY DOCUMENT (if applicable)		
5. TOTAL FEES PAYABLE	CHF 4.295	
Add amounts entered at T, S, I and P, and enter total in the TOTAL box	TOTAL	

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

- ☒ authorization to charge deposit account (see below) ☐ postal money order ☐ cash ☐ coupons
☐ cheque ☐ bank draft ☐ revenue stamps ☐ other (specify):

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

(This mode of payment may not be available at all receiving Offices)

- ☒ Authorization to charge the total fees indicated above.
☒ (This check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.
☐ Authorization to charge the fee for priority document.

Receiving Office: RO/ WIPO

Deposit Account No.: 11725

Date: June 20 2002

Name: PONTI SALES, Adelaida

Signature: _____

See Notes to the fee calculation sheet

2877
N

Brigard & Castro
BOGOTA - COLOMBIA

12.24/4 71.143
Coun-Bin 239

PODER

Yo (nosotros)
LABORATORIOS VITA, S.A.
domiciliado(s) en

Avda. de Barcelona, 68
08970 SANT JOAN DESPI (España)

Nombro(amos) a: RAMIRO CASTRO DUQUE y/o HECTOR GOMEZ MEJIA, de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales y enseñas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

A este efecto, lo(s) facuto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistír a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores, dando el descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeran conducentes al resguardo de mis (nuestros intereses), con todas las demás facultades legales necesarias.

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistír, transigir, comprometer, y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a: RAMIRO CASTRO DUQUE y/o HECTOR GOMEZ MEJIA, domiciliado(s) en la Carrera 7 No. 16-58 Piso 9, mis (nuestros) apoderados en Colombia, con facultades para recibir notificaciones y designar apoderados judiciales o extrajudiciales.

Otorgado y firmado en Barcelona

hoy 26 de Mayo de

Firma

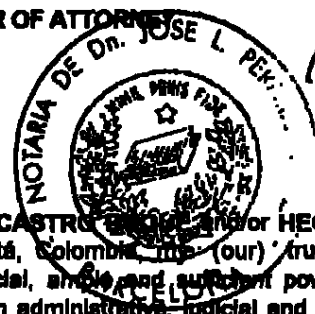
Nombre
Cargo

Santiago Planella, Borl
Consejero-Delegado

I (We)

domiciled in

POWER OF ATTORNEY



Hereby appoint RAMIRO CASTRO DUQUE and/or HECTOR GOMEZ MEJIA, of Bogotá, Colombia, my (our) true and lawful attorneys with special, ample and sufficient power to obtain from the Colombian administrative, judicial and police offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial designs and utility models; registration of commercial names and emblems, registration of copyright and contracts related thereto, certificates of obtainers of vegetable varieties, as well as extensions, renewals and recordal of assignments and changes of name and domicile related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as: oppositions to the registration of trademarks; caducity, cancellation and nullity actions; claim actions derived from the obtaining or exploitation of licenses, action of unfair competition; penal demands, actions of indemnities for damages; claims or observations on patent applications, models, industrial designs and utility models; in the exercise of preventive measures; and in other actions or similar proceedings.

To that effect they hereby empowered to file applications, formulate descriptions, amendments, protests, declarations, oppositions, cancellations, nullities, appeals and claims; to pay taxes, quotas and assessments prescribed by law, renounce or waive the rights granted or in the process of granting; to receive all kinds of documents and valuables, giving the respective release of receipt, and, in general, to take before said authorities the necessary steps to such effect, and any measures that they may deem pertinent to the safeguard of my (our) interest(s) with all the other necessary legal powers.

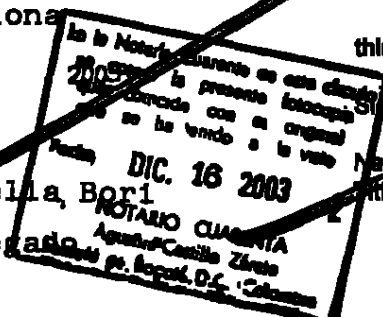
This power includes the faculty to ratify or confirm desist, settle and compromise on my (our) behalf, and to substitute this power in whole or in part and to revoke substitutions. At the same time I (We) hereby appoint RAMIRO CASTRO DUQUE and/or HECTOR GOMEZ MEJIA, domiciled in Carrera 7 No. 16-58, Piso 9, my (our) attorney(s) in fact, with powers to receive notifications and to designate judicial and extra-judicial attorneys.

Granted and signed in

this day of 200_

Signature

Name
Title



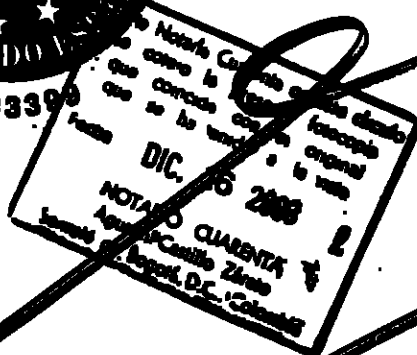
LEGITIMACION. -

Yo, **JOSÉ LUIS PERALES SANZ**, Notario del Ilustre Colegio Notarial de Cataluña, con residencia en Barcelona, DOY FE:

Que legitimo la firma de **DON SANTIAGO PLANELLA BORI**, mayor de edad, provisto de su DNI_NIF., número 46.108.738-V, **CONSEJERO DELEGADO**, de la sociedad "**LABORATORIOS VITA, S.A.**", cargo que ejerce en la actualidad según me consta a mí, el Notario, cuya firma aparece estampada al final del presente documento que consta relacionado en el Acta de Exhibición de Documento con legitimación de firma, por mí el suscrito Notario autorizada en el día de hoy, con el número 1.546 de mi protocolo. -----

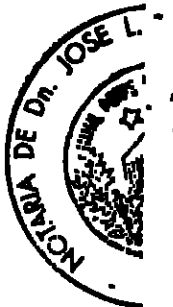
Barcelona, a veintiseis de Mayo de dos mil tres.

SELLO DE
LEGITIMACIONES Y
LEGALIZACIONES

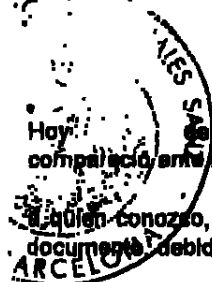


ANOTADO EN EL
LIBRO INDICADOR
TOMO 159
ABRIL 16 2003

[Handwritten signature]



CERTIFICADO NOTARIAL (SOCIEDAD)



Hoy _____ de _____ personalmente
compareció ante mí

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

de _____

Sociedad legalmente constituida para un período de duración
que aún no ha terminado; que el declarante está autorizado
por dicha compañía para conferir este poder; que el sello
estampado por él al ple de tal poder, en nombre y
representación de la expresada compañía, es el sello oficial
de ella; y que el objeto para el cual se confiere este
Instrumento está comprendido dentro del de la sociedad.

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

Estado de _____
con fecha _____

y que quien confiere el presente poder es su representante.

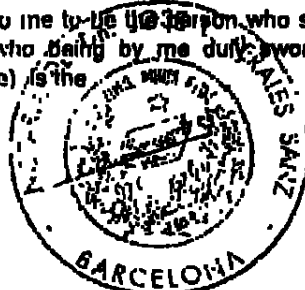
Notario Público (sello)

240
NOTARIAL CERTIFICATE (CORPORATION)

On this _____ day of _____ of _____ personally
appeared before me

to me known, and known to me to be the person who signed
the foregoing instrument who, being by me duly sworn did
depose and say that he (she) is the _____

of _____



Which is legally constituted for a term not yet expired, that
deponent is authorized by said Company to confer this Power
of Attorney: that the seal affixed hereunto by the deponent in
the name and on behalf of said Corporation is the corporate
seal thereof; and that the purpose for which this Instrument is
granted is included within the corporate purpose of company.

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

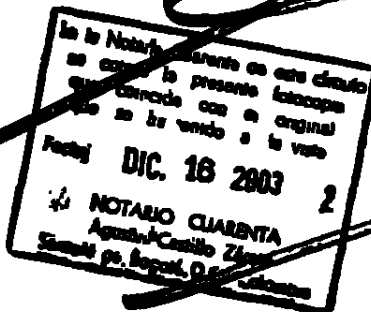
State of _____
under date of _____

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

Public Notary (Seal)

LEGALIZATION BY APOSTILLA IS REQUIRED.

LEGALIZACION POR APOSTILLA ES REQUERIDA.



REQUISITOS NECESARIOS PARA PRESE TRAMITE

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

Firma Responsable:

Edelmi Nacarro

Fecha: 26-12-2003

Français 
1 of 1Images Description and Claims (392 Kb)**(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)****(11) WO 03/002560****(13) A1****(21) PCT/IB02/02408****(22) 24 June 2002 (24.06.2002)****(23) English****(26) English****(30) P 0101559****27 June 2001
(27.06.2001)****ES****(43) 09 January 2003 (09.01.2003)****(51) C07D 413/14, A61K 31/422, A61P 31/04, C07D 471/04****(54) NEW DERIVATIVES OF OXAZOLIDINONES AS ANTIBACTERIAL AGENTS****(71) VITA-INVEST, S.A. [ES/ES]; Fontsaeta, 12-14, E-08970 Sant Joan Despi (ES).****(72) MOURELLE MANCINI, Mariacabel [ES/ES]; Av. Xile, 28, E-08028 Barcelona (ES). HUGUET****(73) CLOTET, Juan [ES/ES]; Riera Nofre, 11-13, E-08970 Sant Joan Despi (ES). HIDALGO RODRIGUEZ, Jose [ES/ES]; Calderon de la Barca, 99 bis 1º 2º, E-08914 Badalona (ES). DEL CASTILLO, Juan Carlos [-/ES]; Castillejos 389 1º 1º, E-08025 Barcelona (ES).****(74) PONTI SALES, Adelaide, et al; Consell de Cent, 322, E-08007 Barcelona (ES).****(81) AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, 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, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW****(84) ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)**For information on time limits for entry into the national phase please click here**Declarations under Rule 4.17**

- *as to the identity of the inventor (Rule 4.17(i)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, 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, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*
- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, 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, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

Published

- *with international search report*

(57) This invention discloses new fluorquinolonic derivatives of oxazolidinones of general formula (I) and processes for obtaining them, the corresponding pharmaceutical compositions and use thereof for manufacturing a medicament for the treatment of microbial infections. These new compounds are useful as antibacterial agents. Formula (I). Furthermore phenalen-type compounds according to general formula (II) are disclosed. Formula (II).

PETITORIO

AS: 92.515

Industria y Comercio 03 112619 00
SUPERINTENDENCIA

Radicación 03-112619
Fecha 26-12-03

SUPERINTENDENCIA Y COMERCIO
Radicación: 03112619 00000000
Fecha (IMP): 2003-12-26 16:29:59
Trámite: 011 PCT-PATENT 279 FASE NACI 411 PRESENTAC
Dependencia: 2129 DIVISION DE MARCAS Y DISEÑOS

Folios: 241

243

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE PCT

Fecha ENTRADA EN FASE NACIONAL 27-01-2004

1 SOLICITUD DE:			
☒ Patente de Invención.		☐ Patente de Modelo de Utilidad.	
☐ Capítulo I.		☒ Capítulo II.	
2 SOLICITANTE (71)	Nombre: LABORATORIOS VITA, S.A. Dirección: Av. De Barcelona, 69, E-08970 Sant Joan Despi, Barcelona, España Nacionalidad o Domicilio: España Lugar de Constitución: España Teléfono: Fax: E-mail:		IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número _____
3 REPRESENTANTE O APODERADO	Nombre: RAMIRO CASTRO DUQUE Dirección: Cra. 7 No. 16-56 Piso 9 Teléfono: 380-2200 Fax: 380-2700 E-mail:		IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número <u>170.322 TP 1003</u>
4 INVENTOR (ES) (72)	Nombre: Marisabel Mourelle Mancini, Juan Huguet Clotet, Jose Hidalgo Rodriguez, Juan Carlos Del Castillo Dirección: Av. Xile, 28, E-08028, Barcelona, ES; Riera Nofre, 11-13, E-08970 Sant Joan Despi, ES; Calderón de la Barca, 99 bis 1º 2º, E-08914 Badalona, ES; Castillejos 389 1º 1ª, E-08025 Barcelona, ESPAÑA (Respectivamente) Nacionalidad o Domicilio: ESPAÑA		
5 PCT (86) Solicitud Internacional No. <u>PCT/IB02/02408</u> Fecha <u>24-08-2002</u> Publicación Internacional No. <u>WO 03/002560 A1</u> Fecha <u>09-01-2003</u>			
6 Título (54): <u>NUEVOS DERIVADOS DE OXAZOLIDINONAS COMO ANTIBACTERIANOS</u>			
7 Clasificación Internacional (51) <u>A61K31/412, A61P31/04</u>			
8 Prioridad	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
SI ☒ NO ☐	<u>ES</u>	<u>27-08-2001</u>	<u>P 0101559</u>

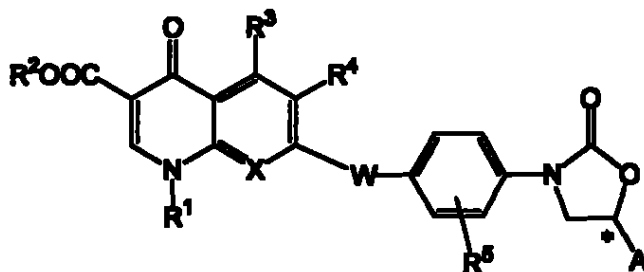
Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

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REIVINDICACIONES

1. Compuesto de fórmula general (I):

5



(I)

10 donde:

X: CR⁶ ó N;

R¹: alquilo C₁-C₄, cicloalquilo C₃-C₆, alquenilo C₂-
15 C₄, 2-hidroxietilo, 2-fluoroetilo, ó fenilo opcionalmente
sustituido por 1 ó 2 átomos de flúor;

R²: H, alquilo C₁-C₄ o fenilo;

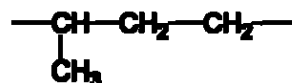
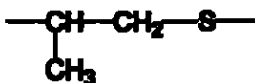
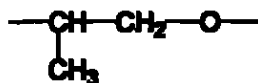
20 R³: H, halógeno, alquilo C₁-C₄, ó alcoxi C₁-C₄,
amino;

R⁴: H ó halógeno;

25 R⁶: H, halógeno, alquilo C₁-C₄, haloalcoxi C₁-C₄, o
bien R¹ y R⁶ juntos forman un puente de estructura

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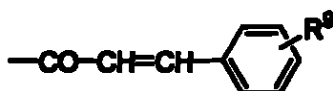
R^5 : H, halógeno, OCH_3 , alcoxi $\text{C}_1\text{--C}_4$, alquilo $\text{C}_1\text{--C}_4$, o haloalquilo $\text{C}_1\text{--C}_4$;

5

A: $-\text{CH}_2\text{---NH---R}^7$, $-\text{CHOH---C}\equiv\text{CH}$;

donde

10 R^7 : isoxazol, $-\text{CO---R}^8$, $-\text{CS---R}^8$, $-\text{CS---OR}^8$, $-\text{COOR}^8$, $-\text{CONHR}^8$, $-\text{CSNHR}^8$, $-\text{SO}_2\text{---R}^8$ o



15

donde

R^8 : alquilo $\text{C}_1\text{--C}_4$, haloalquilo $\text{C}_1\text{--C}_4$, alquenilo $\text{C}_2\text{--C}_4$, arilo, alquilo $\text{C}_1\text{--C}_4$ sustituido por un grupo alcoxi $\text{C}_1\text{--C}_4$, carboxialquilo $\text{C}_1\text{--C}_4$, ciano, o amino;

20

R^9 : H, alquilo $\text{C}_1\text{--C}_4$, alquenilo $\text{C}_2\text{--C}_4$, OH, alcoxi $\text{C}_1\text{--C}_4$, $\text{NR}^{12}\text{R}^{13}$, NO_2 , halógeno, ó CO---R^{12} ;

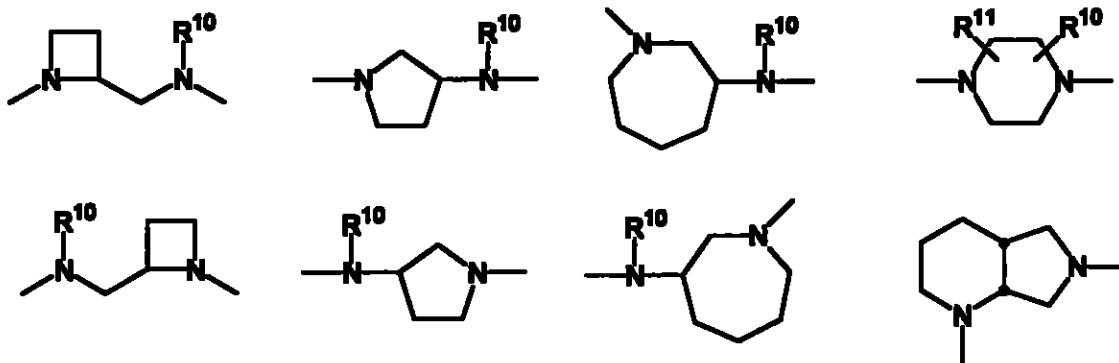
R^{12} y R^{13} : independientemente, H o alquilo $\text{C}_1\text{--C}_4$;

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W:

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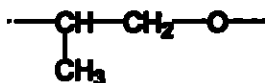


dónde

R¹⁰ y R¹¹ son independientemente H, o alquilo C₁-C₄;

5 una sal o un solvato farmacéuticamente aceptable, o cualquier isómero geométrico, isómero óptico o mezcla de isómeros del mismo en cualquier proporción o polimorfo del mismo.

10 2. Compuesto según la reivindicación 1, caracterizado por el hecho de que R¹ es ciclopropilo, etilo, 2-fluoroetilo, fenilo o difluorofenilo, o bien R¹ y R⁶ juntos forman un puente de estructura:



15

3. Compuesto según la reivindicación 1, caracterizado por el hecho de que R⁶ es H, CH₃, OCH₃, OCHF₂, F o Cl.

20

4. Compuesto según la reivindicación 3, caracterizado por el hecho de que R⁶ es H o F.

5. Compuesto según la reivindicación 1, caracterizado por el hecho de que R⁴ es F o Cl y R³ es H.

25



2020
Bogotá, D.C.,

01638

Doctor:
RAMIRO CASTRO DUQUE
Apoderado
LABORATORIOS VITA, S.A.

Oficio N°

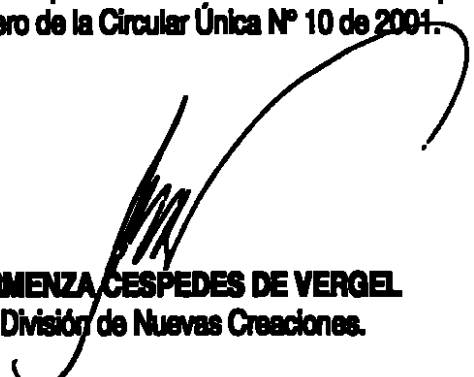
ASUNTO:	Radicación N°	03-112619
	Solicitud Internacional	PCT/IB02/02408
	Fecha inicio fase nacional	21/01/2004
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

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

- ☐ La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486).
- ☐ El solicitante ante la oficina Internacional, es diferente al solicitante ante la oficina nacional. Anexar documentos para aclarar.

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 CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

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

13 FEB. 2004