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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 471/04	A1	(11) International Publication Number: WO 95/15965
		(43) International Publication Date: 15 June 1995 (15.06.95)

(21) International Application Number: PCT/KR94/00175

(22) International Filing Date: 9 December 1994 (09.12.94)

(30) Priority Data:
1993/27071 9 December 1993 (09.12.93) KR

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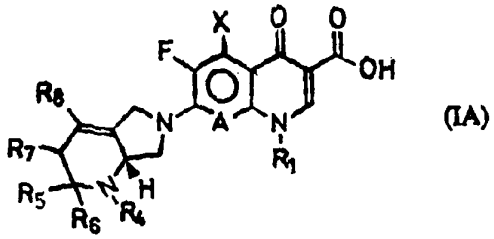
(81) Designated States: AU, CA, JP, NZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: NOVEL QUINOLONE COMPOUNDS AND PROCESSES FOR THE PREPARATION THEREOF



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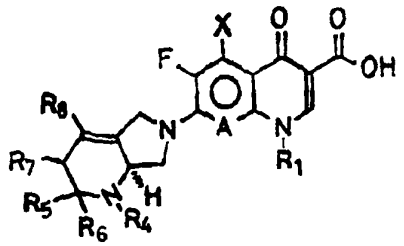

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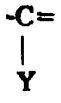
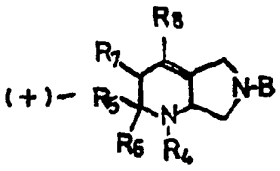
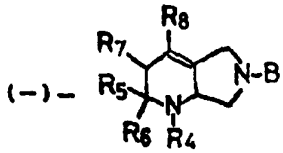


(a)



(Ia)



(Ia')

(57) Abstract

The present invention relates to optical isomers of quinoline compounds of Formula (IA') and their pharmaceutically acceptable salts. In the above formulae, A represent nitrogen or (a), in which Y represents hydrogen, halogen, lower alkyl or lower alkoxy, or together with R_1 forms $-CH_2CH_2CH_2-$, $-CH_2CH_2CH(CH_3)-$, $-OCH_2CH_2-$, $-OCH_2CH(CH_3)-$, $-SCH_2CH_2-$ or $-SCH_2CH(CH_3)-$; R_1 is as defined above or represents an alkyl group having 1 to 3 carbon atoms, which is optionally substituted with a halogen atom, or a cyclopropyl group, which is optionally substituted with a halogen atom, a phenyl group, which is optionally substituted with one or two halogen atoms; R_4 represents hydrogen, a lower alkyl, a lower alkoxy, or an amino-protecting group; R_5, R_6, R_7 and R_8 may be the same or different and represent independently hydrogen, lower alkyl optionally substituted by amino, hydroxy or halogen; and X represents hydrogen, halogen, amino or lower alkyl. The present invention also relates to optical isomers of compounds of Formula (Ia) and Formula (Ia'), wherein, R_4, R_5, R_6, R_7 and R_8 are the same as defined above, and B is hydrogen or an amino-protecting group.

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Novel Quinolone Compounds and Processes for the Preparation Thereof

Technical Field

The present invention relates to novel quinolone compounds, pharmaceutically acceptable salts and optical isomers thereof which possess a broad antibacterial spectrum and exhibit strong antibacterial activity and to processes for preparing these quinolone compounds.

The present invention also relates to optical isomers of diazabicycloalkene derivatives, which may be introduced to the above quinoline compounds, and to processes for preparing the diazabicycloalkene derivatives.

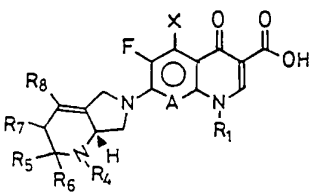
Background Art

Representatives of the commercially available quinolone antibacterial agents include enoxacin, norfloxacin, ofloxacin, ciprofloxacin and tosufloxacin. However, it is generally known that these quinolone antibacterials exhibit relatively weak antibacterial activity against *Gram-positive* bacteria. Furthermore, quinolone-resistant strains have been frequently reported.

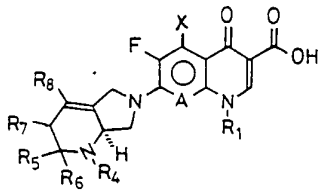
Thus, there is still a need for the development of quinolone antibacterials which not only show a broad antibacterial spectrum but also exert strong antibacterial activity against Gram positive strains, methicillin-resistant staphylococcus and the quinolone-resistant strains. This need is met by the present invention.

Disclosure of Invention

An object of the present invention is to provide optical isomers of quinoline compounds of Formula (IA) or Formula (IA') and their pharmaceutically acceptable salts.



(IA)



(IA')

In the above formulae,

A represent nitrogen or -C=,
|
Y

in which Y represents hydrogen, halogen, lower alkyl or lower alkoxy, or together with R_1 forms $-CH_2CH_2CH_2-$, $-CH_2CH_2CH(CH_3)-$, $-OCH_2CH_2-$, $-OCH_2CH(CH_3)-$, $-SCH_2CH_2-$ or $-SCH_2CH(CH_3)-$;

R_1 is as defined above or represents an alkyl group having 1 to 3 carbon atoms, which is optionally substituted with a halogen atom, or a cyclopropyl group, which is optionally substituted with a halogen atom, a phenyl group, which is optionally substituted with one or two halogen atoms;

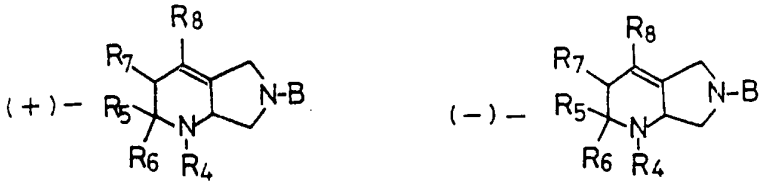
R_4 represents hydrogen, a lower alkyl, a lower alkoxy, or an amino-protecting group;

R_5, R_6, R_7 and R_8 may be the same or different and represent independently hydrogen, lower alkyl optionally substituted by amino, hydroxy or halogen; and

X represents hydrogen, halogen, amino or lower alkyl.

Lower alkyl is preferably C_{1-6} alkyl, more preferably C_{1-4}, such as methyl or ethyl. Lower alkoxy is preferably C_{1-6} alkoxy, more preferably C_{1-4} alkoxy, such as methoxy. Halogen is preferably fluorine or chlorine. Preferred amino-protecting group is t-butoxycarbonyl. An example of substituted phenyl is 2, 4-difluorophenyl.

Another object of the present invention is to provide optical isomers represented by Formula (Ia) or (Ia'):



(Ia) (Ia')

wherein, R_4, R_5, R_6, R_7 and R_8 are the same as defined above, and B is hydrogen or an amino-protecting group.

An example of an amino-protecting group for B is t-butoxycarboxyl.

Preferred compounds of Formula (IA) or (IA') of the present invention which show strong antibacterial activity and possess a broad antibacterial spectrum are:

1-cyclopropyl-6-fluoro-7-(((+)-2,8-diazabicyclo[4.3.0]non-5-en)-8-yl)-8-methoxy-1,4-dihydro-4-oxo-3-quinoline carboxylic acid;

1-cyclopropyl-6-fluoro-7-(((-)-2,8-diazabicyclo[4.3.0]non-5-en)-8-yl)-8-methoxy-1,4-dihydro-4-oxo-3-quinoline carboxylic acid;

1-cyclopropyl-6-fluoro-7-(((+)-2,8-diazabicyclo[4.3.0]non-5-en)-8-yl)-8-chloro-1,4-dihydro-4-oxo-3-quinoline carboxylic acid;

1-cyclopropyl-5-amino-6,8-difluoro-7-(((+)-2,8-diazabicyclo[4.3.0]non-5-en)-8-yl)-1,4-dihydro-4-oxo-3-quinoline carboxylic acid;

9-fluoro-3-(S)-methyl-10-((+)-2,8-diazabicyclo[4.3.0]non-5-en-8-yl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de]-[1,4]-benzoxazin-6-carboxylic acid; and

pharmaceutically acceptable salts thereof.

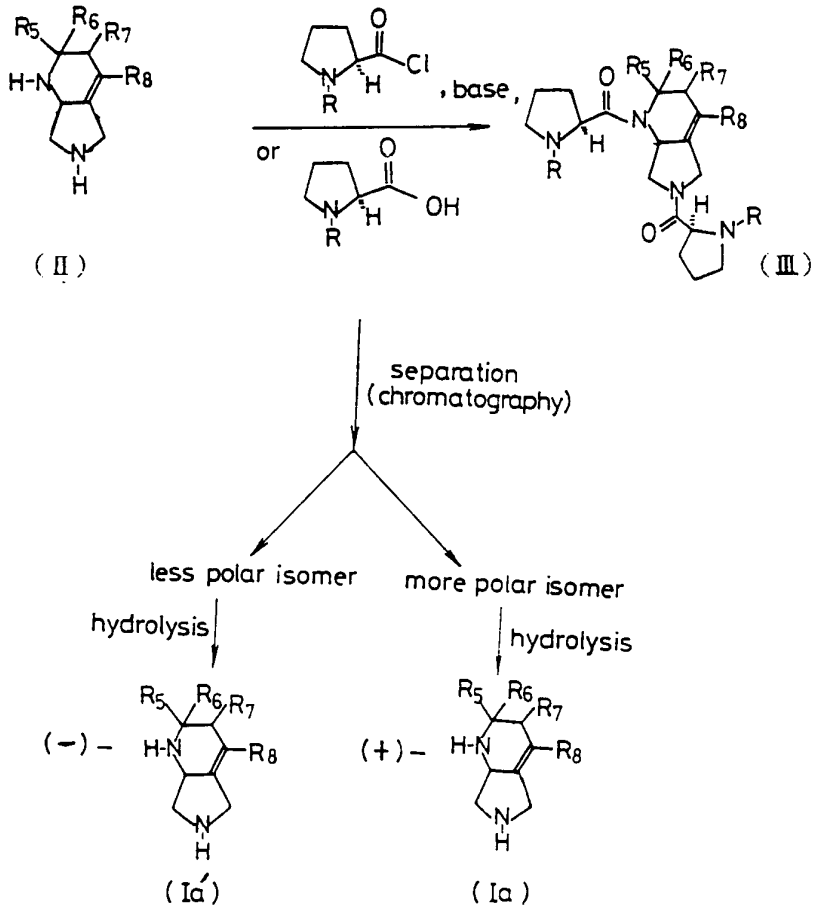
Preferred compounds of Formula (Ia) or (Ia') of the present invention are:

(+)-2,8-diazabicyclo[4.3.0]non-5-ene and

(-)-2,8-diazabicyclo[4.3.0]non-5-ene.

An optical isomer may be present in admixture with up to 45% by weight of the opposite isomer. Preferably, the isomer of a compound of formula (IA), (IA'), (Ia) or (Ia') is in a form containing from 0 to 40%, 0 to 30%, 0 to 20% or 0 to 10% of the opposite isomer. More preferably, the isomer is in a form containing 0 to 5% of the opposite isomer. Most preferably, the isomer is in a form containing 0% or no detectable amount of the opposite isomer. All percentages hereinbefore are percentages of the mixture by weight. The presence of isomers may for example be routinely detected by the comparison of the optical rotation of a sample of the isomeric mixture with that of a pure sample of the desired isomer, by the ^1H nmr spectrum of a sample of the isomeric mixture in the presence of a chiral shift reagent or chiral solvating agent, or by the use of chiral high performance liquid chromatography.

Compounds of Formula (Ia) and (Ia') of the present invention may be prepared by the process illustrated below.

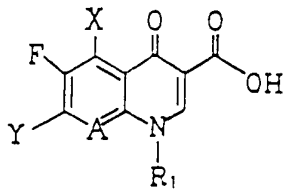


wherein, R_5, R_6, R_7 and R_8 are the same as defined above, and R represents an amino-protecting group such as toluenesulfonyl or t-butoxycarbonyl.

According to the above process, compound (II) is reacted with N-protected-L-prolyl chloride in an organic solvent such as methylene chloride or chloroform or in a mixture of water and the said organic solvents in the presence of an organic base such as triethylamine, DBU (1.8-Diazabicyclo[5.4.0]undec-7-ene) and DBN (1.5-Diazabicyclo[4.3.0]non-5-ene) or an inorganic base such as sodium bicarbonate or sodium carbonate at -20°C to 30°C to give Compound (III). Compound (III) may also be prepared by reacting Compound (II) with N-protected L-proline in a solvent such as DMF (N.N-Dimethylformamide), DMSO (Dimethyl Sulfoxide), acetonitrile or chloroform in the presence of an organic or inorganic base such as triethylamine, DBU or DBN and an acid activator which does not tend to promote amino acid racemisation, such as used in standard peptide synthesis, for example, dicyclohexyl carbodiimide. Compound (III) is subjected to column chromatography and optionally acid-catalized hydrolysis to obtain Compound (Ia) and Compound (Ia'). Examples of N-protecting groups include tosyl.

Compounds of Formula (IA) or Formula (IA') of the present invention may be prepared, using the compounds of Formula (Ia) or (Ia') above, by the process similar to processes described in Korean Patent Application No. 91-25883 and EP 622367A1.

In particular, a compound of Formula (IA) or Formula (IA') may be prepared by condensing a compound of Formula (Ia) or (Ia') with a compound of Formula (III) below.

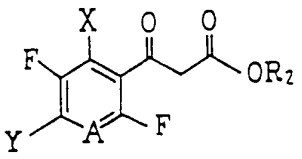


(III)

In the above formulae, R_1, A and X are the same as defined above and Y is a halogen atom or a mesyl or a tosyl group.

Compound of Formula (IA) or (IA') may also be prepared by reacting a compound of Formula (Ia) or (Ia') with a compound of Formula (IV) to obtain a compound of

Formula (V) or (V'); optionally heating under reflux said compound of Formula (V) or (V') with ethyl orthoformate and acetic anhydride; condensing said compound of Formula (V) or (V') with a compound of Formula (VI) to obtain a compound of Formula (VII) or (VII'); cyclizing said compound of Formula (VII) or (VII') to obtain a compound of Formula (VIII) or (VIII'); and hydrolyzing said compound of Formula (VIII) or (VIII') thereby to obtain the compound of formula (IA) or (IA').



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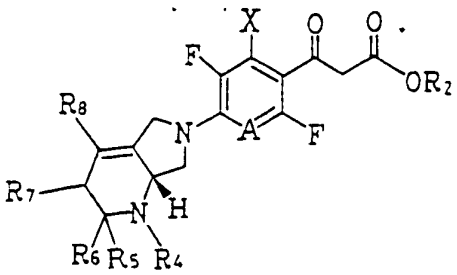

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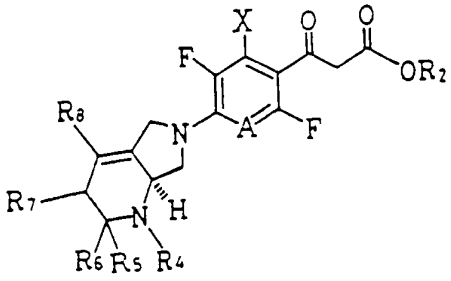
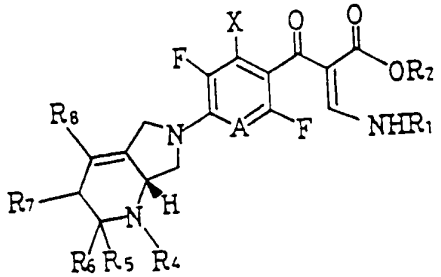


(V') R_1NH_2

(VI)



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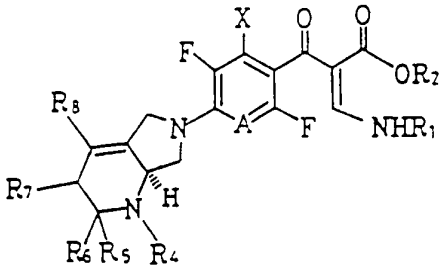

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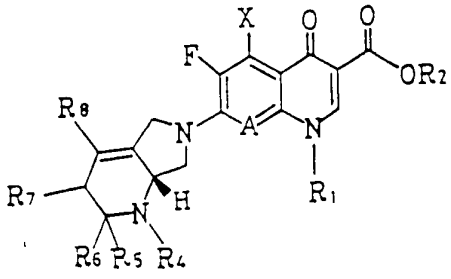

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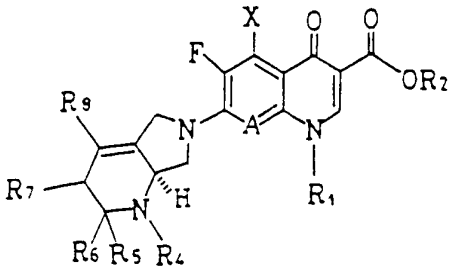


(VIII')

In the above formulae, R_1, R_4, R_5, R_6, R_7, R_8, X, Y and A are the same as defined above ; and R_2 is hydrogen atom or a lower alkyl group.

The following examples are intended to further explain the present invention, without limiting the scope of the invention.

Example 1: Preparation of (+)-2,8-diazabicyclo[4.3.0]non-5-ene dihydrogen chloride

Step (1): Preparation of N,N'-di-(N-tosyl-L-prolyl)-2,8-diazabicyclo[4.3.0]non-5-ene

4.8g of 2,8-diazabicyclo[4.3.0]non-5-ene dihydrogen chloride and 13.5ml of triethylamine were added to 100ml of chloroform and the reaction mixture was stirred for 5 min. 14.0g of N-tosyl-L-prolyl chloride in 100ml of chloroform was added to the reaction mixture under cold temperature (below 0°C) and the resulting reaction mixture was stirred for 3 hours at room temperature. The reaction mixture was diluted with 200ml of chloroform, washed with 5% $NaHCO_3$ solution, next with 1N-HCl, and subsequently with NaCl solution, and dried with anhydrous magnesium sulfate. After evaporating the solvent under reduced pressure, the residue was subjected to silica gel column chromatography (ethyl acetate:methanol(v/v) = 20:1) to obtain 6.6g of more polar optical isomer of N,N'-di-(N-tosyl-L-prolyl)-2,8-diazabicyclo[4.3.0]non-5-ene and 5.79g of less polar optical isomer of N,N'-di-(N-tosyl-L-prolyl)-2,8-diazabicyclo[4.3.0]non-5-ene.

more polar optical isomer: $[\alpha]^{20}_D$ = -3.4° (c=1.0, CH_3CH_2OH)

^{1}H-NMR($CDCl_3$,δ); 1.7~2.35(9H, m), 2.45(3H, s), 2.52(3H, s), 3.25~3.60(6H, m), 3.52(1H, m), 3.29(1H, d), 4.13(1H,d), 4.33(1H, t), 4.40(1H, t), 4.60(2H, m), 5.95(2H, br, s), 7.30(4H, dxd), 7.72(4H, dxd)

less polar optical isomer:$[\alpha]^{20}_D$ = -236.7° (c=1.0, CH_3CH_2OH)

^{1}H-NMR($CDCl_3$,δ); 1.61(1H, m), 1.8~2.2(9H, m), 2.30~2.42(6H, dxd), 3.0~3.55(6H, m), 3.9~4.35(3H, m), 4.40~5.0(4H,m), 6.0(1H, m), 7.30(4H, m), 7.75(4H, m)

Step (2): Preparation of (+)-N,N'-di-t-butoxycarbonyl-2,8-diazabicyclo[4.3.0]non-5-ene

To 20ml of ethanol and 100ml of 8N-HCl solution was added 7.02g of the more polar optical isomer of N,N'-di-(N-tosyl-L-prolyl)-2,8-diazabicyclo[4.3.0]non-5-ene and the reaction mixture was stirred for 3 hours under reflux. The resulting reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. To the residue were added 100ml of methanol and 12.5ml of triethylamine and the resulting mixture was stirred for 10 min. 9.8g of di-t-butyldicarbonate was added to the reaction mixture and stirred for 10 hours at room temperature. The reaction solvent was evaporated under reduced pressure. The residue was dissolved in 100ml of chloroform, washed with water, next with 5% acetic acid and subsequently with NaCl solution, and dried with anhydrous magnesium sulfate. The solovent was evaporated under reduced pressure and the residue was subjected to silica gel column chromatography (ethyl acetate:hexane (v/v) = 6:1) to obtain 3.0g of desired compound (yield: 83%).

^{1}H-NMR($CDCl_3$,δ); 1.45(9H, s), 1.47(9H, s), 2.15(2H, m), 2.8~2.9(2H,m), 3.9(3H, t), 4.05(1H, t), 4.3~4.4(1H, m), 5.85(1H, br,s)

$[\alpha]^{20}_D$ = + 179° (c=1.0, MeOH)

Step (3): Preparation of (+)-2,8-diazabicyclo[4.3.0]non-5-ene dihydrogen chloride

3.02g of (+)-N,N'-di-t-butoxycarbonyl-2,8-diazabicyclo[4.3.0]non-5-ene was dissolved in 18ml of 8% HCl-methanol solution and stirred for 12 hours at room temperature. The solvent was evaporated under reduced pressure and the 5ml of ethanol was added to the residue and stirred to give white solid product. The white solid was filtered, washed with a mixture of ethanol and ethyl ether and dried under reduced pressure to give 1.26g of desired white solid product (yield: 69%).

^{1}H-NMR(D_2O, δ); 2.4(2H, m), 3.1~3.3(2H, m), 3.5~3.65(1H, m), 3.8~4.1(3H,m), 4.2~4.4(1H, m), 6.05(1H, br, s)

$[\alpha]^{20}_D$ = + 1.4° (c=27.2, H_2O)

Example 2: Preparation of (-)-2,8-diazabicyclo[4.3.0]non-5-ene dihydrogen chloride

7.2g of the less polar optical isomer of N,N'-di-(N-tosyl-L-prolyl)-2,8-diazabicyclo[4.3.0]non-5-ene was treated by the process described in Steps (2) and (3) of Example 1 to give 1.14g of desired compound.

$[\alpha]^{20}_D$ = - 1.4° (c=27.2, H_2O)

Example 3: Preparation of 1-cyclopropyl-6-fluoro-7-(((+)-2,8-diazabicyclo[4.3.0]non-5-en)-8-yl)-8-methoxy-1,4-dihydro-4-oxo-3-quinoline carboxylic acid

195mg of (+)-2,8-diazabicyclo[4.3.0]non-5-ene dihydrogen chloride, 457mg of DBU and 295mg of 1-cyclopropyl-6,7-difluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinoline carboxylic acid were added to 2.5ml of acetonitrile and stirred for 10 hours under reflux. The reaction mixture was cooled to room temperature to result in solid products. The resulting solid product was filtered, washed with 3ml of acetonitrile and dried under reduced pressure to give 312mg of desired white solid product.

^{1}H-NMR($CDCl_3$,δ); 1.16(4H, m), 2.11(1H, m), 2.70~4.20(7H, m), 4.02(3H, s), 4.65(1H, d), 5.70(1H, s), 7.84(1H, d), 8.80(1H, s)

Example 4: Preparation of 1-cyclopropyl-6-fluoro-7-(((-)-2,8-diazabicyclo[4.3.0]-non-5-en)-8-yl)-8-methoxy-1,4-dihydro-4-oxo-3-quinoline carboxylic acid

195mg of (-)-2,8-diazabicyclo[4.3.0]non-5-ene dihydrogen chloride was treated by the process described in Example 3 to give 296mg of desired compound.

Example 5: Preparation of 1-cyclopropyl-6-fluoro-7-(((+)-2,8-diazabicyclo[4.3.0]non-5-en)-8-yl)-8-chloro-1,4-dihydro-4-oxo-3-quinoline carboxylic acid

195mg of (+)-2,8-diazabicyclo[4.3.0]non-5-ene dihydrogen chloride and 299.5mg of 1-cyclopropyl-6,7-difluoro-8-chloro-1,4-dihydro-4-oxo-3-quinoline carboxylic acid were treated by the process described in Example 3 to give 346mg of desired compound.

^{1}H-NMR($CDCl_3$,δ); 1.20(4H, m), 2.10(1H, m), 2.30(1H, m), 2.65~4,10(7H, m), 4.93(1H, m), 5.10(1H, m), 5.63(1H, m), 7.56(1H, d), 8.61(1H, s)

Example 6: Preparation of 1-cyclopropyl-5-amino-6,8-difluoro-7-(((+)-2,8-diazabicyclo[4.3.0]non-5-en)-8-yl)-1,4-dihydro-4-oxo-3-quinoline carboxylic acid

195mg of (+)-2,8-diazabicyclo[4.3.0]non-5-ene dihydrogen chloride and 298mg of 1-cyclopropyl-5-amino-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid were treated by the process described in Example 3 to give 298mg of desired compound.

^{1}H-NMR($CDCl_3$,δ); 1.15(4H, m), 2.1(1H, m), 2.3(1H, m), 2.95(1H, m), 3.2~4.0(6H, m), 4.65(1H, d), 5.75(1H, s), 8.90(1H,s)

Example 7: Preparation of 9-fluoro-3-(S)-methyl-10-(((+)-2,8-diazabicyclo[4.3.0]non-5-en)-8-yl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de]-[1,4]-benzoxazin-6-carboxylic acid

200mg of (+)-2,8-diazabicyclo[4.3.0]non-5-ene dihydrogen chloride and 280mg of 9,10-difluoro-3-(S)-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de]-[1,4]-benzoxazin-6-carboxylic acid were treated by the process described in Example 3 to give 250mg of desired compound.

^{1}H-NMR($CDCl_3$,δ); 1.5(3H, d), 2.0(1H, m), 2.85(1H, m), 3.15(1H, m), 3.3~3.6(4H, m), 3.7(1H, m), 3.9(2H, m), 4.2~4.65(4H, m), 5.65(1H, br, s), 7.55(1H, d) 8.5(1H,s)

In vitro antibacterial activity test

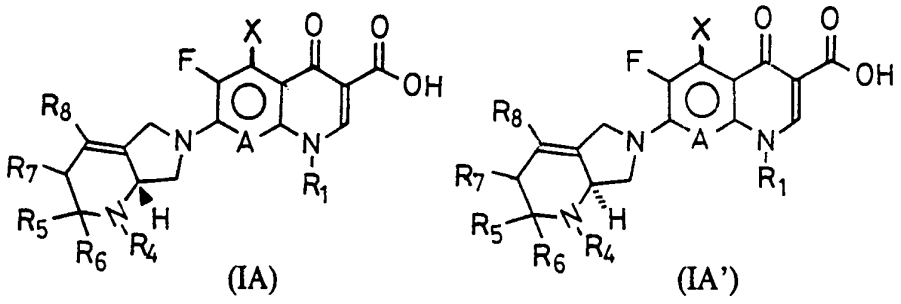
The antibacterial activity of the compounds of the present invention was demonstrated in Table 1. The antibacterial activity was determined in accordance with the agar culture medium two-fold dilution method (Hoechst 345) by using a Muller-Hinton agar medium. Hoechst standard strains were used as the test strains. The strains having 10^7 CFU/ml were inoculated on the culture medium, and the growth of the strains was observed after incubating them at 37°C for 18 hours, in which ciprofloxacin was used as a control material.

Table 1

Strain / Substance	Ex. 3	Ex. 4	Ex. 5	Ex. 6	Ex. 7	ciprof.
Streptococcus pyogenes 308A	0.195	0.781	0.195	0.098	0.781	3.125
Streptococcus pyogenes 77A	0.098	0.391	0.098	0.098	0.195	0.781
Streptococcus faecium MD8b	0.098	0.195	0.098	0.049	0.195	0.781
Staphylococcus aureus SG511	0.025	0.098	0.025	0.007	0.098	0.195
Staphylococcus aureus 285	0.025	0.098	0.025	0.013	0.195	0.391
Staphylococcus aureus 503	0.013	0.049	0.025	0.004	0.098	0.781
Escherichia coli 0 78	0.004	0.025	0.007	<0.002	0.025	<0.002
Escherichia coil DC 0	0.195	1.563	0.195	0.098	0.391	0.195
Escherichia coil DC 2	0.025	0.098	0.025	0.025	0.098	0.098
Escherichia coil TEM	0.013	0.049	0.013	<0.002	0.049	0.007
Escherichia coil 1507E	0.013	0.098	0.013	0.004	0.049	0.007
Pseudomonas aeruginosa 9027	1.563	3.125	0.781	0.781	0.781	0.391
Pseudomonas aeruginosa 1592E	0.781	1.563	0.391	0.391	0.391	0.195
Pseudomonas aeruginosa 1771	0.781	1.563	0.391	0.391	0.781	0.195
Pseudomonas aeruginosa 1771M	0.195	0.781	0.195	0.098	0.195	0.049
Salmonella typhimurium	0.007	0.049	0.007	0.004	0.025	0.007
Klebsiella aerogenes 1082E	<0.002	0.007	<0.002	0.007	0.013	<0.002
Klebsiella aerogenes 1552E	0.025	0.098	0.013	0.007	0.098	0.013
Enterobacter cloacae P 99	0.004	0.025	0.007	<0.002	0.049	0.007
nterobacter cloacae 1321E	0.004	0.025	0.004	<0.002	0.025	<0.002

What is claimed is:

1. Compounds of formula (IA) OR (IA'):



(IA) (IA')

wherein,

A represent nitrogen or -C=,

|

Y

in which Y represents hydrogen, halogen, lower alkyl or lower alkoxy, or together with R_1 forms $-CH_2CH_2CH_2-$, $-CH_2CH_2CH(CH_3)-$, $-OCH_2CH_2-$, $-OCH_2CH(CH_3)-$, $-SCH_2CH_2-$ or $-SCH_2CH(CH_3)-$;

R_1 is as defined above or represents an alkyl group having 1 to 3 carbon atoms, which is optionally substituted with a halogen atom, or a cyclopropyl group, which is optionally substituted with a halogen atom, a phenyl group, which is optionally substituted with one or two halogen atoms;

R_4 represents hydrogen, a lower alkyl, a lower alkoxy, or an amino-protecting group;

R_5, R_6, R_7 and R_8 may be the same or different and represent independently hydrogen, lower alkyl optionally substituted by amino, hydroxy or halogen;

X represents hydrogen, halogen, amino or lower alkyl; and

pharmaceutically acceptable salts thereof.

2. A compound of Claim 1, wherein the compound of Formula (IA) or (IA') is as follows:

1-cyclopropyl-6-fluoro-7-(((+)-2,8-diazabicyclo[4.3.0]non-5-en)-8-yl)-8-methoxy-1,4-dihydro-4-oxo-3-quinoline carboxylic acid;

1-cyclopropyl-6-fluoro-7-(((-)-2,8-diazabicyclo[4.3.0]non-5-en)-8-yl)-8-methoxy-1,4-dihydro-4-oxo-3-quinoline carboxylic acid;

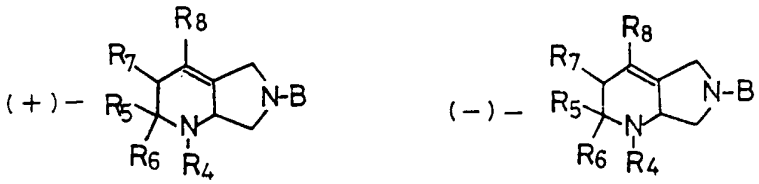
1-cyclopropyl-6-fluoro-7-(((+)-2,8-diazabicyclo[4.3.0]non-5-en)-8-yl)-8-chloro-1,4-dihydro-4-oxo-3-quinoline carboxylic acid;

1-cyclopropyl-5-amino-6,8-difluoro-7-(((+)-2,8-diazabicyclo[4.3.0]non-5-en)-8-yl)-1,4-dihydro-4-oxo-3-quinoline carboxylic acid;

9-fluoro-3-(S)-methyl-10-((+)-2,8-diazabicyclo[4.3.0]non-5-en-8-yl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de]-[1,4]-benzoxazin-6-carboxylic acid; and

pharmaceutically acceptable salts thereof.

3. Compounds of Formla (Ia) or (Ia'):



(Ia) (Ia')

wherein, R_4, R_5, R_6, R_7 and R_8 are the same as defined in Claim 1, and B is hydrogen or an amino-protecting group.

4. A compound of Claim 3, wherein the compound of Formula (Ia) or (Ia') is as follows:

(+)-2,8-diazabicyclo[4.3.0]non-5-ene;

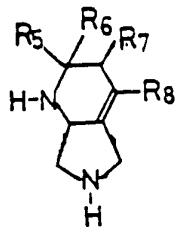
(-)-2,8-diazabicyclo[4.3.0]non-5-ene.

5. A process for preparing compounds of Formula (Ia) or (Ia') which

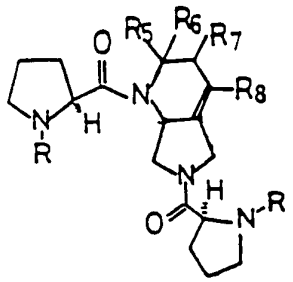
comprises,

(a) reacting the compound (II) with N-protected-L-prolyl chloride in an organic solvent or a mixture of said organic solvent and water in the presence of an organic or inorganic base to give the compound of Formula (III); and

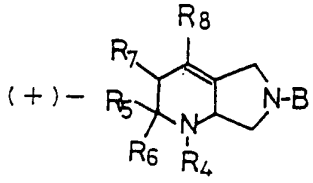
(b) conducting column chromatography, optionally followed by acid-catalized hydrolysis to give the compound (Ia) or (Ia'):



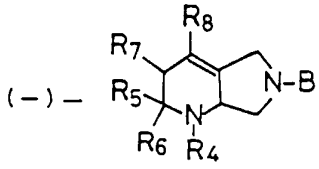
(II)



(III)



(Ia)



(Ia')

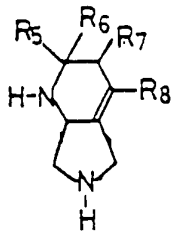
wherein, R_4, R_5, R_6, R_7, R_8 and B are the same as defined in Claim 3, and R is an amino-protecting group.

6. A process for preparing compounds of Formula (Ia) or (Ia') which comprises,

(a) reacting the compound (II) with N-protected L-proline in an organic solvent or a mixture of said organic solvent and water in the presence of an organic or inorganic base and an acid activator to give the compound of Formula

(III); and

(b) conducting column chromatography, optionally followed by acid-catalized hydrolysis to give the compound (Ia) or (Ia'):



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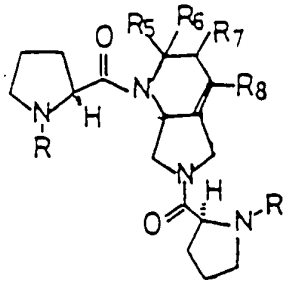
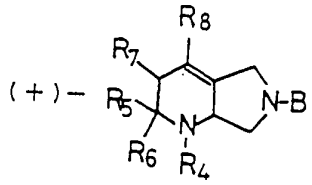
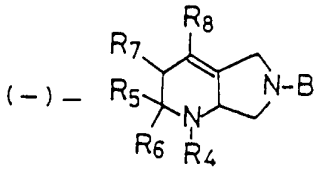


(III)



(Ia)



(Ia')

wherein, R_4, R_5, R_6, R_7, R_8 and B are the same as defined in Claim 3, and R is an amino-protecting group.

7. A process for preparing a compound of formula (IA) or (IA') which process comprises preparing a compound of formula (Ia) or (Ia') according to claim 5 or 6 and thereafter converting the compound of formula (Ia) or (Ia') to (IA) or (IA'):

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 94/00175

A. CLASSIFICATION OF SUBJECT MATTER

IPC[6]: C 07 D 471/04

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[6]: C 07 D 471/04

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

AT, Chemical Abstracts

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Questel: DARC, CAS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE 39 06 365 A1 (BAYER) 18 January 1990 (18.01.90), claims 1,4-6; example 31.	1,5-7
A	EP 05 50 903 A1 (BAYER) 14 July 1993 (14.07.93), claims 1,6,7; example 20.	1,5-7
A	EP 05 23 512 A1 (BAYER) 20 January 1993 (20.01.93), page 19, line 5; claim 7.	1,5-7
A	US 51 40 033 A (SCHRIEWER) 18 August 1992 (18.08.92), examples 1,6,7; columns 11-24.	1,3,4

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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
01 February 1995 (01.02.95)	13 March 1995 (13.03.95)

Name and mailing address of the ISA/ AT	Authorized officer
AUSTRIAN PATENT OFFICE Kohlmarkt 8-10 A-1014 Vienna	Hammer e.h.
Facsimile No. 1/53424/535	Telephone No. 1/5337058/44

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/KR 94/00175

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/KR 94/00175

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